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(54) Titre : VACCIN CONTRE LE VIRUS DE LA GRIPPE A LARGE SPECTRE
(54) Title: BROAD SPECTRUM INFLUENZA VIRUS VACCINE

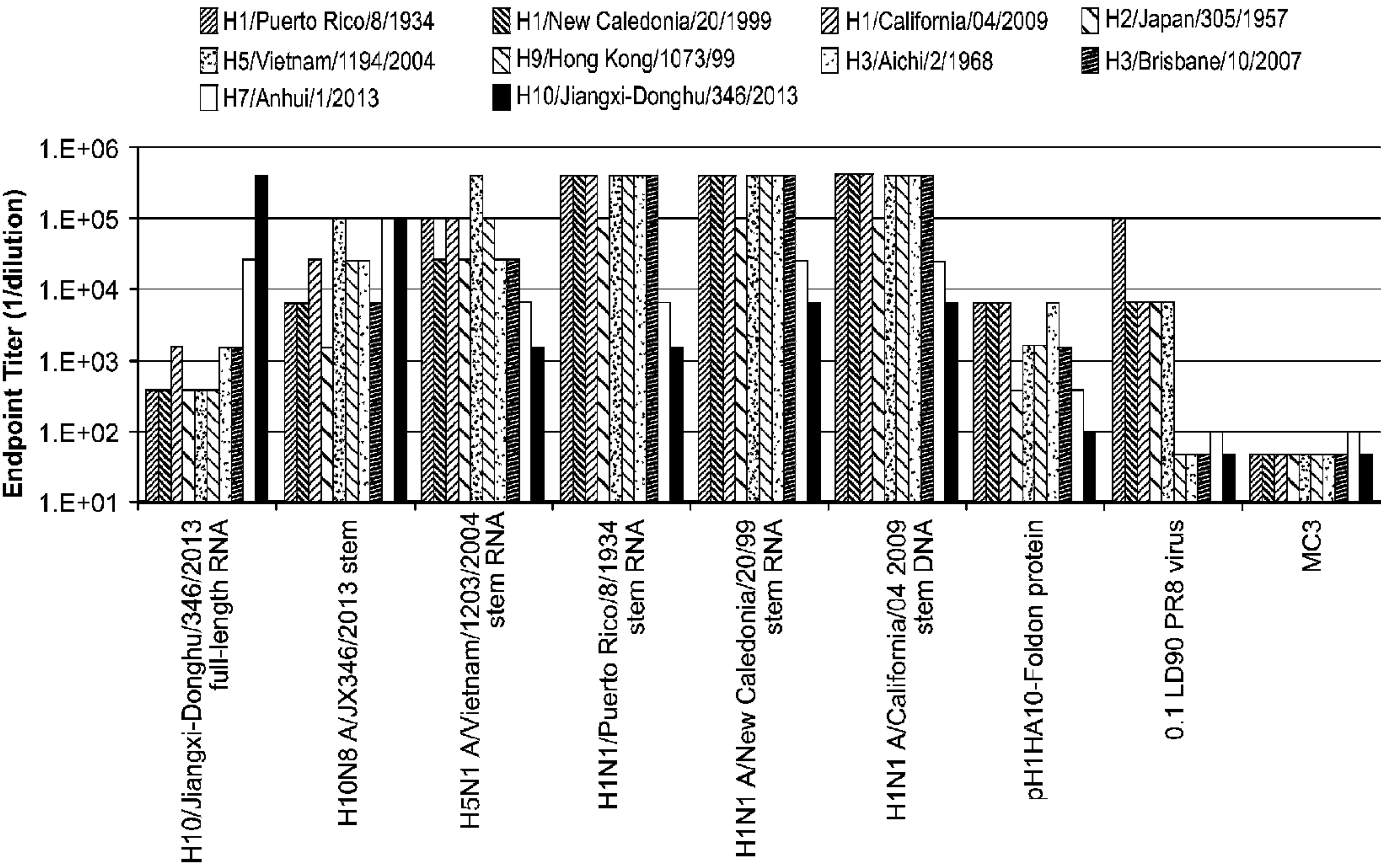


Fig. 1

(57) **Abrégé/Abstract:**
The disclosure relates to influenza virus ribonucleic acid (RNA) vaccines, as well as methods of using the vaccines and compositions comprising the vaccines.

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(54) Title: BROAD SPECTRUM INFLUENZA VIRUS VACCINE

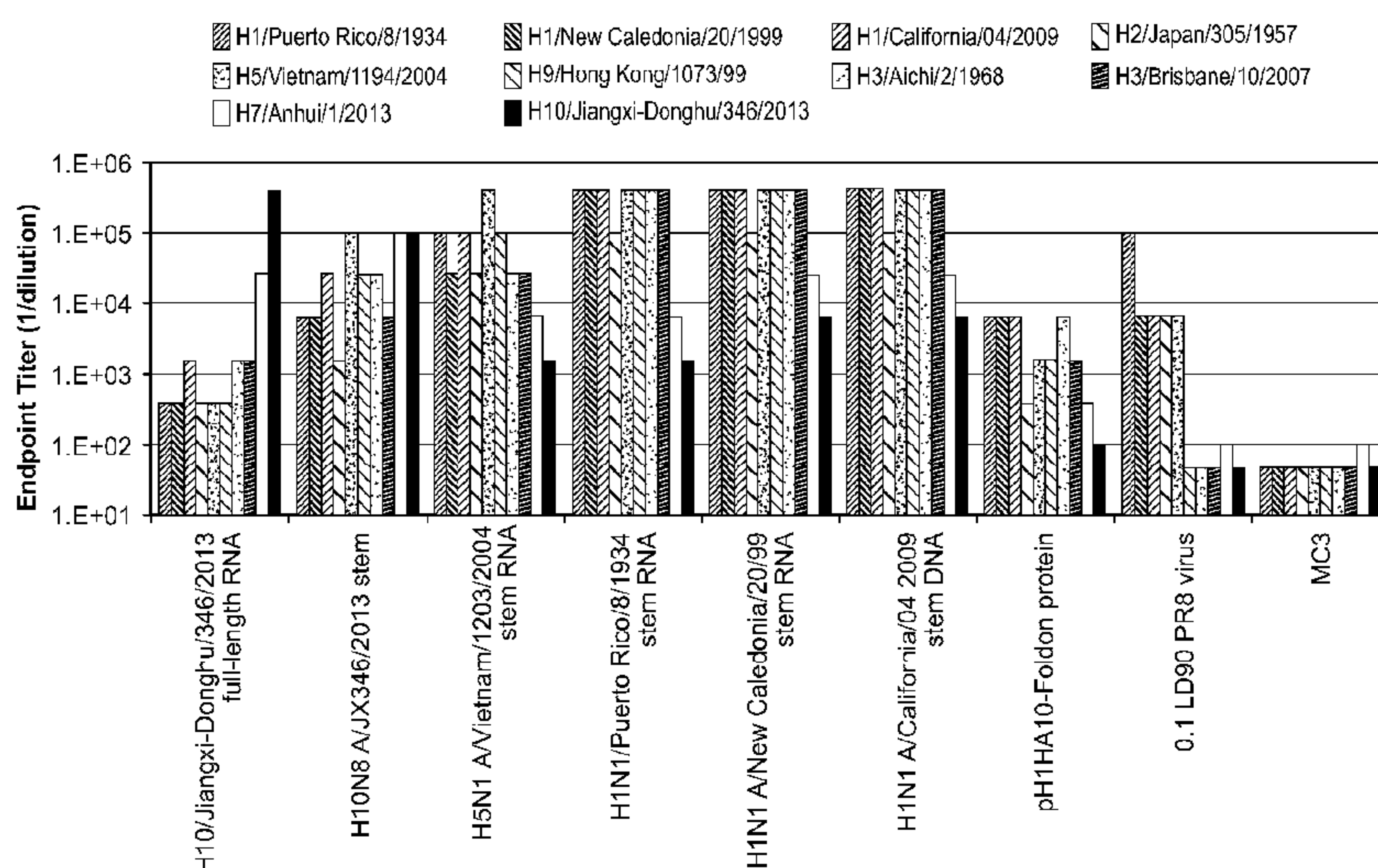


Fig. 1

(57) Abstract: The disclosure relates to influenza virus ribonucleic acid (RNA) vaccines, as well as methods of using the vaccines and compositions comprising the vaccines.

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JUMBO APPLICATIONS/PATENTS

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BROAD SPECTRUM INFLUENZA VIRUS VACCINE

RELATED APPLICATIONS

This application claims the benefit under 35 U.S.C. § 119(e) of U.S. provisional application number 62/245,225, filed October 22, 2015, U.S. provisional application number 62/247,501, filed October 28, 2015, U.S. provisional application number 62/248,248, filed October 29, 2015, and U.S. provisional application number 62/245,031, filed October 22, 2015, each of which is incorporated by reference herein in its entirety.

BACKGROUND

Influenza viruses are members of the orthomyxoviridae family, and are classified into three distinct types (A, B, and C), based on antigenic differences between their nucleoprotein (NP) and matrix (M) protein. The orthomyxoviruses are enveloped animal viruses of approximately 100 nm in diameter. The influenza virions consist of an internal ribonucleoprotein core (a helical nucleocapsid) containing a single-stranded RNA genome, and an outer lipoprotein envelope lined inside by a matrix protein (M1). The segmented genome of influenza A virus consists of eight molecules (seven for influenza C virus) of linear, negative polarity, single-stranded RNAs, which encode several polypeptides including: the RNA-directed RNA polymerase proteins (PB2, PB1 and PA) and nucleoprotein (NP), which form the nucleocapsid; the matrix proteins (M1, M2, which is also a surface-exposed protein embedded in the virus membrane); two surface glycoproteins, which project from the lipoprotein envelope: hemagglutinin (HA) and neuraminidase (NA); and nonstructural proteins (NS1 and NS2). Transcription and replication of the genome takes place in the nucleus and assembly takes place at the plasma membrane.

Hemagglutinin is the major envelope glycoprotein of influenza A and B viruses, and hemagglutinin-esterase (HE) of influenza C viruses is a protein homologous to HA. The rapid evolution of the HA protein of the influenza virus results in the constant emergence of new strains, rendering the adaptive immune response of the host only partially protective to new infections. The biggest challenge for therapy and prophylaxis against influenza and other infections using traditional vaccines is the limitation of vaccines in breadth, providing protection only against closely related subtypes. In addition, the length of time required to complete current standard influenza virus vaccine production processes inhibits the rapid development and production of an adapted vaccine in a pandemic situation.

Deoxyribonucleic acid (DNA) vaccination is one technique used to stimulate humoral and cellular immune responses to foreign antigens, such as influenza antigens. The direct

injection of genetically engineered DNA (*e.g.*, naked plasmid DNA) into a living host results in a small number of its cells directly producing an antigen, resulting in a protective immunological response. With this technique, however, come potential problems, including the possibility of insertional mutagenesis, which could lead to the activation of oncogenes or the inhibition of tumor suppressor genes.

SUMMARY

Provided herein is a ribonucleic acid (RNA) vaccine (or a composition or an immunogenic composition) that builds on the knowledge that RNA (*e.g.*, messenger RNA (mRNA)) can safely direct the body's cellular machinery to produce nearly any protein of interest, from native proteins to antibodies and other entirely novel protein constructs that can have therapeutic activity inside and outside of cells. The RNA vaccines of the present disclosure may be used to induce a balanced immune response against influenza virus, comprising both cellular and humoral immunity, without risking the possibility of insertional mutagenesis, for example.

The RNA (*e.g.*, mRNA) vaccines may be utilized in various settings depending on the prevalence of the infection or the degree or level of unmet medical need. The RNA vaccines may be utilized to treat and/or prevent an influenza virus of various genotypes, strains, and isolates. The RNA vaccines typically have superior properties in that they produce much larger antibody titers and produce responses earlier than commercially available anti-viral therapeutic treatments. While not wishing to be bound by theory, it is believed that the RNA vaccines, as mRNA polynucleotides, are better designed to produce the appropriate protein conformation upon translation as the RNA vaccines co-opt natural cellular machinery. Unlike traditional vaccines, which are manufactured *ex vivo* and may trigger unwanted cellular responses, RNA (*e.g.*, mRNA) vaccines are presented to the cellular system in a more native fashion.

There may be situations where persons are at risk for infection with more than one strain of influenza virus. RNA (*e.g.*, mRNA) therapeutic vaccines are particularly amenable to combination vaccination approaches due to a number of factors including, but not limited to, speed of manufacture, ability to rapidly tailor vaccines to accommodate perceived geographical threat, and the like. Moreover, because the vaccines utilize the human body to produce the antigenic protein, the vaccines are amenable to the production of larger, more complex antigenic proteins, allowing for proper folding, surface expression, antigen presentation, *etc.* in the human subject. To protect against more than one strain of influenza,

a combination vaccine can be administered that includes RNA (*e.g.*, mRNA) encoding at least one antigenic polypeptide protein (or antigenic portion thereof) of a first influenza virus or organism and further includes RNA encoding at least one antigenic polypeptide protein (or antigenic portion thereof) of a second influenza virus or organism. RNA (*e.g.*, mRNA) can be co-formulated, for example, in a single lipid nanoparticle (LNP) or can be formulated in separate LNPs for co-administration.

Some embodiments of the present disclosure provide influenza virus (influenza) vaccines (or compositions or immunogenic compositions) that include at least one RNA polynucleotide having an open reading frame encoding at least one influenza antigenic polypeptide or an immunogenic fragment thereof (*e.g.*, an immunogenic fragment capable of inducing an immune response to influenza).

In some embodiments, the at least one antigenic polypeptide is one of the defined antigenic subdomains of HA, termed HA1, HA2, or a combination of HA1 and HA2, and at least one antigenic polypeptide selected from neuraminidase (NA), nucleoprotein (NP), matrix protein 1 (M1), matrix protein 2 (M2), non-structural protein 1 (NS1) and non-structural protein 2 (NS2).

In some embodiments, the at least one antigenic polypeptide is HA or derivatives thereof comprising antigenic sequences from HA1 and/or HA2, and at least one antigenic polypeptide selected from NA, NP, M1, M2, NS1 and NS2.

In some embodiments, the at least one antigenic polypeptide is HA or derivatives thereof comprising antigenic sequences from HA1 and/or HA2 and at least two antigenic polypeptides selected from NA, NP, M1, M2, NS1 and NS2.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding an influenza virus protein, or an immunogenic fragment thereof.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding multiple influenza virus proteins, or immunogenic fragments thereof.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA protein, or an immunogenic fragment thereof (*e.g.*, at least one HA1, HA2, or a combination of both).

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA protein, or an immunogenic fragment thereof (*e.g.*, at least one HA1, HA2, or a combination of both, of any one of or a combination of any or all of H1, H2, H3, H4, H5, H6, H7, H8, H9, H10, H11, H12, H13,

H14, H15, H16, H17, and/or H18) and at least one other RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a protein selected from a NP protein, a NA protein, a M1 protein, a M2 protein, a NS1 protein and a NS2 protein obtained from influenza virus.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA)

5 polynucleotide having an open reading frame encoding a HA protein, or an immunogenic fragment thereof (*e.g.*, at least one any one of or a combination of any or all of H1, H2, H3, H4, H5, H6, H7, H8, H9, H10, H11, H12, H13, H14, H15, H16, H17, and/or H18) and at least two other RNAs (*e.g.*, mRNAs) polynucleotides having two open reading frames encoding two proteins selected from a NP protein, a NA protein, a M1 protein, a M2 protein,
10 a NS1 protein and a NS2 protein obtained from influenza virus.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA)

polynucleotide having an open reading frame encoding a HA protein, or an immunogenic fragment thereof (*e.g.*, at least one of any one of or a combination of any or all of H1, H2, H3, H4, H5, H6, H7, H8, H9, H10, H11, H12, H13, H14, H15, H16, H17, and/or H18) and at
15 least three other RNAs (*e.g.*, mRNAs) polynucleotides having three open reading frames encoding three proteins selected from a NP protein, a NA protein, a M1 protein, a M2 protein, a NS1 protein and a NS2 protein obtained from influenza virus.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA)

polynucleotide having an open reading frame encoding a HA protein, or an immunogenic
20 fragment thereof (*e.g.*, at least one of any one of or a combination of any or all of H1, H2, H3, H4, H5, H6, H7, H8, H9, H10, H11, H12, H13, H14, H15, H16, H17, and/or H18) and at least four other RNAs (*e.g.*, mRNAs) polynucleotides having four open reading frames encoding four proteins selected from a NP protein, a NA protein, a M1 protein, a M2 protein, a NS1 protein and a NS2 protein obtained from influenza virus.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA)

polynucleotide having an open reading frame encoding a HA protein, or an immunogenic
25 fragment thereof (*e.g.*, at least one of any one of or a combination of any or all of H1, H2, H3, H4, H5, H6, H7, H8, H9, H10, H11, H12, H13, H14, H15, H16, H17, and/or H18) and at least five other RNAs (*e.g.*, mRNAs) polynucleotides having five open reading frames
30 encoding five proteins selected from a NP protein, a NA protein, a M1 protein, a M2 protein, a NS1 protein and a NS2 protein obtained from influenza virus.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA)

polynucleotide having an open reading frame encoding a HA protein or an immunogenic
fragment thereof (*e.g.*, at least one of any one of or a combination of any or all of H1, H2,
35 H3, H4, H5, H6, H7, H8, H9, H10, H11, H12, H13, H14, H15, H16, H17, and/or H18), a NP

protein or an immunogenic fragment thereof, a NA protein or an immunogenic fragment thereof, a M1 protein or an immunogenic fragment thereof, a M2 protein or an immunogenic fragment thereof, a NS1 protein or an immunogenic fragment thereof and a NS2 protein or an immunogenic fragment thereof obtained from influenza virus.

Some embodiments of the present disclosure provide the following novel influenza virus polypeptide sequences: H1HA10-Foldon_ΔNgly1; H1HA10TM-PR8 (H1 A/Puerto Rico/8/34 HA); H1HA10-PR8-DS (H1 A/Puerto Rico/8/34 HA; pH1HA10-Cal04-DS (H1 A/California/04/2009 HA); Pandemic H1HA10 from California 04; pH1HA10-ferritin; HA10; Pandemic H1HA10 from California 04; Pandemic H1HA10 from California 04 strain/without foldon and with K68C/R76C mutation for trimerization; H1HA10 from A/Puerto Rico/8/34 strain, without foldon and with Y94D/N95L mutation for trimerization; H1HA10 from A/Puerto Rico/8/34 strain, without foldon and with K68C/R76C mutation for trimerization; H1N1 A/Viet Nam/850/2009; H3N2 A/Wisconsin/67/2005; H7N9 (A/Anhui/1/2013); H9N2 A/Hong Kong/1073/99; H10N8 A/JX346/2013.

Some embodiments of the present disclosure provide influenza virus (influenza) vaccines that include at least one RNA polynucleotide having an open reading frame encoding at least one influenza antigenic polypeptide or an immunogenic fragment of the novel influenza virus polypeptide sequences described above (*e.g.*, an immunogenic fragment capable of inducing an immune response to influenza). In some embodiments, an influenza vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding at least one influenza antigenic polypeptide comprising a modified sequence that is at least 75% (*e.g.*, any number between 75% and 100%, inclusive, *e.g.*, 70 %, 80%, 85%, 90%, 95%, 99%, and 100%) identity to an amino acid sequence of the novel influenza virus sequences described above. The modified sequence can be at least 75% (*e.g.*, any number between 75% and 100%, inclusive, *e.g.*, 70 %, 80%, 85%, 90%, 95%, 99%, and 100%) identical to an amino acid sequence of the novel influenza virus sequences described above.

Some embodiments of the present disclosure provide an isolated nucleic acid comprising a sequence encoding the novel influenza virus polypeptide sequences described above; an expression vector comprising the nucleic acid; and a host cell comprising the nucleic acid. The present disclosure also provides a method of producing a polypeptide of any of the novel influenza virus sequences described above. A method may include culturing the host cell in a medium under conditions permitting nucleic acid expression of the novel influenza virus sequences described above, and purifying from the cultured cell or the medium of the cell a novel influenza virus polypeptide. The present disclosure also provides

antibody molecules, including full length antibodies and antibody derivatives, directed against the novel influenza virus sequences.

In some embodiments, an open reading frame of a RNA (*e.g.*, mRNA) vaccine is codon-optimized. In some embodiments, at least one RNA polynucleotide encodes at least one antigenic polypeptide comprising an amino acid sequence identified by any one of SEQ ID NO: 1-444, 458, 460, 462-479 (*see also* Tables 7-13) and is codon optimized mRNA.

In some embodiments, a RNA (*e.g.*, mRNA) vaccine further comprising an adjuvant.

Tables 7-13 provide National Center for Biotechnology Information (NCBI) accession numbers of interest. It should be understood that the phrase “an amino acid sequence of Tables 7-13” refers to an amino acid sequence identified by one or more NCBI accession numbers listed in 7-13. Each of the amino acid sequences, and variants having greater than 95% identity or greater than 98% identity to each of the amino acid sequences encompassed by the accession numbers of Tables 7-13 are included within the constructs (polynucleotides/polypeptides) of the present disclosure.

In some embodiments, at least one mRNA polynucleotide is encoded by a nucleic acid comprising a sequence identified by any one of SEQ ID NO: 447-457, 459, 461 and having less than 80% identity to wild-type mRNA sequence. In some embodiments, at least one mRNA polynucleotide is encoded by a nucleic acid comprising a sequence identified by any one SEQ ID NO: 447-457, 459, 461 and having less than 75%, 85% or 95% identity to a wild-type mRNA sequence. In some embodiments, at least one mRNA polynucleotide is encoded by nucleic acid comprising a sequence identified by any one of SEQ ID NO: 447-457, 459, 461 and having less than 50-80%, 60- 80%, 40-80%, 30-80%, 70-80%, 75-80% or 78-80% identity to wild-type mRNA sequence. In some embodiments, at least one mRNA polynucleotide is encoded by a nucleic acid comprising a sequence identified by any one of SEQ ID NO: 447-457, 459, 461 and having less than 40-85%, 50-85%, 60-85%, 30-85%, 70-85%, 75-85% or 80-85% identity to wild-type mRNA sequence. In some embodiments, at least one mRNA polynucleotide is encoded by a nucleic acid comprising a sequence identified by any one of SEQ ID NO: 447-457, 459, 461 and having less than 40-90%, 50-90%, 60-90%, 30-90%, 70-90%, 75-90%, 80-90%, or 85-90% identity to wild-type mRNA sequence.

In some embodiments, at least one mRNA polynucleotide comprises a sequence identified by any one of SEQ ID NO: 491-503 and has less than 80% identity to wild-type mRNA sequence. In some embodiments, at least one mRNA polynucleotide is encoded by a nucleic acid comprising a sequence identified by any one SEQ ID NO: 491-503 and has less than 75%, 85% or 95% identity to a wild-type mRNA sequence. In some embodiments, at

least one mRNA polynucleotide is encoded by nucleic acid comprising a sequence identified by any one of SEQ ID NO: 491-503 and has less than 50-80%, 60- 80%, 40-80%, 30-80%, 70-80%, 75-80% or 78-80% identity to wild-type mRNA sequence. In some embodiments, at least one mRNA polynucleotide is encoded by a nucleic acid comprising a sequence

5 identified by any one of SEQ ID NO: 491-503 and has less than 40-85%, 50-85%, 60-85%, 30-85%, 70-85%, 75-85% or 80-85% identity to wild-type mRNA sequence. In some embodiments, at least one mRNA polynucleotide is encoded by a nucleic acid comprising a sequence identified by any one of SEQ ID NO: 491-503 and has less than 40-90%, 50- 90%, 60-90%, 30-90%, 70-90%, 75-90%, 80-90%, or 85-90% identity to wild-type mRNA
10 sequence.

In some embodiments, at least one RNA polynucleotide encodes at least one antigenic polypeptide comprising an amino acid sequence identified by any one of SEQ ID NO: 1-444, 458, 460, 462-479 (see also Tables 7-13) and having at least 80% (*e.g.*, 85%, 90%, 95%, 98%, 99%) identity to wild-type mRNA sequence, but does not include wild-type mRNA
15 sequence.

In some embodiments, at least one RNA polynucleotide encodes at least one antigenic polypeptide comprising an amino acid sequence identified by any one of SEQ ID NO: 1-444, 458, 460, 462-479 (see also Tables 7-13) and has less than 95%, 90%, 85%, 80% or 75% identity to wild-type mRNA sequence. In some embodiments, at least one RNA
20 polynucleotide encodes at least one antigenic polypeptide comprising an amino acid sequence identified by any one of SEQ ID NO: 1-444, 458, 460, 462-479 (see also Tables 7-13) and has 30-80%, 40-80%, 50-80%, 60-80%, 70-80%, 75-80% or 78-80%, 30-85%, 40-85%, 50-805%, 60-85%, 70-85%, 75-85% or 78-85%, 30-90%, 40-90%, 50-90%, 60-90%, 70-90%, 75-90%, 80-90% or 85-90% identity to wild-type mRNA sequence.

25 In some embodiments, at least one RNA polynucleotide encodes at least one antigenic polypeptide having at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to an amino acid sequence identified by any one of SEQ ID NO: 1-444, 458, 460, 462-479 (see also Tables 7-13). In some embodiments, at least one RNA polynucleotide encodes at least one antigenic polypeptide having 95%-99% identity to an
30 amino acid sequence identified by any one of 1-444, 458, 460, 462-479 (see also Tables 7-13).

In some embodiments, at least one RNA polynucleotide encodes at least one antigenic polypeptide having at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to amino acid sequence identified by any one of SEQ ID NO: 1-444, 458,
35 460, 462-479 (see also Tables 7-13) and having membrane fusion activity. In some

embodiments, at least one RNA polynucleotide encodes at least one antigenic polypeptide having 95%-99% identity to amino acid sequence identified by any one of SEQ ID NO: 1-444, 458, 460, 462-479 (see also Tables 7-13) and having membrane fusion activity.

5 In some embodiments, at least one RNA polynucleotide encodes at least one influenza antigenic polypeptide that attaches to cell receptors.

In some embodiments, at least one RNA polynucleotide encodes at least one influenza antigenic polypeptide that causes fusion of viral and cellular membranes.

In some embodiments, at least one RNA polynucleotide encodes at least one influenza antigenic polypeptide that is responsible for binding of the virus to a cell being infected.

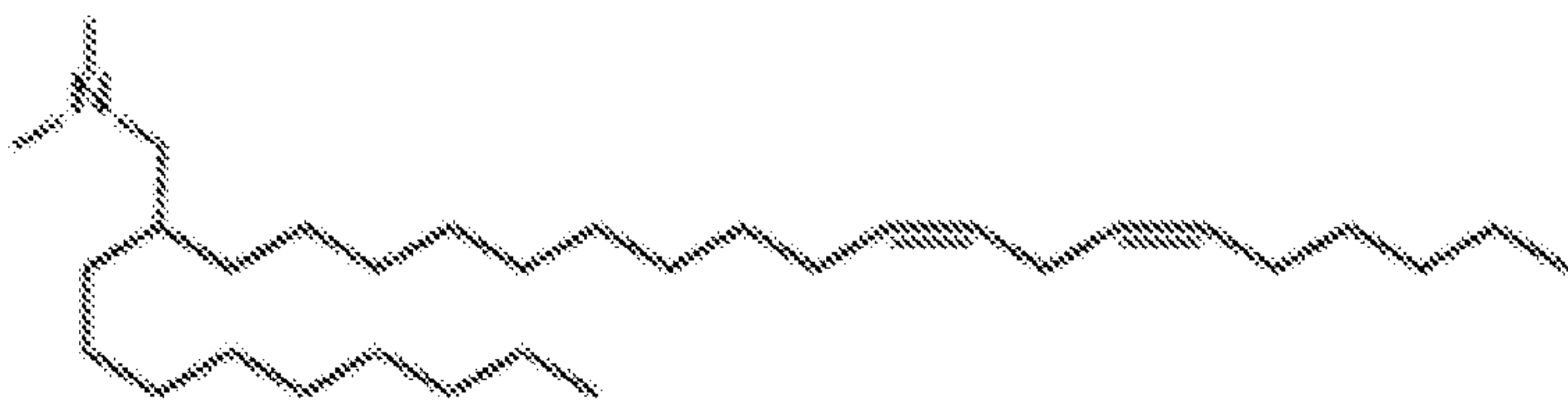
10 Some embodiments of the present disclosure provide a vaccine that includes at least one ribonucleic acid (RNA) (*e.g.*, mRNA) polynucleotide having an open reading frame encoding at least one influenza antigenic polypeptide, at least one 5' terminal cap and at least one chemical modification, formulated within a lipid nanoparticle.

In some embodiments, a 5' terminal cap is 7mG(5')ppp(5')NlmpNp.

15 In some embodiments, at least one chemical modification is selected from pseudouridine, N1-methylpseudouridine, N1-ethylpseudouridine, 2-thiouridine, 4'-thiouridine, 5-methylcytosine, 5-methyluridine, 2-thio-1-methyl-1-deaza-pseudouridine, 2-thio-1-methyl-pseudouridine, 2-thio-5-aza-uridine, 2-thio-dihydropseudouridine, 2-thio-dihydrouridine, 2-thio-pseudouridine, 4-methoxy-2-thio-pseudouridine, 4-methoxy-pseudouridine, 4-thio-1-methyl-pseudouridine, 4-thio-pseudouridine, 5-aza-uridine, 20 dihydropseudouridine, 5-methoxyuridine and 2'-O-methyl uridine. In some embodiments, the chemical modification is in the 5-position of the uracil. In some embodiments, the chemical modification is a N1-methylpseudouridine. In some embodiments, the chemical modification is a N1-ethylpseudouridine.

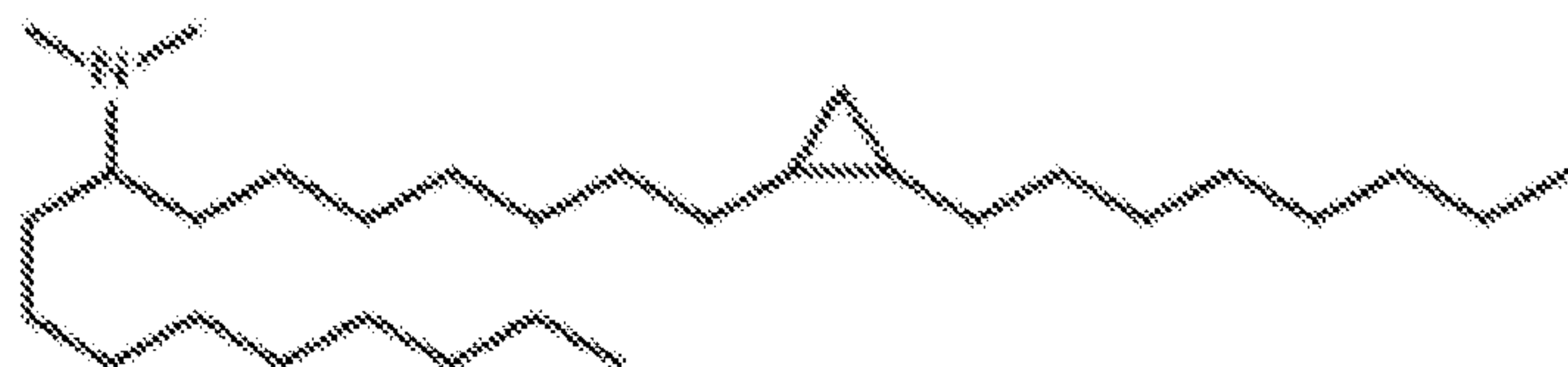
25 In some embodiments, a lipid nanoparticle comprises a cationic lipid, a PEG-modified lipid, a sterol and a non-cationic lipid. In some embodiments, a cationic lipid is an ionizable cationic lipid and the non-cationic lipid is a neutral lipid, and the sterol is a cholesterol. In some embodiments, a cationic lipid is selected from the group consisting of 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-
30 dimethylaminobutyrate (DLin-MC3-DMA), di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), (12Z,15Z)-N,N-dimethyl-2-nonylhenicosa-12,15-dien-1-amine (L608), and N,N-dimethyl-1-[(1S,2R)-2-octylcyclopropyl]heptadecan-8-amine (L530).

In some embodiments, the lipid is



(L608).

In some embodiments, the lipid is



(L530).

Some embodiments of the present disclosure provide a vaccine that includes at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding at least one influenza antigenic polypeptide, wherein at least 80% (*e.g.*, 85%, 90%, 95%, 98%, 99%) of the uracil in the open reading frame have a chemical modification, optionally wherein the vaccine is formulated in a lipid nanoparticle (*e.g.*, a lipid nanoparticle comprises a cationic lipid, a PEG-modified lipid, a sterol and a non-cationic lipid).

In some embodiments, 100% of the uracil in the open reading frame have a chemical modification. In some embodiments, a chemical modification is in the 5-position of the uracil. In some embodiments, a chemical modification is a N1-methyl pseudouridine. In some embodiments, 100% of the uracil in the open reading frame have a N1-methyl pseudouridine in the 5-position of the uracil.

In some embodiments, an open reading frame of a RNA (*e.g.*, mRNA) polynucleotide encodes at least two influenza antigenic polypeptides. In some embodiments, the open reading frame encodes at least five or at least ten antigenic polypeptides. In some embodiments, the open reading frame encodes at least 100 antigenic polypeptides. In some embodiments, the open reading frame encodes 2-100 antigenic polypeptides.

In some embodiments, a vaccine comprises at least two RNA (*e.g.*, mRNA) polynucleotides, each having an open reading frame encoding at least one influenza antigenic polypeptide. In some embodiments, the vaccine comprises at least five or at least ten RNA (*e.g.*, mRNA) polynucleotides, each having an open reading frame encoding at least one antigenic polypeptide or an immunogenic fragment thereof. In some embodiments, the vaccine comprises at least 100 RNA (*e.g.*, mRNA) polynucleotides, each having an open reading frame encoding at least one antigenic polypeptide. In some embodiments, the vaccine comprises 2-100 RNA (*e.g.*, mRNA) polynucleotides, each having an open reading frame encoding at least one antigenic polypeptide.

In some embodiments, at least one influenza antigenic polypeptide is fused to a signal peptide. In some embodiments, the signal peptide is selected from: a HuIgGk signal peptide (METPAQLLFLLLLWLPDTTG; SEQ ID NO: 480); IgE heavy chain epsilon-1 signal peptide (MDWTWILFLVAAATRVHS; SEQ ID NO: 481); Japanese encephalitis PRM
 5 signal sequence (MLGSNSGQRVVFTILLLLVAPAYS; SEQ ID NO: 482), VSVg protein signal sequence (MKCLLYLAFLFIGVNCA; SEQ ID NO: 483) and Japanese encephalitis JEV signal sequence (MWLVSLAIVTACAGA; SEQ ID NO: 484).

In some embodiments, the signal peptide is fused to the N-terminus of at least one antigenic polypeptide. In some embodiments, a signal peptide is fused to the C-terminus of
 10 at least one antigenic polypeptide.

In some embodiments, at least one influenza antigenic polypeptide comprises a mutated N-linked glycosylation site.

Also provided herein is an influenza RNA (*e.g.*, mRNA) vaccine of any one of the foregoing paragraphs formulated in a nanoparticle (*e.g.*, a lipid nanoparticle).

15 In some embodiments, the nanoparticle has a mean diameter of 50-200 nm. In some embodiments, the nanoparticle is a lipid nanoparticle. In some embodiments, the lipid nanoparticle comprises a cationic lipid, a PEG-modified lipid, a sterol and a non-cationic lipid. In some embodiments, the lipid nanoparticle comprises a molar ratio of about 20-60% cationic lipid, 0.5- 15% PEG-modified lipid, 25-55% sterol, and 25% non-cationic lipid. In
 20 some embodiments, the cationic lipid is an ionizable cationic lipid and the non-cationic lipid is a neutral lipid, and the sterol is a cholesterol. In some embodiments, the cationic lipid is selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319).

25 In some embodiments, the nanoparticle has a polydispersity value of less than 0.4 (*e.g.*, less than 0.3, 0.2 or 0.1).

In some embodiments, the nanoparticle has a net neutral charge at a neutral pH value.

In some embodiments, the RNA (*e.g.*, mRNA) vaccine is multivalent.

Some embodiments of the present disclosure provide methods of inducing an antigen
 30 specific immune response in a subject, comprising administering to the subject any of the RNA (*e.g.*, mRNA) vaccine as provided herein in an amount effective to produce an antigen-specific immune response. In some embodiments, the RNA (*e.g.*, mRNA) vaccine is an influenza vaccine. In some embodiments, the RNA (*e.g.*, mRNA) vaccine is a combination vaccine comprising a combination of influenza vaccines (a broad spectrum influenza
 35 vaccine).

In some embodiments, an antigen-specific immune response comprises a T cell response or a B cell response.

In some embodiments, a method of producing an antigen-specific immune response comprises administering to a subject a single dose (no booster dose) of an influenza RNA (e.g., mRNA) vaccine of the present disclosure.

In some embodiments, a method further comprises administering to the subject a second (booster) dose of an influenza RNA (e.g., mRNA) vaccine. Additional doses of an influenza RNA (e.g., mRNA) vaccine may be administered.

In some embodiments, the subjects exhibit a seroconversion rate of at least 80% (e.g., at least 85%, at least 90%, or at least 95%) following the first dose or the second (booster) dose of the vaccine. Seroconversion is the time period during which a specific antibody develops and becomes detectable in the blood. After seroconversion has occurred, a virus can be detected in blood tests for the antibody. During an infection or immunization, antigens enter the blood, and the immune system begins to produce antibodies in response. Before seroconversion, the antigen itself may or may not be detectable, but antibodies are considered absent. During seroconversion, antibodies are present but not yet detectable. Any time after seroconversion, the antibodies can be detected in the blood, indicating a prior or current infection.

In some embodiments, an influenza RNA (e.g., mRNA) vaccine is administered to a subject by intradermal injection, intramuscular injection, or by intranasal administration. In some embodiments, an influenza RNA (e.g., mRNA) vaccine is administered to a subject by intramuscular injection.

Some embodiments, of the present disclosure provide methods of inducing an antigen specific immune response in a subject, including administering to a subject an influenza RNA (e.g., mRNA) vaccine in an effective amount to produce an antigen specific immune response in a subject. Antigen-specific immune responses in a subject may be determined, in some embodiments, by assaying for antibody titer (for titer of an antibody that binds to an influenza antigenic polypeptide) following administration to the subject of any of the influenza RNA (e.g., mRNA) vaccines of the present disclosure. In some embodiments, the anti-antigenic polypeptide antibody titer produced in the subject is increased by at least 1 log relative to a control. In some embodiments, the anti-antigenic polypeptide antibody titer produced in the subject is increased by 1-3 log relative to a control.

In some embodiments, the anti-antigenic polypeptide antibody titer produced in a subject is increased at least 2 times relative to a control. In some embodiments, the anti-antigenic polypeptide antibody titer produced in the subject is increased at least 5 times

relative to a control. In some embodiments, the anti-antigenic polypeptide antibody titer produced in the subject is increased at least 10 times relative to a control. In some embodiments, the anti-antigenic polypeptide antibody titer produced in the subject is increased 2-10 times relative to a control.

5 In some embodiments, the control is an anti-antigenic polypeptide antibody titer produced in a subject who has not been administered a RNA (*e.g.*, mRNA) vaccine of the present disclosure. In some embodiments, the control is an anti-antigenic polypeptide antibody titer produced in a subject who has been administered a live attenuated or inactivated influenza, or wherein the control is an anti-antigenic polypeptide antibody titer
10 produced in a subject who has been administered a recombinant or purified influenza protein vaccine. In some embodiments, the control is an anti-antigenic polypeptide antibody titer produced in a subject who has been administered an influenza virus-like particle (VLP) vaccine (*see, e.g.*, Cox RG *et al.*, *J Virol.* 2014 Jun; 88(11): 6368–6379).

A RNA (*e.g.*, mRNA) vaccine of the present disclosure is administered to a subject in
15 an effective amount (an amount effective to induce an immune response). In some embodiments, the effective amount is a dose equivalent to an at least 2-fold, at least 4-fold, at least 10-fold, at least 100-fold, at least 1000-fold reduction in the standard of care dose of a recombinant influenza protein vaccine, wherein the anti-antigenic polypeptide antibody titer produced in the subject is equivalent to an anti-antigenic polypeptide antibody titer produced
20 in a control subject administered the standard of care dose of a recombinant influenza protein vaccine, a purified influenza protein vaccine, a live attenuated influenza vaccine, an inactivated influenza vaccine, or an influenza VLP vaccine. In some embodiments, the effective amount is a dose equivalent to 2-1000-fold reduction in the standard of care dose of a recombinant influenza protein vaccine, wherein the anti-antigenic polypeptide antibody titer
25 produced in the subject is equivalent to an anti-antigenic polypeptide antibody titer produced in a control subject administered the standard of care dose of a recombinant influenza protein vaccine, a purified influenza protein vaccine, a live attenuated influenza vaccine, an inactivated influenza vaccine, or an influenza VLP vaccine.

In some embodiments, the control is an anti-antigenic polypeptide antibody titer
30 produced in a subject who has been administered a virus-like particle (VLP) vaccine comprising structural proteins of influenza.

In some embodiments, the RNA (*e.g.*, mRNA) vaccine is formulated in an effective amount to produce an antigen specific immune response in a subject.

In some embodiments, the effective amount is a total dose of 25 μ g to 1000 μ g, or 50
35 μ g to 1000 μ g. In some embodiments, the effective amount is a total dose of 100 μ g. In

some embodiments, the effective amount is a dose of 25 µg administered to the subject a total of two times. In some embodiments, the effective amount is a dose of 100 µg administered to the subject a total of two times. In some embodiments, the effective amount is a dose of 400 µg administered to the subject a total of two times. In some embodiments, the effective amount is a dose of 500 µg administered to the subject a total of two times.

In some embodiments, the efficacy (or effectiveness) of a RNA (*e.g.*, mRNA) vaccine is greater than 60%. In some embodiments, the RNA (*e.g.*, mRNA) polynucleotide of the vaccine at least one Influenza antigenic polypeptide.

Vaccine efficacy may be assessed using standard analyses (*see, e.g.*, Weinberg *et al.*, *J Infect Dis.* 2010 Jun 1;201(11):1607-10). For example, vaccine efficacy may be measured by double-blind, randomized, clinical controlled trials. Vaccine efficacy may be expressed as a proportionate reduction in disease attack rate (AR) between the unvaccinated (ARU) and vaccinated (ARV) study cohorts and can be calculated from the relative risk (RR) of disease among the vaccinated group with use of the following formulas:

$$\text{Efficacy} = (\text{ARU} - \text{ARV}) / \text{ARU} \times 100; \text{ and}$$

$$\text{Efficacy} = (1 - \text{RR}) \times 100.$$

Likewise, vaccine effectiveness may be assessed using standard analyses (*see, e.g.*, Weinberg *et al.*, *J Infect Dis.* 2010 Jun 1;201(11):1607-10). Vaccine effectiveness is an assessment of how a vaccine (which may have already proven to have high vaccine efficacy) reduces disease in a population. This measure can assess the net balance of benefits and adverse effects of a vaccination program, not just the vaccine itself, under natural field conditions rather than in a controlled clinical trial. Vaccine effectiveness is proportional to vaccine efficacy (potency) but is also affected by how well target groups in the population are immunized, as well as by other non-vaccine-related factors that influence the ‘real-world’ outcomes of hospitalizations, ambulatory visits, or costs. For example, a retrospective case control analysis may be used, in which the rates of vaccination among a set of infected cases and appropriate controls are compared. Vaccine effectiveness may be expressed as a rate difference, with use of the odds ratio (OR) for developing infection despite vaccination:

$$\text{Effectiveness} = (1 - \text{OR}) \times 100.$$

In some embodiments, the efficacy (or effectiveness) of a RNA (*e.g.*, mRNA) vaccine is at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, or at least 90%.

In some embodiments, the vaccine immunizes the subject against Influenza for up to 2 years. In some embodiments, the vaccine immunizes the subject against Influenza for more than 2 years, more than 3 years, more than 4 years, or for 5-10 years.

In some embodiments, the subject is about 5 years old or younger. For example, the subject may be between the ages of about 1 year and about 5 years (*e.g.*, about 1, 2, 3, 5 or 5 years), or between the ages of about 6 months and about 1 year (*e.g.*, about 6, 7, 8, 9, 10, 11 or 12 months). In some embodiments, the subject is about 12 months or younger (*e.g.*, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2 months or 1 month). In some embodiments, the subject is about 6 months or younger.

In some embodiments, the subject was born full term (*e.g.*, about 37-42 weeks). In some embodiments, the subject was born prematurely, for example, at about 36 weeks of gestation or earlier (*e.g.*, about 36, 35, 34, 33, 32, 31, 30, 29, 28, 27, 26 or 25 weeks). For example, the subject may have been born at about 32 weeks of gestation or earlier. In some embodiments, the subject was born prematurely between about 32 weeks and about 36 weeks of gestation. In such subjects, a RNA (*e.g.*, mRNA) vaccine may be administered later in life, for example, at the age of about 6 months to about 5 years, or older.

In some embodiments, the subject is a young adult between the ages of about 20 years and about 50 years (*e.g.*, about 20, 25, 30, 35, 40, 45 or 50 years old).

In some embodiments, the subject is an elderly subject about 60 years old, about 70 years old, or older (*e.g.*, about 60, 65, 70, 75, 80, 85 or 90 years old).

In some embodiments, the subject has been exposed to influenza (*e.g.*, *C. trachomatis*); the subject is infected with influenza (*e.g.*, *C. trachomatis*); or subject is at risk of infection by influenza (*e.g.*, *C. trachomatis*).

In some embodiments, the subject is immunocompromised (has an impaired immune system, *e.g.*, has an immune disorder or autoimmune disorder).

In some embodiments the nucleic acid vaccines described herein are chemically modified. In other embodiments the nucleic acid vaccines are unmodified.

Yet other aspects provide compositions for and methods of vaccinating a subject comprising administering to the subject a nucleic acid vaccine comprising one or more RNA polynucleotides having an open reading frame encoding a first virus antigenic polypeptide, wherein the RNA polynucleotide does not include a stabilization element, and wherein an adjuvant is not coformulated or co-administered with the vaccine.

In other aspects the invention is a composition for or method of vaccinating a subject comprising administering to the subject a nucleic acid vaccine comprising one or more RNA polynucleotides having an open reading frame encoding a first antigenic polypeptide wherein a dosage of between 10 $\mu\text{g/kg}$ and 400 $\mu\text{g/kg}$ of the nucleic acid vaccine is administered to the subject. In some embodiments the dosage of the RNA polynucleotide is 1-5 μg , 5-10 μg , 10-15 μg , 15-20 μg , 10-25 μg , 20-25 μg , 20-50 μg , 30-50 μg , 40-50 μg , 40-60 μg , 60-80 μg ,

60-100 μ g, 50-100 μ g, 80-120 μ g, 40-120 μ g, 40-150 μ g, 50-150 μ g, 50-200 μ g, 80-200 μ g, 100-200 μ g, 120-250 μ g, 150-250 μ g, 180-280 μ g, 200-300 μ g, 50-300 μ g, 80-300 μ g, 100-300 μ g, 40-300 μ g, 50-350 μ g, 100-350 μ g, 200-350 μ g, 300-350 μ g, 320-400 μ g, 40-380 μ g, 40-100 μ g, 100-400 μ g, 200-400 μ g, or 300-400 μ g per dose. In some embodiments, the
5 nucleic acid vaccine is administered to the subject by intradermal or intramuscular injection. In some embodiments, the nucleic acid vaccine is administered to the subject on day zero. In some embodiments, a second dose of the nucleic acid vaccine is administered to the subject on day twenty one.

In some embodiments, a dosage of 25 micrograms of the RNA polynucleotide is
10 included in the nucleic acid vaccine administered to the subject. In some embodiments, a dosage of 100 micrograms of the RNA polynucleotide is included in the nucleic acid vaccine administered to the subject. In some embodiments, a dosage of 50 micrograms of the RNA polynucleotide is included in the nucleic acid vaccine administered to the subject. In some
15 embodiments, a dosage of 75 micrograms of the RNA polynucleotide is included in the nucleic acid vaccine administered to the subject. In some embodiments, a dosage of 150 micrograms of the RNA polynucleotide is included in the nucleic acid vaccine administered to the subject. In some embodiments, a dosage of 400 micrograms of the RNA polynucleotide is included in the nucleic acid vaccine administered to the subject. In some embodiments, a
20 dosage of 200 micrograms of the RNA polynucleotide is included in the nucleic acid vaccine administered to the subject. In some embodiments, the RNA polynucleotide accumulates at a 100 fold higher level in the local lymph node in comparison with the distal lymph node. In other embodiments the nucleic acid vaccine is chemically modified and in other embodiments the nucleic acid vaccine is not chemically modified.

Aspects of the invention provide a nucleic acid vaccine comprising one or more RNA
25 polynucleotides having an open reading frame encoding a first antigenic polypeptide, wherein the RNA polynucleotide does not include a stabilization element, and a pharmaceutically acceptable carrier or excipient, wherein an adjuvant is not included in the vaccine. In some embodiments, the stabilization element is a histone stem-loop. In some embodiments, the stabilization element is a nucleic acid sequence having increased GC content relative to wild
30 type sequence.

Aspects of the invention provide nucleic acid vaccines comprising one or more RNA
polynucleotides having an open reading frame encoding a first antigenic polypeptide, wherein the RNA polynucleotide is present in the formulation for in vivo administration to a host, which confers an antibody titer superior to the criterion for seroprotection for the first antigen
35 for an acceptable percentage of human subjects. In some embodiments, the antibody titer

produced by the mRNA vaccines of the invention is a neutralizing antibody titer. In some embodiments the neutralizing antibody titer is greater than a protein vaccine. In other embodiments the neutralizing antibody titer produced by the mRNA vaccines of the invention is greater than an adjuvanted protein vaccine. In yet other embodiments the neutralizing antibody titer produced by the mRNA vaccines of the invention is 1,000- 10,000, 1,200- 10,000, 1,400- 10,000, 1,500- 10,000, 1,000- 5,000, 1,000- 4,000, 1,800- 10,000, 2000- 10,000, 2,000- 5,000, 2,000- 3,000, 2,000- 4,000, 3,000- 5,000, 3,000- 4,000, or 2,000- 2,500. A neutralization titer is typically expressed as the highest serum dilution required to achieve a 50% reduction in the number of plaques.

Also provided are nucleic acid vaccines comprising one or more RNA polynucleotides having an open reading frame encoding a first antigenic polypeptide, wherein the RNA polynucleotide is present in a formulation for in vivo administration to a host for eliciting a longer lasting high antibody titer than an antibody titer elicited by an mRNA vaccine having a stabilizing element or formulated with an adjuvant and encoding the first antigenic polypeptide. In some embodiments, the RNA polynucleotide is formulated to produce a neutralizing antibodies within one week of a single administration. In some embodiments, the adjuvant is selected from a cationic peptide and an immunostimulatory nucleic acid. In some embodiments, the cationic peptide is protamine.

Aspects provide nucleic acid vaccines comprising one or more RNA polynucleotides having an open reading frame comprising at least one chemical modification or optionally no modified nucleotides, the open reading frame encoding a first antigenic polypeptide, wherein the RNA polynucleotide is present in the formulation for in vivo administration to a host such that the level of antigen expression in the host significantly exceeds a level of antigen expression produced by an mRNA vaccine having a stabilizing element or formulated with an adjuvant and encoding the first antigenic polypeptide.

Other aspects provide nucleic acid vaccines comprising one or more RNA polynucleotides having an open reading frame comprising at least one chemical modification or optionally no modified nucleotides, the open reading frame encoding a first antigenic polypeptide, wherein the vaccine has at least 10 fold less RNA polynucleotide than is required for an unmodified mRNA vaccine to produce an equivalent antibody titer. In some embodiments, the RNA polynucleotide is present in a dosage of 25-100 micrograms.

Aspects of the invention also provide a unit of use vaccine, comprising between 10ug and 400 ug of one or more RNA polynucleotides having an open reading frame comprising at least one chemical modification or optionally no modified nucleotides, the open reading frame encoding a first antigenic polypeptide, and a pharmaceutically acceptable carrier or

excipient, formulated for delivery to a human subject. In some embodiments, the vaccine further comprises a cationic lipid nanoparticle.

Aspects of the invention provide methods of creating, maintaining or restoring antigenic memory to a virus strain in an individual or population of individuals comprising administering to said individual or population an antigenic memory booster nucleic acid vaccine comprising (a) at least one RNA polynucleotide, said polynucleotide comprising at least one chemical modification or optionally no modified nucleotides and two or more codon-optimized open reading frames, said open reading frames encoding a set of reference antigenic polypeptides, and (b) optionally a pharmaceutically acceptable carrier or excipient. In some embodiments, the vaccine is administered to the individual via a route selected from the group consisting of intramuscular administration, intradermal administration and subcutaneous administration. In some embodiments, the administering step comprises contacting a muscle tissue of the subject with a device suitable for injection of the composition. In some embodiments, the administering step comprises contacting a muscle tissue of the subject with a device suitable for injection of the composition in combination with electroporation.

Aspects of the invention provide methods of vaccinating a subject comprising administering to the subject a single dosage of between 25 ug/kg and 400 ug/kg of a nucleic acid vaccine comprising one or more RNA polynucleotides having an open reading frame encoding a first antigenic polypeptide in an effective amount to vaccinate the subject.

Other aspects provide nucleic acid vaccines comprising one or more RNA polynucleotides having an open reading frame comprising at least one chemical modification, the open reading frame encoding a first antigenic polypeptide, wherein the vaccine has at least 10 fold less RNA polynucleotide than is required for an unmodified mRNA vaccine to produce an equivalent antibody titer. In some embodiments, the RNA polynucleotide is present in a dosage of 25-100 micrograms.

Other aspects provide nucleic acid vaccines comprising an LNP formulated RNA polynucleotide having an open reading frame comprising no nucleotide modifications (unmodified), the open reading frame encoding a first antigenic polypeptide, wherein the vaccine has at least 10 fold less RNA polynucleotide than is required for an unmodified mRNA vaccine not formulated in a LNP to produce an equivalent antibody titer. In some embodiments, the RNA polynucleotide is present in a dosage of 25-100 micrograms.

The data presented in the Examples demonstrate significant enhanced immune responses using the formulations of the invention. Both chemically modified and unmodified RNA vaccines are useful according to the invention. Surprisingly, in contrast to prior art

reports that it was preferable to use chemically unmodified mRNA formulated in a carrier for the production of vaccines, it is described herein that chemically modified mRNA-LNP vaccines required a much lower effective mRNA dose than unmodified mRNA, i.e., tenfold less than unmodified mRNA when formulated in carriers other than LNP. Both the

5 chemically modified and unmodified RNA vaccines of the invention produce better immune responses than mRNA vaccines formulated in a different lipid carrier.

In other aspects the invention encompasses a method of treating an elderly subject age 60 years or older comprising administering to the subject a nucleic acid vaccine comprising one or more RNA polynucleotides having an open reading frame encoding an virus antigenic

10 polypeptide in an effective amount to vaccinate the subject.

In other aspects the invention encompasses a method of treating a young subject age 17 years or younger comprising administering to the subject a nucleic acid vaccine comprising one or more RNA polynucleotides having an open reading frame encoding an virus antigenic polypeptide in an effective amount to vaccinate the subject.

15 In other aspects the invention encompasses a method of treating an adult subject comprising administering to the subject a nucleic acid vaccine comprising one or more RNA polynucleotides having an open reading frame encoding an virus antigenic polypeptide in an effective amount to vaccinate the subject.

In some aspects the invention is a method of vaccinating a subject with a

20 combination vaccine including at least two nucleic acid sequences encoding antigens wherein the dosage for the vaccine is a combined therapeutic dosage wherein the dosage of each individual nucleic acid encoding an antigen is a sub therapeutic dosage. In some embodiments, the combined dosage is 25 micrograms of the RNA polynucleotide in the nucleic acid vaccine administered to the subject. In some embodiments, the combined

25 dosage is 100 micrograms of the RNA polynucleotide in the nucleic acid vaccine administered to the subject. In some embodiments the combined dosage is 50 micrograms of the RNA polynucleotide in the nucleic acid vaccine administered to the subject. In some embodiments, the combined dosage is 75 micrograms of the RNA polynucleotide in the nucleic acid vaccine administered to the subject. In some embodiments, the combined

30 dosage is 150 micrograms of the RNA polynucleotide in the nucleic acid vaccine administered to the subject. In some embodiments, the combined dosage is 400 micrograms of the RNA polynucleotide in the nucleic acid vaccine administered to the subject. In some embodiments, the sub therapeutic dosage of each individual nucleic acid encoding an antigen is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 micrograms. In other

embodiments the nucleic acid vaccine is chemically modified and in other embodiments the nucleic acid vaccine is not nucleotide modified.

The RNA polynucleotide is one of SEQ ID NO: : 447-457, 459, 461 and 491-503 and includes at least one chemical modification. In other embodiments the RNA polynucleotide is one of SEQ ID NO: : 447-457, 459, 461 and 491-503 and does not include any nucleotide modifications, or is unmodified. In yet other embodiments the at least one RNA polynucleotide encodes an antigenic protein of any of SEQ ID NO: 1-444, 458, 460, and 462-479 and includes at least one chemical modification. In other embodiments the RNA polynucleotide encodes an antigenic protein of any of SEQ ID NO: 1-444, 458, 460, and 462-479 and does not include any nucleotide modifications, or is unmodified.

In preferred aspects, vaccines of the invention (e.g., LNP-encapsulated mRNA vaccines) produce prophylactically- and/or therapeutically- efficacious levels, concentrations and/or titers of antigen-specific antibodies in the blood or serum of a vaccinated subject. As defined herein, the term antibody titer refers to the amount of antigen-specific antibody produces in s subject, e.g., a human subject. In exemplary embodiments, antibody titer is expressed as the inverse of the greatest dilution (in a serial dilution) that still gives a positive result. In exemplary embodiments, antibody titer is determined or measured by enzyme-linked immunosorbent assay (ELISA). In exemplary embodiments, antibody titer is determined or measured by neutralization assay, e.g., by microneutralization assay. In certain aspects, antibody titer measurement is expressed as a ratio, such as 1:40, 1:100, etc.

In exemplary embodiments of the invention, an efficacious vaccine produces an antibody titer of greater than 1:40, greater that 1:100, greater than 1:400, greater than 1:1000, greater than 1:2000, greater than 1:3000, greater than 1:4000, greater than 1:500, greater than 1:6000, greater than 1:7500, greater than 1:10000. In exemplary embodiments, the antibody titer is produced or reached by 10 days following vaccination, by 20 days following vaccination, by 30 days following vaccination, by 40 days following vaccination, or by 50 or more days following vaccination. In exemplary embodiments, the titer is produced or reached following a single dose of vaccine administered to the subject. In other embodiments, the titer is produced or reached following multiple doses, e.g., following a first and a second dose (e.g., a booster dose.)

In exemplary aspects of the invention, antigen-specific antibodies are measured in units of $\mu\text{g/ml}$ or are measured in units of IU/L (International Units per liter) or mIU/ml (milli International Units per ml). In exemplary embodiments of the invention, an efficacious vaccine produces $>0.5 \mu\text{g/ml}$, $>0.1 \mu\text{g/ml}$, $>0.2 \mu\text{g/ml}$, $>0.35 \mu\text{g/ml}$, $>0.5 \mu\text{g/ml}$, $>1 \mu\text{g/ml}$, $>2 \mu\text{g/ml}$, $>5 \mu\text{g/ml}$ or $>10 \mu\text{g/ml}$. In exemplary embodiments of the invention, an

efficacious vaccine produces >10 mIU/ml, >20 mIU/ml, >50 mIU/ml, >100 mIU/ml, >200 mIU/ml, >500 mIU/ml or > 1000 mIU/ml. In exemplary embodiments, the antibody level or concentration is produced or reached by 10 days following vaccination, by 20 days following vaccination, by 30 days following vaccination, by 40 days following vaccination, or by 50 or more days following vaccination. In exemplary embodiments, the level or concentration is produced or reached following a single dose of vaccine administered to the subject. In other embodiments, the level or concentration is produced or reached following multiple doses, e.g., following a first and a second dose (e.g., a booster dose.) In exemplary embodiments, antibody level or concentration is determined or measured by enzyme-linked immunosorbent assay (ELISA). In exemplary embodiments, antibody level or concentration is determined or measured by neutralization assay, e.g., by microneutralization assay.

The details of various embodiments of the disclosure are set forth in the description below. Other features, objects, and advantages of the disclosure will be apparent from the description and from the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

The foregoing and other objects, features and advantages will be apparent from the following description of particular embodiments of the invention, as illustrated in the accompanying drawings in which like reference characters refer to the same parts throughout the different views. The drawings are not necessarily to scale, emphasis instead being placed upon illustrating the principles of various embodiments of the invention.

Fig. 1 shows data obtained from an ELISA, demonstrating that vaccination with RNA encoding HA stem protein sequences from different strains induces serum antibodies that bind to diverse panel of recombinant HA (rHA) proteins.

Fig. 2 shows data demonstrating that serum antibody titers obtained from mice vaccinated with a second set of mRNA vaccine antigens induces serum antibodies that bind to a diverse panel of recombinant HA (rHA) proteins.

Fig. 3 shows combining mRNAs encoding HA stem protein from an H1 strain with mRNA encoding HA stem protein from an H3 strain did not result in interference in the immune response to either HA.

Figs. 4A-4B depict endpoint titers of the pooled serum from animals vaccinated with the test vaccines. In Fig. 4A, the vaccines tested are shown on the x-axis and the binding to HA from each of the different strains of influenza is plotted as an endpoint titer. In Fig. 4B, the vaccines tested are shown on the x-axis, and the endpoint titer to NP protein is plotted.

Fig. 5 shows an examination of functional antibody response through an assessment of the ability of serum to neutralize a panel of HA-pseudotyped viruses.

Fig. 6 shows data plotted as fold induction (sample luminescence/background luminescence) versus serum concentration.

5 Fig. 7 is a representation of cell-mediated immune responses following mRNA vaccination. Splenocytes were harvested from vaccinated mice and stimulated with a pool of overlapping NP peptides. The % of CD4 or CD8 T cells secreting one of the three cytokines (IFN- γ , IL-2, or TNF- α) is plotted.

10 Fig. 8 is a representation of cell-mediated immune responses following mRNA vaccination. Splenocytes were harvested from vaccinated mice and stimulated with a pool of overlapping HA peptides. The % of CD4 or CD8 T cells secreting one of the three cytokines (IFN- γ , IL-2, or TNF- α) is plotted.

15 Fig. 9 shows murine weight loss following challenge with a lethal dose of mouse-adapted H1N1 A/Puerto Rico/8/1934. The percentage of weight lost as compared to baseline was calculated for each animal and was averaged across the group. The group average was plotted over time in days. Error bars represent standard error of the mean. Efficacy of the NIHGen6HASS-foldon + NP combination vaccine was better than that of either the NIHGen6HASS-foldon or NP mRNA vaccine alone.

20 Fig. 10 shows vaccine efficacy was similar at all vaccine doses, as well as with all co-formulation and co-delivery methods assessed. Following challenge with a lethal dose of mouse-adapted H1N1 A/Puerto Rico/8/1934, the percentage of weight lost as compared to baseline was calculated for each animal and was averaged across the group. The group average was plotted over time in days. Error bars represent standard error of the mean.

25 Fig. 11A depicts the endpoint titers of the pooled serum from animals vaccinated with the test vaccines. Fig. 11B shows efficacy of the test vaccines (NIHGen6HASS-foldon and NIHGen6HASS-TM2) is similar. Following challenge with a lethal dose of mouse-adapted H1N1 A/Puerto Rico/8/1934, the percentage of group weight lost as compared to baseline was calculated and plotted over time in days.

30 Fig. 12A shows that serum from mice immunized with mRNA encoding consensus HA antigens from the H1 subtype was able to detectably neutralize the PR8 luciferase virus. Fig. 12B shows that serum from mice immunized with mRNA encoding H1 subtype consensus HA antigens with a ferritin fusion sequence was able to detectably neutralize the PR8 luciferase virus, except for the Merck_pH1_Con_ferritin mRNA, while serum from mice vaccinated with an mRNA encoding the consensus H3 antigen with a ferritin fusion sequence
35 was not able to neutralize the PR8 luciferase virus.

Figs. 13A-13B show murine weight loss following challenge with a lethal dose of mouse-adapted H1N1 A/Puerto Rico/8/1934. The percentage of group weight lost as compared to baseline was calculated and plotted over time in days..

Fig. 14 shows the results of neutralization assays performed on a panel of pseudoviruses to assess the breadth of the serum-neutralizing activity elicited by the consensus HA antigens.

Fig. 15A depicts the ELISA endpoint anti-HA antibody titers of the pooled serum from animals vaccinated with the test vaccines. Fig. 15B shows murine weight loss following challenge with a lethal dose of mouse-adapted B/Ann Arbor/1954. The percentage of group weight lost as compared to baseline was calculated and plotted over time in days. Figs. 16A-16C show data depicting the NIHGen6HASS-foldon vaccine's robust antibody response as measured by ELISA assay (plates coated with recombinantly-expressed NIHGen6HASS-foldon [HA stem] or NP proteins). Fig. 16A shows titers to HA stem, over time, for four rhesus macaques previously vaccinated with FLUZONE® and boosted a single time with NIHGen6HASS-foldon mRNA vaccine. Fig. 16B depicts titers to HA stem, over time, from four rhesus macaques vaccinated at days 0, 28 and 56 with the same NIHGen6HASS-foldon RNA vaccine. Fig. 16C illustrates antibody titers to NP, over time, for four rhesus macaques vaccinated at days 0, 28 and 56 with the NP mRNA vaccine and shows that the vaccine elicited a robust antibody response to NP.

Figs. 17A-17B show the results of ELISAs examining the presence of antibody capable of binding to recombinant hemagglutinin (rHA) from a wide variety of influenza strains. Fig. 17A shows the results of rhesus macaques previously vaccinated with FLUZONE® and boosted a single time with NIHGen6HASS-foldon mRNA vaccine, and Fig. 17B shows the results of naive rhesus macaques vaccinated at days 0, 28 and 56 with the same NIHGen6HASS-foldon RNA vaccine..

Fig. 18 is a representation of cell-mediated immune responses following mRNA vaccination. Peripheral blood mononuclear cells were harvested from vaccinated macaques and stimulated with a pool of overlapping NP peptides. The % of CD4 or CD8 T cells secreting one of the three cytokines (IFN- γ , IL-2, or TNF- α) is plotted.

Fig. 19 shows the results of hemagglutination inhibition (HAI) tests. Placebo subjects (targeted to be 25% of each cohort) are included. The data is shown per protocol, and excludes those that did not receive the day 22 injection.

Fig. 20 shows the HAI test kinetics per subject, including the placebo subjects (targeted to be 25% of each cohort).

Fig. 21 shows the results of microneutralization (MN) tests, including placebo subjects (targeted to be 25% of each cohort). The data shown is per protocol, and excludes those that did not receive a day 22 injection.

Fig. 22 shows the MN test kinetics per subject, including the placebo subjects (targeted to be 25% of each cohort).

Fig. 23 is a graph depicting the very strong correlation between HAI and MN. The data includes placebo subjects (targeted to be 25% of each cohort).

DETAILED DESCRIPTION

Embodiments of the present disclosure provide RNA (*e.g.*, mRNA) vaccines that include polynucleotide encoding an influenza virus antigen. Influenza virus RNA vaccines, as provided herein may be used to induce a balanced immune response, comprising both cellular and humoral immunity, without many of the risks associated with DNA vaccination.

In some embodiments, the virus is a strain of Influenza A or Influenza B or combinations thereof. In some embodiments, the strain of Influenza A or Influenza B is associated with birds, pigs, horses, dogs, humans or non-human primates. In some embodiments, the antigenic polypeptide encodes a hemagglutinin protein or immunogenic fragment thereof. In some embodiments, the hemagglutinin protein is H1, H2, H3, H4, H5, H6, H7, H8, H9, H10, H11, H12, H13, H14, H15, H16, H17, H18, or an immunogenic fragment thereof. In some embodiments, the hemagglutinin protein does not comprise a head domain. In some embodiments, the hemagglutinin protein comprises a portion of the head domain. In some embodiments, the hemagglutinin protein does not comprise a cytoplasmic domain. In some embodiments, the hemagglutinin protein comprises a portion of the cytoplasmic domain. In some embodiments, the truncated hemagglutinin protein comprises a portion of the transmembrane domain. In some embodiments, the amino acid sequence of the hemagglutinin protein or fragment thereof comprises at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identify with any of the amino acid sequences having an amino acid sequence identified by any one of SEQ ID NO: 1-444, 458, 460, 462-479 (see also Tables 7-13). In some embodiments, the virus is selected from the group consisting of H1N1, H3N2, H7N9, and H10N8. In some embodiments, the antigenic polypeptide is selected from those proteins having an amino acid sequences identified by any one of SEQ ID NO: 1-444, 458, 460, 462-479 (see also Tables 7-13), or immunogenic fragments thereof.

Some embodiments provide influenza vaccines comprising one or more RNA polynucleotides having an open reading frame encoding a hemagglutinin protein and a pharmaceutically acceptable carrier or excipient, formulated within a cationic lipid

nanoparticle. In some embodiments, the hemagglutinin protein is selected from H1, H7 and H10. In some embodiments, the RNA polynucleotide further encodes neuraminidase protein. In some embodiments, the hemagglutinin protein is derived from a strain of Influenza A virus or Influenza B virus or combinations thereof. In some embodiments, the Influenza virus is
 5 selected from H1N1, H3N2, H7N9, and H10N8.

Some embodiments provide methods of preventing or treating influenza viral infection comprising administering to a subject any of the vaccines described herein. In some embodiments, the antigen specific immune response comprises a T cell response. In some
 10 embodiments, the antigen specific immune response comprises a B cell response. In some
 10 embodiments, the antigen specific immune response comprises both a T cell response and a B cell response. In some embodiments, the method of producing an antigen specific immune response involves a single administration of the vaccine. In some embodiments, the vaccine is administered to the subject by intradermal, intramuscular injection, subcutaneous injection, intranasal inoculation, or oral administration.

15 In some embodiments, the RNA (*e.g.*, mRNA) polynucleotides or portions thereof may encode one or more polypeptides or fragments thereof of an influenza strain as an antigen. Such antigens include, but are not limited to, those antigens encoded by the polynucleotides or portions thereof of the polynucleotides listed in the Tables presented herein. In the Tables, the GenBank Accession Number or GI Accession Number represents
 20 either the complete or partial CDS of the encoded antigen. The RNA (*e.g.*, mRNA) polynucleotides may comprise a region of any of the sequences listed in the Tables or entire coding region of the mRNA listed. They may comprise hybrid or chimeric regions, or mimics or variants.

In the following embodiments, when referring to at least one RNA (*e.g.*, mRNA)
 25 polynucleotide having an open reading frame encoding for a specific influenza virus protein, the polynucleotides may comprise a coding region of the specific influenza virus protein sequence or the entire coding region of the mRNA for that specific influenza virus protein sequence.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA)
 30 polynucleotide having an open reading frame encoding a HA protein or immunogenic fragment thereof (*e.g.*, at least one HA1, HA2, or a combination of both, of H1-H18).

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA protein or immunogenic fragment thereof (*e.g.*, at least one HA1, HA2, or a combination of both, of H1-H18) and at
 35 least one protein, or immunogenic fragment thereof, selected from a NP protein, a NA

protein, a M1 protein, a M2 protein, a NS1 protein and a NS2 protein obtained from influenza virus.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA protein, or immunogenic
5 fragment thereof, (*e.g.*, at least one of H1-H18) and at least two proteins, or immunogenic fragments thereof, selected from a NP protein, a NA protein, a M1 protein, a M2 protein, a NS1 protein and a NS2 protein obtained from influenza virus.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA protein, or immunogenic
10 fragment thereof, (*e.g.*, at least one of H1-H18) and at least three proteins, or immunogenic fragments thereof, selected from a NP protein, a NA protein, a M1 protein, a M2 protein, a NS1 protein and a NS2 protein obtained from influenza virus.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA protein, or immunogenic
15 fragment thereof, (*e.g.*, at least one of H1-H18) and at least four proteins, or immunogenic fragments thereof, selected from a NP protein, a NA protein, a M1 protein, a M2 protein, a NS1 protein and a NS2 protein obtained from influenza virus.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA protein, or immunogenic
20 fragment thereof, (*e.g.*, at least one of H1-H18) and at least five proteins, or immunogenic fragments thereof, selected from a NP protein, a NA protein, a M1 protein, a M2 protein, a NS1 protein and a NS2 protein obtained from influenza virus.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA protein or immunogenic
25 fragment thereof (*e.g.*, at least one of H1-H18), a NP protein, or immunogenic fragment thereof, a NA protein, or immunogenic fragment thereof, a M1 protein, or immunogenic fragment thereof, a M2 protein, or immunogenic fragment thereof, a NS1 protein, or immunogenic fragment thereof, and a NS2 protein, or immunogenic fragment thereof, obtained from influenza virus.

30 In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA protein, or immunogenic fragment thereof, and a NA protein, or immunogenic fragment thereof, obtained from influenza virus.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA)
35 polynucleotide having an open reading frame encoding a HA protein, or immunogenic

fragment thereof, and a M1 protein, or immunogenic fragment thereof, obtained from influenza virus.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA protein, or immunogenic
5 fragment thereof, and a M2 protein, or immunogenic fragment thereof, obtained from influenza virus.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA protein, or immunogenic
10 fragment thereof, and a NS1 protein, or immunogenic fragment thereof, obtained from influenza virus.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA protein, or immunogenic
fragment thereof, and a NS2 protein, or immunogenic fragment thereof, obtained from influenza virus.

15 In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA protein, or immunogenic fragment, thereof, a NP protein and a NA protein obtained from influenza virus.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA protein, a NP protein, or
20 immunogenic fragment, thereof and a M1 protein, or immunogenic fragment thereof, obtained from influenza virus.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA protein, or immunogenic
25 fragment thereof, a NP protein, or immunogenic fragment thereof, and a M2 protein, or immunogenic fragment thereof, obtained from influenza virus.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA protein, or immunogenic
fragment thereof, a NP protein, or immunogenic fragment thereof, and a NS1 protein, or immunogenic fragment thereof, obtained from influenza virus.

30 In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA protein, or immunogenic fragment thereof, a NP protein, or immunogenic fragment thereof, and a NS2 protein, or immunogenic fragment thereof, obtained from influenza virus.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA protein, or immunogenic
35

fragment thereof, a NA protein and a M1 protein, or immunogenic fragment thereof, obtained from influenza virus.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA protein, or immunogenic fragment thereof, a NA protein, or immunogenic fragment thereof, and a M2 protein, or immunogenic fragment thereof, obtained from influenza virus.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA protein, or immunogenic fragment thereof, a NA protein, or immunogenic fragment thereof, and a NS1 protein, or immunogenic fragment thereof, obtained from influenza virus.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA protein, or immunogenic fragment thereof, a NA protein, or immunogenic fragment thereof, and a NS2 protein, or immunogenic fragment thereof, obtained from influenza virus.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA protein, or immunogenic fragment thereof, a M1 protein, or immunogenic fragment thereof, and a M2 protein, or immunogenic fragment thereof, obtained from influenza virus.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA protein, a M1 protein, or immunogenic fragment thereof, and a NS1 protein, or immunogenic fragment thereof, obtained from influenza virus.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA protein, or immunogenic fragment thereof, a M1 protein, or immunogenic fragment thereof, and a NS2 protein, or immunogenic fragment thereof, obtained from influenza virus.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA protein, or immunogenic fragment thereof, a M2 protein, or immunogenic fragment thereof, and a NS1 protein, or immunogenic fragment thereof, obtained from influenza virus.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA protein, or immunogenic fragment thereof, a M2 protein, or immunogenic fragment thereof, and a NS2 protein, or immunogenic fragment thereof, obtained from influenza virus.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA protein, or immunogenic fragment thereof, a NS1 protein, or immunogenic fragment thereof, and a NS2 protein, or immunogenic fragment thereof, obtained from influenza virus.

5 In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA1 protein, or immunogenic fragment thereof, and a NA protein, or immunogenic fragment thereof, obtained from influenza virus.

10 In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA1 protein, or immunogenic fragment thereof, and a M1 protein, or immunogenic fragment thereof, obtained from influenza virus.

15 In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA1 protein, or immunogenic fragment thereof, and a M2 protein, or immunogenic fragment thereof, obtained from influenza virus.

20 In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA1 protein, or immunogenic fragment thereof, and a NS1 protein, or immunogenic fragment thereof, obtained from influenza virus.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA1 protein and a NS2 protein, or immunogenic fragment thereof, obtained from influenza virus.

25 In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA1 protein, or immunogenic fragment thereof, a NP protein, or immunogenic fragment thereof, and a NA protein, or immunogenic fragment thereof, obtained from influenza virus.

30 In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA1 protein, or immunogenic fragment thereof, a NP protein, or immunogenic fragment thereof, and a M1 protein, or immunogenic fragment thereof, obtained from influenza virus.

35 In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA1 protein, or immunogenic fragment thereof, a NP protein, or immunogenic fragment thereof, and a M2 protein, or immunogenic fragment thereof, obtained from influenza virus.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA1 protein, or immunogenic fragment thereof, a NP protein, or immunogenic fragment thereof, and a NS1 protein, or immunogenic fragment thereof, obtained from influenza virus.

5 In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA1 protein, or immunogenic fragment thereof, a NP protein, or immunogenic fragment thereof, and a NS2 protein, or immunogenic fragment thereof, obtained from influenza virus.

10 In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA1 protein, or immunogenic fragment thereof, a NA protein, or immunogenic fragment thereof, and a M1 protein, or immunogenic fragment thereof, obtained from influenza virus.

15 In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA1 protein, or immunogenic fragment thereof, a NA protein, or immunogenic fragment thereof, and a M2 protein, or immunogenic fragment thereof, obtained from influenza virus.

20 In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA1 protein, or immunogenic fragment thereof, a NA protein and a NS1 protein, or immunogenic fragment thereof, obtained from influenza virus.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA1 protein, or immunogenic fragment thereof, a NA protein, or immunogenic fragment thereof, and a NS2 protein, or immunogenic fragment thereof, obtained from influenza virus.

25 In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA1 protein, or immunogenic fragment thereof, a M1 protein, or immunogenic fragment thereof, and a M2 protein, or immunogenic fragment thereof, obtained from influenza virus.

30 In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA1 protein, or immunogenic fragment thereof, a M1 protein, or immunogenic fragment thereof, and a NS1 protein, or immunogenic fragment thereof, obtained from influenza virus.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA1 protein, or immunogenic

fragment thereof, a M1 protein, or immunogenic fragment thereof, and a NS2 protein, or immunogenic fragment thereof, obtained from influenza virus.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA1 protein, or immunogenic fragment thereof, a M2 protein, or immunogenic fragment thereof, and a NS1 protein, or immunogenic fragment thereof, obtained from influenza virus.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA1 protein, or immunogenic fragment thereof, a M2 protein, or immunogenic fragment thereof, and a NS2 protein, or immunogenic fragment thereof, obtained from influenza virus.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA1 protein, or immunogenic fragment thereof, a NS1 protein, or immunogenic fragment thereof, and a NS2 protein, or immunogenic fragment thereof, obtained from influenza virus.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA protein (HA or derivatives thereof comprising antigenic sequences from HA1 and/or HA2), and a NA protein, or immunogenic fragment thereof, obtained from influenza virus.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA protein (HA or derivatives thereof comprising antigenic sequences from HA1 and/or HA2), and a M1 protein, or immunogenic fragment thereof, obtained from influenza virus.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA protein (HA or derivatives thereof comprising antigenic sequences from HA1 and/or HA2), and a M2 protein, or immunogenic fragment thereof, obtained from influenza virus.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA protein (HA or derivatives thereof comprising antigenic sequences from HA1 and/or HA2), and a NS1 protein obtained from influenza virus.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA protein (HA or derivatives thereof comprising antigenic sequences from HA1 and/or HA2), and a NS2 protein, or immunogenic fragment thereof, obtained from influenza virus.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA protein (HA or derivatives thereof comprising antigenic sequences from HA1 and/or HA2), a NP protein, or immunogenic fragment thereof, and a NA protein, or immunogenic fragment thereof, obtained from influenza virus.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA protein (HA or derivatives thereof comprising antigenic sequences from HA1 and/or HA2), a NP protein, or immunogenic fragment thereof, and a M1 protein, or immunogenic fragment thereof, obtained from influenza virus.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA protein (HA or derivatives thereof comprising antigenic sequences from HA1 and/or HA2), a NP protein, or immunogenic fragment thereof, and a M2 protein, or immunogenic fragment thereof, obtained from influenza virus.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA protein (HA or derivatives thereof comprising antigenic sequences from HA1 and/or HA2), a NP protein, or immunogenic fragment thereof, and a NS1 protein, or immunogenic fragment thereof, obtained from influenza virus.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA protein (HA or derivatives thereof comprising antigenic sequences from HA1 and/or HA2), a NP protein and a NS2 protein, or immunogenic fragment thereof, obtained from influenza virus.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA protein (HA or derivatives thereof comprising antigenic sequences from HA1 and/or HA2), a NA protein, or immunogenic fragment thereof, and a M1 protein, or immunogenic fragment thereof, obtained from influenza virus.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA protein (HA or derivatives thereof comprising antigenic sequences from HA1 and/or HA2), a NA protein, or immunogenic fragment thereof, and a M2 protein, or immunogenic fragment thereof, obtained from influenza virus.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA protein (HA or derivatives thereof comprising antigenic sequences from HA1 and/or HA2), a NA protein, or immunogenic fragment thereof, and a NS1 protein, or immunogenic fragment thereof, obtained from influenza virus.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA protein (HA or derivatives thereof comprising antigenic sequences from HA1 and/or HA2), a NA protein, or immunogenic fragment thereof, and a NS2 protein, or immunogenic fragment thereof, obtained from influenza virus.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA protein (HA or derivatives thereof comprising antigenic sequences from HA1 and/or HA2), a M1 protein, or immunogenic fragment thereof, and a M2 protein, or immunogenic fragment thereof, obtained from influenza virus.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA protein (HA or derivatives thereof comprising antigenic sequences from HA1 and/or HA2), a M1 protein, or immunogenic fragment thereof, and a NS1 protein, or immunogenic fragment thereof, obtained from influenza virus.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA protein (HA or derivatives thereof comprising antigenic sequences from HA1 and/or HA2), a M1 protein, or immunogenic fragment thereof, and a NS2 protein, or immunogenic fragment thereof, obtained from influenza virus.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA protein (HA or derivatives thereof comprising antigenic sequences from HA1 and/or HA2), a M2 protein, or immunogenic fragment thereof, and a NS1 protein, or immunogenic fragment thereof, obtained from influenza virus.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA protein (HA or derivatives thereof comprising antigenic sequences from HA1 and/or HA2), a M2 protein, or immunogenic fragment thereof, and a NS2 protein, or immunogenic fragment thereof, obtained from influenza virus.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a HA protein (HA or derivatives thereof comprising antigenic sequences from HA1 and/or HA2), a NS1 protein, or immunogenic fragment thereof, and a NS2 protein, or immunogenic fragment thereof, obtained from influenza virus.

It should be understood that the present disclosure is not intended to be limited by a particular strain of influenza virus. The strain of influenza virus used, as provided herein, may be any strain of influenza virus. Examples of preferred strains of influenza virus and preferred influenza antigens are provided in Tables 7-13 below.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding an influenza antigenic polypeptide (*e.g.*, a HA protein, a NP protein, a NA protein, a M1 protein, a M2 protein, a NS1 protein, a NS2 protein, an immunogenic fragment of any of the foregoing influenza antigens, a variant or homolog of any of the foregoing influenza antigens, or any combination of two or more of the foregoing influenza antigens, variants or homologs) obtained from H1/PuertoRico/8/1934.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding an influenza antigenic polypeptide (*e.g.*, a HA protein, a NP protein, a NA protein, a M1 protein, a M2 protein, a NS1 protein, a NS2 protein, an immunogenic fragment of any of the foregoing influenza antigens, a variant or homolog of any of the foregoing influenza antigens, or any combination of two or more of the foregoing influenza antigens, variants or homologs) obtained from H1/New Caledonia/20/1999.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding an influenza antigenic polypeptide (*e.g.*, a HA protein, a NP protein, a NA protein, a M1 protein, a M2 protein, a NS1 protein, a NS2 protein, an immunogenic fragment of any of the foregoing influenza antigens, a variant or homolog of any of the foregoing influenza antigens, or any combination of two or more of the foregoing influenza antigens, variants or homologs) obtained from H1/California/04/2009.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding an influenza antigenic polypeptide (*e.g.*, a HA protein, a NP protein, a NA protein, a M1 protein, a M2 protein, a NS1 protein, a NS2 protein, an immunogenic fragment of any of the foregoing influenza antigens, a variant or homolog of any of the foregoing influenza antigens, or any combination of two or more of

the foregoing influenza antigens, variants or homologs) obtained from H5/Vietnam/1194/2004.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding an influenza antigenic polypeptide (*e.g.*, a HA protein, a NP protein, a NA protein, a M1 protein, a M2 protein, a NS1 protein, a NS2 protein, an immunogenic fragment of any of the foregoing influenza antigens, a variant or homolog of any of the foregoing influenza antigens, or any combination of two or more of the foregoing influenza antigens, variants or homologs) obtained from H2/Japan/305/1957.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding an influenza antigenic polypeptide (*e.g.*, a HA protein, a NP protein, a NA protein, a M1 protein, a M2 protein, a NS1 protein, a NS2 protein, an immunogenic fragment of any of the foregoing influenza antigens, a variant or homolog of any of the foregoing influenza antigens, or any combination of two or more of the foregoing influenza antigens, variants or homologs) obtained from H9/Hong Kong/1073/99.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding an influenza antigenic polypeptide (*e.g.*, a HA protein, a NP protein, a NA protein, a M1 protein, a M2 protein, a NS1 protein, a NS2 protein, an immunogenic fragment of any of the foregoing influenza antigens, a variant or homolog of any of the foregoing influenza antigens, or any combination of two or more of the foregoing influenza antigens, variants or homologs) obtained from H3/Aichi/2/1968.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding an influenza antigenic polypeptide (*e.g.*, a HA protein, a NP protein, a NA protein, a M1 protein, a M2 protein, a NS1 protein, a NS2 protein, an immunogenic fragment of any of the foregoing influenza antigens, a variant or homolog of any of the foregoing influenza antigens, or any combination of two or more of the foregoing influenza antigens, variants or homologs) obtained from H3/Brisbane/10/2007.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding an influenza antigenic polypeptide (*e.g.*, a HA protein, a NP protein, a NA protein, a M1 protein, a M2 protein, a NS1 protein, a NS2 protein, an immunogenic fragment of any of the foregoing influenza antigens, a variant or homolog of any of the foregoing influenza antigens, or any combination of two or more of the foregoing influenza antigens, variants or homologs) obtained from H7/Anhui/1/2013.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding an influenza antigenic polypeptide

(*e.g.*, a HA protein, a NP protein, a NA protein, a M1 protein, a M2 protein, a NS1 protein, a NS2 protein, an immunogenic fragment of any of the foregoing influenza antigens, a variant or homolog of any of the foregoing influenza antigens, or any combination of two or more of the foregoing influenza antigens, variants or homologs) obtained from H10/Jiangxi-

5 Donghu/346/2013.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding an influenza antigenic polypeptide (*e.g.*, a HA protein, a NP protein, a NA protein, a M1 protein, a M2 protein, a NS1 protein, a NS2 protein, an immunogenic fragment of any of the foregoing influenza antigens, a variant or homolog of any of the foregoing influenza antigens, or any combination of two or more of the foregoing influenza antigens, variants or homologs) obtained from H3/Wisconsin/67/2005.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding an influenza antigenic polypeptide (*e.g.*, a HA protein, a NP protein, a NA protein, a M1 protein, a M2 protein, a NS1 protein, a NS2 protein, an immunogenic fragment of any of the foregoing influenza antigens, a variant or homolog of any of the foregoing influenza antigens, or any combination of two or more of the foregoing influenza antigens, variants or homologs) obtained from H1/Vietnam/850/2009.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding influenza H7N9 HA1 protein, ferritin and a dendritic cell targeting peptide (*see, e.g.*, Ren X *et al. Emerg Infect Dis* 2013;19(11):1881-84; Steel J *et al. mBio* 2010;1(1):e00018-10; Kanekiyo M. *et al. Nature* 2013;499:102-6, each of which is incorporated herein by reference).

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding an avian influenza H7 HA protein.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding influenza H7 HA1 protein (*see, e.g.*, Steel J *et al. mBio* 2010;1(1):e00018-10).

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding influenza H7N9 HA1 protein and ferritin (*see, e.g.*, Kanekiyo M. *et al. Nature* 2013;499:102-6).

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding an influenza H5N1 protein. In some embodiments, the influenza H5N1 protein is from a human strain.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding an influenza H1N1 protein.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding an influenza protein from an influenza A strain, such as human H1N1, H5N1, H9N2 or H3N2.

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding an influenza H1N1 HA having a nanoscaffold (*see, e.g.*, Walker A *et al. Sci Rep* 2011;1(5):1-8, incorporated herein by reference).

In some embodiments, a vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding an aglycosylated influenza H1N1 HA (*see, e.g.*, Chen J *et al. PNAS USA* 2014;111(7):2476-81, incorporated herein by reference).

An influenza vaccine may comprise, for example, at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding at least one influenza HA2 stem antigen selected from the influenza HA2 stem antigens, provided herein, for example, those listed in Table 16, comprising an amino acid sequence identified by any one of SEQ ID NO: 394-412.

The present disclosure also encompasses an influenza vaccine comprising, for example, at least one RNA (*e.g.*, mRNA) polynucleotide having a nucleic acid sequence selected from the influenza sequences listed in SEQ ID NO: 491-503 (*see also*: Mallajosyula VV *et al., Front Immunol.* 2015 Jun 26;6:329.; Mallajosyula VV *et al., Proc Natl Acad Sci U S A.* 2014 Jun 24;111(25):E2514-23.; Bommakanti G, *et al., J Virol.* 2012 Dec;86(24):13434-44; Bommakanti G *et al., Proc Natl Acad Sci U S A.* 2010 Aug 3;107(31):13701-6 and Yassine *et al., Nat Med.* 2015 Sep;21(9):1065-70; Impagliazzo *et al., Science*, 2015 Sep 18;349(6254)).

The entire contents of International Application No. PCT/US2015/02740 is incorporated herein by reference.

In some embodiments the vaccines described herein are consensus sequences. A "consensus sequence" as used herein refers to a polypeptide sequence based on analysis of an alignment of multiple subtypes of a particular influenza antigen. mRNA sequences that encode a consensus polypeptide sequence may be prepared and used to induce broad immunity against multiple subtypes or serotypes of a particular influenza antigen.

The mRNA encoding influenza antigens provided herein can be arranged as a vaccine that causes seroconversion in vaccinated mammals and provides cross-reactivity against a broad range of seasonal strains of influenza and also pandemic strains of influenza. The

seroconversion and broad cross-reactivity can be determined by measuring inhibiting titers against different hemagglutinin strains of influenza. Preferred combinations include at least two antigens from each of the influenza antigens described herein.

It has been discovered that the mRNA vaccines described herein are superior to
5 current vaccines in several ways. First, the lipid nanoparticle (LNP) delivery is superior to other formulations including a protamine base approach described in the literature and no additional adjuvants are to be necessary. The use of LNPs enables the effective delivery of chemically modified or unmodified mRNA vaccines. Additionally it has been demonstrated herein that both modified and unmodified LNP formulated mRNA vaccines were superior to
10 conventional vaccines by a significant degree. In some embodiments the mRNA vaccines of the invention are superior to conventional vaccines by a factor of at least 10 fold, 20 fold, 40 fold, 50 fold, 100 fold, 500 fold or 1,000 fold.

Although attempts have been made to produce functional RNA vaccines, including mRNA vaccines and self-replicating RNA vaccines, the therapeutic efficacy of these RNA
15 vaccines have not yet been fully established. Quite surprisingly, the inventors have discovered, according to aspects of the invention a class of formulations for delivering mRNA vaccines in vivo that results in significantly enhanced, and in many respects synergistic, immune responses including enhanced antigen generation and functional antibody production with neutralization capability. These results can be achieved even when
20 significantly lower doses of the mRNA are administered in comparison with mRNA doses used in other classes of lipid based formulations. The formulations of the invention have demonstrated significant unexpected in vivo immune responses sufficient to establish the efficacy of functional mRNA vaccines as prophylactic and therapeutic agents. Additionally, self-replicating RNA vaccines rely on viral replication pathways to deliver enough RNA to a
25 cell to produce an immunogenic response. The formulations of the invention do not require viral replication to produce enough protein to result in a strong immune response. Thus, the mRNA of the invention are not self-replicating RNA and do not include components necessary for viral replication.

The invention involves, in some aspects, the surprising finding that lipid nanoparticle
30 (LNP) formulations significantly enhance the effectiveness of mRNA vaccines, including chemically modified and unmodified mRNA vaccines. The efficacy of mRNA vaccines formulated in LNP was examined in vivo using several distinct antigens. The results presented herein demonstrate the unexpected superior efficacy of the mRNA vaccines formulated in LNP over other commercially available vaccines.

In addition to providing an enhanced immune response, the formulations of the invention generate a more rapid immune response with fewer doses of antigen than other vaccines tested. The mRNA-LNP formulations of the invention also produce quantitatively and qualitatively better immune responses than vaccines formulated in a different carriers.

5 The data described herein demonstrate that the formulations of the invention produced significant unexpected improvements over existing antigen vaccines. Additionally, the mRNA-LNP formulations of the invention are superior to other vaccines even when the dose of mRNA is lower than other vaccines. mRNA encoding HA protein sequences such as HA stem sequences from different strains have been demonstrated to induce serum antibodies that
10 bind to diverse panel of recombinant HA (rHA) proteins. The vaccine efficacy in mice was similar at all vaccine doses, as well as with all co-formulation and co-delivery methods assessed.

The LNP used in the studies described herein has been used previously to deliver siRNA in various animal models as well as in humans. In view of the observations made in
15 association with the siRNA delivery of LNP formulations, the fact that LNP is useful in vaccines is quite surprising. It has been observed that therapeutic delivery of siRNA formulated in LNP causes an undesirable inflammatory response associated with a transient IgM response, typically leading to a reduction in antigen production and a compromised immune response. In contrast to the findings observed with siRNA, the LNP-mRNA
20 formulations of the invention are demonstrated herein to generate enhanced IgG levels, sufficient for prophylactic and therapeutic methods rather than transient IgM responses.

Nucleic Acids/Polynucleotides

Influenza virus vaccines, as provided herein, comprise at least one (one or more)
25 ribonucleic acid (RNA) (*e.g.*, mRNA) polynucleotide having an open reading frame encoding at least one Influenza antigenic polypeptide. The term “nucleic acid” includes any compound and/or substance that comprises a polymer of nucleotides (nucleotide monomer). These polymers are referred to as polynucleotides. Thus, the terms “nucleic acid” and “polynucleotide” are used interchangeably.

30 Nucleic acids may be or may include, for example, ribonucleic acids (RNAs), deoxyribonucleic acids (DNAs), threose nucleic acids (TNAs), glycol nucleic acids (GNAs), peptide nucleic acids (PNAs), locked nucleic acids (LNAs, including LNA having a β -D-ribo configuration, α -LNA having an α -L-ribo configuration (a diastereomer of LNA), 2'-amino-LNA having a 2'-amino functionalization, and 2'-amino- α -LNA having a 2'-amino

functionalization), ethylene nucleic acids (ENA), cyclohexenyl nucleic acids (CeNA) or chimeras or combinations thereof.

In some embodiments, polynucleotides of the present disclosure function as messenger RNA (mRNA). “Messenger RNA” (mRNA) refers to any polynucleotide that encodes a (at least one) polypeptide (a naturally-occurring, non-naturally-occurring, or modified polymer of amino acids) and can be translated to produce the encoded polypeptide *in vitro*, *in vivo*, *in situ* or *ex vivo*. The skilled artisan will appreciate that, except where otherwise noted, polynucleotide sequences set forth in the instant application will recite “T”s in a representative DNA sequence but where the sequence represents RNA (*e.g.*, mRNA), the “T”s would be substituted for “U”s. Thus, any of the RNA polynucleotides encoded by a DNA identified by a particular sequence identification number may also comprise the corresponding RNA (*e.g.*, mRNA) sequence encoded by the DNA, where each “T” of the DNA sequence is substituted with “U.”

The basic components of an mRNA molecule typically include at least one coding region, a 5' untranslated region (UTR), a 3' UTR, a 5' cap and a poly-A tail. Polynucleotides of the present disclosure may function as mRNA but can be distinguished from wild-type mRNA in their functional and/or structural design features, which serve to overcome existing problems of effective polypeptide expression using nucleic-acid based therapeutics.

In some embodiments, a RNA polynucleotide of an RNA (*e.g.*, mRNA) vaccine encodes 2-10, 2-9, 2-8, 2-7, 2-6, 2-5, 2-4, 2-3, 3-10, 3-9, 3-8, 3-7, 3-6, 3-5, 3-4, 4-10, 4-9, 4-8, 4-7, 4-6, 4-5, 5-10, 5-9, 5-8, 5-7, 5-6, 6-10, 6-9, 6-8, 6-7, 7-10, 7-9, 7-8, 8-10, 8-9 or 9-10 antigenic polypeptides. In some embodiments, a RNA (*e.g.*, mRNA) polynucleotide of an influenza vaccine encodes at least 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 antigenic polypeptides. In some embodiments, a RNA (*e.g.*, mRNA) polynucleotide of an influenza vaccine encodes at least 100 or at least 200 antigenic polypeptides. In some embodiments, a RNA polynucleotide of an influenza vaccine encodes 1-10, 5-15, 10-20, 15-25, 20-30, 25-35, 30-40, 35-45, 40-50, 1-50, 1-100, 2-50 or 2-100 antigenic polypeptides.

Polynucleotides of the present disclosure, in some embodiments, are codon optimized. Codon optimization methods are known in the art and may be used as provided herein. Codon optimization, in some embodiments, may be used to match codon frequencies in target and host organisms to ensure proper folding; bias GC content to increase mRNA stability or reduce secondary structures; minimize tandem repeat codons or base runs that may impair gene construction or expression; customize transcriptional and translational control regions; insert or remove protein trafficking sequences; remove/add post translation modification sites in encoded protein (*e.g.* glycosylation sites); add, remove or shuffle protein domains; insert or

delete restriction sites; modify ribosome binding sites and mRNA degradation sites; adjust translational rates to allow the various domains of the protein to fold properly; or to reduce or eliminate problem secondary structures within the polynucleotide. Codon optimization tools, algorithms and services are known in the art – non-limiting examples include services from GeneArt (Life Technologies), DNA2.0 (Menlo Park CA) and/or proprietary methods. In some embodiments, the open reading frame (ORF) sequence is optimized using optimization algorithms.

In some embodiments, a codon optimized sequence shares less than 95% sequence identity, less than 90% sequence identity, less than 85% sequence identity, less than 80% sequence identity, or less than 75% sequence identity to a naturally-occurring or wild-type sequence (*e.g.*, a naturally-occurring or wild-type mRNA sequence encoding a polypeptide or protein of interest (*e.g.*, an antigenic protein or antigenic polypeptide)).

In some embodiments, a codon-optimized sequence shares between 65% and 85% (*e.g.*, between about 67% and about 85%, or between about 67% and about 80%) sequence identity to a naturally-occurring sequence or a wild-type sequence (*e.g.*, a naturally-occurring or wild-type mRNA sequence encoding a polypeptide or protein of interest (*e.g.*, an antigenic protein or polypeptide)). In some embodiments, a codon-optimized sequence shares between 65% and 75%, or about 80% sequence identity to a naturally-occurring sequence or wild-type sequence (*e.g.*, a naturally-occurring or wild-type mRNA sequence encoding a polypeptide or protein of interest (*e.g.*, an antigenic protein or polypeptide)).

In some embodiments a codon-optimized RNA (*e.g.*, mRNA) may, for instance, be one in which the levels of G/C are enhanced. The G/C-content of nucleic acid molecules may influence the stability of the RNA. RNA having an increased amount of guanine (G) and/or cytosine (C) residues may be functionally more stable than nucleic acids containing a large amount of adenine (A) and thymine (T) or uracil (U) nucleotides. WO02/098443 discloses a pharmaceutical composition containing an mRNA stabilized by sequence modifications in the translated region. Due to the degeneracy of the genetic code, the modifications work by substituting existing codons for those that promote greater RNA stability without changing the resulting amino acid. The approach is limited to coding regions of the RNA.

Antigens/Antigenic Polypeptides

In some embodiments, an antigenic polypeptide (*e.g.*, at least one Influenza antigenic polypeptide) is longer than 25 amino acids and shorter than 50 amino acids. Polypeptides include gene products, naturally occurring polypeptides, synthetic polypeptides, homologs,

orthologs, paralog, fragments and other equivalents, variants, and analogs of the foregoing. A polypeptide may be a single molecule or may be a multi-molecular complex such as a dimer, trimer or tetramer. Polypeptides may also comprise single chain polypeptides or multichain polypeptides, such as antibodies or insulin, and may be associated or linked to each other. Most commonly, disulfide linkages are found in multichain polypeptides. The term “polypeptide” may also apply to amino acid polymers in which at least one amino acid residue is an artificial chemical analogue of a corresponding naturally-occurring amino acid.

A “polypeptide variant” is a molecule that differs in its amino acid sequence relative to a native sequence or a reference sequence. Amino acid sequence variants may possess substitutions, deletions, insertions, or a combination of any two or three of the foregoing, at certain positions within the amino acid sequence, as compared to a native sequence or a reference sequence. Ordinarily, variants possess at least 50% identity to a native sequence or a reference sequence. In some embodiments, variants share at least 80% identity or at least 90% identity with a native sequence or a reference sequence.

In some embodiments “variant mimics” are provided. A “variant mimic” contains at least one amino acid that would mimic an activated sequence. For example, glutamate may serve as a mimic for phospho-threonine and/or phospho-serine. Alternatively, variant mimics may result in deactivation or in an inactivated product containing the mimic. For example, phenylalanine may act as an inactivating substitution for tyrosine, or alanine may act as an inactivating substitution for serine.

“Orthologs” refers to genes in different species that evolved from a common ancestral gene by speciation. Normally, orthologs retain the same function in the course of evolution. Identification of orthologs is important for reliable prediction of gene function in newly sequenced genomes.

“Analog” is meant to include polypeptide variants that differ by one or more amino acid alterations, for example, substitutions, additions or deletions of amino acid residues that still maintain one or more of the properties of the parent or starting polypeptide.

The present disclosure provides several types of compositions that are polynucleotide or polypeptide based, including variants and derivatives. These include, for example, substitutional, insertional, deletion and covalent variants and derivatives. The term “derivative” is synonymous with the term “variant” and generally refers to a molecule that has been modified and/or changed in any way relative to a reference molecule or a starting molecule.

As such, polynucleotides encoding peptides or polypeptides containing substitutions, insertions and/or additions, deletions and covalent modifications with respect to reference

sequences, in particular the polypeptide sequences disclosed herein, are included within the scope of this disclosure. For example, sequence tags or amino acids, such as one or more lysines, can be added to peptide sequences (*e.g.*, at the N-terminal or C-terminal ends). Sequence tags can be used for peptide detection, purification or localization. Lysines can be used to increase peptide solubility or to allow for biotinylation. Alternatively, amino acid residues located at the carboxy and amino terminal regions of the amino acid sequence of a peptide or protein may optionally be deleted providing for truncated sequences. Certain amino acids (*e.g.*, C-terminal residues or N-terminal residues) alternatively may be deleted depending on the use of the sequence, as for example, expression of the sequence as part of a larger sequence that is soluble, or linked to a solid support.

“Substitutional variants” when referring to polypeptides are those that have at least one amino acid residue in a native or starting sequence removed and a different amino acid inserted in its place at the same position. Substitutions may be single, where only one amino acid in the molecule has been substituted, or they may be multiple, where two or more (*e.g.*, 3, 4 or 5) amino acids have been substituted in the same molecule.

As used herein the term “conservative amino acid substitution” refers to the substitution of an amino acid that is normally present in the sequence with a different amino acid of similar size, charge, or polarity. Examples of conservative substitutions include the substitution of a non-polar (hydrophobic) residue such as isoleucine, valine and leucine for another non-polar residue. Likewise, examples of conservative substitutions include the substitution of one polar (hydrophilic) residue for another such as between arginine and lysine, between glutamine and asparagine, and between glycine and serine. Additionally, the substitution of a basic residue such as lysine, arginine or histidine for another, or the substitution of one acidic residue such as aspartic acid or glutamic acid for another acidic residue are additional examples of conservative substitutions. Examples of non-conservative substitutions include the substitution of a non-polar (hydrophobic) amino acid residue such as isoleucine, valine, leucine, alanine, methionine for a polar (hydrophilic) residue such as cysteine, glutamine, glutamic acid or lysine and/or a polar residue for a non-polar residue.

“Features” when referring to polypeptide or polynucleotide are defined as distinct amino acid sequence-based or nucleotide-based components of a molecule respectively. Features of the polypeptides encoded by the polynucleotides include surface manifestations, local conformational shape, folds, loops, half-loops, domains, half-domains, sites, termini and any combination(s) thereof.

As used herein when referring to polypeptides the term “domain” refers to a motif of a polypeptide having one or more identifiable structural or functional characteristics or properties (*e.g.*, binding capacity, serving as a site for protein-protein interactions).

As used herein when referring to polypeptides the terms “site” as it pertains to amino acid based embodiments is used synonymously with “amino acid residue” and “amino acid side chain.” As used herein when referring to polynucleotides the terms “site” as it pertains to nucleotide based embodiments is used synonymously with “nucleotide.” A site represents a position within a peptide or polypeptide or polynucleotide that may be modified, manipulated, altered, derivatized or varied within the polypeptide-based or polynucleotide-based molecules.

As used herein the terms “termini” or “terminus” when referring to polypeptides or polynucleotides refers to an extremity of a polypeptide or polynucleotide respectively. Such extremity is not limited only to the first or final site of the polypeptide or polynucleotide but may include additional amino acids or nucleotides in the terminal regions. Polypeptide-based molecules may be characterized as having both an N-terminus (terminated by an amino acid with a free amino group (NH₂)) and a C-terminus (terminated by an amino acid with a free carboxyl group (COOH)). Proteins are in some cases made up of multiple polypeptide chains brought together by disulfide bonds or by non-covalent forces (multimers, oligomers). These proteins have multiple N- and C-termini. Alternatively, the termini of the polypeptides may be modified such that they begin or end, as the case may be, with a non-polypeptide based moiety such as an organic conjugate.

As recognized by those skilled in the art, protein fragments, functional protein domains, and homologous proteins are also considered to be within the scope of polypeptides of interest. For example, provided herein is any protein fragment (meaning a polypeptide sequence at least one amino acid residue shorter than a reference polypeptide sequence but otherwise identical) of a reference protein having a length of 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 or longer than 100 amino acids. In another example, any protein that includes a stretch of 20, 30, 40, 50, or 100 (contiguous) amino acids that are 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 100% identical to any of the sequences described herein can be utilized in accordance with the disclosure. In some embodiments, a polypeptide includes 2, 3, 4, 5, 6, 7, 8, 9, 10, or more mutations as shown in any of the sequences provided herein or referenced herein. In another example, any protein that includes a stretch of 20, 30, 40, 50, or 100 amino acids that are greater than 80%, 90%, 95%, or 100% identical to any of the sequences described herein, wherein the protein has a stretch of 5, 10, 15, 20, 25, or 30 amino acids that

are less than 80%, 75%, 70%, 65% to 60% identical to any of the sequences described herein can be utilized in accordance with the disclosure.

Polypeptide or polynucleotide molecules of the present disclosure may share a certain degree of sequence similarity or identity with the reference molecules (*e.g.*, reference polypeptides or reference polynucleotides), for example, with art-described molecules (*e.g.*, engineered or designed molecules or wild-type molecules). The term “identity,” as known in the art, refers to a relationship between the sequences of two or more polypeptides or polynucleotides, as determined by comparing the sequences. In the art, identity also means the degree of sequence relatedness between two sequences as determined by the number of matches between strings of two or more amino acid residues or nucleic acid residues. Identity measures the percent of identical matches between the smaller of two or more sequences with gap alignments (if any) addressed by a particular mathematical model or computer program (*e.g.*, “algorithms”). Identity of related peptides can be readily calculated by known methods. “% identity” as it applies to polypeptide or polynucleotide sequences is defined as the percentage of residues (amino acid residues or nucleic acid residues) in the candidate amino acid or nucleic acid sequence that are identical with the residues in the amino acid sequence or nucleic acid sequence of a second sequence after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent identity. Methods and computer programs for the alignment are well known in the art. Identity depends on a calculation of percent identity but may differ in value due to gaps and penalties introduced in the calculation. Generally, variants of a particular polynucleotide or polypeptide have at least 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% but less than 100% sequence identity to that particular reference polynucleotide or polypeptide as determined by sequence alignment programs and parameters described herein and known to those skilled in the art. Such tools for alignment include those of the BLAST suite (Stephen F. Altschul, *et al.* (1997). “Gapped BLAST and PSI-BLAST: a new generation of protein database search programs,” *Nucleic Acids Res.* 25:3389-3402). Another popular local alignment technique is based on the Smith-Waterman algorithm (Smith, T.F. & Waterman, M.S. (1981) “Identification of common molecular subsequences.” *J. Mol. Biol.* 147:195-197). A general global alignment technique based on dynamic programming is the Needleman–Wunsch algorithm (Needleman, S.B. & Wunsch, C.D. (1970) “A general method applicable to the search for similarities in the amino acid sequences of two proteins.” *J. Mol. Biol.* 48:443-453). More recently, a Fast Optimal Global Sequence Alignment Algorithm (FOGSAA) was developed that purportedly produces global alignment of nucleotide and protein sequences faster than other optimal

global alignment methods, including the Needleman–Wunsch algorithm. Other tools are described herein, specifically in the definition of “identity” below.

As used herein, the term “homology” refers to the overall relatedness between polymeric molecules, *e.g.* between nucleic acid molecules (*e.g.* DNA molecules and/or RNA molecules) and/or between polypeptide molecules. Polymeric molecules (*e.g.* nucleic acid molecules (*e.g.* DNA molecules and/or RNA molecules) and/or polypeptide molecules) that share a threshold level of similarity or identity determined by alignment of matching residues are termed homologous. Homology is a qualitative term that describes a relationship between molecules and can be based upon the quantitative similarity or identity. Similarity or identity is a quantitative term that defines the degree of sequence match between two compared sequences. In some embodiments, polymeric molecules are considered to be “homologous” to one another if their sequences are at least 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 99% identical or similar. The term “homologous” necessarily refers to a comparison between at least two sequences (polynucleotide or polypeptide sequences). Two polynucleotide sequences are considered homologous if the polypeptides they encode are at least 50%, 60%, 70%, 80%, 90%, 95%, or even 99% for at least one stretch of at least 20 amino acids. In some embodiments, homologous polynucleotide sequences are characterized by the ability to encode a stretch of at least 4–5 uniquely specified amino acids. For polynucleotide sequences less than 60 nucleotides in length, homology is determined by the ability to encode a stretch of at least 4–5 uniquely specified amino acids. Two protein sequences are considered homologous if the proteins are at least 50%, 60%, 70%, 80%, or 90% identical for at least one stretch of at least 20 amino acids.

Homology implies that the compared sequences diverged in evolution from a common origin. The term “homolog” refers to a first amino acid sequence or nucleic acid sequence (*e.g.*, gene (DNA or RNA) or protein sequence) that is related to a second amino acid sequence or nucleic acid sequence by descent from a common ancestral sequence. The term “homolog” may apply to the relationship between genes and/or proteins separated by the event of speciation or to the relationship between genes and/or proteins separated by the event of genetic duplication. “Orthologs” are genes (or proteins) in different species that evolved from a common ancestral gene (or protein) by speciation. Typically, orthologs retain the same function in the course of evolution. “Paralogs” are genes (or proteins) related by duplication within a genome. Orthologs retain the same function in the course of evolution, whereas paralogs evolve new functions, even if these are related to the original one.

The term “identity” refers to the overall relatedness between polymeric molecules, for example, between polynucleotide molecules (*e.g.* DNA molecules and/or RNA molecules) and/or between polypeptide molecules. Calculation of the percent identity of two polynucleic acid sequences, for example, can be performed by aligning the two sequences for optimal comparison purposes (*e.g.*, gaps can be introduced in one or both of a first and a second nucleic acid sequences for optimal alignment and non-identical sequences can be disregarded for comparison purposes). In certain embodiments, the length of a sequence aligned for comparison purposes is at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, or 100% of the length of the reference sequence. The nucleotides at corresponding nucleotide positions are then compared. When a position in the first sequence is occupied by the same nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences, taking into account the number of gaps, and the length of each gap, which needs to be introduced for optimal alignment of the two sequences. The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm. For example, the percent identity between two nucleic acid sequences can be determined using methods such as those described in Computational Molecular Biology, Lesk, A. M., ed., Oxford University Press, New York, 1988; Biocomputing: Informatics and Genome Projects, Smith, D. W., ed., Academic Press, New York, 1993; Sequence Analysis in Molecular Biology, von Heinje, G., Academic Press, 1987; Computer Analysis of Sequence Data, Part I, Griffin, A. M., and Griffin, H. G., eds., Humana Press, New Jersey, 1994; and Sequence Analysis Primer, Gribskov, M. and Devereux, J., eds., M Stockton Press, New York, 1991; each of which is incorporated herein by reference. For example, the percent identity between two nucleic acid sequences can be determined using the algorithm of Meyers and Miller (CABIOS, 1989, 4:11-17), which has been incorporated into the ALIGN program (version 2.0) using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4. The percent identity between two nucleic acid sequences can, alternatively, be determined using the GAP program in the GCG software package using an NWSgapdna.CMP matrix. Methods commonly employed to determine percent identity between sequences include, but are not limited to those disclosed in Carillo, H., and Lipman, D., *SIAM J Applied Math.*, 48:1073 (1988); incorporated herein by reference. Techniques for determining identity are codified in publicly available computer programs. Exemplary computer software to determine homology between two sequences include, but are not limited to, GCG program package, Devereux, J., *et al.*, *Nucleic Acids*

Research, 12, 387 (1984)), BLASTP, BLASTN, and FASTA Altschul, S. F. *et al.*, *J. Molec. Biol.*, 215, 403 (1990)).

Multiprotein and Multicomponent Vaccines

5 The present disclosure encompasses influenza vaccines comprising multiple RNA (*e.g.*, mRNA) polynucleotides, each encoding a single antigenic polypeptide, as well as influenza vaccines comprising a single RNA polynucleotide encoding more than one antigenic polypeptide (*e.g.*, as a fusion polypeptide). Thus, a vaccine composition comprising a RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a
10 first antigenic polypeptide and a RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding a second antigenic polypeptide encompasses (a) vaccines that comprise a first RNA polynucleotide encoding a first antigenic polypeptide and a second RNA polynucleotide encoding a second antigenic polypeptide, and (b) vaccines that comprise a single RNA polynucleotide encoding a first and second antigenic polypeptide (*e.g.*, as a
15 fusion polypeptide). RNA (*e.g.*, mRNA) vaccines of the present disclosure, in some embodiments, comprise 2-10 (*e.g.*, 2, 3, 4, 5, 6, 7, 8, 9 or 10), or more, RNA polynucleotides having an open reading frame, each of which encodes a different antigenic polypeptide (or a single RNA polynucleotide encoding 2-10, or more, different antigenic polypeptides). The antigenic polypeptides may be selected from any of the influenza antigenic polypeptides
20 described herein.

 In some embodiments, a multicomponent vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide encoding at least one influenza antigenic polypeptide fused to a signal peptide (*e.g.*, SEQ ID NO: 488-490). The signal peptide may be fused at the N-terminus or the C-terminus of an antigenic polypeptide.

Signal peptides

 In some embodiments, antigenic polypeptides encoded by influenza RNA (*e.g.*, mRNA) polynucleotides comprise a signal peptide. Signal peptides, comprising the N-terminal 15-60 amino acids of proteins, are typically needed for the translocation across the
30 membrane on the secretory pathway and, thus, universally control the entry of most proteins both in eukaryotes and prokaryotes to the secretory pathway. Signal peptides generally include three regions: an N-terminal region of differing length, which usually comprises positively charged amino acids; a hydrophobic region; and a short carboxy-terminal peptide region. In eukaryotes, the signal peptide of a nascent precursor protein (pre-protein) directs
35 the ribosome to the rough endoplasmic reticulum (ER) membrane and initiates the transport

of the growing peptide chain across it for processing. ER processing produces mature proteins, wherein the signal peptide is cleaved from precursor proteins, typically by a ER-resident signal peptidase of the host cell, or they remain uncleaved and function as a membrane anchor. A signal peptide may also facilitate the targeting of the protein to the cell membrane. The signal peptide, however, is not responsible for the final destination of the mature protein. Secretory proteins devoid of additional address tags in their sequence are by default secreted to the external environment. During recent years, a more advanced view of signal peptides has evolved, showing that the functions and immunodominance of certain signal peptides are much more versatile than previously anticipated.

Influenza vaccines of the present disclosure may comprise, for example, RNA (*e.g.*, mRNA) polynucleotides encoding an artificial signal peptide, wherein the signal peptide coding sequence is operably linked to and is in frame with the coding sequence of the antigenic polypeptide. Thus, influenza vaccines of the present disclosure, in some embodiments, produce an antigenic polypeptide fused to a signal peptide. In some embodiments, a signal peptide is fused to the N-terminus of the antigenic polypeptide. In some embodiments, a signal peptide is fused to the C-terminus of the antigenic polypeptide.

In some embodiments, the signal peptide fused to the antigenic polypeptide is an artificial signal peptide. In some embodiments, an artificial signal peptide fused to the antigenic polypeptide encoded by the RNA (*e.g.*, mRNA) vaccine is obtained from an immunoglobulin protein, *e.g.*, an IgE signal peptide or an IgG signal peptide. In some embodiments, a signal peptide fused to the antigenic polypeptide encoded by a RNA (*e.g.*, mRNA) vaccine is an Ig heavy chain epsilon-1 signal peptide (IgE HC SP) having the sequence of: MDWTWILFLVAAATRVHS; SEQ ID NO: 481. In some embodiments, a signal peptide fused to the antigenic polypeptide encoded by the (*e.g.*, mRNA) RNA (*e.g.*, mRNA) vaccine is an IgGk chain V-III region HAH signal peptide (IgGk SP) having the sequence of METPAQLLFLLLLWLPDTTG; SEQ ID NO: 480. In some embodiments, the signal peptide is selected from: Japanese encephalitis PRM signal sequence (MLGSNSGQRVVFTILLLLVAPAYS; SEQ ID NO: 482), VSVg protein signal sequence (MKCLLYLAFLFIGVNCA; SEQ ID NO: 483) and Japanese encephalitis JEV signal sequence (MWLVSLAIVTACAGA; SEQ ID NO: 484).

In some embodiments, the antigenic polypeptide encoded by a RNA (*e.g.*, mRNA) vaccine comprises an amino acid sequence identified by any one of SEQ ID NO: 1-444, 458, 460, 462-479 (see also Tables 7-13) fused to a signal peptide identified by any one of SEQ ID NO: 480-484. The examples disclosed herein are not meant to be limiting and any signal peptide that is known in the art to facilitate targeting of a protein to ER for processing and/or

targeting of a protein to the cell membrane may be used in accordance with the present disclosure.

A signal peptide may have a length of 15-60 amino acids. For example, a signal peptide may have a length of 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, or 60 amino acids. In some embodiments, a signal peptide has a length of 20-60, 25-60, 30-60, 35-60, 40-60, 45-60, 50-60, 55-60, 15-55, 20-55, 25-55, 30-55, 35-55, 40-55, 45-55, 50-55, 15-50, 20-50, 25-50, 30-50, 35-50, 40-50, 45-50, 15-45, 20-45, 25-45, 30-45, 35-45, 40-45, 15-40, 20-40, 25-40, 30-40, 35-40, 15-35, 20-35, 25-35, 30-35, 15-30, 20-30, 25-30, 15-25, 20-25, or 15-20 amino acids.

A signal peptide is typically cleaved from the nascent polypeptide at the cleavage junction during ER processing. The mature antigenic polypeptide produced by an influenza RNA (*e.g.*, mRNA) vaccine of the present disclosure typically does not comprise a signal peptide.

Chemical Modifications

Influenza vaccines of the present disclosure, in some embodiments, comprise at least RNA (*e.g.* mRNA) polynucleotide having an open reading frame encoding at least one antigenic polypeptide that comprises at least one chemical modification.

The terms “chemical modification” and “chemically modified” refer to modification with respect to adenosine (A), guanosine (G), uridine (U), thymidine (T) or cytidine (C) ribonucleosides or deoxyribonucleosides in at least one of their position, pattern, percent or population. Generally, these terms do not refer to the ribonucleotide modifications in naturally occurring 5'-terminal mRNA cap moieties. With respect to a polypeptide, the term “modification” refers to a modification relative to the canonical set 20 amino acids. Polypeptides, as provided herein, are also considered “modified” if they contain amino acid substitutions, insertions or a combination of substitutions and insertions.

Polynucleotides (*e.g.*, RNA polynucleotides, such as mRNA polynucleotides), in some embodiments, comprise various (more than one) different modifications. In some embodiments, a particular region of a polynucleotide contains one, two or more (optionally different) nucleoside or nucleotide modifications. In some embodiments, a modified RNA polynucleotide (*e.g.*, a modified mRNA polynucleotide), introduced to a cell or organism, exhibits reduced degradation in the cell or organism, respectively, relative to an unmodified polynucleotide. In some embodiments, a modified RNA polynucleotide (*e.g.*, a modified

mRNA polynucleotide), introduced into a cell or organism, may exhibit reduced immunogenicity in the cell or organism, respectively (*e.g.*, a reduced innate response).

Modifications of polynucleotides include, without limitation, those described herein. Polynucleotides (*e.g.*, RNA polynucleotides, such as mRNA polynucleotides) may comprise
5 modifications that are naturally-occurring, non-naturally-occurring or the polynucleotide may comprise a combination of naturally-occurring and non-naturally-occurring modifications. Polynucleotides may include any useful modification, for example, of a sugar, a nucleobase, or an internucleoside linkage (*e.g.*, to a linking phosphate, to a phosphodiester linkage or to the phosphodiester backbone).

10 Polynucleotides (*e.g.*, RNA polynucleotides, such as mRNA polynucleotides), in some embodiments, comprise non-natural modified nucleotides that are introduced during synthesis or post-synthesis of the polynucleotides to achieve desired functions or properties. The modifications may be present on an internucleotide linkages, purine or pyrimidine bases, or sugars. The modification may be introduced with chemical synthesis or with a polymerase
15 enzyme at the terminal of a chain or anywhere else in the chain. Any of the regions of a polynucleotide may be chemically modified.

The present disclosure provides for modified nucleosides and nucleotides of a polynucleotide (*e.g.*, RNA polynucleotides, such as mRNA polynucleotides). A “nucleoside” refers to a compound containing a sugar molecule (*e.g.*, a pentose or ribose) or a derivative
20 thereof in combination with an organic base (*e.g.*, a purine or pyrimidine) or a derivative thereof (also referred to herein as “nucleobase”). A nucleotide” refers to a nucleoside, including a phosphate group. Modified nucleotides may be synthesized by any useful method, such as, for example, chemically, enzymatically, or recombinantly, to include one or more modified or non-natural nucleosides. Polynucleotides may comprise a region or regions
25 of linked nucleosides. Such regions may have variable backbone linkages. The linkages may be standard phosphodiester linkages, in which case the polynucleotides would comprise regions of nucleotides.

Modified nucleotide base pairing encompasses not only the standard adenosine-thymine, adenosine-uracil, or guanosine-cytosine base pairs, but also base pairs formed
30 between nucleotides and/or modified nucleotides comprising non-standard or modified bases, wherein the arrangement of hydrogen bond donors and hydrogen bond acceptors permits hydrogen bonding between a non-standard base and a standard base or between two complementary non-standard base structures. One example of such non-standard base pairing is the base pairing between the modified nucleotide inosine and adenine, cytosine or

uracil. Any combination of base/sugar or linker may be incorporated into polynucleotides of the present disclosure.

Modifications of polynucleotides (*e.g.*, RNA polynucleotides, such as mRNA polynucleotides) that are useful in the vaccines of the present disclosure include, but are not limited to the following: 2-methylthio-N6-(*cis*-hydroxyisopentenyl)adenosine; 2-methylthio-N6-methyladenosine; 2-methylthio-N6-threonyl carbamoyladenosine; N6-glycinylicarbamoyladenosine; N6-isopentenyladenosine; N6-methyladenosine; N6-threonylicarbamoyladenosine; 1,2'-O-dimethyladenosine; 1-methyladenosine; 2'-O-methyladenosine; 2'-O-ribosyladenosine (phosphate); 2-methyladenosine; 2-methylthio-N6 isopentenyladenosine; 2-methylthio-N6-hydroxynorvalyl carbamoyladenosine; 2'-O-methyladenosine; 2'-O-ribosyladenosine (phosphate); Isopentenyladenosine; N6-(*cis*-hydroxyisopentenyl)adenosine; N6,2'-O-dimethyladenosine; N6,2'-O-dimethyladenosine; N6,N6,2'-O-trimethyladenosine; N6,N6-dimethyladenosine; N6-acetyladenosine; N6-hydroxynorvalylcarbamoyladenosine; N6-methyl-N6-threonylicarbamoyladenosine; 2-methyladenosine; 2-methylthio-N6-isopentenyladenosine; 7-deaza-adenosine; N1-methyladenosine; N6, N6 (dimethyl)adenine; N6-*cis*-hydroxy-isopentenyl-adenosine; α -thioadenosine; 2 (amino)adenine; 2 (aminopropyl)adenine; 2 (methylthio) N6 (isopentenyl)adenine; 2-(alkyl)adenine; 2-(aminoalkyl)adenine; 2-(aminopropyl)adenine; 2-(halo)adenine; 2-(halo)adenine; 2-(propyl)adenine; 2'-Amino-2'-deoxy-ATP; 2'-Azido-2'-deoxy-ATP; 2'-Deoxy-2'-a-aminoadenosine TP; 2'-Deoxy-2'-a-azidoadenosine TP; 6 (alkyl)adenine; 6 (methyl)adenine; 6-(alkyl)adenine; 6-(methyl)adenine; 7 (deaza)adenine; 8 (alkenyl)adenine; 8 (alkynyl)adenine; 8 (amino)adenine; 8 (thioalkyl)adenine; 8-(alkenyl)adenine; 8-(alkyl)adenine; 8-(alkynyl)adenine; 8-(amino)adenine; 8-(halo)adenine; 8-(hydroxyl)adenine; 8-(thioalkyl)adenine; 8-(thiol)adenine; 8-azido-adenosine; aza adenine; deaza adenine; N6 (methyl)adenine; N6-(isopentyl)adenine; 7-deaza-8-aza-adenosine; 7-methyladenine; 1-Deazaadenosine TP; 2'Fluoro-N6-Bz-deoxyadenosine TP; 2'-OMe-2'-Amino-ATP; 2'O-methyl-N6-Bz-deoxyadenosine TP; 2'-a-Ethynyladenosine TP; 2-aminoadenine; 2-Aminoadenosine TP; 2-Amino-ATP; 2'-a-Trifluoromethyladenosine TP; 2-Azidoadenosine TP; 2'-b-Ethynyladenosine TP; 2-Bromoadenosine TP; 2'-b-Trifluoromethyladenosine TP; 2-Chloroadenosine TP; 2'-Deoxy-2',2'-difluoroadenosine TP; 2'-Deoxy-2'-a-mercaptoadenosine TP; 2'-Deoxy-2'-a-thiomethoxyadenosine TP; 2'-Deoxy-2'-b-aminoadenosine TP; 2'-Deoxy-2'-b-azidoadenosine TP; 2'-Deoxy-2'-b-bromoadenosine TP; 2'-Deoxy-2'-b-chloroadenosine TP; 2'-Deoxy-2'-b-fluoroadenosine TP; 2'-Deoxy-2'-b-iodoadenosine TP; 2'-Deoxy-2'-b-mercaptoadenosine TP; 2'-Deoxy-2'-b-thiomethoxyadenosine TP; 2-Fluoroadenosine TP; 2-Iodoadenosine TP; 2-

Mercaptoadenosine TP; 2-methoxy-adenine; 2-methylthio-adenine; 2-
 Trifluoromethyladenosine TP; 3-Deaza-3-bromoadenosine TP; 3-Deaza-3-chloroadenosine
 TP; 3-Deaza-3-fluoroadenosine TP; 3-Deaza-3-iodoadenosine TP; 3-Deazaadenosine TP; 4'-
 Azidoadenosine TP; 4'-Carbocyclic adenosine TP; 4'-Ethynyladenosine TP; 5'-Homo-
 5 adenosine TP; 8-Aza-ATP; 8-bromo-adenosine TP; 8-Trifluoromethyladenosine TP; 9-
 Deazaadenosine TP; 2-aminopurine; 7-deaza-2,6-diaminopurine; 7-deaza-8-aza-2,6-
 diaminopurine; 7-deaza-8-aza-2-aminopurine; 2,6-diaminopurine; 7-deaza-8-aza-adenine, 7-
 deaza-2-aminopurine; 2-thiocytidine; 3-methylcytidine; 5-formylcytidine; 5-
 hydroxymethylcytidine; 5-methylcytidine; N4-acetylcytidine; 2'-O-methylcytidine; 2'-O-
 10 methylcytidine; 5,2'-O-dimethylcytidine; 5-formyl-2'-O-methylcytidine; Lysidine; N4,2'-O-
 dimethylcytidine; N4-acetyl-2'-O-methylcytidine; N4-methylcytidine; N4,N4-Dimethyl-2'-
 OMe-Cytidine TP; 4-methylcytidine; 5-aza-cytidine; Pseudo-iso-cytidine; pyrrolo-cytidine;
 α -thio-cytidine; 2-(thio)cytosine; 2'-Amino-2'-deoxy-CTP; 2'-Azido-2'-deoxy-CTP; 2'-
 Deoxy-2'-a-aminocytidine TP; 2'-Deoxy-2'-a-azidocytidine TP; 3 (deaza) 5 (aza)cytosine; 3
 15 (methyl)cytosine; 3-(alkyl)cytosine; 3-(deaza) 5 (aza)cytosine; 3-(methyl)cytidine; 4,2'-O-
 dimethylcytidine; 5 (halo)cytosine; 5 (methyl)cytosine; 5 (propynyl)cytosine; 5
 (trifluoromethyl)cytosine; 5-(alkyl)cytosine; 5-(alkynyl)cytosine; 5-(halo)cytosine; 5-
 (propynyl)cytosine; 5-(trifluoromethyl)cytosine; 5-bromo-cytidine; 5-iodo-cytidine; 5-
 propynyl cytosine; 6-(azo)cytosine; 6-aza-cytidine; aza cytosine; deaza cytosine; N4
 20 (acetyl)cytosine; 1-methyl-1-deaza-pseudoisocytidine; 1-methyl-pseudoisocytidine; 2-
 methoxy-5-methyl-cytidine; 2-methoxy-cytidine; 2-thio-5-methyl-cytidine; 4-methoxy-1-
 methyl-pseudoisocytidine; 4-methoxy-pseudoisocytidine; 4-thio-1-methyl-1-deaza-
 pseudoisocytidine; 4-thio-1-methyl-pseudoisocytidine; 4-thio-pseudoisocytidine; 5-aza-
 zebularine; 5-methyl-zebularine; pyrrolo-pseudoisocytidine; Zebularine; (E)-5-(2-Bromo-
 25 vinyl)cytidine TP; 2,2'-anhydro-cytidine TP hydrochloride; 2' Fluor-N4-Bz-cytidine TP;
 2'Fluoro-N4-Acetyl-cytidine TP; 2'-O-Methyl-N4-Acetyl-cytidine TP; 2'O-methyl-N4-Bz-
 cytidine TP; 2'-a-Ethynylcytidine TP; 2'-a-Trifluoromethylcytidine TP; 2'-b-Ethynylcytidine
 TP; 2'-b-Trifluoromethylcytidine TP; 2'-Deoxy-2',2'-difluorocytidine TP; 2'-Deoxy-2'-a-
 mercaptocytidine TP; 2'-Deoxy-2'-a-thiomethoxycytidine TP; 2'-Deoxy-2'-b-aminocytidine
 30 TP; 2'-Deoxy-2'-b-azidocytidine TP; 2'-Deoxy-2'-b-bromocytidine TP; 2'-Deoxy-2'-b-
 chlorocytidine TP; 2'-Deoxy-2'-b-fluorocytidine TP; 2'-Deoxy-2'-b-iodocytidine TP; 2'-
 Deoxy-2'-b-mercaptocytidine TP; 2'-Deoxy-2'-b-thiomethoxycytidine TP; 2'-O-Methyl-5-(1-
 propynyl)cytidine TP; 3'-Ethynylcytidine TP; 4'-Azidocytidine TP; 4'-Carbocyclic cytidine
 TP; 4'-Ethynylcytidine TP; 5-(1-Propynyl)ara-cytidine TP; 5-(2-Chloro-phenyl)-2-
 35 thiocytidine TP; 5-(4-Amino-phenyl)-2-thiocytidine TP; 5-Aminoallyl-CTP; 5-Cyanocytidine

TP; 5-Ethynylara-cytidine TP; 5-Ethynylcytidine TP; 5'-Homo-cytidine TP; 5-Methoxycytidine TP; 5-Trifluoromethyl-Cytidine TP; N4-Amino-cytidine TP; N4-Benzoyl-cytidine TP; Pseudoisocytidine; 7-methylguanosine; N2,2'-O-dimethylguanosine; N2-methylguanosine; Wyosine; 1,2'-O-dimethylguanosine; 1-methylguanosine; 2'-O-methylguanosine; 2'-O-ribosylguanosine (phosphate); 2'-O-methylguanosine; 2'-O-ribosylguanosine (phosphate); 7-aminomethyl-7-deazaguanosine; 7-cyano-7-deazaguanosine; Archaeosine; Methylwyosine; N2,7-dimethylguanosine; N2,N2,2'-O-trimethylguanosine; N2,N2,7-trimethylguanosine; N2,N2-dimethylguanosine; N2,7,2'-O-trimethylguanosine; 6-thio-guanosine; 7-deaza-guanosine; 8-oxo-guanosine; N1-methyl-guanosine; α -thio-guanosine; 2 (propyl)guanine; 2-(alkyl)guanine; 2'-Amino-2'-deoxy-GTP; 2'-Azido-2'-deoxy-GTP; 2'-Deoxy-2'-a-aminoguanosine TP; 2'-Deoxy-2'-a-azidoguanosine TP; 6 (methyl)guanine; 6-(alkyl)guanine; 6-(methyl)guanine; 6-methyl-guanosine; 7 (alkyl)guanine; 7 (deaza)guanine; 7 (methyl)guanine; 7-(alkyl)guanine; 7-(deaza)guanine; 7-(methyl)guanine; 8 (alkyl)guanine; 8 (alkynyl)guanine; 8 (halo)guanine; 8 (thioalkyl)guanine; 8-(alkenyl)guanine; 8-(alkyl)guanine; 8-(alkynyl)guanine; 8-(amino)guanine; 8-(halo)guanine; 8-(hydroxyl)guanine; 8-(thioalkyl)guanine; 8-(thiol)guanine; aza guanine; deaza guanine; N (methyl)guanine; N-(methyl)guanine; 1-methyl-6-thio-guanosine; 6-methoxy-guanosine; 6-thio-7-deaza-8-aza-guanosine; 6-thio-7-deaza-guanosine; 6-thio-7-methyl-guanosine; 7-deaza-8-aza-guanosine; 7-methyl-8-oxo-guanosine; N2,N2-dimethyl-6-thio-guanosine; N2-methyl-6-thio-guanosine; 1-Me-GTP; 2'Fluoro-N2-isobutyl-guanosine TP; 2'O-methyl-N2-isobutyl-guanosine TP; 2'-a-Ethynylguanosine TP; 2'-a-Trifluoromethylguanosine TP; 2'-b-Ethynylguanosine TP; 2'-b-Trifluoromethylguanosine TP; 2'-Deoxy-2',2'-difluoroguanosine TP; 2'-Deoxy-2'-a-mercaptoguanosine TP; 2'-Deoxy-2'-a-thiomethoxyguanosine TP; 2'-Deoxy-2'-b-aminoguanosine TP; 2'-Deoxy-2'-b-azidoguanosine TP; 2'-Deoxy-2'-b-bromoguanosine TP; 2'-Deoxy-2'-b-chloroguanosine TP; 2'-Deoxy-2'-b-fluoroguanosine TP; 2'-Deoxy-2'-b-iodoguanosine TP; 2'-Deoxy-2'-b-mercaptoguanosine TP; 2'-Deoxy-2'-b-thiomethoxyguanosine TP; 4'-Azidoguanosine TP; 4'-Carbocyclic guanosine TP; 4'-Ethynylguanosine TP; 5'-Homo-guanosine TP; 8-bromo-guanosine TP; 9-Deazaguanosine TP; N2-isobutyl-guanosine TP; 1-methylinosine; Inosine; 1,2'-O-dimethylinosine; 2'-O-methylinosine; 7-methylinosine; 2'-O-methylinosine; Epoxyqueuosine; galactosyl-queuosine; Mannosylqueuosine; Queuosine; allyamino-thymidine; aza thymidine; deaza thymidine; deoxy-thymidine; 2'-O-methyluridine; 2-thiouridine; 3-methyluridine; 5-carboxymethyluridine; 5-hydroxyuridine; 5-methyluridine; 5-taurinomethyl-2-thiouridine; 5-taurinomethyluridine; Dihydrouridine; Pseudouridine; (3-(3-amino-3-carboxypropyl)uridine; 1-methyl-3-(3-amino-5-carboxypropyl)pseudouridine; 1-methylpseduouridine; 1-methyl-

pseudouridine; 2'-O-methyluridine; 2'-O-methylpseudouridine; 2'-O-methyluridine; 2-thio-2'-O-methyluridine; 3-(3-amino-3-carboxypropyl)uridine; 3,2'-O-dimethyluridine; 3-Methyl-pseudo-Uridine TP; 4-thiouridine; 5-(carboxyhydroxymethyl)uridine; 5-(carboxyhydroxymethyl)uridine methyl ester; 5,2'-O-dimethyluridine; 5,6-dihydro-uridine; 5-aminomethyl-2-thiouridine; 5-carbamoylmethyl-2'-O-methyluridine; 5-carbamoylmethyluridine; 5-carboxyhydroxymethyluridine; 5-carboxyhydroxymethyluridine methyl ester; 5-carboxymethylaminomethyl-2'-O-methyluridine; 5-carboxymethylaminomethyl-2-thiouridine; 5-carboxymethylaminomethyl-2-thiouridine; 5-carboxymethylaminomethyluridine; 5-carboxymethylaminomethyluridine; 5-Carbamoylmethyluridine TP; 5-methoxycarbonylmethyl-2'-O-methyluridine; 5-methoxycarbonylmethyl-2-thiouridine; 5-methoxycarbonylmethyluridine; 5-methoxyuridine; 5-methyl-2-thiouridine; 5-methylaminomethyl-2-selenouridine; 5-methylaminomethyl-2-thiouridine; 5-methylaminomethyluridine; 5-Methyldihydrouridine; 5-Oxyacetic acid-Uridine TP; 5-Oxyacetic acid-methyl ester-Uridine TP; N1-methyl-pseudo-uridine; uridine 5-oxyacetic acid; uridine 5-oxyacetic acid methyl ester; 3-(3-Amino-3-carboxypropyl)-Uridine TP; 5-(iso-Pentenylaminomethyl)-2-thiouridine TP; 5-(iso-Pentenylaminomethyl)-2'-O-methyluridine TP; 5-(iso-Pentenylaminomethyl)uridine TP; 5-propynyl uracil; α -thio-uridine; 1 (aminoalkylamino-carbonylethylenyl)-2(thio)-pseudouracil; 1 (aminoalkylaminocarbonylethylenyl)-2,4-(dithio)pseudouracil; 1 (aminoalkylaminocarbonylethylenyl)-4 (thio)pseudouracil; 1 (aminoalkylaminocarbonylethylenyl)-pseudouracil; 1 (aminocarbonylethylenyl)-2(thio)-pseudouracil; 1 (aminocarbonylethylenyl)-2,4-(dithio)pseudouracil; 1 (aminocarbonylethylenyl)-4 (thio)pseudouracil; 1 (aminocarbonylethylenyl)-pseudouracil; 1 substituted 2(thio)-pseudouracil; 1 substituted 2,4-(dithio)pseudouracil; 1 substituted 4 (thio)pseudouracil; 1 substituted pseudouracil; 1-(aminoalkylamino-carbonylethylenyl)-2-(thio)-pseudouracil; 1-Methyl-3-(3-amino-3-carboxypropyl) pseudouridine TP; 1-Methyl-3-(3-amino-3-carboxypropyl)pseudo-UTP; 1-Methyl-pseudo-UTP; 2 (thio)pseudouracil; 2' deoxy uridine; 2' fluorouridine; 2-(thio)uracil; 2,4-(dithio)pseudouracil; 2' methyl, 2' amino, 2' azido, 2' fluoro-guanosine; 2'-Amino-2'-deoxy-UTP; 2'-Azido-2'-deoxy-UTP; 2'-Azido-deoxyuridine TP; 2'-O-methylpseudouridine; 2' deoxy uridine; 2' fluorouridine; 2'-Deoxy-2'-a-aminouridine TP; 2'-Deoxy-2'-a-azidouridine TP; 2-methylpseudouridine; 3 (3 amino-3 carboxypropyl)uracil; 4 (thio)pseudouracil; 4-(thio)pseudouracil; 4-(thio)uracil; 4-thiouracil; 5 (1,3-diazole-1-alkyl)uracil; 5 (2-aminopropyl)uracil; 5 (aminoalkyl)uracil; 5 (dimethylaminoalkyl)uracil; 5 (guanidiniumalkyl)uracil; 5 (methoxycarbonylmethyl)-2-(thio)uracil; 5 (methoxycarbonyl-methyl)uracil; 5 (methyl) 2 (thio)uracil; 5 (methyl) 2,4

(dithio)uracil; 5 (methyl) 4 (thio)uracil; 5 (methylaminomethyl)-2 (thio)uracil; 5 (methylaminomethyl)-2,4 (dithio)uracil; 5 (methylaminomethyl)-4 (thio)uracil; 5 (propynyl)uracil; 5 (trifluoromethyl)uracil; 5-(2-aminopropyl)uracil; 5-(alkyl)-2-(thio)pseudouracil; 5-(alkyl)-2,4 (dithio)pseudouracil; 5-(alkyl)-4 (thio)pseudouracil; 5-(alkyl)pseudouracil; 5-(alkyl)uracil; 5-(alkynyl)uracil; 5-(allylamino)uracil; 5-(cyanoalkyl)uracil; 5-(dialkylaminoalkyl)uracil; 5-(dimethylaminoalkyl)uracil; 5-(guanidiniumalkyl)uracil; 5-(halo)uracil; 5-(1,3-diazole-1-alkyl)uracil; 5-(methoxy)uracil; 5-(methoxycarbonylmethyl)-2-(thio)uracil; 5-(methoxycarbonyl-methyl)uracil; 5-(methyl) 2(thio)uracil; 5-(methyl) 2,4 (dithio)uracil; 5-(methyl) 4 (thio)uracil; 5-(methyl)-2-(thio)pseudouracil; 5-(methyl)-2,4 (dithio)pseudouracil; 5-(methyl)-4 (thio)pseudouracil; 5-(methyl)pseudouracil; 5-(methylaminomethyl)-2 (thio)uracil; 5-(methylaminomethyl)-2,4(dithio)uracil; 5-(methylaminomethyl)-4-(thio)uracil; 5-(propynyl)uracil; 5-(trifluoromethyl)uracil; 5-aminoallyl-uridine; 5-bromo-uridine; 5-iodo-uridine; 5-uracil; 6 (azo)uracil; 6-(azo)uracil; 6-aza-uridine; allylamino-uracil; aza uracil; deaza uracil; N3 (methyl)uracil; P pseudo-UTP-1-2-ethanoic acid; Pseudouracil; 4-Thio-pseudo-UTP; 1-carboxymethyl-pseudouridine; 1-methyl-1-deaza-pseudouridine; 1-propynyl-uridine; 1-taurinomethyl-1-methyl-uridine; 1-taurinomethyl-4-thio-uridine; 1-taurinomethyl-pseudouridine; 2-methoxy-4-thio-pseudouridine; 2-thio-1-methyl-1-deaza-pseudouridine; 2-thio-1-methyl-pseudouridine; 2-thio-5-aza-uridine; 2-thio-dihydropseudouridine; 2-thio-dihydrouridine; 2-thio-pseudouridine; 4-methoxy-2-thio-pseudouridine; 4-methoxy-pseudouridine; 4-thio-1-methyl-pseudouridine; 4-thio-pseudouridine; 5-aza-uridine; Dihydropseudouridine; ($\pm$)1-(2-Hydroxypropyl)pseudouridine TP; (2R)-1-(2-Hydroxypropyl)pseudouridine TP; (2S)-1-(2-Hydroxypropyl)pseudouridine TP; (E)-5-(2-Bromo-vinyl)ara-uridine TP; (E)-5-(2-Bromo-vinyl)uridine TP; (Z)-5-(2-Bromo-vinyl)ara-uridine TP; (Z)-5-(2-Bromo-vinyl)uridine TP; 1-(2,2,2-Trifluoroethyl)-pseudo-UTP; 1-(2,2,3,3,3-Pentafluoropropyl)pseudouridine TP; 1-(2,2-Diethoxyethyl)pseudouridine TP; 1-(2,4,6-Trimethylbenzyl)pseudouridine TP; 1-(2,4,6-Trimethyl-benzyl)pseudo-UTP; 1-(2,4,6-Trimethyl-phenyl)pseudo-UTP; 1-(2-Amino-2-carboxyethyl)pseudo-UTP; 1-(2-Amino-ethyl)pseudo-UTP; 1-(2-Hydroxyethyl)pseudouridine TP; 1-(2-Methoxyethyl)pseudouridine TP; 1-(3,4-Bis-trifluoromethoxybenzyl)pseudouridine TP; 1-(3,4-Dimethoxybenzyl)pseudouridine TP; 1-(3-Amino-3-carboxypropyl)pseudo-UTP; 1-(3-Amino-propyl)pseudo-UTP; 1-(3-Cyclopropyl-prop-2-ynyl)pseudouridine TP; 1-(4-Amino-4-carboxybutyl)pseudo-UTP; 1-(4-Amino-benzyl)pseudo-UTP; 1-(4-Amino-butyl)pseudo-UTP; 1-(4-Amino-phenyl)pseudo-UTP; 1-(4-Azidobenzyl)pseudouridine TP; 1-(4-Bromobenzyl)pseudouridine TP; 1-(4-Chlorobenzyl)pseudouridine TP; 1-(4-

Fluorobenzyl)pseudouridine TP; 1-(4-Iodobenzyl)pseudouridine TP; 1-(4-Methanesulfonylbenzyl)pseudouridine TP; 1-(4-Methoxybenzyl)pseudouridine TP; 1-(4-Methoxy-benzyl)pseudo-UTP; 1-(4-Methoxy-phenyl)pseudo-UTP; 1-(4-Methylbenzyl)pseudouridine TP; 1-(4-Methyl-benzyl)pseudo-UTP; 1-(4-Nitrobenzyl)pseudouridine TP; 1-(4-Nitro-benzyl)pseudo-UTP; 1-(4-Nitro-phenyl)pseudo-UTP; 1-(4-Thiomethoxybenzyl)pseudouridine TP; 1-(4-Trifluoromethoxybenzyl)pseudouridine TP; 1-(4-Trifluoromethylbenzyl)pseudouridine TP; 1-(5-Amino-pentyl)pseudo-UTP; 1-(6-Amino-hexyl)pseudo-UTP; 1,6-Dimethyl-pseudo-UTP; 1-[3-(2-{2-[2-(2-Aminoethoxy)-ethoxy]-ethoxy}-ethoxy)-propionyl]pseudouridine TP; 1-{3-[2-(2-Aminoethoxy)-ethoxy]-propionyl } pseudouridine TP; 1-Acetylpsudouridine TP; 1-Alkyl-6-(1-propynyl)-pseudo-UTP; 1-Alkyl-6-(2-propynyl)-pseudo-UTP; 1-Alkyl-6-allyl-pseudo-UTP; 1-Alkyl-6-ethynyl-pseudo-UTP; 1-Alkyl-6-homoallyl-pseudo-UTP; 1-Alkyl-6-vinyl-pseudo-UTP; 1-Allylpsudouridine TP; 1-Aminomethyl-pseudo-UTP; 1-Benzoylpsudouridine TP; 1-Benzyloxymethylpsudouridine TP; 1-Benzyl-pseudo-UTP; 1-Biotinyl-PEG2-pseudouridine TP; 1-Biotinylpsudouridine TP; 1-Butyl-pseudo-UTP; 1-Cyanomethylpsudouridine TP; 1-Cyclobutylmethyl-pseudo-UTP; 1-Cyclobutyl-pseudo-UTP; 1-Cycloheptylmethyl-pseudo-UTP; 1-Cycloheptyl-pseudo-UTP; 1-Cyclohexylmethyl-pseudo-UTP; 1-Cyclohexyl-pseudo-UTP; 1-Cyclooctylmethyl-pseudo-UTP; 1-Cyclooctyl-pseudo-UTP; 1-Cyclopentylmethyl-pseudo-UTP; 1-Cyclopentyl-pseudo-UTP; 1-Cyclopropylmethyl-pseudo-UTP; 1-Cyclopropyl-pseudo-UTP; 1-Ethyl-pseudo-UTP; 1-Hexyl-pseudo-UTP; 1-Homoallylpsudouridine TP; 1-Hydroxymethylpsudouridine TP; 1-iso-propyl-pseudo-UTP; 1-Me-2-thio-pseudo-UTP; 1-Me-4-thio-pseudo-UTP; 1-Me-alpha-thio-pseudo-UTP; 1-Methanesulfonylmethylpsudouridine TP; 1-Methoxymethylpsudouridine TP; 1-Methyl-6-(2,2,2-Trifluoroethyl)pseudo-UTP; 1-Methyl-6-(4-morpholino)-pseudo-UTP; 1-Methyl-6-(4-thiomorpholino)-pseudo-UTP; 1-Methyl-6-(substituted phenyl)pseudo-UTP; 1-Methyl-6-amino-pseudo-UTP; 1-Methyl-6-azido-pseudo-UTP; 1-Methyl-6-bromo-pseudo-UTP; 1-Methyl-6-butyl-pseudo-UTP; 1-Methyl-6-chloro-pseudo-UTP; 1-Methyl-6-cyano-pseudo-UTP; 1-Methyl-6-dimethylamino-pseudo-UTP; 1-Methyl-6-ethoxy-pseudo-UTP; 1-Methyl-6-ethylcarboxylate-pseudo-UTP; 1-Methyl-6-ethyl-pseudo-UTP; 1-Methyl-6-fluoro-pseudo-UTP; 1-Methyl-6-formyl-pseudo-UTP; 1-Methyl-6-hydroxyamino-pseudo-UTP; 1-Methyl-6-hydroxy-pseudo-UTP; 1-Methyl-6-iodo-pseudo-UTP; 1-Methyl-6-iso-propyl-pseudo-UTP; 1-Methyl-6-methoxy-pseudo-UTP; 1-Methyl-6-methylamino-pseudo-UTP; 1-Methyl-6-phenyl-pseudo-UTP; 1-Methyl-6-propyl-pseudo-UTP; 1-Methyl-6-tert-butyl-pseudo-UTP; 1-Methyl-6-trifluoromethoxy-pseudo-UTP; 1-Methyl-6-trifluoromethyl-pseudo-UTP; 1-Morpholinomethylpsudouridine TP; 1-Pentyl-

pseudo-UTP; 1-Phenyl-pseudo-UTP; 1-Pivaloylpseudouridine TP; 1-Propargylpseudouridine TP; 1-Propyl-pseudo-UTP; 1-propynyl-pseudouridine; 1-p-tolyl-pseudo-UTP; 1-tert-Butyl-pseudo-UTP; 1-Thiomethoxymethylpseudouridine TP; 1-Thiomorpholinomethylpseudouridine TP; 1-Trifluoroacetylpsudouridine TP; 1-Trifluoromethyl-pseudo-UTP; 1-Vinylpseudouridine TP; 2,2'-anhydro-uridine TP; 2'-bromo-deoxyuridine TP; 2'-F-5-Methyl-2'-deoxy-UTP; 2'-OMe-5-Me-UTP; 2'-OMe-pseudo-UTP; 2'-a-Ethynyluridine TP; 2'-a-Trifluoromethyluridine TP; 2'-b-Ethynyluridine TP; 2'-b-Trifluoromethyluridine TP; 2'-Deoxy-2',2'-difluorouridine TP; 2'-Deoxy-2'-a-mercaptopuridine TP; 2'-Deoxy-2'-a-thiomethoxyuridine TP; 2'-Deoxy-2'-b-aminouridine TP; 2'-Deoxy-2'-b-azidouridine TP; 2'-Deoxy-2'-b-bromouridine TP; 2'-Deoxy-2'-b-chlorouridine TP; 2'-Deoxy-2'-b-fluorouridine TP; 2'-Deoxy-2'-b-iodouridine TP; 2'-Deoxy-2'-b-mercaptopuridine TP; 2'-Deoxy-2'-b-thiomethoxyuridine TP; 2-methoxy-4-thio-uridine; 2-methoxyuridine; 2'-O-Methyl-5-(1-propynyl)uridine TP; 3-Alkyl-pseudo-UTP; 4'-Azidouridine TP; 4'-Carbocyclic uridine TP; 4'-Ethynyluridine TP; 5-(1-Propynyl)ara-uridine TP; 5-(2-Furanyl)uridine TP; 5-Cyanouridine TP; 5-Dimethylaminouridine TP; 5'-Homo-uridine TP; 5-iodo-2'-fluoro-deoxyuridine TP; 5-Phenylethynyluridine TP; 5-Trideuteromethyl-6-deuterouridine TP; 5-Trifluoromethyl-Uridine TP; 5-Vinylarauridine TP; 6-(2,2,2-Trifluoroethyl)-pseudo-UTP; 6-(4-Morpholino)-pseudo-UTP; 6-(4-Thiomorpholino)-pseudo-UTP; 6-(Substituted-Phenyl)-pseudo-UTP; 6-Amino-pseudo-UTP; 6-Azido-pseudo-UTP; 6-Bromo-pseudo-UTP; 6-Butyl-pseudo-UTP; 6-Chloro-pseudo-UTP; 6-Cyano-pseudo-UTP; 6-Dimethylamino-pseudo-UTP; 6-Ethoxy-pseudo-UTP; 6-Ethylcarboxylate-pseudo-UTP; 6-Ethyl-pseudo-UTP; 6-Fluoro-pseudo-UTP; 6-Formyl-pseudo-UTP; 6-Hydroxyamino-pseudo-UTP; 6-Hydroxy-pseudo-UTP; 6-Iodo-pseudo-UTP; 6-iso-Propyl-pseudo-UTP; 6-Methoxy-pseudo-UTP; 6-Methylamino-pseudo-UTP; 6-Methyl-pseudo-UTP; 6-Phenyl-pseudo-UTP; 6-Phenyl-pseudo-UTP; 6-Propyl-pseudo-UTP; 6-tert-Butyl-pseudo-UTP; 6-Trifluoromethoxy-pseudo-UTP; 6-Trifluoromethyl-pseudo-UTP; Alpha-thio-pseudo-UTP; Pseudouridine 1-(4-methylbenzenesulfonic acid) TP; Pseudouridine 1-(4-methylbenzoic acid) TP; Pseudouridine TP 1-[3-(2-ethoxy)]propionic acid; Pseudouridine TP 1-[3-{2-(2-[2-(2-ethoxy)-ethoxy]-ethoxy)-ethoxy}]propionic acid; Pseudouridine TP 1-[3-{2-(2-[2-{2(2-ethoxy)-ethoxy}-ethoxy)-ethoxy}-ethoxy}]propionic acid; Pseudouridine TP 1-[3-{2-(2-[2-ethoxy]-ethoxy)-ethoxy}]propionic acid; Pseudouridine TP 1-methylphosphonic acid; Pseudouridine TP 1-methylphosphonic acid diethyl ester; Pseudo-UTP-N1-3-propionic acid; Pseudo-UTP-N1-4-butanoic acid; Pseudo-UTP-N1-5-pentanoic acid; Pseudo-UTP-N1-6-hexanoic acid; Pseudo-UTP-N1-7-heptanoic acid; Pseudo-UTP-N1-methyl-p-benzoic acid; Pseudo-UTP-N1-p-benzoic acid; Wybutosine;

Hydroxywybutosine; Isowyosine; Peroxywybutosine; undermodified hydroxywybutosine; 4-demethylwyosine; 2,6-(diamino)purine; 1-(aza)-2-(thio)-3-(aza)-phenoxazin-1-yl; 1,3-(diaz)-2-(oxo)-phenthiazin-1-yl; 1,3-(diaz)-2-(oxo)-phenoxazin-1-yl; 1,3,5-(triaz)-2,6-(diox)-naphthalene; 2 (amino)purine; 2,4,5-(trimethyl)phenyl; 2' methyl, 2' amino, 2' azido, 2' fluoro-
 5 cytidine; 2' methyl, 2' amino, 2' azido, 2' fluoro-adenine; 2' methyl, 2' amino, 2' azido, 2' fluoro-uridine; 2'-amino-2'-deoxyribose; 2-amino-6-Chloro-purine; 2-aza-inosinyl; 2'-azido-2'-deoxyribose; 2'fluoro-2'-deoxyribose; 2'-fluoro-modified bases; 2'-O-methyl-ribose; 2-oxo-7-aminopyridopyrimidin-3-yl; 2-oxo-pyridopyrimidine-3-yl; 2-pyridinone; 3 nitropyrrole; 3-(methyl)-7-(propynyl)isocarbostyryl; 3-(methyl)isocarbostyryl; 4-(fluoro)-6-
 10 (methyl)benzimidazole; 4-(methyl)benzimidazole; 4-(methyl)indolyl; 4,6-(dimethyl)indolyl; 5 nitroindole; 5 substituted pyrimidines; 5-(methyl)isocarbostyryl; 5-nitroindole; 6-(aza)pyrimidine; 6-(azo)thymine; 6-(methyl)-7-(aza)indolyl; 6-chloro-purine; 6-phenyl-pyrrolo-pyrimidin-2-on-3-yl; 7-(aminoalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)-phenthiazin-1-yl; 7-(aminoalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)-phenoxazin-1-yl; 7-(aminoalkylhydroxy)-
 15 1,3-(diaz)-2-(oxo)-phenoxazin-1-yl; 7-(aminoalkylhydroxy)-1,3-(diaz)-2-(oxo)-phenthiazin-1-yl; 7-(aminoalkylhydroxy)-1,3-(diaz)-2-(oxo)-phenoxazin-1-yl; 7-(aza)indolyl; 7-(guanidiniumalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)-phenoxazin-1-yl; 7-(guanidiniumalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)-phenthiazin-1-yl; 7-(guanidiniumalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)-phenoxazin-1-yl; 7-(guanidiniumalkylhydroxy)-1,3-(diaz)-2-(oxo)-phenoxazin-1-yl; 7-(guanidiniumalkylhydroxy)-1,3-(diaz)-2-(oxo)-phenthiazin-1-yl; 7-(guanidiniumalkylhydroxy)-1,3-(diaz)-2-(oxo)-phenoxazin-1-yl; 7-(propynyl)isocarbostyryl; 7-(propynyl)isocarbostyryl, propynyl-7-(aza)indolyl; 7-deaza-inosinyl; 7-substituted 1-(aza)-2-(thio)-3-(aza)-phenoxazin-1-yl; 7-substituted 1,3-(diaz)-2-(oxo)-phenoxazin-1-yl; 9-(methyl)-imidizopyridinyl; Aminoindolyl;
 25 Anthracenyl; bis-ortho-(aminoalkylhydroxy)-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl; bis-ortho-substituted-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl; Difluorotolyl; Hypoxanthine; Imidizopyridinyl; Inosinyl; Isocarbostyryl; Isoguanisine; N2-substituted purines; N6-methyl-2-amino-purine; N6-substituted purines; N-alkylated derivative; Napthalenyl; Nitrobenzimidazolyl; Nitroimidazolyl; Nitroindazolyl; Nitropyrazolyl; Nubularine; O6-substituted purines; O-alkylated derivative; ortho-(aminoalkylhydroxy)-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl; ortho-substituted-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl; Oxoformycin
 30 TP; para-(aminoalkylhydroxy)-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl; para-substituted-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl; Pentacenyl; Phenanthracenyl; Phenyl; propynyl-7-(aza)indolyl; Pyrenyl; pyridopyrimidin-3-yl; pyridopyrimidin-3-yl, 2-oxo-7-amino-pyridopyrimidin-3-yl; pyrrolo-pyrimidin-2-on-3-yl; Pyrrolopyrimidinyl; Pyrrolopyrizinyl;
 35

Stilbenzyl; substituted 1,2,4-triazoles; Tetracenyl; Tubercidine; Xanthine; Xanthosine-5'-TP; 2-thio-zebularine; 5-aza-2-thio-zebularine; 7-deaza-2-amino-purine; pyridin-4-one ribonucleoside; 2-Amino-riboside-TP; Formycin A TP; Formycin B TP; Pyrrolosine TP; 2'-OH-ara-adenosine TP; 2'-OH-ara-cytidine TP; 2'-OH-ara-uridine TP; 2'-OH-ara-guanosine TP; 5-(2-carbomethoxyvinyl)uridine TP; and N6-(19-Amino-pentaoxanonadecyl)adenosine TP.

In some embodiments, polynucleotides (*e.g.*, RNA polynucleotides, such as mRNA polynucleotides) include a combination of at least two (*e.g.*, 2, 3, 4 or more) of the aforementioned modified nucleobases.

10 In some embodiments, modified nucleobases in polynucleotides (*e.g.*, RNA polynucleotides, such as mRNA polynucleotides) are selected from the group consisting of pseudouridine (ψ), N1-methylpseudouridine ($m^1\psi$), 2-thiouridine, N1-ethylpseudouridine, 4'-thiouridine, 5-methylcytosine, 2-thio-1-methyl-1-deaza-pseudouridine, 2-thio-1-methyl-pseudouridine, 2-thio-5-aza-uridine, 2-thio-dihydropseudouridine, 2-thio-dihydrouridine, 2-15 thio-pseudouridine, 4-methoxy-2-thio-pseudouridine, 4-methoxy-pseudouridine, 4-thio-1-methyl-pseudouridine, 4-thio-pseudouridine, 5-aza-uridine, dihydropseudouridine, 5-methoxyuridine and 2'-O-methyl uridine. In some embodiments, polynucleotides (*e.g.*, RNA polynucleotides, such as mRNA polynucleotides) include a combination of at least two (*e.g.*, 2, 3, 4 or more) of the aforementioned modified nucleobases.

20 In some embodiments, modified nucleobases in polynucleotides (*e.g.*, RNA polynucleotides, such as mRNA polynucleotides) are selected from the group consisting of 1-methyl-pseudouridine ($m^1\psi$), 5-methoxy-uridine (mo^5U), 5-methyl-cytidine (m^5C), pseudouridine (ψ), α -thio-guanosine and α -thio-adenosine. In some embodiments, polynucleotides includes a combination of at least two (*e.g.*, 2, 3, 4 or more) of the 25 aforementioned modified nucleobases.

In some embodiments, polynucleotides (*e.g.*, RNA polynucleotides, such as mRNA polynucleotides) comprise pseudouridine (ψ) and 5-methyl-cytidine (m^5C). In some embodiments, polynucleotides (*e.g.*, RNA polynucleotides, such as mRNA polynucleotides) comprise 1-methyl-pseudouridine ($m^1\psi$). In some embodiments, polynucleotides (*e.g.*, RNA 30 polynucleotides, such as mRNA polynucleotides) comprise 1-methyl-pseudouridine ($m^1\psi$) and 5-methyl-cytidine (m^5C). In some embodiments, polynucleotides (*e.g.*, RNA polynucleotides, such as mRNA polynucleotides) comprise 2-thiouridine (s^2U). In some embodiments, polynucleotides (*e.g.*, RNA polynucleotides, such as mRNA polynucleotides) comprise 2-thiouridine and 5-methyl-cytidine (m^5C). In some embodiments, polynucleotides 35 (*e.g.*, RNA polynucleotides, such as mRNA polynucleotides) comprise methoxy-uridine

(mo⁵U). In some embodiments, polynucleotides (*e.g.*, RNA polynucleotides, such as mRNA polynucleotides) comprise 5-methoxy-uridine (mo⁵U) and 5-methyl-cytidine (m⁵C). In some embodiments, polynucleotides (*e.g.*, RNA polynucleotides, such as mRNA polynucleotides) comprise 2'-O-methyl uridine. In some embodiments polynucleotides (*e.g.*, RNA polynucleotides, such as mRNA polynucleotides) comprise 2'-O-methyl uridine and 5-methyl-cytidine (m⁵C). In some embodiments, polynucleotides (*e.g.*, RNA polynucleotides, such as mRNA polynucleotides) comprise N6-methyl-adenosine (m⁶A). In some embodiments, polynucleotides (*e.g.*, RNA polynucleotides, such as mRNA polynucleotides) comprise N6-methyl-adenosine (m⁶A) and 5-methyl-cytidine (m⁵C).

In some embodiments, polynucleotides (*e.g.*, RNA polynucleotides, such as mRNA polynucleotides) are uniformly modified (*e.g.*, fully modified, modified throughout the entire sequence) for a particular modification. For example, a polynucleotide can be uniformly modified with 5-methyl-cytidine (m⁵C), meaning that all cytosine residues in the mRNA sequence are replaced with 5-methyl-cytidine (m⁵C). Similarly, a polynucleotide can be uniformly modified for any type of nucleoside residue present in the sequence by replacement with a modified residue such as those set forth above.

Exemplary nucleobases and nucleosides having a modified cytosine include N4-acetyl-cytidine (ac4C), 5-methyl-cytidine (m5C), 5-halo-cytidine (*e.g.*, 5-iodo-cytidine), 5-hydroxymethyl-cytidine (hm5C), 1-methyl-pseudoisocytidine, 2-thio-cytidine (s2C), and 2-thio-5-methyl-cytidine.

In some embodiments, a modified nucleobase is a modified uridine. Exemplary nucleobases and In some embodiments, a modified nucleobase is a modified cytosine. nucleosides having a modified uridine include 5-cyano uridine, and 4'-thio uridine.

In some embodiments, a modified nucleobase is a modified adenine. Exemplary nucleobases and nucleosides having a modified adenine include 7-deaza-adenine, 1-methyl-adenosine (m1A), 2-methyl-adenine (m2A), and N6-methyl-adenosine (m6A).

In some embodiments, a modified nucleobase is a modified guanine. Exemplary nucleobases and nucleosides having a modified guanine include inosine (I), 1-methyl-inosine (m1I), wyosine (imG), methylwyosine (mimG), 7-deaza-guanosine, 7-cyano-7-deaza-guanosine (preQ0), 7-aminomethyl-7-deaza-guanosine (preQ1), 7-methyl-guanosine (m7G), 1-methyl-guanosine (m1G), 8-oxo-guanosine, 7-methyl-8-oxo-guanosine.

The polynucleotides of the present disclosure may be partially or fully modified along the entire length of the molecule. For example, one or more or all or a given type of nucleotide (*e.g.*, purine or pyrimidine, or any one or more or all of A, G, U, C) may be uniformly modified in a polynucleotide of the invention, or in a given predetermined

sequence region thereof (*e.g.*, in the mRNA including or excluding the polyA tail). In some embodiments, all nucleotides X in a polynucleotide of the present disclosure (or in a given sequence region thereof) are modified nucleotides, wherein X may any one of nucleotides A, G, U, C, or any one of the combinations A+G, A+U, A+C, G+U, G+C, U+C, A+G+U, A+G+C, G+U+C or A+G+C.

The polynucleotide may contain from about 1% to about 100% modified nucleotides (either in relation to overall nucleotide content, or in relation to one or more types of nucleotide, *i.e.*, any one or more of A, G, U or C) or any intervening percentage (*e.g.*, from 1% to 20%, from 1% to 25%, from 1% to 50%, from 1% to 60%, from 1% to 70%, from 1% to 80%, from 1% to 90%, from 1% to 95%, from 10% to 20%, from 10% to 25%, from 10% to 50%, from 10% to 60%, from 10% to 70%, from 10% to 80%, from 10% to 90%, from 10% to 95%, from 10% to 100%, from 20% to 25%, from 20% to 50%, from 20% to 60%, from 20% to 70%, from 20% to 80%, from 20% to 90%, from 20% to 95%, from 20% to 100%, from 50% to 60%, from 50% to 70%, from 50% to 80%, from 50% to 90%, from 50% to 95%, from 50% to 100%, from 70% to 80%, from 70% to 90%, from 70% to 95%, from 70% to 100%, from 80% to 90%, from 80% to 95%, from 80% to 100%, from 90% to 95%, from 90% to 100%, and from 95% to 100%). Any remaining percentage is accounted for by the presence of unmodified A, G, U, or C.

The polynucleotides may contain at a minimum 1% and at maximum 100% modified nucleotides, or any intervening percentage, such as at least 5% modified nucleotides, at least 10% modified nucleotides, at least 25% modified nucleotides, at least 50% modified nucleotides, at least 80% modified nucleotides, or at least 90% modified nucleotides. For example, the polynucleotides may contain a modified pyrimidine such as a modified uracil or cytosine. In some embodiments, at least 5%, at least 10%, at least 25%, at least 50%, at least 80%, at least 90% or 100% of the uracil in the polynucleotide is replaced with a modified uracil (*e.g.*, a 5-substituted uracil). The modified uracil can be replaced by a compound having a single unique structure, or can be replaced by a plurality of compounds having different structures (*e.g.*, 2, 3, 4 or more unique structures). In some embodiments, at least 5%, at least 10%, at least 25%, at least 50%, at least 80%, at least 90% or 100% of the cytosine in the polynucleotide is replaced with a modified cytosine (*e.g.*, a 5-substituted cytosine). The modified cytosine can be replaced by a compound having a single unique structure, or can be replaced by a plurality of compounds having different structures (*e.g.*, 2, 3, 4 or more unique structures).

Thus, in some embodiments, the RNA (*e.g.*, mRNA) vaccines comprise a 5'UTR element, an optionally codon optimized open reading frame, and a 3'UTR element, a poly(A) sequence and/or a polyadenylation signal wherein the RNA is not chemically modified.

In some embodiments, the modified nucleobase is a modified uracil. Exemplary
 5 nucleobases and nucleosides having a modified uracil include pseudouridine (ψ), pyridin-4-one ribonucleoside, 5-aza-uridine, 6-aza-uridine, 2-thio-5-aza-uridine, 2-thio-uridine (s^2U), 4-thio-uridine (s^4U), 4-thio-pseudouridine, 2-thio-pseudouridine, 5-hydroxy-uridine (ho^5U), 5-aminoallyl-uridine, 5-halo-uridine (*e.g.*, 5-iodo-uridine or 5-bromo-uridine), 3-methyl-uridine (m^3U), 5-methoxy-uridine (mo^5U), uridine 5-oxyacetic acid (cmo^5U), uridine 5-oxyacetic
 10 acid methyl ester ($mcmo^5U$), 5-carboxymethyl-uridine (cm^5U), 1-carboxymethyl-pseudouridine, 5-carboxyhydroxymethyl-uridine (chm^5U), 5-carboxyhydroxymethyl-uridine methyl ester ($mchm^5U$), 5-methoxycarbonylmethyl-uridine (mcm^5U), 5-methoxycarbonylmethyl-2-thio-uridine (mcm^5s^2U), 5-aminomethyl-2-thio-uridine (nm^5s^2U), 5-methylaminomethyl-uridine (mnm^5U), 5-methylaminomethyl-2-thio-uridine (mnm^5s^2U), 5-methylaminomethyl-2-seleno-uridine (mnm^5se^2U), 5-carbamoylmethyl-uridine (ncm^5U), 5-carboxymethylaminomethyl-uridine ($cmnm^5U$), 5-carboxymethylaminomethyl-2-thio-uridine ($cmnm^5s^2U$), 5-propynyl-uridine, 1-propynyl-pseudouridine, 5-aurinomethyl-uridine (τm^5U), 1-aurinomethyl-pseudouridine, 5-aurinomethyl-2-thio-uridine (τm^5s^2U), 1-aurinomethyl-4-thio-pseudouridine, 5-methyl-uridine (m^5U , *i.e.*, having the nucleobase deoxythymine), 1-methyl-pseudouridine ($m^1\psi$), 5-methyl-2-thio-uridine (m^5s^2U), 1-methyl-4-thio-pseudouridine ($m^1s^4\psi$), 4-thio-1-methyl-pseudouridine, 3-methyl-pseudouridine ($m^3\psi$), 2-thio-1-methyl-pseudouridine, 1-methyl-1-deaza-pseudouridine, 2-thio-1-methyl-1-deaza-pseudouridine, dihydrouridine (D), dihydropseudouridine, 5,6-dihydrouridine, 5-methyl-dihydrouridine (m^5D), 2-thio-dihydrouridine, 2-thio-dihydropseudouridine, 2-methoxy-
 25 uridine, 2-methoxy-4-thio-uridine, 4-methoxy-pseudouridine, 4-methoxy-2-thio-pseudouridine, N1-methyl-pseudouridine, 3-(3-amino-3-carboxypropyl)uridine (acp^3U), 1-methyl-3-(3-amino-3-carboxypropyl)pseudouridine ($acp^3\psi$), 5-(isopentenylaminomethyl)uridine (inm^5U), 5-(isopentenylaminomethyl)-2-thio-uridine (inm^5s^2U), α -thio-uridine, 2'-O-methyl-uridine (Um), 5,2'-O-dimethyl-uridine (m^5Um), 2'-O-methyl-pseudouridine (ψm), 2-thio-2'-O-methyl-uridine (s^2Um), 5-methoxycarbonylmethyl-2'-O-methyl-uridine (mcm^5Um), 5-carbamoylmethyl-2'-O-methyl-uridine (ncm^5Um), 5-carboxymethylaminomethyl-2'-O-methyl-uridine ($cmnm^5Um$), 3,2'-O-dimethyl-uridine (m^3Um), and 5-(isopentenylaminomethyl)-2'-O-methyl-uridine (inm^5Um), 1-thio-uridine, deoxythymidine, 2'-F-ara-uridine, 2'-F-uridine, 2'-OH-ara-uridine, 5-(2-carbomethoxyvinyl)
 35 uridine, and 5-[3-(1-E-propenylamino)]uridine.

In some embodiments, the modified nucleobase is a modified cytosine. Exemplary nucleobases and nucleosides having a modified cytosine include 5-aza-cytidine, 6-aza-cytidine, pseudoisocytidine, 3-methyl-cytidine (m^3C), N4-acetyl-cytidine (ac^4C), 5-formyl-cytidine (f^5C), N4-methyl-cytidine (m^4C), 5-methyl-cytidine (m^5C), 5-halo-cytidine (*e.g.*, 5-iodo-cytidine), 5-hydroxymethyl-cytidine (hm^5C), 1-methyl-pseudoisocytidine, pyrrolo-cytidine, pyrrolo-pseudoisocytidine, 2-thio-cytidine (s^2C), 2-thio-5-methyl-cytidine, 4-thio-pseudoisocytidine, 4-thio-1-methyl-pseudoisocytidine, 4-thio-1-methyl-1-deaza-pseudoisocytidine, 1-methyl-1-deaza-pseudoisocytidine, zebularine, 5-aza-zebularine, 5-methyl-zebularine, 5-aza-2-thio-zebularine, 2-thio-zebularine, 2-methoxy-cytidine, 2-methoxy-5-methyl-cytidine, 4-methoxy-pseudoisocytidine, 4-methoxy-1-methyl-pseudoisocytidine, lysidine (k_2C), α -thio-cytidine, 2'-O-methyl-cytidine (Cm), 5,2'-O-dimethyl-cytidine (m^5Cm), N4-acetyl-2'-O-methyl-cytidine (ac^4Cm), N4,2'-O-dimethyl-cytidine (m^4Cm), 5-formyl-2'-O-methyl-cytidine (f^5Cm), N4,N4,2'-O-trimethyl-cytidine (m^4_2Cm), 1-thio-cytidine, 2'-F-ara-cytidine, 2'-F-cytidine, and 2'-OH-ara-cytidine.

In some embodiments, the modified nucleobase is a modified adenine. Exemplary nucleobases and nucleosides having a modified adenine include 2-amino-purine, 2, 6-diaminopurine, 2-amino-6-halo-purine (*e.g.*, 2-amino-6-chloro-purine), 6-halo-purine (*e.g.*, 6-chloro-purine), 2-amino-6-methyl-purine, 8-azido-adenosine, 7-deaza-adenine, 7-deaza-8-aza-adenine, 7-deaza-2-amino-purine, 7-deaza-8-aza-2-amino-purine, 7-deaza-2,6-diaminopurine, 7-deaza-8-aza-2,6-diaminopurine, 1-methyl-adenosine (m^1A), 2-methyl-adenine (m^2A), N6-methyl-adenosine (m^6A), 2-methylthio-N6-methyl-adenosine (ms^2m^6A), N6-isopentenyl-adenosine (i^6A), 2-methylthio-N6-isopentenyl-adenosine (ms^2i^6A), N6-(cis-hydroxyisopentenyl)adenosine (io^6A), 2-methylthio-N6-(cis-hydroxyisopentenyl)adenosine (ms^2io^6A), N6-glycylcarbamoyl-adenosine (g^6A), N6-threonylcarbamoyl-adenosine (t^6A), N6-methyl-N6-threonylcarbamoyl-adenosine (m^6t^6A), 2-methylthio-N6-threonylcarbamoyl-adenosine (ms^2g^6A), N6,N6-dimethyl-adenosine (m^6_2A), N6-hydroxynorvalylcarbamoyl-adenosine (hn^6A), 2-methylthio-N6-hydroxynorvalylcarbamoyl-adenosine (ms^2hn^6A), N6-acetyl-adenosine (ac^6A), 7-methyl-adenine, 2-methylthio-adenine, 2-methoxy-adenine, α -thio-adenosine, 2'-O-methyl-adenosine (Am), N6,2'-O-dimethyl-adenosine (m^6Am), N6,N6,2'-O-trimethyl-adenosine (m^6_2Am), 1,2'-O-dimethyl-adenosine (m^1Am), 2'-O-ribosyladenosine (phosphate) (Ar(p)), 2-amino-N6-methyl-purine, 1-thio-adenosine, 8-azido-adenosine, 2'-F-ara-adenosine, 2'-F-adenosine, 2'-OH-ara-adenosine, and N6-(19-amino-pentaoxanonadecyl)-adenosine.

In some embodiments, the modified nucleobase is a modified guanine. Exemplary nucleobases and nucleosides having a modified guanine include inosine (I), 1-methyl-inosine

(m¹I), wyosine (imG), methylwyosine (mimG), 4-demethyl-wyosine (imG-14), isowyosine (imG2), wybutosine (yW), peroxywybutosine (o₂yW), hydroxywybutosine (OhyW), undermodified hydroxywybutosine (OhyW*), 7-deaza-guanosine, queuosine (Q), epoxyqueuosine (oQ), galactosyl-queuosine (galQ), mannosyl-queuosine (manQ), 7-cyano-7-deaza-guanosine (preQ₀), 7-aminomethyl-7-deaza-guanosine (preQ₁), archaeosine (G⁺), 7-deaza-8-aza-guanosine, 6-thio-guanosine, 6-thio-7-deaza-guanosine, 6-thio-7-deaza-8-aza-guanosine, 7-methyl-guanosine (m⁷G), 6-thio-7-methyl-guanosine, 7-methyl-inosine, 6-methoxy-guanosine, 1-methyl-guanosine (m¹G), N2-methyl-guanosine (m²G), N2,N2-dimethyl-guanosine (m²₂G), N2,7-dimethyl-guanosine (m^{2,7}G), N2, N2,7-dimethyl-guanosine (m^{2,2,7}G), 8-oxo-guanosine, 7-methyl-8-oxo-guanosine, 1-methyl-6-thio-guanosine, N2-methyl-6-thio-guanosine, N2,N2-dimethyl-6-thio-guanosine, α-thio-guanosine, 2'-O-methyl-guanosine (Gm), N2-methyl-2'-O-methyl-guanosine (m²Gm), N2,N2-dimethyl-2'-O-methyl-guanosine (m²₂Gm), 1-methyl-2'-O-methyl-guanosine (m¹Gm), N2,7-dimethyl-2'-O-methyl-guanosine (m^{2,7}Gm), 2'-O-methyl-inosine (Im), 1,2'-O-dimethyl-inosine (m¹Im), 2'-O-ribosylguanosine (phosphate) (Gr(p)), 1-thio-guanosine, O6-methyl-guanosine, 2'-F-ara-guanosine, and 2'-F-guanosine.

In Vitro Transcription of RNA (e.g., mRNA)

Influenza virus vaccines of the present disclosure comprise at least one RNA polynucleotide, such as a mRNA (e.g., modified mRNA). mRNA, for example, is transcribed *in vitro* from template DNA, referred to as an “*in vitro* transcription template.” In some embodiments, an *in vitro* transcription template encodes a 5' untranslated (UTR) region, contains an open reading frame, and encodes a 3' UTR and a polyA tail. The particular nucleic acid sequence composition and length of an *in vitro* transcription template will depend on the mRNA encoded by the template.

A “5' untranslated region” (5'UTR) refers to a region of an mRNA that is directly upstream (*i.e.*, 5') from the start codon (*i.e.*, the first codon of an mRNA transcript translated by a ribosome) that does not encode a polypeptide.

A “3' untranslated region” (3'UTR) refers to a region of an mRNA that is directly downstream (*i.e.*, 3') from the stop codon (*i.e.*, the codon of an mRNA transcript that signals a termination of translation) that does not encode a polypeptide.

An “open reading frame” is a continuous stretch of DNA beginning with a start codon (*e.g.*, methionine (ATG)), and ending with a stop codon (*e.g.*, TAA, TAG or TGA) and encodes a polypeptide.

A “polyA tail” is a region of mRNA that is downstream, *e.g.*, directly downstream (*i.e.*, 3'), from the 3' UTR that contains multiple, consecutive adenosine monophosphates. A polyA tail may contain 10 to 300 adenosine monophosphates. For example, a polyA tail may contain 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190,
 5 200, 210, 220, 230, 240, 250, 260, 270, 280, 290 or 300 adenosine monophosphates. In some embodiments, a polyA tail contains 50 to 250 adenosine monophosphates. In a relevant biological setting (*e.g.*, in cells, *in vivo*) the poly(A) tail functions to protect mRNA from enzymatic degradation, *e.g.*, in the cytoplasm, and aids in transcription termination, export of the mRNA from the nucleus and translation.

10 In some embodiments, a polynucleotide includes 200 to 3,000 nucleotides. For example, a polynucleotide may include 200 to 500, 200 to 1000, 200 to 1500, 200 to 3000, 500 to 1000, 500 to 1500, 500 to 2000, 500 to 3000, 1000 to 1500, 1000 to 2000, 1000 to 3000, 1500 to 3000, or 2000 to 3000 nucleotides.

15 *Flagellin Adjuvants*

Flagellin is an approximately 500 amino acid monomeric protein that polymerizes to form the flagella associated with bacterial motion. Flagellin is expressed by a variety of flagellated bacteria (*Salmonella typhimurium* for example) as well as non-flagellated bacteria (such as *Escherichia coli*). Sensing of flagellin by cells of the innate immune system
 20 (dendritic cells, macrophages, *etc.*) is mediated by the Toll-like receptor 5 (TLR5) as well as by Nod-like receptors (NLRs) Ipaf and Naip5. TLRs and NLRs have been identified as playing a role in the activation of innate immune response and adaptive immune response. As such, flagellin provides an adjuvant effect in a vaccine.

The nucleotide and amino acid sequences encoding known flagellin polypeptides are
 25 publicly available in the NCBI GenBank database. The flagellin sequences from *S. Typhimurium*, *H. Pylori*, *V. Cholera*, *S. marcesens*, *S. flexneri*, *T. Pallidum*, *L. pneumophila*, *B. burgdorferi*, *C. difficile*, *R. meliloti*, *A. tumefaciens*, *R. lupini*, *B. clarridgeiae*, *P. Mirabilis*, *B. subtilis*, *L. monocytogenes*, *P. aeruginosa*, and *E. coli*, among others are known.

30 A flagellin polypeptide, as used herein, refers to a full length flagellin protein, immunogenic fragments thereof, and peptides having at least 50% sequence identify to a flagellin protein or immunogenic fragments thereof. Exemplary flagellin proteins include flagellin from *Salmonella typhi* (UniPro Entry number: Q56086), *Salmonella typhimurium* (A0A0C9DG09), *Salmonella enteritidis* (A0A0C9BAB7), and *Salmonella choleraesuis*
 35 (Q6V2X8), and proteins having an amino acid sequence identified by any one of SEQ ID NO

1-444, 458, 460, 462-479 (see also Tables 7-13). In some embodiments, the flagellin polypeptide has at least 60%, 70%, 75%, 80%, 90%, 95%, 97%, 98%, or 99% sequence identity to a flagellin protein or immunogenic fragments thereof.

In some embodiments, the flagellin polypeptide is an immunogenic fragment. An immunogenic fragment is a portion of a flagellin protein that provokes an immune response. In some embodiments, the immune response is a TLR5 immune response. An example of an immunogenic fragment is a flagellin protein in which all or a portion of a hinge region has been deleted or replaced with other amino acids. For example, an antigenic polypeptide may be inserted in the hinge region. Hinge regions are the hypervariable regions of a flagellin. Hinge regions of a flagellin are also referred to as “D3 domain or region,” “propeller domain or region,” “hypervariable domain or region” and “variable domain or region.” “At least a portion of a hinge region,” as used herein, refers to any part of the hinge region of the flagellin, or the entirety of the hinge region. In other embodiments an immunogenic fragment of flagellin is a 20, 25, 30, 35, or 40 amino acid C-terminal fragment of flagellin.

The flagellin monomer is formed by domains D0 through D3. D0 and D1, which form the stem, are composed of tandem long alpha helices and are highly conserved among different bacteria. The D1 domain includes several stretches of amino acids that are useful for TLR5 activation. The entire D1 domain or one or more of the active regions within the domain are immunogenic fragments of flagellin. Examples of immunogenic regions within the D1 domain include residues 88-114 and residues 411-431 (in *Salmonella typhimurium* FliC flagellin. Within the 13 amino acids in the 88-100 region, at least 6 substitutions are permitted between *Salmonella* flagellin and other flagellins that still preserve TLR5 activation. Thus, immunogenic fragments of flagellin include flagellin like sequences that activate TLR5 and contain a 13 amino acid motif that is 53% or more identical to the *Salmonella* sequence in 88-100 of FliC (LQRVRELAVQSAN; SEQ ID NO: 504).

In some embodiments, the RNA (*e.g.*, mRNA) vaccine includes an RNA that encodes a fusion protein of flagellin and one or more antigenic polypeptides. A “fusion protein” as used herein, refers to a linking of two components of the construct. In some embodiments, a carboxy-terminus of the antigenic polypeptide is fused or linked to an amino terminus of the flagellin polypeptide. In other embodiments, an amino-terminus of the antigenic polypeptide is fused or linked to a carboxy-terminus of the flagellin polypeptide. The fusion protein may include, for example, one, two, three, four, five, six or more flagellin polypeptides linked to one, two, three, four, five, six or more antigenic polypeptides. When two or more flagellin polypeptides and/or two or more antigenic polypeptides are linked such a construct may be referred to as a “multimer.”

Each of the components of a fusion protein may be directly linked to one another or they may be connected through a linker. For instance, the linker may be an amino acid linker. The amino acid linker encoded for by the RNA (*e.g.*, mRNA) vaccine to link the components of the fusion protein may include, for instance, at least one member selected from the group consisting of a lysine residue, a glutamic acid residue, a serine residue and an arginine residue. In some embodiments the linker is 1-30, 1-25, 1-25, 5-10, 5, 15, or 5-20 amino acids in length.

In other embodiments the RNA (*e.g.*, mRNA) vaccine includes at least two separate RNA polynucleotides, one encoding one or more antigenic polypeptides and the other encoding the flagellin polypeptide. The at least two RNA polynucleotides may be co-formulated in a carrier such as a lipid nanoparticle.

Methods of Treatment

Provided herein are compositions (*e.g.*, pharmaceutical compositions), methods, kits and reagents for prevention and/or treatment of influenza virus in humans and other mammals. Influenza virus RNA vaccines can be used as therapeutic or prophylactic agents. They may be used in medicine to prevent and/or treat infectious disease. In exemplary aspects, the influenza virus RNA vaccines of the present disclosure are used to provide prophylactic protection from influenza virus. Prophylactic protection from influenza virus can be achieved following administration of an influenza virus RNA vaccine of the present disclosure. Vaccines can be administered once, twice, three times, four times or more. It is possible, although less desirable, to administer the vaccine to an infected individual to achieve a therapeutic response. Dosing may need to be adjusted accordingly.

In some embodiments, the influenza virus vaccines of the present disclosure can be used as a method of preventing an influenza virus infection in a subject, the method comprising administering to said subject at least one influenza virus vaccine as provided herein. In some embodiments, the influenza virus vaccines of the present disclosure can be used as a method of inhibiting a primary influenza virus infection in a subject, the method comprising administering to said subject at least one influenza virus vaccine as provided herein. In some embodiments, the influenza virus vaccines of the present disclosure can be used as a method of treating an influenza virus infection in a subject, the method comprising administering to said subject at least one influenza virus vaccine as provided herein. In some embodiments, the influenza virus vaccines of the present disclosure can be used as a method of reducing an incidence of influenza virus infection in a subject, the method comprising administering to said subject at least one influenza virus vaccine as provided herein. In come

embodiments, the influenza virus vaccines of the present disclosure can be used as a method of inhibiting spread of influenza virus from a first subject infected with influenza virus to a second subject not infected with influenza virus, the method comprising administering to at least one of said first subject and said second subject at least one influenza virus vaccine as provided herein.

A method of eliciting an immune response in a subject against an influenza virus is provided in aspects of the invention. The method involves administering to the subject an influenza virus RNA vaccine comprising at least one RNA polynucleotide having an open reading frame encoding at least one influenza virus antigenic polypeptide or an immunogenic fragment thereof, thereby inducing in the subject an immune response specific to influenza virus antigenic polypeptide or an immunogenic fragment thereof, wherein anti-antigenic polypeptide antibody titer in the subject is increased following vaccination relative to anti-antigenic polypeptide antibody titer in a subject vaccinated with a prophylactically effective dose of a traditional vaccine against the influenza virus. An “anti-antigenic polypeptide antibody” is a serum antibody that binds specifically to the antigenic polypeptide.

A prophylactically effective dose is a therapeutically effective dose that prevents infection with the virus at a clinically acceptable level. In some embodiments the therapeutically effective dose is a dose listed in a package insert for the vaccine. A traditional vaccine, as used herein, refers to a vaccine other than the mRNA vaccines of the present disclosure. For instance, a traditional vaccine includes, but is not limited to, live microorganism vaccines, killed microorganism vaccines, subunit vaccines, protein antigen vaccines, DNA vaccines, VLP vaccines, *etc.* In exemplary embodiments, a traditional vaccine is a vaccine that has achieved regulatory approval and/or is registered by a national drug regulatory body, for example the Food and Drug Administration (FDA) in the United States or the European Medicines Agency (EMA).

In some embodiments the anti-antigenic polypeptide antibody titer in the subject is increased 1 log to 10 log following vaccination relative to anti-antigenic polypeptide antibody titer in a subject vaccinated with a prophylactically effective dose of a traditional vaccine against the influenza virus.

In some embodiments the anti-antigenic polypeptide antibody titer in the subject is increased 1 log, 2 log, 3 log, 5 log or 10 log following vaccination relative to anti-antigenic polypeptide antibody titer in a subject vaccinated with a prophylactically effective dose of a traditional vaccine against influenza.

A method of eliciting an immune response in a subject against an influenza virus is provided in other aspects of the present disclosure. The method involves administering to the

subject an influenza virus RNA vaccine comprising at least one RNA polynucleotide having an open reading frame encoding at least one influenza virus antigenic polypeptide or an immunogenic fragment thereof, thereby inducing in the subject an immune response specific to influenza virus antigenic polypeptide or an immunogenic fragment thereof, wherein the immune response in the subject is equivalent to an immune response in a subject vaccinated with a traditional vaccine against the influenza virus at 2 times to 100 times the dosage level relative to the RNA vaccine.

In some embodiments, the immune response in the subject is equivalent to an immune response in a subject vaccinated with a traditional vaccine at 2, 3, 4, 5, 10, 50, 100 times the dosage level relative to the influenza vaccine.

In some embodiments the immune response in the subject is equivalent to an immune response in a subject vaccinated with a traditional vaccine at 10-100 times, or 100-1000 times, the dosage level relative to the influenza vaccine.

In some embodiments the immune response is assessed by determining [protein] antibody titer in the subject.

Some embodiments provide a method of inducing an immune response in a subject by administering to the subject an influenza RNA (*e.g.*, mRNA) vaccine comprising at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding at least one influenza antigenic polypeptide, thereby inducing in the subject an immune response specific to the antigenic polypeptide or an immunogenic fragment thereof, wherein the immune response in the subject is induced 2 days to 10 weeks earlier relative to an immune response induced in a subject vaccinated with a prophylactically effective dose of a traditional vaccine against influenza. In some embodiments, the immune response in the subject is induced in a subject vaccinated with a prophylactically effective dose of a traditional vaccine at 2 times to 100 times the dosage level relative to the influenza RNA (*e.g.*, mRNA) vaccine.

In some embodiments the immune response in the subject is equivalent to an immune response in a subject vaccinated with a traditional vaccine at 2, 3, 4, 5, 10, 50, 100 times the dosage level relative to the influenza RNA (*e.g.*, mRNA) vaccine.

In some embodiments, the immune response in the subject is induced 2 days earlier, or 3 days earlier, relative to an immune response induced in a subject vaccinated with a prophylactically effective dose of a traditional vaccine.

In some embodiments the immune response in the subject is induced 1 week, 2 weeks, 3 weeks, 5 weeks, or 10 weeks earlier relative to an immune response induced in a subject vaccinated with a prophylactically effective dose of a traditional vaccine.

Therapeutic and Prophylactic Compositions

Provided herein are compositions (*e.g.*, pharmaceutical compositions), methods, kits and reagents for prevention, treatment or diagnosis of influenza in humans and other mammals, for example. Influenza RNA (*e.g.* mRNA) vaccines can be used as therapeutic or prophylactic agents. They may be used in medicine to prevent and/or treat infectious disease. In some embodiments, the respiratory RNA (*e.g.*, mRNA) vaccines of the present disclosure are used for the priming of immune effector cells, for example, to activate peripheral blood mononuclear cells (PBMCs) *ex vivo*, which are then infused (re-infused) into a subject.

In some embodiments, influenza vaccine containing RNA (*e.g.*, mRNA) polynucleotides as described herein can be administered to a subject (*e.g.*, a mammalian subject, such as a human subject), and the RNA (*e.g.*, mRNA) polynucleotides are translated *in vivo* to produce an antigenic polypeptide.

The influenza RNA (*e.g.*, mRNA) vaccines may be induced for translation of a polypeptide (*e.g.*, antigen or immunogen) in a cell, tissue or organism. In some embodiments, such translation occurs *in vivo*, although such translation may occur *ex vivo*, in culture or *in vitro*. In some embodiments, the cell, tissue or organism is contacted with an effective amount of a composition containing an influenza RNA (*e.g.*, mRNA) vaccine that contains a polynucleotide that has at least one a translatable region encoding an antigenic polypeptide.

An “effective amount” of an influenza RNA (*e.g.* mRNA) vaccine is provided based, at least in part, on the target tissue, target cell type, means of administration, physical characteristics of the polynucleotide (*e.g.*, size, and extent of modified nucleosides) and other components of the vaccine, and other determinants. In general, an effective amount of the influenza RNA (*e.g.*, mRNA) vaccine composition provides an induced or boosted immune response as a function of antigen production in the cell, preferably more efficient than a composition containing a corresponding unmodified polynucleotide encoding the same antigen or a peptide antigen. Increased antigen production may be demonstrated by increased cell transfection (the percentage of cells transfected with the RNA, *e.g.*, mRNA, vaccine), increased protein translation from the polynucleotide, decreased nucleic acid degradation (as demonstrated, for example, by increased duration of protein translation from a modified polynucleotide), or altered antigen specific immune response of the host cell.

In some embodiments, RNA (*e.g.* mRNA) vaccines (including polynucleotides their encoded polypeptides) in accordance with the present disclosure may be used for treatment of Influenza.

Influenza RNA (*e.g.* mRNA) vaccines may be administered prophylactically or therapeutically as part of an active immunization scheme to healthy individuals or early in infection during the incubation phase or during active infection after onset of symptoms. In some embodiments, the amount of RNA (*e.g.*, mRNA) vaccine of the present disclosure
5 provided to a cell, a tissue or a subject may be an amount effective for immune prophylaxis.

Influenza RNA (*e.g.* mRNA) vaccines may be administered with other prophylactic or therapeutic compounds. As a non-limiting example, a prophylactic or therapeutic compound may be an adjuvant or a booster. As used herein, when referring to a prophylactic composition, such as a vaccine, the term “booster” refers to an extra administration of the
10 prophylactic (vaccine) composition. A booster (or booster vaccine) may be given after an earlier administration of the prophylactic composition. The time of administration between the initial administration of the prophylactic composition and the booster may be, but is not limited to, 1 minute, 2 minutes, 3 minutes, 4 minutes, 5 minutes, 6 minutes, 7 minutes, 8 minutes, 9 minutes, 10 minutes, 15 minutes, 20 minutes, 35 minutes, 40 minutes, 45 minutes,
15 50 minutes, 55 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours, 1 day, 36 hours, 2 days, 3 days, 4 days, 5 days, 6 days, 1 week, 10 days, 2 weeks, 3 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 1 year,
20 18 months, 2 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, 10 years, 11 years, 12 years, 13 years, 14 years, 15 years, 16 years, 17 years, 18 years, 19 years, 20 years, 25 years, 30 years, 35 years, 40 years, 45 years, 50 years, 55 years, 60 years, 65 years, 70 years, 75 years, 80 years, 85 years, 90 years, 95 years or more than 99 years. In some embodiments, the time of administration between the initial administration of the
25 prophylactic composition and the booster may be, but is not limited to, 1 week, 2 weeks, 3 weeks, 1 month, 2 months, 3 months, 6 months or 1 year.

In some embodiments, influenza RNA (*e.g.* mRNA) vaccines may be administered intramuscularly, intradermally, or intranasally, similarly to the administration of inactivated vaccines known in the art. In some embodiments, influenza RNA (*e.g.* mRNA) vaccines are
30 administered intramuscularly.

Influenza RNA (*e.g.* mRNA) vaccines may be utilized in various settings depending on the prevalence of the infection or the degree or level of unmet medical need. As a non-limiting example, the RNA (*e.g.*, mRNA) vaccines may be utilized to treat and/or prevent a variety of influenzas. RNA (*e.g.*, mRNA) vaccines have superior properties in that they

produce much larger antibody titers and produce responses early than commercially available anti-viral agents/compositions.

Provided herein are pharmaceutical compositions including influenza RNA (*e.g.* mRNA) vaccines and RNA (*e.g.* mRNA) vaccine compositions and/or complexes optionally
5 in combination with one or more pharmaceutically acceptable excipients.

Influenza RNA (*e.g.* mRNA) vaccines may be formulated or administered alone or in conjunction with one or more other components. For instance, Influenza RNA (*e.g.*, mRNA) vaccines (vaccine compositions) may comprise other components including, but not limited to, adjuvants.

10 In some embodiments, influenza (*e.g.* mRNA) vaccines do not include an adjuvant (they are adjuvant free).

Influenza RNA (*e.g.* mRNA) vaccines may be formulated or administered in combination with one or more pharmaceutically-acceptable excipients. In some
embodiments, vaccine compositions comprise at least one additional active substances, such
15 as, for example, a therapeutically-active substance, a prophylactically-active substance, or a combination of both. Vaccine compositions may be sterile, pyrogen-free or both sterile and pyrogen-free. General considerations in the formulation and/or manufacture of
pharmaceutical agents, such as vaccine compositions, may be found, for example, in
Remington: The Science and Practice of Pharmacy 21st ed., Lippincott Williams & Wilkins,
20 2005 (incorporated herein by reference in its entirety).

In some embodiments, influenza RNA (*e.g.* mRNA) vaccines are administered to humans, human patients or subjects. For the purposes of the present disclosure, the phrase
“active ingredient” generally refers to the RNA (*e.g.*, mRNA) vaccines or the polynucleotides
contained therein, for example, RNA polynucleotides (*e.g.*, mRNA polynucleotides)
25 encoding antigenic polypeptides.

Formulations of the influenza vaccine compositions described herein may be prepared by any method known or hereafter developed in the art of pharmacology. In general, such preparatory methods include the step of bringing the active ingredient (*e.g.*, mRNA polynucleotide) into association with an excipient and/or one or more other accessory
30 ingredients, and then, if necessary and/or desirable, dividing, shaping and/or packaging the product into a desired single- or multi-dose unit.

Relative amounts of the active ingredient, the pharmaceutically acceptable excipient, and/or any additional ingredients in a pharmaceutical composition in accordance with the disclosure will vary, depending upon the identity, size, and/or condition of the subject treated
35 and further depending upon the route by which the composition is to be administered. By

way of example, the composition may comprise between 0.1% and 100%, *e.g.*, between 0.5 and 50%, between 1-30%, between 5-80%, at least 80% (w/w) active ingredient.

Influenza RNA (*e.g.* mRNA) vaccines can be formulated using one or more excipients to: increase stability; increase cell transfection; permit the sustained or delayed release (*e.g.*, from a depot formulation); alter the biodistribution (*e.g.*, target to specific tissues or cell types); increase the translation of encoded protein *in vivo*; and/or alter the release profile of encoded protein (antigen) *in vivo*. In addition to traditional excipients such as any and all solvents, dispersion media, diluents, or other liquid vehicles, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, excipients can include, without limitation, lipidoids, liposomes, lipid nanoparticles, polymers, lipoplexes, core-shell nanoparticles, peptides, proteins, cells transfected with influenza RNA (*e.g.* mRNA)vaccines (*e.g.*, for transplantation into a subject), hyaluronidase, nanoparticle mimics and combinations thereof.

15 *Stabilizing Elements*

Naturally-occurring eukaryotic mRNA molecules have been found to contain stabilizing elements, including, but not limited to untranslated regions (UTR) at their 5'-end (5'UTR) and/or at their 3'-end (3'UTR), in addition to other structural features, such as a 5'-cap structure or a 3'-poly(A) tail. Both the 5'UTR and the 3'UTR are typically transcribed from the genomic DNA and are elements of the premature mRNA. Characteristic structural features of mature mRNA, such as the 5'-cap and the 3'-poly(A) tail are usually added to the transcribed (premature) mRNA during mRNA processing. The 3'-poly(A) tail is typically a stretch of adenine nucleotides added to the 3'-end of the transcribed mRNA. It can comprise up to about 400 adenine nucleotides. In some embodiments the length of the 3'-poly(A) tail may be an essential element with respect to the stability of the individual mRNA.

In some embodiments the RNA (*e.g.*, mRNA) vaccine may include one or more stabilizing elements. Stabilizing elements may include for instance a histone stem-loop. A stem-loop binding protein (SLBP), a 32 kDa protein has been identified. It is associated with the histone stem-loop at the 3'-end of the histone messages in both the nucleus and the cytoplasm. Its expression level is regulated by the cell cycle; it peaks during the S-phase, when histone mRNA levels are also elevated. The protein has been shown to be essential for efficient 3'-end processing of histone pre-mRNA by the U7 snRNP. SLBP continues to be associated with the stem-loop after processing, and then stimulates the translation of mature histone mRNAs into histone proteins in the cytoplasm. The RNA binding domain of SLBP is conserved through metazoa and protozoa; its binding to the histone stem-loop depends on the

structure of the loop. The minimum binding site includes at least three nucleotides 5' and two nucleotides 3' relative to the stem-loop.

In some embodiments, the RNA (*e.g.*, mRNA) vaccines include a coding region, at least one histone stem-loop, and optionally, a poly(A) sequence or polyadenylation signal.

5 The poly(A) sequence or polyadenylation signal generally should enhance the expression level of the encoded protein. The encoded protein, in some embodiments, is not a histone protein, a reporter protein (*e.g.* Luciferase, GFP, EGFP, β -Galactosidase, EGFP), or a marker or selection protein (*e.g.* alpha-Globin, Galactokinase and Xanthine:guanine phosphoribosyl transferase (GPT)).

10 In some embodiments, the combination of a poly(A) sequence or polyadenylation signal and at least one histone stem-loop, even though both represent alternative mechanisms in nature, acts synergistically to increase the protein expression beyond the level observed with either of the individual elements. It has been found that the synergistic effect of the combination of poly(A) and at least one histone stem-loop does not depend on the order of
15 the elements or the length of the poly(A) sequence.

In some embodiments, the RNA (*e.g.*, mRNA) vaccine does not comprise a histone downstream element (HDE). "Histone downstream element" (HDE) includes a purine-rich polynucleotide stretch of approximately 15 to 20 nucleotides 3' of naturally occurring stem-loops, representing the binding site for the U7 snRNA, which is involved in processing of
20 histone pre-mRNA into mature histone mRNA. Ideally, the inventive nucleic acid does not include an intron.

In some embodiments, the RNA (*e.g.*, mRNA) vaccine may or may not contain a enhancer and/or promoter sequence, which may be modified or unmodified or which may be activated or inactivated. In some embodiments, the histone stem-loop is generally derived
25 from histone genes, and includes an intramolecular base pairing of two neighbored partially or entirely reverse complementary sequences separated by a spacer, including (*e.g.*, consisting of) a short sequence, which forms the loop of the structure. The unpaired loop region is typically unable to base pair with either of the stem loop elements. It occurs more often in RNA, as is a key component of many RNA secondary structures, but may be present
30 in single-stranded DNA as well. Stability of the stem-loop structure generally depends on the length, number of mismatches or bulges, and base composition of the paired region. In some embodiments, wobble base pairing (non-Watson-Crick base pairing) may result. In some embodiments, the at least one histone stem-loop sequence comprises a length of 15 to 45 nucleotides.

In other embodiments the RNA (*e.g.*, mRNA) vaccine may have one or more AU-rich sequences removed. These sequences, sometimes referred to as AURES are destabilizing sequences found in the 3'UTR. The AURES may be removed from the RNA (*e.g.*, mRNA) vaccines. Alternatively the AURES may remain in the RNA (*e.g.*, mRNA) vaccine.

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Nanoparticle Formulations

In some embodiments, influenza RNA (*e.g.* mRNA) vaccines are formulated in a nanoparticle. In some embodiments, influenza RNA (*e.g.* mRNA) vaccines are formulated in a lipid nanoparticle. In some embodiments, influenza RNA (*e.g.* mRNA) vaccines are formulated in a lipid-polycation complex, referred to as a cationic lipid nanoparticle. As a non-limiting example, the polycation may include a cationic peptide or a polypeptide such as, but not limited to, polylysine, polyornithine and/or polyarginine. In some embodiments, influenza RNA (*e.g.*, mRNA) vaccines are formulated in a lipid nanoparticle that includes a non-cationic lipid such as, but not limited to, cholesterol or dioleoyl phosphatidylethanolamine (DOPE).

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A lipid nanoparticle formulation may be influenced by, but not limited to, the selection of the cationic lipid component, the degree of cationic lipid saturation, the nature of the PEGylation, ratio of all components and biophysical parameters such as size. In one example by Semple *et al.* (*Nature Biotech.* 2010 28:172-176), the lipid nanoparticle formulation is composed of 57.1 % cationic lipid, 7.1% dipalmitoylphosphatidylcholine, 34.3% cholesterol, and 1.4% PEG-c-DMA. As another example, changing the composition of the cationic lipid can more effectively deliver siRNA to various antigen presenting cells (Basha *et al.* *Mol Ther.* 2011 19:2186-2200).

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In some embodiments, lipid nanoparticle formulations may comprise 35 to 45% cationic lipid, 40% to 50% cationic lipid, 50% to 60% cationic lipid and/or 55% to 65% cationic lipid. In some embodiments, the ratio of lipid to RNA (*e.g.*, mRNA) in lipid nanoparticles may be 5:1 to 20:1, 10:1 to 25:1, 15:1 to 30:1 and/or at least 30:1.

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In some embodiments, the ratio of PEG in the lipid nanoparticle formulations may be increased or decreased and/or the carbon chain length of the PEG lipid may be modified from C14 to C18 to alter the pharmacokinetics and/or biodistribution of the lipid nanoparticle formulations. As a non-limiting example, lipid nanoparticle formulations may contain 0.5% to 3.0%, 1.0% to 3.5%, 1.5% to 4.0%, 2.0% to 4.5%, 2.5% to 5.0% and/or 3.0% to 6.0% of the lipid molar ratio of PEG-c-DOMG (R-3-[(ω -methoxy-poly(ethyleneglycol)2000)carbamoyl]-1,2-dimyristyloxypropyl-3-amine) (also referred to herein as PEG-DOMG) as compared to the cationic lipid, DSPC and cholesterol. In some

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embodiments, the PEG-c-DOMG may be replaced with a PEG lipid such as, but not limited to, PEG-DSG (1,2-Distearoyl-sn-glycerol, methoxypolyethylene glycol), PEG-DMG (1,2-Dimyristoyl-sn-glycerol) and/or PEG-DPG (1,2-Dipalmitoyl-sn-glycerol, methoxypolyethylene glycol). The cationic lipid may be selected from any lipid known in the art such as, but not limited to, DLin-MC3-DMA, DLin-DMA, C12-200 and DLin-KC2-DMA.

In some embodiments, an influenza RNA (*e.g.* mRNA) vaccine formulation is a nanoparticle that comprises at least one lipid. The lipid may be selected from, but is not limited to, DLin-DMA, DLin-K-DMA, 98N12-5, C12-200, DLin-MC3-DMA, DLin-KC2-DMA, DODMA, PLGA, PEG, PEG-DMG, PEGylated lipids and amino alcohol lipids. In some embodiments, the lipid may be a cationic lipid such as, but not limited to, DLin-DMA, DLin-D-DMA, DLin-MC3-DMA, DLin-KC2-DMA, DODMA and amino alcohol lipids. The amino alcohol cationic lipid may be the lipids described in and/or made by the methods described in U.S. Patent Publication No. US20130150625, herein incorporated by reference in its entirety. As a non-limiting example, the cationic lipid may be 2-amino-3-[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]-2-[[[(9Z,2Z)-octadeca-9,12-dien-1-yloxy]methyl]propan-1-ol (Compound 1 in US20130150625); 2-amino-3-[(9Z)-octadec-9-en-1-yloxy]-2-[[[(9Z)-octadec-9-en-1-yloxy]methyl]propan-1-ol (Compound 2 in US20130150625); 2-amino-3-[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]-2-[(octyloxy)methyl]propan-1-ol (Compound 3 in US20130150625); and 2-(dimethylamino)-3-[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]-2-[[[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]methyl]propan-1-ol (Compound 4 in US20130150625); or any pharmaceutically acceptable salt or stereoisomer thereof.

Lipid nanoparticle formulations typically comprise a lipid, in particular, an ionizable cationic lipid, for example, 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), or di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), and further comprise a neutral lipid, a sterol and a molecule capable of reducing particle aggregation, for example a PEG or PEG-modified lipid.

In some embodiments, a lipid nanoparticle formulation consists essentially of (i) at least one lipid selected from the group consisting of 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319); (ii) a neutral lipid selected from DSPC, DPPC, POPC, DOPE and SM; (iii) a sterol, *e.g.*, cholesterol; and (iv) a PEG-lipid, *e.g.*, PEG-DMG or PEG-cDMA, in a molar ratio of 20-60% cationic lipid: 5-25% neutral lipid: 25-55% sterol; 0.5-15% PEG-lipid.

In some embodiments, a lipid nanoparticle formulation includes 25% to 75% on a molar basis of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), *e.g.*, 35 to 65%, 45 to 65%, 60%, 57.5%, 50% or 40% on a molar basis.

In some embodiments, a lipid nanoparticle formulation includes 0.5% to 15% on a molar basis of the neutral lipid, *e.g.*, 3 to 12%, 5 to 10% or 15%, 10%, or 7.5% on a molar basis. Examples of neutral lipids include, without limitation, DSPC, POPC, DPPC, DOPE and SM. In some embodiments, the formulation includes 5% to 50% on a molar basis of the sterol (*e.g.*, 15 to 45%, 20 to 40%, 40%, 38.5%, 35%, or 31% on a molar basis. A non-limiting example of a sterol is cholesterol. In some embodiments, a lipid nanoparticle formulation includes 0.5% to 20% on a molar basis of the PEG or PEG-modified lipid (*e.g.*, 0.5 to 10%, 0.5 to 5%, 1.5%, 0.5%, 1.5%, 3.5%, or 5% on a molar basis. In some embodiments, a PEG or PEG modified lipid comprises a PEG molecule of an average molecular weight of 2,000 Da. In some embodiments, a PEG or PEG modified lipid comprises a PEG molecule of an average molecular weight of less than 2,000, for example around 1,500 Da, around 1,000 Da, or around 500 Da. Non-limiting examples of PEG-modified lipids include PEG-distearoyl glycerol (PEG-DMG) (also referred herein as PEG-C14 or C14-PEG), PEG-cDMA (further discussed in Reyes *et al.* J. Controlled Release, 107, 276-287 (2005) the contents of which are herein incorporated by reference in their entirety).

In some embodiments, lipid nanoparticle formulations include 25-75% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), 0.5-15% of the neutral lipid, 5-50% of the sterol, and 0.5-20% of the PEG or PEG-modified lipid on a molar basis.

In some embodiments, lipid nanoparticle formulations include 35-65% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), 3-12% of the neutral lipid, 15-45% of the sterol, and 0.5-10% of the PEG or PEG-modified lipid on a molar basis.

In some embodiments, lipid nanoparticle formulations include 45-65% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), 5-10% of the neutral lipid, 25-40% of the sterol, and 0.5-10% of the PEG or PEG-modified lipid on a molar basis.

In some embodiments, lipid nanoparticle formulations include 60% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), 7.5% of the neutral lipid, 31 % of the sterol, and 1.5% of the PEG or PEG-modified lipid on a molar basis.

In some embodiments, lipid nanoparticle formulations include 50% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), 10% of the neutral lipid, 38.5 % of the sterol, and 1.5% of the PEG or PEG-modified lipid on a molar basis.

In some embodiments, lipid nanoparticle formulations include 50% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), 10% of the neutral lipid, 35 % of the sterol, 4.5% or 5% of the PEG or PEG-modified lipid, and 0.5% of the targeting lipid on a molar basis.

In some embodiments, lipid nanoparticle formulations include 40% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), 15% of the neutral lipid, 40% of the sterol, and 5% of the PEG or PEG-modified lipid on a molar basis.

In some embodiments, lipid nanoparticle formulations include 57.2% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), 7.1% of the neutral lipid, 34.3% of the sterol, and 1.4% of the PEG or PEG-modified lipid on a molar basis.

In some embodiments, lipid nanoparticle formulations include 57.5% of a cationic lipid selected from the PEG lipid is PEG-cDMA (PEG-cDMA is further discussed in Reyes *et al.* (J. Controlled Release, 107, 276-287 (2005), the contents of which are herein incorporated by reference in their entirety), 7.5% of the neutral lipid, 31.5 % of the sterol, and 3.5% of the PEG or PEG-modified lipid on a molar basis.

In some embodiments, lipid nanoparticle formulations consists essentially of a lipid mixture in molar ratios of 20-70% cationic lipid: 5-45% neutral lipid: 20-55% cholesterol: 0.5-15% PEG-modified lipid. In some embodiments, lipid nanoparticle formulations consists

essentially of a lipid mixture in a molar ratio of 20-60% cationic lipid: 5-25% neutral lipid: 25-55% cholesterol: 0.5-15% PEG-modified lipid.

In some embodiments, the molar lipid ratio is 50/10/38.5/1.5 (mol% cationic lipid/neutral lipid, *e.g.*, DSPC/Chol/PEG-modified lipid, *e.g.*, PEG-DMG, PEG-DSG or PEG-DPG), 57.2/7.1134.3/1.4 (mol% cationic lipid/ neutral lipid, *e.g.*, DPPC/Chol/ PEG-modified lipid, *e.g.*, PEG-cDMA), 40/15/40/5 (mol% cationic lipid/ neutral lipid, *e.g.*, DSPC/Chol/ PEG-modified lipid, *e.g.*, PEG-DMG), 50/10/35/4.5/0.5 (mol% cationic lipid/ neutral lipid, *e.g.*, DSPC/Chol/ PEG-modified lipid, *e.g.*, PEG-DSG), 50/10/35/5 (cationic lipid/ neutral lipid, *e.g.*, DSPC/Chol/ PEG-modified lipid, *e.g.*, PEG-DMG), 40/10/40/10 (mol% cationic lipid/ neutral lipid, *e.g.*, DSPC/Chol/ PEG-modified lipid, *e.g.*, PEG-DMG or PEG-cDMA), 35/15/40/10 (mol% cationic lipid/ neutral lipid, *e.g.*, DSPC/Chol/ PEG-modified lipid, *e.g.*, PEG-DMG or PEG-cDMA) or 52/13/30/5 (mol% cationic lipid/ neutral lipid, *e.g.*, DSPC/Chol/ PEG-modified lipid, *e.g.*, PEG-DMG or PEG-cDMA).

Non-limiting examples of lipid nanoparticle compositions and methods of making them are described, for example, in Semple *et al.* (2010) *Nat. Biotechnol.* 28:172-176; Jayarama *et al.* (2012), *Angew. Chem. Int. Ed.*, 51: 8529–8533; and Maier *et al.* (2013) *Molecular Therapy* 21, 1570-1578 (the contents of each of which are incorporated herein by reference in their entirety).

In some embodiments, lipid nanoparticle formulations may comprise a cationic lipid, a PEG lipid and a structural lipid and optionally comprise a non-cationic lipid. As a non-limiting example, a lipid nanoparticle may comprise 40-60% of cationic lipid, 5-15% of a non-cationic lipid, 1-2% of a PEG lipid and 30-50% of a structural lipid. As another non-limiting example, the lipid nanoparticle may comprise 50% cationic lipid, 10% non-cationic lipid, 1.5% PEG lipid and 38.5% structural lipid. As yet another non-limiting example, a lipid nanoparticle may comprise 55% cationic lipid, 10% non-cationic lipid, 2.5% PEG lipid and 32.5% structural lipid. In some embodiments, the cationic lipid may be any cationic lipid described herein such as, but not limited to, DLin-KC2-DMA, DLin-MC3-DMA and L319.

In some embodiments, the lipid nanoparticle formulations described herein may be 4 component lipid nanoparticles. The lipid nanoparticle may comprise a cationic lipid, a non-cationic lipid, a PEG lipid and a structural lipid. As a non-limiting example, the lipid nanoparticle may comprise 40-60% of cationic lipid, 5-15% of a non-cationic lipid, 1-2% of a PEG lipid and 30-50% of a structural lipid. As another non-limiting example, the lipid nanoparticle may comprise 50% cationic lipid, 10% non-cationic lipid, 1.5% PEG lipid and 38.5% structural lipid. As yet another non-limiting example, the lipid nanoparticle may comprise 55% cationic lipid, 10% non-cationic lipid, 2.5% PEG lipid and 32.5% structural

lipid. In some embodiments, the cationic lipid may be any cationic lipid described herein such as, but not limited to, DLin-KC2-DMA, DLin-MC3-DMA and L319.

In some embodiments, the lipid nanoparticle formulations described herein may comprise a cationic lipid, a non-cationic lipid, a PEG lipid and a structural lipid. As a non-limiting example, the lipid nanoparticle comprise 50% of the cationic lipid DLin-KC2-DMA, 10% of the non-cationic lipid DSPC, 1.5% of the PEG lipid PEG-DOMG and 38.5% of the structural lipid cholesterol. As a non-limiting example, the lipid nanoparticle comprise 50% of the cationic lipid DLin-MC3-DMA, 10% of the non-cationic lipid DSPC, 1.5% of the PEG lipid PEG-DOMG and 38.5% of the structural lipid cholesterol. As a non-limiting example, the lipid nanoparticle comprise 50% of the cationic lipid DLin-MC3-DMA, 10% of the non-cationic lipid DSPC, 1.5% of the PEG lipid PEG-DMG and 38.5% of the structural lipid cholesterol. As yet another non-limiting example, the lipid nanoparticle comprise 55% of the cationic lipid L319, 10% of the non-cationic lipid DSPC, 2.5% of the PEG lipid PEG-DMG and 32.5% of the structural lipid cholesterol.

Relative amounts of the active ingredient, the pharmaceutically acceptable excipient, and/or any additional ingredients in a vaccine composition may vary, depending upon the identity, size, and/or condition of the subject being treated and further depending upon the route by which the composition is to be administered. For example, the composition may comprise between 0.1% and 99% (w/w) of the active ingredient. By way of example, the composition may comprise between 0.1% and 100%, *e.g.*, between .5 and 50%, between 1-30%, between 5-80%, at least 80% (w/w) active ingredient.

In some embodiments, the influenza RNA (*e.g.* mRNA) vaccine composition may comprise the polynucleotide described herein, formulated in a lipid nanoparticle comprising MC3, Cholesterol, DSPC and PEG2000-DMG, the buffer trisodium citrate, sucrose and water for injection. As a non-limiting example, the composition comprises: 2.0 mg/mL of drug substance, 21.8 mg/mL of MC3, 10.1 mg/mL of cholesterol, 5.4 mg/mL of DSPC, 2.7 mg/mL of PEG2000-DMG, 5.16 mg/mL of trisodium citrate, 71 mg/mL of sucrose and 1.0 mL of water for injection.

In some embodiments, a nanoparticle (*e.g.*, a lipid nanoparticle) has a mean diameter of 10-500 nm, 20-400 nm, 30-300 nm, 40-200 nm. In some embodiments, a nanoparticle (*e.g.*, a lipid nanoparticle) has a mean diameter of 50-150 nm, 50-200 nm, 80-100 nm or 80-200 nm.

Liposomes, Lipoplexes, and Lipid Nanoparticles

The RNA (*e.g.*, mRNA) vaccines of the disclosure can be formulated using one or more liposomes, lipoplexes, or lipid nanoparticles. In some embodiments, pharmaceutical compositions of RNA (*e.g.*, mRNA) vaccines include liposomes. Liposomes are artificially-prepared vesicles which may primarily be composed of a lipid bilayer and may be used as a delivery vehicle for the administration of nutrients and pharmaceutical formulations.

Liposomes can be of different sizes such as, but not limited to, a multilamellar vesicle (MLV) which may be hundreds of nanometers in diameter and may contain a series of concentric bilayers separated by narrow aqueous compartments, a small unimolecular vesicle (SUV) which may be smaller than 50 nm in diameter, and a large unilamellar vesicle (LUV) which may be between 50 and 500 nm in diameter. Liposome design may include, but is not limited to, opsonins or ligands in order to improve the attachment of liposomes to unhealthy tissue or to activate events such as, but not limited to, endocytosis. Liposomes may contain a low or a high pH in order to improve the delivery of the pharmaceutical formulations.

The formation of liposomes may depend on the physicochemical characteristics such as, but not limited to, the pharmaceutical formulation entrapped and the liposomal ingredients, the nature of the medium in which the lipid vesicles are dispersed, the effective concentration of the entrapped substance and its potential toxicity, any additional processes involved during the application and/or delivery of the vesicles, the optimization size, polydispersity and the shelf-life of the vesicles for the intended application, and the batch-to-batch reproducibility and possibility of large-scale production of safe and efficient liposomal products.

In some embodiments, pharmaceutical compositions described herein may include, without limitation, liposomes such as those formed from 1,2-dioleoyloxy-N,N-dimethylaminopropane (DODMA) liposomes, DiLa2 liposomes from Marina Biotech (Bothell, WA), 1,2-dilinoleoyloxy-3-dimethylaminopropane (DLin-DMA), 2,2-dilinoleyl-4-(2-dimethylaminoethyl)-[1,3]-dioxolane (DLin-KC2-DMA), and MC3 (US20100324120; herein incorporated by reference in its entirety) and liposomes which may deliver small molecule drugs such as, but not limited to, DOXIL® from Janssen Biotech, Inc. (Horsham, PA).

In some embodiments, pharmaceutical compositions described herein may include, without limitation, liposomes such as those formed from the synthesis of stabilized plasmid-lipid particles (SPLP) or stabilized nucleic acid lipid particle (SNALP) that have been previously described and shown to be suitable for oligonucleotide delivery *in vitro* and *in vivo* (see Wheeler *et al.* Gene Therapy. 1999 6:271-281; Zhang *et al.* Gene Therapy. 1999 6:1438-1447; Jeffs *et al.* Pharm Res. 2005 22:362-372; Morrissey *et al.*, Nat Biotechnol. 2005 2:1002-1007; Zimmermann *et al.*, Nature. 2006 441:111-114; Heyes *et al.* J Contr Rel.

2005 107:276-287; Semple *et al.* Nature Biotech. 2010 28:172-176; Judge *et al.* J Clin Invest. 2009 119:661-673; deFougerolles Hum Gene Ther. 2008 19:125-132; U.S. Patent Publication No US20130122104; all of which are incorporated herein in their entireties). The original manufacture method by Wheeler *et al.* was a detergent dialysis method, which was later
 5 improved by Jeffs *et al.* and is referred to as the spontaneous vesicle formation method. The liposome formulations are composed of 3 to 4 lipid components in addition to the polynucleotide. As an example a liposome can contain, but is not limited to, 55% cholesterol, 20% distearylphosphatidyl choline (DSPC), 10% PEG-S-DSG, and 15% 1,2-dioleoyloxy-N,N-dimethylaminopropane (DODMA), as described by Jeffs *et al.* As another
 10 example, certain liposome formulations may contain, but are not limited to, 48% cholesterol, 20% DSPC, 2% PEG-c-DMA, and 30% cationic lipid, where the cationic lipid can be 1,2-distearloxy-N,N-dimethylaminopropane (DSDMA), DODMA, DLin-DMA, or 1,2-dilinolenyloxy-3-dimethylaminopropane (DLenDMA), as described by Heyes *et al.*

In some embodiments, liposome formulations may comprise from about 25.0%
 15 cholesterol to about 40.0% cholesterol, from about 30.0% cholesterol to about 45.0% cholesterol, from about 35.0% cholesterol to about 50.0% cholesterol and/or from about 48.5% cholesterol to about 60% cholesterol. In some embodiments, formulations may comprise a percentage of cholesterol selected from the group consisting of 28.5%, 31.5%, 33.5%, 36.5%, 37.0%, 38.5%, 39.0% and 43.5%. In some embodiments, formulations may
 20 comprise from about 5.0% to about 10.0% DSPC and/or from about 7.0% to about 15.0% DSPC.

In some embodiments, the RNA (*e.g.*, mRNA) vaccine pharmaceutical compositions may be formulated in liposomes such as, but not limited to, DiLa2 liposomes (Marina Biotech, Bothell, WA), SMARTICLES® (Marina Biotech, Bothell, WA), neutral DOPC
 25 (1,2-dioleoyl-sn-glycero-3-phosphocholine) based liposomes (*e.g.*, siRNA delivery for ovarian cancer (Landen *et al.* Cancer Biology & Therapy 2006 5(12)1708-1713); herein incorporated by reference in its entirety) and hyaluronan-coated liposomes (Quiet Therapeutics, Israel).

In some embodiments, the cationic lipid may be a low molecular weight cationic lipid
 30 such as those described in U.S. Patent Application No. 20130090372, the contents of which are herein incorporated by reference in their entirety.

In some embodiments, the RNA (*e.g.*, mRNA) vaccines may be formulated in a lipid vesicle, which may have crosslinks between functionalized lipid bilayers.

In some embodiments, the RNA (*e.g.*, mRNA) vaccines may be formulated in a lipid-polycation complex. The formation of the lipid-polycation complex may be accomplished by
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methods known in the art and/or as described in U.S. Pub. No. 20120178702, herein incorporated by reference in its entirety. As a non-limiting example, the polycation may include a cationic peptide or a polypeptide such as, but not limited to, polylysine, polyornithine and/or polyarginine. In some embodiments, the RNA (*e.g.*, mRNA) vaccines may be formulated in a lipid-polycation complex, which may further include a non-cationic lipid such as, but not limited to, cholesterol or dioleoyl phosphatidylethanolamine (DOPE).

In some embodiments, the ratio of PEG in the lipid nanoparticle (LNP) formulations may be increased or decreased and/or the carbon chain length of the PEG lipid may be modified from C14 to C18 to alter the pharmacokinetics and/or biodistribution of the LNP formulations. As a non-limiting example, LNP formulations may contain from about 0.5% to about 3.0%, from about 1.0% to about 3.5%, from about 1.5% to about 4.0%, from about 2.0% to about 4.5%, from about 2.5% to about 5.0% and/or from about 3.0% to about 6.0% of the lipid molar ratio of PEG-c-DOMG (R-3-[(ω -methoxy-poly(ethyleneglycol)2000)carbamoyl]-1,2-dimyristyloxypropyl-3-amine) (also referred to herein as PEG-DOMG) as compared to the cationic lipid, DSPC and cholesterol. In some embodiments, the PEG-c-DOMG may be replaced with a PEG lipid such as, but not limited to, PEG-DSG (1,2-Distearoyl-sn-glycerol, methoxypolyethylene glycol), PEG-DMG (1,2-Dimyristoyl-sn-glycerol) and/or PEG-DPG (1,2-Dipalmitoyl-sn-glycerol, methoxypolyethylene glycol). The cationic lipid may be selected from any lipid known in the art such as, but not limited to, DLin-MC3-DMA, DLin-DMA, C12-200 and DLin-KC2-DMA.

In some embodiments, the RNA (*e.g.*, mRNA) vaccines may be formulated in a lipid nanoparticle.

In some embodiments, the RNA (*e.g.*, mRNA) vaccine formulation comprising the polynucleotide is a nanoparticle which may comprise at least one lipid. The lipid may be selected from, but is not limited to, DLin-DMA, DLin-K-DMA, 98N12-5, C12-200, DLin-MC3-DMA, DLin-KC2-DMA, DODMA, PLGA, PEG, PEG-DMG, PEGylated lipids and amino alcohol lipids. In another aspect, the lipid may be a cationic lipid such as, but not limited to, DLin-DMA, DLin-D-DMA, DLin-MC3-DMA, DLin-KC2-DMA, DODMA and amino alcohol lipids. The amino alcohol cationic lipid may be the lipids described in and/or made by the methods described in U.S. Patent Publication No. US20130150625, herein incorporated by reference in its entirety. As a non-limiting example, the cationic lipid may be 2-amino-3-[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]-2-[[[(9Z,2Z)-octadeca-9,12-dien-1-yloxy]methyl]propan-1-ol (Compound 1 in US20130150625); 2-amino-3-[(9Z)-octadec-9-en-1-yloxy]-2-[[[(9Z)-octadec-9-en-1-yloxy]methyl]propan-1-ol (Compound 2 in

US20130150625); 2-amino-3-[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]-2-[(octyloxy)methyl]propan-1-ol (Compound 3 in US20130150625); and 2-(dimethylamino)-3-[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]-2-[[[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]methyl]propan-1-ol (Compound 4 in US20130150625); or any pharmaceutically acceptable salt or stereoisomer thereof.

Lipid nanoparticle formulations typically comprise a lipid, in particular, an ionizable cationic lipid, for example, 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), or di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), and further comprise a neutral lipid, a sterol and a molecule capable of reducing particle aggregation, for example a PEG or PEG-modified lipid.

In some embodiments, the lipid nanoparticle formulation consists essentially of (i) at least one lipid selected from the group consisting of 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319); (ii) a neutral lipid selected from DSPC, DPPC, POPC, DOPE and SM; (iii) a sterol, *e.g.*, cholesterol; and (iv) a PEG-lipid, *e.g.*, PEG-DMG or PEG-cDMA, in a molar ratio of about 20-60% cationic lipid: 5-25% neutral lipid: 25-55% sterol; 0.5-15% PEG-lipid.

In some embodiments, the formulation includes from about 25% to about 75% on a molar basis of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), *e.g.*, from about 35 to about 65%, from about 45 to about 65%, about 60%, about 57.5%, about 50% or about 40% on a molar basis.

In some embodiments, the formulation includes from about 0.5% to about 15% on a molar basis of the neutral lipid *e.g.*, from about 3 to about 12%, from about 5 to about 10% or about 15%, about 10%, or about 7.5% on a molar basis. Examples of neutral lipids include, but are not limited to, DSPC, POPC, DPPC, DOPE and SM. In some embodiments, the formulation includes from about 5% to about 50% on a molar basis of the sterol (*e.g.*, about 15 to about 45%, about 20 to about 40%, about 40%, about 38.5%, about 35%, or about 31% on a molar basis. An exemplary sterol is cholesterol. In some embodiments, the formulation includes from about 0.5% to about 20% on a molar basis of the PEG or PEG-modified lipid (*e.g.*, about 0.5 to about 10%, about 0.5 to about 5%, about 1.5%, about 0.5%, about 1.5%, about 3.5%, or about 5% on a molar basis. In some embodiments, the PEG or PEG modified lipid comprises a PEG molecule of an average molecular weight of 2,000 Da. In other

embodiments, the PEG or PEG modified lipid comprises a PEG molecule of an average molecular weight of less than 2,000, for example around 1,500 Da, around 1,000 Da, or around 500 Da. Examples of PEG-modified lipids include, but are not limited to, PEG-distearoyl glycerol (PEG-DMG) (also referred herein as PEG-C14 or C14-PEG), PEG-cDMA (further discussed in Reyes *et al. J. Controlled Release*, 107, 276-287 (2005) the contents of which are herein incorporated by reference in their entirety)

In some embodiments, the formulations of the present disclosure include 25-75% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), 0.5-15% of the neutral lipid, 5-50% of the sterol, and 0.5-20% of the PEG or PEG-modified lipid on a molar basis.

In some embodiments, the formulations of the present disclosure include 35-65% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), 3-12% of the neutral lipid, 15-45% of the sterol, and 0.5-10% of the PEG or PEG-modified lipid on a molar basis.

In some embodiments, the formulations of the present disclosure include 45-65% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), 5-10% of the neutral lipid, 25-40% of the sterol, and 0.5-10% of the PEG or PEG-modified lipid on a molar basis.

In some embodiments, the formulations of the present disclosure include about 60% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), about 7.5% of the neutral lipid, about 31 % of the sterol, and about 1.5% of the PEG or PEG-modified lipid on a molar basis.

In some embodiments, the formulations of the present disclosure include about 50% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), about 10% of the neutral lipid, about 38.5 % of the sterol, and about 1.5% of the PEG or PEG-modified lipid on a molar basis.

In some embodiments, the formulations of the present disclosure include about 50% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-

KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), about 10% of the neutral lipid, about 35 % of the sterol, about 4.5% or about 5% of the PEG or PEG-modified lipid, and about 0.5% of the targeting lipid on a molar basis.

5 In some embodiments, the formulations of the present disclosure include about 40% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), about 15% of the neutral lipid, about 40% of the sterol, and about 5% of the PEG or PEG-modified lipid on
10 a molar basis.

In some embodiments, the formulations of the present disclosure include about 57.2% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), about 7.1% of
15 the neutral lipid, about 34.3% of the sterol, and about 1.4% of the PEG or PEG-modified lipid on a molar basis.

In some embodiments, the formulations of the present disclosure include about 57.5% of a cationic lipid selected from the PEG lipid is PEG-cDMA (PEG-cDMA is further discussed in Reyes *et al.* (J. Controlled Release, 107, 276-287 (2005), the contents of which
20 are herein incorporated by reference in their entirety), about 7.5% of the neutral lipid, about 31.5 % of the sterol, and about 3.5% of the PEG or PEG-modified lipid on a molar basis.

In some embodiments, lipid nanoparticle formulation consists essentially of a lipid mixture in molar ratios of about 20-70% cationic lipid: 5-45% neutral lipid: 20-55% cholesterol: 0.5-15% PEG-modified lipid; more preferably in a molar ratio of about 20-60%
25 cationic lipid: 5-25% neutral lipid: 25-55% cholesterol: 0.5-15% PEG-modified lipid.

In some embodiments, the molar lipid ratio is approximately 50/10/38.5/1.5 (mol% cationic lipid/neutral lipid, *e.g.*, DSPC/Chol/PEG-modified lipid, *e.g.*, PEG-DMG, PEG-DSG or PEG-DPG), 57.2/7.1/34.3/1.4 (mol% cationic lipid/ neutral lipid, *e.g.*, DPPC/Chol/ PEG-modified lipid, *e.g.*, PEG-cDMA), 40/15/40/5 (mol% cationic lipid/ neutral lipid, *e.g.*,
30 DSPC/Chol/ PEG-modified lipid, *e.g.*, PEG-DMG), 50/10/35/4.5/0.5 (mol% cationic lipid/ neutral lipid, *e.g.*, DSPC/Chol/ PEG-modified lipid, *e.g.*, PEG-DSG), 50/10/35/5 (cationic lipid/ neutral lipid, *e.g.*, DSPC/Chol/ PEG-modified lipid, *e.g.*, PEG-DMG), 40/10/40/10 (mol% cationic lipid/ neutral lipid, *e.g.*, DSPC/Chol/ PEG-modified lipid, *e.g.*, PEG-DMG or PEG-cDMA), 35/15/40/10 (mol% cationic lipid/ neutral lipid, *e.g.*, DSPC/Chol/ PEG-

modified lipid, *e.g.*, PEG-DMG or PEG-cDMA) or 52/13/30/5 (mol% cationic lipid/ neutral lipid, *e.g.*, DSPC/Chol/ PEG-modified lipid, *e.g.*, PEG-DMG or PEG-cDMA).

Examples of lipid nanoparticle compositions and methods of making same are described, for example, in Semple *et al.* (2010) *Nat. Biotechnol.* 28:172-176; Jayarama *et al.* (2012), *Angew. Chem. Int. Ed.*, 51: 8529–8533; and Maier *et al.* (2013) *Molecular Therapy* 21, 1570-1578 (the contents of each of which are incorporated herein by reference in their entirety).

In some embodiments, the lipid nanoparticle formulations described herein may comprise a cationic lipid, a PEG lipid and a structural lipid and optionally comprise a non-cationic lipid. As a non-limiting example, the lipid nanoparticle may comprise about 40-60% of cationic lipid, about 5-15% of a non-cationic lipid, about 1-2% of a PEG lipid and about 30-50% of a structural lipid. As another non-limiting example, the lipid nanoparticle may comprise about 50% cationic lipid, about 10% non-cationic lipid, about 1.5% PEG lipid and about 38.5% structural lipid. As yet another non-limiting example, the lipid nanoparticle may comprise about 55% cationic lipid, about 10% non-cationic lipid, about 2.5% PEG lipid and about 32.5% structural lipid. In some embodiments, the cationic lipid may be any cationic lipid described herein such as, but not limited to, DLin-KC2-DMA, DLin-MC3-DMA and L319.

In some embodiments, the lipid nanoparticle formulations described herein may be 4 component lipid nanoparticles. The lipid nanoparticle may comprise a cationic lipid, a non-cationic lipid, a PEG lipid and a structural lipid. As a non-limiting example, the lipid nanoparticle may comprise about 40-60% of cationic lipid, about 5-15% of a non-cationic lipid, about 1-2% of a PEG lipid and about 30-50% of a structural lipid. As another non-limiting example, the lipid nanoparticle may comprise about 50% cationic lipid, about 10% non-cationic lipid, about 1.5% PEG lipid and about 38.5% structural lipid. As yet another non-limiting example, the lipid nanoparticle may comprise about 55% cationic lipid, about 10% non-cationic lipid, about 2.5% PEG lipid and about 32.5% structural lipid. In some embodiments, the cationic lipid may be any cationic lipid described herein such as, but not limited to, DLin-KC2-DMA, DLin-MC3-DMA and L319.

In some embodiments, the lipid nanoparticle formulations described herein may comprise a cationic lipid, a non-cationic lipid, a PEG lipid and a structural lipid. As a non-limiting example, the lipid nanoparticle comprise about 50% of the cationic lipid DLin-KC2-DMA, about 10% of the non-cationic lipid DSPC, about 1.5% of the PEG lipid PEG-DOMG and about 38.5% of the structural lipid cholesterol. As a non-limiting example, the lipid nanoparticle comprise about 50% of the cationic lipid DLin-MC3-DMA, about 10% of the

non-cationic lipid DSPC, about 1.5% of the PEG lipid PEG-DOMG and about 38.5% of the structural lipid cholesterol. As a non-limiting example, the lipid nanoparticle comprise about 50% of the cationic lipid DLin-MC3-DMA, about 10% of the non-cationic lipid DSPC, about 1.5% of the PEG lipid PEG-DMG and about 38.5% of the structural lipid cholesterol. As yet another non-limiting example, the lipid nanoparticle comprise about 55% of the cationic lipid L319, about 10% of the non-cationic lipid DSPC, about 2.5% of the PEG lipid PEG-DMG and about 32.5% of the structural lipid cholesterol.

As a non-limiting example, the cationic lipid may be selected from (20Z,23Z)-N,N-dimethylnonacos-20,23-dien-10-amine, (17Z,20Z)-N,N-dimethylhexacos-17,20-dien-9-amine, (1Z,19Z)-N,N-dimethylpentacos-16,19-dien-8-amine, (13Z,16Z)-N,N-dimethyldocos-13,16-dien-5-amine, (12Z,15Z)-N,N-dimethylhenicos-12,15-dien-4-amine, (14Z,17Z)-N,N-dimethyltricos-14,17-dien-6-amine, (15Z,18Z)-N,N-dimethyltetracos-15,18-dien-7-amine, (18Z,21Z)-N,N-dimethylheptacos-18,21-dien-10-amine, (15Z,18Z)-N,N-dimethyltetracos-15,18-dien-5-amine, (14Z,17Z)-N,N-dimethyltricos-14,17-dien-4-amine, (19Z,22Z)-N,N-dimethyloctacos-19,22-dien-9-amine, (18Z,21Z)-N,N-dimethylheptacos-18,21-dien-8-amine, (17Z,20Z)-N,N-dimethylhexacos-17,20-dien-7-amine, (16Z,19Z)-N,N-dimethylpentacos-16,19-dien-6-amine, (22Z,25Z)-N,N-dimethylhentriacont-22,25-dien-10-amine, (21Z,24Z)-N,N-dimethyltriacont-21,24-dien-9-amine, (18Z)-N,N-dimethylheptacos-18-en-10-amine, (17Z)-N,N-dimethylhexacos-17-en-9-amine, (19Z,22Z)-N,N-dimethyloctacos-19,22-dien-7-amine, N,N-dimethylheptacosan-10-amine, (20Z,23Z)-N-ethyl-N-methylnonacos-20,23-dien-10-amine, 1-[(11Z,14Z)-1-nonylicos-11,14-dien-1-yl] pyrrolidine, (20Z)-N,N-dimethylheptacos-20-en-10-amine, (15Z)-N,N-dimethylheptacos-15-en-10-amine, (14Z)-N,N-dimethylnonacos-14-en-10-amine, (17Z)-N,N-dimethylnonacos-17-en-10-amine, (24Z)-N,N-dimethyltritriacont-24-en-10-amine, (20Z)-N,N-dimethylnonacos-20-en-10-amine, (22Z)-N,N-dimethylhentriacont-22-en-10-amine, (16Z)-N,N-dimethylpentacos-16-en-8-amine, (12Z,15Z)-N,N-dimethyl-2-nonylhenicos-12,15-dien-1-amine, (13Z,16Z)-N,N-dimethyl-3-nonyldocos-13,16-dien-1-amine, N,N-dimethyl-1-[(1S,2R)-2-octylcyclopropyl] eptadecan-8-amine, 1-[(1S,2R)-2-hexylcyclopropyl]-N,N-dimethylnonadecan-10-amine, N,N-dimethyl-1-[(1S,2R)-2-octylcyclopropyl]nonadecan-10-amine, N,N-dimethyl-21-[(1S,2R)-2-octylcyclopropyl]henicosan-10-amine, N,N-dimethyl-1-[(1S,2S)-2-[(1R,2R)-2-pentylcyclopropyl]methyl]cyclopropyl]nonadecan-10-amine, N,N-dimethyl-1-[(1S,2R)-2-octylcyclopropyl]hexadecan-8-amine, N,N-dimethyl-[(1R,2S)-2-undecylcyclopropyl]tetradecan-5-amine, N,N-dimethyl-3-{7-[(1S,2R)-2-octylcyclopropyl]heptyl} dodecan-1-amine, 1-[(1R,2S)-2-heptylcyclopropyl]-N,N-

dimethyloctadecan-9-amine, 1-[(1S,2R)-2-decylcyclopropyl]-N,N-dimethylpentadecan-6-amine, N,N-dimethyl-1-[(1S,2R)-2-octylcyclopropyl]pentadecan-8-amine, R-N,N-dimethyl-1-[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]-3-(octyloxy)propan-2-amine, S-N,N-dimethyl-1-[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]-3-(octyloxy)propan-2-amine, 1-{2-[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]-1-[(octyloxy)methyl]ethyl}pyrrolidine, (2S)-N,N-dimethyl-1-[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]-3-[(5Z)-oct-5-en-1-yloxy]propan-2-amine, 1-{2-[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]-1-[(octyloxy)methyl]ethyl}azetidine, (2S)-1-(hexyloxy)-N,N-dimethyl-3-[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]propan-2-amine, (2S)-1-(heptyloxy)-N,N-dimethyl-3-[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]propan-2-amine, N,N-dimethyl-1-(nonyloxy)-3-[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]propan-2-amine, N,N-dimethyl-1-[(9Z)-octadec-9-en-1-yloxy]-3-(octyloxy)propan-2-amine; (2S)-N,N-dimethyl-1-[(6Z,9Z,12Z)-octadeca-6,9,12-trien-1-yloxy]-3-(octyloxy)propan-2-amine, (2S)-1-[(11Z,14Z)-icosa-11,14-dien-1-yloxy]-N,N-dimethyl-3-(pentyloxy)propan-2-amine, (2S)-1-(hexyloxy)-3-[(11Z,14Z)-icosa-11,14-dien-1-yloxy]-N,N-dimethylpropan-2-amine, 1-[(11Z,14Z)-icosa-11,14-dien-1-yloxy]-N,N-dimethyl-3-(octyloxy)propan-2-amine, 1-[(13Z,16Z)-docosa-13,16-dien-1-yloxy]-N,N-dimethyl-3-(octyloxy)propan-2-amine, (2S)-1-[(13Z,16Z)-docosa-13,16-dien-1-yloxy]-3-(hexyloxy)-N,N-dimethylpropan-2-amine, (2S)-1-[(13Z)-docos-13-en-1-yloxy]-3-(hexyloxy)-N,N-dimethylpropan-2-amine, 1-[(13Z)-docos-13-en-1-yloxy]-N,N-dimethyl-3-(octyloxy)propan-2-amine, 1-[(9Z)-hexadec-9-en-1-yloxy]-N,N-dimethyl-3-(octyloxy)propan-2-amine, (2R)-N,N-dimethyl-H(1-metoyloctyl)oxy]-3-[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]propan-2-amine, (2R)-1-[(3,7-dimethyloctyl)oxy]-N,N-dimethyl-3-[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]propan-2-amine, N,N-dimethyl-1-(octyloxy)-3-({8-[(1S,2S)-2-[(1R,2R)-2-pentylcyclopropyl]methyl}cyclopropyl]octyl}oxy)propan-2-amine, N,N-dimethyl-1-{[8-(2-octylcyclopropyl)octyl]oxy}-3-(octyloxy)propan-2-amine and (11E,20Z,23Z)-N,N-dimethylnonacos-11,20,2-trien-10-amine or a pharmaceutically acceptable salt or stereoisomer thereof.

In some embodiments, the LNP formulations of the RNA (*e.g.*, mRNA) vaccines may contain PEG-c-DOMG at 3% lipid molar ratio. In some embodiments, the LNP formulations of the RNA (*e.g.*, mRNA) vaccines may contain PEG-c-DOMG at 1.5% lipid molar ratio.

In some embodiments, the pharmaceutical compositions of the RNA (*e.g.*, mRNA) vaccines may include at least one of the PEGylated lipids described in International Publication No. WO2012099755, the contents of which are herein incorporated by reference in their entirety.

In some embodiments, the LNP formulation may contain PEG-DMG 2000 (1,2-dimyristoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-2000]). In some embodiments, the LNP formulation may contain PEG-DMG 2000, a cationic lipid known in the art and at least one other component. In some embodiments, the LNP formulation may contain PEG-DMG 2000, a cationic lipid known in the art, DSPC and cholesterol. As a non-limiting example, the LNP formulation may contain PEG-DMG 2000, DLin-DMA, DSPC and cholesterol. As another non-limiting example the LNP formulation may contain PEG-DMG 2000, DLin-DMA, DSPC and cholesterol in a molar ratio of 2:40:10:48 (*see e.g.*, Geall *et al.*, Nonviral delivery of self-amplifying RNA (*e.g.*, mRNA) vaccines, PNAS 2012; PMID: 22908294, the contents of each of which are herein incorporated by reference in their entirety).

The lipid nanoparticles described herein may be made in a sterile environment.

In some embodiments, the LNP formulation may be formulated in a nanoparticle such as a nucleic acid-lipid particle. As a non-limiting example, the lipid particle may comprise one or more active agents or therapeutic agents; one or more cationic lipids comprising from about 50 mol % to about 85 mol % of the total lipid present in the particle; one or more non-cationic lipids comprising from about 13 mol % to about 49.5 mol % of the total lipid present in the particle; and one or more conjugated lipids that inhibit aggregation of particles comprising from about 0.5 mol % to about 2 mol % of the total lipid present in the particle.

The nanoparticle formulations may comprise a phosphate conjugate. The phosphate conjugate may increase *in vivo* circulation times and/or increase the targeted delivery of the nanoparticle. As a non-limiting example, the phosphate conjugates may include a compound of any one of the formulas described in International Application No. WO2013033438, the contents of which are herein incorporated by reference in its entirety.

The nanoparticle formulation may comprise a polymer conjugate. The polymer conjugate may be a water soluble conjugate. The polymer conjugate may have a structure as described in U.S. Patent Application No. 20130059360, the contents of which are herein incorporated by reference in its entirety. In some embodiments, polymer conjugates with the polynucleotides of the present disclosure may be made using the methods and/or segmented polymeric reagents described in U.S. Patent Application No. 20130072709, the contents of which are herein incorporated by reference in its entirety. In some embodiments, the polymer conjugate may have pendant side groups comprising ring moieties such as, but not limited to, the polymer conjugates described in U.S. Patent Publication No. US20130196948, the contents which are herein incorporated by reference in its entirety.

The nanoparticle formulations may comprise a conjugate to enhance the delivery of nanoparticles of the present disclosure in a subject. Further, the conjugate may inhibit phagocytic clearance of the nanoparticles in a subject. In one aspect, the conjugate may be a “self” peptide designed from the human membrane protein CD47 (*e.g.*, the “self” particles described by Rodriguez *et al.* (*Science* 2013 339, 971-975), herein incorporated by reference in its entirety). As shown by Rodriguez *et al.*, the self peptides delayed macrophage-mediated clearance of nanoparticles which enhanced delivery of the nanoparticles. In another aspect, the conjugate may be the membrane protein CD47 (*e.g.*, see Rodriguez *et al.* *Science* 2013 339, 971-975, herein incorporated by reference in its entirety). Rodriguez *et al.* showed that, similarly to “self” peptides, CD47 can increase the circulating particle ratio in a subject as compared to scrambled peptides and PEG coated nanoparticles.

In some embodiments, the RNA (*e.g.*, mRNA) vaccines of the present disclosure are formulated in nanoparticles which comprise a conjugate to enhance the delivery of the nanoparticles of the present disclosure in a subject. The conjugate may be the CD47 membrane or the conjugate may be derived from the CD47 membrane protein, such as the “self” peptide described previously. In some embodiments, the nanoparticle may comprise PEG and a conjugate of CD47 or a derivative thereof. In some embodiments, the nanoparticle may comprise both the “self” peptide described above and the membrane protein CD47.

In some embodiments, a “self” peptide and/or CD47 protein may be conjugated to a virus-like particle or pseudovirion, as described herein for delivery of the RNA (*e.g.*, mRNA) vaccines of the present disclosure.

In some embodiments, RNA (*e.g.*, mRNA) vaccine pharmaceutical compositions comprising the polynucleotides of the present disclosure and a conjugate that may have a degradable linkage. Non-limiting examples of conjugates include an aromatic moiety comprising an ionizable hydrogen atom, a spacer moiety, and a water-soluble polymer. As a non-limiting example, pharmaceutical compositions comprising a conjugate with a degradable linkage and methods for delivering such pharmaceutical compositions are described in U.S. Patent Publication No. US20130184443, the contents of which are herein incorporated by reference in their entirety.

The nanoparticle formulations may be a carbohydrate nanoparticle comprising a carbohydrate carrier and a RNA (*e.g.*, mRNA) vaccine. As a non-limiting example, the carbohydrate carrier may include, but is not limited to, an anhydride-modified phytoglycogen or glycogen-type material, phytoglycogen octenyl succinate, phytoglycogen beta-dextrin,

anhydride-modified phytylglycogen beta-dextrin. (*See e.g.*, International Publication No. WO2012109121; the contents of which are herein incorporated by reference in their entirety).

Nanoparticle formulations of the present disclosure may be coated with a surfactant or polymer in order to improve the delivery of the particle. In some embodiments, the
5 nanoparticle may be coated with a hydrophilic coating such as, but not limited to, PEG coatings and/or coatings that have a neutral surface charge. The hydrophilic coatings may help to deliver nanoparticles with larger payloads such as, but not limited to, RNA (*e.g.*, mRNA) vaccines within the central nervous system. As a non-limiting example
10 nanoparticles comprising a hydrophilic coating and methods of making such nanoparticles are described in U.S. Patent Publication No. US20130183244, the contents of which are herein incorporated by reference in their entirety.

In some embodiments, the lipid nanoparticles of the present disclosure may be hydrophilic polymer particles. Non-limiting examples of hydrophilic polymer particles and methods of making hydrophilic polymer particles are described in U.S. Patent Publication
15 No. US20130210991, the contents of which are herein incorporated by reference in their entirety.

In some embodiments, the lipid nanoparticles of the present disclosure may be hydrophobic polymer particles.

Lipid nanoparticle formulations may be improved by replacing the cationic lipid with
20 a biodegradable cationic lipid which is known as a rapidly eliminated lipid nanoparticle (reLNP). Ionizable cationic lipids, such as, but not limited to, DLinDMA, DLin-KC2-DMA, and DLin-MC3-DMA, have been shown to accumulate in plasma and tissues over time and may be a potential source of toxicity. The rapid metabolism of the rapidly eliminated lipids can improve the tolerability and therapeutic index of the lipid nanoparticles by an order of
25 magnitude from a 1 mg/kg dose to a 10 mg/kg dose in rat. Inclusion of an enzymatically degraded ester linkage can improve the degradation and metabolism profile of the cationic component, while still maintaining the activity of the reLNP formulation. The ester linkage can be internally located within the lipid chain or it may be terminally located at the terminal end of the lipid chain. The internal ester linkage may replace any carbon in the lipid chain.

30 In some embodiments, the internal ester linkage may be located on either side of the saturated carbon.

In some embodiments, an immune response may be elicited by delivering a lipid nanoparticle which may include a nanospecies, a polymer and an immunogen. (U.S. Publication No. 20120189700 and International Publication No. WO2012099805; each of
35 which is herein incorporated by reference in their entirety). The polymer may encapsulate

the nanospecies or partially encapsulate the nanospecies. The immunogen may be a recombinant protein, a modified RNA and/or a polynucleotide described herein. In some embodiments, the lipid nanoparticle may be formulated for use in a vaccine such as, but not limited to, against a pathogen.

5 Lipid nanoparticles may be engineered to alter the surface properties of particles so the lipid nanoparticles may penetrate the mucosal barrier. Mucus is located on mucosal tissue such as, but not limited to, oral (*e.g.*, the buccal and esophageal membranes and tonsil tissue), ophthalmic, gastrointestinal (*e.g.*, stomach, small intestine, large intestine, colon, rectum), nasal, respiratory (*e.g.*, nasal, pharyngeal, tracheal and bronchial membranes),
10 genital (*e.g.*, vaginal, cervical and urethral membranes). Nanoparticles larger than 10-200 nm which are preferred for higher drug encapsulation efficiency and the ability to provide the sustained delivery of a wide array of drugs have been thought to be too large to rapidly diffuse through mucosal barriers. Mucus is continuously secreted, shed, discarded or digested and recycled so most of the trapped particles may be removed from the mucosa
15 tissue within seconds or within a few hours. Large polymeric nanoparticles (200nm -500nm in diameter) which have been coated densely with a low molecular weight polyethylene glycol (PEG) diffused through mucus only 4 to 6-fold lower than the same particles diffusing in water (Lai *et al.* PNAS 2007 104:1482-487; Lai *et al.* *Adv Drug Deliv Rev.* 2009 61: 158-171; each of which is herein incorporated by reference in their entirety). The transport of
20 nanoparticles may be determined using rates of permeation and/or fluorescent microscopy techniques including, but not limited to, fluorescence recovery after photobleaching (FRAP) and high resolution multiple particle tracking (MPT). As a non-limiting example, compositions which can penetrate a mucosal barrier may be made as described in U.S. Pat. No. 8,241,670 or International Patent Publication No. WO2013110028, the contents of each
25 of which are herein incorporated by reference in its entirety.

The lipid nanoparticle engineered to penetrate mucus may comprise a polymeric material (*i.e.* a polymeric core) and/or a polymer-vitamin conjugate and/or a tri-block co-polymer. The polymeric material may include, but is not limited to, polyamines, polyethers, polyamides, polyesters, polycarbamates, polyureas, polycarbonates, poly(styrenes),
30 polyimides, polysulfones, polyurethanes, polyacetylenes, polyethylenes, polyethyleneimines, polyisocyanates, polyacrylates, polymethacrylates, polyacrylonitriles, and polyarylates. The polymeric material may be biodegradable and/or biocompatible. Non-limiting examples of biocompatible polymers are described in International Patent Publication No. WO2013116804, the contents of which are herein incorporated by reference in their entirety.
35 The polymeric material may additionally be irradiated. As a non-limiting example, the

polymeric material may be gamma irradiated (*see e.g.*, International App. No. WO201282165, herein incorporated by reference in its entirety). Non-limiting examples of specific polymers include poly(caprolactone) (PCL), ethylene vinyl acetate polymer (EVA), poly(lactic acid) (PLA), poly(L-lactic acid) (PLLA), poly(glycolic acid) (PGA), poly(lactic acid-co-glycolic acid) (PLGA), poly(L-lactic acid-co-glycolic acid) (PLLGA), poly(D,L-lactide) (PDLA), poly(L-lactide) (PLLA), poly(D,L-lactide-co-caprolactone), poly(D,L-lactide-co-caprolactone-co-glycolide), poly(D,L-lactide-co-PEO-co-D,L-lactide), poly(D,L-lactide-co-PPO-co-D,L-lactide), polyalkyl cyanoacrylate, polyurethane, poly-L-lysine (PLL), hydroxypropyl methacrylate (HPMA), polyethyleneglycol, poly-L-glutamic acid,

poly(hydroxy acids), polyanhydrides, polyorthoesters, poly(ester amides), polyamides, poly(ester ethers), polycarbonates, polyalkylenes such as polyethylene and polypropylene, polyalkylene glycols such as poly(ethylene glycol) (PEG), polyalkylene oxides (PEO), polyalkylene terephthalates such as poly(ethylene terephthalate), polyvinyl alcohols (PVA), polyvinyl ethers, polyvinyl esters such as poly(vinyl acetate), polyvinyl halides such as poly(vinyl chloride) (PVC), polyvinylpyrrolidone, polysiloxanes, polystyrene (PS), polyurethanes, derivatized celluloses such as alkyl celluloses, hydroxyalkyl celluloses, cellulose ethers, cellulose esters, nitro celluloses, hydroxypropylcellulose, carboxymethylcellulose, polymers of acrylic acids, such as poly(methyl(meth)acrylate) (PMMA), poly(ethyl(meth)acrylate), poly(butyl(meth)acrylate), poly(isobutyl(meth)acrylate), poly(hexyl(meth)acrylate), poly(isodecyl(meth)acrylate), poly(lauryl(meth)acrylate), poly(phenyl(meth)acrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), poly(octadecyl acrylate) and copolymers and mixtures thereof, polydioxanone and its copolymers, polyhydroxyalkanoates, polypropylene fumarate, polyoxymethylene, poloxamers, poly(ortho)esters, poly(butyric acid), poly(valeric acid), poly(lactide-co-caprolactone), PEG-PLGA-PEG and trimethylene carbonate, polyvinylpyrrolidone. The lipid nanoparticle may be coated or associated with a co-polymer such as, but not limited to, a block co-polymer (such as a branched polyether-polyamide block copolymer described in International Publication No. WO2013012476, herein incorporated by reference in its entirety), and (poly(ethylene glycol))-(poly(propylene oxide))-(poly(ethylene glycol)) triblock copolymer (*see e.g.*, U.S. Publication 20120121718 and U.S. Publication 20100003337 and U.S. Pat. No. 8,263,665, the contents of each of which is herein incorporated by reference in their entirety). The co-polymer may be a polymer that is generally regarded as safe (GRAS) and the formation of the lipid nanoparticle may be in such a way that no new chemical entities are created. For example, the lipid nanoparticle may comprise poloxamers coating PLGA nanoparticles without forming new chemical entities

which are still able to rapidly penetrate human mucus (Yang *et al.* Angew. Chem. Int. Ed. 2011 50:2597-2600; the contents of which are herein incorporated by reference in their entirety). A non-limiting scalable method to produce nanoparticles which can penetrate human mucus is described by Xu *et al.* (*see, e.g.*, J Control Release 2013, 170:279-86; the contents of which are herein incorporated by reference in their entirety).

The vitamin of the polymer-vitamin conjugate may be vitamin E. The vitamin portion of the conjugate may be substituted with other suitable components such as, but not limited to, vitamin A, vitamin E, other vitamins, cholesterol, a hydrophobic moiety, or a hydrophobic component of other surfactants (*e.g.*, sterol chains, fatty acids, hydrocarbon chains and alkylene oxide chains).

The lipid nanoparticle engineered to penetrate mucus may include surface altering agents such as, but not limited to, polynucleotides, anionic proteins (*e.g.*, bovine serum albumin), surfactants (*e.g.*, cationic surfactants such as for example dimethyldioctadecylammonium bromide), sugars or sugar derivatives (*e.g.*, cyclodextrin), nucleic acids, polymers (*e.g.*, heparin, polyethylene glycol and poloxamer), mucolytic agents (*e.g.*, N-acetylcysteine, mugwort, bromelain, papain, clerodendrum, acetylcysteine, bromhexine, carbocysteine, eprazinone, mesna, ambroxol, sobrerol, domiodol, letosteine, stepronin, tiopronin, gelsolin, thymosin β 4 dornase alfa, neltexine, erdosteine) and various DNases including rhDNase. The surface altering agent may be embedded or enmeshed in the particle's surface or disposed (*e.g.*, by coating, adsorption, covalent linkage, or other process) on the surface of the lipid nanoparticle. (*see e.g.*, U.S. Publication 20100215580 and U.S. Publication 20080166414 and US20130164343; the contents of each of which are herein incorporated by reference in their entirety).

In some embodiments, the mucus penetrating lipid nanoparticles may comprise at least one polynucleotide described herein. The polynucleotide may be encapsulated in the lipid nanoparticle and/or disposed on the surface of the particle. The polynucleotide may be covalently coupled to the lipid nanoparticle. Formulations of mucus penetrating lipid nanoparticles may comprise a plurality of nanoparticles. Further, the formulations may contain particles which may interact with the mucus and alter the structural and/or adhesive properties of the surrounding mucus to decrease mucoadhesion, which may increase the delivery of the mucus penetrating lipid nanoparticles to the mucosal tissue.

In some embodiments, the mucus penetrating lipid nanoparticles may be a hypotonic formulation comprising a mucosal penetration enhancing coating. The formulation may be hypotonic for the epithelium to which it is being delivered. Non-limiting examples of

hypotonic formulations may be found in International Patent Publication No.

WO2013110028, the contents of which are herein incorporated by reference in their entirety.

In some embodiments, in order to enhance the delivery through the mucosal barrier the RNA (*e.g.*, mRNA) vaccine formulation may comprise or be a hypotonic solution.

5 Hypotonic solutions were found to increase the rate at which mucoinert particles such as, but not limited to, mucus-penetrating particles, were able to reach the vaginal epithelial surface (*see e.g.*, Ensign *et al.* Biomaterials 2013 34(28):6922-9, the contents of which are herein incorporated by reference in their entirety).

In some embodiments, the RNA (*e.g.*, mRNA) vaccine is formulated as a lipoplex,
 10 such as, without limitation, the ATUPLEX™ system, the DACC system, the DBTC system and other siRNA-lipoplex technology from Silence Therapeutics (London, United Kingdom), STEMFECT™ from STEMGENT® (Cambridge, MA), and polyethylenimine (PEI) or protamine-based targeted and non-targeted delivery of nucleic acids (Aleku *et al.* Cancer Res. 2008 68:9788-9798; Strumberg *et al.* Int J Clin Pharmacol Ther 2012 50:76-78; Santel *et al.*,
 15 Gene Ther 2006 13:1222-1234; Santel *et al.*, Gene Ther 2006 13:1360-1370; Gutbier *et al.*, Pulm Pharmacol. Ther. 2010 23:334-344; Kaufmann *et al.* Microvasc Res 2010 80:286-293; Weide *et al.* J Immunother. 2009 32:498-507; Weide *et al.* J Immunother. 2008 31:180-188; Pascolo Expert Opin. Biol. Ther. 4:1285-1294; Fotin-Mleczek *et al.*, 2011 J. Immunother. 34:1-15; Song *et al.*, Nature Biotechnol. 2005, 23:709-717; Peer *et al.*, Proc
 20 Natl Acad Sci U S A. 2007 6;104:4095-4100; deFougerolles Hum Gene Ther. 2008 19:125-132, the contents of each of which are incorporated herein by reference in their entirety).

In some embodiments, such formulations may also be constructed or compositions altered such that they passively or actively are directed to different cell types *in vivo*, including but not limited to hepatocytes, immune cells, tumor cells, endothelial cells, antigen
 25 presenting cells, and leukocytes (Akinc *et al.* Mol Ther. 2010 18:1357-1364; Song *et al.*, Nat Biotechnol. 2005 23:709-717; Judge *et al.*, J Clin Invest. 2009 119:661-673; Kaufmann *et al.*, Microvasc Res 2010 80:286-293; Santel *et al.*, Gene Ther 2006 13:1222-1234; Santel *et al.*, Gene Ther 2006 13:1360-1370; Gutbier *et al.*, Pulm Pharmacol. Ther. 2010 23:334-344; Basha *et al.*, Mol. Ther. 2011 19:2186-2200; Fenske and Cullis, Expert Opin Drug Deliv.
 30 2008 5:25-44; Peer *et al.*, Science. 2008 319:627-630; Peer and Lieberman, Gene Ther. 2011 18:1127-1133, the contents of each of which are incorporated herein by reference in their entirety). One example of passive targeting of formulations to liver cells includes the DLin-DMA, DLin-KC2-DMA and DLin-MC3-DMA-based lipid nanoparticle formulations, which have been shown to bind to apolipoprotein E and promote binding and uptake of these
 35 formulations into hepatocytes *in vivo* (Akinc *et al.* Mol Ther. 2010 18:1357-1364, the

contents of which are incorporated herein by reference in their entirety). Formulations can also be selectively targeted through expression of different ligands on their surface as exemplified by, but not limited by, folate, transferrin, N-acetylgalactosamine (GalNAc), and antibody targeted approaches (Kolhatkar *et al.*, Curr Drug Discov Technol. 2011 8:197-206; Musacchio and Torchilin, Front Biosci. 2011 16:1388-1412; Yu *et al.*, Mol Membr Biol. 2010 27:286-298; Patil *et al.*, Crit Rev Ther Drug Carrier Syst. 2008 25:1-61; Benoit *et al.*, Biomacromolecules. 2011 12:2708-2714; Zhao *et al.*, Expert Opin Drug Deliv. 2008 5:309-319; Akinc *et al.*, Mol Ther. 2010 18:1357-1364; Srinivasan *et al.*, Methods Mol Biol. 2012 820:105-116; Ben-Arie *et al.*, Methods Mol Biol. 2012 757:497-507; Peer 2010 J Control Release. 20:63-68; Peer *et al.*, Proc Natl Acad Sci U S A. 2007 104:4095-4100; Kim *et al.*, Methods Mol Biol. 2011 721:339-353; Subramanya *et al.*, Mol Ther. 2010 18:2028-2037; Song *et al.*, Nat Biotechnol. 2005 23:709-717; Peer *et al.*, Science. 2008 319:627-630; Peer and Lieberman, Gene Ther. 2011 18:1127-1133, the contents of each of which are incorporated herein by reference in their entirety).

In some embodiments, the RNA (*e.g.*, mRNA) vaccine is formulated as a solid lipid nanoparticle. A solid lipid nanoparticle (SLN) may be spherical with an average diameter between 10 to 1000 nm. SLN possess a solid lipid core matrix that can solubilize lipophilic molecules and may be stabilized with surfactants and/or emulsifiers. In some embodiments, the lipid nanoparticle may be a self-assembly lipid-polymer nanoparticle (*see* Zhang *et al.*, ACS Nano, 2008, 2 , pp 1696–1702; the contents of which are herein incorporated by reference in their entirety). As a non-limiting example, the SLN may be the SLN described in International Patent Publication No. WO2013105101, the contents of which are herein incorporated by reference in their entirety. As another non-limiting example, the SLN may be made by the methods or processes described in International Patent Publication No. WO2013105101, the contents of which are herein incorporated by reference in their entirety.

Liposomes, lipoplexes, or lipid nanoparticles may be used to improve the efficacy of polynucleotides directed protein production as these formulations may be able to increase cell transfection by the RNA (*e.g.*, mRNA) vaccine; and/or increase the translation of encoded protein. One such example involves the use of lipid encapsulation to enable the effective systemic delivery of polyplex plasmid DNA (Heyes *et al.*, Mol Ther. 2007 15:713-720; the contents of which are incorporated herein by reference in their entirety). The liposomes, lipoplexes, or lipid nanoparticles may also be used to increase the stability of the polynucleotide.

In some embodiments, the RNA (*e.g.*, mRNA) vaccines of the present disclosure can be formulated for controlled release and/or targeted delivery. As used herein, “controlled

release” refers to a pharmaceutical composition or compound release profile that conforms to a particular pattern of release to effect a therapeutic outcome. In some embodiments, the RNA (*e.g.*, mRNA) vaccines may be encapsulated into a delivery agent described herein and/or known in the art for controlled release and/or targeted delivery. As used herein, the term “encapsulate” means to enclose, surround or encase. As it relates to the formulation of the compounds of the disclosure, encapsulation may be substantial, complete or partial. The term “substantially encapsulated” means that at least greater than 50, 60, 70, 80, 85, 90, 95, 96, 97, 98, 99, 99.9, 99.9 or greater than 99.999% of the pharmaceutical composition or compound of the disclosure may be enclosed, surrounded or encased within the delivery agent. “Partially encapsulation” means that less than 10, 10, 20, 30, 40 50 or less of the pharmaceutical composition or compound of the disclosure may be enclosed, surrounded or encased within the delivery agent. Advantageously, encapsulation may be determined by measuring the escape or the activity of the pharmaceutical composition or compound of the disclosure using fluorescence and/or electron micrograph. For example, at least 1, 5, 10, 20, 30, 40, 50, 60, 70, 80, 85, 90, 95, 96, 97, 98, 99, 99.9, 99.99 or greater than 99.99% of the pharmaceutical composition or compound of the disclosure are encapsulated in the delivery agent.

In some embodiments, the controlled release formulation may include, but is not limited to, tri-block co-polymers. As a non-limiting example, the formulation may include two different types of tri-block co-polymers (International Pub. No. WO2012131104 and WO2012131106, the contents of each of which are incorporated herein by reference in their entirety).

In some embodiments, the RNA (*e.g.*, mRNA) vaccines may be encapsulated into a lipid nanoparticle or a rapidly eliminated lipid nanoparticle and the lipid nanoparticles or a rapidly eliminated lipid nanoparticle may then be encapsulated into a polymer, hydrogel and/or surgical sealant described herein and/or known in the art. As a non-limiting example, the polymer, hydrogel or surgical sealant may be PLGA, ethylene vinyl acetate (EVAc), poloxamer, GELSITE® (Nanotherapeutics, Inc. Alachua, FL), HYLENEX® (Halozyme Therapeutics, San Diego CA), surgical sealants such as fibrinogen polymers (Ethicon Inc. Cornelia, GA), TISSELL® (Baxter International, Inc Deerfield, IL), PEG-based sealants, and COSEAL® (Baxter International, Inc Deerfield, IL).

In some embodiments, the lipid nanoparticle may be encapsulated into any polymer known in the art which may form a gel when injected into a subject. As another non-limiting example, the lipid nanoparticle may be encapsulated into a polymer matrix which may be biodegradable.

In some embodiments, the RNA (*e.g.*, mRNA) vaccine formulation for controlled release and/or targeted delivery may also include at least one controlled release coating. Controlled release coatings include, but are not limited to, OPADRY®, polyvinylpyrrolidone/vinyl acetate copolymer, polyvinylpyrrolidone, hydroxypropyl methylcellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, EUDRAGIT RL®, EUDRAGIT RS® and cellulose derivatives such as ethylcellulose aqueous dispersions (AQUACOAT® and SURELEASE®).

In some embodiments, the RNA (*e.g.*, mRNA) vaccine controlled release and/or targeted delivery formulation may comprise at least one degradable polyester which may contain polycationic side chains. Degradable polyesters include, but are not limited to, poly(serine ester), poly(L-lactide-co-L-lysine), poly(4-hydroxy-L-proline ester), and combinations thereof. In some embodiments, the degradable polyesters may include a PEG conjugation to form a PEGylated polymer.

In some embodiments, the RNA (*e.g.*, mRNA) vaccine controlled release and/or targeted delivery formulation comprising at least one polynucleotide may comprise at least one PEG and/or PEG related polymer derivatives as described in U.S. Patent No. 8,404,222, the contents of which are incorporated herein by reference in their entirety.

In some embodiments, the RNA (*e.g.*, mRNA) vaccine controlled release delivery formulation comprising at least one polynucleotide may be the controlled release polymer system described in US20130130348, the contents of which are incorporated herein by reference in their entirety.

In some embodiments, the RNA (*e.g.*, mRNA) vaccines of the present disclosure may be encapsulated in a therapeutic nanoparticle, referred to herein as “therapeutic nanoparticle RNA (*e.g.*, mRNA) vaccines.” Therapeutic nanoparticles may be formulated by methods described herein and known in the art such as, but not limited to, International Pub Nos. WO2010005740, WO2010030763, WO2010005721, WO2010005723, WO2012054923, U.S. Publication Nos. US20110262491, US20100104645, US20100087337, US20100068285, US20110274759, US20100068286, US20120288541, US20130123351 and US20130230567 and U.S. Patent No. 8,206,747, 8,293,276, 8,318,208 and 8,318,211; the contents of each of which are herein incorporated by reference in their entirety. In some embodiments, therapeutic polymer nanoparticles may be identified by the methods described in US Pub No. US20120140790, the contents of which are herein incorporated by reference in their entirety.

In some embodiments, the therapeutic nanoparticle RNA (*e.g.*, mRNA) vaccine may be formulated for sustained release. As used herein, “sustained release” refers to a pharmaceutical composition or compound that conforms to a release rate over a specific

period of time. The period of time may include, but is not limited to, hours, days, weeks, months and years. As a non-limiting example, the sustained release nanoparticle may comprise a polymer and a therapeutic agent such as, but not limited to, the polynucleotides of the present disclosure (see International Pub No. 2010075072 and US Pub No.

5 US20100216804, US20110217377 and US20120201859, the contents of each of which are incorporated herein by reference in their entirety). In another non-limiting example, the sustained release formulation may comprise agents which permit persistent bioavailability such as, but not limited to, crystals, macromolecular gels and/or particulate suspensions (see U.S. Patent Publication No US20130150295, the contents of each of which are incorporated
10 herein by reference in their entirety).

In some embodiments, the therapeutic nanoparticle RNA (*e.g.*, mRNA) vaccines may be formulated to be target specific. As a non-limiting example, the therapeutic nanoparticles may include a corticosteroid (see International Pub. No. WO2011084518, the contents of which are incorporated herein by reference in their entirety). As a non-limiting example, the
15 therapeutic nanoparticles may be formulated in nanoparticles described in International Pub No. WO2008121949, WO2010005726, WO2010005725, WO2011084521 and US Pub No. US20100069426, US20120004293 and US20100104655, the contents of each of which are incorporated herein by reference in their entirety.

In some embodiments, the nanoparticles of the present disclosure may comprise a
20 polymeric matrix. As a non-limiting example, the nanoparticle may comprise two or more polymers such as, but not limited to, polyethylenes, polycarbonates, polyanhydrides, polyhydroxyacids, polypropylfumerates, polycaprolactones, polyamides, polyacetals, polyethers, polyesters, poly(orthoesters), polycyanoacrylates, polyvinyl alcohols, polyurethanes, polyphosphazenes, polyacrylates, polymethacrylates, polycyanoacrylates,
25 polyureas, polystyrenes, polyamines, polylysine, poly(ethylene imine), poly(serine ester), poly(L-lactide-co-L-lysine), poly(4-hydroxy-L-proline ester) or combinations thereof.

In some embodiments, the therapeutic nanoparticle comprises a diblock copolymer. In some embodiments, the diblock copolymer may include PEG in combination with a polymer such as, but not limited to, polyethylenes, polycarbonates, polyanhydrides,
30 polyhydroxyacids, polypropylfumerates, polycaprolactones, polyamides, polyacetals, polyethers, polyesters, poly(orthoesters), polycyanoacrylates, polyvinyl alcohols, polyurethanes, polyphosphazenes, polyacrylates, polymethacrylates, polycyanoacrylates, polyureas, polystyrenes, polyamines, polylysine, poly(ethylene imine), poly(serine ester), poly(L-lactide-co-L-lysine), poly(4-hydroxy-L-proline ester) or combinations thereof. In yet
35 another embodiment, the diblock copolymer may be a high-X diblock copolymer such as

those described in International Patent Publication No. WO2013120052, the contents of which are incorporated herein by reference in their entirety.

As a non-limiting example the therapeutic nanoparticle comprises a PLGA-PEG block copolymer (*see* U.S. Publication No. US20120004293 and U.S. Patent No. 8,236,330, each of which is herein incorporated by reference in their entirety). In another non-limiting example, the therapeutic nanoparticle is a stealth nanoparticle comprising a diblock copolymer of PEG and PLA or PEG and PLGA (*see* U.S. Patent No 8,246,968 and International Publication No. WO2012166923, the contents of each of which are herein incorporated by reference in their entirety). In yet another non-limiting example, the therapeutic nanoparticle is a stealth nanoparticle or a target-specific stealth nanoparticle as described in U.S. Patent Publication No. US20130172406, the contents of which are herein incorporated by reference in their entirety.

In some embodiments, the therapeutic nanoparticle may comprise a multiblock copolymer (*see e.g.*, U.S. Pat. No. 8,263,665 and 8,287,910 and U.S. Patent Pub. No. US20130195987, the contents of each of which are herein incorporated by reference in their entirety).

In yet another non-limiting example, the lipid nanoparticle comprises the block copolymer PEG-PLGA-PEG (*see e.g.*, the thermosensitive hydrogel (PEG-PLGA-PEG) was used as a TGF-beta1 gene delivery vehicle in Lee *et al.* Thermosensitive Hydrogel as a TGF- β 1 Gene Delivery Vehicle Enhances Diabetic Wound Healing. *Pharmaceutical Research*, 2003 20(12): 1995-2000; as a controlled gene delivery system in Li *et al.* Controlled Gene Delivery System Based on Thermosensitive Biodegradable Hydrogel. *Pharmaceutical Research* 2003 20:884-888; and Chang *et al.*, Non-ionic amphiphilic biodegradable PEG-PLGA-PEG copolymer enhances gene delivery efficiency in rat skeletal muscle. *J Controlled Release*. 2007 118:245-253, the contents of each of which are herein incorporated by reference in their entirety). The RNA (*e.g.*, mRNA) vaccines of the present disclosure may be formulated in lipid nanoparticles comprising the PEG-PLGA-PEG block copolymer.

In some embodiments, the therapeutic nanoparticle may comprise a multiblock copolymer (*see e.g.*, U.S. Pat. No. 8,263,665 and 8,287,910 and U.S. Patent Pub. No. US20130195987, the contents of each of which are herein incorporated by reference in their entirety).

In some embodiments, the block copolymers described herein may be included in a polyion complex comprising a non-polymeric micelle and the block copolymer. (*see e.g.*, U.S. Publication No. 20120076836, the contents of which are herein incorporated by reference in their entirety).

In some embodiments, the therapeutic nanoparticle may comprise at least one acrylic polymer. Acrylic polymers include but are not limited to, acrylic acid, methacrylic acid, acrylic acid and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, amino alkyl methacrylate copolymer, poly(acrylic acid), poly(methacrylic acid), polycyanoacrylates and combinations thereof.

In some embodiments, the therapeutic nanoparticles may comprise at least one poly(vinyl ester) polymer. The poly(vinyl ester) polymer may be a copolymer such as a random copolymer. As a non-limiting example, the random copolymer may have a structure such as those described in International Application No. WO2013032829 or U.S. Patent Publication No US20130121954, the contents of each of which are herein incorporated by reference in their entirety. In some embodiments, the poly(vinyl ester) polymers may be conjugated to the polynucleotides described herein.

In some embodiments, the therapeutic nanoparticle may comprise at least one diblock copolymer. The diblock copolymer may be, but it not limited to, a poly(lactic) acid-poly(ethylene)glycol copolymer (*see, e.g.*, International Patent Publication No. WO2013044219, the contents of which are herein incorporated by reference in their entirety). As a non-limiting example, the therapeutic nanoparticle may be used to treat cancer (*see* International publication No. WO2013044219, the contents of which are herein incorporated by reference in their entirety).

In some embodiments, the therapeutic nanoparticles may comprise at least one cationic polymer described herein and/or known in the art.

In some embodiments, the therapeutic nanoparticles may comprise at least one amine-containing polymer such as, but not limited to polylysine, polyethylene imine, poly(amidoamine) dendrimers, poly(beta-amino esters) (*see, e.g.*, U.S. Patent No. 8,287,849, the contents of which are herein incorporated by reference in their entirety) and combinations thereof.

In some embodiments, the nanoparticles described herein may comprise an amine cationic lipid such as those described in International Patent Application No. WO2013059496, the contents of which are herein incorporated by reference in their entirety.

In some embodiments, the cationic lipids may have an amino-amine or an amino-amide moiety.

In some embodiments, the therapeutic nanoparticles may comprise at least one degradable polyester which may contain polycationic side chains. Degradable polyesters include, but are not limited to, poly(serine ester), poly(L-lactide-co-L-lysine), poly(4-

hydroxy-L-proline ester), and combinations thereof. In some embodiments, the degradable polyesters may include a PEG conjugation to form a PEGylated polymer.

In some embodiments, the synthetic nanocarriers may contain an immunostimulatory agent to enhance the immune response from delivery of the synthetic nanocarrier. As a non-limiting example, the synthetic nanocarrier may comprise a Th1 immunostimulatory agent, which may enhance a Th1-based response of the immune system (*see* International Pub No. WO2010123569 and U.S. Publication No. US20110223201, the contents of each of which are herein incorporated by reference in their entirety).

In some embodiments, the synthetic nanocarriers may be formulated for targeted release. In some embodiments, the synthetic nanocarrier is formulated to release the polynucleotides at a specified pH and/or after a desired time interval. As a non-limiting example, the synthetic nanoparticle may be formulated to release the RNA (*e.g.*, mRNA) vaccines after 24 hours and/or at a pH of 4.5 (*see* International Publication Nos. WO2010138193 and WO2010138194 and US Pub Nos. US20110020388 and US20110027217, each of which is herein incorporated by reference in their entirety).

In some embodiments, the synthetic nanocarriers may be formulated for controlled and/or sustained release of the polynucleotides described herein. As a non-limiting example, the synthetic nanocarriers for sustained release may be formulated by methods known in the art, described herein and/or as described in International Pub No. WO2010138192 and US Pub No. 20100303850, each of which is herein incorporated by reference in their entirety.

In some embodiments, the RNA (*e.g.*, mRNA) vaccine may be formulated for controlled and/or sustained release wherein the formulation comprises at least one polymer that is a crystalline side chain (CYSC) polymer. CYSC polymers are described in U.S. Patent No. 8,399,007, herein incorporated by reference in its entirety.

In some embodiments, the synthetic nanocarrier may be formulated for use as a vaccine. In some embodiments, the synthetic nanocarrier may encapsulate at least one polynucleotide which encode at least one antigen. As a non-limiting example, the synthetic nanocarrier may include at least one antigen and an excipient for a vaccine dosage form (*see* International Publication No. WO2011150264 and U.S. Publication No. US20110293723, the contents of each of which are herein incorporated by reference in their entirety). As another non-limiting example, a vaccine dosage form may include at least two synthetic nanocarriers with the same or different antigens and an excipient (*see* International Publication No. WO2011150249 and U.S. Publication No. US20110293701, the contents of each of which are herein incorporated by reference in their entirety). The vaccine dosage form may be selected by methods described herein, known in the art and/or described in International

Publication No. WO2011150258 and U.S. Publication No. US20120027806, the contents of each of which are herein incorporated by reference in their entirety).

In some embodiments, the synthetic nanocarrier may comprise at least one polynucleotide which encodes at least one adjuvant. As non-limiting example, the adjuvant may comprise dimethyldioctadecylammonium-bromide, dimethyldioctadecylammonium-chloride, dimethyldioctadecylammonium-phosphate or dimethyldioctadecylammonium-acetate (DDA) and an apolar fraction or part of said apolar fraction of a total lipid extract of a mycobacterium (*see, e.g.*, U.S. Patent No. 8,241,610, the content of which is herein incorporated by reference in its entirety). In some embodiments, the synthetic nanocarrier may comprise at least one polynucleotide and an adjuvant. As a non-limiting example, the synthetic nanocarrier comprising and adjuvant may be formulated by the methods described in International Publication No. WO2011150240 and U.S. Publication No. US20110293700, the contents of each of which are herein incorporated by reference in their entirety.

In some embodiments, the synthetic nanocarrier may encapsulate at least one polynucleotide that encodes a peptide, fragment or region from a virus. As a non-limiting example, the synthetic nanocarrier may include, but is not limited to, any of the nanocarriers described in International Publication No. WO2012024621, WO201202629, WO2012024632 and U.S. Publication No. US20120064110, US20120058153 and US20120058154, the contents of each of which are herein incorporated by reference in their entirety.

In some embodiments, the synthetic nanocarrier may be coupled to a polynucleotide which may be able to trigger a humoral and/or cytotoxic T lymphocyte (CTL) response (*see, e.g.*, International Publication No. WO2013019669, the contents of which are herein incorporated by reference in their entirety).

In some embodiments, the RNA (*e.g.*, mRNA) vaccine may be encapsulated in, linked to and/or associated with zwitterionic lipids. Non-limiting examples of zwitterionic lipids and methods of using zwitterionic lipids are described in U.S. Patent Publication No. US20130216607, the contents of which are herein incorporated by reference in their entirety. In some aspects, the zwitterionic lipids may be used in the liposomes and lipid nanoparticles described herein.

In some embodiments, the RNA (*e.g.*, mRNA) vaccine may be formulated in colloid nanocarriers as described in U.S. Patent Publication No. US20130197100, the contents of which are herein incorporated by reference in their entirety.

In some embodiments, the nanoparticle may be optimized for oral administration. The nanoparticle may comprise at least one cationic biopolymer such as, but not limited to, chitosan or a derivative thereof. As a non-limiting example, the nanoparticle may be

formulated by the methods described in U.S. Publication No. 20120282343, the contents of which are herein incorporated by reference in their entirety.

In some embodiments, LNPs comprise the lipid KL52 (an amino-lipid disclosed in U.S. Application Publication No. 2012/0295832, the contents of which are herein incorporated by reference in their entirety. Activity and/or safety (as measured by examining one or more of ALT/AST, white blood cell count and cytokine induction, for example) of LNP administration may be improved by incorporation of such lipids. LNPs comprising KL52 may be administered intravenously and/or in one or more doses. In some embodiments, administration of LNPs comprising KL52 results in equal or improved mRNA and/or protein expression as compared to LNPs comprising MC3.

In some embodiments, RNA (*e.g.*, mRNA) vaccine may be delivered using smaller LNPs. Such particles may comprise a diameter from below 0.1 μm up to 100 nm such as, but not limited to, less than 0.1 μm , less than 1.0 μm , less than 5 μm , less than 10 μm , less than 15 μm , less than 20 μm , less than 25 μm , less than 30 μm , less than 35 μm , less than 40 μm , less than 50 μm , less than 55 μm , less than 60 μm , less than 65 μm , less than 70 μm , less than 75 μm , less than 80 μm , less than 85 μm , less than 90 μm , less than 95 μm , less than 100 μm , less than 125 μm , less than 150 μm , less than 175 μm , less than 200 μm , less than 225 μm , less than 250 μm , less than 275 μm , less than 300 μm , less than 325 μm , less than 350 μm , less than 375 μm , less than 400 μm , less than 425 μm , less than 450 μm , less than 475 μm , less than 500 μm , less than 525 μm , less than 550 μm , less than 575 μm , less than 600 μm , less than 625 μm , less than 650 μm , less than 675 μm , less than 700 μm , less than 725 μm , less than 750 μm , less than 775 μm , less than 800 μm , less than 825 μm , less than 850 μm , less than 875 μm , less than 900 μm , less than 925 μm , less than 950 μm , less than 975 μm , or less than 1000 μm .

In some embodiments, RNA (*e.g.*, mRNA) vaccines may be delivered using smaller LNPs, which may comprise a diameter from about 1 nm to about 100 nm, from about 1 nm to about 10 nm, about 1 nm to about 20 nm, from about 1 nm to about 30 nm, from about 1 nm to about 40 nm, from about 1 nm to about 50 nm, from about 1 nm to about 60 nm, from about 1 nm to about 70 nm, from about 1 nm to about 80 nm, from about 1 nm to about 90 nm, from about 5 nm to about 100 nm, from about 5 nm to about 10 nm, about 5 nm to about 20 nm, from about 5 nm to about 30 nm, from about 5 nm to about 40 nm, from about 5 nm to about 50 nm, from about 5 nm to about 60 nm, from about 5 nm to about 70 nm, from about 5 nm to about 80 nm, from about 5 nm to about 90 nm, about 10 to about 50 nm, from about 20 to about 50 nm, from about 30 to about 50 nm, from about 40 to about 50 nm, from about 20 to about 60 nm, from about 30 to about 60 nm, from about 40 to about 60 nm, from

about 20 to about 70 nm, from about 30 to about 70 nm, from about 40 to about 70 nm, from about 50 to about 70 nm, from about 60 to about 70 nm, from about 20 to about 80 nm, from about 30 to about 80 nm, from about 40 to about 80 nm, from about 50 to about 80 nm, from about 60 to about 80 nm, from about 20 to about 90 nm, from about 30 to about 90 nm, from about 40 to about 90 nm, from about 50 to about 90 nm, from about 60 to about 90 nm and/or from about 70 to about 90 nm.

In some embodiments, such LNPs are synthesized using methods comprising microfluidic mixers. Examples of microfluidic mixers may include, but are not limited to, a slit interdigital micromixer including, but not limited to those manufactured by Microinova (Allerheiligen bei Wildon, Austria) and/or a staggered herringbone micromixer (SHM) (Zhigaltsev, I.V. *et al.*, Bottom-up design and synthesis of limit size lipid nanoparticle systems with aqueous and triglyceride cores using millisecond microfluidic mixing have been published (Langmuir. 2012. 28:3633-40; Belliveau, N.M. *et al.*, Microfluidic synthesis of highly potent limit-size lipid nanoparticles for *in vivo* delivery of siRNA. Molecular Therapy-Nucleic Acids. 2012. 1:e37; Chen, D. *et al.*, Rapid discovery of potent siRNA-containing lipid nanoparticles enabled by controlled microfluidic formulation. J Am Chem Soc. 2012. 134(16):6948-51, the contents of each of which are herein incorporated by reference in their entirety). In some embodiments, methods of LNP generation comprising SHM, further comprise the mixing of at least two input streams wherein mixing occurs by microstructure-induced chaotic advection (MICA). According to this method, fluid streams flow through channels present in a herringbone pattern causing rotational flow and folding the fluids around each other. This method may also comprise a surface for fluid mixing wherein the surface changes orientations during fluid cycling. Methods of generating LNPs using SHM include those disclosed in U.S. Application Publication Nos. 2004/0262223 and 2012/0276209, the contents of each of which are herein incorporated by reference in their entirety.

In some embodiments, the RNA (*e.g.*, mRNA) vaccine of the present disclosure may be formulated in lipid nanoparticles created using a micromixer such as, but not limited to, a Slit Interdigital Microstructured Mixer (SIMM-V2) or a Standard Slit Interdigital Micro Mixer (SSIMM) or Caterpillar (CPMM) or Impinging-jet (IJMM) from the Institut für Mikrotechnik Mainz GmbH, Mainz Germany).

In some embodiments, the RNA (*e.g.*, mRNA) vaccines of the present disclosure may be formulated in lipid nanoparticles created using microfluidic technology (*see, e.g.*, Whitesides, George M. The Origins and the Future of Microfluidics. Nature, 2006 442: 368-373; and Abraham *et al.* Chaotic Mixer for Microchannels. Science, 2002 295: 647-651; each

of which is herein incorporated by reference in its entirety). As a non-limiting example, controlled microfluidic formulation includes a passive method for mixing streams of steady pressure-driven flows in micro channels at a low Reynolds number (*see, e.g., Abraham et al. Chaotic Mixer for Microchannels. Science, 2002 295: 647-651, the contents of which are*
5 herein incorporated by reference in their entirety).

In some embodiments, the RNA (*e.g., mRNA*) vaccines of the present disclosure may be formulated in lipid nanoparticles created using a micromixer chip such as, but not limited to, those from Harvard Apparatus (Holliston, MA) or Dolomite Microfluidics (Royston, UK). A micromixer chip can be used for rapid mixing of two or more fluid streams with a split and
10 recombine mechanism.

In some embodiments, the RNA (*e.g., mRNA*) vaccines of the disclosure may be formulated for delivery using the drug encapsulating microspheres described in International Patent Publication No. WO2013063468 or U.S. Patent No. 8,440,614, the contents of each of which are herein incorporated by reference in their entirety. The microspheres may comprise
15 a compound of the formula (I), (II), (III), (IV), (V) or (VI) as described in International Patent Publication No. WO2013063468, the contents of which are herein incorporated by reference in their entirety. In some embodiments, the amino acid, peptide, polypeptide, lipids (APPL) are useful in delivering the RNA (*e.g., mRNA*) vaccines of the disclosure to cells (see International Patent Publication No. WO2013063468, the contents of which are herein
20 incorporated by reference in their entirety).

In some embodiments, the RNA (*e.g., mRNA*) vaccines of the disclosure may be formulated in lipid nanoparticles having a diameter from about 10 to about 100 nm such as, but not limited to, about 10 to about 20 nm, about 10 to about 30 nm, about 10 to about 40 nm, about 10 to about 50 nm, about 10 to about 60 nm, about 10 to about 70 nm, about 10 to
25 about 80 nm, about 10 to about 90 nm, about 20 to about 30 nm, about 20 to about 40 nm, about 20 to about 50 nm, about 20 to about 60 nm, about 20 to about 70 nm, about 20 to about 80 nm, about 20 to about 90 nm, about 20 to about 100 nm, about 30 to about 40 nm, about 30 to about 50 nm, about 30 to about 60 nm, about 30 to about 70 nm, about 30 to about 80 nm, about 30 to about 90 nm, about 30 to about 100 nm, about 40 to about 50 nm,
30 about 40 to about 60 nm, about 40 to about 70 nm, about 40 to about 80 nm, about 40 to about 90 nm, about 40 to about 100 nm, about 50 to about 60 nm, about 50 to about 70 nm, about 50 to about 80 nm, about 50 to about 90 nm, about 50 to about 100 nm, about 60 to about 70 nm, about 60 to about 80 nm, about 60 to about 90 nm, about 60 to about 100 nm, about 70 to about 80 nm, about 70 to about 90 nm, about 70 to about 100 nm, about 80 to
35 about 90 nm, about 80 to about 100 nm and/or about 90 to about 100 nm.

In some embodiments, the lipid nanoparticles may have a diameter from about 10 to 500 nm.

In some embodiments, the lipid nanoparticle may have a diameter greater than 100 nm, greater than 150 nm, greater than 200 nm, greater than 250 nm, greater than 300 nm, greater than 350 nm, greater than 400 nm, greater than 450 nm, greater than 500 nm, greater than 550 nm, greater than 600 nm, greater than 650 nm, greater than 700 nm, greater than 750 nm, greater than 800 nm, greater than 850 nm, greater than 900 nm, greater than 950 nm or greater than 1000 nm.

In some embodiments, the lipid nanoparticle may be a limit size lipid nanoparticle described in International Patent Publication No. WO2013059922, the contents of which are herein incorporated by reference in their entirety. The limit size lipid nanoparticle may comprise a lipid bilayer surrounding an aqueous core or a hydrophobic core; where the lipid bilayer may comprise a phospholipid such as, but not limited to, diacylphosphatidylcholine, a diacylphosphatidylethanolamine, a ceramide, a sphingomyelin, a dihydrosphingomyelin, a cephalin, a cerebroside, a C8-C20 fatty acid diacylphosphatidylcholine, and 1-palmitoyl-2-oleoyl phosphatidylcholine (POPC). In some embodiments, the limit size lipid nanoparticle may comprise a polyethylene glycol-lipid such as, but not limited to, DLPE-PEG, DMPE-PEG, DPPC-PEG and DSPE-PEG.

In some embodiments, the RNA (*e.g.*, mRNA) vaccines may be delivered, localized and/or concentrated in a specific location using the delivery methods described in International Patent Publication No. WO2013063530, the contents of which are herein incorporated by reference in their entirety. As a non-limiting example, a subject may be administered an empty polymeric particle prior to, simultaneously with or after delivering the RNA (*e.g.*, mRNA) vaccines to the subject. The empty polymeric particle undergoes a change in volume once in contact with the subject and becomes lodged, embedded, immobilized or entrapped at a specific location in the subject.

In some embodiments, the RNA (*e.g.*, mRNA) vaccines may be formulated in an active substance release system (*see, e.g.*, U.S. Patent Publication No. US20130102545, the contents of which are herein incorporated by reference in their entirety). The active substance release system may comprise 1) at least one nanoparticle bonded to an oligonucleotide inhibitor strand which is hybridized with a catalytically active nucleic acid and 2) a compound bonded to at least one substrate molecule bonded to a therapeutically active substance (*e.g.*, polynucleotides described herein), where the therapeutically active substance is released by the cleavage of the substrate molecule by the catalytically active nucleic acid.

In some embodiments, the RNA (*e.g.*, mRNA) vaccines may be formulated in a nanoparticle comprising an inner core comprising a non-cellular material and an outer surface comprising a cellular membrane. The cellular membrane may be derived from a cell or a membrane derived from a virus. As a non-limiting example, the nanoparticle may be made by the methods described in International Patent Publication No. WO2013052167, the contents of which are herein incorporated by reference in their entirety. As another non-limiting example, the nanoparticle described in International Patent Publication No. WO2013052167, the contents of which are herein incorporated by reference in their entirety, may be used to deliver the RNA (*e.g.*, mRNA) vaccines described herein.

In some embodiments, the RNA (*e.g.*, mRNA) vaccines may be formulated in porous nanoparticle-supported lipid bilayers (protocells). Protocells are described in International Patent Publication No. WO2013056132, the contents of which are herein incorporated by reference in their entirety.

In some embodiments, the RNA (*e.g.*, mRNA) vaccines described herein may be formulated in polymeric nanoparticles as described in or made by the methods described in U.S. Patent Nos. 8,420,123 and 8,518,963 and European Patent No. EP2073848B1, the contents of each of which are herein incorporated by reference in their entirety. As a non-limiting example, the polymeric nanoparticle may have a high glass transition temperature such as the nanoparticles described in or nanoparticles made by the methods described in U.S. Patent No. 8,518,963, the contents of which are herein incorporated by reference in their entirety. As another non-limiting example, the polymer nanoparticle for oral and parenteral formulations may be made by the methods described in European Patent No. EP2073848B1, the contents of which are herein incorporated by reference in their entirety.

In some embodiments, the RNA (*e.g.*, mRNA) vaccines described herein may be formulated in nanoparticles used in imaging. The nanoparticles may be liposome nanoparticles such as those described in U.S. Patent Publication No US20130129636, herein incorporated by reference in its entirety. As a non-limiting example, the liposome may comprise gadolinium(III)2-{4,7-bis-carboxymethyl-10-[(N,N-distearylamidomethyl-N'-amido-methyl]-1,4,7,10-tetra-azacyclododec-1-yl}-acetic acid and a neutral, fully saturated phospholipid component (*see, e.g.*, U.S. Patent Publication No US20130129636, the contents of which are herein incorporated by reference in their entirety).

In some embodiments, the nanoparticles which may be used in the present disclosure are formed by the methods described in U.S. Patent Application No. US20130130348, the contents of which are herein incorporated by reference in their entirety.

The nanoparticles of the present disclosure may further include nutrients such as, but not limited to, those which deficiencies can lead to health hazards from anemia to neural tube defects (*see, e.g.*, the nanoparticles described in International Patent Publication No WO2013072929, the contents of which are herein incorporated by reference in their entirety).

5 As a non-limiting example, the nutrient may be iron in the form of ferrous, ferric salts or elemental iron, iodine, folic acid, vitamins or micronutrients.

In some embodiments, the RNA (*e.g.*, mRNA) vaccines of the present disclosure may be formulated in a swellable nanoparticle. The swellable nanoparticle may be, but is not limited to, those described in U.S. Patent No. 8,440,231, the contents of which are herein
10 incorporated by reference in their entirety. As a non-limiting embodiment, the swellable nanoparticle may be used for delivery of the RNA (*e.g.*, mRNA) vaccines of the present disclosure to the pulmonary system (*see, e.g.*, U.S. Patent No. 8,440,231, the contents of which are herein incorporated by reference in their entirety).

The RNA (*e.g.*, mRNA) vaccines of the present disclosure may be formulated in
15 polyanhydride nanoparticles such as, but not limited to, those described in U.S. Patent No. 8,449,916, the contents of which are herein incorporated by reference in their entirety.

The nanoparticles and microparticles of the present disclosure may be geometrically engineered to modulate macrophage and/or the immune response. In some embodiments, the geometrically engineered particles may have varied shapes, sizes and/or surface charges in
20 order to incorporated the polynucleotides of the present disclosure for targeted delivery such as, but not limited to, pulmonary delivery (*see, e.g.*, International Publication No WO2013082111, the contents of which are herein incorporated by reference in their entirety). Other physical features the geometrically engineering particles may have include, but are not limited to, fenestrations, angled arms, asymmetry and surface roughness, charge which can
25 alter the interactions with cells and tissues. As a non-limiting example, nanoparticles of the present disclosure may be made by the methods described in International Publication No WO2013082111, the contents of which are herein incorporated by reference in their entirety.

In some embodiments, the nanoparticles of the present disclosure may be water soluble nanoparticles such as, but not limited to, those described in International Publication
30 No. WO2013090601, the contents of which are herein incorporated by reference in their entirety. The nanoparticles may be inorganic nanoparticles which have a compact and zwitterionic ligand in order to exhibit good water solubility. The nanoparticles may also have small hydrodynamic diameters (HD), stability with respect to time, pH, and salinity and a low level of non-specific protein binding.

In some embodiments the nanoparticles of the present disclosure may be developed by the methods described in U.S. Patent Publication No. US20130172406, the contents of which are herein incorporated by reference in their entirety.

In some embodiments, the nanoparticles of the present disclosure are stealth nanoparticles or target-specific stealth nanoparticles such as, but not limited to, those described in U.S. Patent Publication No. US20130172406, the contents of which are herein incorporated by reference in their entirety. The nanoparticles of the present disclosure may be made by the methods described in U.S. Patent Publication No. US20130172406, the contents of which are herein incorporated by reference in their entirety.

In some embodiments, the stealth or target-specific stealth nanoparticles may comprise a polymeric matrix. The polymeric matrix may comprise two or more polymers such as, but not limited to, polyethylenes, polycarbonates, polyanhydrides, polyhydroxyacids, polypropylfumerates, polycaprolactones, polyamides, polyacetals, polyethers, polyesters, poly(orthoesters), polycyanoacrylates, polyvinyl alcohols, polyurethanes, polyphosphazenes, polyacrylates, polymethacrylates, polycyanoacrylates, polyureas, polystyrenes, polyamines, polyesters, polyanhydrides, polyethers, polyurethanes, polymethacrylates, polyacrylates, polycyanoacrylates or combinations thereof.

In some embodiments, the nanoparticle may be a nanoparticle-nucleic acid hybrid structure having a high density nucleic acid layer. As a non-limiting example, the nanoparticle-nucleic acid hybrid structure may be made by the methods described in U.S. Patent Publication No. US20130171646, the contents of which are herein incorporated by reference in their entirety. The nanoparticle may comprise a nucleic acid such as, but not limited to, polynucleotides described herein and/or known in the art.

At least one of the nanoparticles of the present disclosure may be embedded in the core a nanostructure or coated with a low density porous 3-D structure or coating which is capable of carrying or associating with at least one payload within or on the surface of the nanostructure. Non-limiting examples of the nanostructures comprising at least one nanoparticle are described in International Patent Publication No. WO2013123523, the contents of which are herein incorporated by reference in their entirety.

In some embodiments the RNA (*e.g.*, mRNA) vaccine may be associated with a cationic or polycationic compounds, including protamine, nucleoline, spermine or spermidine, or other cationic peptides or proteins, such as poly-L-lysine (PLL), polyarginine, basic polypeptides, cell penetrating peptides (CPPs), including HIV-binding peptides, HIV-1 Tat (HIV), Tat-derived peptides, Penetratin, VP²² derived or analog peptides, Pestivirus Erns, HSV, VP²² (Herpes simplex), MAP, KALA or protein transduction domains (PTDs),

PpT620, prolin-rich peptides, arginine-rich peptides, lysine-rich peptides, MPG-peptide(s), Pep-1, L-oligomers, Calcitonin peptide(s), Antennapedia-derived peptides (particularly from *Drosophila antennapedia*), pAntp, pIsl, FGF, Lactoferrin, Transportan, Buforin-2, Bac715-24, SynB, SynB, pVEC, hCT-derived peptides, SAP, histones, cationic polysaccharides, for example chitosan, polybrene, cationic polymers, *e.g.* polyethyleneimine (PEI), cationic lipids, *e.g.* DOTMA: [1-(2,3-dioleoyloxy)propyl]-N,N,N-trimethylammonium chloride, DMRIE, di-C14-amidine, DOTIM, SAINT, DC-Chol, BGTC, CTAP, DOPC, DODAP, DOPE: Dioleoyl phosphatidylethanol-amine, DOSPA, DODAB, DOIC, DMEPC, DOGS: Dioctadecylamidoglycylspermin, DIMRI: Dimyristooxypropyl dimethyl hydroxyethyl ammonium bromide, DOTAP: dioleoyloxy-3-(trimethylammonio)propane, DC-6-14: O,O-ditetradecanoyl-N-.alpha.-trimethylammonioacetyl)diethanolamine chloride, CLIP 1: rac-[(2,3-dioctadecyloxypropyl)(2-hydroxyethyl)]-dimethylammonium chloride, CLIP6: rac-[2(2,3-dihexadecyloxypropyloxymethyloxy)ethyl]-trimethylammonium, CLIP9: rac-[2(2,3-dihexadecyloxypropyloxysuccinyloxy)ethyl]-trimethylammonium, oligofectamine, or cationic or polycationic polymers, *e.g.* modified polyaminoacids, such as beta-aminoacid-polymers or reversed polyamides, *etc.*, modified polyethylenes, such as PVP (poly(N-ethyl-4-vinylpyridinium bromide)), *etc.*, modified acrylates, such as pDMAEMA (poly(dimethylaminoethyl methylacrylate)), *etc.*, modified amidoamines such as pAMAM (poly(amidoamine)), *etc.*, modified polybetaminoester (PBAE), such as diamine end modified 1,4 butanediol diacrylate-co-5-amino-1-pentanol polymers, *etc.*, dendrimers, such as polypropylamine dendrimers or pAMAM based dendrimers, *etc.*, polyimine(s), such as PEI: poly(ethyleneimine), poly(propyleneimine), *etc.*, polyallylamine, sugar backbone based polymers, such as cyclodextrin based polymers, dextran based polymers, chitosan, *etc.*, silan backbone based polymers, such as PMOXA-PDMS copolymers, *etc.*, blockpolymers consisting of a combination of one or more cationic blocks (*e.g.* selected from a cationic polymer as mentioned above) and of one or more hydrophilic or hydrophobic blocks (*e.g.* polyethyleneglycole), *etc.*

In other embodiments the RNA (*e.g.*, mRNA) vaccine is not associated with a cationic or polycationic compounds.

Modes of Vaccine Administration

Influenza RNA (*e.g.* mRNA) vaccines may be administered by any route which results in a therapeutically effective outcome. These include, but are not limited, to intradermal, intramuscular, intranasal and/or subcutaneous administration. The present disclosure provides methods comprising administering RNA (*e.g.*, mRNA) vaccines to a

subject in need thereof. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the disease, the particular composition, its mode of administration, its mode of activity, and the like. Influenza RNA (*e.g.*, mRNA) vaccines compositions are typically formulated in dosage unit form for ease of administration and uniformity of dosage. It will be understood, however, that the total daily usage of RNA (*e.g.*, mRNA) vaccine compositions may be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective, prophylactically effective, or appropriate imaging dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well known in the medical arts.

In some embodiments, influenza disease RNA (*e.g.* mRNA) vaccines compositions may be administered at dosage levels sufficient to deliver 0.0001 mg/kg to 100 mg/kg, 0.001 mg/kg to 0.05 mg/kg, 0.005 mg/kg to 0.05 mg/kg, 0.001 mg/kg to 0.005 mg/kg, 0.05 mg/kg to 0.5 mg/kg, 0.01 mg/kg to 50 mg/kg, 0.1 mg/kg to 40 mg/kg, 0.5 mg/kg to 30 mg/kg, 0.01 mg/kg to 10 mg/kg, 0.1 mg/kg to 10 mg/kg, or 1 mg/kg to 25 mg/kg, of subject body weight per day, one or more times a day, per week, per month, etc. to obtain the desired therapeutic, diagnostic, prophylactic, or imaging effect (*see, e.g.*, the range of unit doses described in International Publication No WO2013078199, the contents of which are herein incorporated by reference in their entirety). The desired dosage may be delivered three times a day, two times a day, once a day, every other day, every third day, every week, every two weeks, every three weeks, every four weeks, every 2 months, every three months, every 6 months, *etc.* In some embodiments, the desired dosage may be delivered using multiple administrations (*e.g.*, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or more administrations). When multiple administrations are employed, split dosing regimens such as those described herein may be used. In exemplary embodiments, influenza RNA (*e.g.*, mRNA) vaccines compositions may be administered at dosage levels sufficient to deliver 0.0005 mg/kg to 0.01 mg/kg, *e.g.*, about 0.0005 mg/kg to about 0.0075 mg/kg, *e.g.*, about 0.0005 mg/kg, about 0.001 mg/kg, about 0.002 mg/kg, about 0.003 mg/kg, about 0.004 mg/kg or about 0.005 mg/kg.

In some embodiments, influenza disease RNA (*e.g.*, mRNA) vaccine compositions may be administered once or twice (or more) at dosage levels sufficient to deliver 0.025 mg/kg to 0.250 mg/kg, 0.025 mg/kg to 0.500 mg/kg, 0.025 mg/kg to 0.750 mg/kg, or 0.025 mg/kg to 1.0 mg/kg.

5 In some embodiments, influenza disease RNA (*e.g.*, mRNA) vaccine compositions may be administered twice (*e.g.*, Day 0 and Day 7, Day 0 and Day 14, Day 0 and Day 21, Day 0 and Day 28, Day 0 and Day 60, Day 0 and Day 90, Day 0 and Day 120, Day 0 and Day 150, Day 0 and Day 180, Day 0 and 3 months later, Day 0 and 6 months later, Day 0 and 9 months later, Day 0 and 12 months later, Day 0 and 18 months later, Day 0 and 2 years later, Day 0 and 5 years later, or Day 0 and 10 years later) at a total dose of or at dosage levels sufficient to deliver a total dose of 0.0100 mg, 0.025 mg, 0.050 mg, 0.075 mg, 0.100 mg, 0.125 mg, 0.150 mg, 0.175 mg, 0.200 mg, 0.225 mg, 0.250 mg, 0.275 mg, 0.300 mg, 0.325 mg, 0.350 mg, 0.375 mg, 0.400 mg, 0.425 mg, 0.450 mg, 0.475 mg, 0.500 mg, 0.525 mg, 0.550 mg, 0.575 mg, 0.600 mg, 0.625 mg, 0.650 mg, 0.675 mg, 0.700 mg, 0.725 mg, 10 0.750 mg, 0.775 mg, 0.800 mg, 0.825 mg, 0.850 mg, 0.875 mg, 0.900 mg, 0.925 mg, 0.950 mg, 0.975 mg, or 1.0 mg. Higher and lower dosages and frequency of administration are encompassed by the present disclosure. For example, an influenza RNA (*e.g.*, mRNA) vaccine composition may be administered three or four times.

In some embodiments, influenza RNA (*e.g.*, mRNA) vaccine compositions may be administered twice (*e.g.*, Day 0 and Day 7, Day 0 and Day 14, Day 0 and Day 21, Day 0 and Day 28, Day 0 and Day 60, Day 0 and Day 90, Day 0 and Day 120, Day 0 and Day 150, Day 0 and Day 180, Day 0 and 3 months later, Day 0 and 6 months later, Day 0 and 9 months later, Day 0 and 12 months later, Day 0 and 18 months later, Day 0 and 2 years later, Day 0 and 5 years later, or Day 0 and 10 years later) at a total dose of or at dosage levels sufficient 20 to deliver a total dose of 0.010 mg, 0.025 mg, 0.100 mg or 0.400 mg.

In some embodiments, the influenza RNA (*e.g.*, mRNA) vaccine for use in a method of vaccinating a subject is administered to the subject as a single dosage of between 10 µg/kg and 400 µg/kg of the nucleic acid vaccine (in an effective amount to vaccinate the subject). In some embodiments the RNA (*e.g.*, mRNA) vaccine for use in a method of vaccinating a subject is administered to the subject as a single dosage of between 10 µg and 400 µg of the nucleic acid vaccine (in an effective amount to vaccinate the subject). In some embodiments, an influenza RNA (*e.g.*, mRNA) vaccine for use in a method of vaccinating a subject is administered to the subject as a single dosage of 25-1000 µg. In some embodiments, an influenza RNA (*e.g.*, mRNA) vaccine is administered to the subject as a single dosage of 25, 30 50, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950

or 1000 μ g. For example, an influenza RNA (*e.g.*, mRNA) vaccine may be administered to a subject as a single dose of 25-100, 25-500, 50-100, 50-500, 50-1000, 100-500, 100-1000, 250-500, 250-1000, or 500-1000 μ g. In some embodiments, an influenza RNA (*e.g.*, mRNA) vaccine for use in a method of vaccinating a subject is administered to the subject as two
5 dosages, the combination of which equals 25-1000 μ g of the influenza RNA (*e.g.*, mRNA) vaccine.

An influenza RNA (*e.g.* mRNA) vaccine pharmaceutical composition described herein can be formulated into a dosage form described herein, such as an intranasal, intratracheal, or injectable (*e.g.*, intravenous, intraocular, intravitreal, intramuscular,
10 intradermal, intracardiac, intraperitoneal, intranasal and subcutaneous).

Influenza Virus RNA (e.g., mRNA) vaccine formulations and methods of use

Some aspects of the present disclosure provide formulations of the influenza RNA (*e.g.*, mRNA) vaccine, wherein the RNA (*e.g.*, mRNA) vaccine is formulated in an effective
15 amount to produce an antigen specific immune response in a subject (*e.g.*, production of antibodies specific to an influenza antigenic polypeptide). “An effective amount” is a dose of an RNA (*e.g.*, mRNA) vaccine effective to produce an antigen-specific immune response. Also provided herein are methods of inducing an antigen-specific immune response in a subject.

20 In some embodiments, the antigen-specific immune response is characterized by measuring an anti- influenza antigenic polypeptide antibody titer produced in a subject administered an influenza RNA (*e.g.*, mRNA) vaccine as provided herein. An antibody titer is a measurement of the amount of antibodies within a subject, for example, antibodies that are specific to a particular antigen (*e.g.*, an influenza antigenic polypeptide) or epitope of an
25 antigen. Antibody titer is typically expressed as the inverse of the greatest dilution that provides a positive result. Enzyme-linked immunosorbent assay (ELISA) is a common assay for determining antibody titers, for example.

In some embodiments, an antibody titer is used to assess whether a subject has had an infection or to determine whether immunizations are required. In some embodiments, an
30 antibody titer is used to determine the strength of an autoimmune response, to determine whether a booster immunization is needed, to determine whether a previous vaccine was effective, and to identify any recent or prior infections. In accordance with the present disclosure, an antibody titer may be used to determine the strength of an immune response induced in a subject by the influenza RNA (*e.g.*, mRNA) vaccine.

In some embodiments, an anti-influenza antigenic polypeptide antibody titer produced in a subject is increased by at least 1 log relative to a control. For example, anti-antigenic polypeptide antibody titer produced in a subject may be increased by at least 1.5, at least 2, at least 2.5, or at least 3 log relative to a control. In some embodiments, the anti-antigenic polypeptide antibody titer produced in the subject is increased by 1, 1.5, 2, 2.5 or 3 log relative to a control. In some embodiments, the anti-antigenic polypeptide antibody titer produced in the subject is increased by 1-3 log relative to a control. For example, the anti-antigenic polypeptide antibody titer produced in a subject may be increased by 1-1.5, 1-2, 1-2.5, 1-3, 1.5-2, 1.5-2.5, 1.5-3, 2-2.5, 2-3, or 2.5-3 log relative to a control.

In some embodiments, the anti-influenza antigenic polypeptide antibody titer produced in a subject is increased at least 2 times relative to a control. For example, the anti-antigenic polypeptide antibody titer produced in a subject may be increased at least 3 times, at least 4 times, at least 5 times, at least 6 times, at least 7 times, at least 8 times, at least 9 times, or at least 10 times relative to a control. In some embodiments, the anti-antigenic polypeptide antibody titer produced in the subject is increased 2, 3, 4, 5, 6, 7, 8, 9, or 10 times relative to a control. In some embodiments, the anti-antigenic polypeptide antibody titer produced in a subject is increased 2-10 times relative to a control. For example, the anti-antigenic polypeptide antibody titer produced in a subject may be increased 2-10, 2-9, 2-8, 2-7, 2-6, 2-5, 2-4, 2-3, 3-10, 3-9, 3-8, 3-7, 3-6, 3-5, 3-4, 4-10, 4-9, 4-8, 4-7, 4-6, 4-5, 5-10, 5-9, 5-8, 5-7, 5-6, 6-10, 6-9, 6-8, 6-7, 7-10, 7-9, 7-8, 8-10, 8-9, or 9-10 times relative to a control.

A control, in some embodiments, is the anti-influenza antigenic polypeptide antibody titer produced in a subject who has not been administered an influenza RNA (*e.g.*, mRNA) vaccine of the present disclosure. In some embodiments, a control is an anti-influenza antigenic polypeptide antibody titer produced in a subject who has been administered a live attenuated influenza vaccine. An attenuated vaccine is a vaccine produced by reducing the virulence of a viable (live). An attenuated virus is altered in a manner that renders it harmless or less virulent relative to live, unmodified virus. In some embodiments, a control is an anti-influenza antigenic polypeptide antibody titer produced in a subject administered inactivated influenza vaccine. In some embodiments, a control is an anti-influenza antigenic polypeptide antibody titer produced in a subject administered a recombinant or purified influenza protein vaccine. Recombinant protein vaccines typically include protein antigens that either have been produced in a heterologous expression system (*e.g.*, bacteria or yeast) or purified from large amounts of the pathogenic organism. In some embodiments, a control is an anti-influenza antigenic polypeptide antibody titer produced in a subject who has been administered an influenza virus-like particle (VLP) vaccine.

In some embodiments, an effective amount of an influenza RNA (*e.g.*, mRNA) vaccine is a dose that is reduced compared to the standard of care dose of a recombinant influenza protein vaccine. A “standard of care,” as provided herein, refers to a medical or psychological treatment guideline and can be general or specific. “Standard of care” specifies appropriate treatment based on scientific evidence and collaboration between medical professionals involved in the treatment of a given condition. It is the diagnostic and treatment process that a physician/clinician should follow for a certain type of patient, illness or clinical circumstance. A “standard of care dose,” as provided herein, refers to the dose of a recombinant or purified influenza protein vaccine, or a live attenuated or inactivated influenza vaccine, that a physician/clinician or other medical professional would administer to a subject to treat or prevent influenza, or a related condition, while following the standard of care guideline for treating or preventing influenza, or a related condition.

In some embodiments, the anti-influenza antigenic polypeptide antibody titer produced in a subject administered an effective amount of an influenza RNA (*e.g.*, mRNA) vaccine is equivalent to an anti-influenza antigenic polypeptide antibody titer produced in a control subject administered a standard of care dose of a recombinant or purified influenza protein vaccine or a live attenuated or inactivated influenza vaccine.

In some embodiments, an effective amount of an influenza RNA (*e.g.*, mRNA) vaccine is a dose equivalent to an at least 2-fold reduction in a standard of care dose of a recombinant or purified influenza protein vaccine. For example, an effective amount of an influenza RNA (*e.g.*, mRNA) vaccine may be a dose equivalent to an at least 3-fold, at least 4-fold, at least 5-fold, at least 6-fold, at least 7-fold, at least 8-fold, at least 9-fold, or at least 10-fold reduction in a standard of care dose of a recombinant or purified influenza protein vaccine. In some embodiments, an effective amount of an influenza RNA (*e.g.*, mRNA) vaccine is a dose equivalent to an at least at least 100-fold, at least 500-fold, or at least 1000-fold reduction in a standard of care dose of a recombinant or purified influenza protein vaccine. In some embodiments, an effective amount of an influenza RNA (*e.g.*, mRNA) vaccine is a dose equivalent to a 2-, 3-, 4-, 5-, 6-, 7-, 8-, 9-, 10-, 20-, 50-, 100-, 250-, 500-, or 1000-fold reduction in a standard of care dose of a recombinant or purified influenza protein vaccine. In some embodiments, the anti-influenza antigenic polypeptide antibody titer produced in a subject administered an effective amount of an influenza RNA (*e.g.*, mRNA) vaccine is equivalent to an anti-influenza antigenic polypeptide antibody titer produced in a control subject administered the standard of care dose of a recombinant or protein influenza protein vaccine or a live attenuated or inactivated influenza vaccine. In some embodiments, an effective amount of an influenza RNA (*e.g.*, mRNA) vaccine is a dose equivalent to a 2-

fold to 1000-fold (*e.g.*, 2-fold to 100-fold, 10-fold to 1000-fold) reduction in the standard of care dose of a recombinant or purified influenza protein vaccine, wherein the anti-influenza antigenic polypeptide antibody titer produced in the subject is equivalent to an anti-influenza antigenic polypeptide antibody titer produced in a control subject administered the standard of care dose of a recombinant or purified influenza protein vaccine or a live attenuated or inactivated influenza vaccine.

In some embodiments, the effective amount of an influenza RNA (*e.g.*, mRNA) vaccine is a dose equivalent to a 2 to 1000-, 2 to 900-, 2 to 800-, 2 to 700-, 2 to 600-, 2 to 500-, 2 to 400-, 2 to 300-, 2 to 200-, 2 to 100-, 2 to 90-, 2 to 80-, 2 to 70-, 2 to 60-, 2 to 50-, 2 to 40-, 2 to 30-, 2 to 20-, 2 to 10-, 2 to 9-, 2 to 8-, 2 to 7-, 2 to 6-, 2 to 5-, 2 to 4-, 2 to 3-, 3 to 1000-, 3 to 900-, 3 to 800-, 3 to 700-, 3 to 600-, 3 to 500-, 3 to 400-, 3 to 300-, 3 to 200-, 3 to 100-, 3 to 90-, 3 to 80-, 3 to 70-, 3 to 60-, 3 to 50-, 3 to 40-, 3 to 30-, 3 to 20-, 3 to 10-, 3 to 9-, 3 to 8-, 3 to 7-, 3 to 6-, 3 to 5-, 3 to 4-, 4 to 1000-, 4 to 900-, 4 to 800-, 4 to 700-, 4 to 600-, 4 to 500-, 4 to 400-, 4 to 300-, 4 to 200-, 4 to 100-, 4 to 90-, 4 to 80-, 4 to 70-, 4 to 60-, 4 to 50-, 4 to 40-, 4 to 30-, 4 to 20-, 4 to 10-, 4 to 9-, 4 to 8-, 4 to 7-, 4 to 6-, 4 to 5-, 4 to 4-, 5 to 1000-, 5 to 900-, 5 to 800-, 5 to 700-, 5 to 600-, 5 to 500-, 5 to 400-, 5 to 300-, 5 to 200-, 5 to 100-, 5 to 90-, 5 to 80-, 5 to 70-, 5 to 60-, 5 to 50-, 5 to 40-, 5 to 30-, 5 to 20-, 5 to 10-, 5 to 9-, 5 to 8-, 5 to 7-, 5 to 6-, 6 to 1000-, 6 to 900-, 6 to 800-, 6 to 700-, 6 to 600-, 6 to 500-, 6 to 400-, 6 to 300-, 6 to 200-, 6 to 100-, 6 to 90-, 6 to 80-, 6 to 70-, 6 to 60-, 6 to 50-, 6 to 40-, 6 to 30-, 6 to 20-, 6 to 10-, 6 to 9-, 6 to 8-, 6 to 7-, 7 to 1000-, 7 to 900-, 7 to 800-, 7 to 700-, 7 to 600-, 7 to 500-, 7 to 400-, 7 to 300-, 7 to 200-, 7 to 100-, 7 to 90-, 7 to 80-, 7 to 70-, 7 to 60-, 7 to 50-, 7 to 40-, 7 to 30-, 7 to 20-, 7 to 10-, 7 to 9-, 7 to 8-, 8 to 1000-, 8 to 900-, 8 to 800-, 8 to 700-, 8 to 600-, 8 to 500-, 8 to 400-, 8 to 300-, 8 to 200-, 8 to 100-, 8 to 90-, 8 to 80-, 8 to 70-, 8 to 60-, 8 to 50-, 8 to 40-, 8 to 30-, 8 to 20-, 8 to 10-, 8 to 9-, 9 to 1000-, 9 to 900-, 9 to 800-, 9 to 700-, 9 to 600-, 9 to 500-, 9 to 400-, 9 to 300-, 9 to 200-, 9 to 100-, 9 to 90-, 9 to 80-, 9 to 70-, 9 to 60-, 9 to 50-, 9 to 40-, 9 to 30-, 9 to 20-, 9 to 10-, 10 to 1000-, 10 to 900-, 10 to 800-, 10 to 700-, 10 to 600-, 10 to 500-, 10 to 400-, 10 to 300-, 10 to 200-, 10 to 100-, 10 to 90-, 10 to 80-, 10 to 70-, 10 to 60-, 10 to 50-, 10 to 40-, 10 to 30-, 10 to 20-, 20 to 1000-, 20 to 900-, 20 to 800-, 20 to 700-, 20 to 600-, 20 to 500-, 20 to 400-, 20 to 300-, 20 to 200-, 20 to 100-, 20 to 90-, 20 to 80-, 20 to 70-, 20 to 60-, 20 to 50-, 20 to 40-, 20 to 30-, 30 to 1000-, 30 to 900-, 30 to 800-, 30 to 700-, 30 to 600-, 30 to 500-, 30 to 400-, 30 to 300-, 30 to 200-, 30 to 100-, 30 to 90-, 30 to 80-, 30 to 70-, 30 to 60-, 30 to 50-, 30 to 40-, 40 to 1000-, 40 to 900-, 40 to 800-, 40 to 700-, 40 to 600-, 40 to 500-, 40 to 400-, 40 to 300-, 40 to 200-, 40 to 100-, 40 to 90-, 40 to 80-, 40 to 70-, 40 to 60-, 40 to 50-, 50 to 1000-, 50 to 900-, 50 to 800-, 50 to 700-, 50 to 600-, 50 to 500-, 50 to 400-, 50 to 300-, 50 to 200-, 50 to 100-,

50 to 90-, 50 to 80-, 50 to 70-, 50 to 60-, 60 to 1000-, 60 to 900-, 60 to 800-, 60 to 700-, 60 to 600-, 60 to 500-, 60 to 400-, 60 to 300-, 60 to 200-, 60 to 100-, 60 to 90-, 60 to 80-, 60 to 70-, 70 to 1000-, 70 to 900-, 70 to 800-, 70 to 700-, 70 to 600-, 70 to 500-, 70 to 400-, 70 to 300-, 70 to 200-, 70 to 100-, 70 to 90-, 70 to 80-, 80 to 1000-, 80 to 900-, 80 to 800-, 80 to 700-, 80 to 600-, 80 to 500-, 80 to 400-, 80 to 300-, 80 to 200-, 80 to 100-, 80 to 90-, 90 to 1000-, 90 to 900-, 90 to 800-, 90 to 700-, 90 to 600-, 90 to 500-, 90 to 400-, 90 to 300-, 90 to 200-, 90 to 100-, 100 to 1000-, 100 to 900-, 100 to 800-, 100 to 700-, 100 to 600-, 100 to 500-, 100 to 400-, 100 to 300-, 100 to 200-, 200 to 1000-, 200 to 900-, 200 to 800-, 200 to 700-, 200 to 600-, 200 to 500-, 200 to 400-, 200 to 300-, 300 to 1000-, 300 to 900-, 300 to 800-, 300 to 700-, 300 to 600-, 300 to 500-, 300 to 400-, 400 to 1000-, 400 to 900-, 400 to 800-, 400 to 700-, 400 to 600-, 400 to 500-, 500 to 1000-, 500 to 900-, 500 to 800-, 500 to 700-, 500 to 600-, 600 to 1000-, 600 to 900-, 600 to 800-, 600 to 700-, 700 to 1000-, 700 to 900-, 700 to 800-, 800 to 1000-, 800 to 900-, or 900 to 1000-fold reduction in the standard of care dose of a recombinant influenza protein vaccine. In some embodiments, the anti-antigenic polypeptide antibody titer produced in the subject is equivalent to an anti-antigenic polypeptide antibody titer produced in a control subject administered the standard of care dose of a recombinant or purified influenza protein vaccine or a live attenuated or inactivated influenza vaccine. In some embodiments, the effective amount is a dose equivalent to (or equivalent to an at least) 2-, 3 -,4 -,5 -,6-, 7-, 8-, 9-, 10-, 20-, 30-, 40-, 50-, 60-, 70-, 80-, 90-, 100-, 110-, 120-, 130-, 140-, 150-, 160-, 170-, 1280-, 190-, 200-, 210-, 220-, 230-, 240-, 250-, 260-, 270-, 280-, 290-, 300-, 310-, 320-, 330-, 340-, 350-, 360-, 370-, 380-, 390-, 400-, 410-, 420-, 430-, 440-, 450-, 4360-, 470-, 480-, 490-, 500-, 510-, 520-, 530-, 540-, 550-, 560-, 5760-, 580-, 590-, 600-, 610-, 620-, 630-, 640-, 650-, 660-, 670-, 680-, 690-, 700-, 710-, 720-, 730-, 740-, 750-, 760-, 770-, 780-, 790-, 800-, 810-, 820--, 830-, 840-, 850-, 860-, 870-, 880-, 890-, 900-, 910-, 920-, 930-, 940-, 950-, 960-, 970-, 980-, 990-, or 1000-fold reduction in the standard of care dose of a recombinant influenza protein vaccine. In some embodiments, an anti- antigenic polypeptide antibody titer produced in the subject is equivalent to an anti-antigenic polypeptide antibody titer produced in a control subject administered the standard of care dose of a recombinant or purified influenza protein vaccine or a live attenuated or inactivated an influenza vaccine.

In some embodiments, the effective amount of an influenza RNA (*e.g.*, mRNA) vaccine is a total dose of 50-1000 µg. In some embodiments, the effective amount of an influenza RNA (*e.g.*, mRNA) vaccine is a total dose of 50-1000, 50- 900, 50-800, 50-700, 50-600, 50-500, 50-400, 50-300, 50-200, 50-100, 50-90, 50-80, 50-70, 50-60, 60-1000, 60- 900, 60-800, 60-700, 60-600, 60-500, 60-400, 60-300, 60-200, 60-100, 60-90, 60-80, 60-70, 70-

1000, 70- 900, 70-800, 70-700, 70-600, 70-500, 70-400, 70-300, 70-200, 70-100, 70-90, 70-80, 80-1000, 80- 900, 80-800, 80-700, 80-600, 80-500, 80-400, 80-300, 80-200, 80-100, 80-90, 90-1000, 90- 900, 90-800, 90-700, 90-600, 90-500, 90-400, 90-300, 90-200, 90-100, 100-1000, 100- 900, 100-800, 100-700, 100-600, 100-500, 100-400, 100-300, 100-200, 200-1000, 200-900, 200-800, 200-700, 200-600, 200-500, 200-400, 200-300, 300-1000, 300-900, 300-800, 300-700, 300-600, 300-500, 300-400, 400-1000, 400-900, 400-800, 400-700, 400-600, 400-500, 500-1000, 500-900, 500-800, 500-700, 500-600, 600-1000, 600-900, 600-800, 600-700, 700-1000, 700-900, 700-800, 800-1000, 800-900, or 900-1000 µg. In some embodiments, the effective amount of an influenza RNA (*e.g.*, mRNA) vaccine is a total dose of 50, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950 or 1000 µg. In some embodiments, the effective amount is a dose of 25-500 µg administered to the subject a total of two times. In some embodiments, the effective amount of an influenza RNA (*e.g.*, mRNA) vaccine is a dose of 25-500, 25-400, 25-300, 25-200, 25-100, 25-50, 50-500, 50-400, 50-300, 50-200, 50-100, 100-500, 100-400, 100-300, 100-200, 150-500, 150-400, 150-300, 150-200, 200-500, 200-400, 200-300, 250-500, 250-400, 250-300, 300-500, 300-400, 350-500, 350-400, 400-500 or 450-500 µg administered to the subject a total of two times. In some embodiments, the effective amount of an influenza RNA (*e.g.*, mRNA) vaccine is a total dose of 25, 50, 100, 150, 200, 250, 300, 350, 400, 450, or 500 µg administered to the subject a total of two times.

Additional Embodiments

1. An influenza virus vaccine or composition or immunogenic composition, comprising: at least one messenger ribonucleic acid (mRNA) polynucleotide having a 5' terminal cap, an open reading frame encoding at least one influenza antigenic polypeptide, and a 3' polyA tail.
2. The vaccine of paragraph 1, wherein the at least one mRNA polynucleotide is encoded by a sequence identified by SEQ ID NO: 447-457, 459, 461.
3. The vaccine of paragraph 1, wherein the at least one mRNA polynucleotide comprises a sequence identified by SEQ ID NO: 491-503.
4. The vaccine of paragraph 1, wherein the at least one antigenic polypeptide comprises a sequence identified by SEQ ID NO: 1-444, 458, 460, 462-479.
5. The vaccine of paragraph 1, wherein the at least one mRNA polynucleotide is encoded by a sequence identified by SEQ ID NO: 457.

6. The vaccine of paragraph 1, wherein the at least one mRNA polynucleotide comprises a sequence identified by SEQ ID NO: 501.
7. The vaccine of paragraph 1, wherein the at least one antigenic polypeptide comprises a sequence identified by SEQ ID NO: 458.
- 5 8. The vaccine of paragraph 1, wherein the at least one mRNA polynucleotide is encoded by a sequence identified by SEQ ID NO: 459.
9. The vaccine of paragraph 1, wherein the at least one mRNA polynucleotide comprises a sequence identified by SEQ ID NO: 502.
- 10 10. The vaccine of paragraph 1, wherein the at least one antigenic polypeptide comprises a sequence identified by SEQ ID NO: 460.
11. The vaccine of paragraph 1, wherein the at least one mRNA polynucleotide is encoded by a sequence identified by SEQ ID NO: 461.
12. The vaccine of paragraph 1, wherein the at least one mRNA polynucleotide comprises a sequence identified by SEQ ID NO: 503.
- 15 13. The vaccine of paragraph 1, wherein the at least one antigenic polypeptide comprises a sequence identified by SEQ ID NO: 462.
14. The vaccine of any one of paragraphs 1-13, wherein the 5' terminal cap is or comprises 7mG(5')ppp(5')NlmpNp.
15. The vaccine of any one of paragraphs 1-14, wherein 100% of the uracil in the open
20 reading frame is modified to include N1-methyl pseudouridine at the 5-position of the uracil.
16. The vaccine of any one of paragraphs 1-15, wherein the vaccine is formulated in a lipid nanoparticle comprising: DLin-MC3-DMA; cholesterol; 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC); and polyethylene glycol (PEG)2000-DMG.
17. The vaccine of paragraph 16, wherein the lipid nanoparticle further comprises
25 trisodium citrate buffer, sucrose and water.
18. A influenza virus vaccine or composition or immunogenic composition, comprising:
at least one messenger ribonucleic acid (mRNA) polynucleotide having a 5' terminal cap 7mG(5')ppp(5')NlmpNp, a sequence identified by SEQ ID NO: 501 and a 3' polyA tail,
wherein the uracil nucleotides of the sequence identified by SEQ ID NO: 501 are modified to
30 include N1-methyl pseudouridine at the 5-position of the uracil nucleotide.
19. A influenza virus vaccine, comprising:
at least one messenger ribonucleic acid (mRNA) polynucleotide having a 5' terminal cap 7mG(5')ppp(5')NlmpNp, a sequence identified by SEQ ID NO: 502 and a 3' polyA tail,
wherein the uracil nucleotides of the sequence identified by SEQ ID NO: 502 are modified to
35 include N1-methyl pseudouridine at the 5-position of the uracil nucleotide.

20. A influenza virus vaccine or composition or immunogenic composition, comprising:
 at least one messenger ribonucleic acid (mRNA) polynucleotide having a 5' terminal
 cap 7mG(5')ppp(5')NlmpNp, a sequence identified by SEQ ID NO: 503 and a 3' polyA tail,
 wherein the uracil nucleotides of the sequence identified by SEQ ID NO: 503 are modified to
 5 include N1-methyl pseudouridine at the 5-position of the uracil nucleotide.

21. The vaccine of any one of paragraphs 18-20 formulated in a lipid nanoparticle
 comprising DLin-MC3-DMA, cholesterol, 1,2-Distearoyl-sn-glycero-3-phosphocholine
 (DSPC), and polyethylene glycol (PEG)2000-DMG.

This invention is not limited in its application to the details of construction and the
 10 arrangement of components set forth in the following description or illustrated in the
 drawings. The invention is capable of other embodiments and of being practiced or of being
 carried out in various ways. Also, the phraseology and terminology used herein is for the
 purpose of description and should not be regarded as limiting. The use of "including,"
 "comprising," or "having," "containing," "involving," and variations thereof herein, is meant
 15 to encompass the items listed thereafter and equivalents thereof as well as additional items.

EXAMPLES

Example 1: Manufacture of Polynucleotides

20 According to the present disclosure, the manufacture of polynucleotides and/or parts
 or regions thereof may be accomplished utilizing the methods taught in International
 Publication WO2014/152027, entitled "Manufacturing Methods for Production of RNA
 Transcripts," the contents of which is incorporated herein by reference in its entirety.

Purification methods may include those taught in International Publication
 25 WO2014/152030 and International Publication WO2014/152031, each of which is
 incorporated herein by reference in its entirety.

Detection and characterization methods of the polynucleotides may be performed as
 taught in International Publication WO2014/144039, which is incorporated herein by
 reference in its entirety.

30 Characterization of the polynucleotides of the disclosure may be accomplished using
 polynucleotide mapping, reverse transcriptase sequencing, charge distribution analysis,
 detection of RNA impurities, or any combination of two or more of the foregoing.
 "Characterizing" comprises determining the RNA transcript sequence, determining the purity
 of the RNA transcript, or determining the charge heterogeneity of the RNA transcript, for
 35 example. Such methods are taught in, for example, International Publication

WO2014/144711 and International Publication WO2014/144767, the content of each of which is incorporated herein by reference in its entirety.

Example 2: Chimeric polynucleotide synthesis

5 According to the present disclosure, two regions or parts of a chimeric polynucleotide may be joined or ligated using triphosphate chemistry. A first region or part of 100 nucleotides or less is chemically synthesized with a 5' monophosphate and terminal 3' desOH or blocked OH, for example. If the region is longer than 80 nucleotides, it may be synthesized as two strands for ligation.

10 If the first region or part is synthesized as a non-positionally modified region or part using *in vitro* transcription (IVT), conversion the 5' monophosphate with subsequent capping of the 3' terminus may follow.

 Monophosphate protecting groups may be selected from any of those known in the art.

15 The second region or part of the chimeric polynucleotide may be synthesized using either chemical synthesis or IVT methods. IVT methods may include an RNA polymerase that can utilize a primer with a modified cap. Alternatively, a cap of up to 130 nucleotides may be chemically synthesized and coupled to the IVT region or part.

 For ligation methods, ligation with DNA T4 ligase, followed by treatment with DNase
20 should readily avoid concatenation.

 The entire chimeric polynucleotide need not be manufactured with a phosphate-sugar backbone. If one of the regions or parts encodes a polypeptide, then such region or part may comprise a phosphate-sugar backbone.

 Ligation is then performed using any known click chemistry, orthoclick chemistry,
25 solulink, or other bioconjugate chemistries known to those in the art.

Synthetic route

 The chimeric polynucleotide may be made using a series of starting segments. Such segments include:

 (a) a capped and protected 5' segment comprising a normal 3'OH (SEG. 1)
30 (b) a 5' triphosphate segment, which may include the coding region of a polypeptide and a normal 3'OH (SEG. 2)

 (c) a 5' monophosphate segment for the 3' end of the chimeric polynucleotide (*e.g.*, the tail) comprising cordycepin or no 3'OH (SEG. 3)

 After synthesis (chemical or IVT), segment 3 (SEG. 3) may be treated with
35 cordycepin and then with pyrophosphatase to create the 5' monophosphate.

Segment 2 (SEG. 2) may then be ligated to SEG. 3 using RNA ligase. The ligated polynucleotide is then purified and treated with pyrophosphatase to cleave the diphosphate. The treated SEG.2-SEG. 3 construct may then be purified and SEG. 1 is ligated to the 5' terminus. A further purification step of the chimeric polynucleotide may be performed.

5 Where the chimeric polynucleotide encodes a polypeptide, the ligated or joined segments may be represented as: 5'UTR (SEG. 1), open reading frame or ORF (SEG. 2) and 3'UTR+PolyA (SEG. 3).

The yields of each step may be as much as 90-95%.

10 **Example 3: PCR for cDNA Production**

PCR procedures for the preparation of cDNA may be performed using 2x KAPA HIFI™ HotStart ReadyMix by Kapa Biosystems (Woburn, MA). This system includes 2x KAPA ReadyMix 12.5 µl; Forward Primer (10 µM) 0.75 µl; Reverse Primer (10 µM) 0.75 µl; Template cDNA 100 ng; and dH₂O diluted to 25.0 µl. The reaction conditions may be at 95 °C for 5 min. The reaction may be performed for 25 cycles of 98 °C for 20 sec, then 58 °C for 15 sec, then 72 °C for 45 sec, then 72 °C for 5 min, then 4 °C to termination.

The reaction may be cleaned up using Invitrogen's PURELINK™ PCR Micro Kit (Carlsbad, CA) per manufacturer's instructions (up to 5 µg). Larger reactions may require a cleanup using a product with a larger capacity. Following the cleanup, the cDNA may be 20 quantified using the NANODROP™ and analyzed by agarose gel electrophoresis to confirm that the cDNA is the expected size. The cDNA may then be submitted for sequencing analysis before proceeding to the *in vitro* transcription reaction.

Example 4: In vitro Transcription (IVT)

25 The *in vitro* transcription reaction generates RNA polynucleotides. Such polynucleotides may comprise a region or part of the polynucleotides of the disclosure, including chemically modified RNA (*e.g.*, mRNA) polynucleotides. The chemically modified RNA polynucleotides can be uniformly modified polynucleotides. The *in vitro* transcription reaction utilizes a custom mix of nucleotide triphosphates (NTPs). The NTPs 30 may comprise chemically modified NTPs, or a mix of natural and chemically modified NTPs, or natural NTPs.

A typical *in vitro* transcription reaction includes the following:

- | | | |
|----|---------------------------------|--------|
| 1) | Template cDNA | 1.0 µg |
| 2) | 10x transcription buffer | 2.0 µl |
| 35 | (400 mM Tris-HCl pH 8.0, 190 mM | |

MgCl₂, 50 mM DTT, 10 mM Spermidine)

- 3) Custom NTPs (25 mM each) 0.2 µl
- 4) RNase Inhibitor 20 U
- 5) T7 RNA polymerase 3000 U
- 5 6) dH₂O up to 20.0 µl. and
- 7) Incubation at 37 °C for 3 hr-5 hrs.

The crude IVT mix may be stored at 4 °C overnight for cleanup the next day. 1 U of RNase-free DNase may then be used to digest the original template. After 15 minutes of incubation at 37 °C, the mRNA may be purified using Ambion's MEGACLEAR™ Kit
 10 (Austin, TX) following the manufacturer's instructions. This kit can purify up to 500 µg of RNA. Following the cleanup, the RNA polynucleotide may be quantified using the NANODROP™ and analyzed by agarose gel electrophoresis to confirm the RNA polynucleotide is the proper size and that no degradation of the RNA has occurred.

15 **Example 5: Enzymatic Capping**

Capping of a RNA polynucleotide is performed as follows where the mixture includes: IVT RNA 60 µg-180µg and dH₂O up to 72 µl. The mixture is incubated at 65 °C for 5 minutes to denature RNA, and then is transferred immediately to ice.

The protocol then involves the mixing of 10x Capping Buffer (0.5 M Tris-HCl (pH
 20 8.0), 60 mM KCl, 12.5 mM MgCl₂) (10.0 µl); 20 mM GTP (5.0 µl); 20 mM S-Adenosyl Methionine (2.5 µl); RNase Inhibitor (100 U); 2'-O-Methyltransferase (400U); Vaccinia capping enzyme (Guanylyl transferase) (40 U); dH₂O (Up to 28 µl); and incubation at 37 °C for 30 minutes for 60 µg RNA or up to 2 hours for 180 µg of RNA.

The RNA polynucleotide may then be purified using Ambion's MEGACLEAR™ Kit
 25 (Austin, TX) following the manufacturer's instructions. Following the cleanup, the RNA may be quantified using the NANODROP™ (ThermoFisher, Waltham, MA) and analyzed by agarose gel electrophoresis to confirm the RNA polynucleotide is the proper size and that no degradation of the RNA has occurred. The RNA polynucleotide product may also be sequenced by running a reverse-transcription-PCR to generate the cDNA for sequencing.

30

Example 6: PolyA Tailing Reaction

Without a poly-T in the cDNA, a poly-A tailing reaction must be performed before cleaning the final product. This is done by mixing capped IVT RNA (100 µl); RNase
 35 Inhibitor (20 U); 10x Tailing Buffer (0.5 M Tris-HCl (pH 8.0), 2.5 M NaCl, 100 mM MgCl₂) (12.0 µl); 20 mM ATP (6.0 µl); Poly-A Polymerase (20 U); dH₂O up to 123.5 µl and

incubation at 37 °C for 30 min. If the poly-A tail is already in the transcript, then the tailing reaction may be skipped and proceed directly to cleanup with Ambion's MEGACLEAR™ kit (Austin, TX) (up to 500 µg). Poly-A Polymerase may be a recombinant enzyme expressed in yeast.

5 It should be understood that the processivity or integrity of the polyA tailing reaction may not always result in an exact size polyA tail. Hence, polyA tails of approximately between 40-200 nucleotides, *e.g.*, about 40, 50, 60, 70, 80, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 150-165, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164 or 165 are within the scope of the present disclosure.

10

Example 7: Natural 5' Caps and 5' Cap Analogues

5'-capping of polynucleotides may be completed concomitantly during the *in vitro*-transcription reaction using the following chemical RNA cap analogs to generate the 5'-guanosine cap structure according to manufacturer protocols: 3'-O-Me-m7G(5')ppp(5') G [the
15 ARCA cap]; G(5')ppp(5')A; G(5')ppp(5')G; m7G(5')ppp(5')A; m7G(5')ppp(5')G (New England BioLabs, Ipswich, MA). 5'-capping of modified RNA may be completed post-transcriptionally using a Vaccinia Virus Capping Enzyme to generate the "Cap 0" structure: m7G(5')ppp(5')G (New England BioLabs, Ipswich, MA). Cap 1 structure may be generated using both Vaccinia Virus Capping Enzyme and a 2'-O methyl-transferase to generate:
20 m7G(5')ppp(5')G-2'-O-methyl. Cap 2 structure may be generated from the Cap 1 structure followed by the 2'-O-methylation of the 5'-antepenultimate nucleotide using a 2'-O methyl-transferase. Cap 3 structure may be generated from the Cap 2 structure followed by the 2'-O-methylation of the 5'-preantepenultimate nucleotide using a 2'-O methyl-transferase. Enzymes are preferably derived from a recombinant source.

25 When transfected into mammalian cells, the modified mRNAs have a stability of between 12-18 hours or more than 18 hours, *e.g.*, 24, 36, 48, 60, 72 or greater than 72 hours.

Example 8: Capping Assays

Protein Expression Assay

30 Polynucleotides (*e.g.*, mRNA) encoding a polypeptide, containing any of the caps taught herein, can be transfected into cells at equal concentrations. The amount of protein secreted into the culture medium can be assayed by ELISA at 6, 12, 24 and/or 36 hours post-transfection. Synthetic polynucleotides that secrete higher levels of protein into the medium correspond to a synthetic polynucleotide with a higher translationally-competent cap
35 structure.

Purity Analysis Synthesis

RNA (*e.g.*, mRNA) polynucleotides encoding a polypeptide, containing any of the caps taught herein can be compared for purity using denaturing Agarose-Urea gel electrophoresis or HPLC analysis. RNA polynucleotides with a single, consolidated band by electrophoresis correspond to the higher purity product compared to polynucleotides with multiple bands or streaking bands. Chemically modified RNA polynucleotides with a single HPLC peak also correspond to a higher purity product. The capping reaction with a higher efficiency provides a more pure polynucleotide population.

Cytokine Analysis

RNA (*e.g.*, mRNA) polynucleotides encoding a polypeptide, containing any of the caps taught herein can be transfected into cells at multiple concentrations. The amount of pro-inflammatory cytokines, such as TNF-alpha and IFN-beta, secreted into the culture medium can be assayed by ELISA at 6, 12, 24 and/or 36 hours post-transfection. RNA polynucleotides resulting in the secretion of higher levels of pro-inflammatory cytokines into the medium correspond to a polynucleotides containing an immune-activating cap structure.

Capping Reaction Efficiency

RNA (*e.g.*, mRNA) polynucleotides encoding a polypeptide, containing any of the caps taught herein can be analyzed for capping reaction efficiency by LC-MS after nuclease treatment. Nuclease treatment of capped polynucleotides yield a mixture of free nucleotides and the capped 5'-5-triphosphate cap structure detectable by LC-MS. The amount of capped product on the LC-MS spectra can be expressed as a percent of total polynucleotide from the reaction and correspond to capping reaction efficiency. The cap structure with a higher capping reaction efficiency has a higher amount of capped product by LC-MS.

Example 9: Agarose Gel Electrophoresis of Modified RNA or RT PCR Products

Individual RNA polynucleotides (200-400 ng in a 20 μ l volume) or reverse transcribed PCR products (200-400 ng) may be loaded into a well on a non-denaturing 1.2% Agarose E-Gel (Invitrogen, Carlsbad, CA) and run for 12-15 minutes, according to the manufacturer protocol.

Example 10: NANODROP™ Modified RNA Quantification and UV Spectral Data

Chemically modified RNA polynucleotides in TE buffer (1 μ l) are used for NANODROP™ UV absorbance readings to quantitate the yield of each polynucleotide from an chemical synthesis or *in vitro* transcription reaction.

5 **Example 11: Formulation of Modified mRNA Using Lipidoids**

RNA (*e.g.*, mRNA) polynucleotides may be formulated for *in vitro* experiments by mixing the polynucleotides with the lipidoid at a set ratio prior to addition to cells. *In vivo* formulation may require the addition of extra ingredients to facilitate circulation throughout the body. To test the ability of these lipidoids to form particles suitable for *in vivo* work, a
10 standard formulation process used for siRNA-lipidoid formulations may be used as a starting point. After formation of the particle, polynucleotide is added and allowed to integrate with the complex. The encapsulation efficiency is determined using a standard dye exclusion assays.

15 **Example 12: Mouse Immunogenicity Studies**

Comparison of HA stem antigens

In this example, assays were carried out to evaluate the immune response to influenza virus vaccine antigens delivered using an mRNA/LNP platform in comparison to protein antigens. The instant study was designed to test the immunogenicity in mice of candidate
20 influenza virus vaccines comprising an mRNA polynucleotide encoding HA stem protein obtained from different strains of influenza virus. Animals tested were 6-8 week old female BALB/c mice obtained from Charles River Laboratories. Test vaccines included the following mRNAs formulated in MC3 LNP: stem of H1/Puerto Rico/8/1934 (based on Mallajosyula V *et al.* *PNAS* 2014 Jun 24;111(25):E2514-23), stem of H1/New
25 Caledonia/20/1999 (based on Mallajosyula V *et al.* *PNAS* 2014 Jun 24;111(25):E2514-23), stem of H1/California/04/2009 (based on Mallajosyula V *et al.* *PNAS* 2014 Jun 24;111(25):E2514-23), stem of H5/Vietnam/1194/2004 (based on Mallajosyula V *et al.* *PNAS* 2014 Jun 24;111(25):E2514-23), stem of H10/Jiangxi-Donghu/346/2013, and full-length H10/Jiangxi-Donghu/346/2013.

30 Protein vaccines tested in this study included the pH1HA10-Foldon protein, as described in Mallajosyula *et al.* *Proc Natl Acad Sci U S A.* 2014;111(25):E2514-23. Additional controls included MC3 (control for effects of LNP) and PR8 influenza virus.

Mice were immunized intramuscularly with a total volume of 100 μ L of each test vaccine, which was administered in a 50 μ L immunization to each quadricep, except for
35 administration of the PR8 influenza virus control which was delivered intranasally in a

volume of 20 μ L while the animals were sedated with a mixture of Ketamine and Xylazine. The group numbers for each test vaccine along with the vaccine dose are outlined in the table below:

5 **Table 1. RNA Test Vaccines**

Group #	Antigen	dose	formulation
1	H10/Jiangxi-Donghu/346/2013 full-length RNA	10 μ g	MC3
2	H10N8 A/JX346/2013 stem RNA	10 μ g	MC3
3	H1N1 A/Puerto Rico/8/1934 stem RNA	10 μ g	MC3
4	H1N1 A/New Caledonia/20/99 stem RNA	10 μ g	MC3
5	H1N1 A/California/04/2009 stem RNA	10 μ g	MC3
6	H5N1 A/Vietnam/1203/2004 stem RNA	10 μ g	MC3
7	pH1HA10-Foldon protein	20 μ g	CpG 7909
8	MC3	0 μ g	MC3
9	0.1 LD90 PR8 virus	0.1 LD90	None

Mice were immunized with two doses of the various influenza virus RNA vaccine formulations at weeks 0 and 3, and serum was collected two weeks after immunization with the second dose.

To test the sera for the presence of antibodies capable of binding to hemagglutinin (HA) from a wide variety of influenza strains, ELISA plates were coated with 100 ng of the following recombinant HAs obtained from Sino Biological Inc.: Influenza A H1N1 (A/New Caledonia/20/99), cat # 11683-V08H; Influenza A H3N2 (A/Aichi/2/1968), cat # 11707-V08H; Influenza A H1N1 (A/California/04/2009) cat # 11055-V08H; Influenza A H1N1 (A/Puerto Rico/8/34) cat # 11684-V08H; Influenza A H3N2 (A/Brisbane/10/2007), cat # 11056-V08H; Influenza A H2N2 (A/Japan/305/1957) cat # 11088-V08H; Influenza A H7N9 (A/Anhui/1/2013) cat # 40103-V08H; Influenza H5N1 (A/Vietnam/1194/2004) cat # 11062-V08H1; Influenza H9N2 (A/Hong Kong/1073/99) cat # 11229-V08H and Influenza A H10N8 (A/Jiangxi-Donghu/346/2013) cat # 40359-V08B. After coating, the plates were washed, blocked with Phosphate Buffered Saline with 0.05% Tween-20 (PBST) + 3% milk, and 100 μ L of control antibodies or sera from immunized mice (diluted in PBST + 3% milk) were added to the top well of each plate and serially diluted. Plates were sealed and incubated at room temperature for 2 hours. Plates were washed, and goat anti-mouse IgG

(H+L)-HRP conjugate (Novex, diluted 1:2000 in PBST/3% milk) was added to each well containing mouse sera. Plates were incubated at room temperature for 1 hr, washed, and incubated with TMB substrate (Thermo Scientific). The color was allowed to develop for 10 minutes and then quenched with 100 μ L of 2N sulfuric acid. The plates were read at 450 nM on a microplate reader. Endpoint titers (2.5-fold above background) were calculated.

In Fig. 1, the vaccines tested are shown on the y-axis and the endpoint titer to HA from each of the different strains of influenza are plotted. HAs from group 1 (H1, H2, H5, H9) strains of influenza are indicated by filled circles while HAs from group 2 (H3, H7, H10) strains of influenza are indicated by open circles. Fig. 1 illustrates that mRNA based vaccines encoding HA-based antigens that are encapsulated in the MC3 lipid nanoparticle induced high antibody binding titers to HA. Fig. 1 also illustrates that mRNA vaccines designed to express a portion of the stem domain from different H1N1 or H5N1 strains of influenza elicited high antibody titers that were capable of binding all strains of group 1 HA tested as well as several group 2 strains. Fig. 1 also illustrates that mRNA vaccines designed to express a portion of the H1N1 A/California/04/2009 stem domain induced higher titers than a protein vaccine of the same stem domain.

In another mouse immunogenicity study, the immune response to additional influenza virus vaccine antigens delivered using an mRNA/LNP platform was evaluated. The purpose of this study was to evaluate the ability of a second set of mRNA vaccine antigens to elicit cross-protective immune responses in the mouse and to assess the potential for mRNA vaccines encoding influenza HA antigens to be co-dosed. Animals tested were 6-8 week old female BALB/c mice obtained from Charles River Laboratories. Test vaccines included the following mRNAs formulated in MC3 LNP: H1HA6 (based on Bommakanti G et al. *J Virol.* 2012 Dec;86(24):13434-44); H3HA6 (based on Bommakanti G et al. *PNAS* 2010 Aug 3;107(31):13701-6); H1HA10-Foldon_delta Ngly; eH1HA (ectodomain of HA from H1N1 A/Puerto Rico/8/34); eH1HA_native signal seq (eH1HA with its native signal sequence); H3N2 A/Wisconsin/67/2005 stem; H3N2 A/Hong Kong/1/1968 stem (based on Mallajosyula V et al. *Front Immunol.* 2015 Jun 26;6:329); H7N9 A/Anhui/1/2013 stem; H1N1 A/California/04/2009 stem RNA (based on Mallajosyula V et al. *PNAS* 2014 Jun 24;111(25):E2514-23); and H1N1 A/Puerto Rico/8/1934 stem RNA (based on Mallajosyula V et al. *PNAS* 2014 Jun 24;111(25):E2514-23).

Controls included: MC3 (control for effects of LNP); Naïve (unvaccinated animals); and vaccination with H1N1 A/PR/8/34 and H3N2 A/HK/1/68 influenza viruses (positive controls).

Mice were immunized intramuscularly with a total volume of 100 μ L of each test vaccine, which was administered in a 50 μ L immunization to each quadricep, except for administration of the H1N1 A/PR/8/34 and H3N2 A/HK/1/68 virus influenza virus controls which were delivered intranasally in a volume of 20 μ L while the animals were sedated with a mixture of Ketamine and Xylazine. The group numbers for each test vaccine along with the vaccine dose are outlined in the table below:

Table 2. Test Vaccines

Group #	Antigen	Antigen dose	Formulation	Volume, Route
1	H1HA6 RNA	10 μ g	MC3	100 μ l, i.m.
2	H3HA6 RNA	10 μ g	MC3	100 μ l, i.m.
3	H1HA10-Foldon_delta Ngly	10 μ g	MC3	100 μ l, i.m.
4	eH1HA	10 μ g	MC3	100 μ l, i.m.
5	eH1HA_native signal seq	10 μ g	MC3	100 μ l, i.m.
6	H3N2 A/Wisconsin/67/2005 stem RNA	10 μ g	MC3	100 μ l, i.m.
7	H3N2 A/Hong Kong/1/1968 stem RNA	10 μ g	MC3	100 μ l, i.m.
8	H7N9 A/Anhui/1/2013 stem RNA	10 μ g	MC3	100 μ l, i.m.
9	H1N1 A/Puerto Rico/8/1934 stem RNA AND H3N2 A/Wisconsin/67/2005 stem RNA (RNAs mixed prior to formulation)	10 μ g	MC3	100 μ l, i.m.
10	H1N1 A/Puerto Rico/8/1934 stem RNA AND H3N2 A/Wisconsin/67/2005 stem RNA (RNAs formulated and then mixed)	10 μ g	MC3	100 μ l, i.m.
11	H1N1 A/California/04/2009 stem RNA	10 μ g	MC3	100 μ l, i.m.
12	H1N1 A/Puerto Rico/8/1934 stem RNA	10 μ g	MC3	100 μ l, i.m.
13	MC3	0 μ g	MC3	100 μ l, i.m.
14	Naïve	0 μ g	None	None
15	H3N2 A/HK/1/68 virus	0.1 LD90	None	20 μ l, i.n.
16	H1N1 A/PR/8/34 virus	0.1 LD90	None	20 μ l, i.n.

Animals were immunized on the study start day and then again three weeks after the initial immunization. Sera were collected from the animals two weeks after the second dose. To test the sera for the presence of antibodies capable of binding to hemagglutinin (HA) from a wide variety of influenza strains, ELISA plates were coated with 100 ng of the following

recombinant HAs obtained from Sino Biological Inc.: Influenza A H1N1 (A/New Caledonia/20/99), cat # 11683-V08H; Influenza A H3N2 (A/Aichi/2/1968), cat # 11707-V08H; Influenza A H1N1 (A/California/04/2009) cat # 11055-V08H; Influenza A H1N1 (A/Puerto Rico/8/34) cat # 11684-V08H; Influenza A H3N2 (A/Brisbane/10/2007), cat # 11056-V08H; Influenza A H2N2 (A/Japan/305/1957) cat # 11088-V08H; Influenza A H7N9 (A/Anhui/1/2013) cat # 40103-V08H and Influenza A H3N2 (A/Moscow/10/99) cat #40154-V08. The ELISA assay was performed and endpoint titers were calculated as described above. Figs. 2 and 3 show the endpoint anti-HA antibody titers following the second immunization with the test vaccines. The vaccines tested are shown on the x-axis and the binding to HA from each of the different strains of influenza is plotted. All mRNA vaccines encoding HA stem were immunogenic and elicited a robust antibody response recognizing HA from a diverse set of influenza A virus strains. The H1HA6, eH1HA, and eH1HA_native-signal-sequence mRNAs elicited the highest overall binding titers across the panel of group 1 HAs, while the H3HA6 RNA elicited the highest overall binding titers across group 2 HAs (Fig. 2). Immunogenicity of combinations of stem mRNA vaccines was also tested. In this study, individual mRNAs were mixed prior to formulation with LNP (Group 9, co-form) or individual mRNAs were formulated with LNP prior to mixing (Group 10, mix-form). As shown in Fig. 3, combining H1 and H3 stem-based mRNAs did not result in interference in the immune response to either antigen, regardless of the method of formulation.

Example 13: Mouse Efficacy studies

Influenza A challenge #1

This study was designed to test the immunogenicity and efficacy in mice of candidate influenza virus vaccines. Animals tested were 6-8 week old female BALB/c mice obtained from Charles River Laboratories. Test vaccines included the following mRNAs formulated in MC3 LNP: NIHGen6HASS-foldon mRNA (based on Yassine et al. *Nat. Med.* 2015 Sep; 21(9):1065-70), an mRNA encoding the nucleoprotein NP from an H3N2 strain, or one of several combinations of NIHGen6HASS-foldon and NP mRNAs. Several methods of vaccine antigen co-delivery were tested including: mixing individual mRNAs prior to formulation with LNP (co-form), formulation of individual mRNAs prior to mixing (mix and LNPs), and formulating mRNAs individually and injecting distal sites (opposite legs) (ind LNPs remote). Control animals were vaccinated with an RNA encoding the ectodomain of the HA from H1N1 A/Puerto Rico/8/1934 (eH1HA, positive control) or empty MC3 LNP (to control for effects of the LNP) or were not vaccinated (naïve).

At week 0 and week 3, animals were immunized intramuscularly (IM) with a total volume of 100 μ L of each test vaccine, which was administered in a 50 μ L immunization to each quadricep. Candidate influenza virus vaccines evaluated in this study were described above and are outlined in the table below. Sera were collected from all animals two weeks after the second dose. At week 6, spleens were harvested from a subset of the animals (n=4). The remaining animals (n=6) were challenged intranasally while sedated with a mixture of Ketamine and Xylazine with a lethal dose of mouse-adapted influenza virus strain H1N1 A/Puerto Rico/8/1934. Mortality was recorded and individual mouse weight was assessed daily for 20 days post-infection.

10

Table 3. Test Vaccines

Group #	Antigen	Antigen dose	Formulation	Volume, Route
1	NIHGen6HASS-foldon RNA	10 μ g	MC3	100 μ l, i.m.
2	NIHGen6HASS-foldon RNA	5 μ g	MC3	100 μ l, i.m.
3	NIHGen6HASS-foldon RNA	2 μ g	MC3	100 μ l, i.m.
4	NP RNA	5 μ g	MC3	100 μ l, i.m.
5	NIHGen6HASS-foldon RNA + NP RNA	5 μ g of each RNA mixed, then formulated	MC3	100 μ l, i.m.
6	NIHGen6HASS-foldon RNA + NP RNA	5 μ g of each RNA formulated, then mixed	MC3	100 μ l, i.m.
7	NIHGen6HASS-foldon RNA + NP RNA	5 μ g of each RNA formulated and injected into separate legs	MC3	100 μ l, i.m.
8	NIHGen6HASS-foldon RNA + NP RNA	5 μ g of NP + 2 μ g of NIHGen6HASS-foldon RNA mixed, then formulated	MC3	100 μ l, i.m.
9	eH1HA RNA	10 μ g	MC3	100 μ l, i.m.
10	MC3	0 μ g	MC3	100 μ l, i.m.
11	Naïve	0 μ g	None	None

To test the sera for the presence of antibodies capable of binding to hemagglutinin (HA) from a wide variety of influenza strains or nucleoprotein (NP), ELISA plates were

coated with 100 ng of the following recombinant proteins obtained from Sino Biological Inc.: Influenza A H1N1 (A/New Caledonia/20/99) HA, cat # 11683-V08H; Influenza A H3N2 (A/Aichi/2/1968) HA, cat # 11707-V08H; Influenza A H1N1 (A/California/04/2009) HA, cat # 11055-V08H; Influenza A H1N1 (A/Puerto Rico/8/34) HA, cat # 11684-V08H; Influenza A H1N1 (A/Brisbane/59/2007) HA, cat # 11052-V08H; Influenza A H2N2 (A/Japan/305/1957) HA, cat # 11088-V08H; Influenza A H7N9 (A/Anhui/1/2013) HA, cat # 40103-V08H, Influenza A H3N2 (A/Moscow/10/99) HA, cat #40154-V08 and Influenza A H3N2 (A/Aichi/2/1968) Nucleoprotein cat # 40207-V08B. The ELISA assay was performed and endpoint titers were calculated as described above. Fig. 4 depicts the endpoint titers of the pooled serum from animals vaccinated with the test vaccines. The vaccines tested are shown on the x-axis of Fig. 4A and the binding to HA from each of the different strains of influenza is plotted. The NIHGen6HASS-foldon mRNA vaccine elicited high titers of antibodies that bound all H1, H2 and H7 HAs tested. Combining the NIHGen6HASS-foldon mRNA with one that encodes NP did not negatively affect the observed anti-HA response, regardless of the method of mRNA co-formulation or co-delivery. In serum collected from identical groups from a separate study, a robust antibody response to NP protein was also detected in serum from animals vaccinated with NP mRNA containing vaccines, either NP alone or co-formulated with NIHGen6HASS-foldon mRNA(Fig. 4B).

To probe the functional antibody response, the ability of serum to neutralize a panel of HA-pseudotyped viruses was assessed (Fig. 5). Briefly, 293 cells were co-transfected with a replication-defective retroviral vector containing a firefly luciferase gene, an expression vector encoding a human airway serine protease, and expression vectors encoding influenza hemagglutinin (HA) and neuraminidase (NA) proteins. The resultant pseudoviruses were harvested from the culture supernatant, filtered, and titered. Serial dilutions of serum were incubated in 96 well plates at 37 °C for one hour with pseudovirus stocks (30,000 – 300,000 relative light units per well) before 293 cells were added to each well. The cultures were incubated at 37 °C for 72 hours, luciferase substrate and cell lysing reagents were added, and relative light units (RLU) were measured on a luminometer. Neutralization titers are expressed as the reciprocal of the serum dilution that inhibited 50% of pseudovirus infection (IC50).

For each sample tested (listed along the x-axis), each bar represents the IC50 for neutralization of a different virus pseudotype. While the serum from naïve or NP RNA vaccinated mice was unable to inhibit pseudovirus infection, the serum from mice vaccinated with 10 µg or 5 µg of NIHGen6HASS-foldon mRNA or with a combination of

NIHGen6HASS-foldon and NP mRNAs neutralized, to a similar extent, all H1 and H5 virus pseudotypes tested.

The ability of NIHGen6HASS-foldon antisera to mediate antibody-dependent cell cytotoxicity (ADCC) surrogate activity *in vitro* was also assessed. Briefly, serially titrated mouse serum samples were incubated with A549 cells stably expressing HA from H1N1 A/Puerto Rico/8/1934 on the cell surface. Subsequently, ADCC Bioassay Effector cells (Promega, mouse FcγRIV NFAT-Luc effector cells) were added to the serum/target cell mixture. Approximately 6 hours later, Bio-glo reagent (Promega) was added to sample wells and luminescence was measured. Data was plotted as fold induction (sample luminescence/background luminescence) versus serum concentration (Fig. 6). When incubated with the appropriate target cells, serum from NIHGen6HASS-foldon mRNA vaccinated mice was able to stimulate the surrogate ADCC effector cell line, suggesting that the vaccine may induce antibodies capable of mediating *in vivo* ADCC activity.

Three weeks after the administration of the second vaccine dose, spleens were harvested from a subset of animals in each group and splenocytes from animals in the same group were pooled. Splenic lymphocytes were stimulated with a pool of HA or NP peptides, and IFN-γ, IL-2 or TNF-α production was measured by intracellular staining and flow cytometry. Figure 7 is a representation of responses following stimulation with a pool of NP peptides, and Figure 8 is a representation of responses following stimulation with a pool of H1 HA peptides. Following vaccination with NP mRNA, either in the presence or absence of NIHGen6HASS-foldon mRNA, antigen-specific CD4 and CD8 T cells were found in the spleen. Following vaccination with NIHGen6HASS-foldon RNA or delivery of NIHGen6HASS-foldon and NP RNAs to distal injection sites (dist. site), only HA-specific CD4 cells were observed. However, when NIHGen6HASS-foldon and NP RNAs were co-administered to the same injection site (co-form, mix), an HA-specific CD8 T cell response was detected.

Following lethal challenge with mouse-adapted H1N1 A/Puerto Rico/8/1934, all naïve animals succumbed to infection by day 12 post-infection (Fig. 9). In contrast, all animals vaccinated with NIHGen6HASS-foldon mRNA, NP mRNA, any combination of NIHGen6HASS-foldon and NP mRNAs, or eH1HA mRNA survived the challenge. As seen in Fig. 9, although there was no mortality, mice that were vaccinated with an H3N2 NP mRNA and challenged with H1N1 virus lost a significant amount (~15%) of weight prior to recovery. Those vaccinated with NIHGen6HASS-foldon RNA also lost ~5% body weight. In contrast, mice vaccinated with a combination of NIHGen6HASS-foldon and NP mRNAs appeared to be completely protected from lethal influenza virus challenge, similar to those

vaccinated with mRNA expressing an HA antigen homologous to that of the challenge virus (eH1HA). Vaccine efficacy was similar at all vaccine doses, as well as with all co-formulation and co-delivery methods assessed (Fig. 10).

5 *Influenza A challenge #2*

This study was designed to test the immunogenicity and efficacy in mice of candidate influenza virus vaccines. Animals tested were 6-8 week old female BALB/c mice obtained from Charles River Laboratories. Test vaccines included the following mRNAs formulated in MC3 LNP: NIHGen6HASS-foldon mRNA (based on Yassine et al. *Nat. Med.* 2015 Sep; 21(9):1065-70) and NIHGen6HASS-TM2 mRNA. Control animals were vaccinated with an mRNA encoding the ectodomain of the HA from H1N1 A/Puerto Rico/8/1934 (eH1HA, positive control) or were not vaccinated (naïve).

At week 0 and week 3, animals were immunized intramuscularly (IM) with a total volume of 100 μ L of each test vaccine, which was administered in a 50 μ L immunization to each quadricep. Candidate influenza virus vaccines evaluated in this study were described above and outlined in the table below. Sera were collected from all animals two weeks after the second dose. At week 6, all animals were challenged intranasally while sedated with a mixture of Ketamine and Xylazine with a lethal dose of mouse-adapted influenza virus strain H1N1 A/Puerto Rico/8/1934. Mortality was recorded and group mouse weight was assessed daily for 20 days post-infection.

25 **Table 4. Test Vaccines**

Group #	Antigen	Antigen dose	Formulation	Volume, Route
1	NIHGen6HASS-foldon RNA	5 μ g	MC3	100 μ l, i.m.
2	NIHGen6HASS-foldon-TM2 RNA	5 μ g	MC3	100 μ l, i.m.
3	eH1HA RNA	10 μ g	MC3	100 μ l, i.m.
4	Naïve	0 μ g	None	None

To test the sera for the presence of antibody capable of binding to hemagglutinin (HA) from a wide variety of influenza strains, ELISA plates were coated with 100 ng of the following recombinant HAs obtained from Sino Biological Inc.: Influenza A H1N1 (A/New

Caledonia/20/99), cat # 11683-V08H; Influenza A H3N2 (A/Aichi/2/1968), cat # 11707-V08H; Influenza A H1N1 (A/California/04/2009) cat # 11055-V08H; Influenza A H1N1 (A/Puerto Rico/8/34) cat # 11684-V08H; Influenza A H1N1 (A/Brisbane/59/2007), cat # 11052-V08H; Influenza A H2N2 (A/Japan/305/1957) cat # 11088-V08H; Influenza A H7N9 (A/Anhui/1/2013) cat # 40103-V08H and Influenza A H3N2 (A/Moscow/10/99) cat #40154-V08. The ELISA assay was performed and endpoint titers were calculated as described above. Fig. 11A depicts the endpoint titers of the pooled serum from animals vaccinated with the test vaccines. The vaccines tested are shown on the x-axis and the binding to HA from each of the different strains of influenza is plotted. The NIHGen6HASS-foldon mRNA vaccine elicited high titers of antibodies that bound all H1, H2 and H7 HAs tested. The binding titers from NIHGen6HASS-TM2 mRNA vaccinated mice were reduced as compared to those from NIHGen6HASS-foldon mRNA vaccinated mice.

Following lethal challenge with mouse-adapted H1N1 A/Puerto Rico/8/1934, all naïve animals succumbed to infection by day 16 post-infection (Fig. 11B). In contrast, all animals vaccinated with NIHGen6HASS-foldon mRNA, NIHGen6HASS-TM2 mRNA, or eH1HA RNA survived the challenge. As shown in Fig. 11B, the efficacy of the NIHGen6HASS-TM2 vaccine was equivalent to that of the NIHGen6HASS-foldon vaccine.

Influenza A challenge #3

In this example, two animal studies and assays were carried out to evaluate the immune response to influenza virus consensus hemagglutinin (HA) vaccine antigens delivered using an mRNA/LNP platform. The purpose of these studies was to evaluate the ability of consensus HA mRNA vaccine antigens to elicit cross-protective immune responses in the mouse.

To generate consensus HA sequences, 2415 influenza A serotype H1 HA sequences were obtained from the NIAID Influenza Research Database (IRD) (Squires et al., *Influenza Other Respir Viruses*. 2012 Nov; 6(6): 404–416.) through the web site at <http://www.fludb.org>. After removal of duplicate sequences and lab strains, 2385 entries remained, including 1735 H1 sequences from pandemic H1N1 strains (pH1N1) and 650 from seasonal H1N1 strains (sH1N1). Pandemic and seasonal H1 sequences were separately aligned and a consensus sequence was generated for each group using the Matlab 9.0 Bioinformatics toolbox (MathWorks, Natick, MA). Sequence profiles were generated for both groups separately using a modified Seq2Logo program (Thomsen et al., *Nucleic Acids Res*. 2012 Jul;40 (Web Server issue):W281-7).

Animals tested were 6-8 week old female BALB/c mice obtained from Charles River Laboratories. Test vaccines included the following mRNAs formulated in MC3 LNP: ConH1 and ConH3 (based on Webby et al., *PLoS One*. 2015 Oct 15;10(10):e0140702.); Cobra_P1 and Cobra_X3 (based on Carter et al., *J Virol*. 2016 Apr 14;90(9):4720-34); MRK_pH1_Con and MRK_sH1_Con (pandemic and seasonal consensus sequences described above); and each of the above mentioned six antigens with a ferritin fusion sequence for potential particle formation.

Controls included: MC3 (control for effects of LNP); Naïve (unvaccinated animals); and vaccination with eH1HA RNA, which encode the ectodomain of HA from strain H1N1 A/PR/8/34 (positive control for the virus challenge).

At week 0 and week 3, animals were immunized intramuscularly (IM) with a total volume of 100 μ L of each test vaccine, which was administered in a 50 μ L immunization to each quadriceps. Candidate influenza virus vaccines evaluated in this study were described above and are outlined in the table below. Sera were collected from all animals two weeks after the second dose (week 5). At week 6, the animals were challenged intranasally while sedated with a mixture of Ketamine and Xylazine with a lethal dose of mouse-adapted influenza virus strain H1N1 A/Puerto Rico/8/1934 (PR8). Mortality was recorded and group weight was assessed daily for 20 days post-infection.

Table 5. Test Vaccines

Group #	Antigen	Antigen dose	Formulation	Volume, Route
1	Con_H1 RNA	10 μ g	MC3	100 μ l, i.m.
2	Con_H3 RNA	10 μ g	MC3	100 μ l, i.m.
3	Merck_pH1_Con RNA	10 μ g	MC3	100 μ l, i.m.
4	Merck_sH1_Con RNA	10 μ g	MC3	100 μ l, i.m.
5	Cobra_P1 RNA	10 μ g	MC3	100 μ l, i.m.
6	Cobra_X3 RNA	10 μ g	MC3	100 μ l, i.m.
7	ConH1_ferritin RNA	10 μ g	MC3	100 μ l, i.m.
8	ConH3_ferritin RNA	10 μ g	MC3	100 μ l, i.m.
9	Merck_pH1_Con_ferritin RNA	10 μ g	MC3	100 μ l, i.m.
10	Merck_sH1_Con_ferritin RNA	10 μ g	MC3	100 μ l, i.m.
11	Cobra_P1_ferritin RNA	10 μ g	MC3	100 μ l, i.m.
12	Cobra_X3_ferritin RNA	10 μ g	MC3	100 μ l, i.m.
13	eH1HA	10 μ g	MC3	100 μ l, i.m.
14	MC3	0 μ g	MC3	100 μ l, i.m.
15	Naïve	0 μ g	None	None

To test the ability of the serum antibodies to neutralize the challenge virus strain, a microneutralization assay using a modified PR8 virus with a Gaussia luciferase reporter gene (Pan et al., *Nat Commun.* 2013;4:2369) was performed. Briefly, PR8 luciferase virus was diluted in virus diluent with TPCK-treated trypsin. Serum samples were diluted 1:10 and then serially diluted 3-fold in 96-well cell culture plates. 50 μ L of each diluted serum sample and an equal volume of diluted virus were mixed in the well and incubated at 37 °C with 5% CO₂ for 1 hr before 100 μ L of MDCK cells at 1.5×10^5 cells/mL were added. Plates were then incubated at 37 °C with 5% CO₂ for 72 hrs. Luminescence signal was read with a Gaussia Luciferase Glow Assay Kit (Pierce) on an EnVision reader (Perkin Elmer). As shown in Figure 12A, serum from mice immunized with mRNA encoding consensus HA antigens from the H1 subtype was able to detectably neutralize the PR8 luciferase virus, even though the HA sequences of these antigens were 8-19% different from that of the PR8 strain. The HA sequence-matched antigen (eH1HA) elicited a much higher serum neutralizing antibody response against this virus. Serum from mice vaccinated with RNA encoding the consensus H3 antigen (ConH3), in contrast, was not able to neutralize the PR8 luciferase virus, suggesting that the consensus sequences from different subtypes (H1 and H3, for example) may not cross-react. Similarly, serum from mice immunized with mRNA encoding H1 subtype consensus HA antigens with a ferritin fusion sequence was able to detectably neutralize the PR8 luciferase virus, except for the Merck_pH1_Con_ferritin mRNA, while serum from mice vaccinated with an mRNA encoding the consensus H3 antigen with a ferritin fusion sequence was not able to neutralize the PR8 luciferase virus (Fig. 12B). Consistent with the serum neutralization data, mice immunized with the consensus H1 HA antigens (with or without ferritin fusion) survived the lethal PR8 virus challenge and showed no weight loss, except for the Merck_pH1_Con_ferritin mRNA group, while mice in the ConH3, naïve and LNP only control groups rapidly lost weight upon challenge (Fig. 13). Mice immunized with Merck_pH1_Con_ferritin mRNA survived the lethal PR8 virus challenge and showed 5-10% weight loss, suggesting that partial protection may be mediated by mechanism(s) other than virus neutralization.

To assess the breadth of the serum neutralizing activity elicited by the consensus HA antigens, neutralization assays were performed on a panel of pseudoviruses as described above (Fig. 14). As expected, serum from mice immunized with influenza virus H1N1 A/Puerto Rico/8/1934 (from studies described in Example 12) was only able to neutralize a matched pseudovirus strain (PR8). In contrast, serum from mice immunized with the consensus H1 HA antigens, as well as the eH1HA antigen, were able to neutralize a panel of diverse group 1 pseudoviruses, including strains from subtypes H1 and H5, but not a strain

from group 2 (subtype H3). Consistently, serum from mice immunized with the consensus H3 HA antigen was able to neutralize a strain from group 2 (subtype H3) but not any of the group 1 pseudoviruses.

5 *Influenza B challenge*

This study was designed to test the immunogenicity and efficacy in mice of candidate influenza virus vaccines. Animals tested were 6-8 week old female BALB/c mice obtained from Charles River Laboratories. Test vaccines included the following mRNAs formulated in MC3 LNP: B/Phuket/3073/2013 sHA (soluble HA), B/Phuket/3073/2013 mHA (full-length HA with membrane anchor), B/Brisbane/60/2008 sHA, B/Victoria/02/1987 sHA, B/Victoria/02/1987 mHA, B/Yamagata/16/1988 mHA, or BHA10 (HA stem design). Control animals were vaccinated with a nonlethal dose of mouse-adapted B/Ann Arbor/1954 (positive control) or empty MC3 LNP (to control for effects of the LNP) or were not vaccinated (naïve).

At week 0 and week 3, animals were immunized intramuscularly (IM) with a total volume of 100 μ L of each test vaccine, which was administered in a 50 μ L immunization to each quadriceps. Candidate influenza virus vaccines evaluated in this study were described above and are outlined in the table below. Sera were collected from all animals two weeks after the second dose. At week 6, all animals (n=10 per group) were challenged intranasally while sedated with a mixture of Ketamine and Xylazine with a lethal dose of mouse-adapted influenza virus strain B/Ann Arbor/1954. Mortality was recorded and group mouse weight was assessed daily for 20 days post-infection.

Each of the sequences described herein encompasses a chemically modified sequence or an unmodified sequence which includes no nucleotide modifications.

25 **Table 6. Test Vaccines**

Group #	Antigen	Antigen dose	Formulation	Volume, Route
1	B/Phuket/3073/2013 sHA RNA	10 μ g	MC3	100 μ l, i.m.
2	B/Phuket/3073/2013 mHA RNA	10 μ g	MC3	100 μ l, i.m.
3	B/Brisbane/60/2008 sHA RNA	10 μ g	MC3	100 μ l, i.m.
4	B/Victoria/02/1987 sHA RNA	10 μ g	MC3	100 μ l, i.m.
5	B/Victoria/02/1987 mHA RNA	10 μ g	MC3	100 μ l, i.m.
6	B/Yamagata/16/1988 mHA RNA	10 μ g	MC3	100 μ l, i.m.

Group #	Antigen	Antigen dose	Formulation	Volume, Route
7	BHA10 RNA	10 µg	MC3	100 µl, i.m.
8	MC3	0 µg	MC3	100 µl, i.m.
9	Naive	0 µg	None	100 µl, i.m.
10	B/Ann Arbor/1954	0.1 LD90	None	20 µl, i.n.

Fig. 15A depicts the ELISA endpoint anti-HA antibody titers of the pooled serum from animals vaccinated with the test vaccines. The vaccines tested are shown on the x-axis and the binding to HA from each of the different strains of influenza is plotted. All vaccines tested, except for those derived from B/Phuket/3073/2013 were immunogenic, and serum antibody bound to HA from both B/Yamagata/16/1988 (Yamagata lineage) and B/Florida/4/2006 (Victoria lineage).

Following lethal challenge with mouse-adapted B/Ann Arbor/1954, 90% of MC3-vaccinated and naïve animals succumbed to infection by day 16 post-infection (Fig. 15B). The B/Phuket/3073/2013 sHA and mHA mRNA vaccines showed no efficacy against lethal challenge, and the BHA10 stem mRNA vaccine protected only half of the animals. All other vaccines tested protected mice completely from mortality (Fig 15B), but only the B/Yamagata/16/1988 mHA RNA vaccine was able to prevent lethality and weight loss in animals challenged with a heterologous virus strain (Fig 15B).

Example 14: Non-Human Primate Immunogenicity

This study was designed to test the immunogenicity in rhesus macaques of candidate influenza virus vaccines. Test vaccines included the following mRNAs formulated in MC3 LNP: NIHGen6HASS-foldon mRNA (based on Yassine et al. *Nat. Med.* 2015 Sep; 21(9):1065-70) and NP mRNA encoding NP protein from an H3N2 influenza strain.

Animals in Group 1 had been previously vaccinated with seasonal inactivated influenza vaccine (FLUZONE[®]) and were boosted intramuscularly (IM) at day 0 with 300 µg of NIHGen6HASS-foldon mRNA. Animals in Groups 2 and 3 were influenza naïve at the study start and were vaccinated at days 0, 28 and 56 with 300 µg of NIHGen6HASS-foldon mRNA or 300 µg of NP mRNA, respectively. Serum was collected from all animals prior to the study start (day -8) as well as at days 14, 28, 42, 56, 70, 84, 112, 140 and 168.

The NIHGen6HASS-foldon vaccine elicited a robust antibody response as measured by ELISA assay (plates coated with recombinantly-expressed NIHGen6HASS-foldon [HA stem] or NP proteins), and the data is depicted in Fig. 16. Fig. 16A shows titers to HA stem, over time, for four rhesus macaques previously vaccinated with FLUZONE[®] and boosted a

single time with NIHGen6HASS-foldon mRNA vaccine. Fig. 16B depicts titers to HA stem, over time, from four rhesus macaques vaccinated at days 0, 28 and 56 with the same NIHGen6HASS-foldon RNA vaccine. The NIHGen6HASS-foldon RNA vaccine was able to boost anti-HA stem antibody binding titers in animal previously vaccinated with inactivated influenza vaccine as well as elicited a robust response in naïve animals. In both groups, HA stem titers remained elevated over baseline to at least study day 168. Fig. 16C illustrates antibody titers to NP, over time, for four rhesus macaques vaccinated at days 0, 28 and 56 with the NP mRNA vaccine and shows that the vaccine elicited a robust antibody response to NP.

To test the Group 1 and 2 sera for the presence of antibody capable of binding to hemagglutinin (HA) from a wide variety of influenza strains, ELISA plates were coated with recombinant HAs from a diverse set of influenza strains as described above. EC10 titers were calculated as the reciprocal of the serum dilution that reached 10% of the maximal signal. For animals in Group 1 (Fig. 17A), a single dose of NIHGen6HASS-foldon vaccine boosted titers to H1 HAs ~ 40 – 60 fold, and titers peaked approximately 28 days post-vaccination. Titers decreased from days 28 – 70, but day 70 titers were still ~ 10 – 30-fold above the titers measured prior to vaccination. The NIHGen6HASS-foldon mRNA vaccine did not boost titers to HAs from H3 or H7 influenza strains. For animals in Group 2 (Fig. 17B), antibody titers to H1 and H2 HAs rose after each dose of NIHGen6HASS-foldon mRNA vaccine, and titers appeared to rise most dramatically after dose 2.

In addition to robust antibody responses, the NP mRNA vaccine also elicited cell-mediated immunity in rhesus. On study day 0, 42, 70 and 140, PBMCs were collected from Group 3 NP mRNA vaccinated rhesus macaques. Lymphocytes were stimulated with a pool of NP peptides, and IFN- γ , IL-2 or TNF- α production were measured by intracellular staining and flow cytometry. Figure 18 is a representation of responses following NP peptide pool stimulation. Following vaccination with NP mRNA, antigen-specific CD4 and CD8 T cells were found in the peripheral blood, and these cells were maintained above baseline to at least study day 140.

Example 15: H7N9 Immunogenicity Studies

The instant study was designed to test H7N9 immunogenicity. Intramuscular immunizations of 25 μ M were administered on days 1 and 22 to 40 animals, and blood was collected on days 1, 8, 22, and 43. Hemagglutination inhibition (HAI) and microneutralization tests were conducted using the blood samples.

The HAI test showed a geometric mean titer (GMT) of 45 for all of the animals, including the placebo group. The GMT of the responders only was 116 (Fig. 19). The HAI kinetics for each individual subject are given in Fig. 20.

5 The microneutralization (MN) test showed a geometric mean titer (GMT) of 36 for all of the animals, including the placebo group. The GMT of the responders only was 84 (Fig. 21). The MN test kinetics for each subject are given in Fig. 22.

HAI and MN showed a very strong correlation (Fig. 23). Only one subject had a protective titer in one assay , but not in the other. Also, 10 subjects had no detectable HAI or MN titer at Day 43.

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Table 7. Influenza H1N1 Antigens

Strain/Protein	Length	GenBank / GI Accession No.
Influenza A virus (A/Bayern/7/95(H1N1)) NA gene for neuraminidase, genomic RNA	1,459 bp linear mRNA	AJ518104.1 GI:31096418
Influenza A virus (A/Brazil/11/1978(X-71)(H1N1)) mRNA for hemagglutinin HA1, escape variant 1	1,072 bp linear mRNA	X86654.1 GI:995549
Influenza A virus (A/Brazil/11/1978(X-71)(H1N1)) mRNA for hemagglutinin HA1, escape variant 2	1,072 bp linear mRNA	X86655.1 GI:995550
Influenza A virus (A/Brazil/11/1978(X-71)(H1N1)) mRNA for hemagglutinin HA1, escape variant 3	1,072 bp linear mRNA	X86656.1 GI:995551
Influenza A virus (A/Brazil/11/1978(X-71)(H1N1)) mRNA for hemagglutinin HA1, escape variant 4	1,072 bp linear mRNA	X86657.1 GI:995552
Influenza A virus (A/Brevig_Mission/1/18(H1N1)) hemagglutinin (HA) mRNA, partial cds	1,220 bp linear mRNA	AF116575.1 GI:4325017
Influenza A virus (A/Brevig_Mission/1/18(H1N1)) neuraminidase (NA) gene, complete cds	1,410 bp linear mRNA	AF250356.2 GI:13260556
Influenza A virus (A/Brevig_Mission/1/1918(H1N1)) nucleoprotein (np) mRNA, complete cds	1,497 bp linear mRNA	AY744935.1 GI:55273940
Influenza A virus (A/Brevig_Mission/1/1918(H1N1)) polymerase PB2 (PB2) mRNA, complete cds	2,280 bp linear mRNA	DQ208309.1 GI:76786704
Influenza A virus (A/Brevig_Mission/1/1918(H1N1)) polymerase PB1 (PB1) mRNA, complete cds	2,274 bp linear mRNA	DQ208310.1 GI:76786706
Influenza A virus (A/Brevig_Mission/1/1918(H1N1)) polymerase PA (PA) mRNA, complete cds	2,151 bp linear mRNA	DQ208311.1 GI:76786708
Influenza A virus (A/camel/Mongolia/1982(H1N1)) hemagglutinin mRNA, partial cds	366 bp linear mRNA	M73975.1 GI:324242
Influenza A virus (A/camel/Mongolia/1982(H1N1)) matrix protein mRNA, partial cds	460 bp linear mRNA	M73978.1 GI:324402
Influenza A virus (A/camel/Mongolia/1982(H1N1)) neuraminidase (NA) mRNA, partial cds	310 bp linear mRNA	M73976.1 GI:324579

Strain/Protein	Length	GenBank / GI Accession No.
Influenza A Virus A/camel/Mongolia/82 NS1 protein mRNA, partial cds	273 bp linear mRNA	M73977.1 GI:324768
Influenza A virus (A/camel/Mongolia/1982(H1N1)) PA polymerase mRNA, partial cds	227 bp linear mRNA	M73974.1 GI:324931
Influenza A virus (A/camel/Mongolia/1982(H1N1)) PB1 protein mRNA, partial cds	531 bp linear mRNA	M73973.1 GI:324971
Influenza A Virus (A/camel/Mongolia/82(H1N1)) polymerase 2 (P2) mRNA, partial cds	379 bp linear mRNA	M73972.1 GI:324993
Influenza A virus (A/chicken/Hong Kong/14/1976(H1N1)) hemagglutinin precursor (HA) mRNA, partial cds	1,169 bp linear mRNA	U46782.1 GI:1912328
Influenza A virus (A/Chonnam/07/2002(H1N1)) neuraminidase (NA) mRNA, complete cds	1,452 bp linear mRNA	AY297141.1 GI:31871990
Influenza A virus (A/Chonnam/07/2002(H1N1)) hemagglutinin (HA) mRNA, partial cds	1,137 bp linear mRNA	AY297154.1 GI:32140347
Influenza A virus (A/Chonnam/18/2002(H1N1)) neuraminidase (NA) mRNA, complete cds	1,458 bp linear mRNA	AY297143.1 GI:31871994
Influenza A virus (A/Chonnam/18/2002(H1N1)) hemagglutinin (HA) mRNA, partial cds	1,176 bp linear mRNA	AY297156.1 GI:32140355
Influenza A virus (A/Chonnam/19/2002(H1N1)) neuraminidase (NA) mRNA, complete cds	1,458 bp linear mRNA	AY310410.1 GI:31872389
Influenza A virus (A/Chonnam/19/2002(H1N1)) hemagglutinin (HA) mRNA, partial cds	1,167 bp linear mRNA	AY299502.1 GI:32140392
Influenza A virus (A/Chonnam/51/2002(H1N1)) neuraminidase (NA) mRNA, complete cds	1,443 bp linear mRNA	AY310412.1 GI:31873090
Influenza A virus (A/Chonnam/51/2002(H1N1)) hemagglutinin (HA) mRNA, partial cds	1,161 bp linear mRNA	AY299498.1 GI:32140384
Influenza A virus (A/Chungbuk/50/2002(H1N1)) neuraminidase (NA) mRNA, partial cds	1,425 bp linear mRNA	AY297150.1 GI:31872010
Influenza A virus (A/Chungbuk/50/2002(H1N1)) hemagglutinin (HA) mRNA, partial cds	1,161 bp linear mRNA	AY299506.1 GI:32140400
Influenza A virus (A/Denmark/40/2000(H1N1)) NA gene for neuraminidase, genomic RNA	1,458 bp linear mRNA	AJ518095.1 GI:31096400
Influenza A virus (A/Denver/1/57(H1N1)) neuraminidase mRNA, partial cds	379 bp linear mRNA	AF305216.1 GI:10732818
Influenza A virus (A/Denver/1/57(H1N1)) matrix protein gene, partial cds	442 bp linear mRNA	AF305217.1 GI:10732820
Influenza A virus (A/Denver/1/57(H1N1)) hemagglutinin gene, partial cds	215 bp linear mRNA	AF305218.1 GI:10732822
Influenza A virus (A/duck/Australia/749/80(H1N1)) hemagglutinin precursor (HA) mRNA, partial cds	981 bp linear mRNA	U47309.1 GI:1912348
Influenza A virus (A/duck/Australia/749/80(H1N1)) segment 4 hemagglutinin precursor (HA) mRNA, complete cds	1,777 bp linear mRNA	AF091312.1 GI:4585166
Influenza A virus (A/duck/Bavaria/1/77(H1N1)) segment 4 hemagglutinin precursor (HA) mRNA, complete cds	1,777 bp linear mRNA	AF091313.1 GI:4585168
Influenza A virus (A/duck/Bavaria/2/77(H1N1)) hemagglutinin precursor (HA) mRNA, partial cds	981 bp linear mRNA	U47308.1 GI:1912346
Influenza A virus (A/duck/Eastern China/103/2003(H1N1)) segment 6 neuraminidase (NA) mRNA, complete cds	1,458 bp linear mRNA	EU429749.1 GI:167859463
Influenza A virus (A/duck/Eastern China/152/2003(H1N1)) segment 6 neuraminidase (NA) mRNA, complete cds	1,461 bp linear mRNA	EU429751.1 GI:167859467

Strain/Protein	Length	GenBank / GI Accession No.
Influenza A virus (A/Duck/Ohio/118C/93 (H1N1)) neuraminidase (NA) gene, complete cds	1,410 bp linear mRNA	AF250361.2 GI:13260576
Influenza A virus (A/Duck/Ohio/175/86 (H1N1)) neuraminidase (NA) gene, complete cds	1,410 bp linear mRNA	AF250358.2 GI:13260565
Influenza A virus (A/Duck/Ohio/194/86 (H1N1)) neuraminidase (NA) gene, complete cds	1,410 bp linear mRNA	AF250360.2 GI:13260573
Influenza A virus (A/Duck/Ohio/30/86 (H1N1)) neuraminidase (NA) gene, complete cds	1,410 bp linear mRNA	AF250359.2 GI:13260570
Influenza A virus strain A/Fiji/15899/83(H1N1) mRNA for neuraminidase	1,460 bp linear mRNA	AJ006954.1 GI:4210707
Influenza A Virus (A/Fiji/15899/83(H1N1)) mRNA for PB2 protein	2,341 bp linear mRNA	AJ564805.1 GI:31442134
Influenza A Virus (A/Fiji/15899/83(H1N1)) partial mRNA for PB1 protein	2,113 bp linear mRNA	AJ564807.1 GI:31442138
Influenza A virus (A/FM/1/47 (H1N1)) neuraminidase (NA) gene, complete cds	1,395 bp linear mRNA	AF250357.2 GI:13260561
Influenza A virus (A/goose/Hong Kong/8/1976(H1N1)) hemagglutinin precursor (HA) mRNA, partial cds	1,091 bp linear mRNA	U46021.1 GI:1912326
Influenza A virus (A/goose/Hong Kong/8/1976(H1N1)) polymerase (PB1) mRNA, partial cds	261 bp linear mRNA	U48284.1 GI:1912372
Influenza A virus (A/goose/Hong Kong/8/1976(H1N1)) nucleoprotein (NP) mRNA, partial cds	1,395 bp linear mRNA	U49093.1 GI:1912384
Influenza A virus (A/Guangzhou/1561/2006(H1N1)) segment 4 hemagglutinin (HA) mRNA, complete cds	1,775 bp linear mRNA	EU382986.1 GI:170762603
Influenza A virus (A/Guangzhou/1561/2006(H1N1)) segment 6 neuraminidase (NA) mRNA, complete cds	1,462 bp linear mRNA	EU382993.1 GI:170762617
Influenza A virus (A/Guangzhou/1684/2006(H1N1)) segment 4 hemagglutinin (HA) mRNA, complete cds	1,775 bp linear mRNA	EU382987.1 GI:170762605
Influenza A virus (A/Guangzhou/1684/2006(H1N1)) segment 6 neuraminidase (NA) mRNA, complete cds	1,462 bp linear mRNA	EU382994.1 GI:170762619
Influenza A virus (A/Guangzhou/483/2006(H1N1)) segment 4 hemagglutinin (HA) mRNA, complete cds	1,775 bp linear mRNA	EU382981.1 GI:170762593
Influenza A virus (A/Guangzhou/483/2006(H1N1)) segment 6 neuraminidase (NA) mRNA, complete cds	1,462 bp linear mRNA	EU382988.1 GI:170762607
Influenza A virus (A/Guangzhou/506/2006(H1N1)) segment 4 hemagglutinin (HA) mRNA, complete cds	1,775 bp linear mRNA	EU382982.1 GI:170762595
Influenza A virus (A/Guangzhou/506/2006(H1N1)) segment 6 neuraminidase (NA) mRNA, complete cds	1,461 bp linear mRNA	EU382989.1 GI:170762609
Influenza A virus (A/Guangzhou/555/2006(H1N1)) segment 4 hemagglutinin (HA) mRNA, complete cds	1,775 bp linear mRNA	EU382983.1 GI:170762597
Influenza A virus (A/Guangzhou/555/2006(H1N1)) segment 6 neuraminidase (NA) mRNA, complete cds	1,462 bp linear mRNA	EU382990.1 GI:170762611
Influenza A virus (A/Guangzhou/657/2006(H1N1)) segment 4 hemagglutinin (HA) mRNA, complete cds	1,775 bp linear mRNA	EU382984.1 GI:170762599

Strain/Protein	Length	GenBank / GI Accession No.
Influenza A virus (A/Guangzhou/657/2006(H1N1)) segment 6 neuraminidase (NA) mRNA, complete cds	1,462 bp linear mRNA	EU382991.1 GI:170762613
Influenza A virus (A/Guangzhou/665/2006(H1N1)) segment 4 hemagglutinin (HA) mRNA, complete cds	1,775 bp linear mRNA	EU382985.1 GI:170762601
Influenza A virus (A/Guangzhou/665/2006(H1N1)) segment 6 neuraminidase (NA) mRNA, complete cds	1,462 bp linear mRNA	EU382992.1 GI:170762615
Influenza A virus (A/Gwangju/55/2002(H1N1)) neuraminidase (NA) mRNA, complete cds	1,431 bp linear mRNA	AY297151.1 GI:31872012
Influenza A virus (A/Gwangju/55/2002(H1N1)) hemagglutinin (HA) mRNA, partial cds	1,179 bp linear mRNA	AY299507.1 GI:32140402
Influenza A virus (A/Gwangju/57/2002(H1N1)) neuraminidase (NA) mRNA, complete cds	1,446 bp linear mRNA	AY297152.1 GI:31872014
Influenza A virus (A/Gwangju/57/2002(H1N1)) hemagglutinin (HA) mRNA, partial cds	1,167 bp linear mRNA	AY299508.1 GI:32140404
Influenza A virus (A/Gwangju/58/2002(H1N1)) neuraminidase (NA) mRNA, complete cds	1,434 bp linear mRNA	AY297153.1 GI:31872016
Influenza A virus (A/Gwangju/58/2002(H1N1)) hemagglutinin (HA) mRNA, partial cds	1,176 bp linear mRNA	AY299509.1 GI:32140406
Influenza A virus (A/Gwangju/90/2002(H1N1)) neuraminidase (NA) mRNA, complete cds	1,446 bp linear mRNA	AY297147.1 GI:31872002
Influenza A virus (A/Gwangju/90/2002(H1N1)) hemagglutinin (HA) mRNA, partial cds	1,164 bp linear mRNA	AY299499.1 GI:32140386
Influenza A virus (A/Hong Kong/437/2002(H1N1)) partial NA gene for neuraminidase, genomic RNA	1,403 bp linear mRNA	AJ518101.1 GI:31096412
Influenza A virus (A/Hong Kong/747/2001(H1N1)) partial NA gene for neuraminidase, genomic RNA	1,352 bp linear mRNA	AJ518102.1 GI:31096414
Influenza A virus (A/London/1/1918(H1N1)) hemagglutinin (HA) mRNA, partial cds	563 bp linear mRNA	AY184805.1 GI:32395285
Influenza A virus (A/London/1/1919(H1N1)) hemagglutinin (HA) mRNA, partial cds	563 bp linear mRNA	AY184806.1 GI:32395287
Influenza A virus (A/Loygang/4/1957(H1N1)) nucleoprotein mRNA, complete cds	1,565 bp linear mRNA	M76604.1 GI:324255
Influenza A virus (A/Lyon/651/2001(H1N1)) partial NA gene for neuraminidase, genomic RNA	1,318 bp linear mRNA	AJ518103.1 GI:31096416
Influenza A virus (A/mallard/Alberta/119/98 (H1N1)) nonfunctional matrix protein mRNA, partial sequence	947 bp linear mRNA	AY664487.1 GI:51011891
Influenza A virus (A/duck/Alberta/35/76(H1N1)) hemagglutinin precursor (HA) mRNA, partial cds	981 bp linear mRNA	U47310.1 GI:1912350
Influenza A virus (A/duck/Alberta/35/76(H1N1)) segment 4 hemagglutinin precursor (HA) mRNA, complete cds	1,777 bp linear mRNA	AF091309.1 GI:4585160
Influenza A virus (A/duck/Alberta/35/76(H1N1)) neuraminidase (NA) gene, complete cds	1,410 bp linear mRNA	AF250362.2 GI:13260579
Influenza A virus (A/mallard/Tennessee/11464/85 (H1N1)) hemagglutinin precursor (HA) mRNA, partial cds	981 bp linear mRNA	U47307.1 GI:1912344

Strain/Protein	Length	GenBank / GI Accession No.
Influenza A virus (A/mallard/Tennessee/11464/85 (H1N1)) segment 4 hemagglutinin precursor (HA) mRNA, complete cds	1,777 bp linear mRNA	AF091311.1 GI:4585164
Influenza A virus (A/New Caledonia/20/1999(H1N1)) segment 7 matrix protein 2 (M2) mRNA, complete cds	294 bp linear mRNA	HQ008884.1 GI:302566794
Influenza A virus (A/New Jersey/4/1976(H1N1)) nucleoprotein mRNA, complete cds	1,565 bp linear mRNA	M76605.1 GI:324581
Influenza A virus (A/New Jersey/8/1976(H1N1)) nucleoprotein mRNA, complete cds	1,565 bp linear mRNA	M76606.1 GI:324583
Influenza A virus (A/New_York/1/18(H1N1)) hemagglutinin (HA) mRNA, partial cds	1,220 bp linear mRNA	AF116576.1 GI:4325019
Influenza A virus (A/Ohio/3523/1988(H1N1)) nucleoprotein mRNA, complete cds	1,565 bp linear mRNA	M76602.1 GI:324889
Influenza A virus (A/Pusan/22/2002(H1N1)) neuraminidase (NA) mRNA, complete cds	1,455 bp linear mRNA	AY310411.1 GI:31872391
Influenza A virus (A/Pusan/22/2002(H1N1)) hemagglutinin (HA) mRNA, partial cds	1,149 bp linear mRNA	AY299503.1 GI:32140394
Influenza A virus (A/Pusan/23/2002(H1N1)) neuraminidase (NA) mRNA, complete cds	1,440 bp linear mRNA	AY297144.1 GI:31871996
Influenza A virus (A/Pusan/23/2002(H1N1)) hemagglutinin (HA) mRNA, partial cds	1,158 bp linear mRNA	AY297157.1 GI:32140357
Influenza A virus (A/Pusan/24/2002(H1N1)) neuraminidase (NA) mRNA, complete cds	1,449 bp linear mRNA	AY297145.1 GI:31871998
Influenza A virus (A/Pusan/24/2002(H1N1)) hemagglutinin (HA) mRNA, partial cds	1,128 bp linear mRNA	AY299494.1 GI:32140376
Influenza A virus (A/Pusan/44/2002(H1N1)) neuraminidase (NA) mRNA, complete cds	1,431 bp linear mRNA	AY297148.1 GI:31872004
Influenza A virus (A/Pusan/44/2002(H1N1)) hemagglutinin (HA) mRNA, partial cds	1,167 bp linear mRNA	AY299504.1 GI:32140396
Influenza A virus (A/Pusan/45/2002(H1N1)) neuraminidase (NA) mRNA, complete cds	1,434 bp linear mRNA	AY297146.1 GI:31872000
Influenza A virus (A/Pusan/45/2002(H1N1)) hemagglutinin (HA) mRNA, partial cds	1,167 bp linear mRNA	AY299496.1 GI:32140380
Influenza A virus (A/Pusan/46/2002(H1N1)) neuraminidase (NA) mRNA, complete cds	1,422 bp linear mRNA	AY310408.1 GI:31872385
Influenza A virus (A/Pusan/46/2002(H1N1)) hemagglutinin (HA) mRNA, partial cds	1,176 bp linear mRNA	AY299497.1 GI:32140382
Influenza A virus (A/Pusan/47/2002(H1N1)) neuraminidase (NA) mRNA, complete cds	1,437 bp linear mRNA	AY297149.1 GI:31872008
Influenza A virus (A/Pusan/47/2002(H1N1)) hemagglutinin (HA) mRNA, partial cds	1,170 bp linear mRNA	AY299505.1 GI:32140398
Influenza A virus (A/Saudi Arabia/7971/2000(H1N1)) partial NS1 gene for non structural protein 1 and partial NS2 gene for non structural protein 2, genomic RNA	789 bp linear mRNA	AJ519463.1 GI:31096450
Influenza A virus (A/Seoul/11/2002(H1N1)) neuraminidase (NA) mRNA, complete cds	1,452 bp linear mRNA	AY297142.1 GI:31871992
Influenza A virus (A/Seoul/11/2002(H1N1)) hemagglutinin (HA) mRNA, partial cds	1,176 bp linear mRNA	AY297155.1 GI:32140349
Influenza A virus (A/Seoul/13/2002(H1N1)) neuraminidase (NA) mRNA, complete cds	1,452 bp linear mRNA	AY310409.1 GI:31872387
Influenza A virus (A/Seoul/13/2002(H1N1)) hemagglutinin (HA) mRNA, partial cds	1,167 bp linear mRNA	AY299500.1 GI:32140388
Influenza A virus (A/Seoul/15/2002(H1N1)) neuraminidase (NA) mRNA, complete cds	1,449 bp linear mRNA	AY297140.1 GI:31871988
Influenza A virus (A/Seoul/15/2002(H1N1)) hemagglutinin (HA) mRNA, partial cds	1,149 bp linear mRNA	AY299501.1 GI:32140390

Strain/Protein	Length	GenBank / GI Accession No.
Influenza A virus (A/Seoul/33/2002(H1N1)) neuraminidase (NA) mRNA, complete cds	1,437 bp linear mRNA	AY310407.1 GI:31872383
Influenza A virus (A/Seoul/33/2002(H1N1)) hemagglutinin (HA) mRNA, partial cds	1,167 bp linear mRNA	AY299495.1 GI:32140378
Influenza A virus (A/swine/Arnsberg/6554/1979(H1N1)) mRNA for hemagglutinin HA1	1,050 bp linear mRNA	Z46437.1 GI:565609
Influenza A virus (A/swine/Beijing/47/1991(H1N1)) hemagglutinin precursor (HA) mRNA, partial cds	1,595 bp linear mRNA	U46783.1 GI:1912330
Influenza A virus (A/swine/Beijing/94/1991(H1N1)) nucleoprotein (NP) mRNA, complete cds	1,565 bp linear mRNA	U49091.1 GI:1912380
Influenza A virus (A/swine/Belgium/1/83(H1N1)) segment 4 hemagglutinin precursor (HA) mRNA, complete cds	1,778 bp linear mRNA	AF091316.1 GI:4585174
Influenza A virus (A/swine/Cotes d'Armor/0118/2006(H1N1)) partial mRNA for haemagglutinin precursor (HA1 gene)	1,116 bp linear mRNA	AM490219.1 GI:222062898
Influenza A virus (A/swine/Cotes d'Armor/0136_18/2006(H1N1)) partial mRNA for haemagglutinin precursor (HA1 gene)	1,043 bp linear mRNA	AM490223.1 GI:222062906
Influenza A virus (A/swine/Cotes d'Armor/0184/2006(H1N1)) partial mRNA for haemagglutinin precursor (HA1 gene)	1,089 bp linear mRNA	AM490220.1 GI:222062900
Influenza A virus (A/swine/Cotes d'Armor/0227/2005(H1N1)) partial mRNA for haemagglutinin precursor (HA1 gene)	1,068 bp linear mRNA	AM490221.1 GI:222062902
Influenza A virus (A/swine/Cotes d'Armor/0250/2006(H1N1)) partial mRNA for haemagglutinin precursor (HA1 gene)	1,024 bp linear mRNA	AM490222.1 GI:222062904
Influenza A virus (A/swine/Cotes d'Armor/736/2001(H1N1)) partial HA gene for Haemagglutinin, genomic RNA	1,011 bp linear mRNA	AJ517820.1 GI:38422533
Influenza A virus (A/Swine/England/195852/92 (H1N1)) neuraminidase (NA) gene, complete cds	1,410 bp linear mRNA	AF250366.2 GI:13260593
Influenza A virus PB2 gene for Polymerase 2 protein, genomic RNA, strain A/Swine/Finistere/2899/82	2,268 bp linear mRNA	AJ311457.1 GI:13661037
Influenza A virus PB1 gene for Polymerase 1 protein, genomic RNA, strain A/Swine/Finistere/2899/82	2,341 bp linear mRNA	AJ311462.1 GI:13661047
Influenza A virus PA gene for Polymerase A protein, genomic RNA, strain A/Swine/Finistere/2899/82	2,233 bp linear mRNA	AJ311463.1 GI:13661049
Influenza A virus (A/swine/Finistere/2899/82(H1N1)) M1 gene for matrix protein 1 and M2 gene for matrix protein 2, genomic RNA	1,002 bp linear mRNA	AJ316059.1 GI:20068128
Influenza A virus (A/swine/Finistere/2899/82(H1N1)) NS1 gene for non structural protein 1 and NS2 gene for non structural protein 2, genomic RNA	864 bp linear mRNA	AJ344037.1 GI:20068185
Influenza A virus (A/swine/Germany/2/1981(H1N1)) mRNA for PA polymerase	838 bp linear mRNA	X75786.1 GI:438106
Influenza A virus (A/swine/Germany/2/1981(H1N1)) mRNA for neuraminidase (partial)	305 bp linear mRNA	Z30277.1 GI:530399

Strain/Protein	Length	GenBank / GI Accession No.
Influenza A virus (A/swine/Germany/2/1981(H1N1)) mRNA for hemagglutinin	1,730 bp linear mRNA	Z30276.1 GI:563490
165. Influenza A virus (A/swine/Germany/8533/1991(H1N1)) mRNA for hemagglutinin precursor	1,730 bp linear mRNA	Z46434.1 GI:565611
Influenza A virus (A/swine/Guangdong/711/2001(H1N1)) nonfunctional hemagglutinin (HA) mRNA, partial sequence	1,690 bp linear mRNA	AY852271.1 GI:60327789
Influenza A virus (A/swine/Haseluenne/IDT2617/03(H1N1)) hemagglutinin mRNA, complete cds	1,809 bp linear mRNA	EU163946.1 GI:157679548
Influenza A virus (A/swine/Hokkaido/2/81(H1N1)) hemagglutinin precursor (HA) mRNA, partial cds	981 bp linear mRNA	U47306.1 GI:1912342
Influenza A virus (A/swine/Hokkaido/2/81(H1N1)) segment 4 hemagglutinin precursor (HA) mRNA, complete cds	1,778 bp linear mRNA	AF091306.1 GI:4585154
Influenza A virus (A/swine/Hong Kong/168/1993(H1N1)) hemagglutinin precursor (HA) mRNA, partial cds	1,113 bp linear mRNA	U44482.1 GI:1912318
Influenza A virus (A/swine/Hong Kong/168/1993(H1N1)) neuraminidase (NA) mRNA, partial cds	416 bp linear mRNA	U47817.1 GI:1912354
Influenza A virus (A/swine/Hong Kong/168/1993(H1N1)) polymerase (PB2) mRNA, partial cds	286 bp linear mRNA	U48286.1 GI:1912358
Influenza A virus (A/swine/Hong Kong/168/1993(H1N1)) polymerase (PB1) mRNA, partial cds	379 bp linear mRNA	U48283.1 GI:1912370
Influenza A virus (A/swine/Hong Kong/168/1993(H1N1)) polymerase (PA) mRNA, partial cds	308 bp linear mRNA	U48850.1 GI:1912376
Influenza A virus (A/swine/Hong Kong/168/1993(H1N1)) nucleoprotein (NP) mRNA, partial cds	1,397 bp linear mRNA	U49096.1 GI:1912390
Influenza A virus (A/swine/Hong Kong/172/1993(H1N1)) hemagglutinin precursor (HA) mRNA, partial cds	1,315 bp linear mRNA	U46020.1 GI:1912324
Influenza A virus (A/swine/Hong Kong/176/1993(H1N1)) hemagglutinin precursor (HA) mRNA, partial cds	1,113 bp linear mRNA	U45451.1 GI:1912320
Influenza A virus (A/swine/Hong Kong/273/1994(H1N1)) hemagglutinin precursor (HA) mRNA, partial cds	1,330 bp linear mRNA	U45452.1 GI:1912322
Influenza A virus (A/swine/Hong Kong/273/1994(H1N1)) neuraminidase (NA) mRNA, partial cds	241 bp linear mRNA	U47818.1 GI:1912356
Influenza A virus (A/swine/Hong Kong/273/1994(H1N1)) polymerase (PB2) mRNA, partial cds	328 bp linear mRNA	U48287.1 GI:1912360
Influenza A virus (A/swine/Hong Kong/273/1994(H1N1)) polymerase (PB1) mRNA, partial cds	240 bp linear mRNA	U48282.1 GI:1912368
Influenza A virus (A/swine/Hong Kong/273/1994(H1N1)) polymerase (PA) mRNA, partial cds	336 bp linear mRNA	U48851.1 GI:1912378

Strain/Protein	Length	GenBank / GI Accession No.
Influenza A virus (A/swine/Hong Kong/273/1994(H1N1)) nucleoprotein (NP) mRNA, partial cds	1,422 bp linear mRNA	U49092.1 GI:1912382
Influenza A virus (A/swine/IDT/Re230/92hp(H1N1)) hemagglutinin mRNA, complete cds	1,761 bp linear mRNA	EU163947.1 GI:157679550
Influenza A virus (A/swine/IN/1726/1988(H1N1)) nucleoprotein (segment 5) mRNA, complete cds	1,550 bp linear mRNA	L46849.1 GI:954755
Influenza A virus (A/swine/Iowa/15/30(H1N1)) hemagglutinin precursor (HA) mRNA, partial cds	981 bp linear mRNA	U47305.1 GI:1912340
Influenza A virus (A/swine/Iowa/15/30 (H1N1)) segment 4 hemagglutinin precursor (HA) mRNA, complete cds	1,778 bp linear mRNA	AF091308.1 GI:4585158
Influenza A virus (A/Swine/Iowa/30 (H1N1)) neuraminidase (NA) gene, complete cds	1,410 bp linear mRNA	AF250364.2 GI:13260586
Influenza A virus (A/swine/Iowa/17672/88 (H1N1)) hemagglutinin precursor (HA) mRNA, partial cds	981 bp linear mRNA	U47304.1 GI:1912338
Influenza A virus (A/swine/Italy/3364/00(H1N1)) partial NS1 gene for non structural protein 1 and partial NS2 gene for non structural protein 2, genomic RNA	864 bp linear mRNA	AJ519462.1 GI:31096447
Influenza A virus (A/swine/Italy-Virus/671/87(H1N1)) segment 4 hemagglutinin precursor (HA) mRNA, complete cds	1,777 bp linear mRNA	AF091315.1 GI:4585172
Influenza A Virus (A/swine/Italy/v.147/1981(H1N1)) mRNA for hemagglutinin HA1	1,028 bp linear mRNA	Z46436.1 GI:854214
Influenza A virus (A/swine/Morbihan/0070/2005(H1N1)) partial mRNA for haemagglutinin precursor (HA1 gene)	1,118 bp linear mRNA	AM490218.1 GI:222062896
Influenza A virus (A/swine/Nebraska/1/92(H1N1)) HA protein mRNA, complete cds	1,770 bp linear mRNA	L09063.1 GI:290722
Influenza A virus (A/swine/Nebraska/1/1992(H1N1)) segment 5 nucleoprotein (NP) mRNA, complete cds	1,550 bp linear mRNA	L11164.1 GI:290724
Influenza A virus (A/swine/Netherlands/12/1985(H1N1)) hemagglutinin (HA) mRNA, partial cds	981 bp linear mRNA	U46943.1 GI:1912336
Influenza A virus (A/swine/Netherlands/12/85(H1N1)) segment 4 hemagglutinin precursor (HA) mRNA, complete cds	1,776 bp linear mRNA	AF091317.1 GI:4585176
Influenza A virus (A/swine/Netherlands/25/1980(H1N1)) mRNA for nucleoprotein	539 bp linear mRNA	X75791.1 GI:438105
Influenza A virus (A/swine/Netherlands/3/1980(H1N1)) hemagglutinin (HA) mRNA, partial cds	981 bp linear mRNA	U46942.1 GI:1912334
Influenza A virus (A/swine/Netherlands/3/80(H1N1)) segment 4 hemagglutinin precursor (HA) mRNA, complete cds	1,778 bp linear mRNA	AF091314.1 GI:4585170
Influenza A virus (A/NJ/11/76 (H1N1)) neuraminidase (NA) gene, complete cds	1,410 bp linear mRNA	AF250363.2 GI:13260583

Strain/Protein	Length	GenBank / GI Accession No.
Influenza A virus (A/Swine/Quebec/192/81 (SwQc81)) neuraminidase mRNA, complete cds	1,438 bp linear mRNA	U86144.1 GI:4099318
Influenza A virus (A/Swine/Quebec/5393/91 (SwQc91)) neuraminidase mRNA, complete cds	1,438 bp linear mRNA	U86145.1 GI:4099320
Influenza A virus (A/swine/Schleswig-Holstein/1/1992(H1N1)) mRNA for hemagglutinin precursor	1,730 bp linear mRNA	Z46435.1 GI:854216
Influenza A Virus (A/swine/Schleswig-Holstein/1/1993(H1N1)) mRNA for nucleoprotein	1,554 bp linear mRNA	Z46438.1 GI:854222
Influenza A virus (A/swine/Wisconsin/1/61(H1N1)) segment 4 hemagglutinin precursor (HA) mRNA, complete cds	1,778 bp linear mRNA	AF091307.1 GI:4585156
212. Influenza A virus (A/swine/Wisconsin/1/1967(H1N1)) nucleoprotein mRNA, complete cds	1,565 bp linear mRNA	M76607.1 GI:325086
Influenza A virus (A/swine/Wisconsin/1915/1988(H1N1)) nucleoprotein mRNA, complete cds	1,565 bp linear mRNA	M76608.1 GI:325088
Influenza A virus (A/swine/WI/1915/1988(H1N1)) nucleoprotein (segment 5) mRNA, complete cds	1,550 bp linear mRNA	L46850.1 GI:954757
Influenza A virus (A/Switzerland/8808/2002(H1N1)) partial m1 gene for matrix protein 1 and partial m2 gene for matrix protein 2, genomic RNA	729 bp linear mRNA	AJ532568.1 GI:31096461
Influenza A virus (A/human/Taiwan/0012/00(H1N1)) hemagglutinin (HA) mRNA, partial cds	561 bp linear mRNA	AF362803.1 GI:14571975
Influenza A virus (A/human/Taiwan/0016/00(H1N1)) hemagglutinin (HA) mRNA, partial cds	561 bp linear mRNA	AF362779.1 GI:14571927
Influenza A virus (A/Taiwan/0016/2000 (H1N1)) polymerase basic protein 1 (PB1) mRNA, partial cds	303 bp linear mRNA	AY303752.1 GI:32330993
Influenza A virus (A/human/Taiwan/0030/00(H1N1)) hemagglutinin (HA) mRNA, partial cds	561 bp linear mRNA	AF362780.1 GI:14571929
Influenza A virus (A/Taiwan/0030/2000 (H1N1)) polymerase basic protein 1 (PB1) mRNA, partial cds	303 bp linear mRNA	AY303704.1 GI:32330897
Influenza A virus (A/Taiwan/0032/2002(H1N1)) hemagglutinin mRNA, partial cds	494 bp linear mRNA	AY604804.1 GI:50727488
Influenza A virus (A/Taiwan/0061/2002(H1N1)) hemagglutinin mRNA, partial cds	494 bp linear mRNA	AY604795.1 GI:50727470
Influenza A virus (A/Taiwan/0069/2002(H1N1)) hemagglutinin mRNA, partial cds	494 bp linear mRNA	AY604803.1 GI:50727486
Influenza A virus (A/Taiwan/0078/2002(H1N1)) hemagglutinin mRNA, partial cds	494 bp linear mRNA	AY604805.1 GI:50727490
Influenza A virus (A/Taiwan/0094/2002(H1N1)) hemagglutinin mRNA, partial cds	494 bp linear mRNA	AY604797.1 GI:50727474
Influenza A virus (A/Taiwan/0116/2002(H1N1)) hemagglutinin mRNA, partial cds	494 bp linear mRNA	AY604796.1 GI:50727472
Influenza A virus (A/human/Taiwan/0130/96(H1N1)) hemagglutinin (HA) mRNA, partial cds	564 bp linear mRNA	AF362781.1 GI:14571931
Influenza A virus (A/Taiwan/0130/96 (H1N1)) polymerase basic protein 1 (PB1) mRNA, partial cds	303 bp linear mRNA	AY303707.1 GI:32330903

Strain/Protein	Length	GenBank / GI Accession No.
Influenza A virus (A/human/Taiwan/0132/96(H1N1)) hemagglutinin (HA) mRNA, partial cds	564 bp linear mRNA	AF362782.1 GI:14571933
Influenza A virus (A/Taiwan/0132/96 (H1N1)) polymerase basic protein 1 (PB1) mRNA, partial cds	303 bp linear mRNA	AY303708.1 GI:32330905
Influenza A virus (A/human/Taiwan/0211/96(H1N1)) hemagglutinin (HA) mRNA, partial cds	564 bp linear mRNA	AF362783.1 GI:14571935
Influenza A virus (A/Taiwan/0211/96 (H1N1)) polymerase basic protein 1 (PB1) mRNA, partial cds	303 bp linear mRNA	AY303709.1 GI:32330907
Influenza A virus (A/human/Taiwan/0235/96(H1N1)) hemagglutinin (HA) mRNA, partial cds	564 bp linear mRNA	AF362784.1 GI:14571937
Influenza A virus (A/Taiwan/0235/96 (H1N1)) polymerase basic protein 1 (PB1) mRNA, partial cds	303 bp linear mRNA	AY303710.1 GI:32330909
Influenza A virus (A/human/Taiwan/0255/96(H1N1)) hemagglutinin (HA) mRNA, partial cds	564 bp linear mRNA	AF362785.1 GI:14571939
Influenza A virus (A/Taiwan/0255/96 (H1N1)) polymerase basic protein 1 (PB1) mRNA, partial cds	303 bp linear mRNA	AY303711.1 GI:32330911
Influenza A virus (A/human/Taiwan/0337/96(H1N1)) hemagglutinin (HA) mRNA, partial cds	564 bp linear mRNA	AF362786.1 GI:14571941
Influenza A virus (A/human/Taiwan/0342/96(H1N1)) hemagglutinin (HA) mRNA, partial cds	564 bp linear mRNA	AF362787.1 GI:14571943
Influenza A virus (A/Taiwan/0342/96 (H1N1)) polymerase basic protein 1 (PB1) mRNA, partial cds	303 bp linear mRNA	AY303714.1 GI:32330917
Influenza A virus (A/human/Taiwan/0464/99(H1N1)) hemagglutinin (HA) mRNA, partial cds	561 bp linear mRNA	AF362788.1 GI:14571945
Influenza A virus (A/human/Taiwan/0562/95(H1N1)) hemagglutinin (HA) mRNA, partial cds	564 bp linear mRNA	AF362789.1 GI:14571947
Influenza A virus (A/Taiwan/0562/95 (H1N1)) polymerase basic protein 1 (PB1) mRNA, partial cds	303 bp linear mRNA	AY303720.1 GI:32330929
Influenza A virus (A/human/Taiwan/0563/95(H1N1)) hemagglutinin (HA) mRNA, partial cds	564 bp linear mRNA	AF362790.1 GI:14571949
Influenza A virus (A/Taiwan/0563/95 (H1N1)) polymerase basic protein 1 (PB1) mRNA, partial cds	303 bp linear mRNA	AY303721.1 GI:32330931
Influenza A virus (A/human/Taiwan/0657/95(H1N1)) hemagglutinin (HA) mRNA, partial cds	564 bp linear mRNA	AF362791.1 GI:14571951
Influenza A virus (A/Taiwan/0657/95 (H1N1)) polymerase basic protein 1 (PB1) mRNA, partial cds	303 bp linear mRNA	AY303724.1 GI:32330937
Influenza A virus (A/Taiwan/0859/2002(H1N1)) hemagglutinin mRNA, partial cds	494 bp linear mRNA	AY604801.1 GI:50727482
Influenza A virus (A/human/Taiwan/0892/99(H1N1)) hemagglutinin (HA) mRNA, partial cds	561 bp linear mRNA	AF362792.1 GI:14571953

Strain/Protein	Length	GenBank / GI Accession No.
Influenza A virus (A/Taiwan/0983/2002(H1N1)) hemagglutinin mRNA, partial cds	494 bp linear mRNA	AY604800.1 GI:50727480
Influenza A virus (A/Taiwan/1007/2006(H1N1)) hemagglutinin (HA) mRNA, partial cds	507 bp linear mRNA	EU068163.1 GI:158452199
Influenza A virus (A/Taiwan/1015/2006(H1N1)) hemagglutinin (HA) mRNA, partial cds	507 bp linear mRNA	EU068171.1 GI:158452215
Influenza A virus (A/Taiwan/112/1996-1(H1N1)) haemagglutinin (HA) mRNA, partial cds	1,176 bp linear mRNA	AF026153.1 GI:2554950
Influenza A virus (A/Taiwan/112/1996-2(H1N1)) haemagglutinin (HA) mRNA, partial cds	1,176 bp linear mRNA	AF026154.1 GI:2554952
Influenza A virus (A/Taiwan/117/1996-1(H1N1)) haemagglutinin (HA) mRNA, partial cds	1,176 bp linear mRNA	AF026155.1 GI:2554954
Influenza A virus (A/Taiwan/117/1996-2(H1N1)) haemagglutinin (HA) mRNA, partial cds	1,176 bp linear mRNA	AF026156.1 GI:2554956
Influenza A virus (A/Taiwan/117/1996-3(H1N1)) haemagglutinin (HA) mRNA, partial cds	1,176 bp linear mRNA	AF026157.1 GI:2554958
Influenza A virus (A/Taiwan/118/1996-1(H1N1)) haemagglutinin (HA) mRNA, partial cds	1,176 bp linear mRNA	AF026158.1 GI:2554960
Influenza A virus (A/Taiwan/118/1996-2(H1N1)) haemagglutinin (HA) mRNA, partial cds	1,176 bp linear mRNA	AF026159.1 GI:2554962
Influenza A virus (A/Taiwan/118/1996-3(H1N1)) haemagglutinin (HA) mRNA, partial cds	1,176 bp linear mRNA	AF026160.1 GI:2554964
Influenza A virus (A/human/Taiwan/1184/99(H1N1)) hemagglutinin (HA) mRNA, partial cds	561 bp linear mRNA	AF362793.1 GI:14571955
Influenza A virus (A/Taiwan/1184/99 (H1N1)) polymerase basic protein 1 (PB1) mRNA, partial cds	303 bp linear mRNA	AY303726.1 GI:32330941
Influenza A virus (A/human/Taiwan/1190/95(H1N1)) hemagglutinin (HA) mRNA, partial cds	564 bp linear mRNA	AF362794.1 GI:14571957
Influenza A virus (A/Taiwan/1190/95 (H1N1)) polymerase basic protein 1 (PB1) mRNA, partial cds	303 bp linear mRNA	AY303727.1 GI:32330943
Influenza A virus (A/Taiwan/1523/2003(H1N1)) hemagglutinin mRNA, partial cds	494 bp linear mRNA	AY604808.1 GI:50727496
Influenza A virus (A/Taiwan/1566/2003(H1N1)) hemagglutinin mRNA, partial cds	494 bp linear mRNA	AY604806.1 GI:50727492
Influenza A virus (A/Taiwan/1769/96(H1N1)) matrix protein M1 (M) mRNA, partial cds	875 bp linear mRNA	AF138710.2 GI:4996871
Influenza A virus (A/Taiwan/1906/2002(H1N1)) hemagglutinin mRNA, partial cds	494 bp linear mRNA	AY604799.1 GI:50727478
Influenza A virus (A/Taiwan/1922/2002(H1N1)) hemagglutinin mRNA, partial cds	494 bp linear mRNA	AY604802.1 GI:50727484
Influenza A virus (A/Taiwan/2069/2006(H1N1)) hemagglutinin (HA) mRNA, partial cds	507 bp linear mRNA	EU068168.1 GI:158452209
Influenza A virus (A/Taiwan/2157/2001 (H1N1)) polymerase basic protein 1 (PB1) mRNA, partial cds	303 bp linear mRNA	AY303733.1 GI:32330955
Influenza A virus (A/Taiwan/2175/2001 (H1N1)) hemagglutinin (HA) mRNA, partial cds	561 bp linear mRNA	AY303734.1 GI:32330957
Influenza A virus (A/human/Taiwan/2200/95(H1N1)) hemagglutinin (HA) mRNA, partial cds	564 bp linear mRNA	AF362795.1 GI:14571959
Influenza A virus (A/Taiwan/2200/95 (H1N1)) polymerase basic protein 1 (PB1) mRNA, partial cds	303 bp linear mRNA	AY303737.1 GI:32330963
Influenza A virus (A/Taiwan/2966/2006(H1N1)) hemagglutinin (HA) mRNA, partial cds	507 bp linear mRNA	EU068170.1 GI:158452213

Strain/Protein	Length	GenBank / GI Accession No.
Influenza A virus (A/Taiwan/3168/2005(H1N1)) hemagglutinin (HA) mRNA, partial cds	507 bp linear mRNA	EU068174.1 GI:158452221
Influenza A virus (A/human/Taiwan/3355/97(H1N1)) hemagglutinin (HA) mRNA, partial cds	561 bp linear mRNA	AF362796.1 GI:14571961
Influenza A virus (A/Taiwan/3355/97 (H1N1)) polymerase basic protein 1 (PB1) mRNA, partial cds	303 bp linear mRNA	AY303739.1 GI:32330967
Influenza A virus (A/Taiwan/3361/2001 (H1N1)) polymerase basic protein 1 (PB1) mRNA, partial cds	303 bp linear mRNA	AY303740.1 GI:32330969
Influenza A virus (A/Taiwan/3361/2001 (H1N1)) hemagglutinin (HA) mRNA, partial cds	561 bp linear mRNA	AY303741.1 GI:32330971
Influenza A virus (A/Taiwan/3518/2006(H1N1)) hemagglutinin (HA) mRNA, partial cds	507 bp linear mRNA	EU068169.1 GI:158452211
Influenza A virus (A/human/Taiwan/3825/00(H1N1)) hemagglutinin (HA) mRNA, partial cds	581 bp linear mRNA	AF362797.1 GI:14571963
Influenza A virus (A/Taiwan/3896/2001 (H1N1)) polymerase basic protein 1 (PB1) mRNA, partial cds	303 bp linear mRNA	AY303746.1 GI:32330981
Influenza A virus (A/Taiwan/3896/2001 (H1N1)) hemagglutinin (HA) mRNA, partial cds	561 bp linear mRNA	AY303747.1 GI:32330983
Influenza A virus (A/Taiwan/4050/2003(H1N1)) hemagglutinin mRNA, partial cds	494 bp linear mRNA	AY604807.1 GI:50727494
Influenza A virus (A/Taiwan/4054/2006(H1N1)) hemagglutinin (HA) mRNA, partial cds	507 bp linear mRNA	EU068160.1 GI:158452193
Influenza A virus (A/human/Taiwan/4360/99(H1N1)) hemagglutinin (HA) mRNA, partial cds	561 bp linear mRNA	AF362798.1 GI:14571965
Influenza A virus (A/Taiwan/4360/99 (H1N1)) polymerase basic protein 1 (PB1) mRNA, partial cds	303 bp linear mRNA	AY303748.1 GI:32330985
Influenza A virus (A/human/Taiwan/4415/99(H1N1)) hemagglutinin (HA) mRNA, partial cds	561 bp linear mRNA	AF362799.1 GI:14571967
Influenza A virus (A/Taiwan/4415/99 (H1N1)) polymerase basic protein 1 (PB1) mRNA, partial cds	303 bp linear mRNA	AY303749.1 GI:32330987
Influenza A virus (A/Taiwan/4509/2006(H1N1)) hemagglutinin (HA) mRNA, partial cds	507 bp linear mRNA	EU068165.1 GI:158452203
Influenza A virus (A/human/Taiwan/4845/99(H1N1)) hemagglutinin (HA) mRNA, partial cds	561 bp linear mRNA	AF362800.1 GI:14571969
Influenza A virus (A/Taiwan/4845/99 (H1N1)) polymerase basic protein 1 (PB1) mRNA, partial cds	303 bp linear mRNA	AY303750.1 GI:32330989
Influenza A virus (A/human/Taiwan/4943/99(H1N1)) hemagglutinin (HA) mRNA, partial cds	561 bp linear mRNA	AF362801.1 GI:14571971
Influenza A virus (A/Taiwan/5010/2006(H1N1)) hemagglutinin (HA) mRNA, partial cds	507 bp linear mRNA	EU068167.1 GI:158452207
Influenza A virus (A/human/Taiwan/5063/99(H1N1)) hemagglutinin (HA) mRNA, partial cds	561 bp linear mRNA	AF362802.1 GI:14571973
Influenza A virus (A/Taiwan/5063/99 (H1N1)) polymerase basic protein 1 (PB1) mRNA, partial cds	303 bp linear mRNA	AY303751.1 GI:32330991
Influenza A virus (A/Taiwan/5084/2006(H1N1)) hemagglutinin (HA) mRNA, partial cds	507 bp linear mRNA	EU068166.1 GI:158452205

Strain/Protein	Length	GenBank / GI Accession No.
Influenza A virus (A/Taiwan/511/96(H1N1)) matrix protein M1 (M) mRNA, partial cds	875 bp linear mRNA	AF138708.2 GI:4996867
Influenza A virus (A/Taiwan/557/2006(H1N1)) hemagglutinin (HA) mRNA, partial cds	507 bp linear mRNA	EU068156.1 GI:158452185
Influenza A virus (A/Taiwan/562/2006(H1N1)) hemagglutinin (HA) mRNA, partial cds	507 bp linear mRNA	EU068159.1 GI:158452191
Influenza A virus (A/human/Taiwan/5779/98(H1N1)) hemagglutinin (HA) mRNA, partial cds	561 bp linear mRNA	AF362778.1 GI:14571925
Influenza A virus (A/Taiwan/5779/98 (H1N1)) polymerase basic protein 1 (PB1) mRNA, partial cds	303 bp linear mRNA	AY303702.1 GI:32330893
Influenza A virus (A/Taiwan/6025/2005(H1N1)) hemagglutinin (HA) mRNA, partial cds	507 bp linear mRNA	EU068172.1 GI:158452217
Influenza A virus (A/Taiwan/607/2006(H1N1)) hemagglutinin (HA) mRNA, partial cds	507 bp linear mRNA	EU068157.1 GI:158452187
Influenza A virus (A/Taiwan/615/2006(H1N1)) hemagglutinin (HA) mRNA, partial cds	507 bp linear mRNA	EU068162.1 GI:158452197
Influenza A virus (A/Taiwan/645/2006(H1N1)) hemagglutinin (HA) mRNA, partial cds	507 bp linear mRNA	EU068164.1 GI:158452201
Influenza A virus (A/Taiwan/680/2005(H1N1)) hemagglutinin (HA) mRNA, partial cds	507 bp linear mRNA	EU068173.1 GI:158452219
Influenza A virus (A/Taiwan/719/2006(H1N1)) hemagglutinin (HA) mRNA, partial cds	507 bp linear mRNA	EU068158.1 GI:158452189
Influenza A virus (A/Thailand/CU124/2006(H3N2)) neuraminidase (NA) mRNA, complete cds	1,410 bp linear mRNA	EU021285.1 GI:154224724
Influenza A virus (A/Thailand/CU32/2006(H1N1)) neuraminidase (NA) mRNA, complete cds	1,413 bp linear mRNA	EU021265.1 GI:154224704
Influenza A virus (A/Thailand/CU32/2006(H1N1)) hemagglutinin (HA) mRNA, complete cds	1,698 bp linear mRNA	EU021264.1 GI:154224775
Influenza A virus (A/Thailand/CU41/2006(H1N1)) neuraminidase (NA) mRNA, complete cds	1,413 bp linear mRNA	EU021247.1 GI:154224686
Influenza A virus (A/Thailand/CU41/2006(H1N1)) hemagglutinin (HA) mRNA, complete cds	1,698 bp linear mRNA	EU021246.1 GI:154224757
Influenza A virus (A/Thailand/CU44/2006(H1N1)) neuraminidase (NA) mRNA, complete cds	1,413 bp linear mRNA	EU021259.1 GI:154224698
Influenza A virus (A/Thailand/CU44/2006(H1N1)) hemagglutinin (HA) mRNA, complete cds	1,698 bp linear mRNA	EU021258.1 GI:154224769
Influenza A virus (A/Thailand/CU51/2006(H1N1)) neuraminidase (NA) mRNA, complete cds	1,413 bp linear mRNA	EU021255.1 GI:154224694
Influenza A virus (A/Thailand/CU51/2006(H1N1)) hemagglutinin (HA) mRNA, complete cds	1,698 bp linear mRNA	EU021254.1 GI:154224765
Influenza A virus (A/Thailand/CU53/2006(H1N1)) neuraminidase (NA) mRNA, complete cds	1,413 bp linear mRNA	EU021249.1 GI:154224688
Influenza A virus (A/Thailand/CU53/2006(H1N1)) hemagglutinin (HA) mRNA, complete cds	1,698 bp linear mRNA	EU021248.1 GI:154224759
Influenza A virus (A/Thailand/CU57/2006(H1N1)) neuraminidase (NA) mRNA, complete cds	1,413 bp linear mRNA	EU021257.1 GI:154224696

Strain/Protein	Length	GenBank / GI Accession No.
Influenza A virus (A/Thailand/CU57/2006(H1N1)) hemagglutinin (HA) mRNA, complete cds	1,698 bp linear mRNA	EU021256.1 GI:154224767
Influenza A virus (A/Thailand/CU67/2006(H1N1)) neuraminidase (NA) mRNA, complete cds	1,413 bp linear mRNA	EU021251.1 GI:154224690
Influenza A virus (A/Thailand/CU67/2006(H1N1)) hemagglutinin (HA) mRNA, complete cds	1,698 bp linear mRNA	EU021250.1 GI:154224761
Influenza A virus (A/Thailand/CU68/2006(H1N1)) neuraminidase (NA) mRNA, complete cds	1,413 bp linear mRNA	EU021261.1 GI:154224700
Influenza A virus (A/Thailand/CU68/2006(H1N1)) hemagglutinin (HA) mRNA, complete cds	1,698 bp linear mRNA	EU021260.1 GI:154224771
Influenza A virus (A/Thailand/CU75/2006(H1N1)) neuraminidase (NA) mRNA, complete cds	1,413 bp linear mRNA	EU021263.1 GI:154224702
Influenza A virus (A/Thailand/CU75/2006(H1N1)) hemagglutinin (HA) mRNA, complete cds	1,698 bp linear mRNA	EU021262.1 GI:154224773
Influenza A virus (A/Thailand/CU88/2006(H1N1)) neuraminidase (NA) mRNA, complete cds	1,413 bp linear mRNA	EU021253.1 GI:154224692
Influenza A virus (A/Thailand/CU88/2006(H1N1)) hemagglutinin (HA) mRNA, complete cds	1,698 bp linear mRNA	EU021252.1 GI:154224763
Influenza A virus (A/turkey/England/647/1977(H1N1)) nucleoprotein mRNA, complete cds	1,565 bp linear mRNA	M76603.1 GI:325094
Influenza A virus (A/turkey/France/87075/87(H1N1)) N1 gene for neuraminidase, genomic RNA	1,445 bp linear mRNA	AJ416626.1 GI:39840719
Influenza A virus (A/turkey/Germany/3/91(H1N1)) mRNA for PB2 polymerase (partial)	394 bp linear mRNA	Z30272.1 GI:456652
Influenza A virus (A/turkey/Germany/3/91(H1N1)) mRNA for neuraminidase (UTR)	97 bp linear mRNA	Z30275.1 GI:530398
Influenza A virus (A/turkey/Germany/3/91(H1N1)) mRNA for PA polymerase	264 bp linear mRNA	Z30274.1 GI:530401
Influenza A virus (A/turkey/Germany/3/91(H1N1)) mRNA for PBI polymerase (partial)	247 bp linear mRNA	Z30273.1 GI:530403
Influenza A virus (A/turkey/Germany/3/91(H1N1)) mRNA for hemagglutinin HA1	1,038 bp linear mRNA	Z46441.1 GI:854218
Influenza A virus (A/turkey/Minnesota/1661/1981(H1N1)) hemagglutinin (HA) mRNA, partial cds	981 bp linear mRNA	U46941.1 GI:1912332
Influenza A virus (A/turkey/Minnesota/1661/81(H1N1)) segment 4 hemagglutinin precursor (HA) mRNA, complete cds	1,777 bp linear mRNA	AF091310.1 GI:4585162
Influenza A virus (A/turkey/North Carolina/1790/1988(H1N1)) nucleoprotein mRNA, complete cds	1,565 bp linear mRNA	M76609.1 GI:325096
Influenza A virus (A/Weiss/43 (H1N1)) neuraminidase (NA) gene, complete cds	1,410 bp linear mRNA	AF250365.2 GI:13260589

Strain/Protein	Length	GenBank / GI Accession No.
Influenza A virus (A/Wilson-Smith/1933(H1N1)) nucleocapsid protein (NP) mRNA, complete cds	1,497 bp linear mRNA	EU330203.1 GI:167989512
Influenza A virus (A/Wisconsin/3523/1988(H1N1)) neuraminidase (NA) mRNA, partial cds	241 bp linear mRNA	U47816.1 GI:1912352
Influenza A virus (A/Wisconsin/3623/1988(H1N1)) nucleoprotein mRNA, complete cds	1,565 bp linear mRNA	M76610.1 GI:325103
Influenza A virus (A/WI/4754/1994(H1N1)) PB1 (PB1) mRNA, partial cds	235 bp linear mRNA	U53156.1 GI:1399590
Influenza A virus (A/WI/4754/1994(H1N1)) PB2 (PB2) mRNA, partial cds	168 bp linear mRNA	U53158.1 GI:1399594
Influenza A virus (A/WI/4754/1994(H1N1)) PA (PA) mRNA, partial cds	621 bp linear mRNA	U53160.1 GI:1399598
Influenza A virus (A/WI/4754/1994(H1N1)) hemagglutinin (HA) mRNA, complete cds	1,778 bp linear mRNA	U53162.1 GI:1399602
Influenza A virus (A/WI/4754/1994(H1N1)) NP (NP) mRNA, partial cds	200 bp linear mRNA	U53164.1 GI:1399606
Influenza A virus (A/WI/4754/1994(H1N1)) neuraminidase (NA) mRNA, complete cds	1,458 bp linear mRNA	U53166.1 GI:1399610
Influenza A virus (A/WI/4754/1994(H1N1)) M (M) mRNA, complete cds	1,027 bp linear mRNA	U53168.1 GI:1399614
Influenza A virus (A/WI/4754/1994(H1N1)) NS (NS) mRNA, complete cds	890 bp linear mRNA	U53170.1 GI:1399618
Influenza A virus (A/WI/4755/1994(H1N1)) PB1 (PB1) mRNA, partial cds	203 bp linear mRNA	U53157.1 GI:1399592
Influenza A virus (A/WI/4755/1994(H1N1)) PB2 (PB2) mRNA, partial cds	173 bp linear mRNA	U53159.1 GI:1399596
Influenza A virus (A/WI/4755/1994(H1N1)) PA (PA) mRNA, partial cds	621 bp linear mRNA	U53161.1 GI:1399600
Influenza A virus (A/WI/4755/1994(H1N1)) hemagglutinin (HA) mRNA, complete cds	1,778 bp linear mRNA	U53163.1 GI:1399604
Influenza A virus (A/WI/4755/1994(H1N1)) NP (NP) mRNA, partial cds	215 bp linear mRNA	U53165.1 GI:1399608
Influenza A virus (A/WI/4755/1994(H1N1)) neuraminidase (NA) mRNA, partial cds	209 bp linear mRNA	U53167.1 GI:1399612
Influenza A virus (A/WI/4755/1994(H1N1)) M (M) mRNA, complete cds	1,027 bp linear mRNA	U53169.1 GI:1399616
Influenza A virus (A/WI/4755/1994(H1N1)) NS (NS) mRNA, complete cds	890 bp linear mRNA	U53171.1 GI:1399620
Influenza A virus (A/WSN/33) segment 5 nucleocapsid protein (NP) mRNA, partial cds	543 bp linear mRNA	AF306656.1 GI:11935089

Table 8. Influenza H3N2 Antigens

Strain/Protein	Length	GenBank / GI Accession No.
1. Influenza A virus (A/Aichi/2/1968(H3N2)) hemagglutinin (HA) mRNA, complete cds	1,704 bp linear mRNA	EF614248.1 GI:148910819
2. Influenza A virus (A/Aichi/2/1968(H3N2)) hemagglutinin (HA) mRNA, partial cds	1,698 bp linear mRNA	EF614249.1 GI:148910821
3. Influenza A virus (A/Aichi/2/1968(H3N2)) hemagglutinin (HA) mRNA, partial cds	1,698 bp linear mRNA	EF614250.1 GI:148910823
4. Influenza A virus (A/Aichi/2/1968(H3N2)) hemagglutinin (HA) mRNA, partial cds	1,698 bp linear mRNA	EF614251.1 GI:148910825
5. Influenza A virus (A/Akita/1/1995(H3N2)) haemagglutinin mRNA, partial cds	1,032 bp linear mRNA	U48444.1 GI:1574989

Strain/Protein	Length	GenBank / GI Accession No.
6. Influenza A virus (A/Beijing/32/1992(H3N2)) mRNA for haemagglutinin	1,041 bp linear mRNA	Z46392.1 GI:609020
7. Influenza A virus (A/Canada/33312/99(H3N2)) hemagglutinin (HA) mRNA, partial cds	987 bp linear mRNA	AF501516.1 GI:21314288
8. Influenza A virus (A/Charlottesville/10/99 (H3N2)) hemagglutinin mRNA, partial cds	987 bp linear mRNA	AF297094.1 GI:11228917
9. Influenza A virus (A/Charlottesville/49/99 (H3N2)) hemagglutinin mRNA, partial cds	987 bp linear mRNA	AF297096.1 GI:11228921
10. Influenza A virus (A/Charlottesville/69/99 (H3N2)) hemagglutinin mRNA, partial cds	987 bp linear mRNA	AF297097.1 GI:11228923
11. Influenza A virus (A/Charlottesville/73/99 (H3N2)) hemagglutinin mRNA, partial cds	987 bp linear mRNA	AF297095.1 GI:11228919
12. Influenza A virus (A/England/1/1993(H3N2)) mRNA for haemagglutinin	1,041 bp linear mRNA	Z46393.1 GI:609024
13. Influenza A virus (A/England/247/1993(H3N2)) mRNA for haemagglutinin	1,041 bp linear mRNA	Z46394.1 GI:609025
14. Influenza A virus (A/England/269/93(H3N2)) mRNA for haemagglutinin	1,041 bp linear mRNA	Z46395.1 GI:609027
15. Influenza A virus (A/England/284/1993(H3N2)) mRNA for haemagglutinin	1,041 bp linear mRNA	Z46396.1 GI:609029
16. Influenza A virus (A/England/286/1993(H3N2)) mRNA for haemagglutinin	1,041 bp linear mRNA	Z46397.1 GI:609031
17. Influenza A virus (A/England/289/1993(H3N2)) mRNA for haemagglutinin	1,041 bp linear mRNA	Z46398.1 GI:609033
18. Influenza A virus (A/England/328/1993(H3N2)) mRNA for haemagglutinin	1,041 bp linear mRNA	Z46399.1 GI:609035
19. Influenza A virus (A/England/346/1993(H3N2)) mRNA for haemagglutinin	1,041 bp linear mRNA	Z46400.1 GI:609037
20. Influenza A virus (A/England/347/1993(H3N2)) mRNA for haemagglutinin	1,041 bp linear mRNA	Z46401.1 GI:609039
21. Influenza A virus (A/England/42/72(H3N2)) hemagglutinin mRNA, partial cds	1,091 bp linear mRNA	AF201875.1 GI:6470274
22. Influenza A virus (A/England/471/1993(H3N2)) mRNA for haemagglutinin	1,041 bp linear mRNA	Z46402.1 GI:609041
23. Influenza A virus (A/England/67/1994(H3N2)) mRNA for haemagglutinin	1,041 bp linear mRNA	Z46403.1 GI:609043
24. Influenza A virus (A/England/68/1994(H3N2)) mRNA for haemagglutinin	1,041 bp linear mRNA	Z46404.1 GI:609045
25. Influenza A virus (A/England/7/1994(H3N2)) mRNA for haemagglutinin	1,041 bp linear mRNA	Z46405.1 GI:609047

Strain/Protein	Length	GenBank / GI Accession No.
28. Influenza A virus (A/Guangdong/25/1993(H3N2)) mRNA for haemagglutinin	1,041 bp linear mRNA	Z46406.1 GI:609049
29. Influenza A virus (A/Hong Kong/1/68(H3N2)) hemagglutinin mRNA, partial cds	1,091 bp linear mRNA	AF201874.1 GI:6470272
30. Influenza A virus (A/Hong Kong/1/1994(H3N2)) mRNA for haemagglutinin	1,041 bp linear mRNA	Z46407.1 GI:609051
31. Influenza A virus (A/Hong Kong/1143/99(H3N2)) hemagglutinin mRNA, complete cds	1,762 bp linear mRNA	AF382319.1 GI:14487957
32. Influenza A virus (A/Hong Kong/1143/99(H3N2)) hemagglutinin mRNA, complete cds	1,762 bp linear mRNA	AF382320.1 GI:14487959
33. Influenza A virus (A/Hong Kong/1143/99(H3N2)) neuraminidase mRNA, complete cds	1,466 bp linear mRNA	AF382329.1 GI:14487977
34. Influenza A virus (A/Hong Kong/1143/99(H3N2)) neuraminidase mRNA, complete cds	1,466 bp linear mRNA	AF382330.1 GI:14487979
35. Influenza A virus (A/Hong Kong/1144/99(H3N2)) hemagglutinin mRNA, complete cds	1,762 bp linear mRNA	AY035589.1 GI:14486403
36. Influenza A virus (A/Hong Kong/1144/99(H3N2)) hemagglutinin mRNA, complete cds	1,762 bp linear mRNA	AF382321.1 GI:14487961
37. Influenza A virus (A/Hong Kong/1144/99(H3N2)) hemagglutinin mRNA, complete cds	1,762 bp linear mRNA	AF382322.1 GI:14487963
38. Influenza A virus (A/Hong Kong/1144/99(H3N2)) neuraminidase mRNA, complete cds	1,466 bp linear mRNA	AF382331.1 GI:14487981
39. Influenza A virus (A/Hong Kong/1144/99(H3N2)) neuraminidase mRNA, complete cds	1,466 bp linear mRNA	AF382332.1 GI:14487983
40. Influenza A virus (A/Hong Kong/1179/99(H3N2)) hemagglutinin mRNA, complete cds	1,762 bp linear mRNA	AY035590.1 GI:14486405
41. Influenza A virus (A/Hong Kong/1179/99(H3N2)) hemagglutinin mRNA, complete cds	1,762 bp linear mRNA	AF382323.1 GI:14487965
42. Influenza A virus (A/Hong Kong/1179/99(H3N2)) hemagglutinin mRNA, complete cds	1,762 bp linear mRNA	AF382324.1 GI:14487967
43. Influenza A virus (A/Hong Kong/1180/99(H3N2)) hemagglutinin mRNA, complete cds	1,762 bp linear mRNA	AY035591.1 GI:14486407
44. Influenza A virus (A/Hong Kong/1180/99(H3N2)) hemagglutinin mRNA, complete cds	1,762 bp linear mRNA	AF382325.1 GI:14487969
45. Influenza A virus (A/Hong Kong/1180/99(H3N2)) hemagglutinin mRNA, complete cds	1,762 bp linear mRNA	AF382326.1 GI:14487971
46. Influenza A virus (A/Hong Kong/1182/99(H3N2)) hemagglutinin mRNA, complete cds	1,762 bp linear mRNA	AF382327.1 GI:14487973
47. Influenza A virus (A/Hong Kong/1182/99(H3N2)) hemagglutinin mRNA, complete cds	1,762 bp linear mRNA	AF382328.1 GI:14487975

Strain/Protein	Length	GenBank / GI Accession No.
48. Influenza A virus (A/Hong Kong/2/1994(H3N2)) mRNA for haemagglutinin	1,041 bp linear mRNA	Z46408.1 GI:609055
49. Influenza A virus (A/Hong Kong/23/1992(H3N2)) mRNA for haemagglutinin	1,041 bp linear mRNA	Z46410.1 GI:609053
50. Influenza A virus (A/Hong Kong/34/1990(H3N2)) mRNA for haemagglutinin	1,041 bp linear mRNA	Z46409.1 GI:609057
51. Influenza A virus (A/England/286/1993(H3N2)) mRNA for haemagglutinin	1,041 bp linear mRNA	Z46397.1 GI:609031
52. Influenza A virus (A/England/289/1993(H3N2)) mRNA for haemagglutinin	1,041 bp linear mRNA	Z46398.1 GI:609033
53. Influenza A virus (A/England/328/1993(H3N2)) mRNA for haemagglutinin	1,041 bp linear mRNA	Z46399.1 GI:609035
54. Influenza A virus (A/England/346/1993(H3N2)) mRNA for haemagglutinin	1,041 bp linear mRNA	Z46400.1 GI:609037
55. Influenza A virus (A/England/347/1993(H3N2)) mRNA for haemagglutinin	1,041 bp linear mRNA	Z46401.1 GI:609039
56. Influenza A virus (A/England/42/72(H3N2)) hemagglutinin mRNA, partial cds	1,091 bp linear mRNA	AF201875.1 GI:6470274
57. Influenza A virus (A/England/471/1993(H3N2)) mRNA for haemagglutinin	1,041 bp linear mRNA	Z46402.1 GI:609041
58. Influenza A virus (A/England/67/1994(H3N2)) mRNA for haemagglutinin	1,041 bp linear mRNA	Z46403.1 GI:609043
59. Influenza A virus (A/England/68/1994(H3N2)) mRNA for haemagglutinin	1,041 bp linear mRNA	Z46404.1 GI:609045
60. Influenza A virus (A/England/7/1994(H3N2)) mRNA for haemagglutinin	1,041 bp linear mRNA	Z46405.1 GI:609047
63. Influenza A virus (A/Guandong/28/1994(H3N2)) haemagglutinin mRNA, partial cds	1,032 bp linear mRNA	U48442.1 GI:1574985
64. Influenza A virus (A/Guangdong/25/1993(H3N2)) mRNA for haemagglutinin	1,041 bp linear mRNA	Z46406.1 GI:609049
65. Influenza A virus (A/Hebei/19/1995(H3N2)) haemagglutinin mRNA, partial cds	1,032 bp linear mRNA	U48447.1 GI:1574995
66. Influenza A virus (A/Hebei/41/1994(H3N2)) haemagglutinin mRNA, partial cds	1,032 bp linear mRNA	U48441.1 GI:1574983
67. Influenza A virus (A/Hong Kong/1/68(H3N2)) hemagglutinin mRNA, partial cds	1,091 bp linear mRNA	AF201874.1 GI:6470272
68. Influenza A virus (A/Hong Kong/1/1994(H3N2)) mRNA for haemagglutinin	1,041 bp linear mRNA	Z46407.1 GI:609051
69. Influenza A virus (A/Hong Kong/1143/99(H3N2)) hemagglutinin mRNA, complete cds	1,762 bp linear mRNA	AY035588.1 GI:14486401
70. Influenza A virus (A/Hong Kong/1143/99(H3N2)) hemagglutinin mRNA, complete cds	1,762 bp linear mRNA	AF382319.1 GI:14487957

Strain/Protein	Length	GenBank / GI Accession No.
71. Influenza A virus (A/Hong Kong/1143/99(H3N2)) hemagglutinin mRNA, complete cds	1,762 bp linear mRNA	AF382320.1 GI:14487959
72. Influenza A virus (A/Hong Kong/1143/99(H3N2)) neuraminidase mRNA, complete cds	1,466 bp linear mRNA	AF382329.1 GI:14487977
73. Influenza A virus (A/Hong Kong/1143/99(H3N2)) neuraminidase mRNA, complete cds	1,466 bp linear mRNA	AF382330.1 GI:14487979
74. Influenza A virus (A/Hong Kong/1144/99(H3N2)) hemagglutinin mRNA, complete cds	1,762 bp linear mRNA	AY035589.1 GI:14486403
75. Influenza A virus (A/Hong Kong/1144/99(H3N2)) hemagglutinin mRNA, complete cds	1,762 bp linear mRNA	AF382321.1 GI:14487961
76. Influenza A virus (A/Hong Kong/1144/99(H3N2)) hemagglutinin mRNA, complete cds	1,762 bp linear mRNA	AF382322.1 GI:14487963
77. Influenza A virus (A/Hong Kong/1144/99(H3N2)) neuraminidase mRNA, complete cds	1,466 bp linear mRNA	AF382331.1 GI:14487981
78. Influenza A virus (A/Hong Kong/1144/99(H3N2)) neuraminidase mRNA, complete cds	1,466 bp linear mRNA	AF382332.1 GI:14487983
79. Influenza A virus (A/Hong Kong/1179/99(H3N2)) hemagglutinin mRNA, complete cds	1,762 bp linear mRNA	AY035590.1 GI:14486405
80. Influenza A virus (A/Hong Kong/1179/99(H3N2)) hemagglutinin mRNA, complete cds	1,762 bp linear mRNA	AF382323.1 GI:14487965
81. Influenza A virus (A/Hong Kong/1179/99(H3N2)) hemagglutinin mRNA, complete cds	1,762 bp linear mRNA	AF382324.1 GI:14487967
82. Influenza A virus (A/Hong Kong/1180/99(H3N2)) hemagglutinin mRNA, complete cds	1,762 bp linear mRNA	AY035591.1 GI:14486407
83. Influenza A virus (A/Hong Kong/1180/99(H3N2)) hemagglutinin mRNA, complete cds	1,762 bp linear mRNA	AF382325.1 GI:14487969
84. Influenza A virus (A/Hong Kong/1180/99(H3N2)) hemagglutinin mRNA, complete cds	1,762 bp linear mRNA	AF382326.1 GI:14487971
85. Influenza A virus (A/Hong Kong/1182/99(H3N2)) hemagglutinin mRNA, complete cds	1,762 bp linear mRNA	AY035592.1 GI:14486409
86. Influenza A virus (A/Hong Kong/1182/99(H3N2)) hemagglutinin mRNA, complete cds	1,762 bp linear mRNA	AF382327.1 GI:14487973
87. Influenza A virus (A/Hong Kong/1182/99(H3N2)) hemagglutinin mRNA, complete cds	1,762 bp linear mRNA	AF382328.1 GI:14487975
88. Influenza A virus (A/Hong Kong/2/1994(H3N2)) mRNA for haemagglutinin	1,041 bp linear mRNA	Z46408.1 GI:609055
89. Influenza A virus (A/Hong Kong/23/1992(H3N2)) mRNA for haemagglutinin	1,041 bp linear mRNA	Z46410.1 GI:609053
90. Influenza A virus (A/Hong Kong/34/1990(H3N2)) mRNA for haemagglutinin	1,041 bp linear mRNA	Z46409.1 GI:609057
91. Influenza A virus (A/Indiana/28170/99(H3N2)) hemagglutinin (HA) mRNA, partial cds	987 bp linear mRNA	AF501534.1 GI:21314324

Strain/Protein	Length	GenBank / GI Accession No.
92. Influenza A virus (A/Kinmen/618/03(H3N2)) hemagglutinin (HA) mRNA, partial cds	529 bp linear mRNA	AY961997.1 GI:68138151
93. Influenza A virus (A/Kinmen/618/03(H3N2)) neuraminidase (NA) mRNA, partial cds	383 bp linear mRNA	AY973325.1 GI:70673206
94. Influenza A virus (A/Kinmen/618/03(H3N2)) nucleoprotein (NP) mRNA, partial cds	882 bp linear mRNA	AY986986.1 GI:70728099
95. Influenza A virus (A/Kinmen/621/03(H3N2)) hemagglutinin (HA) mRNA, partial cds	545 bp linear mRNA	AY962017.1 GI:68138191
96. Influenza A virus (A/Kinmen/621/03(H3N2)) neuraminidase (NA) mRNA, partial cds	386 bp linear mRNA	AY973326.1 GI:70673208
97. Influenza A virus (A/Kinmen/621/03(H3N2)) nucleoprotein (NP) mRNA, partial cds	882 bp linear mRNA	AY986987.1 GI:70728101
98. Influenza A virus (A/Kinmen/639/04(H3N2)) hemagglutinin (HA) mRNA, partial cds	786 bp linear mRNA	AY962008.1 GI:68138173
99. Influenza A virus (A/Kinmen/639/04(H3N2)) neuraminidase (NA) mRNA, partial cds	381 bp linear mRNA	AY973327.1 GI:70673210
100. Influenza A virus (A/Kinmen/639/04(H3N2)) nucleoprotein (NP) mRNA, partial cds	882 bp linear mRNA	AY986988.1 GI:70728103
101. Influenza A virus (A/Kinmen/641/04(H3N2)) hemagglutinin (HA) mRNA, partial cds	596 bp linear mRNA	AY962004.1 GI:68138165
102. Influenza A virus (A/Kinmen/641/04(H3N2)) neuraminidase (NA) mRNA, partial cds	785 bp linear mRNA	AY973328.1 GI:70673212
103. Influenza A virus (A/Kinmen/642/04(H3N2)) hemagglutinin (HA) mRNA, partial cds	576 bp linear mRNA	AY962001.1 GI:68138159
104. Influenza A virus (A/Kinmen/642/04(H3N2)) neuraminidase (NA) mRNA, partial cds	580 bp linear mRNA	AY973329.1 GI:70673214
105. Influenza A virus (A/Kinmen/642/04(H3N2)) nucleoprotein (NP) mRNA, partial cds	882 bp linear mRNA	AY986989.1 GI:70728105
106. Influenza A virus (A/Kinmen/645/04(H3N2)) hemagglutinin (HA) mRNA, partial cds	789 bp linear mRNA	AY962009.1 GI:68138175
107. Influenza A virus (A/Kinmen/645/04(H3N2)) neuraminidase (NA) mRNA, partial cds	581 bp linear mRNA	AY973330.1 GI:70673216
108. Influenza A virus (A/Kinmen/645/04(H3N2)) nucleoprotein (NP) mRNA, partial cds	981 bp linear mRNA	AY986990.1 GI:70728107
109. Influenza A virus (A/LosAngeles/2/1987(H3N2)) polymerase protein basic 2 (PB2) mRNA, complete cds	2,341 bp linear mRNA	U62543.1 GI:1480737
110. Influenza A virus (A/Madrid/252/1993(H3N2)) mRNA for haemagglutinin	1,041 bp linear mRNA	Z46411.1 GI:609067
111. Influenza A virus (A/Michigan/22568/99(H3N2)) hemagglutinin (HA) mRNA, partial cds	987 bp linear mRNA	AF501531.1 GI:21314318

Strain/Protein	Length	GenBank / GI Accession No.
112. Influenza A virus (A/Michigan/22692/99(H3N2)) hemagglutinin (HA) mRNA, partial cds	987 bp linear mRNA	AF501518.1 GI:21314292
113. Influenza A virus (A/Moscow/10/99(H3N2)) partial NS1 gene for non structural protein 1 and partial NS2 gene for non structural protein 2, genomic RNA	754 bp linear mRNA	AJ519454.1 GI:31096423
114. Influenza A virus (A/ningbo/17/2002(H3N2)) hemagglutinin (HA) mRNA, partial cds	987 bp linear mRNA	AY138518.1 GI:24895178
115. Influenza A virus (A/ningbo/25/2002(H3N2)) hemagglutinin (HA) mRNA, partial cds	987 bp linear mRNA	AY138517.1 GI:24895169
116. Influenza A virus (A/NT/60/68/29C(H3N2)) mRNA for haemagglutinin (HA1 and HA2 genes)	1,765 bp linear mRNA	V01103.1 GI:60800
117. Influenza A virus (A/Oklahoma/323/03(H3N2)) hemagglutinin mRNA, complete cds	1,701 bp linear mRNA	DQ059385.1 GI:66933143
118. Influenza A virus (A/Oklahoma/323/03(H3N2)) neuraminidase mRNA, complete cds	1,410 bp linear mRNA	DQ059384.2 GI:75859981
119. Influenza A virus (A/Panama/2007/99(H3N2)) partial NS1 gene for non structural protein 1 and partial NS2 gene for non structural protein 2, genomic RNA	766 bp linear mRNA	AJ519458.1 GI:31096435
120. Influenza A virus (A/Pennsylvania/20109/99(H3N2)) hemagglutinin (HA) mRNA, partial cds	987 bp linear mRNA	AF501526.1 GI:21314308
121. Influenza A virus (A/Philippines/2/82(H3N2)) hemagglutinin mRNA, partial cds	1,091 bp linear mRNA	AF233691.1 GI:7331124
122. Influenza A virus (A/Pingtung/303/04(H3N2)) hemagglutinin (HA) mRNA, partial cds	767 bp linear mRNA	AY962000.1 GI:68138157
123. Influenza A virus (A/Pingtung/303/04(H3N2)) neuraminidase (NA) mRNA, partial cds	783 bp linear mRNA	AY973331.1 GI:70673218
124. Influenza A virus (A/Pingtung/303/04(H3N2)) nucleoprotein (NP) mRNA, partial cds	928 bp linear mRNA	AY986991.1 GI:70728109
125. Influenza A virus (A/Pingtung/313/04(H3N2)) hemagglutinin (HA) mRNA, partial cds	788 bp linear mRNA	AY961999.1 GI:68138155
126. Influenza A virus (A/Pingtung/313/04(H3N2)) neuraminidase (NA) mRNA, partial cds	787 bp linear mRNA	AY973332.1 GI:70673220
127. Influenza A virus (A/Pingtung/313/04(H3N2)) nucleoprotein (NP) mRNA, partial cds	882 bp linear mRNA	AY986992.1 GI:70728111
128. Influenza A virus (A/ruddy turnstone/Delaware/142/99 (H3N2)) nonfunctional matrix protein mRNA, partial sequence	927 bp linear mRNA	AY664458.1 GI:51011862
129. Influenza A virus (A/Scotland/142/1993(H3N2)) mRNA for haemagglutinin	1,041 bp linear mRNA	Z46413.1 GI:609059

Strain/Protein	Length	GenBank / GI Accession No.
130. Influenza A virus (A/Scotland/160/1993(H3N2)) mRNA for haemagglutinin	1,041 bp linear mRNA	Z46414.1 GI:609061
131. Influenza A virus (A/Scotland/173/1993(H3N2)) mRNA for haemagglutinin	1,041 bp linear mRNA	Z46416.1 GI:609063
132. Influenza A virus (A/Scotland/174/1993(H3N2)) mRNA for haemagglutinin	1,041 bp linear mRNA	Z46415.1 GI:609065
133. Influenza A virus (A/Scotland/2/1993(H3N2)) mRNA for haemagglutinin	1,041 bp linear mRNA	Z46412.1 GI:609069
134. Influenza A virus (A/Sendai/c182/1994(H3N2)) haemagglutinin mRNA, partial cds	1,032 bp linear mRNA	U48439.1 GI:1574979
135. Influenza A virus (A/Sendai/c373/1995(H3N2)) haemagglutinin mRNA, partial cds	1,032 bp linear mRNA	U48445.1 GI:1574991
136. Influenza A virus (A/Sendai/c384/1994(H3N2)) haemagglutinin mRNA, partial cds	1,032 bp linear mRNA	U48440.1 GI:1574981
137. Influenza A virus (A/Shangdong/9/1993(H3N2)) mRNA for haemagglutinin	1,041 bp linear mRNA	Z46417.1 GI:609071
138. Influenza A virus (A/Shanghai/11/1987/X99aE high yield reassortant(H3N2)) hemagglutinin (HA) mRNA, partial cds	987 bp linear mRNA	L19416.1 GI:348117
139. Influenza A virus (A/sw/Shizuoka/110/97(H3N2)) polymerase basic 2 (PB2) mRNA, complete cds	2,280 bp linear mRNA	AF225514.1 GI:27462098
140. Influenza A virus (A/sw/Shizuoka/110/97(H3N2)) polymerase basic 1 (PB1) mRNA, complete cds	2,274 bp linear mRNA	AF225518.1 GI:27462106
141. Influenza A virus (A/sw/Shizuoka/110/97(H3N2)) polymerase acidic (PA) mRNA, complete cds	2,151 bp linear mRNA	AF225522.1 GI:27462114
142. Influenza A virus (A/sw/Shizuoka/110/97(H3N2)) nucleoprotein (NP) mRNA, complete cds	1,497 bp linear mRNA	AF225534.1 GI:27462146
143. Influenza A virus (A/sw/Shizuoka/110/97(H3N2)) neuraminidase (NA) mRNA, complete cds	1,410 bp linear mRNA	AF225538.1 GI:27462154
144. Influenza A virus (A/sw/Shizuoka/110/97(H3N2)) hemagglutinin (HA1) mRNA, partial cds	984 bp linear mRNA	AF225542.1 GI:27462162
145. Influenza A virus (A/sw/Shizuoka/115/97(H3N2)) polymerase basic 2 (PB2) mRNA, complete cds	2,280 bp linear mRNA	AF225515.1 GI:27462100
146. Influenza A virus (A/sw/Shizuoka/115/97(H3N2)) polymerase basic 1 (PB1) mRNA, complete cds	2,274 bp linear mRNA	AF225519.1 GI:27462108
147. Influenza A virus (A/sw/Shizuoka/115/97(H3N2)) polymerase acidic (PA) mRNA, complete cds	2,151 bp linear mRNA	AF225523.1 GI:27462116
148. Influenza A virus (A/sw/Shizuoka/115/97(H3N2)) nucleoprotein (NP) mRNA, complete cds	1,497 bp linear mRNA	AF225535.1 GI:27462148

Strain/Protein	Length	GenBank / GI Accession No.
149. Influenza A virus (A/sw/Shizuoka/115/97(H3N2)) neuraminidase (NA) mRNA, complete cds	1,410 bp linear mRNA	AF225539.1 GI:27462156
150. Influenza A virus (A/sw/Shizuoka/115/97(H3N2)) hemagglutinin (HA1) mRNA, partial cds	984 bp linear mRNA	AF225543.1 GI:27462164
151. Influenza A virus (A/sw/Shizuoka/119/97(H3N2)) polymerase basic 2 (PB2) mRNA, complete cds	2,280 bp linear mRNA	AF225516.1 GI:27462102
152. Influenza A virus (A/sw/Shizuoka/119/97(H3N2)) polymerase basic 1 (PB1) mRNA, complete cds	2,274 bp linear mRNA	AF225520.1 GI:27462110
153. Influenza A virus (A/sw/Shizuoka/119/97(H3N2)) polymerase acidic (PA) mRNA, complete cds	2,151 bp linear mRNA	AF225524.1 GI:27462118
154. Influenza A virus (A/sw/Shizuoka/119/97(H3N2)) nucleoprotein (NP) mRNA, complete cds	1,497 bp linear mRNA	AF225536.1 GI:27462150
155. Influenza A virus (A/sw/Shizuoka/119/97(H3N2)) neuraminidase (NA) mRNA, complete cds	1,410 bp linear mRNA	AF225540.1 GI:27462158
156. Influenza A virus (A/sw/Shizuoka/119/97(H3N2)) hemagglutinin (HA1) mRNA, partial cds	984 bp linear mRNA	AF225544.1 GI:27462166
159. Influenza A virus (A/swine/Bakum/IDT1769/2003(H3N2)) neuraminidase mRNA, complete cds	1,410 bp linear mRNA	EU163948.1 GI:157679552
163. Influenza A virus (A/swine/Fujian/668/01(H3N2)) nonfunctional hemagglutinin mRNA, complete sequence	1,738 bp linear mRNA	AY857957.1 GI:58042507
164. Influenza A virus PB2 gene for Polymerase 2 protein, genomic RNA, strain A/Swine/Italy/1523/98	2,280 bp linear mRNA	AJ311459.1 GI:13661041
165. Influenza A virus PB1 gene for Polymerase 1 protein, genomic RNA, strain A/Swine/Italy/1523/98	2,274 bp linear mRNA	AJ311460.1 GI:13661043
166. Influenza A virus (A/swine/Italy/1523/98(H3N2)) NS1 gene for non structural protein 1 and NS2 gene for non structural protein 2, genomic RNA	821 bp linear mRNA	AJ344024.1 GI:20068146
167. Influenza A virus (A/swine/Re220/92hp(H3N2)) neuraminidase mRNA, complete cds	1,465 bp linear mRNA	EU163949.1 GI:157679554
168. Influenza A virus (A/sw/Shizuoka/120/97(H3N2)) polymerase basic 2 (PB2) mRNA, complete cds	2,280 bp linear mRNA	AF225517.1 GI:27462104
169. Influenza A virus (A/sw/Shizuoka/120/97(H3N2)) polymerase basic 1 (PB1) mRNA, complete cds	2,274 bp linear mRNA	AF225521.1 GI:27462112
170. Influenza A virus (A/sw/Shizuoka/120/97(H3N2)) polymerase acidic (PA) mRNA, complete cds	2,151 bp linear mRNA	AF225525.1 GI:27462120
171. Influenza A virus (A/sw/Shizuoka/120/97(H3N2)) nucleoprotein (NP) mRNA, complete cds	1,497 bp linear mRNA	AF225537.1 GI:27462152
172. Influenza A virus (A/sw/Shizuoka/120/97(H3N2)) neuraminidase (NA) mRNA, complete cds	1,410 bp linear mRNA	AF225541.1 GI:27462160

Strain/Protein	Length	GenBank / GI Accession No.
173. Influenza A virus (A/sw/Shizuoka/120/97(H3N2)) hemagglutinin (HA1) mRNA, partial cds	984 bp linear mRNA	AF225545.1 GI:27462168
174. Influenza A virus (A/Switzerland/7729/98(H3N2)) hemagglutinin mRNA, complete cds	1,762 bp linear mRNA	AY032978.1 GI:14161723
175. Influenza A virus (A/Switzerland/7729/98(H3N2)) hemagglutinin mRNA, complete cds	1,762 bp linear mRNA	AF382318.1 GI:14487955
176. Influenza A virus (A/Tainan/704/03(H3N2)) hemagglutinin (HA) mRNA, partial cds	528 bp linear mRNA	AY962011.1 GI:68138179
177. Influenza A virus (A/Tainan/704/03(H3N2)) neuraminidase (NA) mRNA, partial cds	384 bp linear mRNA	AY973333.1 GI:70673222
178. Influenza A virus (A/Tainan/704/03(H3N2)) nucleoprotein (NP) mRNA, partial cds	882 bp linear mRNA	AY986993.1 GI:70728113
179. Influenza A virus (A/Tainan/712/03(H3N2)) hemagglutinin (HA) mRNA, partial cds	519 bp linear mRNA	AY962012.1 GI:68138181
180. Influenza A virus (A/Tainan/712/03(H3N2)) neuraminidase (NA) mRNA, partial cds	383 bp linear mRNA	AY973334.1 GI:70673224
181. Influenza A virus (A/Tainan/712/03(H3N2)) nucleoprotein (NP) mRNA, partial cds	882 bp linear mRNA	AY986994.1 GI:70728115
182. Influenza A virus (A/Tainan/722/03(H3N2)) hemagglutinin (HA) mRNA, partial cds	784 bp linear mRNA	AY962005.1 GI:68138167
183. Influenza A virus (A/Tainan/722/03(H3N2)) neuraminidase (NA) mRNA, partial cds	592 bp linear mRNA	AY973335.1 GI:70673226
184. Influenza A virus (A/Tainan/722/03(H3N2)) nucleoprotein (NP) mRNA, partial cds	936 bp linear mRNA	AY986995.1 GI:70728117
185. Influenza A virus (A/Taipei/407/03(H3N2)) hemagglutinin (HA) mRNA, partial cds	788 bp linear mRNA	AY961998.1 GI:68138153
186. Influenza A virus (A/Taipei/407/03(H3N2)) neuraminidase (NA) mRNA, partial cds	787 bp linear mRNA	AY973336.1 GI:70673228
187. Influenza A virus (A/Taipei/407/03(H3N2)) nucleoprotein (NP) mRNA, partial cds	882 bp linear mRNA	AY986996.1 GI:70728119
188. Influenza A virus (A/Taipei/416/03(H3N2)) hemagglutinin (HA) mRNA, partial cds	787 bp linear mRNA	AY962007.1 GI:68138171
189. Influenza A virus (A/Taipei/416/03(H3N2)) neuraminidase (NA) mRNA, partial cds	782 bp linear mRNA	AY973337.1 GI:70673230
190. Influenza A virus (A/Taipei/416/03(H3N2)) nucleoprotein (NP) mRNA, partial cds	882 bp linear mRNA	AY986997.1 GI:70728121
191. Influenza A virus (A/Taiwan/0020/98 (H3N2)) polymerase basic protein 1 (PB1) mRNA, partial cds	297 bp linear mRNA	AY303703.1 GI:32330895
192. Influenza A virus (A/Taiwan/0040/2003(H3N2)) hemagglutinin mRNA, partial cds	791 bp linear mRNA	AY604817.1 GI:50727514

Strain/Protein	Length	GenBank / GI Accession No.
193. Influenza A virus (A/Taiwan/0045/98 (H3N2)) polymerase basic protein 1 (PB1) mRNA, partial cds	297 bp linear mRNA	AY303705.1 GI:32330899
194. Influenza A virus (A/human/Taiwan/0095/96 (H3N2)) hemagglutinin (HA) mRNA, partial cds	844 bp linear mRNA	AF362820.1 GI:15055140
195. Influenza A virus (A/Taiwan/0097/2003 (H3N2)) hemagglutinin mRNA, partial cds	791 bp linear mRNA	AY604828.1 GI:50727536
196. Influenza A virus (A/Taiwan/0104/2001 (H3N2)) polymerase basic protein 1 (PB1) mRNA, partial cds	297 bp linear mRNA	AY303706.1 GI:32330901
197. Influenza A virus (A/human/Taiwan/0118/98 (H3N2)) hemagglutinin (HA) mRNA, partial cds	844 bp linear mRNA	AF362805.1 GI:15055110
198. Influenza A virus (A/Taiwan/0122/2003 (H3N2)) hemagglutinin mRNA, partial cds	791 bp linear mRNA	AY604823.1 GI:50727526
199. Influenza A virus (A/human/Taiwan/0149/00 (H3N2)) hemagglutinin (HA) mRNA, partial cds	844 bp linear mRNA	AF362806.1 GI:15055112
200. Influenza A virus (A/Taiwan/0275/2000 (H3N2)) polymerase basic protein 1 (PB1) mRNA, partial cds	297 bp linear mRNA	AY303712.1 GI:32330913
201. Influenza A virus (A/Taiwan/0275/2000 (H3N2)) hemagglutinin (HA) mRNA, partial cds	844 bp linear mRNA	AY303713.1 GI:32330915
202. Influenza A virus (A/human/Taiwan/0293/98 (H3N2)) hemagglutinin (HA) mRNA, partial cds	844 bp linear mRNA	AF362807.1 GI:15055114
203. Influenza A virus (A/Taiwan/0346/98 (H3N2)) polymerase basic protein 1 (PB1) mRNA, partial cds	297 bp linear mRNA	AY303715.1 GI:32330919
204. Influenza A virus (A/Taiwan/0379/2000 (H3N2)) polymerase basic protein 1 (PB1) mRNA, partial cds	297 bp linear mRNA	AY303716.1 GI:32330921
205. Influenza A virus (A/Taiwan/0379/2000 (H3N2)) hemagglutinin (HA) mRNA, partial cds	844 bp linear mRNA	AY303717.1 GI:32330923
206. Influenza A virus (A/Taiwan/0388/2001 (H3N2)) hemagglutinin (HA) mRNA, partial cds	791 bp linear mRNA	AY625729.1 GI:50604415
207. Influenza A virus (A/human/Taiwan/0389/99 (H3N2)) hemagglutinin (HA) mRNA, partial cds	844 bp linear mRNA	AF362808.1 GI:15055116
208. Influenza A virus (A/human/Taiwan/0423/98 (H3N2)) hemagglutinin (HA) mRNA, partial cds	844 bp linear mRNA	AF362809.1 GI:15055118
209. Influenza A virus (A/Taiwan/0423/98 (H3N2)) polymerase basic protein 1 (PB1) mRNA, partial cds	297 bp linear mRNA	AY303718.1 GI:32330925
210. Influenza A virus (A/human/Taiwan/0464/98 (H3N2)) hemagglutinin (HA) mRNA, partial cds	844 bp linear mRNA	AF362810.1 GI:15055120
211. Influenza A virus (A/Taiwan/0464/98 (H3N2)) polymerase basic protein 1 (PB1) mRNA, partial cds	297 bp linear mRNA	AY303719.1 GI:32330927
212. Influenza A virus (A/Taiwan/0568/2001 (H3N2)) hemagglutinin (HA) mRNA, partial cds	791 bp linear mRNA	AY625730.1 GI:50604440

Strain/Protein	Length	GenBank / GI Accession No.
213. Influenza A virus (A/Taiwan/0570/2003(H3N2)) hemagglutinin mRNA, partial cds	791 bp linear mRNA	AY604822.1 GI:50727524
214. Influenza A virus (A/Taiwan/0572/2003(H3N2)) hemagglutinin mRNA, partial cds	791 bp linear mRNA	AY604827.1 GI:50727534
215. Influenza A virus (A/Taiwan/0578/2003(H3N2)) hemagglutinin mRNA, partial cds	791 bp linear mRNA	AY604821.1 GI:50727522
216. Influenza A virus (A/Taiwan/0583/2003(H3N2)) hemagglutinin mRNA, partial cds	791 bp linear mRNA	AY604820.1 GI:50727520
217. Influenza A virus (A/Taiwan/0646/2000 (H3N2)) polymerase basic protein 1 (PB1) mRNA, partial cds	297 bp linear mRNA	AY303722.1 GI:32330933
218. Influenza A virus (A/Taiwan/0646/2000 (H3N2)) hemagglutinin (HA) mRNA, partial cds	844 bp linear mRNA	AY303723.1 GI:32330935
219. Influenza A virus (A/human/Taiwan/0830/99(H3N2)) hemagglutinin (HA) mRNA, partial cds	844 bp linear mRNA	AF362811.1 GI:15055122
220. Influenza A virus (A/Taiwan/0964/2001(H3N2)) hemagglutinin (HA) mRNA, partial cds	791 bp linear mRNA	AY625731.1 GI:50604469
221. Influenza A virus (A/human/Taiwan/1008/99(H3N2)) hemagglutinin (HA) mRNA, partial cds	844 bp linear mRNA	AF362812.1 GI:15055124
222. Influenza A virus (A/Taiwan/1008/99 (H3N2)) polymerase basic protein 1 (PB1) mRNA, partial cds	297 bp linear mRNA	AY303725.1 GI:32330939
223. Influenza A virus (A/Taiwan/1219/2004(H3N2)) hemagglutinin (HA) mRNA, partial cds	750 bp linear mRNA	EU068138.1 GI:158452149
224. Influenza A virus (A/Taiwan/1315/2005(H3N2)) hemagglutinin (HA) mRNA, partial cds	750 bp linear mRNA	EU068125.1 GI:158452123
225. Influenza A virus (A/Taiwan/1511/2004(H3N2)) hemagglutinin (HA) mRNA, partial cds	750 bp linear mRNA	EU068153.1 GI:158452179
226. Influenza A virus (A/Taiwan/1533/2003(H3N2)) hemagglutinin (HA) mRNA, partial cds	750 bp linear mRNA	EU068119.1 GI:158452111
227. Influenza A virus (A/human/Taiwan/1537/99(H3N2)) hemagglutinin (HA) mRNA, partial cds	844 bp linear mRNA	AF362813.1 GI:15055126
228. Influenza A virus (A/Taiwan/1537/99 (H3N2)) polymerase basic protein 1 (PB1) mRNA, partial cds	297 bp linear mRNA	AY303728.1 GI:32330945
229. Influenza A virus (A/Taiwan/1566/2003(H3N2)) hemagglutinin mRNA, partial cds	791 bp linear mRNA	AY604826.1 GI:50727532
230. Influenza A virus (A/Taiwan/1568/2003(H3N2)) hemagglutinin mRNA, partial cds	791 bp linear mRNA	AY604819.1 GI:50727518
231. Influenza A virus (A/Taiwan/158/2003(H3N2)) hemagglutinin (HA) mRNA, partial cds	750 bp linear mRNA	EU068116.1 GI:158452105
232. Influenza A virus (A/Taiwan/1600/96(H3N2)) matrix protein M1 (M) mRNA, partial cds	875 bp linear mRNA	AF138709.2 GI:4996869

Strain/Protein	Length	GenBank / GI Accession No.
233. Influenza A virus (A/Taiwan/1613/2003(H3N2)) hemagglutinin (HA) mRNA, partial cds	750 bp linear mRNA	EU068117.1 GI:158452107
234. Influenza A virus (A/Taiwan/1651/2004(H3N2)) hemagglutinin (HA) mRNA, partial cds	750 bp linear mRNA	EU068148.1 GI:158452169
235. Influenza A virus (A/human/Taiwan/1748/97(H3N2)) hemagglutinin (HA) mRNA, partial cds	844 bp linear mRNA	AF362814.1 GI:15055128
236. Influenza A virus (A/Taiwan/1748/97(H3N2)) polymerase basic protein 1 (PB1) mRNA, partial cds	297 bp linear mRNA	AY303729.1 GI:32330947
237. Influenza A virus (A/Taiwan/179/96(H3N2)) matrix protein M1 (M) mRNA, partial cds	872 bp linear mRNA	AF138707.2 GI:4996865
238. Influenza A virus (A/Taiwan/1817/2004(H3N2)) hemagglutinin (HA) mRNA, partial cds	750 bp linear mRNA	EU068139.1 GI:158452151
239. Influenza A virus (A/Taiwan/1904/2003(H3N2)) hemagglutinin (HA) mRNA, partial cds	750 bp linear mRNA	EU068154.1 GI:158452181
240. Influenza A virus (A/Taiwan/1921/2003(H3N2)) hemagglutinin (HA) mRNA, partial cds	750 bp linear mRNA	EU068155.1 GI:158452183
241. Influenza A virus (A/human/Taiwan/1986/96(H3N2)) hemagglutinin (HA) mRNA, partial cds	844 bp linear mRNA	AF362815.1 GI:15055130
242. Influenza A virus (A/Taiwan/1990/96(H3N2)) polymerase basic protein 1 (PB1) mRNA, partial cds	297 bp linear mRNA	AY303730.1 GI:32330949
243. Influenza A virus (A/Taiwan/1990/96(H3N2)) hemagglutinin (HA) mRNA, partial cds	844 bp linear mRNA	AY303731.1 GI:32330951
244. Influenza A virus (A/Taiwan/20/98(H3N2)) H3 hemagglutinin (HA) mRNA, partial cds	861 bp linear mRNA	AF139938.1 GI:4972940
245. Influenza A virus (A/Taiwan/20/98(H3N2)) N2 neuraminidase (NA) mRNA, partial cds	392 bp linear mRNA	AF140627.1 GI:4972988
246. Influenza A virus (A/Taiwan/20/98(H3N2)) matrix protein M1 (M) mRNA, partial cds	875 bp linear mRNA	AF138715.2 GI:4996879
247. Influenza A virus (A/human/Taiwan/2031/97(H3N2)) hemagglutinin (HA) mRNA, partial cds	844 bp linear mRNA	AF362816.1 GI:15055132
248. Influenza A virus (A/Taiwan/2034/96(H3N2)) H3 hemagglutinin (HA) mRNA, partial cds	861 bp linear mRNA	AF139937.1 GI:4972938
249. Influenza A virus (A/Taiwan/2034/96(H3N2)) N2 neuraminidase (NA) mRNA, partial cds	392 bp linear mRNA	AF140620.1 GI:4972974
250. Influenza A virus (A/Taiwan/2034/96(H3N2)) polymerase basic protein 1 (PB1) mRNA, partial cds	297 bp linear mRNA	AY303732.1 GI:32330953
251. Influenza A virus (A/Taiwan/2040/2003(H3N2)) hemagglutinin mRNA, partial cds	791 bp linear mRNA	AY604818.1 GI:50727516
252. Influenza A virus (A/Taiwan/2072/2006(H3N2)) hemagglutinin (HA) mRNA, partial cds	750 bp linear mRNA	EU068131.1 GI:158452135

Strain/Protein	Length	GenBank / GI Accession No.
253. Influenza A virus (A/Taiwan/21/98(H3N2)) H3 hemagglutinin (HA) mRNA, partial cds	861 bp linear mRNA	AF139934.1 GI:4972932
254. Influenza A virus (A/Taiwan/21/98(H3N2)) N2 neuraminidase (NA) mRNA, partial cds	392 bp linear mRNA	AF140624.1 GI:4972982
255. Influenza A virus (A/Taiwan/21/98(H3N2)) matrix protein M1 (M) mRNA, partial cds	875 bp linear mRNA	AF138716.2 GI:4996881
256. Influenza A virus (A/Taiwan/2191/96(H3N2)) H3 hemagglutinin (HA) mRNA, partial cds	861 bp linear mRNA	AF139932.1 GI:4972928
257. Influenza A virus (A/Taiwan/2191/96(H3N2)) N2 neuraminidase (NA) mRNA, partial cds	392 bp linear mRNA	AF140622.1 GI:4972978
258. Influenza A virus (A/Taiwan/2191/96(H3N2)) matrix protein M1 (M) mRNA, partial cds	875 bp linear mRNA	AF138711.3 GI:156147502
259. Influenza A virus (A/Taiwan/2192/96(H3N2)) H3 hemagglutinin (HA) mRNA, partial cds	861 bp linear mRNA	AF139936.1 GI:4972936
260. Influenza A virus (A/Taiwan/2192/96(H3N2)) N2 neuraminidase (NA) mRNA, partial cds	392 bp linear mRNA	AF140626.1 GI:4972986
261. Influenza A virus (A/Taiwan/2195/96(H3N2)) polymerase basic protein 1 (PB1) mRNA, partial cds	297 bp linear mRNA	AY303735.1 GI:32330959
262. Influenza A virus (A/Taiwan/2195/96(H3N2)) hemagglutinin (HA) mRNA, partial cds	844 bp linear mRNA	AY303736.1 GI:32330961
263. Influenza A virus (A/Taiwan/224/98(H3N2)) matrix protein M1 (M) mRNA, partial cds	875 bp linear mRNA	AF138718.2 GI:4996885
264. Influenza A virus (A/human/Taiwan/2548/99(H3N2)) hemagglutinin (HA) mRNA, partial cds	844 bp linear mRNA	AF362817.1 GI:15055134
265. Influenza A virus (A/Taiwan/268/2005(H3N2)) hemagglutinin (HA) mRNA, partial cds	750 bp linear mRNA	EU068120.1 GI:158452113
266. Influenza A virus (A/Taiwan/3008/2004(H3N2)) hemagglutinin (HA) mRNA, partial cds	750 bp linear mRNA	EU068149.1 GI:158452171
267. Influenza A virus (A/Taiwan/3075/2003(H3N2)) hemagglutinin (HA) mRNA, partial cds	750 bp linear mRNA	EU068152.1 GI:158452177
268. Influenza A virus (A/human/Taiwan/3083/00(H3N2)) hemagglutinin (HA) mRNA, partial cds	940 bp linear mRNA	AF362818.1 GI:15055136
269. Influenza A virus (A/Taiwan/3131/2002(H3N2)) hemagglutinin mRNA, partial cds	791 bp linear mRNA	AY604811.1 GI:50727502
270. Influenza A virus (A/Taiwan/3154/2004(H3N2)) hemagglutinin (HA) mRNA, partial cds	750 bp linear mRNA	EU068145.1 GI:158452163
271. Influenza A virus (A/Taiwan/3187/2004(H3N2)) hemagglutinin (HA) mRNA, partial cds	750 bp linear mRNA	EU068141.1 GI:158452155
272. Influenza A virus (A/Taiwan/3245/2004(H3N2)) hemagglutinin (HA) mRNA, partial cds	750 bp linear mRNA	EU068134.1 GI:158452141

Strain/Protein	Length	GenBank / GI Accession No.
273. Influenza A virus (A/Taiwan/3294/2005(H3N2)) hemagglutinin (HA) mRNA, partial cds	750 bp linear mRNA	EU068133.1 GI:158452139
274. Influenza A virus (A/Taiwan/3351/97(H3N2)) H3 hemagglutinin (HA) mRNA, partial cds	861 bp linear mRNA	AF139935.1 GI:4972934
275. Influenza A virus (A/Taiwan/3351/97(H3N2)) N2 neuraminidase (NA) mRNA, partial cds	392 bp linear mRNA	AF140625.1 GI:4972984
276. Influenza A virus (A/Taiwan/3351/97(H3N2)) matrix protein M1 (M) mRNA, partial cds	875 bp linear mRNA	AF138713.2 GI:4996875
277. Influenza A virus (A/Taiwan/3351/97(H3N2)) polymerase basic protein 1 (PB1) mRNA, partial cds	297 bp linear mRNA	AY303738.1 GI:32330965
278. Influenza A virus (A/Taiwan/3387/2005(H3N2)) hemagglutinin (HA) mRNA, partial cds	750 bp linear mRNA	EU068132.1 GI:158452137
279. Influenza A virus (A/Taiwan/3396/97(H3N2)) polymerase basic protein 1 (PB1) mRNA, partial cds	297 bp linear mRNA	AY303742.1 GI:32330973
280. Influenza A virus (A/Taiwan/3396/97(H3N2)) hemagglutinin (HA) mRNA, partial cds	844 bp linear mRNA	AY303743.1 GI:32330975
281. Influenza A virus (A/Taiwan/3427/97(H3N2)) H3 hemagglutinin (HA) mRNA, partial cds	861 bp linear mRNA	AF139930.1 GI:4972924
282. Influenza A virus (A/Taiwan/3427/97(H3N2)) N2 neuraminidase (NA) mRNA, partial cds	392 bp linear mRNA	AF140619.1 GI:4972972
283. Influenza A virus (A/Taiwan/346/98(H3N2)) H3 hemagglutinin (HA) mRNA, partial cds	861 bp linear mRNA	AF139940.1 GI:4972944
284. Influenza A virus (A/Taiwan/346/98(H3N2)) N2 neuraminidase (NA) mRNA, partial cds	392 bp linear mRNA	AF140787.1 GI:4972992
285. Influenza A virus (A/Taiwan/346/98(H3N2)) matrix protein M1 (M) mRNA, partial cds	875 bp linear mRNA	AF138719.2 GI:4996887
286. Influenza A virus (A/human/Taiwan/3460/00(H3N2)) truncated hemagglutinin (HA) mRNA, partial cds	942 bp linear mRNA	AF362819.1 GI:15055138
287. Influenza A virus (A/Taiwan/3469/97(H3N2)) H3 hemagglutinin (HA) mRNA, partial cds	861 bp linear mRNA	AF139933.1 GI:4972930
288. Influenza A virus (A/Taiwan/3469/97(H3N2)) N2 neuraminidase (NA) mRNA, partial cds	392 bp linear mRNA	AF140623.1 GI:4972980
289. Influenza A virus (A/Taiwan/3469/97(H3N2)) matrix protein M1 (M) mRNA, partial cds	875 bp linear mRNA	AF138714.2 GI:4996877
290. Influenza A virus (A/Taiwan/3503/97(H3N2)) polymerase basic protein 1 (PB1) mRNA, partial cds	297 bp linear mRNA	AY303744.1 GI:32330977
291. Influenza A virus (A/Taiwan/3503/97(H3N2)) hemagglutinin (HA) mRNA, partial cds	844 bp linear mRNA	AY303745.1 GI:32330979
292. Influenza A virus (A/Taiwan/3513/96(H3N2)) matrix protein M1 (M) mRNA, partial cds	919 bp linear mRNA	AF138712.1 GI:4928900

Strain/Protein	Length	GenBank / GI Accession No.
293. Influenza A virus (A/Taiwan/3513/97(H3N2)) H3 hemagglutinin (HA) mRNA, partial cds	861 bp linear mRNA	AF139931.1 GI:4972926
294. Influenza A virus (A/Taiwan/3513/97(H3N2)) N2 neuraminidase (NA) mRNA, partial cds	392 bp linear mRNA	AF140621.1 GI:4972976
295. Influenza A virus (A/Taiwan/3744/2002(H3N2)) hemagglutinin mRNA, partial cds	791 bp linear mRNA	AY604814.1 GI:50727508
296. Influenza A virus (A/human/Taiwan/3760/00(H3N2)) hemagglutinin (HA) mRNA, partial cds	940 bp linear mRNA	AF362804.1 GI:15055108
297. Influenza A virus (A/Taiwan/3896/2001(H1N1)) hemagglutinin (HA) mRNA, partial cds	561 bp linear mRNA	AY303747.1 GI:32330983
298. Influenza A virus (A/Taiwan/4050/2003(H3N2)) hemagglutinin mRNA, partial cds	791 bp linear mRNA	AY604825.1 GI:50727530
299. Influenza A virus (A/Taiwan/4063/2003(H3N2)) hemagglutinin mRNA, partial cds	791 bp linear mRNA	AY604824.1 GI:50727528
300. Influenza A virus (A/Taiwan/41/2004(H3N2)) hemagglutinin (HA) mRNA, partial cds	750 bp linear mRNA	EU068137.1 GI:158452147
301. Influenza A virus (A/Taiwan/45/98(H3N2)) H3 hemagglutinin (HA) mRNA, partial cds	861 bp linear mRNA	AF139939.1 GI:4972942
302. Influenza A virus (A/Taiwan/45/98(H3N2)) N2 neuraminidase (NA) mRNA, partial cds	392 bp linear mRNA	AF140628.1 GI:4972990
303. Influenza A virus (A/Taiwan/45/98(H3N2)) matrix protein M1 (M) mRNA, partial cds	875 bp linear mRNA	AF138717.2 GI:4996883
304. Influenza A virus (A/Taiwan/4548/2003(H3N2)) hemagglutinin (HA) mRNA, partial cds	750 bp linear mRNA	EU068114.1 GI:158452101
305. Influenza A virus (A/Taiwan/4673/2002(H3N2)) hemagglutinin mRNA, partial cds	791 bp linear mRNA	AY604813.1 GI:50727506
306. Influenza A virus (A/Taiwan/4680/2002(H3N2)) hemagglutinin mRNA, partial cds	791 bp linear mRNA	AY604812.1 GI:50727504
307. Influenza A virus (A/Taiwan/4735/2004(H3N2)) hemagglutinin (HA) mRNA, partial cds	750 bp linear mRNA	EU068136.1 GI:158452145
308. Influenza A virus (A/Taiwan/4829/2005(H3N2)) hemagglutinin (HA) mRNA, partial cds	750 bp linear mRNA	EU068142.1 GI:158452157
309. Influenza A virus (A/Taiwan/4836/2005(H3N2)) hemagglutinin (HA) mRNA, partial cds	750 bp linear mRNA	EU068130.1 GI:158452133
310. Influenza A virus (A/Taiwan/4865/2005(H3N2)) hemagglutinin (HA) mRNA, partial cds	750 bp linear mRNA	EU068143.1 GI:158452159
311. Influenza A virus (A/Taiwan/4883/2005(H3N2)) hemagglutinin (HA) mRNA, partial cds	750 bp linear mRNA	EU068121.1 GI:158452115
312. Influenza A virus (A/Taiwan/4938/2002(H3N2)) hemagglutinin mRNA, partial cds	791 bp linear mRNA	AY604809.1 GI:50727498

Strain/Protein	Length	GenBank / GI Accession No.
313. Influenza A virus (A/Taiwan/4954/2002(H3N2)) hemagglutinin mRNA, partial cds	791 bp linear mRNA	AY604815.1 GI:50727510
314. Influenza A virus (A/Taiwan/4963/2002(H3N2)) hemagglutinin mRNA, partial cds	791 bp linear mRNA	AY604810.1 GI:50727500
315. Influenza A virus (A/Taiwan/4987/2005(H3N2)) hemagglutinin (HA) mRNA, partial cds	750 bp linear mRNA	EU068122.1 GI:158452117
316. Influenza A virus (A/Taiwan/4990/2005(H3N2)) hemagglutinin (HA) mRNA, partial cds	750 bp linear mRNA	EU068127.1 GI:158452127
317. Influenza A virus (A/Taiwan/5/2003(H3N2)) hemagglutinin (HA) mRNA, partial cds	750 bp linear mRNA	EU068118.1 GI:158452109
318. Influenza A virus (A/Taiwan/5153/2002(H3N2)) hemagglutinin mRNA, partial cds	791 bp linear mRNA	AY604816.1 GI:50727512
319. Influenza A virus (A/Taiwan/5267/2005(H3N2)) hemagglutinin (HA) mRNA, partial cds	750 bp linear mRNA	EU068128.1 GI:158452129
320. Influenza A virus (A/Taiwan/556/2004(H3N2)) hemagglutinin (HA) mRNA, partial cds	750 bp linear mRNA	EU068146.1 GI:158452165
321. Influenza A virus (A/Taiwan/5694/2005(H3N2)) hemagglutinin (HA) mRNA, partial cds	750 bp linear mRNA	EU068126.1 GI:158452125
322. Influenza A virus (A/Taiwan/587/2004(H3N2)) hemagglutinin (HA) mRNA, partial cds	750 bp linear mRNA	EU068147.1 GI:158452167
323. Influenza A virus (A/Taiwan/592/2004(H3N2)) hemagglutinin (HA) mRNA, partial cds	750 bp linear mRNA	EU068151.1 GI:158452175
324. Influenza A virus (A/Taiwan/7099/2003(H3N2)) hemagglutinin mRNA, partial cds	791 bp linear mRNA	AY604829.1 GI:50727538
325. Influenza A virus (A/Taiwan/7100/2003(H3N2)) hemagglutinin mRNA, partial cds	791 bp linear mRNA	AY604830.1 GI:50727540
326. Influenza A virus (A/Taiwan/7196/2003(H3N2)) hemagglutinin (HA) mRNA, partial cds	750 bp linear mRNA	EU068150.1 GI:158452173
327. Influenza A virus (A/Taiwan/7568/2004(H3N2)) hemagglutinin (HA) mRNA, partial cds	750 bp linear mRNA	EU068135.1 GI:158452143
328. Influenza A virus (A/Taiwan/7601/2005(H3N2)) hemagglutinin (HA) mRNA, partial cds	750 bp linear mRNA	EU068144.1 GI:158452161
329. Influenza A virus (A/Taiwan/7681/2005(H3N2)) hemagglutinin (HA) mRNA, partial cds	750 bp linear mRNA	EU068124.1 GI:158452121
330. Influenza A virus (A/Taiwan/7702/2005(H3N2)) hemagglutinin (HA) mRNA, partial cds	750 bp linear mRNA	EU068123.1 GI:158452119
331. Influenza A virus (A/Taiwan/7873/2005(H3N2)) hemagglutinin (HA) mRNA, partial cds	750 bp linear mRNA	EU068129.1 GI:158452131
332. Influenza A virus (A/Taiwan/8/2003(H3N2)) hemagglutinin (HA) mRNA, partial cds	750 bp linear mRNA	EU068115.1 GI:158452103

Strain/Protein	Length	GenBank / GI Accession No.
333. Influenza A virus (A/Taiwan/93/2004(H3N2)) hemagglutinin (HA) mRNA, partial cds	750 bp linear mRNA	EU068140.1 GI:158452153
334. Influenza A virus (A/Taoyuan/108/02(H3N2)) hemagglutinin (HA) mRNA, partial cds	528 bp linear mRNA	AY962016.1 GI:68138189
335. Influenza A virus (A/Taoyuan/108/02(H3N2)) neuraminidase (NA) mRNA, partial cds	754 bp linear mRNA	AY973338.1 GI:70673232
336. Influenza A virus (A/Taoyuan/108/02(H3N2)) nucleoprotein (NP) mRNA, partial cds	882 bp linear mRNA	AY986998.1 GI:70728123
337. Influenza A virus (A/Thailand/CU124/2006(H3N2)) neuraminidase (NA) mRNA, complete cds	1,410 bp linear mRNA	EU021285.1 GI:154224724
338. Influenza A virus (A/Thailand/CU124/2006(H3N2)) hemagglutinin (HA) mRNA, complete cds	1,701 bp linear mRNA	EU021284.1 GI:154224795
339. Influenza A virus (A/Thailand/CU228/2006(H3N2)) neuraminidase (NA) mRNA, complete cds	1,410 bp linear mRNA	EU021275.1 GI:154224714
340. Influenza A virus (A/Thailand/CU228/2006(H3N2)) hemagglutinin (HA) mRNA, complete cds	1,701 bp linear mRNA	EU021274.1 GI:154224785
341. Influenza A virus (A/Thailand/CU23/2006(H3N2)) neuraminidase (NA) mRNA, partial cds	1,347 bp linear mRNA	EU021267.1 GI:154224706
342. Influenza A virus (A/Thailand/CU23/2006(H3N2)) hemagglutinin (HA) mRNA, complete cds	1,701 bp linear mRNA	EU021266.1 GI:154224777
343. Influenza A virus (A/Thailand/CU231/2006(H3N2)) neuraminidase (NA) mRNA, complete cds	1,410 bp linear mRNA	EU021283.1 GI:154224722
344. Influenza A virus (A/Thailand/CU231/2006(H3N2)) hemagglutinin (HA) mRNA, complete cds	1,701 bp linear mRNA	EU021282.1 GI:154224793
345. Influenza A virus (A/Thailand/CU259/2006(H3N2)) neuraminidase (NA) mRNA, complete cds	1,410 bp linear mRNA	EU021279.1 GI:154224718
346. Influenza A virus (A/Thailand/CU259/2006(H3N2)) hemagglutinin (HA) mRNA, complete cds	1,701 bp linear mRNA	EU021278.1 GI:154224789
347. Influenza A virus (A/Thailand/CU260/2006(H3N2)) neuraminidase (NA) mRNA, complete cds	1,410 bp linear mRNA	EU021281.1 GI:154224720
348. Influenza A virus (A/Thailand/CU260/2006(H3N2)) hemagglutinin (HA) mRNA, partial cds	1,129 bp linear mRNA	EU021280.1 GI:154224791
349. Influenza A virus (A/Thailand/CU272/2007(H3N2)) neuraminidase (NA) mRNA, complete cds	1,410 bp linear mRNA	EU021271.1 GI:154224710
350. Influenza A virus (A/Thailand/CU272/2007(H3N2)) hemagglutinin (HA) mRNA, complete cds	1,701 bp linear mRNA	EU021270.1 GI:154224781
351. Influenza A virus (A/Thailand/CU280/2007(H3N2)) neuraminidase (NA) mRNA, complete cds	1,410 bp linear mRNA	EU021273.1 GI:154224712
352. Influenza A virus (A/Thailand/CU280/2007(H3N2)) hemagglutinin (HA) mRNA, complete cds	1,701 bp linear mRNA	EU021272.1 GI:154224783

Strain/Protein	Length	GenBank / GI Accession No.
353. Influenza A virus (A/Thailand/CU282/2007(H3N2)) neuraminidase (NA) mRNA, complete cds	1,410 bp linear mRNA	EU021277.1 GI:154224716
354. Influenza A virus (A/Thailand/CU282/2007(H3N2)) hemagglutinin (HA) mRNA, complete cds	1,701 bp linear mRNA	EU021276.1 GI:154224787
355. Influenza A virus (A/Thailand/CU32/2006(H1N1)) neuraminidase (NA) mRNA, complete cds	1,413 bp linear mRNA	EU021265.1 GI:154224704
361. Influenza A virus (A/Thailand/CU46/2006(H3N2)) neuraminidase (NA) mRNA, complete cds	1,410 bp linear mRNA	EU021269.1 GI:154224708
362. Influenza A virus (A/Thailand/CU46/2006(H3N2)) hemagglutinin (HA) mRNA, complete cds	1,701 bp linear mRNA	EU021268.1 GI:154224779
377. Influenza A virus (A/Tottori/849AM1AL3/1994(H3N2)) hemagglutinin (HA) mRNA, partial cds	987 bp linear mRNA	U77837.1 GI:2992515
378. Influenza A virus (A/Tottori/849AM2/1994(H3N2)) hemagglutinin (HA) mRNA, partial cds	987 bp linear mRNA	U77833.1 GI:2992507
379. Influenza A virus (A/Tottori/849AM2AL3/1994(H3N2)) hemagglutinin (HA) mRNA, partial cds	987 bp linear mRNA	U77839.1 GI:2992519
380. Influenza A virus (A/Tottori/849AM4/1994(H3N2)) hemagglutinin (HA) mRNA, partial cds	987 bp linear mRNA	U77835.1 GI:2992511
382. Influenza A virus (A/Tottori/872AM2/1994(H3N2)) hemagglutinin (HA) mRNA, partial cds	987 bp linear mRNA	U77834.1 GI:2992509
383. Influenza A virus (A/Tottori/872AM2AL3/1994(H3N2)) hemagglutinin (HA) mRNA, partial cds	987 bp linear mRNA	U77840.1 GI:2992521
384. Influenza A virus (A/Tottori/872AM4/1994(H3N2)) hemagglutinin (HA) mRNA, partial cds	987 bp linear mRNA	U77836.1 GI:2992513
385. Influenza A virus (A/Tottori/872K4/1994(H3N2)) hemagglutinin (HA) mRNA, partial cds	987 bp linear mRNA	U77832.1 GI:2992505
386. Influenza A virus (A/United Kingdom/26554/99(H3N2)) hemagglutinin (HA) mRNA, partial cds	987 bp linear mRNA	AF501529.1 GI:21314314
387. Influenza A virus (A/United Kingdom/34300/99(H3N2)) hemagglutinin (HA) mRNA, partial cds	987 bp linear mRNA	AF501527.1 GI:21314310
388. Influenza A virus (A/Utah/20997/99(H3N2)) hemagglutinin (HA) mRNA, partial cds	987 bp linear mRNA	AF501533.1 GI:21314322
389. Influenza A virus (A/Victoria/3/75) segment 5 nucleoprotein mRNA, complete cds	1,565 bp linear mRNA	AF072545.1 GI:4218933
390. Influenza A virus (A/Vienna/47/96M(H3N2)) hemagglutinin (HA) mRNA, complete cds	1,762 bp linear mRNA	AF017270.2 GI:14286338
391. Influenza A virus (A/Vienna/47/96V(H3N2)) hemagglutinin (HA) mRNA, complete cds	1,762 bp linear mRNA	AF017272.2 GI:15004991
392. Influenza A virus (A/Vienna/81/96V(H3N2)) hemagglutinin (HA) mRNA, partial cds	1,069 bp linear mRNA	AF017271.1 GI:2407251

Strain/Protein	Length	GenBank / GI Accession No.
393. Influenza A virus (A/Virginia/21712/99(H3N2)) hemagglutinin (HA) mRNA, partial cds	987 bp linear mRNA	AF501532.1 GI:21314320
394. Influenza A virus (A/Virginia/21716/99(H3N2)) hemagglutinin (HA) mRNA, partial cds	987 bp linear mRNA	AF501515.1 GI:21314286
395. Influenza A virus (A/Virginia/21735/99(H3N2)) hemagglutinin (HA) mRNA, partial cds	987 bp linear mRNA	AF501530.1 GI:21314316
396. Influenza A virus (A/Virginia/21743/99(H3N2)) hemagglutinin (HA) mRNA, partial cds	987 bp linear mRNA	AF501524.1 GI:21314304
397. Influenza A virus (A/Virginia/21754/99(H3N2)) hemagglutinin (HA) mRNA, partial cds	987 bp linear mRNA	AF501519.1 GI:21314294
398. Influenza A virus (A/Virginia/21799/99(H3N2)) hemagglutinin (HA) mRNA, partial cds	987 bp linear mRNA	AF501523.1 GI:21314302
399. Influenza A virus (A/Virginia/21817/99(H3N2)) hemagglutinin (HA) mRNA, partial cds	987 bp linear mRNA	AF501525.1 GI:21314306
400. Influenza A virus (A/Virginia/21822/99(H3N2)) hemagglutinin (HA) mRNA, partial cds	987 bp linear mRNA	AF501520.1 GI:21314296
401. Influenza A virus (A/Virginia/21828/99(H3N2)) hemagglutinin (HA) mRNA, partial cds	987 bp linear mRNA	AF501528.1 GI:21314312
402. Influenza A virus (A/Virginia/21833/99(H3N2)) hemagglutinin (HA) mRNA, partial cds	987 bp linear mRNA	AF501517.1 GI:21314290
403. Influenza A virus (A/Virginia/21845/99(H3N2)) hemagglutinin (HA) mRNA, partial cds	987 bp linear mRNA	AF501522.1 GI:21314300
404. Influenza A virus (A/Virginia/21847/99(H3N2)) hemagglutinin (HA) mRNA, partial cds	987 bp linear mRNA	AF501535.1 GI:21314326
405. Influenza A virus (A/Virginia/G1/99(H3N2)) hemagglutinin (HA) mRNA, partial cds	987 bp linear mRNA	AF501521.1 GI:21314298
406. Influenza A virus (A/Yilan/508/03(H3N2)) neuraminidase (NA) mRNA, partial cds	755 bp linear mRNA	AY973339.1 GI:70673234
407. Influenza A virus (A/Yilan/508/03(H3N2)) nucleoprotein (NP) mRNA, partial cds	882 bp linear mRNA	AY986999.1 GI:70728125
408. Influenza A virus (A/Yilan/513/03(H3N2)) hemagglutinin (HA) mRNA, partial cds	740 bp linear mRNA	AY962015.1 GI:68138187
409. Influenza A virus (A/Yilan/513/03(H3N2)) neuraminidase (NA) mRNA, partial cds	396 bp linear mRNA	AY973340.1 GI:70673236
410. Influenza A virus (A/Yilan/513/03(H3N2)) nucleoprotein (NP) mRNA, partial cds	882 bp linear mRNA	AY987000.1 GI:70728127
411. Influenza A virus (A/Yilan/515/03(H3N2)) hemagglutinin (HA) mRNA, partial cds	511 bp linear mRNA	AY962010.1 GI:68138177
412. Influenza A virus (A/Yilan/515/03(H3N2)) neuraminidase (NA) mRNA, partial cds	394 bp linear mRNA	AY973341.1 GI:70673238

Strain/Protein	Length	GenBank / GI Accession No.
413. Influenza A virus (A/Yilan/516/03(H3N2)) nucleoprotein (NP) mRNA, partial cds	882 bp linear mRNA	AY987001.1 GI:70728129
414. Influenza A virus (A/Yilan/518/03(H3N2)) hemagglutinin (HA) mRNA, partial cds	530 bp linear mRNA	AY962006.1 GI:68138169
415. Influenza A virus (A/Yilan/518/03(H3N2)) neuraminidase (NA) mRNA, partial cds	397 bp linear mRNA	AY973342.1 GI:70673240
416. Influenza A virus (A/Yilan/518/03(H3N2)) nucleoprotein (NP) mRNA, partial cds	882 bp linear mRNA	AY987002.1 GI:70728131
417. Influenza A virus (A/Yilan/538/04(H3N2)) hemagglutinin (HA) mRNA, partial cds	777 bp linear mRNA	AY962002.1 GI:68138161
418. Influenza A virus (A/Yilan/538/04(H3N2)) neuraminidase (NA) mRNA, partial cds	783 bp linear mRNA	AY973343.1 GI:70673242
419. Influenza A virus (A/Yilan/538/04(H3N2)) nucleoprotein (NP) mRNA, partial cds	882 bp linear mRNA	AY987003.1 GI:70728133
420. Influenza A virus (A/Yilan/549/04(H3N2)) hemagglutinin (HA) mRNA, partial cds	788 bp linear mRNA	AY962003.1 GI:68138163
421. Influenza A virus (A/Yilan/549/04(H3N2)) neuraminidase (NA) mRNA, partial cds	779 bp linear mRNA	AY973344.1 GI:70673244
422. Influenza A virus (A/Yilan/549/04(H3N2)) nucleoprotein (NP) mRNA, partial cds	882 bp linear mRNA	AY987004.1 GI:70728135
423. Influenza A virus (A/Yilan/557/04(H3N2)) hemagglutinin (HA) mRNA, partial cds	776 bp linear mRNA	AY962013.1 GI:68138183
424. Influenza A virus (A/Yilan/557/04(H3N2)) neuraminidase (NA) mRNA, partial cds	796 bp linear mRNA	AY973345.1 GI:70673246
425. Influenza A virus (A/Yilan/557/04(H3N2)) nucleoprotein (NP) mRNA, partial cds	882 bp linear mRNA	AY987005.1 GI:70728137
426. Influenza A virus (A/Yilan/566/04(H3N2)) hemagglutinin (HA) mRNA, partial cds	753 bp linear mRNA	AY962014.1 GI:68138185
427. Influenza A virus (A/Yilan/566/04(H3N2)) neuraminidase (NA) mRNA, partial cds	808 bp linear mRNA	AY973346.1 GI:70673248
428. Influenza A virus (A/Yilan/566/04(H3N2)) nucleoprotein (NP) mRNA, partial cds	882 bp linear mRNA	AY987006.1 GI:70728139
429. Influenza A virus (A/zhejiang/06/99(H3N2)) hemagglutinin (HA) mRNA, partial cds	987 bp linear mRNA	AY138513.1 GI:24895131
430. Influenza A virus (A/zhejiang/10/98(H3N2)) hemagglutinin (HA) mRNA, partial cds	987 bp linear mRNA	AY138515.1 GI:24895149
431. Influenza A virus (A/zhejiang/11/2002(H3N2)) hemagglutinin (HA) mRNA, partial cds	987 bp linear mRNA	AY138516.1 GI:24895159
432. Influenza A virus (A/zhejiang/12/99(H3N2)) hemagglutinin-like (HA) mRNA, partial sequence	987 bp linear mRNA	AY138514.1 GI:24895141

Strain/Protein	Length	GenBank / GI Accession No.
433. Influenza A virus (A/zhejiang/8/2002(H3N2)) hemagglutinin (HA) mRNA, partial cds	987 bp linear mRNA	AY138519.1 GI:24895188
434. Influenza A virus H3N2 strain A/Akita/1/94 nonstructural protein 1 and nonstructural protein 2 mRNAs, complete cds	840 bp linear mRNA	U65670.1 GI:3929405
435. Influenza A virus H3N2 strain A/Akita/1/95 nonstructural protein 1 and nonstructural protein 2 mRNAs, complete cds	840 bp linear mRNA	U65671.1 GI:3929408
436. Influenza A virus H3N2 strain A/Shiga/20/95 nonstructural protein 1 and nonstructural protein 2 mRNAs, complete cds	840 bp linear mRNA	U65673.1 GI:3929411
437. Influenza A virus H3N2 strain A/Miyagi/69/95 nonstructural protein 1 and nonstructural protein 2 mRNAs, complete cds	840 bp linear mRNA	U65674.1 GI:3929414
438. Influenza A virus H3N2 strain A/Hebei/19/95 nonstructural protein 1 and nonstructural protein 2 mRNAs, complete cds	840 bp linear mRNA	U65672.1 GI:6468319
A/Aichi/69/1994(H3N2) haemagglutinin		U48446.1
A/Bangkok/1/1979 (H3N2) hemagglutinin (HA)		AF201843.1
A/Beijing/353/89(H3) hemagglutinin (HA)		U97740.1
A/Beijing/353/1989(H3N2) haemagglutinin		Z46391.1
A/chicken/Singapore/2002(H3N2) M2 protein		EU014143.1
A/Christ Hospital/231/82(H3N2)) hemagglutinin (HA)		U77830.1
A/duck/Eastern China/36/2002(H3N2) segment 6 neuraminidase (NA)		EU429701.1
A/duck/Eastern China/160/2003(H3N2) segment 6 neuraminidase (NA)		EU429732.1
A/duck/Eastern China/848/2003(H3N2) segment 6 neuraminidase (NA)		EU429721.1
A/duck/Eastern China/770/2003(H3N2) segment 6 neuraminidase (NA)		EU429736.1
A/duck/Eastern China/855/2003(H3N2) segment 6 neuraminidase (NA)		EU429737.1
A/duck/Eastern China/875/2003(H3N2) segment 6 neuraminidase (NA)		EU429738.1
A/duck/Eastern China/901/2003(H3N2) segment 6 neuraminidase (NA)		EU429739.1
A/duck/Eastern China/866/2003(H3N2) segment 6 neuraminidase (NA)		EU429756.1
A/duck/Eastern China/857/2003(H3N2) segment 6 neuraminidase (NA)		EU429761.1
A/duck/Eastern China/852/2003(H3N2) segment 6 neuraminidase (NA)		EU429767.1
A/duck/Eastern China/838/2003(H3N2) segment 6 neuraminidase (NA)		EU429720.1
A/duck/Eastern China/6/2004(H3N2) segment 6 neuraminidase (NA)		EU429745.1
A/duck/Eastern China/03/2005(H3N2) segment 6 neuraminidase (NA)		EU429781.1
A/duck/Eastern China/02/2006(H3N2) segment 6 neuraminidase (NA)		EU429769.1
A/duck/Eastern China/04/2006(H3N2) segment 6 neuraminidase (NA)		EU429770.1
A/duck/Eastern China/21/2006(H3N2) segment 6 neuraminidase (NA)		EU429771.1
A/duck/Eastern China/23/2006(H3N2) segment 6 neuraminidase (NA)		EU429772.1

Strain/Protein	Length	GenBank / GI Accession No.
A/duck/Eastern China/31/2006(H3N2) segment 6 neuraminidase (NA)		EU429773.1
A/duck/Eastern China/35/2006(H3N2) segment 6 neuraminidase (NA)		EU429768.1
A/duck/Eastern China/42/2006(H3N2) segment 6 neuraminidase (NA)		EU429774.1
A/duck/Eastern China/53/2006(H3N2) segment 6 neuraminidase (NA)		EU429775.1
A/duck/Eastern China/60/2006(H3N2) segment 6 neuraminidase (NA)		EU429776.1
A/duck/Eastern China/62/2006(H3N2) segment 6 neuraminidase (NA)		EU429784.1
A/duck/Eastern China/63/2006(H3N2) segment 6 neuraminidase (NA)		EU429777.1
A/duck/Eastern China/142/2006(H3N2) segment 6 neuraminidase (NA)		EU429742.1
A/Dunedin/4/1973 (H3N2) hemagglutinin (HA)		AF201842.1

Table 9. Influenza H5N1 Antigens

Strain/Protein	Length	GenBank / GI Accession No.
1. Influenza A virus (A/chicken/Burkina Faso/01.03/2006(H5N1)) mRNA for non-structural protein (ns gene)	827 bp linear mRNA	AM503036.1 GI:147846308
2. Influenza A virus (A/chicken/Burkina Faso/13.1/2006(H5N1)) partial mRNA for matrix protein 1 (m1 gene)	990 bp linear mRNA	AM503007.1 GI:147846250
3. Influenza A virus (A/chicken/Burkina Faso/13.1/2006(H5N1)) mRNA for nucleoprotein (np gene)	1,529 bp linear mRNA	AM503029.1 GI:147846294
4. Influenza A virus (A/chicken/Burkina Faso/13.1/2006(H5N1)) mRNA for non-structural protein (ns gene)	827 bp linear mRNA	AM503037.1 GI:147846310
5. Influenza A virus (A/chicken/Burkina Faso/13.1/2006(H5N1)) partial mRNA for polymerase (pa gene)	2,169 bp linear mRNA	AM503046.1 GI:147846328
6. Influenza A virus (A/chicken/Burkina Faso/13.1/2006(H5N1)) partial mRNA for polymerase basic protein 1 (pb1 gene)	2,259 bp linear mRNA	AM503056.1 GI:147846348
7. Influenza A virus (A/chicken/Burkina Faso/13.1/2006(H5N1)) partial mRNA for polymerase basic protein 2 (pb2 gene)	2,315 bp linear mRNA	AM503067.1 GI:147846859
8. Influenza A virus (A/chicken/China/1/02(H5N1)) hemagglutinin (HA) mRNA, complete cds	1,736 bp linear mRNA	DQ023145.1 GI:66775624
9. Influenza A virus (A/chicken/China/1/02(H5N1)) nucleoprotein (NP) mRNA, complete cds	1,509 bp linear mRNA	DQ023146.1 GI:66775626
10. Influenza A virus (A/chicken/China/1/02(H5N1)) neuraminidase (NA) mRNA, complete cds	1,379 bp linear mRNA	DQ023147.1 GI:66775628
11. Influenza A virus (A/chicken/Crimea/04/2005(H5N1)) matrix protein (M) mRNA, complete cds	999 bp linear mRNA	DQ650660.1 GI:109692767
12. Influenza A virus (A/chicken/Crimea/04/2005(H5N1)) nonstructural protein (NS) mRNA, complete cds	850 bp linear mRNA	DQ650662.1 GI:109692771

Strain/Protein	Length	GenBank / GI Accession No.
13. Influenza A virus (A/chicken/Crimea/08/2005(H5N1)) matrix protein (M) mRNA, complete cds	994 bp linear mRNA	DQ650664.1 GI:109692775
14. Influenza A virus (A/chicken/Crimea/08/2005(H5N1)) nucleoprotein (NP) mRNA, complete cds	1,532 bp linear mRNA	DQ650666.1 GI:109692779
15. Influenza A virus (A/chicken/Crimea/08/2005(H5N1)) nonstructural protein (NS) mRNA, complete cds	850 bp linear mRNA	DQ650667.1 GI:109692781
16. Influenza A virus (A/chicken/Crimea/08/2005(H5N1)) polymerase acidic protein (PA) mRNA, complete cds	2,208 bp linear mRNA	DQ650668.1 GI:109692783
17. Influenza A virus (A/chicken/Crimea/08/2005(H5N1)) polymerase basic protein 2 (PB2) mRNA, complete cds	2,305 bp linear mRNA	DQ650670.1 GI:109692787
18. Influenza A virus (A/chicken/Dovolnoe/03/2005(H5N1)) hemagglutinin (HA) mRNA, partial cds	1,015 bp linear mRNA	DQ676838.1 GI:108782527
20. Influenza A virus (A/chicken/Guangxi/12/2004(H5N1)) polymerase PB2 mRNA, complete cds	2,341 bp linear mRNA	DQ366327.1 GI:86753731
21. Influenza A virus (A/chicken/Guangxi/12/2004(H5N1)) polymerase PB1 mRNA, complete cds	2,341 bp linear mRNA	DQ366328.1 GI:86753741
22. Influenza A virus (A/chicken/Guangxi/12/2004(H5N1)) PA protein mRNA, complete cds	2,233 bp linear mRNA	DQ366329.1 GI:86753751
23. Influenza A virus (A/chicken/Guangxi/12/2004(H5N1)) nucleocapsid mRNA, complete cds	1,565 bp linear mRNA	DQ366331.1 GI:86753771
24. Influenza A virus (A/chicken/Guangxi/12/2004(H5N1)) matrix protein mRNA, complete cds	1,027 bp linear mRNA	DQ366333.1 GI:86753791
25. Influenza A virus (A/chicken/Hong Kong/258/97(H5N1)) hemagglutinin mRNA, complete cds	1,718 bp linear mRNA	AF057291.1 GI:3068720
26. Influenza A virus (A/chicken/Hong Kong/258/97(H5N1)) neuraminidase mRNA, partial cds	1,318 bp linear mRNA	AF057292.1 GI:3068722
27. Influenza A virus (A/chicken/Hong Kong/258/97(H5N1)) nucleoprotein mRNA, complete cds	1,508 bp linear mRNA	AF057293.1 GI:3068724
28. Influenza A virus (A/Chicken/Hong Kong/728/97 (H5N1)) hemagglutinin H5 mRNA, complete cds	1,726 bp linear mRNA	AF082034.1 GI:4240435
29. Influenza A virus (A/Chicken/Hong Kong/786/97 (H5N1)) hemagglutinin H5 mRNA, complete cds	1,726 bp linear mRNA	AF082035.1 GI:4240437
30. Influenza A virus (A/chicken/Hong Kong/915/97(H5N1)) hemagglutinin H5 mRNA, complete cds	1,726 bp linear mRNA	AF082036.1 GI:4240439
31. Influenza A virus (A/chicken/Hong Kong/990/97 (H5N1)) hemagglutinin H5 mRNA, partial cds	1,091 bp linear mRNA	AF082037.1 GI:4240441
32. Influenza A virus (A/chicken/Krasnodar/01/2006(H5N1)) matrix protein 1 (M) mRNA, complete cds	1,002 bp linear mRNA	DQ676835.1 GI:108782521

Strain/Protein	Length	GenBank / GI Accession No.
33. Influenza A virus (A/chicken/Krasnodar/01/2006(H5N1)) nonstructural protein (NS) mRNA, complete cds	850 bp linear mRNA	DQ676837.1 GI:108782525
34. Influenza A virus (A/chicken/Kurgan/05/2005(H5N1)) hemagglutinin (HA) mRNA, complete cds	1,754 bp linear mRNA	DQ449632.1 GI:90289625
35. Influenza A virus (A/chicken/Kurgan/05/2005(H5N1)) matrix protein 1 (M) mRNA, complete cds	1,002 bp linear mRNA	DQ449633.1 GI:90289627
36. Influenza A virus (A/chicken/Kurgan/05/2005(H5N1)) neuraminidase (NA) mRNA, complete cds	1,373 bp linear mRNA	DQ449634.1 GI:90289629
37. Influenza A virus (A/chicken/Kurgan/05/2005(H5N1)) nucleoprotein (NP) mRNA, complete cds	1,540 bp linear mRNA	DQ449635.1 GI:90289631
38. Influenza A virus (A/chicken/Kurgan/05/2005(H5N1)) nonstructural protein (NS) mRNA, complete cds	850 bp linear mRNA	DQ449636.1 GI:90289633
39. Influenza A virus (A/chicken/Kurgan/05/2005(H5N1)) polymerase acidic protein (PA) mRNA, complete cds	2,208 bp linear mRNA	DQ449637.1 GI:90289635
40. Influenza A virus (A/chicken/Kurgan/05/2005(H5N1)) polymerase basic protein 1 (PB1) mRNA, complete cds	2,316 bp linear mRNA	DQ449638.1 GI:90289637
41. Influenza A virus (A/chicken/Kurgan/05/2005(H5N1)) polymerase basic protein 2 (PB2) mRNA, complete cds	2,316 bp linear mRNA	DQ449639.1 GI:90289646
42. Influenza A virus (A/chicken/Lobzenko/01/2008(H5N1)) hemagglutinin (HA) mRNA, partial cds	184 bp linear mRNA	EU447276.1 GI:168998217
43. Influenza A virus (A/chicken/Mahachkala/05/2006(H5N1)) matrix protein 1 (M) mRNA, complete cds	1,002 bp linear mRNA	DQ676831.1 GI:108782513
44. Influenza A virus (A/chicken/Mahachkala/05/2006(H5N1)) nonstructural protein (NS) mRNA, complete cds	850 bp linear mRNA	DQ676833.1 GI:108782517
45. Influenza A virus (A/chicken/Nigeria/AB13/2006(H5N1)) mRNA for nucleoprotein (np gene)	1,531 bp linear mRNA	AM503030.1 GI:147846296
46. Influenza A virus (A/chicken/Nigeria/AB13/2006(H5N1)) mRNA for non-structural protein (ns gene)	827 bp linear mRNA	AM503040.1 GI:147846316
47. Influenza A virus (A/chicken/Nigeria/AB13/2006(H5N1)) partial mRNA for polymerase (pa gene)	2,169 bp linear mRNA	AM503051.1 GI:147846338
48. Influenza A virus (A/chicken/Nigeria/AB13/2006(H5N1)) partial mRNA for polymerase basic protein 1 (pb1 gene)	2,259 bp linear mRNA	AM503060.1 GI:147846845
49. Influenza A virus (A/chicken/Nigeria/AB13/2006(H5N1)) partial mRNA for polymerase basic protein 2 (pb2 gene)	2,315 bp linear mRNA	AM503071.1 GI:147846867
70. Influenza A virus (A/chicken/Hong Kong/3123.1/2002(H5N1)) neuraminidase (NA) mRNA, partial cds	1,055 bp linear mRNA	DQ250158.1 GI:82412012

Strain/Protein	Length	GenBank / GI Accession No.
75. Influenza A virus (A/chicken/Krasnodar/01/2006(H5N1)) hemagglutinin (HA) mRNA, complete cds	1,754 bp linear mRNA	DQ676834.1 GI:108782519
78. Influenza A virus (A/chicken/Krasnodar/01/2006(H5N1)) neuraminidase (NA) mRNA, complete cds	1,373 bp linear mRNA	DQ676836.2 GI:115520953
91. Influenza A virus (A/chicken/Lobzenko/01/2008(H5N1)) hemagglutinin (HA) mRNA, partial cds	184 bp linear mRNA	EU447276.1 GI:168998217
92. Influenza A virus (A/chicken/Mahachkala/05/2006(H5N1)) hemagglutinin (HA) mRNA, complete cds	1,683 bp linear mRNA	DQ676830.1 GI:108782511
94. Influenza A virus (A/chicken/Mahachkala/05/2006(H5N1)) neuraminidase (NA) mRNA, complete cds	1,373 bp linear mRNA	DQ676832.1 GI:108782515
96. Influenza A virus (A/chicken/Malaysia/01/2004(H5N1)) neuramidase (NA) mRNA, partial cds	433 bp linear mRNA	DQ096567.1 GI:69145364
97. Influenza A virus (A/chicken/Nigeria/AB13/2006(H5N1)) partial mRNA for hemagglutinin (ha gene)	1,722 bp linear mRNA	AM503002.1 GI:147846240
98. Influenza A virus (A/chicken/Nigeria/AB13/2006(H5N1)) partial mRNA for neuraminidase (na gene)	1,329 bp linear mRNA	AM503020.1 GI:147846276
105. Influenza A virus (A/chicken/Nigeria/AB14/2006(H5N1)) partial mRNA for hemagglutinin (ha gene)	1,719 bp linear mRNA	AM503003.1 GI:147846242
106. Influenza A virus (A/chicken/Nigeria/AB14/2006(H5N1)) partial mRNA for matrix protein 1 (m1 gene)	953 bp linear mRNA	AM503011.1 GI:147846258
107. Influenza A virus (A/chicken/Nigeria/AB14/2006(H5N1)) partial mRNA for neuraminidase (na gene)	1,343 bp linear mRNA	AM503025.1 GI:147846286
108. Influenza A virus (A/chicken/Nigeria/AB14/2006(H5N1)) mRNA for non-structural protein (ns gene)	827 bp linear mRNA	AM503041.1 GI:147846318
109. Influenza A virus (A/chicken/Nigeria/AB14/2006(H5N1)) partial mRNA for polymerase (pa gene)	2,169 bp linear mRNA	AM503054.1 GI:147846344
110. Influenza A virus (A/chicken/Nigeria/AB14/2006(H5N1)) partial mRNA for polymerase basic protein 1 (pb1 gene)	2,259 bp linear mRNA	AM503061.1 GI:147846847
111. Influenza A virus (A/chicken/Nigeria/AB14/2006(H5N1)) partial mRNA for polymerase basic protein 2 (pb2 gene)	2,315 bp linear mRNA	AM503072.1 GI:147846869
112. Influenza A virus (A/chicken/Nigeria/AB14/2006(H5N1)) mRNA for nucleoprotein (np gene)	1,548 bp linear mRNA	AM503034.2 GI:149773117
113. Influenza A virus (A/chicken/Nigeria/BA210/2006(H5N1)) partial mRNA for neuraminidase (na gene)	1,342 bp linear mRNA	AM503022.1 GI:147846280
114. Influenza A virus (A/chicken/Nigeria/BA211/2006(H5N1)) partial mRNA for neuraminidase (na gene)	1,321 bp linear mRNA	AM503021.1 GI:147846278
115. Influenza A virus (A/chicken/Nigeria/BA211/2006(H5N1)) partial mRNA for polymerase basic protein 2 (pb2 gene)	2,315 bp linear mRNA	AM503073.1 GI:147846871

Strain/Protein	Length	GenBank / GI Accession No.
116. Influenza A virus (A/chicken/Nigeria/FA4/2006(H5N1)) partial mRNA for hemagglutinin (ha gene)	1,717 bp linear mRNA	AM503004.1 GI:147846244
117. Influenza A virus (A/chicken/Nigeria/FA4/2006(H5N1)) partial mRNA for matrix protein 1 (m1 gene)	989 bp linear mRNA	AM503013.1 GI:147846262
118. Influenza A virus (A/chicken/Nigeria/FA4/2006(H5N1)) partial mRNA for neuraminidase (na gene)	1,321 bp linear mRNA	AM503026.1 GI:147846288
119. Influenza A virus (A/chicken/Nigeria/FA4/2006(H5N1)) mRNA for non-structural protein (ns gene)	827 bp linear mRNA	AM503045.1 GI:147846326
120. Influenza A virus (A/chicken/Nigeria/FA4/2006(H5N1)) partial mRNA for polymerase (pa gene)	2,169 bp linear mRNA	AM503055.1 GI:147846346
121. Influenza A virus (A/chicken/Nigeria/FA4/2006(H5N1)) partial mRNA for polymerase basic protein 1 (pb1 gene)	2,259 bp linear mRNA	AM503064.1 GI:147846853
122. Influenza A virus (A/chicken/Nigeria/FA4/2006(H5N1)) partial mRNA for polymerase basic protein 2 (pb2 gene)	2,224 bp linear mRNA	AM503074.1 GI:147846873
123. Influenza A virus (A/chicken/Nigeria/FA6/2006(H5N1)) partial mRNA for hemagglutinin (ha gene)	1,717 bp linear mRNA	AM502998.1 GI:147846232
124. Influenza A virus (A/chicken/Nigeria/FA6/2006(H5N1)) partial mRNA for matrix protein 1 (m1 gene)	965 bp linear mRNA	AM503012.1 GI:147846260
125. Influenza A virus (A/chicken/Nigeria/FA6/2006(H5N1)) partial mRNA for neuraminidase (na gene)	1,327 bp linear mRNA	AM503023.1 GI:147846282
126. Influenza A virus (A/chicken/Nigeria/FA6/2006(H5N1)) mRNA for nucleoprotein (np gene)	1,543 bp linear mRNA	AM503031.1 GI:147846298
127. Influenza A virus (A/chicken/Nigeria/FA6/2006(H5N1)) partial mRNA for polymerase (pa gene)	2,169 bp linear mRNA	AM503052.1 GI:147846340
128. Influenza A virus (A/chicken/Nigeria/FA6/2006(H5N1)) partial mRNA for polymerase basic protein 1 (pb1 gene)	2,259 bp linear mRNA	AM503063.1 GI:147846851
129. Influenza A virus (A/chicken/Nigeria/FA7/2006(H5N1)) partial mRNA for hemagglutinin (ha gene)	1,710 bp linear mRNA	AM502999.1 GI:147846234
130. Influenza A virus (A/chicken/Nigeria/FA7/2006(H5N1)) partial mRNA for matrix protein 1 (m1 gene)	1,001 bp linear mRNA	AM503009.1 GI:147846254
131. Influenza A virus (A/chicken/Nigeria/FA7/2006(H5N1)) partial mRNA for neuraminidase (na gene)	1,331 bp linear mRNA	AM503018.1 GI:147846272
132. Influenza A virus (A/chicken/Nigeria/FA7/2006(H5N1)) mRNA for nucleoprotein (np gene)	1,531 bp linear mRNA	AM503035.1 GI:147846306
133. Influenza A virus (A/chicken/Nigeria/FA7/2006(H5N1)) mRNA for non-structural protein (ns gene)	827 bp linear mRNA	AM503042.1 GI:147846320
134. Influenza A virus (A/chicken/Nigeria/FA7/2006(H5N1)) partial mRNA for polymerase (pa gene)	2,169 bp linear mRNA	AM503049.1 GI:147846334

Strain/Protein	Length	GenBank / GI Accession No.
135. Influenza A virus (A/chicken/Nigeria/FA7/2006(H5N1)) partial mRNA for polymerase basic protein 1 (pb1 gene)	2,259 bp linear mRNA	AM503057.1 GI:147846350
136. Influenza A virus (A/chicken/Nigeria/FA7/2006(H5N1)) partial mRNA for polymerase basic protein 2 (pb2 gene)	2,315 bp linear mRNA	AM503068.1 GI:147846861
137. Influenza A virus (A/chicken/Nigeria/IF10/2006(H5N1)) partial mRNA for hemagglutinin (ha gene)	1,714 bp linear mRNA	AM503001.1 GI:147846238
138. Influenza A virus (A/chicken/Nigeria/IF10/2006(H5N1)) partial mRNA for matrix protein 1 (m1 gene)	990 bp linear mRNA	AM503010.1 GI:147846256
139. Influenza A virus (A/chicken/Nigeria/IF10/2006(H5N1)) partial mRNA for neuraminidase (na gene)	1,332 bp linear mRNA	AM503024.1 GI:147846284
140. Influenza A virus (A/chicken/Nigeria/IF10/2006(H5N1)) mRNA for non-structural protein (ns gene)	827 bp linear mRNA	AM503044.1 GI:147846324
141. Influenza A virus (A/chicken/Nigeria/IF10/2006(H5N1)) partial mRNA for polymerase (pa gene)	2,169 bp linear mRNA	AM503053.1 GI:147846342
142. Influenza A virus (A/chicken/Nigeria/IF10/2006(H5N1)) partial mRNA for polymerase basic protein 1 (pb1 gene)	2,259 bp linear mRNA	AM503059.1 GI:147846843
143. Influenza A virus (A/chicken/Nigeria/IF10/2006(H5N1)) partial mRNA for polymerase basic protein 2 (pb2 gene)	2,315 bp linear mRNA	AM503069.1 GI:147846863
144. Influenza A virus (A/chicken/Nigeria/IF10/2006(H5N1)) mRNA for nucleoprotein (np gene)	1,550 bp linear mRNA	AM503033.2 GI:149773115
145. Influenza A virus (A/chicken/Nigeria/OD8/2006(H5N1)) partial mRNA for hemagglutinin (ha gene)	1,719 bp linear mRNA	AM503005.1 GI:147846246
146. Influenza A virus (A/chicken/Nigeria/OD8/2006(H5N1)) partial mRNA for matrix protein 1 (m1 gene)	989 bp linear mRNA	AM503014.1 GI:147846264
147. Influenza A virus (A/chicken/Nigeria/OD9/2006(H5N1)) partial mRNA for hemagglutinin (ha gene)	1,720 bp linear mRNA	AM503000.1 GI:147846236
148. Influenza A virus (A/chicken/Nigeria/OD9/2006(H5N1)) partial mRNA for matrix protein 1 (m1 gene)	988 bp linear mRNA	AM503015.1 GI:147846266
149. Influenza A virus (A/chicken/Nigeria/OD9/2006(H5N1)) partial mRNA for neuraminidase (na gene)	1,330 bp linear mRNA	AM503019.1 GI:147846274
150. Influenza A virus (A/chicken/Nigeria/OD9/2006(H5N1)) mRNA for nucleoprotein (np gene)	1,531 bp linear mRNA	AM503032.1 GI:147846300
151. Influenza A virus (A/chicken/Nigeria/OD9/2006(H5N1)) mRNA for non-structural protein (ns gene)	827 bp linear mRNA	AM503043.1 GI:147846322
152. Influenza A virus (A/chicken/Nigeria/OD9/2006(H5N1)) partial mRNA for polymerase (pa gene)	2,169 bp linear mRNA	AM503050.1 GI:147846336

Strain/Protein	Length	GenBank / GI Accession No.
153. Influenza A virus (A/chicken/Nigeria/OD9/2006(H5N1)) partial mRNA for polymerase basic protein 1 (pb1 gene)	2,259 bp linear mRNA	AM503058.1 GI:147846841
154. Influenza A virus (A/chicken/Nigeria/OD9/2006(H5N1)) partial mRNA for polymerase basic protein 2 (pb2 gene)	2,315 bp linear mRNA	AM503070.1 GI:147846865
155. Influenza A virus (A/chicken/Scotland/59(H5N1)) mRNA for haemagglutinin precursor	1,768 bp linear mRNA	X07869.1 GI:60482
156. Influenza A virus (A/chicken/Scotland/59(H5N1)) N1 gene for neuraminidase, genomic RNA	1,445 bp linear mRNA	AJ416625.1 GI:39840717
161. Influenza A virus (A/chicken/zz/02/2004(H5N1)) nucleoprotein mRNA, complete cds	1,497 bp linear mRNA	DQ208502.1 GI:77158587
162. Influenza A virus (A/common coot/Switzerland/V544/2006(H5N1)) hemagglutinin (HA) gene, complete cds	1,707 bp linear mRNA	EF110519.1 GI:119394676
163. Influenza A virus (A/domestic goose/Pavlodar/1/2005(H5N1)) hemagglutinin (HA) mRNA, complete cds	1,735 bp linear mRNA	EU190482.1 GI:158516739
164. Influenza A virus (A/duck/Eastern China/145/2003(H5N1)) segment 6 neuraminidase (NA) mRNA, complete cds	1,401 bp linear mRNA	EU429750.1 GI:167859465
165. Influenza A virus (A/duck/Eastern China/150/2003(H5N1)) segment 6 neuraminidase (NA) mRNA, complete cds	1,407 bp linear mRNA	EU429731.1 GI:167859427
166. Influenza A virus (A/duck/Eastern China/22/2005(H5N1)) segment 6 neuraminidase (NA) mRNA, complete cds	1,398 bp linear mRNA	EU429783.1 GI:167859531
167. Influenza A virus (A/duck/Eastern China/304/2002(H5N1)) segment 6 neuraminidase (NA) mRNA, complete cds	1,398 bp linear mRNA	EU429747.1 GI:167859459
168. Influenza A virus (A/duck/Eastern China/318/2002(H5N1)) segment 6 neuraminidase (NA) mRNA, complete cds	1,401 bp linear mRNA	EU429727.1 GI:167859419
169. Influenza A virus (A/duck/Eastern China/37/2006(H5N1)) segment 6 neuraminidase (NA) mRNA, complete cds	1,399 bp linear mRNA	EU429778.1 GI:167859521
170. Influenza A virus (A/duck/Eastern China/40/2005(H5N1)) segment 6 neuraminidase (NA) mRNA, complete cds	1,398 bp linear mRNA	EU429757.1 GI:167859479
171. Influenza A virus (A/duck/Eastern China/48/2006(H5N1)) segment 6 neuraminidase (NA) mRNA, complete cds	1,398 bp linear mRNA	EU429779.1 GI:167859523
172. Influenza A virus (A/duck/Eastern China/51/2005(H5N1)) segment 6 neuraminidase (NA) mRNA, complete cds	1,398 bp linear mRNA	EU429763.1 GI:167859491
173. Influenza A virus (A/duck/Eastern China/54/2005(H5N1)) segment 6 neuraminidase (NA) mRNA, complete cds	1,398 bp linear mRNA	EU429758.1 GI:167859481
174. Influenza A virus (A/duck/Eastern China/58/2005(H5N1)) segment 6 neuraminidase (NA) mRNA, complete cds	1,398 bp linear mRNA	EU429764.1 GI:167859493
175. Influenza A virus (A/duck/Eastern China/59/2005(H5N1)) segment 6 neuraminidase (NA) mRNA, complete cds	1,398 bp linear mRNA	EU429759.1 GI:167859483

Strain/Protein	Length	GenBank / GI Accession No.
176. Influenza A virus (A/duck/Eastern China/89/2005(H5N1)) segment 6 neuraminidase (NA) mRNA, complete cds	1,398 bp linear mRNA	EU429765.1 GI:167859495
177. Influenza A virus (A/duck/Eastern China/89/2006(H5N1)) segment 6 neuraminidase (NA) mRNA, complete cds	1,399 bp linear mRNA	EU429785.1 GI:167859535
178. Influenza A virus (A/duck/Eastern China/97/2001(H5N1)) segment 6 neuraminidase (NA) mRNA, complete cds	1,398 bp linear mRNA	EU429717.1 GI:167859399
179. Influenza A virus (A/duck/Fujian/01/2002(H5N1)) polymerase basic protein 2 (PB2) mRNA, complete cds	2,281 bp linear mRNA	AY585504.1 GI:47156226
180. Influenza A virus (A/duck/Fujian/01/2002(H5N1)) matrix protein mRNA, complete cds	760 bp linear mRNA	AY585378.1 GI:47156310
181. Influenza A virus (A/duck/Fujian/01/2002(H5N1)) neuraminidase (NA) mRNA, complete cds	1,357 bp linear mRNA	AY585399.1 GI:47156352
182. Influenza A virus (A/duck/Fujian/01/2002(H5N1)) nucleoprotein (NP) mRNA, complete cds	1,497 bp linear mRNA	AY585420.1 GI:47156394
183. Influenza A virus (A/duck/Fujian/01/2002(H5N1)) nonstructural protein 1 (NS1) mRNA, partial cds	686 bp linear mRNA	AY585441.1 GI:47156436
184. Influenza A virus (A/duck/Fujian/13/2002(H5N1)) polymerase basic protein 2 (PB2) mRNA, complete cds	2,281 bp linear mRNA	AY585505.1 GI:47156228
185. Influenza A virus (A/duck/Fujian/13/2002(H5N1)) matrix protein mRNA, complete cds	761 bp linear mRNA	AY585379.1 GI:47156312
186. Influenza A virus (A/duck/Fujian/13/2002(H5N1)) neuraminidase (NA) mRNA, complete cds	1,357 bp linear mRNA	AY585400.1 GI:47156354
187. Influenza A virus (A/duck/Fujian/13/2002(H5N1)) nucleoprotein (NP) mRNA, complete cds	1,499 bp linear mRNA	AY585421.1 GI:47156396
188. Influenza A virus (A/duck/Fujian/13/2002(H5N1)) nonstructural protein 1 (NS1) mRNA, partial cds	685 bp linear mRNA	AY585442.1 GI:47156438
189. Influenza A virus (A/duck/Fujian/17/2001(H5N1)) polymerase basic protein 2 (PB2) mRNA, complete cds	2,281 bp linear mRNA	AY585506.1 GI:47156230
190. Influenza A virus (A/duck/Fujian/17/2001(H5N1)) matrix protein mRNA, complete cds	759 bp linear mRNA	AY585380.1 GI:47156314
191. Influenza A virus (A/duck/Fujian/17/2001(H5N1)) neuraminidase (NA) mRNA, complete cds	1,418 bp linear mRNA	AY585401.1 GI:47156356
192. Influenza A virus (A/duck/Fujian/17/2001(H5N1)) nucleoprotein (NP) mRNA, complete cds	1,498 bp linear mRNA	AY585422.1 GI:47156398
193. Influenza A virus (A/duck/Fujian/17/2001(H5N1)) nonstructural protein 1 (NS1) mRNA, complete cds	686 bp linear mRNA	AY585443.1 GI:47156440
194. Influenza A virus (A/duck/Fujian/19/2000(H5N1)) polymerase basic protein 2 (PB2) mRNA, complete cds	2,281 bp linear mRNA	AY585507.1 GI:47156232
195. Influenza A virus (A/duck/Fujian/19/2000(H5N1)) matrix protein mRNA, complete cds	760 bp linear mRNA	AY585381.1 GI:47156316

Strain/Protein	Length	GenBank / GI Accession No.
196. Influenza A virus (A/duck/Fujian/19/2000(H5N1)) neuraminidase (NA) mRNA, complete cds	1,355 bp linear mRNA	AY585402.1 GI:47156358
197. Influenza A virus (A/duck/Fujian/19/2000(H5N1)) nucleoprotein (NP) mRNA, complete cds	1,498 bp linear mRNA	AY585423.1 GI:47156400
198. Influenza A virus (A/duck/Fujian/19/2000(H5N1)) nonstructural protein 1 (NS1) mRNA, complete cds	687 bp linear mRNA	AY585444.1 GI:47156442
199. Influenza A virus (A/duck/Guangdong/01/2001(H5N1)) polymerase basic protein 2 (PB2) mRNA, complete cds	2,281 bp linear mRNA	AY585508.1 GI:47156234
200. Influenza A virus (A/duck/Guangdong/01/2001(H5N1)) matrix protein mRNA, complete cds	760 bp linear mRNA	AY585382.1 GI:47156318
201. Influenza A virus (A/duck/Guangdong/01/2001(H5N1)) neuraminidase (NA) mRNA, complete cds	1,414 bp linear mRNA	AY585403.1 GI:47156360
202. Influenza A virus (A/duck/Guangdong/01/2001(H5N1)) nucleoprotein (NP) mRNA, complete cds	1,497 bp linear mRNA	AY585424.1 GI:47156402
203. Influenza A virus (A/duck/Guangdong/01/2001(H5N1)) nonstructural protein 1 (NS1) mRNA, complete cds	687 bp linear mRNA	AY585445.1 GI:47156444
204. Influenza A virus (A/duck/Guangdong/07/2000(H5N1)) polymerase basic protein 2 (PB2) mRNA, complete cds	2,280 bp linear mRNA	AY585509.1 GI:47156236
205. Influenza A virus (A/duck/Guangdong/07/2000(H5N1)) matrix protein mRNA, complete cds	759 bp linear mRNA	AY585383.1 GI:47156320
206. Influenza A virus (A/duck/Guangdong/07/2000(H5N1)) neuraminidase (NA) mRNA, complete cds	1,417 bp linear mRNA	AY585404.1 GI:47156362
207. Influenza A virus (A/duck/Guangdong/07/2000(H5N1)) nucleoprotein (NP) mRNA, complete cds	1,497 bp linear mRNA	AY585425.1 GI:47156404
208. Influenza A virus (A/duck/Guangdong/07/2000(H5N1)) nonstructural protein 1 (NS1) mRNA, partial cds	690 bp linear mRNA	AY585446.1 GI:47156446
209. Influenza A virus (A/duck/Guangdong/12/2000(H5N1)) polymerase basic protein 2 (PB2) mRNA, complete cds	2,281 bp linear mRNA	AY585510.1 GI:47156238
210. Influenza A virus (A/duck/Guangdong/12/2000(H5N1)) matrix protein mRNA, complete cds	760 bp linear mRNA	AY585384.1 GI:47156322
211. Influenza A virus (A/duck/Guangdong/12/2000(H5N1)) neuraminidase (NA) mRNA, complete cds	1,359 bp linear mRNA	AY585405.1 GI:47156364
212. Influenza A virus (A/duck/Guangdong/12/2000(H5N1)) nucleoprotein (NP) mRNA, complete cds	1,498 bp linear mRNA	AY585426.1 GI:47156406
213. Influenza A virus (A/duck/Guangdong/12/2000(H5N1)) nonstructural protein 1 (NS1) mRNA, partial cds	685 bp linear mRNA	AY585447.1 GI:47156448
214. Influenza A virus (A/duck/Guangdong/22/2002(H5N1)) polymerase basic protein 2 (PB2) mRNA, complete cds	2,281 bp linear mRNA	AY585511.1 GI:47156240

Strain/Protein	Length	GenBank / GI Accession No.
215. Influenza A virus (A/duck/Guangdong/22/2002(H5N1)) matrix protein mRNA, complete cds	760 bp linear mRNA	AY585385.1 GI:47156324
216. Influenza A virus (A/duck/Guangdong/22/2002(H5N1)) neuraminidase (NA) mRNA, complete cds	1,412 bp linear mRNA	AY585406.1 GI:47156366
217. Influenza A virus (A/duck/Guangdong/22/2002(H5N1)) nucleoprotein (NP) mRNA, complete cds	1,499 bp linear mRNA	AY585427.1 GI:47156408
218. Influenza A virus (A/duck/Guangdong/22/2002(H5N1)) nonstructural protein 1 (NS1) mRNA, complete cds	682 bp linear mRNA	AY585448.1 GI:47156450
219. Influenza A virus (A/duck/Guangdong/40/2000(H5N1)) polymerase basic protein 2 (PB2) mRNA, complete cds	2,281 bp linear mRNA	AY585512.1 GI:47156242
220. Influenza A virus (A/duck/Guangdong/40/2000(H5N1)) matrix protein mRNA, complete cds	760 bp linear mRNA	AY585386.1 GI:47156326
221. Influenza A virus (A/duck/Guangdong/40/2000(H5N1)) neuraminidase (NA) mRNA, partial cds	1,401 bp linear mRNA	AY585407.1 GI:47156368
222. Influenza A virus (A/duck/Guangdong/40/2000(H5N1)) nucleoprotein (NP) mRNA, complete cds	1,499 bp linear mRNA	AY585428.1 GI:47156410
223. Influenza A virus (A/duck/Guangdong/40/2000(H5N1)) nonstructural protein 1 (NS1) mRNA, partial cds	689 bp linear mRNA	AY585449.1 GI:47156452
224. Influenza A virus (A/duck/Guangxi/07/1999(H5N1)) polymerase basic protein 2 (PB2) mRNA, complete cds	2,281 bp linear mRNA	AY585513.1 GI:47156244
225. Influenza A virus (A/duck/Guangxi/07/1999(H5N1)) matrix protein mRNA, complete cds	760 bp linear mRNA	AY585387.1 GI:47156328
226. Influenza A virus (A/duck/Guangxi/07/1999(H5N1)) neuraminidase (NA) mRNA, complete cds	1,421 bp linear mRNA	AY585408.1 GI:47156370
227. Influenza A virus (A/duck/Guangxi/07/1999(H5N1)) nucleoprotein (NP) mRNA, complete cds	1,501 bp linear mRNA	AY585429.1 GI:47156412
228. Influenza A virus (A/duck/Guangxi/07/1999(H5N1)) nonstructural protein 1 (NS1) mRNA, partial cds	687 bp linear mRNA	AY585450.1 GI:47156454
229. Influenza A virus (A/duck/Guangxi/13/2004(H5N1)) nonstructural protein 1 mRNA, complete cds	875 bp linear mRNA	DQ366342.1 GI:86753723
230. Influenza A virus (A/duck/Guangxi/13/2004(H5N1)) polymerase PB2 mRNA, complete cds	2,341 bp linear mRNA	DQ366335.1 GI:86753733
231. Influenza A virus (A/duck/Guangxi/13/2004(H5N1)) polymerase PB1 mRNA, complete cds	2,341 bp linear mRNA	DQ366336.1 GI:86753743
232. Influenza A virus (A/duck/Guangxi/13/2004(H5N1)) PA protein mRNA, complete cds	2,233 bp linear mRNA	DQ366337.1 GI:86753753
233. Influenza A virus (A/duck/Guangxi/13/2004(H5N1)) hemagglutinin mRNA, complete cds	1,776 bp linear mRNA	DQ366338.1 GI:86753763

Strain/Protein	Length	GenBank / GI Accession No.
234. Influenza A virus (A/duck/Guangxi/13/2004(H5N1)) nucleocapsid mRNA, complete cds	1,565 bp linear mRNA	DQ366339.1 GI:86753773
235. Influenza A virus (A/duck/Guangxi/13/2004(H5N1)) neuraminidase mRNA, complete cds	1,378 bp linear mRNA	DQ366340.1 GI:86753783
236. Influenza A virus (A/duck/Guangxi/13/2004(H5N1)) matrix protein mRNA, complete cds	1,027 bp linear mRNA	DQ366341.1 GI:86753793
237. Influenza A virus (A/duck/Guangxi/22/2001(H5N1)) polymerase basic protein 2 (PB2) mRNA, complete cds	2,281 bp linear mRNA	AY585514.1 GI:47156246
238. Influenza A virus (A/duck/Guangxi/22/2001(H5N1)) matrix protein mRNA, partial cds	757 bp linear mRNA	AY585388.1 GI:47156330
239. Influenza A virus (A/duck/Guangxi/22/2001(H5N1)) neuraminidase (NA) mRNA, complete cds	1,414 bp linear mRNA	AY585409.1 GI:47156372
240. Influenza A virus (A/duck/Guangxi/22/2001(H5N1)) nucleoprotein (NP) mRNA, complete cds	1,498 bp linear mRNA	AY585430.1 GI:47156414
241. Influenza A virus (A/duck/Guangxi/22/2001(H5N1)) nonstructural protein 1 (NS1) mRNA, complete cds	687 bp linear mRNA	AY585451.1 GI:47156456
242. Influenza A virus (A/duck/Guangxi/35/2001(H5N1)) polymerase basic protein 2 (PB2) mRNA, complete cds	2,281 bp linear mRNA	AY585515.1 GI:47156248
243. Influenza A virus (A/duck/Guangxi/35/2001(H5N1)) matrix protein mRNA, complete cds	760 bp linear mRNA	AY585389.1 GI:47156332
244. Influenza A virus (A/duck/Guangxi/35/2001(H5N1)) neuraminidase (NA) mRNA, complete cds	1,414 bp linear mRNA	AY585410.1 GI:47156374
245. Influenza A virus (A/duck/Guangxi/35/2001(H5N1)) nucleoprotein (NP) mRNA, complete cds	1,498 bp linear mRNA	AY585431.1 GI:47156416
246. Influenza A virus (A/duck/Guangxi/35/2001(H5N1)) nonstructural protein 1 (NS1) mRNA, complete cds	685 bp linear mRNA	AY585452.1 GI:47156458
247. Influenza A virus (A/duck/Guangxi/50/2001(H5N1)) polymerase basic protein 2 (PB2) mRNA, complete cds	2,281 bp linear mRNA	AY585516.1 GI:47156250
248. Influenza A virus (A/duck/Guangxi/50/2001(H5N1)) matrix protein mRNA, complete cds	760 bp linear mRNA	AY585398.1 GI:47156350
249. Influenza A virus (A/duck/Guangxi/50/2001(H5N1)) neuraminidase (NA) mRNA, complete cds	1,354 bp linear mRNA	AY585411.1 GI:47156376
250. Influenza A virus (A/duck/Guangxi/50/2001(H5N1)) nucleoprotein (NP) mRNA, complete cds	1,498 bp linear mRNA	AY585432.1 GI:47156418
251. Influenza A virus (A/duck/Guangxi/50/2001(H5N1)) nonstructural protein 1 (NS1) mRNA, complete cds	686 bp linear mRNA	AY585453.1 GI:47156460
252. Influenza A virus (A/duck/Guangxi/53/2002(H5N1)) polymerase basic protein 2 (PB2) mRNA, complete cds	2,281 bp linear mRNA	AY585517.1 GI:47156252
253. Influenza A virus (A/duck/Guangxi/53/2002(H5N1)) matrix protein mRNA, complete cds	760 bp linear mRNA	AY585390.1 GI:47156334

Strain/Protein	Length	GenBank / GI Accession No.
254. Influenza A virus (A/duck/Guangxi/53/2002(H5N1)) neuraminidase (NA) mRNA, complete cds	1,361 bp linear mRNA	AY585412.1 GI:47156378
255. Influenza A virus (A/duck/Guangxi/53/2002(H5N1)) nucleoprotein (NP) mRNA, complete cds	1,498 bp linear mRNA	AY585433.1 GI:47156420
256. Influenza A virus (A/duck/Guangxi/53/2002(H5N1)) nonstructural protein 1 (NS1) mRNA, partial cds	687 bp linear mRNA	AY585454.1 GI:47156462
257. Influenza A virus (A/duck/Kurgan/08/2005(H5N1)) hemagglutinin (HA) mRNA, complete cds	1,754 bp linear mRNA	DQ449640.1 GI:90289674
258. Influenza A virus (A/duck/Kurgan/08/2005(H5N1)) matrix protein 1 (M) mRNA, complete cds	1,002 bp linear mRNA	DQ449641.1 GI:90289689
259. Influenza A virus (A/duck/Kurgan/08/2005(H5N1)) neuraminidase (NA) mRNA, complete cds	1,373 bp linear mRNA	DQ449642.1 GI:90289708
260. Influenza A virus (A/duck/Kurgan/08/2005(H5N1)) nucleoprotein (NP) mRNA, complete cds	1,540 bp linear mRNA	DQ449643.1 GI:90289731
261. Influenza A virus (A/duck/Kurgan/08/2005(H5N1)) nonstructural protein (NS) mRNA, complete cds	850 bp linear mRNA	DQ449644.1 GI:90289739
262. Influenza A virus (A/duck/Kurgan/08/2005(H5N1)) polymerase acidic protein (PA) mRNA, complete cds	2,208 bp linear mRNA	DQ449645.1 GI:90289756
263. Influenza A virus (A/duck/Kurgan/08/2005(H5N1)) polymerase basic protein 1 (PB1) mRNA, complete cds	2,316 bp linear mRNA	DQ449646.1 GI:90289774
264. Influenza A virus (A/duck/Kurgan/08/2005(H5N1)) polymerase basic protein 2 (PB2) mRNA, complete cds	2,316 bp linear mRNA	DQ449647.1 GI:90289783
266. Influenza A virus (A/duck/Shanghai/08/2001(H5N1)) polymerase basic protein 2 (PB2) mRNA, complete cds	2,281 bp linear mRNA	AY585518.1 GI:47156254
267. Influenza A virus (A/duck/Shanghai/08/2001(H5N1)) matrix protein mRNA, complete cds	760 bp linear mRNA	AY585391.1 GI:47156336
268. Influenza A virus (A/duck/Shanghai/08/2001(H5N1)) neuraminidase (NA) mRNA, complete cds	1,357 bp linear mRNA	AY585413.1 GI:47156380
269. Influenza A virus (A/duck/Shanghai/08/2001(H5N1)) nucleoprotein (NP) mRNA, complete cds	1,498 bp linear mRNA	AY585434.1 GI:47156422
270. Influenza A virus (A/duck/Shanghai/08/2001(H5N1)) nonstructural protein 1 (NS1) mRNA, partial cds	685 bp linear mRNA	AY585455.1 GI:47156464
271. Influenza A virus (A/duck/Shanghai/13/2001(H5N1)) polymerase basic protein 2 (PB2) mRNA, complete cds	2,281 bp linear mRNA	AY585519.1 GI:47156256
272. Influenza A virus (A/duck/Shanghai/13/2001(H5N1)) matrix protein mRNA, complete cds	760 bp linear mRNA	AY585392.1 GI:47156338
273. Influenza A virus (A/duck/Shanghai/13/2001(H5N1)) neuraminidase (NA) mRNA, complete cds	1,417 bp linear mRNA	AY585414.1 GI:47156382

Strain/Protein	Length	GenBank / GI Accession No.
274. Influenza A virus (A/duck/Shanghai/13/2001(H5N1)) nucleoprotein (NP) mRNA, complete cds	1,499 bp linear mRNA	AY585435.1 GI:47156424
275. Influenza A virus (A/duck/Shanghai/13/2001(H5N1)) nonstructural protein 1 (NS1) mRNA, complete cds	685 bp linear mRNA	AY585456.1 GI:47156466
276. Influenza A virus (A/duck/Shanghai/35/2002(H5N1)) polymerase basic protein 2 (PB2) mRNA, complete cds	2,281 bp linear mRNA	AY585520.1 GI:47156258
277. Influenza A virus (A/duck/Shanghai/35/2002(H5N1)) matrix protein mRNA, complete cds	760 bp linear mRNA	AY585393.1 GI:47156340
278. Influenza A virus (A/duck/Shanghai/35/2002(H5N1)) neuraminidase (NA) mRNA, complete cds	1,363 bp linear mRNA	AY585415.1 GI:47156384
279. Influenza A virus (A/duck/Shanghai/35/2002(H5N1)) nucleoprotein (NP) mRNA, complete cds	1,498 bp linear mRNA	AY585436.1 GI:47156426
280. Influenza A virus (A/duck/Shanghai/35/2002(H5N1)) nonstructural protein 1 (NS1) mRNA, partial cds	685 bp linear mRNA	AY585457.1 GI:47156468
281. Influenza A virus (A/duck/Shanghai/37/2002(H5N1)) polymerase basic protein 2 (PB2) mRNA, complete cds	2,281 bp linear mRNA	AY585521.1 GI:47156260
282. Influenza A virus (A/duck/Shanghai/37/2002(H5N1)) matrix protein mRNA, complete cds	760 bp linear mRNA	AY585394.1 GI:47156342
283. Influenza A virus (A/duck/Shanghai/37/2002(H5N1)) neuraminidase (NA) mRNA, complete cds	1,361 bp linear mRNA	AY585416.1 GI:47156386
284. Influenza A virus (A/duck/Shanghai/37/2002(H5N1)) nucleoprotein (NP) mRNA, complete cds	1,497 bp linear mRNA	AY585437.1 GI:47156428
285. Influenza A virus (A/duck/Shanghai/37/2002(H5N1)) nonstructural protein 1 (NS1) mRNA, partial cds	685 bp linear mRNA	AY585458.1 GI:47156470
286. Influenza A virus (A/duck/Shanghai/38/2001(H5N1)) polymerase basic protein 2 (PB2) mRNA, complete cds	2,282 bp linear mRNA	AY585522.1 GI:47156262
287. Influenza A virus (A/duck/Shanghai/38/2001(H5N1)) matrix protein mRNA, complete cds	760 bp linear mRNA	AY585395.1 GI:47156344
288. Influenza A virus (A/duck/Shanghai/38/2001(H5N1)) neuraminidase (NA) mRNA, complete cds	1,355 bp linear mRNA	AY585417.1 GI:47156388
289. Influenza A virus (A/duck/Shanghai/38/2001(H5N1)) nucleoprotein (NP) mRNA, complete cds	1,499 bp linear mRNA	AY585438.1 GI:47156430
290. Influenza A virus (A/duck/Shanghai/38/2001(H5N1)) nonstructural protein 1 (NS1) mRNA, partial cds	692 bp linear mRNA	AY585459.1 GI:47156472
291. Influenza A virus (A/duck/Sheyang/1/2005(H5N1)) nonstructural protein (NS) mRNA, complete cds	875 bp linear mRNA	DQ354059.1 GI:87128643

Strain/Protein	Length	GenBank / GI Accession No.
292. Influenza A virus (A/duck/Tuva/01/2006(H5N1)) hemagglutinin (HA) mRNA, complete cds	1,748 bp linear mRNA	DQ861291.1 GI:112820195
293. Influenza A virus (A/duck/Tuva/01/2006(H5N1)) matrix protein 1 (M1) mRNA, complete cds	991 bp linear mRNA	DQ861292.1 GI:112820197
294. Influenza A virus (A/duck/Tuva/01/2006(H5N1)) neuraminidase (NA) mRNA, complete cds	1,364 bp linear mRNA	DQ861293.1 GI:112820199
295. Influenza A virus (A/duck/Tuva/01/2006(H5N1)) nucleoprotein (NP) mRNA, complete cds	1,531 bp linear mRNA	DQ861294.1 GI:112820201
296. Influenza A virus (A/duck/Tuva/01/2006(H5N1)) nonstructural protein (NS) mRNA, complete cds	842 bp linear mRNA	DQ861295.1 GI:112820203
297. Influenza A virus (A/duck/Vietnam/1/2005(H5N1)) nonstructural protein 1 mRNA, complete cds	890 bp linear mRNA	DQ366310.1 GI:86753715
298. Influenza A virus (A/duck/Vietnam/1/2005(H5N1)) polymerase PB2 mRNA, complete cds	2,341 bp linear mRNA	DQ366303.1 GI:86753725
299. Influenza A virus (A/duck/Vietnam/1/2005(H5N1)) polymerase PB1 mRNA, complete cds	2,341 bp linear mRNA	DQ366304.1 GI:86753735
300. Influenza A virus (A/duck/Vietnam/1/2005(H5N1)) PA protein mRNA, complete cds	2,233 bp linear mRNA	DQ366305.1 GI:86753745
301. Influenza A virus (A/duck/Vietnam/1/2005(H5N1)) hemagglutinin mRNA, complete cds	1,779 bp linear mRNA	DQ366306.1 GI:86753755
302. Influenza A virus (A/duck/Vietnam/1/2005(H5N1)) nucleocapsid mRNA, complete cds	1,565 bp linear mRNA	DQ366307.1 GI:86753765
303. Influenza A virus (A/duck/Vietnam/1/2005(H5N1)) neuraminidase mRNA, complete cds	1,401 bp linear mRNA	DQ366308.1 GI:86753775
304. Influenza A virus (A/duck/Vietnam/1/2005(H5N1)) matrix protein mRNA, complete cds	1,027 bp linear mRNA	DQ366309.1 GI:86753785
305. Influenza A virus (A/duck/Vietnam/8/05(H5N1)) nonstructural protein 1 mRNA, complete cds	890 bp linear mRNA	DQ366326.1 GI:86753719
306. Influenza A virus (A/duck/Vietnam/8/05(H5N1)) polymerase PB2 mRNA, complete cds	2,341 bp linear mRNA	DQ366319.1 GI:86753729
307. Influenza A virus (A/duck/Vietnam/8/05(H5N1)) polymerase PB1 mRNA, complete cds	2,341 bp linear mRNA	DQ366320.1 GI:86753739
308. Influenza A virus (A/duck/Vietnam/8/05(H5N1)) PA protein mRNA, complete cds	2,233 bp linear mRNA	DQ366321.1 GI:86753749
309. Influenza A virus (A/duck/Vietnam/8/05(H5N1)) hemagglutinin mRNA, complete cds	1,779 bp linear mRNA	DQ366322.1 GI:86753759
310. Influenza A virus (A/duck/Vietnam/8/05(H5N1)) nucleocapsid mRNA, complete cds	1,565 bp linear mRNA	DQ366323.1 GI:86753769
311. Influenza A virus (A/duck/Vietnam/8/05(H5N1)) neuraminidase mRNA, complete cds	1,401 bp linear mRNA	DQ366324.1 GI:86753779

Strain/Protein	Length	GenBank / GI Accession No.
312. Influenza A virus (A/duck/Vietnam/8/05(H5N1)) matrix protein mRNA, complete cds	1,027 bp linear mRNA	DQ366325.1 GI:86753789
313. Influenza A virus (A/duck/Yangzhou/232/2004(H5N1)) nonfunctional nonstructural protein (NS) mRNA, complete sequence	876 bp linear mRNA	DQ354060.1 GI:87128645
314. Influenza A virus (A/duck/Zhejiang/11/2000(H5N1)) polymerase basic protein 2 (PB2) mRNA, complete cds	2,281 bp linear mRNA	AY585523.1 GI:47156264
315. Influenza A virus (A/duck/Zhejiang/11/2000(H5N1)) matrix protein mRNA, complete cds	760 bp linear mRNA	AY585396.1 GI:47156346
316. Influenza A virus (A/duck/Zhejiang/11/2000(H5N1)) neuraminidase (NA) mRNA, complete cds	1,352 bp linear mRNA	AY585418.1 GI:47156390
317. Influenza A virus (A/duck/Zhejiang/11/2000(H5N1)) nucleoprotein (NP) mRNA, complete cds	1,498 bp linear mRNA	AY585439.1 GI:47156432
318. Influenza A virus (A/duck/Zhejiang/11/2000(H5N1)) nonstructural protein 1 (NS1) mRNA, partial cds	687 bp linear mRNA	AY585460.1 GI:47156474
319. Influenza A virus (A/duck/Zhejiang/52/2000(H5N1)) polymerase basic protein 2 (PB2) mRNA, complete cds	2,281 bp linear mRNA	AY585524.1 GI:47156266
320. Influenza A virus (A/duck/Zhejiang/52/2000(H5N1)) matrix protein mRNA, complete cds	760 bp linear mRNA	AY585397.1 GI:47156348
321. Influenza A virus (A/duck/Zhejiang/52/2000(H5N1)) neuraminidase (NA) mRNA, complete cds	1,423 bp linear mRNA	AY585419.1 GI:47156392
322. Influenza A virus (A/duck/Zhejiang/52/2000(H5N1)) nucleoprotein (NP) mRNA, complete cds	1,499 bp linear mRNA	AY585440.1 GI:47156434
323. Influenza A virus (A/duck/Zhejiang/52/2000(H5N1)) nonstructural protein 1 (NS1) mRNA, complete cds	686 bp linear mRNA	AY585461.1 GI:47156476
324. Influenza A virus (A/Egypt/0636-NAMRU3/2007(H5N1)) hemagglutinin (HA) mRNA, complete cds	1,749 bp linear mRNA	EF382359.1 GI:124244205
325. Influenza A virus (A/goosander/Switzerland/V82/06 (H5N1)) hemagglutinin (HA) gene, complete cds	1,707 bp linear mRNA	EF110518.1 GI:119394674
326. Influenza A virus (A/goose/Guangdong/1/96/(H5N1)) hemagglutinin mRNA, complete cds	1,707 bp linear mRNA	AF148678.1 GI:5007022
327. Influenza A virus (A/Goose/Huadong/1/2000(H5N1)) hemagglutinin (HA) mRNA, complete cds	1,779 bp linear mRNA	DQ201829.1 GI:76786306
328. Influenza A virus (A/Goose/Huadong/1/2000(H5N1)) neuraminidase (NA) mRNA, complete cds	1,458 bp linear mRNA	DQ201830.1 GI:76786308
329. Influenza A virus (A/goose/Hungary/2823/2/2007(H5N1)) polymerase PB1 (PB1) mRNA, partial cds	2,287 bp linear mRNA	EF446768.1 GI:126428373
330. Influenza A virus (A/goose/Hungary/2823/2/2007(H5N1)) polymerase PB2 (PB2) mRNA, partial cds	2,274 bp linear mRNA	EF446769.1 GI:126428375

Strain/Protein	Length	GenBank / GI Accession No.
331. Influenza A virus (A/goose/Hungary/2823/2/2007(H5N1)) polymerase PA (PA) mRNA, complete cds	2,175 bp linear mRNA	EF446770.1 GI:126428377
332. Influenza A virus (A/goose/Hungary/2823/2/2007(H5N1)) hemagglutinin (HA) mRNA, complete cds	1,735 bp linear mRNA	EF446771.1 GI:126428379
333. Influenza A virus (A/goose/Hungary/2823/2/2007(H5N1)) nucleocapsid protein (NP) mRNA, partial cds	1,473 bp linear mRNA	EF446772.1 GI:126428381
334. Influenza A virus (A/goose/Hungary/2823/2/2007(H5N1)) neuraminidase (NA) mRNA, partial cds	1,311 bp linear mRNA	EF446773.1 GI:126428383
335. Influenza A virus (A/goose/Hungary/2823/2/2007(H5N1)) matrix protein 1 (M1) mRNA, partial cds	971 bp linear mRNA	EF446774.1 GI:126428385
336. Influenza A virus (A/goose/Hungary/2823/2/2007(H5N1)) nonstructural protein 1 (NS1) mRNA, partial cds	795 bp linear mRNA	EF446775.1 GI:126428387
337. Influenza A virus (A/goose/Hungary/3413/2007(H5N1)) polymerase PB1 (PB1) mRNA, partial cds	2,277 bp linear mRNA	EF446776.1 GI:126428389
338. Influenza A virus (A/goose/Hungary/3413/2007(H5N1)) polymerase PB2 (PB2) mRNA, partial cds	2,274 bp linear mRNA	EF446777.1 GI:126428391
339. Influenza A virus (A/goose/Hungary/3413/2007(H5N1)) polymerase PA (PA) mRNA, partial cds	2,163 bp linear mRNA	EF446778.1 GI:126428393
340. Influenza A virus (A/goose/Hungary/3413/2007(H5N1)) hemagglutinin (HA) mRNA, complete cds	1,722 bp linear mRNA	EF446779.1 GI:126428395
341. Influenza A virus (A/goose/Hungary/3413/2007(H5N1)) nucleocapsid protein (NP) mRNA, partial cds	1,463 bp linear mRNA	EF446780.1 GI:126428397
342. Influenza A virus (A/goose/Hungary/3413/2007(H5N1)) neuraminidase (NA) mRNA, partial cds	1,289 bp linear mRNA	EF446781.1 GI:126428399
343. Influenza A virus (A/goose/Hungary/3413/2007(H5N1)) matrix protein 1 (M1) mRNA, partial cds	955 bp linear mRNA	EF446782.1 GI:126428401
344. Influenza A virus (A/goose/Hungary/3413/2007(H5N1)) nonstructural protein 1 (NS1) mRNA, complete cds	805 bp linear mRNA	EF446783.1 GI:126428403
345. Influenza A virus (A/goose/Jiangsu/131/2002(H5N1)) nonfunctional nonstructural protein (NS) mRNA, complete sequence	877 bp linear mRNA	DQ354061.1 GI:87128646
346. Influenza A virus (A/goose/Jiangsu/220/2003(H5N1)) nonstructural protein (NS) mRNA, complete cds	875 bp linear mRNA	DQ354062.1 GI:87128647
347. Influenza A virus (A/goose/Krasnoozerka/627/2005(H5N1)) hemagglutinin (HA) mRNA, complete cds	1,754 bp linear mRNA	DQ676840.1 GI:108782531
348. Influenza A virus (A/goose/Krasnoozerka/627/2005(H5N1)) nucleoprotein (NP) mRNA, complete cds	1,530 bp linear mRNA	DQ676841.1 GI:108782533

Strain/Protein	Length	GenBank / GI Accession No.
349. Influenza A virus (A/goose/Krasnoozerka/627/2005(H5N1)) nonstructural protein (NS) mRNA, complete cds	850 bp linear mRNA	DQ676842.1 GI:108782535
350. Influenza A virus (A/goose/Vietnam/3/05(H5N1)) nonstructural protein 1 mRNA, complete cds	890 bp linear mRNA	DQ366318.1 GI:86753717
351. Influenza A virus (A/goose/Vietnam/3/05(H5N1)) polymerase PB2 mRNA, complete cds	2,341 bp linear mRNA	DQ366311.1 GI:86753727
352. Influenza A virus (A/goose/Vietnam/3/05(H5N1)) polymerase PB1 mRNA, complete cds	2,341 bp linear mRNA	DQ366312.1 GI:86753737
353. Influenza A virus (A/goose/Vietnam/3/05(H5N1)) PA protein mRNA, complete cds	2,233 bp linear mRNA	DQ366313.1 GI:86753747
354. Influenza A virus (A/goose/Vietnam/3/05(H5N1)) hemagglutinin mRNA, complete cds	1,779 bp linear mRNA	DQ366314.1 GI:86753757
355. Influenza A virus (A/goose/Vietnam/3/05(H5N1)) nucleocapsid mRNA, complete cds	1,565 bp linear mRNA	DQ366315.1 GI:86753767
356. Influenza A virus (A/goose/Vietnam/3/05(H5N1)) neuraminidase mRNA, complete cds	1,401 bp linear mRNA	DQ366316.1 GI:86753777
357. Influenza A virus (A/goose/Vietnam/3/05(H5N1)) matrix protein mRNA, complete cds	1,027 bp linear mRNA	DQ366317.1 GI:86753787
358. Influenza A virus (A/gull/Pennsylvania/4175/83(H5N1)) hemagglutinin H5 mRNA, partial cds	1,700 bp linear mRNA	AF082043.1 GI:4240453
360. Influenza A virus (A/HongKong/156/97(H5N1)) neuraminidase mRNA, complete cds	1,388 bp linear mRNA	AF028708.1 GI:2865377
361. Influenza A virus (A/HongKong/156/97(H5N1)) hemagglutinin mRNA, complete cds	1,741 bp linear mRNA	AF028709.1 GI:2865379
362. Influenza A virus (A/HongKong/156/97(H5N1)) nucleoprotein mRNA, complete cds	1,549 bp linear mRNA	AF028710.1 GI:2865381
363. Influenza A virus (A/hooded vulture/Burkina Faso/1/2006(H5N1)) partial mRNA for nucleoprotein (np gene)	1,451 bp linear mRNA	AM503028.1 GI:147846292
364. Influenza A virus (A/hooded vulture/Burkina Faso/1/2006(H5N1)) mRNA for non-structural protein (ns gene)	827 bp linear mRNA	AM503038.1 GI:147846312
365. Influenza A virus (A/hooded vulture/Burkina Faso/1/2006(H5N1)) partial mRNA for polymerase (pa gene)	2,169 bp linear mRNA	AM503047.1 GI:147846330
366. Influenza A virus (A/hooded vulture/Burkina Faso/1/2006(H5N1)) partial mRNA for polymerase basic protein 1 (pb1 gene)	1,686 bp linear mRNA	AM503065.1 GI:147846855
367. Influenza A virus (A/hooded vulture/Burkina Faso/2/2006(H5N1)) partial mRNA for matrix protein 1 (m1 gene)	977 bp linear mRNA	AM503006.1 GI:147846248
368. Influenza A virus (A/hooded vulture/Burkina Faso/2/2006(H5N1)) partial mRNA for neuraminidase (na gene)	1,336 bp linear mRNA	AM503017.1 GI:147846270

Strain/Protein	Length	GenBank / GI Accession No.
369. Influenza A virus (A/hooded vulture/Burkina Faso/2/2006(H5N1)) partial mRNA for nucleoprotein (np gene)	1,499 bp linear mRNA	AM503027.1 GI:147846290
370. Influenza A virus (A/hooded vulture/Burkina Faso/2/2006(H5N1)) mRNA for non-structural protein (ns gene)	827 bp linear mRNA	AM503039.1 GI:147846314
371. Influenza A virus (A/hooded vulture/Burkina Faso/2/2006(H5N1)) partial mRNA for polymerase (pa gene)	2,169 bp linear mRNA	AM503048.1 GI:147846332
372. Influenza A virus (A/hooded vulture/Burkina Faso/2/2006(H5N1)) partial mRNA for polymerase basic protein 1 (pb1 gene)	2,259 bp linear mRNA	AM503062.1 GI:147846849
373. Influenza A virus (A/hooded vulture/Burkina Faso/2/2006(H5N1)) partial mRNA for polymerase basic protein 2 (pb2 gene)	2,315 bp linear mRNA	AM503066.1 GI:147846857
374. Influenza A virus (A/Indonesia/CDC177/2005(H5N1)) M2 protein mRNA, complete cds	294 bp linear mRNA	EU014135.1 GI:151336850
375. Influenza A virus (A/Indonesia/CDC298/2005(H5N1)) M2 protein mRNA, complete cds	294 bp linear mRNA	EU014138.1 GI:151336856
376. Influenza A virus (A/Indonesia/CDC485/2006(H5N1)) M2 protein mRNA, complete cds	294 bp linear mRNA	EU014136.1 GI:151336852
377. Influenza A virus (A/Indonesia/CDC530/2006(H5N1)) M2 protein mRNA, complete cds	294 bp linear mRNA	EU014134.1 GI:151336848
378. Influenza A virus (A/Indonesia/CDC535/2006(H5N1)) M2 protein mRNA, complete cds	294 bp linear mRNA	EU014133.1 GI:151336846
379. Influenza A virus (A/Indonesia/CDC540/2006(H5N1)) M2 protein mRNA, complete cds	294 bp linear mRNA	EU014132.1 GI:151336844
380. Influenza A virus (A/Indonesia/CDC561/2006(H5N1)) M2 protein mRNA, complete cds	294 bp linear mRNA	EU014137.1 GI:151336854
381. Influenza A virus (A/Indonesia/CDC60/2005(H5N1)) M2 protein mRNA, complete cds	294 bp linear mRNA	EU014139.1 GI:151336858
382. Influenza A virus (A/mallard/Wisconsin/428/75(H5N1)) hemagglutinin mRNA, partial cds	996 bp linear mRNA	U79453.1 GI:1840071
383. Influenza A virus (A/ostrich/VRLCU/Egypt/2011(H5N1)) segment 4 hemagglutinin (HA) mRNA, partial cds	441 bp linear mRNA	JN157759.1 GI:338223304
384. Influenza A virus (A/quail/yunnan/092/2002(H5N1)) nonstructural protein (NS) mRNA, complete cds	875 bp linear mRNA	DQ354063.1 GI:87128649
385. Influenza A virus (A/R(Turkey/Ontario/7732/66-Bellamy/42)(H5N1)) HA mRNA for hemagglutinin, partial cds	1,472 bp linear mRNA	AB241613.1 GI:82581222
386. Influenza A virus (A/Thailand/LFPN-2004/2004(H5N1)) neuraminidase mRNA, complete cds	1,350 bp linear mRNA	AY679513.1 GI:50843945

Strain/Protein	Length	GenBank / GI Accession No.
387. Influenza A virus (A/Thailand/LFPN-2004/2004(H5N1)) hemagglutinin mRNA, complete cds	1,704 bp linear mRNA	AY679514.1 GI:50843949
388. Influenza A virus (A/tiger/Thailand/CU-T4/04(H5N1)) polymerase basic protein 2 (PB2) mRNA, partial cds	534 bp linear mRNA	DQ017251.1 GI:65329524
389. Influenza A virus (A/tiger/Thailand/CU-T5/04(H5N1)) polymerase basic protein 2 (PB2) mRNA, partial cds	582 bp linear mRNA	DQ017252.1 GI:65329536
390. Influenza A virus (A/tiger/Thailand/CU-T6/04(H5N1)) polymerase basic protein 2 (PB2) mRNA, partial cds	564 bp linear mRNA	DQ017253.1 GI:65329553
391. Influenza A virus (A/tiger/Thailand/CU-T8/04(H5N1)) polymerase basic protein 2 (PB2) mRNA, partial cds	582 bp linear mRNA	DQ017254.1 GI:65329568
392. Influenza A virus (A/turkey/England/250/2007(H5N1)) hemagglutinin (HA) mRNA, partial cds	1,695 bp linear mRNA	EF441263.1 GI:129307104
393. Influenza A virus (A/turkey/England/250/2007(H5N1)) matrix protein (M) mRNA, partial cds	943 bp linear mRNA	EF441264.1 GI:129307106
394. Influenza A virus (A/turkey/England/250/2007(H5N1)) nonstructural protein 1 (NS1) mRNA, complete cds	812 bp linear mRNA	EF441265.1 GI:129307109
395. Influenza A virus (A/turkey/England/250/2007(H5N1)) polymerase PA (PA) mRNA, complete cds	2,185 bp linear mRNA	EF441266.1 GI:129307111
396. Influenza A virus (A/turkey/England/250/2007(H5N1)) polymerase PB2 (PB2) mRNA, partial cds	2,272 bp linear mRNA	EF441267.1 GI:129307113
397. Influenza A virus (A/turkey/England/250/2007(H5N1)) nucleocapsid (NP) mRNA, partial cds	1,396 bp linear mRNA	EF441268.1 GI:129307115
398. Influenza A virus (A/turkey/England/250/2007(H5N1)) polymerase PB1 (PB1) mRNA, partial cds	2,288 bp linear mRNA	EF441269.1 GI:129307117
399. Influenza A virus (A/turkey/England/250/2007(H5N1)) neuraminidase (NA) mRNA, partial cds	1,276 bp linear mRNA	EF441270.1 GI:129307119
A/chicken/Burkina Faso/13.1/2006(H5N1) neuraminidase (NA)		AM503016.1
A/chicken/Crimea/04/2005(H5N1) neuraminidase (NA)		DQ650661.1
A/chicken/Crimea/04/2005(H5N1) hemagglutinin		DQ650659.1
A/chicken/Crimea/08/2005(H5N1) polymerase basic protein 1 (PB1)		DQ650669.1
A/chicken/Crimea/08/2005(H5N1) neuraminidase (NA)		DQ650665.1
A/chicken/Crimea/08/2005(H5N1) hemagglutinin (HA)		DQ650663.1
A/chicken/Guangxi/12/2004(H5N1) nonstructural protein 1		DQ366334.1
A/chicken/Guangxi/12/2004(H5N1) neuraminidase		DQ366332.1
A/chicken/Guangxi/12/2004(H5N1) hemagglutinin		DQ366330.1
A/duck/Kurgan/08/2005(H5N1) nucleoprotein (NP)		DQ449643.1

Table 10. Other Influenza A Antigens (H1N*, H2N*, H3N*)

Strain/Protein	Length	GenBank / GI Accession Nos.
H1N*		
Influenza A virus (A/duck/Hong Kong/193/1977(H1N2)) nucleoprotein (NP) mRNA, partial cds	1,402 bp linear mRNA	U49097.1 GI:1912392
Influenza A virus (A/duck/Hong Kong/193/1977(H1N2)) polymerase (PB1) mRNA, partial cds	258 bp linear mRNA	U48285.1 GI:1912374
Influenza A virus (A/England/2/2002(H1N2)) partial NS1 gene for non structural protein 1 and partial NS2 gene for non structural protein 2, genomic RNA	795 bp linear mRNA	AJ519455.1 GI:31096426
Influenza A virus (A/England/3/02(H1N2)) partial mRNA for nucleoprotein (np gene)	384 bp linear mRNA	AJ489497.1 GI:27526856
Influenza A virus (A/England/3/02(H1N2)) partial mRNA for polymerase subunit 2 (pb2 gene)	442 bp linear mRNA	AJ489488.1 GI:27526838
Influenza A virus (A/England/5/02(H1N2)) partial mRNA for nucleoprotein (np gene)	384 bp linear mRNA	AJ489498.1 GI:27526858
Influenza A virus (A/England/5/02(H1N2)) partial mRNA for polymerase subunit 2 (pb2 gene)	442 bp linear mRNA	AJ489489.1 GI:27526840
Influenza A virus (A/England/57/02(H1N2)) partial mRNA for nucleoprotein (np gene)	384 bp linear mRNA	AJ489499.1 GI:27526860
Influenza A virus (A/England/57/02(H1N2)) partial mRNA for polymerase subunit 2 (pb2 gene)	442 bp linear mRNA	AJ489492.1 GI:27526846
Influenza A virus (A/England/691/01(H1N2)) partial mRNA for nucleoprotein (np gene)	384 bp linear mRNA	AJ489496.1 GI:27526854
Influenza A virus (A/England/73/02(H1N2)) partial mRNA for nucleoprotein (np gene)	384 bp linear mRNA	AJ489500.1 GI:27526862
Influenza A virus (A/England/73/02(H1N2)) partial mRNA for polymerase subunit 2 (pb2 gene)	442 bp linear mRNA	AJ489493.1 GI:27526848
Influenza A virus (A/England/90/02(H1N2)) partial mRNA for nucleoprotein (np gene)	384 bp linear mRNA	AJ489501.1 GI:27526864
Influenza A virus (A/England/90/02(H1N2)) partial mRNA for polymerase subunit 2 (pb2 gene)	442 bp linear mRNA	AJ489490.1 GI:27526842
Influenza A virus (A/England/97/02(H1N2)) partial mRNA for nucleoprotein (np gene)	384 bp linear mRNA	AJ489502.1 GI:27526866
Influenza A virus (A/England/97/02(H1N2)) partial mRNA for polymerase subunit 2 (pb2 gene)	442 bp linear mRNA	AJ489491.1 GI:27526844
Influenza A virus (A/England/627/01(H1N2)) partial mRNA for nucleoprotein (np gene)	384 bp linear mRNA	AJ489494.1 GI:27526850
Influenza A virus (A/England/627/01(H1N2)) partial mRNA for polymerase subunit 2 (pb2 gene)	442 bp linear mRNA	AJ489485.1 GI:27526832
Influenza A virus (A/England/691/01(H1N2)) partial mRNA for polymerase subunit 2 (pb2 gene)	442 bp linear mRNA	AJ489487.1 GI:27526836
Influenza A virus (A/Egypt/96/2002(H1N2)) partial NS1 gene for non structural protein 1 and partial NS2 gene for non structural protein 2, genomic RNA	747 bp linear mRNA	AJ519457.1 GI:31096432

Strain/Protein	Length	GenBank / GI Accession Nos.
Influenza A virus (A/Israel/6/2002(H1N2)) partial NS1 gene for non structural protein 1 and partial NS2 gene for non structural protein 2, genomic RNA	773 bp linear mRNA	AJ519456.1 GI:31096429
Influenza A virus (A/Saudi Arabia/2231/2001(H1N2)) partial NS1 gene for non structural protein 1 and partial NS2 gene for non structural protein 2, genomic RNA	772 bp linear mRNA	AJ519453.1 GI:31096420
Influenza A virus (A/Scotland/122/01(H1N2)) partial mRNA for nucleoprotein (np gene)	384 bp linear mRNA	AJ489495.1 GI:27526852
Influenza A virus (A/Scotland/122/01(H1N2)) partial mRNA for polymerase subunit 2 (pb2 gene)	442 bp linear mRNA	AJ489486.1 GI:27526834
Influenza A virus (A/swine/Bakum/1832/2000(H1N2)) hemagglutinin (HA) mRNA, partial cds	832 bp linear mRNA	AY861443.1 GI:57791765
Influenza A virus (A/swine/Bakum/1832/2000(H1N2)) neuraminidase mRNA, partial cds	467 bp linear mRNA	AY870645.1 GI:58042754
Influenza A virus (A/swine/Cotes d'Armor/0040/2007(H1N2)) segment 4 partial mRNA	1,039 bp linear mRNA	AM503547.1 GI:225578611
Influenza A virus (A/swine/Cotes d'Armor/0136_17/2006(H1N2)) partial mRNA for haemagglutinin precursor (HA1 gene)	1,136 bp linear mRNA	AM490224.3 GI:222062921
Influenza A virus (A/swine/England/72685/96(H1N2)) haemagglutinin precursor, mRNA, complete cds	1,778 bp linear mRNA	AF085417.1 GI:3831770
Influenza A virus (A/swine/England/17394/96(H1N2)) haemagglutinin precursor, mRNA, complete cds	1,778 bp linear mRNA	AF085416.1 GI:3831768
Influenza A virus (A/swine/England/690421/95(H1N2)) haemagglutinin precursor, mRNA, complete cds	1,778 bp linear mRNA	AF085415.1 GI:3831766
Influenza A virus (A/swine/England/438207/94(H1N2)) haemagglutinin precursor, mRNA, complete cds	1,778 bp linear mRNA	AF085414.1 GI:3831764
Influenza A virus (A/Swine/Korea/CY02/02(H1N2)) neuraminidase (NA) mRNA, complete cds	1,427 bp linear mRNA	AY129157.1 GI:24286064
Influenza A virus (A/Swine/Korea/CY02/02(H1N2)) matrix protein (M) mRNA, complete cds	952 bp linear mRNA	AY129158.1 GI:24286066
Influenza A virus (A/Swine/Korea/CY02/02(H1N2)) nucleoprotein (NP) mRNA, complete cds	1,542 bp linear mRNA	AY129159.1 GI:24286069
Influenza A virus (A/Swine/Korea/CY02/02(H1N2)) nonstructural protein (NS) mRNA, complete cds	842 bp linear mRNA	AY129160.1 GI:24286081
Influenza A virus (A/Swine/Korea/CY02/02(H1N2)) polymerase acidic protein 2 (PA) mRNA, complete cds	2,165 bp linear mRNA	AY129161.1 GI:24286087
Influenza A virus (A/Swine/Korea/CY02/02(H1N2)) polymerase subunit 1 (PB1) mRNA, complete cds	2,274 bp linear mRNA	AY129162.1 GI:24286096
Influenza A virus (A/Swine/Korea/CY02/02(H1N2)) polymerase subunit 2 (PB2) mRNA, complete cds	2,334 bp linear mRNA	AY129163.1 GI:24286100

Strain/Protein	Length	GenBank / GI Accession Nos.
Influenza A virus (A/swine/Scotland/410440/94(H1N2)) haemagglutinin precursor, mRNA, complete cds	1,778 bp linear mRNA	AF085413.1 GI:3831762
Influenza A virus (A/swine/Spain/80598-LP4/2007(H1N2)) matrix protein 2 (M2) mRNA, partial cds	291 bp linear mRNA	EU305436.1 GI:168830657
Influenza A virus (A/Switzerland/3100/2002(H1N2)) partial HA gene for Haemagglutinin, genomic RNA	975 bp linear mRNA	AJ517813.1 GI:38422519
Influenza A virus (A/duck/Hong Kong/717/1979(H1N3)) nucleoprotein (NP) mRNA, partial cds	1,387 bp linear mRNA	U49095.1 GI:1912388
Influenza A virus (A/duck/Hong Kong/717/1979(H1N3)) polymerase (PB1) mRNA, partial cds	265 bp linear mRNA	U48281.1 GI:1912366
Influenza A virus (A/herring gull/New Jersey/780/86 (H1N3)) nonfunctional matrix protein mRNA, partial sequence	971 bp linear mRNA	AY664422.1 GI:51011826
Influenza A virus (A/mallard/Alberta/42/77(H1N6)) nonfunctional matrix protein mRNA, partial sequence	997 bp linear mRNA	AY664426.1 GI:51011830
Influenza A virus (A/swine/England/191973/92(H1N7)) matrix protein M1 mRNA, complete cds	1,020 bp linear mRNA	U85985.1 GI:1835733
Influenza A virus (A/swine/England/191973/92(H1N7)) nucleoprotein mRNA, complete cds	1,524 bp linear mRNA	U85987.1 GI:1835737
Influenza A virus (A/swine/England/191973/92(H1N7)) neuraminidase mRNA, complete cds	1,458 bp linear mRNA	U85988.1 GI:1835739
Influenza A virus (A/swine/England/191973/92(H1N7)) haemagglutinin HA mRNA, partial cds	1,698 bp linear mRNA	U85986.1 GI:1835735
H2N*		
Influenza A virus (A/ruddy turnstone/Delaware/81/93 (H2N1)) nonfunctional matrix protein mRNA, partial sequence	917 bp linear mRNA	AY664465.1 GI:51011869
Influenza A virus (A/ruddy turnstone/Delaware/34/93 (H2N1)) nonfunctional matrix protein mRNA, partial sequence	968 bp linear mRNA	AY664429.1 GI:51011833
Influenza A virus (A/Shorebird/Delaware/122/97(H2N1)) nonfunctional matrix protein mRNA, partial sequence	925 bp linear mRNA	AY664466.1 GI:51011870
Influenza A virus (A/shorebird/Delaware/138/97 (H2N1)) nonfunctional matrix protein mRNA, partial sequence	958 bp linear mRNA	AY664454.1 GI:51011858
Influenza A virus (A/shorebird/Delaware/111/97 (H2N1)) nonfunctional matrix protein mRNA, partial sequence	958 bp linear mRNA	AY664457.1 GI:51011861
Influenza A virus (A/shorebird/Delaware/24/98 (H2N1)) nonfunctional matrix protein mRNA, partial sequence	979 bp linear mRNA	AY664442.1 GI:51011846

Strain/Protein	Length	GenBank / GI Accession Nos.
Influenza virus type A/Leningrad/134/17/57 (H2N2) PA RNA, complete cds	2,233 bp linear mRNA	M81579.1 GI:324935
Influenza A virus (STRAIN A/MALLARD/NEW YORK/6750/78) partial mRNA for PA protein	2,151 bp linear mRNA	AJ243994.1 GI:5918195
Influenza A virus (A/X-7(F1)/(H2N2)) neuraminidase mRNA, complete cds	1,467 bp linear mRNA	M11205.1 GI:323969
Influenza A virus (A/mallard/Alberta/77/77 (H2N3)) nonfunctional matrix protein mRNA, partial sequence	1,009 bp linear mRNA	AY664425.1 GI:51011829
Influenza A virus (A/mallard/Alberta/226/98 (H2N3)) nonfunctional matrix protein mRNA, partial sequence	968 bp linear mRNA	AY664447.1 GI:51011851
Influenza A virus (A/sanderling/New Jersey/766/86 (H2N7)) nonfunctional matrix protein mRNA, partial sequence	846 bp linear mRNA	AY664477.1 GI:51011881
Influenza A virus (A/laughing gull/New Jersey/798/86 (H2N7)) nonfunctional matrix protein mRNA, partial sequence	907 bp linear mRNA	AY664471.1 GI:51011875
Influenza A virus (A/herring gull/Delaware/471/1986 (H2N7)) nonfunctional matrix protein mRNA, partial sequence	960 bp linear mRNA	AY664440.1 GI:51011844
Influenza A virus (A/ruddy turnstone/Delaware/142/98 (H2N8)) nonfunctional matrix protein mRNA, partial sequence	1,011 bp linear mRNA	AY664423.1 GI:51011827
Influenza A virus (A/pintail/Alberta/293/77 (H2N9)) nonfunctional matrix protein mRNA, partial sequence	906 bp linear mRNA	AY664473.1 GI:51011877
Influenza A virus (A/blue-winged teal/Alberta/16/97 (H2N9)) nonfunctional matrix protein mRNA, partial sequence	961 bp linear mRNA	AY664449.1 GI:51011853
Influenza A virus (A/Laughing gull/New Jersey/75/85 (H2N9)) nonfunctional matrix protein mRNA, partial sequence	952 bp linear mRNA	AY664437.1 GI:51011841
Influenza A virus (A/mallard/Alberta/205/98 (H2N9)) nonfunctional matrix protein mRNA, partial sequence	959 bp linear mRNA	AY664450.1 GI:51011854
H3N*		
Influenza A virus (A/duck/Eastern China/267/2003 (H3N1)) segment 6 neuraminidase (NA) mRNA, complete cds	1,458 bp linear mRNA	EU429755.1 GI:167859475
Influenza A virus (A/duck/Eastern China/253/2003 (H3N1)) segment 6 neuraminidase (NA) mRNA, complete cds	1,458 bp linear mRNA	EU429754.1 GI:167859473
Influenza A virus (A/duck/Eastern China/252/2003 (H3N1)) segment 6 neuraminidase (NA) mRNA, complete cds	1,458 bp linear mRNA	EU429753.1 GI:167859471
Influenza A virus (A/duck/Eastern China/243/2003 (H3N1)) segment 6 neuraminidase (NA) mRNA, complete cds	1,458 bp linear mRNA	EU429752.1 GI:167859469
Influenza A virus (A/duck/Eastern China/262/2003 (H3N1)) segment 6 neuraminidase (NA) mRNA, complete cds	1,458 bp linear mRNA	EU429734.1 GI:167859433
Influenza A virus (A/duck/Eastern China/233/2003 (H3N1)) segment 6 neuraminidase (NA) mRNA, complete cds	1,459 bp linear mRNA	EU429733.1 GI:167859431

Strain/Protein	Length	GenBank / GI Accession Nos.
Influenza A virus (A/duck/Eastern China/213/2003(H3N1)) segment 6 neuraminidase (NA) mRNA, complete cds	1,458 bp linear mRNA	EU429723.1 GI:167859411
Influenza A virus (A/duck/Eastern China/341/2003(H3N1)) segment 6 neuraminidase (NA) mRNA, complete cds	1,458 bp linear mRNA	EU429719.1 GI:167859403
Influenza A virus (A/duck/Eastern China/01/2002(H3N1)) segment 6 neuraminidase (NA) mRNA, complete cds	1,458 bp linear mRNA	EU429718.1 GI:167859401
Influenza A virus (A/mallard/Alberta/22/76 (H3N6)) nonfunctional matrix protein mRNA, partial sequence	1,013 bp linear mRNA	AY664434.1 GI:51011838
Influenza A virus (A/mallard/Alberta/199/99(H3N6)) nonfunctional matrix protein mRNA, partial sequence	970 bp linear mRNA	AY664443.1 GI:51011847
Influenza A virus (A/shorebird/Delaware/222/97 (H3N6)) nonfunctional matrix protein mRNA, partial sequence	922 bp linear mRNA	AY664461.1 GI:51011865
Influenza A virus (A/Duck/Hokkaido/8/80 (H3N8)) hemagglutinin precursor, mRNA, partial cds	984 bp linear mRNA	AF079570.1 GI:3414978
Influenza A virus (A/Duck/Hokkaido/8/80 (H3N8)) nucleoprotein mRNA, complete cds	1,497 bp linear mRNA	AF079571.1 GI:3414980
Influenza A virus (A/duck/Ukraine/1/1963(H3N8)) segment 6 neuraminidase (NA) mRNA, complete cds	1,461 bp linear mRNA	EU429797.1 GI:167859559
Influenza A virus (A/duck/Eastern China/19/2004(H3N8)) segment 6 neuraminidase (NA) mRNA, complete cds	1,460 bp linear mRNA	EU429698.1 GI:167859361
Influenza A virus (A/duck/Eastern China/90/2004(H3N8)) segment 6 neuraminidase (NA) mRNA, complete cds	1,460 bp linear mRNA	EU429700.1 GI:167859365
Influenza A virus (A/duck/Eastern China/18/2005(H3N8)) segment 6 neuraminidase (NA) mRNA, complete cds	1,460 bp linear mRNA	EU429787.1 GI:167859539
Influenza A virus (A/duck/Eastern China/119/2005(H3N8)) segment 6 neuraminidase (NA) mRNA, complete cds	1,460 bp linear mRNA	EU429788.1 GI:167859541
Influenza A virus (A/equine/Argentina/1/96(H3N8)) hemagglutinin precursor (HA1) mRNA, partial cds	1,061 bp linear mRNA	AF197246.1 GI:6651512
Influenza A virus (A/equine/Argentina/2/94(H3N8)) hemagglutinin precursor (HA1) mRNA, partial cds	1,061 bp linear mRNA	AF197245.1 GI:6651510
Influenza A virus (A/equine/Argentina/1/95(H3N8)) hemagglutinin precursor (HA1) mRNA, partial cds	1,061 bp linear mRNA	AF197244.1 GI:6651508
Influenza A virus HA partial gene for haemagglutinin, genomic RNA, strain A/equine/Berlin/3/89(H3N8)	1,026 bp linear mRNA	AJ223194.1 GI:2780201
Influenza A virus HA partial gene for haemagglutinin, genomic RNA, strain A/equine/Berlin/4/89(H3N8)	1,006 bp linear mRNA	AJ223195.1 GI:2780203

Strain/Protein	Length	GenBank / GI Accession Nos.
Influenza A virus (A/equine/Florida/1/94(H3N8)) hemagglutinin precursor (HA1) mRNA, partial cds	1,061 bp linear mRNA	AF197242.1 GI:6651504
Influenza A virus (A/equine/Grobois/1/98(H3N8)) nonstructural protein NS1 mRNA, complete cds	695 bp linear mRNA	AY328471.1 GI:32966577
Influenza A virus (A/equi 2/Gotland/01(H3N8)) hemagglutinin HA1 subunit mRNA, partial cds	473 bp linear mRNA	AY919314.1 GI:60250543
Influenza A virus (A/eq/Kentucky/81(H3N8)) hemagglutinin mRNA, complete cds	1,763 bp linear mRNA	U58195.1 GI:1377873
Influenza A virus (A/equine/Kentucky/9/95(H3N8)) hemagglutinin precursor (HA1) mRNA, partial cds	1,061 bp linear mRNA	AF197247.1 GI:6651514
Influenza A virus (A/equine/Kentucky/1/96(H3N8)) hemagglutinin precursor (HA1) mRNA, partial cds	1,061 bp linear mRNA	AF197248.1 GI:6651516
Influenza A virus (A/equine/Kentucky/1/97(H3N8)) hemagglutinin precursor (HA1) mRNA, partial cds	1,061 bp linear mRNA	AF197249.1 GI:6651518
Influenza A virus (A/equine/Kentucky/1/98(H3N8)) hemagglutinin precursor (HA1) mRNA, partial cds	1,061 bp linear mRNA	AF197241.1 GI:6651502
Influenza A virus (A/equine/Santiago/85(H3N8)) nucleoprotein mRNA, complete cds	1,497 bp linear mRNA	AY383753.1 GI:37223511
Influenza A virus (A/equine/Santiago/85(H3N8)) hemagglutinin mRNA, complete cds	1,698 bp linear mRNA	AY383755.1 GI:37223515
Influenza A virus (A/equine/Santiago/85(H3N8)) neuraminidase mRNA, complete cds	1,413 bp linear mRNA	AY383754.1 GI:37223513
Influenza A virus (A/equine/Saskatoon/1/90(H3N8)) hemagglutinin precursor (HA1) mRNA, partial cds	1,061 bp linear mRNA	AF197243.1 GI:6651506
Influenza A virus (A/mallard/Alberta/114/97(H3N8)) nonfunctional matrix protein mRNA, partial sequence	1,010 bp linear mRNA	AY664432.1 GI:51011836
Influenza A virus (A/mallard/Alberta/167/98(H3N8)) nonfunctional matrix protein mRNA, partial sequence	961 bp linear mRNA	AY664489.1 GI:51011893
Influenza A virus (A/pintail/Alberta/37/99(H3N8)) nonfunctional matrix protein mRNA, partial sequence	970 bp linear mRNA	AY664445.1 GI:51011849
Influenza A virus (A/sanderling/Delaware/65/99 (H3N8)) nonfunctional matrix protein mRNA, partial sequence	922 bp linear mRNA	AY664455.1 GI:51011859

Table 11. Other Influenza A Antigens (H4N*-H13N*)

Strain/Protein	GenBank Access No.
A/chicken/Singapore/1992(H4N1) M2 protein	EU014144.1
A/mallard/Alberta/47/98(H4N1) nonfunctional matrix protein	AY664488.1
A/duck/Hong Kong/412/1978(H4N2) polymerase (PB1)	U48279.1

Strain/Protein	GenBank Access No.
A/mallard/Alberta/300/77 (H4N3) nonfunctional matrix protein	AY664480.1
A/Duck/Czechoslovakia/56(H4N6) segment 4 hemagglutinin	AF290436.1
A/duck/Eastern China/376/2004(H4N6) segment 6neuraminidase (NA)	EU429792.1
A/duck/Eastern China/01/2007(H4N6) segment 6 neuraminidase (NA)	EU429790.1
A/duck/Eastern China/216/2007(H4N6) segment 6 neuraminidase (NA)	EU429789.1
A/duck/Eastern China/166/2004(H4N6) segment 6 neuraminidase (NA)	EU429746.1
A/duck/Eastern China/02/2003(H4N6) segment 6 neuraminidase (NA)	EU429713.1
A/duck/Eastern China/160/2002(H4N6) segment 6 neuraminidase (NA)	EU429706.1
A/mallard/Alberta/111/99(H4N6) nonfunctional matrix protein	AY664482.1
A/mallard/Alberta/213/99 (H4N6) nonfunctional matrix protein	AY664460.1
A/mallard/Alberta/30/98 (H4N6) nonfunctional matrix protein	AY664484.1
A/blue-winged teal/Alberta/96/76 (H4N8) nonfunctional matrix protein	AY664420.1
A/chicken/Florida/25717/1993(H5N2) hemagglutinin	U05332.1
A/chicken/Hidalgo/26654-1368/1994(H5N2) hemagglutinin (HA)	U37172.1
A/chicken/Jalisco/14585-660/1994(H5N2) hemagglutinin (HA)	U37181.1
A/chicken/Mexico/26654-1374/1994(H5N2) hemagglutinin (HA)	U37173.1
A/chicken/Mexico/31381-3/1994(H5N2) hemagglutinin (HA)	U37176.1
A/chicken/Mexico/31381-6/1994(H5N2) hemagglutinin (HA)	U37175.1
A/chicken/Mexico/31381-4/1994(H5N2) hemagglutinin (HA)	U37174.1
A/chicken/Mexico/31381-5/1994(H5N2) hemagglutinin (HA)	U37169.1
A/chicken/Mexico/31381-8/1994(H5N2) hemagglutinin (HA)	U37170.1
A/Chicken/Mexico/31381-Avilab/94(H5N2)hemagglutinin (HA)	L46585.1
A/chicken/Mexico/31382-1/1994(H5N2)hemagglutinin (HA)	U37168.1
A/chicken/Mexico/31381-2/1994(H5N2) hemagglutinin (HA)	U37167.1
A/chicken/Mexico/31381-1/1994(H5N2) hemagglutinin (HA)	U37166.1
A/chicken/Mexico/31381-7/1994(H5N2) hemagglutinin (HA)	U37165.1
A/chicken/Pennsylvania/13609/1993(H5N2) hemagglutinin	U05331.1
A/chicken/Pennsylvania/1/1983(H5N2) hemagglutinin esterase precursor	M18001.1
A/chicken/Pennsylvania/1370/1983(H5N2) hemagglutinin esterase precursor	M10243.1
A/Chicken/Puebla/8623-607/94(H5N2) hemagglutinin (HA)	L46586.1
A/chicken/Puebla/14586-654/1994(H5N2) hemagglutinin (HA)	U37180.1
A/chicken/Puebla/14585-622/1994(H5N2) hemagglutinin (HA)	U37179.1
A/chicken/Puebla/8623-607/1994(H5N2)hemagglutinin (HA)	U37178.1
A/chicken/Puebla/8624-604/1994(H5N2) hemagglutinin (HA)	U37177.1
A/Chicken/Queretaro/14588-19/95(H5N2) hemagglutinin (HA)	L46587.1
A/chicken/Queretaro/7653-20/95(H5N2) hemagglutinin (HA)	U79448.1
A/chicken/Queretaro/26654-1373/1994(H5N2) hemagglutinin (HA)	U37171.1
A/chicken/Queretaro/14588-19/1994(H5N2)hemagglutinin (HA)	U37182.1
A/chicken/Singapore/98(H5N2) matrix protein 2 (M2)	EF682127.1
A/chicken/Taiwan/1209/03(H5N2) hemagglutinin protein (HA)	AY573917.1
A/chicken/Taiwan/1209/03(H5N2) neuraminidase	AY573918.1

Strain/Protein	GenBank Access No.
A/duck/Eastern China/64/2004(H5N2) segment 6 neuraminidase (NA)	EU429791.1
A/duck/Eastern China/264/2002(H5N2) segment 6 neuraminidase (NA)	EU429744.1
A/duck/Eastern China/01/2001(H5N2) segment 6 neuraminidase (NA)	EU429728.1
A/duck/Eastern China/06/2000(H5N2) segment 6 neuraminidase (NA)	EU429722.1
A/duck/Hong Kong/342/78(H5N2) matrix protein 1 (M) and matrix protein 2 (M)	DQ107452.1
A/duck/Hong Kong/342/78(H5N2) hemagglutinin precursor	U20475.1
A/duck/Michigan/80(H5N2) hemagglutinin 1 chain	U20474.1
A/duck/Michigan/80(H5N2) hemagglutinin	U79449.1
A/duck/MN/1564/81(H5N2) matrix protein 1 (M) and matrix protein 2 (M)	DQ107467.1
A/duck/Mongolia/54/2001(H5N2) hemagglutinin (HA)	AB241614.2
A/duck/Primorie/2621/01(H5N2) hemagglutinin (HA)	AJ621811.3
A/duck/Primorie/2621/01(H5N2)nucleoprotein (NP)	AJ621812.1
A/duck/Primorie/2621/01(H5N2) nonstructural protein (NS)	AJ621813.1
A/duck/Pennsylvania/84(H5N2) hemagglutinin 1chain	U20473.1
A/duck/Potsdam/1402-6/86(H5N2) hemagglutinin H5	AF082042.1
A/emu/Texas/39442/93(H5N2) hemagglutinin	U28920.1
A/emu/Texas/39442/93(H5N2) hemagglutinin	U28919.1
A/mallard/Alberta/645/80(H5N2) matrix protein 1 (M) and matrix protein 2 (M)	DQ107471.1
A/mallard/AR/1C/2001(H5N2) matrix protein 1 (M) and matrix protein 2 (M)	DQ107463.1
A/mallard/NY/189/82(H5N2) matrix protein 1 (M) and matrix protein 2 (M)	DQ107465.1
A/mallard/MN/25/80(H5N2) matrix protein 1 (M) and matrix protein 2 (M)	DQ107473.1
A/mallard/MI/18/80(H5N2) matrix protein 1 (M) and matrix protein 2 (M)	DQ107470.1
A/mallard/Ohio/345/88(H5N2) hemagglutinin	U79450.1
A/parrot/CA/6032/04(H5N2) polymerase basic protein 2 (PB2)	DQ256390.1
A/parrot/CA/6032/04(H5N2) polymerase basic protein 1 (PB1)	DQ256389.1
A/parrot/CA/6032/04(H5N2) matrix protein (M)	DQ256384.2
A/parrot/CA/6032/04(H5N2) hemagglutinin (HA)	DQ256383.1
A/parrot/CA/6032/04(H5N2) neuraminidase (NA)	DQ256385.1
A/parrot/CA/6032/04(H5N2) polymerase basic protein 2 (PB2)	DQ256390.1
A/parrot/CA/6032/04(H5N2) nucleoprotein (NP)	DQ256386.1
A/parrot/CA/6032/04(H5N2)) polymerase (PA)	DQ256388.1
A/ruddy turnstone/Delaware/244/91 (H5N2) nonfunctional matrix protein	AY664474.1
A/ruddy turnstone/Delaware/244/91 (H5N2)	U05330.1
A/turkey/Colorado/72(H5N2) hemagglutinin 1 chain (HA)	U20472.1
A/turkey/England/N28/73 (H5N2) hemagglutinin	AY500365.1
A/turkey/TX/14082/81(H5N2) matrix protein 1 (M) and matrix protein 2 (M)	DQ107464.1
A/turkey/MN/1704/82(H5N2)) matrix protein 1 (M) and matrix protein 2 (M)	DQ107472.1
A/turkey/Minnesota/10734/95(H5N2)) hemagglutinin	U79455.1

Strain/Protein	GenBank Access No.
A/turkey/Minnesota/3689-1551/81(H5N2) hemagglutinin	U79454.1
A/chicken/Singapore/1997(H5N3) M2 protein	EU014141.1
A/duck/Hokkaido/299/04(H5N3) hemagglutinin (HA)	AB241626.1
A/duck/Hokkaido/193/04(H5N3) hemagglutinin (HA)	AB241625.1
A/duck/Hokkaido/101/04(H5N3) hemagglutinin (HA)	AB241624.1
A/duck/Hokkaido/447/00(H5N3) hemagglutinin (HA)	AB241620.1
A/duck/Hokkaido/69/00(H5N3) hemagglutinin (HA)	AB241619.1
A/duck/Hong Kong/205/77(H5N3) hemagglutinin H5	AF082038.1
A/duck/Hong Kong/698/79(H5N3) hemagglutinin H5	AF082039.1
A/duck/Hong Kong/308/78(H5N3) matrix protein 1 (M) and matrix protein 2 (M)	DQ107457.1
A/duck/Hong Kong/825/80(H5N3) matrix protein 1 (M) and matrix protein 2 (M)	DQ107455.1
A/duck/Hong Kong/820/80(H5N3) matrix protein 1 (M) and matrix protein 2 (M)	DQ107453.1
A/duck/Hong Kong/205/77(H5N3) matrix protein 1 (M) and matrix protein 2 (M)	DQ107456.1
A/Duck/Ho Chi Minh/014/78(H5N3) segment 4 hemagglutinin	AF290443.1
A/duck/Jiangxi/6151/2003(H5N3) matrix protein 1 (M) and matrix protein 2 (M)	DQ107451.1
A/duck/Malaysia/F119-3/97(H5N3) hemagglutinin	AF303057.1
A/duck/Miyagi/54/76(H5N3)hemagglutinin (HA)	AB241615.1
A/duck/Mongolia/596/01(H5N3) hemagglutinin HA)	AB241622.1
A/duck/Mongolia/500/01(H5N3)hemagglutinin (HA)	AB241621.1
A/duck/Primorie/2633/01(H5N3) matrix protein (M1)	AJ621810.1
A/duck/Primorie/2633/01(H5N3)nucleoprotein (NP)	AJ621808.1
A/duck/Primorie/2633/01(H5N3)hemagglutinin (HA)	AJ621807.1
A/duck/Primorie/2633/01(H5N3)nucleoprotein (NP)	AJ621809.1
A/goose/Hong Kong/23/78(H5N3) matrix protein 1 (M) and matrix protein 2 (M)	DQ107454.1
A/mallard/Wisconsin/169/75(H5N3) hemagglutinin	U79452.1
A/swan/Hokkaido/51/96(H5N3)hemagglutinin (HA)	AB241617.1
A/swan/Hokkaido/4/96(H5N3) hemagglutinin (HA)	AB241616.1
A/turkey/CA/6878/79(H5N3) matrix protein 1 (M) and matrix protein 2 (M)	DQ107469.1
A/tern/South Africa/61(H5N3) hemagglutinin precursor (HA)	U20460.1
A/gull/Delaware/5/2000(H5N4) matrix protein 1 (M) and matrix protein 2 (M)	DQ107459.1
A/gull/Delaware/4/2000(H5N4) matrix protein 1 (M) and matrix protein 2 (M)	DQ107458.1
A/shorebird/Delaware/109/2000(H5N4) matrix protein 1 (M)	DQ107460.1
A/shorebird/Delaware/243/2000(H5N4) matrix protein 1 (M) and matrix protein 2 (M)	DQ107462.1
A/shorebird/Delaware/230/2000(H5N4) matrix protein 1 (M) and matrix protein 2 (M)	DQ107461.1
A/mallard/Wisconsin/34/75(H5N6) hemagglutinin	U79451.1
A/duck/Potsdam/2216-4/1984(H5N6) hemagglutinin H5	AF082041.1
A/shorebird/Delaware/207/98 (H5N8) nonfunctional matrix protein	AY664456.1
A/shorebird/Delaware/27/98 (H5N8) nonfunctional matrix protein	AY664453.1

Strain/Protein	GenBank Access No.
A/herring gull/Delaware/281/98 (H5N8) nonfunctional matrix protein	AY664452.1
A/mallard/Ohio/556/1987(H5N9) hemagglutinin (HA)	U67783.2
A/turkey/Wisconsin/68(H5N9) hemagglutinin	U79456.1
A/blue-winged teal/Alberta/685/82(H6N1) matrix protein 1 (M) and matrix protein 2 (M)	DQ107448.1
A/chicken/Taiwan/7-5/99(H6N1) nucleocapsid protein (NP)	AF261750.1
A/chicken/Taiwan/7-5/99(H6N1) matrix protein	AF262213.1
A/chicken/Taiwan/7-5/99(H6N1) nonstructural protein	AF262212.1
A/chicken/Taiwan/7-5/99(H6N1) polymerase (PA)	AF262211.1
A/chicken/Taiwan/7-5/99(H6N1) polymerase subunit PB1	AF262210.1
A/chicken/Taiwan/7-5/99(H6N1) nucleocapsid protein (NP)	AF261750.1
A/chicken/Taiwan/ns2/99(H6N1) segment 4 hemagglutinin (HA1)	AF310985.1
A/chicken/Taiwan/na3/98(H6N1) segment 4 hemagglutinin (HA1)	AF310984.1
A/chicken/Taiwan/7-5/99(H6N1) segment 4 hemagglutinin (HA1)	AF310983.1
A/duck/Hong Kong/D73/76(H6N1) matrix protein 1 (M) and matrix protein 2 (M)	DQ107432.1
A/duck/Taiwan/9/23-3/2000(H6N1) matrix protein 1 (M) and matrix protein 2 (M)	DQ107407.1
A/pheasant/Hong Kong/FY479/2000(H6N1) matrix protein 1 (M) and matrix protein 2 (M)	DQ107409.1
A/pheasant/Hong Kong/SSP44/2002(H6N1) matrix protein 1 (M) and matrix protein 2 (M)	DQ107412.1
A/quail/Hong Kong/YU421/2002(H6N1) matrix protein 1 (M) and matrix protein 2 (M)	DQ107414.1
A/avian/NY/17150-7/2000(H6N2) matrix protein 1 (M) and matrix protein 2 (M)	DQ107423.1
A/chicken/CA/285/2003(H6N2) matrix protein 1 (M) and matrix protein 2 (M)	DQ107429.1
A/chicken/CA/375TR/2002(H6N2) matrix protein 1 (M) and matrix protein 2 (M)	DQ107428.1
A/chicken/CA/203/2003(H6N2) matrix protein 1 (M) and matrix protein 2 (M)	DQ107426.1
A/chicken/NY/101250-7/2001(H6N2) matrix protein 1 (M) and matrix protein 2 (M)	DQ107419.1
A/chicken/CA/625/2002(H6N2) matrix protein 1 (M) and matrix protein 2 (M)	DQ107418.1
A/Chicken/California/0139/2001(H6N2)nucleoprotein (NP)	AF474070.1
A/Chicken/California/650/2000(H6N2) nucleoprotein (NP)	AF474069.1
A/Chicken/California/9420/2001(H6N2) neuraminidase N2 (N2)	AF474048.1
A/Chicken/California/9174/2001(H6N2) neuraminidase N2 (N2)	AF474047.1
A/Chicken/California/8892/2001(H6N2)neuraminidase N2 (N2)	AF474046.1
A/Chicken/California/6643/2001(H6N2) neuraminidase N2 (N2)	AF474045.1
A/Chicken/California/1316/2001(H6N2)neuraminidase N2 (N2)	AF474044.1
A/Chicken/California/0139/2001(H6N2) neuraminidase N2 (N2)	AF474043.1
A/Chicken/California/1002/2000(H6N2) neuraminidase N2 (N2)	AF474042.1
A/Chicken/California/650/2000(H6N2) neuraminidase N2 (N2)	AF474041.1
A/Chicken/California/465/2000(H6N2) neuraminidase N2 (N2)	AF474040.1
A/Chicken/California/431/2000(H6N2) neuraminidase N2 (N2)	AF474039.1
A/Chicken/California/6643/2001(H6N2) hemagglutinin H6 (H6)	AF474035.1

Strain/Protein	GenBank Access No.
A/Chicken/California/431/2000(H6N2) hemagglutinin H6 (H6)	AF474029.1
A/Chicken/California/9420/2001(H6N2) hemagglutinin H6 (H6)	AF474038.1
A/Chicken/California/9174/2001(H6N2) hemagglutinin H6 (H6)	AF474037.1
A/Chicken/California/8892/2001(H6N2) hemagglutinin H6 (H6)	AF474036.1
A/Chicken/California/1316/2001(H6N2) hemagglutinin H6 (H6)	AF474034.1
A/Chicken/California/0139/2001(H6N2) hemagglutinin H6 (H6)	AF474033.1
A/Chicken/California/1002/2000(H6N2) hemagglutinin H6 (H6)	AF474032.1
A/Chicken/California/650/2000(H6N2) hemagglutinin H6 (H6)	AF474031.1
A/Chicken/California/465/2000(H6N2) hemagglutinin H6 (H6)	AF474030.1
A/cornish cross/CA/139/2001(H6N2) matrix protein 1 (M) and matrix protein 2 (M)	DQ107424.1
A/duck/Eastern China/164/2002(H6N2) segment 6 neuraminidase (NA)	EU429762.1
A/duck/Eastern China/729/2003(H6N2) segment 6 neuraminidase (NA)	EU429760.1
A/duck/Eastern China/262/2002(H6N2) segment 6 neuraminidase (NA)	EU429743.1
A/duck/Eastern China/74/2006(H6N2) segment 6 neuraminidase (NA)	EU429741.1
A/duck/Eastern China/161/2002(H6N2) segment 6 neuraminidase (NA)	EU429740.1
A/duck/Hong Kong/960/80(H6N2)) matrix protein 1 (M) and matrix protein 2 (M)	DQ107435.1
A/duck/Hong Kong/D134/77(H6N2)) matrix protein 1 (M) and matrix protein 2 (M)	DQ107433.1
A/duck/CA/10221/2002(H6N2) matrix protein 1 (M) and matrix protein 2 (M)	DQ107421.1
A/duck/Shantou/5540/2001(H6N2) matrix protein 1 (M) and matrix protein 2 (M)	DQ107431.1
A/guinea fowl/Hong Kong/SSP99/2002(H6N2) matrix protein 1 (M) and matrix protein 2 (M)	DQ107413.1
A/mallard/NY/016/83(H6N2) matrix protein 1 (M) and matrix protein 2 (M)	DQ107449.1
A/mallard/NY/046/83(H6N2) matrix protein 1 (M) and matrix protein 2 (M)	DQ107450.1
A/pintail/Alberta/644/81(H6N2) matrix protein 1 (M) and matrix protein 2 (M)	DQ107445.1
A/quail/Hong Kong/SF792/2000(H6N2) matrix protein 1 (M) and matrix protein 2 (M)	DQ107410.1
A/ruddy turnstone/Delaware/106/98 (H6N2) nonfunctional matrix protein	AY664439.1
A/Shorebird/Delaware/127/97(H6N2) nonfunctional matrix protein	AY664467.1
A/shorebird/Delaware/124/2001(H6N2) matrix protein 1 (M) and matrix protein 2 (M)	DQ107417.1
A/shorebird/Delaware/208/2001(H6N2) matrix protein 1 (M) and matrix protein 2 (M)	DQ107427.1
A/turkey/CA/527/2002(H6N2) matrix protein 1 (M) and matrix protein 2 (M)	DQ107420.1
A/turkey/CA/1623CT/2002(H6N2) matrix protein 1 (M) and matrix protein 2 (M)	DQ107425.1
A/turkey/MN/836/80(H6N2) matrix protein 1 (M) and matrix protein 2 (M)	DQ107440.1
A/turkey/MN/735/79(H6N2) matrix protein 1 (M) and matrix protein 2 (M)	DQ107437.1
A/chicken/Hong Kong/17/77(H6N4)) matrix protein 1 (M) and matrix protein 2 (M)	DQ107436.1

Strain/Protein	GenBank Access No.
A/chicken/Hong Kong/CSW106/2001(H6N4) matrix protein 1 (M) and matrix protein 2 (M)	DQ107406.1
A/gull/Delaware/18/2000(H6N4) matrix protein 1 (M) and matrix protein 2 (M)	DQ107415.1
A/pheasant/Hong Kong/CSW2573/2001(H6N4) matrix protein 1 (M) and matrix protein 2 (M)	DQ107411.1
A/quail/Hong Kong/CSW106/2001(H6N4) matrix protein 1 (M) and matrix protein 2 (M)	DQ107430.1
A/Shorebird/Delaware/194/98(H6N4) nonfunctional matrix protein	AY664424.1
A/shorebird/Delaware/259/2000(H6N4) matrix protein 1 (M) and matrix protein 2 (M)	DQ107416.1
A/shearwater/Australia/1/1972(H6N5) segment 6 neuraminidase (NA)	EU429794.1
A/shearwater/Australia/1/1972(H6N5) polymerase A (PA)	L25832.1
A/pintail/Alberta/1040/79(H6N5) matrix protein 1 (M) and matrix protein 2 (M)	DQ107439.1
A/blue-winged teal/MN/993/80(H6N6)) matrix protein 1 (M) and matrix protein 2 (M)	DQ107441.1
A/duck/NY/83779/2002(H6N6) matrix protein 1 (M) and matrix protein 2 (M)	DQ107422.1
A/duck/MN/1414/81(H6N6) matrix protein 1 (M) and matrix protein 2 (M)	DQ107444.1
A/mallard/Alberta/289/82(H6N6) matrix protein 1 (M) and matrix protein 2 (M)	DQ107447.1
A/mallard duck/MN/1041/80(H6N6) matrix protein 1 (M) and matrix protein 2 (M)	DQ107442.1
A/pintail/Alberta/189/82(H6N6) matrix protein 1 (M) and matrix protein 2 (M)	DQ107446.1
A/sanderling/Delaware/1258/86(H6N6) nonfunctional matrix protein	AY664436.1
A/blue-winged teal/Alberta/368/78(H6N8)) matrix protein 1 (M) and matrix protein 2 (M)	DQ107438.1
A/ruddy turnstone/Delaware/105/98 (H6N8) nonfunctional matrix protein	AY664428.1
A/domestic duck/NY/81(H6N8)) matrix protein (M)	DQ107443.1
A/duck/Eastern China/163/2002(H6N8) segment 6 neuraminidase (NA)	EU429786.1
A/duck/Hong Kong/D182/77(H6N9) matrix protein 1 (M) and matrix protein 2 (M)	DQ107434.1
A/chicken/Hong Kong/SF3/2001(H6) matrix protein 1 (M) and matrix protein 2 (M)	DQ107408.1
A/African starling/England/983/79(H7N1) neuraminidase (N1)	AJ416629.1
A/Afri.Star./Eng-Q/938/79(H7N1) hemagglutinin precursors	AF149295.1
A/chicken/Italy/1067/99(H7N1) matrix protein 1 (M1)	AJ416630.1
A/chicken/Italy/1067/99(H7N1) neuraminidase (N1)	AJ416627.1
A/chicken/Italy/4575/99 (H7N1) hemagglutinin (HA)	AJ493469.1
A/chicken/Italy/13474/99(H7N1) haemagglutinin (HA)	AJ491720.1
A/chicken/Italy/445/1999(H7N1)	AX537385.1
A/Chicken/Italy/267/00(H7N1) hemagglutinin (HA)	AJ493215.1
A/Chicken/Italy/13489/99(H7N1) hemagglutinin (HA)	AJ493214.1
A/Chicken/Italy/13307/99(H7N1) hemagglutinin (HA)	AJ493212.1
A/chicken/Singapore/1994(H7N1) M2 protein	EU014140.1
A/duck/Hong Kong/301/78(H7N1) matrix protein 1 (M) and matrix protein 2 (M)	DQ107475.1
A/Hong Kong/301/78(H7N1) hemagglutinin (HA)	AY672090.1

Strain/Protein	GenBank Access No.
A/fowl plaguq virus/Rostock/34 (H7N1) NP protein	AJ243993.1
A/fowl plaguq virus/Rostock/34 (H7N1) PA protein	AJ243992.1
A/fowl plaguq virus/Rostock/34 (H7N1) PB2 protein	AJ243991.1
A/fowl plaguq virus/Rostock/34 (H7N1) PB1 protein	AJ243990.1
A/ostrich/South Africa/5352/92(H7N1) hemagglutinin precursor (HA)	U20458.1
A/rhea/North Carolina/39482/93(H7N1) hemagglutinin precursor (HA)	U20468.1
A/turkey/Italy/3775/99 (H7N1) hemagglutinin (HA)	AJ493472.1
A/turkey/Italy/4603/99 (H7N1) hemagglutinin (HA)	AJ493471.1
A/turkey/Italy/4602/99 (H7N1) hemagglutinin (HA)	AJ493470.1
A/turkey/Italy/4169/99 (H7N1) hemagglutinin (HA)	AJ493468.1
A/turkey/Italy/4073/99 (H7N1) hemagglutinin (HA)	AJ493467.1
A/turkey/Italy/3889/99 (H7N1) hemagglutinin (HA)	AJ493466.1
A/turkey/Italy/12598/99(H7N1) haemagglutinin (HA)	AJ489520.1
A/turkey/Italy/4580/99(H7N1) haemagglutinin (HA)	AJ416628.1
A/Turkey/Italy/335/00(H7N1) haemagglutinin (HA)	AJ493217.1
A/Turkey/Italy/13468/99(H7N1) haemagglutinin (HA)	AJ493216.1
A/Turkey/Italy/13467/99(H7N1) haemagglutinin (HA)	AJ493213.1
A/chicken/CT/9407/2003(H7N2) matrix protein 1 (M) and matrix protein 2 (M)	DQ107478.1
A/chicken/NY/116124/2003(H7N2) matrix protein 1 (M) and matrix protein 2 (M)	DQ107479.1
A/chicken/PA/143586/2002(H7N2) matrix protein 1 (M) and matrix protein 2 (M)	DQ107477.1
A/duck/Hong Kong/293/78(H7N2) matrix protein 1 (M) and matrix protein 2 (M)	DQ107474.1
A/duck/Hong Kong/293/78(H7N2) hemagglutinin precursor (HA)	U20461.1
A/laughing gull/Delaware/2838/87 (H7N2) nonfunctional matrix protein	AY664427.1
A/pheasant/NJ/30739-9/2000(H7N2) matrix protein 1 (M) and matrix protein 2 (M)	DQ107481.1
A/ruddy turnstone/Delaware/130/99 (H7N2) onfunctional matrix protein	AY664451.1
A/unknown/149717-12/2002(H7N2) matrix protein 1 (M) and matrix protein 2 (M)	DQ107480.1
A/unknown/NY/74211-5/2001(H7N2) matrix protein 1 (M) and matrix protein 2 (M)	DQ107476.1
A/unknown/149717-12/2002(H7N2) matrix protein 1 (M) and matrix protein 2(M)	DQ107480.1
A/unknown/NY/74211-5/2001(H7N2) matrix protein 1(M) and matrix protein 2 (M)	DQ107476.1
A/chicken/British Columbia/CN7-3/04 (H7N3) hemagglutinin (HA)	AY644402.1
A/chicken/British Columbia/CN7-3/04 (H7N3) matrix protein (M1)	AY677732.1
A/chicken/Italy/270638/02(H7N3) hemagglutinin (HA)	EU158111.1
A/gadwall/MD/3495/83(H7N3) matrix protein 1 (M) and matrix protein 2 (M)	DQ107488.1
A/mallard/Alberta/22/2001(H7N3) matrix protein 1 (M) and matrix protein 2 (M)	DQ107482.1
A/mallard/Alberta/699/81(H7N3) matrix protein 1 (M) and matrix protein 2 (M)	DQ107487.1

Strain/Protein	GenBank Access No.
A/pintail/Alberta/25/2001(H7N3) matrix protein 1 (M) and matrix protein 2 (M)	DQ107483.1
A/Quail/Arkansas/16309-7/94 (H7N3) hemagglutinin protein subunit 1 precursor (HA1)	AF072401.1
A/ruddy turnstone/New Jersey/65/85(H7N3) nonfunctional matrix protein	AY664433.1
A/turkey/England/63(H7N3) hemagglutinin precursor (HA)	U20462.1
A/Turkey/Colorado/13356/91 (H7N3) hemagglutinin protein subunit 1 precursor (HA1)	AF072400.1
A/turkey/MN/1200/80(H7N3)) matrix protein 1 (M) and matrix protein 2 (M)	DQ107486.1
A/turkey/MN/1818/82(H7N3) matrix protein 1 (M) and matrix protein 2 (M)	DQ107489.1
A/turkey/Minnesota/1237/80(H7N3) hemagglutinin precursor (HA)	U20466.1
A/turkey/TX/1/79(H7N3) matrix protein 1 (M) and matrix protein 2 (M)	DQ107484.1
A/Turkey/Oregon/71(H7N3) hemagglutinin	AF497557.1
A/Turkey/Utah/24721-10/95 (H7N3) hemagglutinin protein subunit 1 precursor (HA1)	AF072402.1
A/softbill/South Africa/142/92(H7N4) hemagglutinin precursor (HA)	U20464.1
A/ruddy turnstone/Delaware/2770/87 (H7N5) nonfunctional matrix protein	AY664476.1
A/chicken/Brescia/1902(H7N7) hemagglutinin 1 chain (HA)	U20471.1
A/chicken/Jena/1816/87(H7N7) hemagglutinin precursor (HA)	U20469.1
A/chicken/Leipzig/79(H7N7) hemagglutinin precursor (HA)	U20459.1
A/duck/Heinersdorf/S495/6/86(H7N7) hemagglutinin precursor (HA)	U20465.1
A/equine/Prague/1/56 (H7N7) neuraminidase	U85989.1
A/equine/Santiago/77(H7N7) nucleoprotein	AY383752.1
A/equine/Santiago/77(H7N7) neuraminidase	AY383757.1
A/equine/Santiago/77(H7N7) hemagglutinin	AY383756.1
A/FPV/Weybridge(H7N7) matrix protein	M38299.1
A/goose/Leipzig/187/7/1979(H7N7) hemagglutinin	L43914.1
A/goose/Leipzig/192/7/1979(H7N7) hemagglutinin	L43915.1
A/goose/Leipzig/137/8/1979(H7N7) hemagglutinin	L43913.1
A/ruddy turnstone/Delaware/134/99 (H7N7) nonfunctional matrix protein	AY664468.1
A/seal/Mass/1/80 H7N7 recombinant	S73497.1
A/swan/Potsdam/63/6/81(H7N7) hemagglutinin precursor (HA)	U20467.1
A/tern/Potsdam/342/6/79(H7N7) hemagglutinin precursor (HA)	U20470.1
A/pintail/Alberta/121/79(H7N8) matrix protein 1 (M) and matrix protein 2 (M)	DQ107485.1
A/Turkey/Minnesota/38429/88(H7N9) hemagglutinin	AF497551.1
A/turkey/Ontario/6118/1968(H8N4) segment 6 neuraminidase (NA)	EU429793.1
A/Mallard Duck/Alberta/357/84(H8N4) segment 4 hemagglutinin (HA1)	AF310988.1
A/Pintail Duck/Alberta/114/79(H8N4) segment 4 hemagglutinin (HA1)	AF310987.1
A/duck/Eastern China/01/2005(H8N4) segment 6 neuraminidase (NA)	EU429780.1
A/Red Kont/Delaware/254/94(H8N4) segment 4 hemagglutinin (HA1)	AF310989.1
A/chicken/Amioz/1527/03(H9N2) nucleoprotein	DQ116511.1

Strain/Protein	GenBank Access No.
A/chicken/Amioz/1527/03(H9N2) neuraminidase	DQ116081.1
A/chicken/Amioz/1527/03(H9N2) hemagglutinin	DQ108911.1
A/chicken/Alonim/1953/104(H9N2) hemagglutinin	DQ108928.1
A/chicken/Alonim/1552/03(H9N2) hemagglutinin	DQ108914.1
A/chicken/Alonim/1552/03(H9N2) nucleoprotein	DQ116514.1
A/chicken/Alonim/1965/04(H9N2) hemagglutinin	DQ108929.1
A/Chicken/Anhui/1/98(H9N2) hemagglutinin (HA)	AF461511.1
A/Chicken/Beijing/1/95(H9N2) nonfunctional matrix protein	AF536719.1
A/Chicken/Beijing/1/95(H9N2) nucleoprotein (NP)	AF536699.1
A/Chicken/Beijing/1/95(H9N2) nonfunctional nonstructural protein	AF536729.1
A/Chicken/Beijing/1/95(H9N2) segment 6 neuraminidase (NA)	AF536709.1
A/Chicken/Beijing/2/97(H9N2) nucleoprotein (NP)	AF536700.1
A/Chicken/Beijing/2/97(H9N2) nonfunctional matrix protein	AF536720.1
A/Chicken/Beijing/2/97(H9N2) nonfunctional nonstructural protein	AF536730.1
A/Chicken/Beijing/2/97(H9N2) segment 6 neuraminidase (NA)	AF536710.1
A/Chicken/Beijing/1/97(H9N2) hemagglutinin (HA)	AF461530.1
A/Chicken/Beijing/3/99(H9N2) nonfunctional matrix protein	AF536721.1
A/Chicken/Beijing/3/99(H9N2) nucleoprotein (NP)	AF536701.1
A/Chicken/Beijing/3/99(H9N2) nonfunctional nonstructural protein	AF536731.1
A/Chicken/Beijing/3/99(H9N2) segment 6 neuraminidase (NA)	AF536711.1
A/chicken/Beit Alfa/1282/03(H9N2)hemagglutinin	DQ104476.1
A/chicken/Beit-Aran/29/05(H9N2) hemagglutinin	DQ108931.1
A/chicken/Bnei Darom/1557/03(H9N2) hemagglutinin	DQ108915.1
A/chicken/Ein Habsor/1808/04(H9N2) hemagglutinin	DQ108925.1
A/Chicken/Gangxi/2/00(H9N2) hemagglutinin (HA)	AF461514.1
A/Chicken/Gangxi/1/00(H9N2) hemagglutinin (HA)	AF461513.1
A/chicken/Gan Shomron/1465/03(H9N2) hemagglutinin	DQ104480.1
A/chicken/Gan Shomron/1292/03(H9N2) hemagglutinin	DQ104478.1
A/chicken/Gan_Shomron/1465/03(H9N2) nucleoprotein	DQ116506.1
A/chicken/Gan_Shomron/1465/03(H9N2) neuraminidase	DQ116077.1
A/chicken/Gan Shomron/1543/04(H9N2) nucleoprotein	DQ116512.1
A/chicken/Gan Shomron/1543/04(H9N2) hemagglutinin	DQ108912.1
A/Chicken/Guangdong/97(H9N2) nonfunctional matrix protein	AF536722.1
A/Chicken/Guangdong/97(H9N2) nucleoprotein (NP)	AF536702.1
A/Chicken/Guangdong/97(H9N2) nonfunctional nonstructural protein	AF536732.1
A/Chicken/Guangdong/97(H9N2) segment 6 neuraminidase (NA)	AF536712.1
A/Chicken/Gansu/1/99(H9N2) hemagglutinin (HA)	AF461512.1
A/chicken/Gujrat/India/3697/2004(H9N2) polymerase basic 2 (PB2)	DQ979865.1
A/chicken/Haryana/India/2424/2004(H9N2) polymerase basic 2 (PB2)	DQ979862.1
A/Chicken/Henan/98(H9N2) nonfunctional matrix protein	AF536726.1
A/Chicken/Henan/98(H9N2) nucleoprotein (NP)	AF536706.1

Strain/Protein	GenBank Access No.
A/Chicken/Henan/98(H9N2) nonfunctional nonstructural protein	AF536736.1
A/Chicken/Henan/2/98(H9N2) hemagglutinin (HA)	AF461517.1
A/Chicken/Henan/1/99(H9N2) hemagglutinin (HA)	AF461516.1
A/Chicken/Henan/98(H9N2) segment 6 neuraminidase (NA)	AF536716.1
A/Chicken/Hebei/1/96(H9N2) nonfunctional matrix protein	AF536723.1
A/Chicken/Hebei/1/96(H9N2) segment 6 nonfunctional neuraminidase protein	AF536713.1
A/Chicken/Hebei/1/96(H9N2) nucleoprotein (NP)	AF536703.1
A/Chicken/Hebei/1/96(H9N2) nonfunctional nonstructural protein	AF536733.1
A/Chicken/Hebei/1/96(H9N2) segment 6 nonfunctional neuraminidase protein	AF536713.1
A/Chicken/Hebei/2/00(H9N2) hemagglutinin (HA)	AF461531.1
A/Chicken/Hebei/2/98(H9N2) nonfunctional matrix protein	AF536724.1
A/Chicken/Hebei/2/98(H9N2) nucleoprotein (NP)	AF536704.1
A/Chicken/Hebei/2/98(H9N2) nonfunctional nonstructural protein	AF536734.1
A/Chicken/Hebei/2/98(H9N2) segment 6 neuraminidase (NA)	AF536714.1
A/Chicken/Hebei/1/00(H9N2) hemagglutinin (HA)	AF461515.1
A/Chicken/Hebei/3/98(H9N2) nucleoprotein (NP)	AF536705.1
A/Chicken/Hebei/3/98(H9N2) nonfunctional matrix protein	AF536725.1
A/Chicken/Hebei/3/98(H9N2) nonfunctional onstructural protein	AF536735.1
A/Chicken/Hebei/3/98(H9N)) segment 6 neuraminidase (NA)	AF536715.1
A/chicken/Hong Kong/FY313/2000(H9N2) matrix protein 1 (M) and matrix protein 2 (M)	DQ107508.1
A/chicken/Hong Kong/WF208/2001(H9N2) matrix protein 1 (M) and matrix protein 2 (M)	DQ107513.1
A/chicken/Hong Kong/NT471/2002(H9N2) matrix protein 1 (M) and matrix protein 2 (M)	DQ107514.1
A/chicken/Hong Kong/WF2/99(H9N2) hemagglutinin	AY206677.1
A/chicken/Iarah/1376/03(H9N2) nucleoprotein	DQ116504.1
A/chicken/Iarah/1376/03(H9N2) neuraminidase	DQ116075.1
A/chicken/Iarah/1376/03(H9N2) hemagglutinin	DQ108910.1
A/chicken/India/2793/2003(H9N2) hemagglutinin (HA)	AY336597.1
A/chicken/Iran/101/1998(H9N2) matrix protein 2 (M2)	EU477375.1
A/Chicken/Jiangsu/1/99(H9N)) hemagglutinin (HA)	AF461509.1
A/Chicken/Jiangsu/2/98(H9N2) hemagglutinin (HA)	AF461510.1
A/chicken/Kfar Monash/636/02(H9N2) hemagglutinin	DQ104464.1
A/chicken/Kalanit/1966/06.12.04(H9N2) hemagglutinin	DQ108930.1
A/chicken/Kalanit/1946/04(H9N2) hemagglutinin	DQ108927.1
A/chicken/Korea/S4/2003(H9N2) matrix protein 1 (M) and matrix protein 2 (M)	DQ107517.1
A/Chicken/Korea/MS96/96(H9N2) matrix protein 1 and 2 (M)	AF203788.1
A/Chicken/Korea/MS96/96(H9N2) neuraminidase subtype 2	AF203786.1
A/Chicken/Korea/MS96/96(H9N2) nucleoprotein	AF203787.1
A/Chicken/Liaoning/99(H9N2) nonfunctional matrix protein	AF536727.1
A/Chicken/Liaoning/1/00(H9N2) hemagglutinin (HA)	AF461518.1
A/Chicken/Liaoning/99(H9N2) nucleoprotein (NP)	AF536707.1
A/Chicken/Liaoning/99(H9N2) nonfunctional matrix protein	AF536727.1

Strain/Protein	GenBank Access No.
A/Chicken/Liaoning/99(H9N2) nonfunctional onstructural protein	AF536737.1
A/Chicken/Liaoning/2/00(H9N2) hemagglutinin (HA)	AF461519.1
A/chicken/Liaoning/99(H9N2) segment 6 neuraminidase (NA)	AF536717.1
A/chicken/Mudanjiang/0823/2000(H9N2) nucleoprotein (NP)	AY496851.1
A/Chicken/Mudanjiang/0823/2000 (H9N2) nonstructural protein	AY631868.1
A/Chicken/Mudanjiang/0823/00 (H9N2) hemagglutinin (HA)	AY513715.1
A/chicken/Mudanjiang/0823/2000(H9N2) matrix protein (M1)	AY496852.1
A/chicken/Mudanjiang/0823/2000(H9N2) nucleoprotein (np)	AY496851.1
A/chicken/Maale HaHamisha/90658/00(H9N2) hemagglutinin	DQ104472.1
A/chicken/Maanit/1477/03(H9N2) hemagglutinin	DQ104483.1
A/chicken/Maanit/1291/03(H9N2) hemagglutinin	DQ104477.1
A/chicken/Maanit/1275/03(H9N2) hemagglutinin	DQ104457.1
A/chicken/Maanit/1477/03(H9N2) nucleoprotein	DQ116508.1
A/chicken/Netohah/1373/03 (H9N2) nucleoprotein	DQ116503.1
A/chicken/Netohah/1373/03 (H9N2) neuraminidase	DQ116074.1
A/chicken/Netohah/1373/03 (H9N2) hemagglutinin	DQ108909.1
A/chicken/Neve Ilan/1504/03(H9N2) hemagglutinin	DQ104484.1
A/chicken/Neve_Ilan/1504/03(H9N2) nucleoprotein	DQ116509.1
A/chicken/Neve_Ilan/1504/03(H9N2) neuraminidase	DQ116079.1
A/chicken/Orissa/India/2317/2004(H9N2) polymerase basic 2 (PB2)	DQ979861.1
A/chicken/Pardes-Hana-Carcur/1475/03(H9N2) hemagglutinin	DQ104482.1
A/chicken/Pardes-Hana-Carcur/1475/03(H9N2) neuraminidase	DQ116078.1
A/chicken/Saar/1456/03(H9N2) hemagglutinin	DQ104479.1
A/chicken/Sde_Uziahuh/1747/04(H9N2) neuraminidase	DQ116068.1
A/chicken/Sede Uzziyyahu/1651/04(H9N2) hemagglutinin	DQ108923.1
A/chicken/Sde Uziahuh/1747/04(H9N2)	DQ108905.1
A/chicken/Singapore/1998(H9N2) M2 protein	EU014142.1
A/chicken/Singapore/1998(H9N2) M2 protein	EU014142.1
A/Chicken/Shandong/98(H9N2) nonfunctional matrix protein	AF536728.1
A/Chicken/Shandong/1/98(H9N2) hemagglutinin (HA)	AF461520.1
A/Chicken/Shandong/98(H9N2) nucleoprotein (NP)	AF536708.1
A/Chicken/Shandong/98(H9N2) nonfunctional nonstructural protein	AF536738.1
A/Chicken/Shandong/98(H9N2) segment 6 neuraminidase (NA)	AF536718.1
A/Chicken/Shandong/2/99(H9N2) hemagglutinin (HA)	AF461521.1
A/chicken/Shandong/1/02(H9N2) neuraminidase (NA)	AY295761.1
A/Chicken/Shanghai/F/98(H9N2) hemagglutinin	AF461532.1
A/Chicken/Shanghai/1/02(H9N2) hemagglutinin	AY281745.1
A/Chicken/Shanghai/2/99(H9N2)) hemagglutinin (HA)	AF461522.1
A/Chicken/Shanghai/3/00(H9N2)) hemagglutinin (HA)	AF461523.1
A/Chicken/Shanghai/F/98(H9N2) hemagglutinin (HA)	AY743216.1
A/Chicken/Shanghai/4-2/01(H9N2) hemagglutinin (HA)	AF461525.1
A/Chicken/Shanghai/4-1/01(H9N2) hemagglutinin (HA)	AF461524.1
A/Chicken/Shanghai/4/01(H9N2) hemagglutinin (HA)	AY083841.1
A/Chicken/Shanghai/3/01(H9N2) hemagglutinin HA)	AY083840.1

Strain/Protein	GenBank Access No.
A/chicken/Talmei_Elazar/1304/03 (H9N2) nucleoprotein	DQ116530.1
A/chicken/Talmei_Elazar/1304/03 (H9N2) neuraminidase	DQ116072.1
A/Chicken/Tianjing/2/96 (H9N2) hemagglutinin	AF461527.1
A/Chicken/Tianjing/1/96 (H9N2) hemagglutinin (HA)	AF461526.1
A/chicken/Tel Adashim/811/01 (H9N2) hemagglutinin	DQ104467.1
A/chicken/Tel Adashim/811/01 (H9N2) nucleoprotein	DQ116527.1
A/ck/Tel_Adashim/811/01 (H9N2) neuraminidase	DQ116064.1
A/chicken/Tel Adashim/812/01 (H9N2) nucleoprotein	DQ116528.1
A/chicken/Tel Adashim/812/01 (H9N2) hemagglutinin	DQ104468.1
A/ck/Tel_Adashim/812/01 (H9N2) neuraminidase	DQ116065.1
A/chicken/Tel Adashim/786/01 (H9N2) nucleoprotein	DQ116524.1
A/chicken/Tel Adashim/809/01 (H9N2) hemagglutinin	DQ104465.1
A/chicken/Tel Adashim/809/01 (H9N2) nucleoprotein	DQ116525.1
A/chicken/Tel Adashim/1469/03 (H9N2) nucleoprotein	DQ116507.1
A/chicken/Tel Adashim/1469/303 (H9N2) hemagglutinin	DQ104481.1
A/chicken/Tel Adashim/1506/03 (H9N2) neuraminidase	DQ116080.1
A/chicken/Tel Adashim/1506/03 (H9N2) hemagglutinin	DQ104474.1
A/chicken/Tel Adashim/1506/03 (H9N2) nucleoprotein	DQ116510.1
A/chicken/Tel Adashim/1332/03 (H9N2) nucleoprotein	DQ116501.1
A/chicken/Tel Adashim/1321/03 (H9N2) nucleoprotein	DQ116500.1
A/chicken/Tel Adashim/1332/03 (H9N2) hemagglutinin	DQ108907.1
A/chicken/Tel Adashim/1321/03 (H9N2) hemagglutinin	DQ108906.1
A/chicken/Telmond/1308/03 (H9N2) nucleoprotein	DQ116499.1
A/chicken/Telmond/1308/03 (H9N2) neuraminidase	DQ116073.1
A/chicken/Telmond/1308/03 (H9N2) hemagglutinin	DQ108921.1
A/chicken/Tzrofa/1568/04 (H9N2) nucleoprotein	DQ116519.1
A/chicken/Tzrofa/1568/04 (H9N2) hemagglutinin	DQ108919.1
A/chicken/UP/India/2544/2004 (H9N2) polymerase basic 2 (PB2)	DQ979864.1
A/chicken/UP/India/2543/2004 (H9N2) polymerase basic 2 (PB2)	DQ979863.1
A/chicken/Wangcheng/4/2001 (H9N2) nucleoprotein	AY268949.1
A/chicken/Ysodot/1362/03 (H9N2) nucleoprotein	DQ116502.1
A/chicken/Ysodot/1362/03 (H9N2) hemagglutinin	DQ108908.1
A/Chicken/Yunnan/2/00 (H9N2) hemagglutinin (HA)	AF461529.1
A/Chicken/Yunnan/1/99 (H9N2) hemagglutinin (HA)	AF461528.1
A/duck/Eastern China/01/2000 (H9N2) segment 6 neuraminidase (NA)	EU429725.1
A/duck/Eastern China/48/2001 (H9N2) segment 6 neuraminidase (NA)	EU429707.1
A/duck/Eastern China/66/2003 (H9N2) segment 6 neuraminidase (NA)	EU429699.1
A/duck/Eastern China/80/2004 (H9N2) segment 6 neuraminidase (NA)	EU429726.1
A/duck/Hong Kong/448/78 (H9N2) matrix protein 1 (M) and matrix protein 2 (M)	DQ107494.1
A/duck/Hong Kong/448/78 (H9N2) hemagglutinin precursor	AY206673.1
A/duck/Hong Kong/366/78 (H9N2) hemagglutinin precursor	AY206674.1
A/duck/Hong Kong/784/79 (H9N2)) matrix protein 1 (M) and matrix protein 2 (M)	DQ107496.1
A/duck/Hong Kong/702/79 (H9N2) matrix protein 1 (M) and matrix protein 2 (M)	DQ107495.1

Strain/Protein	GenBank Access No.
/duck/Hong Kong/702/79(H9N2) hemagglutinin precursor	AY206672.1
A/duck/Hong Kong/610/79(H9N2) hemagglutinin precursor	AY206680.1
A/duck/Hong Kong/552/79(H9N2) hemagglutinin precursor	AY206679.1
A/duck/Hong Kong/644/79(H9N2) hemagglutinin precursor	AY206678.1
A/duck/Korea/S13/2003(H9N2) matrix protein 1 (M) and matrix protein 2 (M)	DQ107518.1
A/duck/Nanchang/4-361/2001(H9N2) matrix protein 1 (M) and matrix protein 2 (M)	DQ107511.1
A/duck/NY/83793/2002(H9N2) matrix protein 1 (M) and matrix protein 2 (M)	DQ107499.1
A/goose/MN/5733-1243/80(H9N2) matrix protein 1 (M) and matrix protein 2 (M)	DQ107492.1
A/geese/Tel Adashim/829/01(H9N2) hemagglutinin	DQ104469.1
A/geese/Tel Adashim/830/01(H9N2) hemagglutinin	DQ104470.1
A/ostrich/Eshkol/1436/03(H9N2) neuraminidase	DQ116076.1
A/ostrich/Eshkol/1436/03(H9N2) nucleoprotein	DQ116505.1
A/pigeon/Hong Kong/WF286/2000(H9N2) matrix protein 1 (M) and matrix protein 2 (M)	DQ107509.1
A/quail/Hong Kong/YU415/2002(H9N2) matrix protein 1 (M) and matrix protein 2 (M)	DQ107516.1
A/quail/Hong Kong/SSP225/2001(H9) matrix protein 1 (M) and matrix protein 2 (M)	DQ107512.1
A/quail/Hong Kong/YU1495/2000(H9N2) matrix protein 1 (M) and matrix protein 2 (M)	DQ107510.1
A/quail/Hong Kong/A28945/88(H9N2) hemagglutinin precursor	AY206675.1
A/shorebird/Delaware/276/99 (H9N2) nonfunctional matrix protein	AY664464.1
A/shorebird/Delaware/113/2001(H9N2) matrix protein 1 (M) and matrix protein 2 (M)	DQ107505.1
A/silky chicken/Hong Kong/WF266/2002(H9N2) matrix protein 2 (M) and matrix protein 1 (M)	DQ107515.1
A/shorebird/Delaware/77/2001(H9N2) matrix protein 1 (M) and matrix protein 2 (M)	DQ107497.1
A/guinea fowl/Hong Kong/WF10/99(H9N2) hemagglutinin precursor	AY206676.1
A/swine/Hangzhou/1/2006(H9N2) nucleocapsid protein (NP)	DQ907704.1
A/swine/Hangzhou/1/2006(H9N2)) matrix protein 1 (M1)	EF055887.1
A/swine/Hangzhou/1/2006(H9N2)) nonstructural protein 1 (NS1)	DQ823385.1
A/Sw/ShanDong/1/2003(H9N2) hemagglutinin (HA)	AY294658.1
A/turkey/CA/6889/80(H9N2) matrix protein 1 (M) and matrix protein 2 (M)	DQ107491.1
A/turkey/TX/28737/81(H9N2) matrix protein 1 (M) and matrix protein 2 (M)	DQ107493.1
A/turkey/MN/511/78(H9N2) matrix protein 1 (M) and matrix protein 2 (M)	DQ107490.1
A/turkey/Beit Herut/1267/03(H9N2) hemagglutinin	DQ104485.1
A/turkey/Beit HaLevi/1009/02(H9N2) hemagglutinin	DQ104473.1
A/turkey/Beit Herut/1265/03(H9N2) hemagglutinin	DQ104456.1
A/turkey/Beit_HaLevi/1562/03(H9N2) nucleoprotein	DQ116515.1
A/turkey/Beit_HaLevi/1566/04(H9N2) nucleoprotein	DQ116517.1
A/turkey/Beit_HaLevi/1562/03(H9N2) neuraminidase	DQ116083.1
A/turkey/Beit_HaLevi/1566/04(H9N2) neuraminidase	DQ116084.1
A/turkey/Beit_Herut/1267/03(H9N2) neuraminidase	DQ116070.1

Strain/Protein	GenBank Access No.
A/turkey/Beit_Herut/1265/03(H9N2) neuraminidase	DQ116069.1
A/turkey/Beit HaLevi/1566/04(H9N2) hemagglutinin	DQ108917.1
A/turkey/Bezat/89/05(H9N2) hemagglutinin	DQ108922.1
A/turkey/Brosh/1276/03(H9N2) hemagglutinin	DQ104458.1
A/turkey/Brosh/1276/03(H9N2) neuraminidase	DQ116071.1
A/turkey/Emek Hefer/1272/03(H9N2) hemagglutinin	DQ104475.1
A/turkey/Ein Habsor/1804/04(H9N2) hemagglutinin	DQ108924.1
A/turkey/Ein Tzurim/1172/02(H9N2) hemagglutinin	DQ104451.1
A/turkey/Ein Tzurim/1738/04(H9N2) hemagglutinin	DQ108920.1
A/turkey/Ein_Tzurim/1738/04(H9N2) neuraminidase	DQ116085.1
A/turkey/Gyvat Haim Ehud/1544/03(H9N2)hemagglutinin	DQ108913.1
A/turkey/Givat Haim/810/01 (H9N2) hemagglutinin	DQ104466.1
A/turkey/Givat Haim/810/01 (H9N2) nucleoprotein	DQ116526.1
A/turkey/Givat Haim/868/02(H9N2) hemagglutinin	DQ104471.1
A/turkey/Givat Haim/622/02(H9N2) hemagglutinin	DQ104462.1
A/turkey/Givat_Haim/965/02(H9N2) nucleoprotein	DQ116498.1
A/turkey/Gyvat_Haim_Ehud/1544/03(H9N2) nucleoprotein	DQ116513.1
A/turkey/Gyvat_Haim_Ehud/1544/03(H9N2) neuraminidase	DQ116082.1
A/tk/Givat_Haim/810/25.12.01(H9N2) neuraminidase	DQ116063.1
A/turkey/Givat_Haim/622/02(H9N2)) neuraminidase	DQ116060.1
A/turkey/Givat_Haim/965/02(H9N2) neuraminidase	DQ116057.1
A/turkey/Hod_Ezyon/699/02(H9N2) neuraminidase	DQ116062.1
A/turkey/Mishmar Hasharon/619/02 (H9N2) hemagglutinin	DQ104461.1
A/turkey/Mishmar_Hasharon/619/02(H9N2) neuraminidase	DQ116059.1
A/turkey/Kfar_Vitkin/616/02(H9N2) neuraminidase	DQ116058.1
A/turkey/Kfar Vitkin/616/02 (H9N2) hemagglutinin	DQ104460.1
A/turkey/Kfar Vitkin/615/02 (H9N2)hemagglutinin	DQ104459.1
A/turkey/Kfar Vitkin/615/02 (H9N2) nucleoprotein	DQ116520.1
A/turkey/Kfar_Vitkin/616/02(H9N2)) nucleoprotein	DQ116521.1
A/turkey/Kfar Warburg/1224/03(H9N2) hemagglutinin	DQ104455.1
A/tk/Kfar_Vitkin/615/02(H9N)) neuraminidase	DQ116067.1
A/turkey/Mishmar_Hasharon/619/02(H9N2) nucleoprotein	DQ116522.1
A/turkey/Naharia/1013/02(H9N2) hemagglutinin	DQ104449.1
A/turkey/Nahalal/1547/04(H9N2) hemagglutinin	DQ108932.1
A/turkey/Neve Ilan/90710/00 (H9N2) nucleoprotein	DQ116529.1
A/tk/Neve_Ilan/90710/00(H9N2) neuraminidase	DQ116066.1
A/turkey/Qevuzat_Yavne/1242/03(H9N2) neuraminidase	DQ116086.1
A/turkey/Sapir/1199/02(H9N2) hemagglutinin	DQ104452.1
A/turkey/Shadmot Dvorah/1567/04(H9N2) nucleoprotein	DQ116518.1
A/turkey/Shadmot Dvorah/1567/04(H9N2) hemagglutinin	DQ108918.1
A/turkey/Tzur Moshe/1565/04(H9N2) nucleoprotein	DQ116516.1
A/turkey/Tzur Moshe/1565/04(H9N2) hemagglutinin	DQ108916.1
A/turkey/Yedidia/625/02 (H9N2) hemagglutinin	DQ104463.1
A/turkey/Yedidia/625/02 (H9N2) nucleoprotein	DQ116523.1

Strain/Protein	GenBank Access No.
A/turkey/Yedidia/625/02 (H9N2) neuraminidase	DQ116061.1
A/turkey/Yedidia/911/02 (H9N2) hemagglutinin	DQ104448.1
A/turkey/Avigdor/1215/03 (H9N2) hemagglutinin	DQ104454.1
A/turkey/Avigdor/1209/03 (H9N2) hemagglutinin	DQ104453.1
A/turkey/Avichail/1075/02 (H9N2) hemagglutinin	DQ104450.1
A/turkey/Avigdor/1920/04 (H9N2) hemagglutinin	DQ108926.1
A/pintail/Alberta/49/2003 (H9N5) matrix protein 1 (M) and matrix protein 2 (M)	DQ107498.1
A/red knot/Delaware/2552/87 (H9N5) nonfunctional matrix protein	AY664472.1
A/duck/Hong Kong/147/77 (H9N6) hemagglutinin precursor	AY206671.1
A/shorebird/Delaware/270/2001 (H9N7) matrix protein 1 (M) and matrix protein 2 (M)	DQ107504.1
A/shorebird/Delaware/277/2000 (H9N7) matrix protein 1 (M) and matrix protein 2 (M)	DQ107507.1
A/shorebird/Delaware/275/2001 (H9N7) matrix protein 2 (M) and matrix protein 1 (M)	DQ107506.1
A/ruddy turnstone/Delaware/116/98 (H9N8) nonfunctional matrix protein	AY664435.1
A/shorebird/Delaware/141/2002 (H9N9) matrix protein 1 (M) and matrix protein 2 (M)	DQ107503.1
A/ruddy turnstone/Delaware/103/2002 (H9N9) matrix protein 1 (M) and matrix protein 2 (M)	DQ107502.1
A/shorebird/Delaware/29/2002 (H9N9) matrix protein 1 (M) and matrix protein 2 (M)	DQ107501.1
A/shorebird/Delaware/18/2002 (H9N9) matrix protein 1 (M) and matrix protein 2 (M)	DQ107500.1
A/ruddy turnstone/Delaware/259/98 (H9N9) nonfunctional matrix protein	AY664469.1
A/duck/Eastern China/527/2003 (H10N3) segment 6 neuraminidase (NA)	EU429716.1
A/duck/Eastern China/495/2003 (H10N3) segment 6 neuraminidase (NA)	EU429715.1
A/duck/Eastern China/372/2003 (H10N3) segment 6 neuraminidase (NA)	EU429714.1
A/duck/Eastern China/488/2003 (H10N3) segment 6 neuraminidase (NA)	EU429712.1
A/duck/Eastern China/453/2002 (H10N3) segment 6 neuraminidase (NA)	EU429711.1
A/duck/Eastern China/412/2003 (H10N3) segment 6 neuraminidase (NA)	EU429710.1
A/duck/Eastern China/404/2003 (H10N3) segment 6 neuraminidase (NA)	EU429709.1
A/duck/Eastern China/397/2003 (H10N3) segment 6 neuraminidase (NA)	EU429708.1
A/duck/Eastern China/502/2003 (H10N3) segment 6 neuraminidase (NA)	EU429705.1
A/duck/Eastern China/395/2003 (H10N3) segment 6 neuraminidase (NA)	EU429704.1
A/duck/Eastern China/356/2003 (H10N3) segment 6 neuraminidase (NA)	EU429703.1
A/duck/Eastern China/368/2003 (H10N3) segment 6 neuraminidase (NA)	EU429702.1
A/chicken/Singapore/1993 (H10N5) M2 protein	EU014145.1
A/red knot/Delaware/2561/87 (H10N5) nonfunctional matrix protein	AY664441.1
A/chicken/Germany/N/1949 (H10N7) segment 6 neuraminidase (NA)	EU429796.1

Strain/Protein	GenBank Access No.
A/ruddy turnstone/Delaware/2764/87 (H10N7) nonfunctional matrix protein	AY664462.1
A/mallard/Alberta/71/98 (H10N7) nonfunctional matrix protein	AY664485.1
A/mallard/Alberta/90/97 (H10N7) nonfunctional matrix protein	AY664446.1
A/mallard/Alberta/110/99 (H10N7) nonfunctional matrix protein	AY664481.1
A/mallard/Alberta/297/77 (H10N7) nonfunctional matrix protein	AY664430.1
A/mallard/Alberta/223/98 (H10N8) nonfunctional matrix protein	AY664486.1
A/ruddy turnstone/New Jersey/51/85 (H11N1) nonfunctional matrix protein	AY664479.1
A/duck/Nanchang/1749/1992 (H11N2) nucleoprotein (NP)	U49094.1
A/duck/Hong Kong/62/1976 (H11N2) polymerase (PB1)	U48280.1
A/duck/Yangzhou/906/2002 (H11N2) hemagglutinin	DQ080993.1
A/shorebird/Delaware/86/99 (H11N2) nonfunctional matrix protein	AY664463.1
A/ruddy turnstone/Delaware Bay/2762/1987 (H11N2) polymerase PB2 (PB2)	CY126279.1
A/ruddy turnstone/Delaware/2762/87 (H11N2) nonfunctional matrix protein	AY664459.1
A/ruddy turnstone/Delaware Bay/2762/1987 (H11N2) polymerase PB1 (PB1) and PB1-F2 protein (PB1-F2)	CY126278.1
A/ruddy turnstone/Delaware/2589/87 (H11N4) nonfunctional matrix protein	AY664478.1
A/duck/England/1/1956 (H11N6) segment 6 neuraminidase (NA)	EU429795.1
A/mallard/Alberta/125/99 (H11N6) nonfunctional matrix protein	AY664483.1
A/duck/Memphis/546/1974 (H11N9) segment 6 neuraminidase (NA)	EU429798.1
A/mallard/Alberta/122/99 (H11N9) nonfunctional matrix protein	AY664444.1
A/Mallard Duck/Alberta/342/83 (H12N1) segment 4 hemagglutinin (HA1)	AF310991.1
A/ruddy turnstone/Delaware/67/98 (H12N4) nonfunctional matrix protein	AY664470.1
A/Ruddy Turnstone/Delaware/67/98 (H12N4) segment 4 hemagglutinin (HA1)	AF310990.1
A/mallard/Alberta/52/97 (H12N5) nonfunctional matrix protein	AY664448.1
A/mallard/Alberta/223/77 (H12N5) nonfunctional matrix protein	AY664431.1
A/Laughing Gull/New Jersey/171/92 (H12N5) segment 4 hemagglutinin (HA1)	AF310992.1
A/ruddy turnstone/Delaware/265/98 (H12N8) nonfunctional matrix protein	AY664438.1
A/herring gull/New Jersey/782/86 (H13N2) nonfunctional matrix protein	AY664475.1
A/shorebird/Delaware/224/97 (H13N6) nonfunctional matrix protein	AY664421.1
A/PR/8/34 (H1N1) x A/England/939/69 (H3N2) PB1 protein	AJ564806.1
A/PR/8/34 (H1N1) x A/England/939/69 (H3N2) PB2 protein	AJ564804.1
A/duck/Czechslovakia/56 (H4N6) x A/USSR/90/77 (H1N1)) neuraminidase (NA)	EU643639.1
A/duck/Czechslovakia/56 (H4N6) x A/USSR/90/77 (H1N1)) neuraminidase (NA)	EU643638.1
A/duck/Ukraine/63 (H3N8) x A/USSR/90/77 (H1N1)) neuraminidase (NA)	EU643637.1
A/duck/Ukraine/63 (H3N8) x A/USSR/90/77 (H1N1)) neuraminidase (NA)	EU643636.1
RCB1-XXI: A/USSR/90/77 (H1N1) x A/Duck/Czechoslov 56 (H4N6) segment 4 hemagglutinin	AF290438.1

Strain/Protein	GenBank Access No.
RCB1: A/USSR/90/77(H1N1)xA/Duck/Czechoslov 56 (H4N6) hemagglutinin	AF290437.1
PX14-XIII (A/USSR/90/77(H1N1)xA/Pintail Duck/Primorie/695/76(H2N3)) segment 4 hemagglutinin	AF290442.1
PX14(A/USSR/90/77(H1N1)xA/Pintail Duck/Primorie/695/76(H2N3)) segment 4 hemagglutinin	AF290441.1
PX8-XIII(A/USSR/90/77(H1N1)xA/Pintail Duck/Primorie/695/76(H2N3)) segment 4 hemagglutinin	
PX8(A/USSR/90/77(H1N1)xA/Pintail Duck/Primorie/695/76(H2N3)) segment 4 hemagglutinin	AF290439.1
A/swine/Schleswig-Holstein/1/93 hemagglutinin (HA)	U72669.1
A/swine/England/283902/93 hemagglutinin (HA)	U72668.1
A/swine/England/195852/92 hemagglutinin (HA)	U72667.1
A/swine/England/117316/86 hemagglutinin (HA)	U72666.1
A/turkey/Germany/2482/90) hemagglutinin (HA)	U96766.1

Table 12. Influenza B Antigens

Strain/Protein	GenBank Access No.
B/Daeku/47/97 hemagglutinin	AF521237.1
B/Daeku/45/97 hemagglutinin	AF521236.1
B/Daeku/10/97 hemagglutinin	AF521221.1
B/Daeku/9/97 hemagglutinin	AF521220.1
B/Gyeonggi/592/2005 neuraminidase	DQ231543.1
B/Gyeonggi/592/2005 hemagglutinin	DQ231538.1
B/Hong Kong/5/72 neuraminidase	AF305220.1
B/Hong Kong/5/72 hemagglutinin	AF305219.1
B/Hong Kong/157/99 hemagglutinin	AF387503.1
B/Hong Kong/157/99 hemagglutinin	AF387502.1
B/Hong Kong/156/99 hemagglutinin	AF387501.1
B/Hong Kong/156/99 hemagglutinin	AF387500.1
B/Hong Kong/147/99 hemagglutinin	AF387499.1
B/Hong Kong/147/99 hemagglutinin	AF387498.1
B/Hong Kong/110/99 hemagglutinin	AF387497.1
B/Hong Kong/110/99 hemagglutinin	AF387496.1
B/Incheon/297/2005 hemagglutinin	DQ231539.1
B/Incheon/297/2005 neuraminidase	DQ231542.1
B/Lee/40 polymerase protein (PB1)	D00004.1
B/Michigan/22572/99 hemagglutinin	AY129961.1
B/Michigan/22723/99 hemagglutinin (HA)	AY112992.1
B/Michigan/22631/99 hemagglutinin (HA)	AY112991.1
B/Michigan/22587/99 hemagglutinin (HA)	AY112990.1
B/New York/20139/99 hemagglutinin	AY129960.1
B/Panama/45/90 nucleoprotein	AF005739.1
B/Panama/45/90 polymerase (PA)	AF005738.1
B/Panama/45/90 polymerase (PB2)	AF005737.1
B/Panama/45/90 polymerase (PB1)	AF005736.1

Strain/Protein	GenBank Access No.
B/Pusan/250/99 hemagglutinin	AF521218.1
B/Pusan/255/99 hemagglutinin	AF521226.1
B/Pusan/270/99 hemagglutinin	AF521219.1
B/Pusan/285/99 hemagglutinin	AF521217.1
B/Riyadh/01/2007 segment 8 nuclear export protein (NEP) and non structural protein 1 (NS1)	GU135839.1
B/Seoul/6/88 hemagglutinin	AF521238.1
B/Seoul/12/88 hemagglutinin	AF521239.1
B/Seoul/1/89 hemagglutinin	AF521230.1
B/Seoul/37/91 hemagglutinin	AF521229.1
B/Seoul/38/91 hemagglutinin	AF521227.1
B/Seoul/40/91 hemagglutinin	AF521235.1
B/Seoul/41/91 hemagglutinin	AF521228.1
B/Seoul/13/95 hemagglutinin	AF521225.1
B/Seoul/12/95 hemagglutinin	AF521223.1
B/Seoul/17/95 hemagglutinin	AF521222.1
B/Seoul/21/95 hemagglutinin	AF521224.1
B/Seoul/16/97 hemagglutinin	AF521233.1
B/Seoul/19/97 hemagglutinin	AF521231.1
B/Seoul/28/97 hemagglutinin	AF521234.1
B/Seoul/31/97 hemagglutinin	AF521232.1
B/Seoul/232/2004 neuraminidase	DQ231541.1
B/Seoul/1163/2004 neuraminidase	DQ231540.1
B/Seoul/1163/2004 hemagglutinin	DQ231537.1
B/Sichuan/379/99 hemagglutinin (HA)	AF319590.1
B/Sichuan/38/2000 hemagglutinin (HA)	AF319589.1
B/South Carolina/25723/99 hemagglutinin	AY129962.1
B/Switzerland/4291/97 hemagglutinin	AF387505.1
B/Switzerland/4291/97 hemagglutinin	AF387504.1
B/Taiwan/21706/97 nonstructural protein 1 (NS1)	AF492479.1
B/Taiwan/21706/97 hemagglutinin (HA)	AF026162.1
B/Taiwan/3143/97 nonstructural protein 1 (NS1)	AF492478.1
B/Taiwan/3143/97 haemagglutinin (HA)	AF026161.1
B/Taiwan/2026/99 nonstructural protein 1 (NS1)	AF492481.1
B/Taiwan/2026/99 hemagglutinin	AY604741.1
B/Taiwan/2027/99 nonstructural protein 1 (NS1)	AF492480.1
B/Taiwan/2027/99 hemagglutinin	AY604742.1
B/Taiwan/1243/99 nonstructural protein NS1(NS1)	AF380504.1
B/Taiwan/1243/99 hemagglutinin	AY604740.1
B/Taiwan/2195/99 hemagglutinin	AY604743.1
B/Taiwan/2195/99 nonstructural protein 1 (NS1)	AF492482.1
B/Taiwan/1293/2000 nonstructural protein NS1(NS1)	AF380509.1
B/Taiwan/1293/00 hemagglutinin	AY604746.1
B/Taiwan/1293/2000 hemagglutinin (HA)	AF492477.1
B/Taiwan/1265/2000 nonstructural protein NS1 (NS1)	AF380508.1

Strain/Protein	GenBank Access No.
B/Taiwan/1265/00 hemagglutinin	AY604745.1
B/Taiwan/4184/2000 nonstructural protein NS1 (NS1)	AF380507.1
B/Taiwan/4184/00 hemagglutinin (HA)	AY604750.1
B/Taiwan/31511/2000 nonstructural protein NS1 (NS1)	AF380505.1
B/Taiwan/31511/00 hemagglutinin (HA)	AY604748.1
B/Taiwan/12192/2000 hemagglutinin	AY604747.1
B/Taiwan/41010/00 hemagglutinin (HA)	AY604749.1
B/Taiwan/41010/2000 nonstructural protein NS1 (NS1)	AF380506.1
B/Taiwan/0409/00 hemagglutinin (HA)	AY604744.1
B/Taiwan/202/2001 nonstructural protein 1 (NS1)	AF380512.1
B/Taiwan/202/2001 hemagglutinin (HA)	AF366076.1
B/Taiwan/11515/2001 nonstructural protein 1 (NS1)	AF380511.1
B/Taiwan/11515/01 hemagglutinin	AY604754.1
B/Taiwan/11515/2001 hemagglutinin (HA)	AF366075.1
B/Taiwan/1103/2001 nonstructural protein NS1 (NS1)	AF380510.1
B/Taiwan/1103/01 hemagglutinin	AY604755.1
B/Taiwan/114/2001 hemagglutinin (HA), HA-4 allele	AF492476.1
B/Taiwan/2805/2001 hemagglutinin (HA)	AF400581.1
B/Taiwan/2805/01 hemagglutinin (HA)	AY604752.1
B/Taiwan/0114/01 hemagglutinin (HA)	AY604753.1
B/Taiwan/0202/01 hemagglutinin (HA)	AY604751.1
B/Taiwan/4119/02 hemagglutinin (HA)	AY604778.1
B/Taiwan/4602/02 hemagglutinin (HA)	AY604777.1
B/Taiwan/1950 /02 hemagglutinin (HA)	AY604776.1
B/Taiwan/1949/02 hemagglutinin (HA)	AY604775.1
B/Taiwan/1584 /02 hemagglutinin (HA)	AY604774.1
B/Taiwan/1561 /02 hemagglutinin (HA)	AY604773.1
B/Taiwan/ 1536/02 hemagglutinin (HA)	AY604772.1
B/Taiwan/1534 /02 hemagglutinin (HA)	AY604771.1
B/Taiwan/1503 /02 hemagglutinin (HA)	AY604770.1
B/Taiwan/1502/02 hemagglutinin (HA)	AY604769.1
B/Taiwan/1013 /02 hemagglutinin (HA)	AY604768.1
B/Taiwan/0993 /02 hemagglutinin (HA)	AY604766.1
B/Taiwan/0932 /02 hemagglutinin (HA)	AY604765.1
B/Taiwan/0927/02 hemagglutinin (HA)	AY604764.1
B/Taiwan/0880 /02 hemagglutinin (HA)	AY604763.1
B/Taiwan/0874/02 hemagglutinin (HA)	AY604762.1
B/Taiwan/0730 /02 hemagglutinin (HA)	AY604761.1
B/Taiwan/0722/02 hemagglutinin (HA)	AY604760.1
B/Taiwan/0702 /02 hemagglutinin (HA)	AY604759.1
B/Taiwan/0654/02 hemagglutinin (HA)	AY604758.1
B/Taiwan/0600/02 hemagglutinin (HA)	AY604757.1
B/Taiwan/0409 /02 hemagglutinin (HA)	AY604756.1
B/Taiwan/0879/02 nonfunctional hemagglutinin	AY604767.1

Strain/Protein	GenBank Access No.
B/Taiwan/ 3532/03 hemagglutinin (HA)	AY604794.1
B/Taiwan/2551 /03 hemagglutinin (HA)	AY604793.1
B/Taiwan/ 1618/03 hemagglutinin (HA)	AY604792.1
B/Taiwan/ 1574/03 hemagglutinin (HA)	AY604791.1
B/Taiwan/1013 /03 hemagglutinin (HA)	AY604790.1
B/Taiwan/0833 /03 hemagglutinin (HA)	AY604789.1
B/Taiwan/0735 /03 hemagglutinin (HA)	AY604788.1
B/Taiwan/0699/03 hemagglutinin (HA)	AY604787.1
B/Taiwan/0684/03 hemagglutinin (HA)	AY604786.1
B/Taiwan/0616 /03 hemagglutinin (HA)	AY604785.1
B/Taiwan/0615 /03 hemagglutinin (HA)	AY604784.1
B/Taiwan/0610 /03 hemagglutinin (HA)	AY604783.1
B/Taiwan/0576 /03 hemagglutinin (HA)	AY604782.1
B/Taiwan/0569/03 hemagglutinin (HA)	AY604781.1
B/Taiwan/0562/03 hemagglutinin (HA)	AY604780.1
B/Taiwan/0002 /03 hemagglutinin (HA)	AY604779.1
B/Taiwan/773/2004 hemagglutinin (HA)	EU068195.1
B/Taiwan/187/2004 hemagglutinin (HA)	EU068194.1
B/Taiwan/3892/2004 hemagglutinin (HA)	EU068193.1
B/Taiwan/562/2004 hemagglutinin (HA)	EU068191.1
B/Taiwan/234/2004 hemagglutinin (HA)	EU068188.1
B/Taiwan/4897/2004 hemagglutinin (HA)	EU068186.1
B/Taiwan/8579/2004 hemagglutinin (HA)	EU068184.1
B/Taiwan/184/2004 hemagglutinin (HA)	EU068183.1
B/Taiwan/647/2005 hemagglutinin (HA)	EU068196.1
B/Taiwan/877/2005 hemagglutinin (HA)	EU068198.1
B/Taiwan/521/2005 hemagglutinin (HA)	EU068189.1
B/Taiwan/1064/2005 hemagglutinin (HA)	EU068192.1
B/Taiwan/3722/2005 hemagglutinin (HA)	EU068197.1
B/Taiwan/5049/2005 hemagglutinin (HA)	EU068190.1
B/Taiwan/5011/2005 hemagglutinin (HA)	EU068187.1
B/Taiwan/4659/2005 hemagglutinin (HA)	EU068185.1
B/Taiwan/25/2005 hemagglutinin (HA)	EU068182.1
B/Taiwan/1037/2005 hemagglutinin (HA)	EU068181.1
B/Taiwan/62/2005 hemagglutinin (HA)	EU068180.1
B/Taiwan/591/2005 hemagglutinin (HA)	EU068179.1
B/Taiwan/649/2005 hemagglutinin (HA)	EU068178.1
B/Taiwan/4554/2005 hemagglutinin (HA)	EU068177.1
B/Taiwan/987/2005 hemagglutinin (HA)	EU068176.1
B/Taiwan/2607/2006 hemagglutinin (HA)	EU068175.1
B/Vienna/1/99 hemagglutinin	AF387495.1
B/Vienna/1/99 hemagglutinin	AF387494.1
B/Vienna/1/99 hemagglutinin	AF387493.1
B/Vienna/1/99 hemagglutinin	AF387492.1

Table 13. Influenza C Antigens

Strain/Protein	GenBank Access No.
C/JHB/1/66) hemagglutinin-esterase-fusion protein (HEF) mRNA, complete cds.	AY880247.1
STRAIN C/ANN ARBOR/1/50) persistent variant segment 7 non-structural protein 1 (NS1) mRNA, complete cds	AF102027.1
(STRAIN C/ANN ARBOR/1/50) wild type segment 7 non-structural protein 1 (NS1) mRNA, complete cds	AF102026.1
(C/JHB/1/66) hemagglutinin-esterase-fusion protein (HEF) mRNA, complete cds	AY880247.1
(STRAIN C/BERLIN/1/85) mRNA for basic polymerase 2 precursor	X55992.1

Table 14: H7 Hemagglutinin Amino Acid Sequences

Accession No / Strain / Protein	Amino Acid Sequence	SEQ ID NO:
AAM19228 A/turkey/Minnesota/38429/1988 1988// HA 20335017	ACVLVEAKGDKICLGHHAVVNGTKVNTLTEKGIEVVNATETVETANIGKICTQGKRPTDLGQCGLLGTIGPPQCDQFLEFESDLIIERR EGNDVCYPGKFTNEESLRQILRGSGGIDKESMGFTYSGIITNGAT SACRRSGSSFYAEMKWLLSNSDNAAFPQMTKSYRNP RNPALIVWGIHHSGSTTEQTKLYGSGNKLITVGSSNYQQSFVPS PGARPQVNGQSGRIDFHWMLLDPNPNDTVTFNNGAFIAPDRASFFK GESLGVQSDVPLDSSCGGDCFHSGGTIVSSLPFQININPRTVGKCP RYVKQPSLLLATGMRNVPENPKTRGLFGAIAGFIEKDGGSHYG	1
AAY46211 A/mallard/Sweden/91/2002 2002// HA 66394828	MNTQILVFALVAIIPINADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNPVPRICSRGKRTVDLGQCGLLGTITGPPQCDQFLEF SADLIIERREGSDVCYPGKFVNEEALRQILRESGGIDKETMGFTY SGIRTNGAPSACRRSGSSFYAEMKWLLSNTDNAAFPQMTKSYKNT RNDPALIIWGIHHSGSTTEQTKLYGSGNKLITVGSSNYQQSFVPS PGARPQVNGQSGRIDFHWMLLDPNPNDTVTFNNGAFIAPDRASFLR GKSMGIQSGVQIDANCEGDCYHSGGTIISNLPFQININRAVVGKCP RYVKQESLLLATGMRNVPENPKTRGLFGAIAGFIEGWEGLIDGW YGFRRHQAQGEQTAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFTEVEKQIGNVINWTRDSMTEVWSYNAELLVAMENQHTIDLA DSEMKNLYERVRRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASC FILLAIAMGLVFMCMVKNNGNMRCTICI	2
ABI84694 A/turkey/Minnesota/1/1988 1988/07/13 HA 115278573	MNTQILVFIACVLVEAKGDKICLGHHAVVNGTKVNTLTEKGIEVV NATETVETANIGKICTQGKRPTDLGQCGLLGTIGPPQCDQFLEF ESDLIIERRREGNDVCYPGKFTNEESLRQILRGSGGIDKESMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNSDNAAFPQMTKSYRNP RNPALIVWGIHHSGSTTEQTKLYGSGNKLITVGSSKYQQSFTPS PGARPQVNGQSGRIDFHWMLLDPNPNDTVTFNNGAFIAPDRASFFK GESLGVQSDVPLDSSCGGDCFHSGGTIVSSLPFQININPRTVGKCP RYVKQPSLLLATGMRNVPENPKTRGLFGAIAGFIEGWEGLIDGW YGFKHQAQGEQTAADYKSTQSAIDQITGKLNRLIDKTNQQFELI DNEFSEIEQQIGNVINWTRDSMTEVWSYNAELLVAMENQHTIDLA DSEMKNLYERVRRQLRENAEEDGTGCFEIFHKCDDQCMESIRNNT YDHAQYRAESLQNRIQIDPVKLSSGYKDIILWFSFGASC FLLLAIAMGLVFICIKNNGNMRCTICI	3

Accession No / Strain / Protein	Amino Acid Sequence	SEQ ID NO:
ABS89409 A/blue-winged teal/Ohio/566/ 2006 2006// HA 155016324	MNTQILALIAACMLIGAKGDKICLGHHAVANGTKVNTLTERGIEVV NATETVETANIKKICTQGKRPTDLGQCGLLGTLLIGPPQCDQFLEF DTDLLIERREGTDVCYPGKFTNEESLRQILRGSGGIDKESMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNSDNAAFPQMTKSYRNP RNKPALIIWGVHHS GSATEQTKLYGSGNKLITVGSSKYQQSFTPS PGARPQVNGQSGRIDFHWLLLDPN DTVTFTFN GAFIAPDRASFFR GESLGVQSDVPLDSGCEGDCFHSGGTIVSSLPFQNI NPRTV GKCP RYVKQTSLLLATGMRNVPENPKTRGLFGA IAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRLIDKTNQQFELI DNEFSEIEQQIGNVINWTRDSMTEVWSYNAELLVAMENQHTIDLA DSEMKNKLYERVRKQLRENAEEDGTGCFEIFHKCDDQCMESIRNNT YDHTQYRTESLQNRIQIDPVRLSSGYKDIILWFSFGASCFLLLAI AMGLVFICIKNGNMRCTICI	4
ACD03594 A/ruddy turnstone/DE/1 538/2000 2000// HA 187384848	MNTQILAFIACMLVGVRGDKICLGHHAVANGTKVNTLTEKGIEVV NATETVESANIKKICTQGKRPTDLGQCGLLGTLLIGPPQCDQFLEF DSDLIIERREGTDVCYPGKFTNEESLRQILRGSGGIDKESMGFTY SGIRTNGATSACRRLGSSFYAEMKWLLSNSDNAAFPQMTKSYRNP RNKPALIIWGVHHS GSANEQTKLYGSGNKLITVGSSKYQQSFTPS PGARPQVNGQSGRIDFHWLLLDPN DTVTFTFN GAFIAPDRASFFR GESLGIQSDVPLDSSCGGDCFHSGGTIVSSLPFQNI NPRTV GKCP RYVKQTSLLLATGMRNVPENPKTRGLFGA IAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRLIDKTNQQFELM DNEFNEIEQQIGNVINWTRDSMTEVWSYNAELLVAMENQHTIDLA DSEMKNKLYERVRKQLRENAEEDGTGCFEIFHKCDDQCMESIRNNT YDHTQYRTESLQNRIQIDPVKLSSGYKDIILWFSFGASCFLLLAI AMGLIFICIKNGNMRCTICI	5
BAH22785 A/duck/Mongoli a/119/2008 2008// HA 223717820	MNTQILVFALVAIIPTNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKRTVDLGQCGLLGTITGPPQCDQFLEF SADLIIERREGSDVCYPGKFVN EEARLQILRESGGIGKETMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNTDNAAFPQMTKSYKNT RKDPALIIWGIHHS GSTTEQTKLYGSGNKLITVGSSNYQQSFVPS PGARPQVNGQSGRIDFHWLMLNPNDTVTFSFN GAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHNGGTII SNLPFQNI NSRTV GKCP RYVKQESLLLATGMKNVPEIPKGRGLFGA IAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRLIERTNQQFELI DNEFTEVEKQIGNVINWTRDSMTEVWSYNAELLVAMENQHTIDLA DSEMKNKLYERVRKQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSNGYKDVILWFSFGASC FILLAI AMGLVFICVKNGNMRCTICI	6
CAY39406 A/Anas crecca/Spain/1 460/2008 2008/01/26 HA 254674376	MNTQILVFALVAIIPTNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNVPRICSKGKRTVDLGQCGLLGTITGPPQCDQFLEF SADLIIERREGSDVCYPGKFVN EEARLQILRESGGIDKETMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNTDNAAFPQMTKSYKNT RKDPALIIWGIHHS GSTTEQTKLYGSGSKLITVGSSNYQQSFVPS PGARPQVNGQSGRIDFHWLMLNPNDTVTFSFN GAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTII SNLPFQNI NSRAV GKCP RYVKQESLMLATGMKNVPEIPKGRGLFGA IAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFTEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMKNKLYERVRKQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSNGYKDVILWFSFGASC FILLAI AMGLVFICVKNGNMRCTICI	7

Accession No / Strain / Protein	Amino Acid Sequence	SEQ ID NO:
ACX53683 A/goose/Czech Republic/1848- K9/2009 2009/02/04 HA 260907763	MNIQILVFALVAIIPTNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNVPRICSKGKRTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERRGGSDVCYPGKFTVNEEALRQILRGSGGIDKETMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNSDNAAFPQMTKSYKNT RKDPALIIWGIHHSGSTTEQTKLYGSGSKLITVGSSNYQQSFVPS PGARPQVNGQSGRIDFHWMLNPNNDTVTFNNGAFIAPDRASFLK GKSMGIQSGVQVDANCEGDCYHSGGTIIISNLPFQININRAVGKCP RYVKQESLMLATGMKNVPELPKGRGLFGAIIAGFIENGWEGLIDGW YGFRHQNAQGEETAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFTEVEKQIGNVINWTRDSMTEVWSYNAELLVAMENQHTIDLA DSEMKNKLYERVKRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQINPVKLSSGYKDVILWFSFGASCFILLAI AMGLVFICVKNNGNMRCTICI	8
ACZ48625 A/turkey/Minne sota/38429/198 8 1988// HA 269826341	MNTQILVFIACVLVEAKGDKICLGHHAVVNGTKVNTLTEKGIEVV NATETVETANIGKICTQGKRPTDLGQCGLLGTLIGPPQCDQFLEF ESDLIIERREGNDVCYPGKFTNEESLRQILRGSGGIDKESMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNSDNAAFPQMTKSYRNP RNKPALIVWGIHHSGSTTEQTKLYGSGNKLITVGSSKYQQSFTPS PGARPQVNGQSGRIDFHWMLLDPNNDTVTFNNGAFIAPDRASFFK GESLGVQSDVPLDSSCGGDCFHSGGTIVSSLPFQININPRTVKGKCP RYVKQPSLLLATGMRNVPENPKTRGLFGAIIAGFIENGWEGLIDGW YGFKHQNAQGEETAADYKSTQSAIDQITGKLNRLIDKTNQQFEL	9
ADC29485 A/mallard/Spai n/08.00991.3/2 005 2005/11/ HA 284927336	STQSAIDQITGKLNRLIEKTNQQFELIDNEFTEVEKQIGNVINWT RDSMTEVWSYNAELLVAMENQHTIDLADSEMKNKLYERVKRQLREN AEEDGTGCFEIFHKCDDDCMASIRNNTYDHSKYREEAMQNRIQID PVKLSSGYKDVILWFSFGASCFILL	10
ADK71137 A/blue-winged teal/Guatemala /CIP049- 01/2008 2008/02/07 HA 301333785	MNTQILALIAACMLIGAKGDKICLGHHAVANGTKVNTLTERGIEVV NATETVETANIKKICTQGKRPTDLGQCGLLGTLIGPPQCDQFLEF DADLIIERREGTDVCYPGKFTNEESLRQILRGSGGIDKESMGFTY SGIRTNGATSACRRSGSSSYAEMKWLLSNSDNAAFPQMTKSYRNP RNKPALIIWGVHHSGSATEQTKLYGSGNKLITVGSSKYQQSFTPS PGTRPQVNGQSGRIDFHWMLLDPNNDTVTFNNGAFIAPDRASFLR GKSLGIQSDVPLDSGCEGDCFHSGGTIVSSLPFQININPRTVKGKCP RYVKQTSLLLATGMRNVPENPKTRGLFGAIIAGFIENGWEGLIDGW YGFRHQNAQGEETAADYKSTQSAIDQITGKLNRLIDKTNQHFELI DNEFSEIEQQIGNVINWTRDSMTEVWSYNAELLVAMENQHTIDLA DSEMKNKLYERVKRQLRENAEEDGTGCFEIFHKCDDQCMESIRNNT YDHTQYRTESLQNRIQIDPVKLSSGYKDIIILWFSFGASCFLLLAI AMGLVFICIKNGNMRCTICI	11
ADK71148 A/blue-winged teal/Guatemala /CIP049- 02/2008 2008/03/05 HA 301333804	MNTQILALIAACMLIGAKGDKICLGHHAVANGTKVNTLTERGIEVV NXTETVETANIKKICTHGRPTDLGQCGLLGTLIGPPQCDRFLEF DADLIIERREGTDVCYPGKFTNEESLRQILRGSGGIDKESMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNSDNAAFPQMTKSYRNP RNKPALIIWGVHHSGSATEQTKLYGSGNKLITVGSSKYQQSFTPS PGTRPQVNGQSGRIDFHWMLLDPNNDTVTFNNGAFIAPDRASFLR GKSLGIQSDVPLDSGCEGDCFHSGGTIVSSLPFQININPRTVKGKCP RYVKQTSLLLATGMRNVPENPKTRGLFGAIIAGFIENGWEGLIDGW YGFRHQNAQGEETAADYKSTQSAIDQITGKLNRLIDKTNQQFELI DNEFSEIEQQIGNVINWTRDSMTEVWSYNAELLVAMENQHTIDLA DSEMKNKLYERVKRQLRENAEEDGTGCFEIFHKCDDQCMESIRNNT YDHTQYRTESLQNRIQIDPVKLSSGYKDIIILWFSFGASCFLLLAI AMGLVFICIKNGNMRCTICI	12

Accession No / Strain / Protein	Amino Acid Sequence	SEQ ID NO:
ADN34727 A/goose/Czech Republic/1848- T14/2009 2009/02/04 HA 307141869	MNIQILVFALVAIIPTNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNVPRICSKGKRTVDLGQCGLLGTTITGPPQCDQFLEF SADLI IERRGGSDVCYPGKFVNEEALRQILRESGGIDKETMGFTY SGIRTNGXTSACRRSGSSFYAEMKWLLSNTDNAAFPQMTKSYKNT RKDPALIIWGIHHSGSTTEQTKLYGSGSKLITVGSSNYQQSFVPS PGARPQVNGQSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLK GKSMGIQSGVQVDANCEGDCYHSGGTII SNLPFQNINSRAVGKCP RYVKQESLMLATGMKNVPELPKGRGLFGAIAGFIENGWEGLIDGW YGFRHQNAQGEETAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFTEVEKQIGNVINWTRDSMTEVWSYNAELLVAMENQHTIDLA DSEMKNLYERVQRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI AMGLVFICVKNGNMRCTICI	13
AEK84760 A/wild bird/Korea/A14 /2011 2011/02/ HA 341610308	PAFIAPDRASFLRGKSMGIQSGVQVDASCEGDCYHSGGTII SNLP FQNINSRAVGKCPRYVKQESLMLATGMKNVPELPKGRGLFGAIAG FIENGWEGLIDGWYGFRHQNAQGEETAADYKSTQSAIDQITGKLN RLIEKTNQQFELIDNEFTEVEKQIGNVINWTRDSMTEVWSYNAEL LVAMENQHTIDLADSEMKNLYERVRRQLRENAEEDGTGCFEIFHK CDDDCMASIRNNTYDHSKYREEAMQNRIQIDPVKLSSGYKDVILW FSFGASCFILLAIAMGLVFICVKNGNMRCTICI	14
AEK84761 A/wild bird/Korea/A3/ 2011 2011/02/ HA 341610310	ILVFALVAIIPTNANKIGLGHHAVSNGTKVNTLTERGVEVFNATE TVERTNVPRICSKGKKTVDLGQCGLRGTITGPPQCDQFLKFSPDL I IERQKGS DVCYPGKFVNEKPLRQILRESGGIDKETMGFAYNGIK TNGPPIACRKSGSSFYAKMKWLLSNTDKAAFPQMTKSYKNTRRNP ALIVWGIHHSGSTTKQTKLYGIGSNLITVGSSNYQQSFVPSPGAR PQVNGQSGRIDFHWLILNPNDTVTF SFNGAFIPDRASFLRGKSM GIQSGVQVDASCEGDCYHSGGTII SNLPFQNINSRAVGKCPRYVK QESLMLATGMKNVPELPKGRGLFGAIAGFIENGWEGLIDGWYGFR HQNAQGEETAADYKSTQSAIDQITGKLNRLIEKTNQQFELIDNEF TEVEKQIGNVINWTRDSMTEVWSYNAELLVAMENQHTIDLADSEM NKLYERVRRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNTYDHS KYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAIAMGL VFICVKNGNMRCTICI	15
AEK84763 A/wild bird/Korea/A9/ 2011 2011/02/ HA 341610314	ILVFALVAIIPTNANKIGLGHHAVSNGTKVNTLTERGVEFFNATE TVEPTNVPRICSKGKKTVDLGQCGLLGTTITGPPQCDQFLEFSADLI I IERREGSDVCYPGKFVNEKALRQILRESGGIDKETMGFAYSGIK TNGPPIACRKSGSSFYAKMKWLLSNTDKAAFPQMTKSYKNIRRDPA ALIVWGIHHSGSTTKQTNLYGIGSNLITVGSSNYQQSFVPSPGAR PQVNGQSGRIDFHWLILNPNDTVTF IFNGAFIAPDRASFLIGKSM GIQSGVQVDASCEGDCYHSGGTII SNLPFQNINSRAVGKCPRYVK QESLMLATGMKNVPELPKGRGLFGAIAGFIENGWEGLIDGWYGFR HQNAQGEETAADYKSTQSAIDQITGKLNRLIEKTNQQFELIDNEF TEVEKQIGNVINWTRDSMTEVWSYNAELLVAMENQHTIDLADSEM NKLYERVRRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNTYDHS KYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAIAMGL VFICVKNGNMRCTICI	16
AEK84765 A/spot-billed duck/Korea/447 /2011 2011/04/ HA 341610318	LVFALVAIIPTNADKICLGHHAVSNGTKVNTLTERGVEVVNATET VERTNVPRICSKGKRTVDLGQCGLLGTTITGPPQCDQFLEFSADLI IERREGSDVCYPGKFVNEEALRQILRESGGIDKETMGFTYSGIRT NGATSACRRSGSSFYAEMKWLLSNTDNAAFPQMTKSYKNTRRDPA LIVWGIHHSGSTTEQTKLYGSGSKLITVGSSNYQQSFVPSPGAR QVNGQSGRIDFHWLILNPNDTVTF SFNGAFIAPDRASFLRGKSMG IQSGVQVDASCEGDCYHSGGTII SNLPFQNINSRAVGKCPRYVKQ ESLMLATGMKNVPEPPKGRGLFGAIAGFIENGWEGLIDGWYGFRH QNAQGEETAADYKSTQSAIDQITGKLNRLIEKTNQQFELIDNEFT EVEKQIGNVINWTRDSMTEVWSYNAELLVAMENQHTIDLADSEM KNLYERVRRQLRENAEEDGTGCFEIFHKCDDDCMARIRNNTYDHSK YREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAIAMGLV FICVKNGNMRCTICI	17

Accession No / Strain / Protein	Amino Acid Sequence	SEQ ID NO:
AEM98291 A/wild duck/Mongolia/ 1-241/2008 2008/04/ HA 344196120	SILVFALVAIIPTNADKICLGHHAVSNGTKVNTLTERGVEVVNAT ETVERTNVPRICSKGKRTVDLGQCGLLGTITGPPQCDQFLEFSAD LIIERREGSDVCYPGKFVNEEALRQILRESGGIDKETMGFTYSGI RTNGATSACRRSGSSFYAEMKWLLSNTDNAAFPMTKSYKNTRKD PALIIWGIHHSGSTTEQTKLYGSGSKLITVGSSNYQQSFVPSGA RPQVNGQSGRIDFWLMLNPNDTVTFNFNGAFIAPDRASFLRGKS MGIQSGVQVDANCEGDCYHSGGSIISNLPFQNINSRAVGKCPRYV KQESLMLATGMKNVPELPKGRGLFGAIAAGFIENGWEGLIDGWYGF RHQNAQQEGTAADYKSTQSAIDQITGKLNRLIEKTNQQFELIDNE FTEVEKQIGNVINWTRDSMTEVWSYNAELLVAMENQHTIDLADSE MNKLYERVVRKQLRENAEEDGTGCFEIFHKCDDDCMASIRNNTYDH SKYREEAMQNRIQINPVKLSSGYKDVILWFSFGASCFILLAIAMG LVFICVKNGNMRCTI	18
AFM09439 A/emperor goose/Alaska/4 4063-061/2006 2006/05/23 HA 390535062	QILAFIACMLIGAKGDKICLGHHAVANGTKVNTLTERGIEVVNAT ETVETVNIKKICTQGKRPTDLGQCGLLGTILIGPPQCDQFLEFDAD LIIERRKGTDCYPGKFTNEESLRQILRGSGGIDKESMGFTYSGI RTNGATSACRRSGSSFYAEMKWLLSNSDNAAFPMTKSYRNPRNK PALIIWGVHHSGSATEQTKLYGSGNKLITVGSSKYQQSFVPSGA RPQVNGQSGRIDFWLMLLDPNDTVTFNFNGAFIAPERASFFRGES LGVQSDVPLDSGCEGDCFHSGGTIVSSLPFQNINPRTVGKCPRYV KQTSLLLATGMRNVPENPKTRGLFGAIAAGFIENGWEGLIDGWYGF RHQNAQQEGTAADYKSTQSAIDQITGKLNRLIDKTNQQFELIDNE FSEIEQQIGNVINWTRDSMTEVWSYNAELLVAMENQHTIDLADSE MNKLYERVVRKQLRENAEEDGTGCFEIFHKCDDQCMESIRNNTYDH TQYRTESLQNRIQINPVKLSSGYKDIILWFSFGASCFLLLAIAMG LVFICIKNGNMRCTICI	19
AFV33945 A/guinea fowl/Nebraska/ 17096-1/2011 2011/04/05 HA 409676820	MNTQILALIACMLIGAKGDKICLGHHAVANGTKVNTLTERRIE VV NATETVETANIKKICTQGKRPTDLGQCGLLGTILIGPPQCDQFLEF DADLIIERREGTDVCYPGKFTNEESLRQILRGSGGIDKESMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNSNNAAFPMTKSYRNP RNKPALIVWGVHHSGSATEQTKLYGSGSKLITVGSSKYQQSFTPS PGARPQVNGQSGRIDFWLMLLDPNDTVTFNFNGAFIAPDRASFFR GESLGVQSDVPLDSGCEGDCFHKG GTIVSSLPFQNINPRTVGKCP RYVKQTSLLLATGMRNVPENPKTRGLFGAIAAGFIENGWEGLIDGW YGFRHQNAQQEGTAADYKSTQSAIDQITGKLNRLIDKTNQQFELI DNEFSEIEQQIGNVINWTRDSMTEIWSYNAELLVAMENQHTIDLA DSEMKNKLYERVVRKQLRENAEEDGTGCFEIFHKCDDQCMESIRNNT YDHTQYRAESLQNRIQIDPVKLSSGYKDIILWFSFGASCFLLLAI AMGLVFICIKNGNMRCTICI	20
AFV33947 A/goose/Nebras ka/17097- 4/2011 2011/04/05 HA 409676827	MNTQILALIACMLIGAKGDKICLGHHAVANGTKVNTLTERGIEVV NATETVETANIKKICTQGKRPTDLGQCGLLGTILIGPPQCDQFLEF DADLIIERREGTDVCYPGKFTNEESLRQILRGSGGIDKESMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNSDNAAFPMTKSYRNP RNKPALIVWGVHHSASATEQTKLYGSGSKLITVGSSKYQQSFTPS PGARPQVNGQSGRIDFWLMLLDPNDTVTFNFNGAFIAPDRASFFR GESLGVQSDVPLDSGCEGDCFHKG GTIVSSLPFQNINPRTVGKCP RYVKQTSLLLATGMRNVPENPKTRGLFGAIAAGFIENGWEGLIDGW YGFRHQNAQQEGTAADYKSTQSAIDQITGKLNRLIDKTNQQFELI DNEFSEIEQQIGNVINWTRDSMTEIWSYNAELLVAMENQHTIDLA DSEMKNKLYERVVRKQLRENAEEDGTGCFEIFHKCDDQCMESIRNNT YDHTQYRAESLQNRIQIDPVKLSSGYKDIILWFSFGASCFLLLAI AMGLVFICIKNGNMRCTICI	21

Accession No / Strain / Protein	Amino Acid Sequence	SEQ ID NO:
AFX85260 A/ruddy turnstone/Dela ware Bay/220/1995 1995/05/21 HA 423514912	MNTQILAFIACMLIGINGDKICLGHHAVANGTKVNTLTERGIEVV NATETVETANIKRICTQGKRPIDLGQCGLLGTIGPPQCDQFLEF DSDLIIERREGTDVCYPGKFTNEESLRQILRGSGGIDKESMGFTY SGIRTNGATSACIRLGSSFYAEMKWLLSNSDNAAFPQMTKSYRNP RNKPALIIWGVHHSANEQTKLYGSGNKLITVGSSKYQQSFTPS PGARPQVNGQSGRIDFHWLLLDPNDDTVTFTFNGAFIAPDRASFFR GESLGVQSDVPLDSSCGGDCFHSGGTIVSSLPFQININPRTVGRCP RYVKQTSLLLATGMKNVPENPKTRGLFGAIAAGFIENGWEGLIDGW YGFRHQNAQGEETAADYKSTQSAIDQITGKLNRLIDKTNQQFELI DNEFNEIEQQIGNVINWTRDSMTEVWSYNAELLVAMENQHTIDLA DSEMKNLYERVVRKQLRENAEEDGTGCFEIFHKCDDQCMESIRNNT YDHTQYRTESLQNRIQIDPVKLSSGYKDIILWFSFGASCFLLLAI AMGLVFICIKNGNMRCTICI	22
AGE08098 A/northern shoverl/Missis sippi/110S145/ 2011 2011/01/08 HA 444344488	MNTQILTTLIACMLIGAKGDKICLGHHAVANGTKVNTLTERGIEVV NATETVETANIKKICTQGKRPTDLGQCGLLGTIGPPQCDQFLEF DADLIIERREGTDVCYPGKFTNEESLRQILRGSGGIDKESMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNSDNAAFPQMTKSYRNP RNKPALIIWGVHHSASATEQTKLYGSGNKLITVGSSKYQQSFTPS PGARPQVNGQSGRIDFHWLLLDPNDDTVTFTFNGAFIAPDRASFFR GESLGVQSDVPLDSGCEGDCFHNGGTIVSSLPFQININPRTVKGCP RYVKQTSLLLATGMKNVPENPKTRGLFGAIAAGFIENGWEGLIDGW YGFRHQNAQGEETAADYKSTQSAIDQITGKLNRLIDKTNQQFELI DNEFSEIEQQIGNVINWTRDSMTEVWSYNAELLVAMENQHTIDLA DSEMKNLYERVVRKQLRENAEEDGTGCFEIFHKCDDQCMESIRNNT YDHTQYRAESLQNRIQIDPVKLSSGYKDIILWFSFGASCFLLLAI AMGLVFICIKNGNMRCTICI	23
AGI60301 A/Hangzhou/1/2 013 2013/03/24 HA 475662454	MNTQILVFALIAIIPNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKRTVDLGQCGLLGTITGPPQCDQFLEF SADLIIERREGSDVCYPGKFVNEEALRQILRESGGIDKEAMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNTDNAAFPQMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGISGRIDFHWLMLNPNDDTVTFSFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTIISNLPFQINIDSRVKGCP RYVKQRSLLLATGMKNVPEIPKGRGLFGAIAAGFIENGWEGLIDGW YGFRHQNAQGEETAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVVRKQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	24
AGI60292 A/Shanghai/466 4T/2013 2013/03/05 HA 476403560	MNTQILVFALIAIIPANADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKRTVDLGQCGLLGTITGPPQCDQFLEF SADLIIERREGSDVCYPGKFVNEEALRQILRESGGIDKEAMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNTDNAAFPQMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDDTVTFSFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCHSGGTIISNLPFQINIDSRVKGCP RYVKQRSLLLATGMKNVPEIPKGRGLFGAIAAGFIENGWEGLIDGW YGFRHQNAQGEETAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVVRKQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	25

Accession No / Strain / Protein	Amino Acid Sequence	SEQ ID NO:
AGJ72861 A/chicken/Zhejiang/DTID- ZJU01/2013 2013/04/ HA 479280294	MNTQILVFALIAIIPNADKICLGHHAVSNGTKVNTLTERGGEVV NATETVERTNIPRICSKGKKTVDLGQGGPRGTITGPPQCDQFLEF SADLIMERREGSDVCYPGKFFVNEEALRQILRESGGIDKEAMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNTDNAAFPMQTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGQSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTII SNLPFQNI DSRVAGKCP RYVKQRSLLLATGMKNVPEIPKGRGLFGAIIAGFIENGWEGLIDGW YGFRHQNAQGEETAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	26
AGJ73503 A/Nanjing/1/20 13 2013/03/28 HA 479285761	MNTQILVFALIAIIPNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKMTVDLGQCGLLGTITGPPQCDQFLEF SADLIIERREGSDVCYPGKFFVNEEALRQILRESGGIDKEAMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNTDNAAFPMQTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTII SNLPFQNI DSRVAGKCP RYVKQRSLLLATGMKNVPEIPKGRGLFGAIIAGFIENGWEGLIDGW YGFRHQNAQGEETAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	27
BAN16711 A/duck/Gunma/4 66/2011 2011// HA 482661571	MNTQVLVFAIMAIIPNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNVPRICSKGKRTVDLGQCGLLGTITGPPQCDQFLEF SADLIIERREGSDVCYPGKFFVNEEALRQILRESGGIDKETMGFTY SGIRTNGTTSACRRSGSSFYAEMKWLLSNTDNAAFPMQTKSYKNT RRDPALIAWGIHHSGSTTEQTKLYGSGSKLITVGSSNYQQSFVPS PGARPQVNGQSGRIDFHWLILNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDASCEGDCYHSGGTII SNLPFQNI NSRAVAGKCP RYVKQESLMLATGMKNVPELPKGRGLFGAIIAGFIENGWEGLIDGW YGFRHQNAQGEETAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFTEVEKQIGNVINWTRDSMTEVWSYNAELLVAMENQHTIDLA DSEMKNLYERVRRQLRENAEEDDTGCFEIFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI AMGLVFICVKNGNMRCTICI	28
AGK84857 A/Hangzhou/2/2 013 2013/04/01 HA 485649824	MNTQILVFALIAIIPNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKRTVDLGQCGLLGTITGPPQCDQFLEF SADLIIERREGSDVCYPGKFFVNEEALRQILRESGGIDKEAMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNTDNAAFPMQTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTII SNLPFQNI DSRVAGKCP RYVKQRSLLLATGMKNVPEIPKGRGLFGAIIAGFIENGWEGLIDGW YGFRHQNAQGEETAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	29

Accession No / Strain / Protein	Amino Acid Sequence	SEQ ID NO:
AGL44438 A/Shanghai/02/ 2013 2013/03/05 HA 496493389	MNTQILVFALIAIPTNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKRTVDLGQCGLLGTITGPPQCDQFLEF SADLIIERREGSDVCYPGKFVNEEALRQILRESGGIDKEAMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNTDNAAFPMQTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTIISNLPFQNIIDSRVAGKCP RYVKQRSLLLATGMKNVPEIPKGRGLFGAIAAGFIENGWEGLIDGW YGFRHQNAQGEFTAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNNGNMRTCTICI	30
AGL33692 A/Shanghai/465 5T/2013 2013/02/26 HA 491874175	GMIDGWYGFRHQNAQGEFTAADYKSTQSAIDQITGKLNRLIEKTN QQFELIDNEFTEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQ HTIDLADSEMDKLYERVKRQLRENAEEDGTGCFEIFHKCDDDCMA SIRNNTYDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASC FILLAIAMGLVFICVKNNGNMRTCTICI	31
AGL33693 A/Shanghai/465 9T/2013 2013/02/27 HA 491874186	GMIDGWYGFRHQNAQGEFTAADYKSTQSAIDQITGKLNRLIEKTN QQFELIDNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQ HTIDLADSEMDKLYERVKRQLRENAEEDGTGCFEIFHKCDDDCMA SIRNNTYDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASC FILLAIAMGLVFICVKNNGNMRTCTICI	32
AGL95088 A/Taiwan/S0207 6/2013 2013/04/22 HA 501485301	VFALIAIPTNADKICLGHHAVSNGTKVNTLTERGVEVVNATETV ERTNIPRICSKGKRTVDLGQCGLLGTITGPPQCDQFLEFSADLI I ERREGSDVCYPGKFVNEEALRQILRESGGIDKEAMGFTYSGIRTN GATSACRRSGSSFYAEMKWLLSNTDNAAFPMQTKSYKNTRKSPAL IVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPSPGARPQ VNGLSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLRGKSMGI QSGVQVDANCEGDCYHSGGTIISNLPFQNIIDSRVAGKCPRYVKQR SLLLATGMKNVPEIPKGRGLFGAIAAGFIENGWEGLIDGWYGFRHQ NAQGEFTAADYKSTQSAIDQITGKLNRLIEKTNQQFELIDNEFNE VEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLADSEMDK LYERVKRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNTYDHSKY REEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAIAMGLVF ICVKNNGNMR	33
AGL95098 A/Taiwan/T0208 1/2013 2013/04/22 HA 501485319	LVFALIAIPTNADKICLGHHAVSNGTKVNTLTERGVEVVNATET VERTNIPRICSKGKRTVDLGQCGLLGTITGPPQCDQFLEFSADLI IERREGSDVCYPGKFVNEEALRQILRESGGIDKEAMGFTYSGIRT NGATSACRRSGSSFYAEMKWLLSNTDNAAFPMQTKSYKNTRKSPA LIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPSPGARP QVNGLSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLRGKSMG IQSGVQVDANCEGDCYHSGGTIISNLPFQNIIDSRVAGKCPRYVKQ RSLLLATGMKNVPEIPKGRGLFGAIAAGFIENGWEGLIDGWYGFRH QNAQGEFTAADYKSTQSAIDQITGKLNRLIEKTNQQFELIDNEFN EVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLADSEMD KLYERVKRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNTYDHSK YREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAIAMGLV FICVKNNGNMRT	34
AGM53883 A/Shanghai/508 3T/2013 2013/04/20 HA 507593986	GFRHQNAQGEFTAADYKSTQSAIDQITGKLNRLIEKTNQQFELID NEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLAD SEMDKLYERVKRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNTY DHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI MGLVFICVKNNGNMRT	35
AGM53884 A/Shanghai/518 0T/2013 2013/04/23 HA 507593988	AQGEFTAADYKSTQSAIDQITGKLNRLIEKTNQQFELIDNEFNEV EKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLADSEMDKL YERVKRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNTYDHSKYR EEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAIAMGLVFI CVKNNGNMRTCTICI	36

Accession No / Strain / Protein	Amino Acid Sequence	SEQ ID NO:
AGM53885 A/Shanghai/524 0T/2013 2013/04/25 HA 507593990	QNAQGEGETAADYKSTQSAIDQITGKLNRLIEKTNQQFELIDNEFN EVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLADSEMD KLYERVKRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNTYDHSK YREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLV FICVKNGNMRCT	37
AGM53886 A/Shanghai/484 2T/2013 2013/04/13 HA 507593992	NAQGEGETAADYKSTQSAIDQITGKLNRLIEKTNQQFELIDNEFNE VEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLADSEMDK LYERVKRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNTYDHSKY REEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVF ICVKNGNMRCT	38
AGM53887 A/Shanghai/470 1T/2013 2013/04/06 HA 507593994	NAQGEGETAADYKSTQSAIDQITGKLNRLIEKTNQQFELIDNEFNE VEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLADSEMDK LYERVKRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNTYDHSKY REEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVF ICVKNGNMRCTIC	39
AGN69462 A/Wuxi/2/2013 2013/03/31 HA 511105778	MNTQILVFALIAIIP TNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKRTVDLGQCGLLG TITGPPQCDQFLEF SADLIIERREGSDVCYPGK FVNEEALRQILRESGGIDKEAMGFTY SGIRTNGSTSACRRSGSSFYAEMKWLLSNTDNAAFPM TKS YKNT RKSPALIVWGIHHSVSTAEQTKLYGSGSKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTII SNLPFQNI DSRAVGKCP RYVKQRSLLLATGMKNVPEIPKGRGLFGAIAGFIENGWEGLIDGW YGFRHQNAQGEGETAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	40
AGN69474 A/Wuxi/1/2013 2013/03/31 HA 511105798	MNTQILVFALIAIIP TNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKRTVDLGQCGLLG TITGPPQCDQFLEF SADLIIERREGSDVCYPGK FVNEEALRQILRESGGIDKEAMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNTDNAAFPM TKS YKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTII SNLPFQNI DSRAVGKCP RYVKQRSLLLATGMKNVPEIPKGRGLFGAIAGFIENGWEGLINGW YGFRHQNAQGEGETAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	41
AGO51387 A/Jiangsu/2/20 13 2013/04/20 HA 514390990	MNTQILVFALIAIIP TNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKMTVDLGQCGLLG TITGPPQCDQFLEF SADLIIERREGSDVCYPGK FVNEEALRQILRESGGIDKEAMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNTDNAAFPM TKS YKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTII SNLPFQNI DSRAVGKCP RYVKQRSLLLATGMKNVPEIPKGRGLFGAIAGFIENGWEGLIDGW YGFRHQNAQGEGETAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDHSKYRXEAMXBXI QIDPVKLSSGYKDVXJWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	42

Accession No / Strain / Protein	Amino Acid Sequence	SEQ ID NO:
BAN59726 A/duck/Mongolia/147/2008 2008/08/29 HA 519661951	MNTQILVFALVAIIPTNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKRTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDVCYPGKFFVNEEALRQILRESGGIGKETMGFTY SGIRTNGATSACRRSRSSFYAEMKWLLSNTDNAAFPMTRSYKNT RKDPALIIWGIHHSGSTTEQTKLYGSGNKLITVGSSNYQQSFVPS PGARPQVNGQSGRIDFHWMLNPNNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHNGGTII SNLPFQNINSRTVGKCP RYVKQESLLLATGMKNVPEIPKGRGLFGAIIAGFIENGWEGLIDGW YGFRHQNAQGEETAADYKSTQSAIDQITGKLNRLIERTNQQFELI DNEFTEVEKQIGNVINWTRDSMTEVWSYNAELLVAMENQHTIDLA DSEMKNLYERVKRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSNGYKDVILWFSFGASCFILLAI AMGLVFICVKNGNMRCTICI	43
BAN59727 A/duck/Mongolia/129/2010 2010// HA 519661954	MNTQILVFALVAIIPTNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERINVPRICSKGKRTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDVCYPGKFFVNEEALRQILRESGGIDKETMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNTDNAAFPMTKSYKNT RKDPALIIWGIHHSGSTTEQTKLYGSGSKLITVGSSNYQQSFVPS PGARPQVNGQSGRIDFHWMLNPNNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDASCEGDCYHSGGTII SNLPFQNINSRAVGKCP RYVKQESLMLLATGMKNVPELPKGRGLFGAIIAGFIENGWEGLIDGW YGFRHQNAQGEETAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFTEVEKQIGNVINWTRDSMTEVWSYNAELLVAMENQHTIDLA DSEMKNLYERVKRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQINPVKLSSGYKDVILWFSFGASCFILLAI AMGLVFICVKNGNMRCTICI	44
AGQ80952 A/duck/Jiangxi/3096/2009 2009// HA 523788794	MNTQILVFALVAIIPTNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTSIPRICSKGKRAVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDVCYPGKFFVNEEALRQILRESGGIDKETMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNTDNAAFQTTKSYKNT RKDPALIIWGIHHSGSTTEQTKLYGSGNKLITVGSSNYQQSFVPS PGARPQVNGQSGRIDFHWMLNPNNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHNGGTII SNLPFQNINSRAVGKCP RYVKQESLLLATGMKNVPEIPKGRGLFGAIIAGFIENGWEGLIDGW YGFRHQNAQGEETAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFTEVERQIGNVINWTRDSMTEVWSYNAELLVAMENQHTIDLA DSEMKNLYERVRRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI AMGLVFICVKNGNMRCTICI	45
AGQ80989 A/duck/Jiangxi/3257/2009 2009// HA 523788868	MNTQILVFALVAIIPTNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTSIPRICSKGKRAVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDVCYPGKFFVNEEALRQILRESGGIDKETMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNTDNAAFQTTKSYKNT RKDPALIIWGIHHSGSTTEQTKLYGSGNKLITVGXSNYQQSFVPS PGARPQVNGQSGRIDFHWMLNPNNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHNGGTII SNLPFQNINSRAVGKCP RYVKQESLLLATGMKNVPEIPKGRGLFGAIIAGFIENGWEGLIDGW YGFRHQNAQGEETAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFTEVERQIGNVINWTRDSMTEVWSYNAELLVAMENQHTIDLA DSEMKNLYERVRRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI AMGLVFICVKNGNMRCTICI	46

Accession No / Strain / Protein	Amino Acid Sequence	SEQ ID NO:
AGQ81043 A/chicken/Rizhao/515/2013 2013// HA 523788976	MNTQILVFALIAIIP TNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKRTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDVCYPGK FVN E EALRQILRESGGIDKEEMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNTDNAAFPMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTII SNLPFQNI DSRVAGKCP RYVKQRSLLLATGMKNVPEIPKGRGLFGA IAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	47
AGR33894 A/chicken/Rizhao/719b/2013 2013// HA 524845213	MNTQILVFALIAIIP TNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKRTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDVCYPGK FVN E EALRQILRESGGIDKEAMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNTDNAAFPMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTII SNLPFQNI DSRVAGKCP RYVKQRSLLLATGMKNVPEIPKGRGLFGA IAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDRSKYREEAMQNRXXXXXXXXXXXXXKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	48
AGR49399 A/chicken/Jiangxi/SD001/2013 2013/05/03 HA 525338528	MNTQILVFALIAIIP TNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKRTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDVCYPGK FVN E EALRQILRKSGGIDKEAMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNTDNAAFPMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTII SNLPFQNI DSRVAGKCP RYVKQRSLLLATGMKNVPEIPKGRGLFGA IAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	49
AGR49495 A/chicken/Shanghai/S1358/2013 2013/04/03 HA 525338689	MNTQILVFALIAIIP TNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKMTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDVCYPGK FVN E EALRQILRESGGIDKEAMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNTDNAAFPMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTII SNLPFQNI DSRVAGKCP RYVKQRSLLLATGMKNVPEIPKGRGLFGA IAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFEIFHKCDDDCMASIKNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	50

Accession No / Strain / Protein	Amino Acid Sequence	SEQ ID NO:
AGR49506 A/chicken/Shanghai/S1410/2013 2013/04/03 HA 525338708	MNTQILVFALIAIIP TNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKRTVDLGQCGLLGTITGPPQCDQFLEF SADLIIERREGSDVCYPGK FVN E EALRQILRESGGIDKEAMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNTDNAAFPMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGQSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTII SNLPFQNI DSR AVGKCP RYVKQRSLLLATGMKNVPEIPKGRGLFGA IAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFE I FHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	51
AGR49554 A/chicken/Zhejiang/SD033/2013 2013/04/11 HA 525338789	MNTQILVFALIAIIP TNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKRTVDLGQCGLLGTITGPPQCDQFLEF SADLIIERREGSDVCYPGK FVN E EALRQILRESGGIDKEAMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNTDNAAFPMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTII SNLPFQNI DSR AVGKCP RYVKQRSLLLATGMKNVPEIPKGRGLFGA IAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVRRQLRENAEEDGTGCFE I FHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	52
AGR49566 A/duck/Anhui/SC702/2013 2013/04/16 HA 525338809	MNTQILVFALIAIIP TNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKRTVDLGQCGLLGTITGPPQCDQFLEF SADLIIERREGSDVCYPGK FVN E EALRQILRESGGIDKEAMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNTDNAAFPMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTII SNLPFQNI DNR AVGKCP RYVKQRSLLLATGMKNVPEIPKGRGLFGA IAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFE I FHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	53
AGR49722 A/homing pigeon/Jiangsu/SD184/2013 2013/04/20 HA 525339071	MNTQILVFALIAIIP TNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKRTVDLGQCGLLGTITGPPQCDQFLEF SADLIIERREGSDVCYPGK FVN E EALRQILRESGGIDKEAMGFTY SEIRTNGATSACRRSGSSFYAEMKWLLSNTDNAAFPMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGQSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTII SNLPFQNI DSR AVGKCP RYVKQRSLLLATGMKNVPEIPKGRGLFGA IAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFE I FHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	54

Accession No / Strain / Protein	Amino Acid Sequence	SEQ ID NO:
AGR49734 A/pigeon/Shang hai/S1069/2013 2013/04/02 HA 525339091	MNTQILVFALIAIIP TNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKRTVDLGQCGLLGTITGPPQCDQFLEF SADLIIERREGSDVCYPGK FVN E EALRQILRESGGIDKEAMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNTDNAAFPMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDTITFSFN GAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTII SNLPFQNI DSRAVGKCP RYVKQRSLLLATGMKNVPEIPKGRGLFGAIAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	55
AGR49770 A/wild pigeon/Jiangsu /SD001/2013 2013/04/17 HA 525339151	MNTQILVFALIAIIP TNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKKTVDLGQCGLLGTITGPPQCDQFLEF SADLIIERREGSDVCYPGK FVN E EALRQILRESGGIDKEAMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNTDNAAFPMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGQSGRIDFHWLMLNPNDTVTF S FN GAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTII SNLPFQNI DSRAVGKCP RYVKQRSLLLATGMKNVPEIPKGRGLFGAIAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	56
AGY41893 A/Huizhou/01/2 013 2013/08/08 HA 552049496	MNTQILVFALIAIIP TNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKKTVDLGQCGLLGTITGPPQCDQFLEF SADLIIERREGSDVCYPGK FVN E EALRQILRESGGIDKEAMGFTY SGIRANGATSACRRSGSSFYAEMKWLLSNTDNAAFPMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDTVTF S FN GAFIAPDRASFLR GKSMGIQSGVQVDADCEGDCYHSGGTII SNLPFQNI DSRAVGKCP RYVKQRSLLLATGMKNVPEIPKGRGLFGAIAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	57
AGY42258 A/mallard/Swed en/91/2002 2002/12/12 HA 552052155	FALVAIIPINADKICLGHHAVSNGTKVNTLTERGVEVVNATETVE RTNVPRICSRGKRTVDLGQCGLLGTIXGPPQCDQFLEFSADLIE RREGSDVCYPGK FVN E EALRQILRESGGIDKETMGFTYSGIRTNG AXSACRRSGSSFYAEMKWLLSNTDNAAFPMTKSYKNTRNDPALI IWGIHHSGSTTEQTKLYGSGNKLITVGSSNYQQSFVPSPGARPQV NGQSGRIDFHWLILNPNDTVTF S FN GAFIAPDRASFLRGKSMGIQ SGVQIDANCEGDCYHSGGTII SNLPFQNI NSRAVGKCPRYVKQES LLLATGMKNVPEIPKGRGLFGAIAGFIENGWEGLIDGWYGFRHQ NAQGE GTAADYKSTQSAIDQITGKLNRLIEKTNQQFELIDNEFTEV EKQIGNVINWTRDSMTEVWSYNAELLVAMENQHTIDLADSEMKNL YERVRRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNTYDHSKYR EAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAIAMGLVFM CVKNGNMRCTICI	58

Accession No / Strain / Protein	Amino Acid Sequence	SEQ ID NO:
AHA11441 A/guinea fowl/Nebraska/ 17096/2011 2011/04/10 HA 557478572	MNTQILALIALCMLIGAKGDKICLGHHAVANGTKVNTLTERGIEVV NATETVETANIKKICTQGKRPTDLGQCGLLGTLIGPPQCDQFLEF DADLIIERREGTDVCYPGKFTNEESLRQILRGSGGIDKESMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNSNNAAFPQMTKSYRNP RNKPALIVWGVHHS GSATEQTKLYGSGSKLITVGSSKYQQSFTPS PGARPQVNGQSGRIDFHWLLLDPN DTVTFTFNGAFIAPDRASFFR GESLGVQSDVPLDSGCEGDCFHKG GTIVSSLPFQNI NPRTV GKCP RYVKQTSLLLATGMRNVPENPKTRGLFGA IAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRLIDKTNQQFELI DNEFSEIEQQIGNVINWTRDSMTEIWSYNAELLVAMENQHTIDLA DSEMKNLYERVRKQLRENAEEDGTGCFEIFHKCDDQCMESIRNNT YDHTQYRAESLQNRIQIDPVKLSSGYKDIILWFSFGASCFLLLAI AMGLVFICIKNGNMRCTICI	59
AHA11452 A/turkey/Minne sota/32710/201 1 2011/07/12 HA 557478591	MNTQILALIALCMLVGTKGDKICLGHHAVANGTKVNTLTERGIEVV NATETVETANIKKICTQGKRPTDLGQCGLLGTLIGPPQCDQFLEF DADLIIERREGTDVCYPGKFTNEEPLRQILRGSGGIDKESMGFTY SGIRTNGATSTCRRSGSSFYAEMKWLLSNSNNAAFPQMTKSYRNP RNKPALIVWGVHHS GSATEQTKLYGSGSKLITVGSSKYQQSFTPS PGARPQVNGQSGRIDFHWLLLDPN DTVTFTFNGAFIAPDRASFFR GESLGVQSDVPLDSGCEGDCFHKG GTIVSSLPFQNI NPRTV GKCP RYVKQTSLLLATGMRNVPENPKTRGLFGA IAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRLIDKTNQQFEMI DNEFSEIEQQIGNVINWTRDSMTEIWSYNAELLVAMENQHTIDLA DSEMKNLYERVRKQLRENAEEDGTGCFEIFHKCDDQCMESIRNNT YDHTQYRAESLQNRIQIDPVKLSSGYKDIILWFSFGASCFLLLAI AMGLVFICIKNGNMRCTICI	60
AHA11461 A/turkey/Minne sota/31900/201 1 2011/07/05 HA 557478606	MNTQILALIALCMLVGTKGDKICLGHHAVANGTKVNTLTERGIEVV NATETVETANIKKICTQGKRPTDLGQCGLLGTLIGPPQCDQFLEF DADLIIERREGTDVCYPGKFTNEEPLRQILRGSGGIDKESMGFTY SGIRTNGATSTCRRSGSSFYAEMKWLLSNSNNAAFPQMTKSYRNP RNKPALIVWGVHHS GSATEQTKLYGSGSKLITVGSSKYQQSFTPS PGARPQVNGQSGRIDFHWLLLDPN DTVTFTFNGAFIAPDRASFFR GESLGVQSDVPLDSGCEGDCFHKG GTIVSSLPFQNI NPRTV GKCP RYVKQTSLLLATGMRNVPENPKTRGLFGA IAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRLIDKTNQQFELI DNEFSEIEQQIGNVINWTRDSMTEIWSYNAELLVAMENQHTIDLA DSEMKNLYERVRKQLRENAEEDGTGCFEIFHKCDDQCMESIRNNT YDHTQYRAESLQNRIQIDPVKLSSGYKDIILWFSFGASCFLLLAI AMGLVFICIKNGNMRCTICI	61
AHK10585 A/chicken/Guan gdong/G1/2013 2013/05/05 HA 587680636	MNTQILVFALIAIIP TNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKKTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDVCYPGKFVNEEALRQILRESGGIDKEAMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNTDNAAFPQMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDTVTFSFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTIISNLPFQNI DSRVVGKCP RYVKQRSLLLATGMKNVPEIPKGRGLFGA IAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVRKQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNNGNMRCTICI	62

Accession No / Strain / Protein	Amino Acid Sequence	SEQ ID NO:
AGG53366 A/wild duck/Korea/CSM 42-34/2011 2011/03/ HA 459252887	MNTQILVFALVAIIPTNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNVPRICSKGKRTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDVCYPGKFFVNEEALRQILRESGGIDKETMGLTY SGIRTNGATSACRRSGSSFYAEMKWLLSNTDNAAFPMTKSYKNT RRDPALIVWGIHHSGSSTEQTKLYGSGSKLITVGSSNYQQSFVPS PGARPQVNGQSGRIDFHWLILNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDASCEGDCYHSGGTII SNLPFQNINSRAVGKCP RYVKQESLMLATGMKNVPELPKGRGLFGAIIAGFIENGWEGLIDGW YGFRHQNAQGEETAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFTEVEKQIGNVINWTRDSMTEVWSYNAELLVAMENQHTIDLA DSEMKNLYERVRRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVRLSSGYKDVILWFSFGASCFILLAI AMGLVFICVKNGNMRCTICI	63
AGG53377 A/wild duck/Korea/CSM 42-1/2011 2011/03/ HA 459252925	MNTQILVFALVAIIPTNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNVPRICSKGKRTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDVCYPGKFFVNEEALRQILRESGGIDKETMGLTY SGIRTNGATSACRRSGSSFYAEMKWLLSNTDNAAFPMTKSYKNT RRDPALIVWGIHHSGSSTEQTKLYGSGSKLITVGSSNYQQSFVPS PGARPQVNGQSGRIDFHWLILNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDASCEGDCYHSGGTII SNLPFQNINSRAVGKCP RYVKQESLMLATGMKNVPELPKGRGLFGAIIAGFIENGWEGLIDGW YGFRHQNAQGEETAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFTEVEKQIGNVINWTRDSMTEVWSYNAELLVAMENQHTIDLA DSEMKNLYERVRRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVRLSSGYKDVILWFSFGASCFILLAI AMGLVFICVKNGNMRCT	64
AGG53399 A/wild duck/Korea/MHC 39-26/2011 2011/03/ HA 459253005	MNTQILVFALVAIIPTNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNVPRICSKGKRTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDVCYPGKFFVNEEALRQILRESGGIDKETMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNTDNAAFPMTKSYKNT RRDPALIVWGIHHSGSTTEQTKLYGSGSKLITVGSSNYQQSFVPS PGARPQVNGQSGRIDFHWLILNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDASCEGDCYHSGGTII SNLPFQNINSRAVGKCP RYVKQESLMLATGMKNVPEPPKGRGLFGAIIAGFIENGWEGLIDGW YGFRHQNAQGEETAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFTEVEKQIGNVINWTRDSMTEVWSYNAELLVAMENQHTIDLA DSEMKNLYERVRRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI AMGLVFICVKNGNMRCTICI	65
AGG53432 A/wild duck/Korea/MHC 35-41/2011 2011/03/ HA 459253136	MNTQILVFALVAIIPTNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNVPRICSKGKRTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDVCYPGKFFVNEEALRQILRESGGIDKETMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNTDNAAFPMTKSYKNT RRDPALIVWGIHHSGSTTEQTKLYGSGSKLITVGSSNYQQSFVPS PGARPQVNGQSGRIDFHWLILNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDASCEGDCYHSGGTII SNLPFQNINSRAVGKCP RYVKQESLMLATGMKNVPEPPKGRGLFGAIIAGFIENGWEGLIDGW YGFRHQNAQGEETAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFTEVEKQIGNVINWTRDSMTEVWSYNAELLVAMENQHTIDLA DSEMKNLYERVRRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI AMGLVFICVKNGNMRCT	66

Accession No / Strain / Protein	Amino Acid Sequence	SEQ ID NO:
AGG53476 A/wild duck/Korea/SH1 9-27/2010 2010/12/ HA 459253257	MNTQILVFALVAIIPTNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNVPRICSKGKRTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDVCYPGKFFVNEEALRQILRESGGIDKETMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNTDNAAFPMTKSYKNT RRDPALIVWGIHHSGSTTEQTKLYGSGSKLITVGSSNYQQSFVPS PGARPQVNGQSGRIDFHWLILNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDASCEGDCYHSGGTII SNLPFQNINSRAVGKCP RYVKQESLMLATGMKNVPELPKGRGLFGAIIAGFIENGWEGLIDGW YGFRHQNAQGEETAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFTEVEKQIGNVINWTRDSMTEVWSYNAELLVAMENQHTIDLA DSEMKNLYERVRRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI AMGLVFICVKNGNMRCTI	67
AGG53487 A/wild duck/Korea/SH1 9-50/2010 2010/01/ HA 459253278	MNTQILVFALVAIIPTNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNVPRICSKGKRTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDVCYPGKFFVNEEALRQILRESGGIDKETMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNTDNAAFPMTKSYKNT RRDPALIVWGIHHSGSTTEQTKLYGSGSKLITVGSSNYQQSFVPS PGARPQVNGQSGRIDFHWLILNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDASCEGDCYHSGGTII SNLPFQNINSRAVGKCP RYVKQESLMLATGMKNVPELPKGRGLFGAIIAGFIENGWEGLIDGW YGFRHQNAQGEETAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFTEVEKQIGNVINWTRDSMTEVWSYNAELLVAMENQHTIDLA DSEMKNLYERVRRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI AMGLVFICVKNGNMRCTICI	68
AGG53520 A/wild duck/Korea/SH2 0-27/2008 2008/12/ HA 459253409	QILVFALVAIIPTNADKICLGHHAVSNGTKVNTLTERGVEVVNAT ETVERTNVPRICSKGKRTVDLGQCGLLGTTITGPPQCDQLLEFSAD LIIERREGTDVCYPGKFFVNEEALRQILRESGGIEKETMGFTYSGI RTNGATSACRRSGSSFYAEMKWLLSNTDNAAFPMTKSYKNTRKD PALIIWGIHHSGSTTEQTKLYGSGSKLITVGSSNYQQSFVPSGA RPQVNGQSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLRGKS MGIQSGVQVDANCEGDCYHSGGTII SNLPFQNINSRAVGKCPRYV KQESLMLATGMKNVPELPKGRGLFGAIIAGFIENGWEGLIDGWYGF RHQNAQGEETAADYKSTQSAIDQITGKLNRLIEKTNQQFELIDNE FTEVEKQIGNVINWTRDSMTEVWSYNAELLVAMENQHTIDLADSE MNKLYERVKRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNTYDH SKYREEAMQNRIQINPVKLSSGYKDVILWFSFGASCFILLAIAMG LVFICVKNGNMR	69
AGL43637 A/Taiwan/1/201 3 2013// HA 496297389	MNTQILVFALIAIIPTNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKRTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDVCYPGKFFVNEEALRQILRESGGIDKEAMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNTDNAAFPMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGPSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTIINNLPFQNIDSRAVGKCP RYVKQRSLLLATGMKNVPEIPKGRGLFGAIIAGFIENGWEGLIDGW YGFRHQNAQGEETAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	70

Accession No / Strain / Protein	Amino Acid Sequence	SEQ ID NO:
AGL97639 A/mallard/Minn esota/AI09- 3770/2009 2009/09/12 HA 505555371	IACMLVGAKGDKICLGHHAVANGTKVNTLTERGIEVVNATETVET ANIKKLCTQGKRPTDLGQCGLLGTITGPPQCDQFLEFDADLIIE REGTDVCYPGKFTNEESLRQILRGSGGIDKESMGFTYSGIRTINGA TSACRRSGSSFYAEMKWLLSNSDNAAFPQMTKSYRNPRNKPALII WGVHHSGSATEQTKLYGSGNKLITVGSSKYQQSFTSPSGARPQVN GQSGRIDFHWLLLDPNDDTVTFTFNGAFIAPDRASFFRGESLGVQS DVPLDSGCEGDCFHSGGTIVSSLPFQNNINPRTVGKCPRYVKQTS LLATGMRNVPENPKTRGLFGAIAGFIENGWEGLIDGWYGRHQNA QGEFTAADYKSTQSAIDQITGKLNRLIDKTNQQFELIDNEFSEIE QQIGNVINWTRDSMTELWSYNAELLVAMENQHTIDLADSEMKNLY ERVVKQLRENAEEDGTGCFEIFHKCDDQCMESIRNNTYDHTQYRT ESLQNRIQIDPVKLS	71
AGO02477 A/Xuzhou/1/201 3 2013/04/25 HA 512403688	MNTQILVFALIAIIPNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKRTVDLGQCGLLGTITGPPQCDQFLEF SADLIIEERREGSDVCYPGKVFVNEEALRQILRESGGIDKEAMGFTY SGIRTINGATSACRRSGSSFYAEMKWLLSNTDNAAFPQMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGSKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDDTVTFNFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTIISNLPFQNNIDSRVKGCP RYVKQRSLLLATGMKNVPEIPKGRGLFGAIAGFIENGWEGLIDGW YGRHQNAQGEFTAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVVKQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKSRNMRCTICI	72
AGR84942 A/Suzhou/5/201 3 2013/04/12 HA 526304561	MNTQILVFALIAIIPNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKRTVDLGQCGLLGTITGPPQCDQFLEF SADLIIEERREGSDVCYPGKVFVNEEALRQILRESGGIDKEAMGFTY SGIRTINGATSACRRSGSSFYAEMKWLLSNTDNAAFPQMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGSKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDDTVTFNFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTIISNLPFQNNIDSRVKGCP RYVKQRSLLLATGMKNVPEIPKGRGLFGAIAGFIENGWEGLIDGW YGRHQNAQGEFTAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVVKQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	73
AGR84954 A/Nanjing/6/20 13 2013/04/11 HA 526304594	MNTQILVFALIAIIPNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKRTVDLGQCGLLGTITGPPQCDQFLEF SADLIIEERREGSDVCYPGKVFVNEEALRQILRESGGIDKEAMGFTY SGIRTINGATSACRRSGSSFYAEMKWLLSNTDNAAFPQMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDDTVTFNFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTIISNLPFQNNIDSRVKGCP RYVKQRSLLLATGMKNVPEIPKGRGLFGAIAGFIENGWEGLIDGW YGRHQNAQGEFTAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVVKQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNRNMRCTICI	74

Accession No / Strain / Protein	Amino Acid Sequence	SEQ ID NO:
AGR84978 A/Wuxi/4/2013 2013/04/07 HA 526304656	MNTQILVFALIAIIP TNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKKTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDVCYPGK FVN E EALRQILRESGGIDKEAMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNTDNAAFPMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTII SNLPFQNI DSRVKGCP RYVKQRSLLLATGMKNVPEIPKGRGLFGAIAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKSRNMRCTICI	75
AGR84990 A/Wuxi/3/2013 2013/04/07 HA 526304688	MNTQILVFALIAIIP TNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKRTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDVCYPGK FVN E EALRQILRESGGIDKEAMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNTDNAAFPMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTII SNLPFQNI DSRVKGCP RYVKQRSLLLATGMKNVPEIPKGRGLFGAIAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKSRNMRCTICI	76
AGR85002 A/Zhenjiang/1/ 2013 2013/04/07 HA 526304708	MNTQILVFALIAIIP TNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKMTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDVCYPGK FVN E EALRQILRESGGIDKEAMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNTDNAAFPMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTII SNLPFQNI DSRVKGCP RYVKQRSLLLATGMKNVPEIPKGRGLFGAIAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKSRNKRCTICI	77
AGR85026 A/Nanjing/2/20 13 2013/04/05 HA 526304762	MNTQILVFALIAIIP TNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKMTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDVCYPGK FVN E EALRQILRESGGIDKEAMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNTDNAAFPMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTII SNLPFQNI DSRVKGCP RYVKQRSLLLATGMKNVPEIPKGRGLFGAIAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKSRNMRCTICI	78

Accession No / Strain / Protein	Amino Acid Sequence	SEQ ID NO:
AGU02230 A/Zhejiang/DTI D-ZJU05/2013 2013/04/ HA 532808765	LVFALIAIIPTNADKICLGHHAVSNGTKVNTLTERGGGEVVNATET VERTNIPRICSKGKRTVDLGQCGLRGTTITGPPQCDQFLEFSADLI IERREGSDVCYPGKFVNEEALRQILRESGGIDKEAMGFTYSGIRT NGATSACRRSGSSFYAEMKWLLSNTDNAAFPQMTKSYKNTRKSPA LIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPSPGARP QVNGLSGRIDFHWLMLNPNDTVTFSFNGAFIAPDRASFLRGKSMG IQSGVQVDANCEGDCYHSGGTIISNLPFQNIIDSRVKGKCPRYVKQ RSLLLATGMKNVPEIPKGRGLFGAIIAGFIENGWEGLIDGWYGFRH QNAQGEFTAADYKSTQSAIDQITGKLNRLIEKTNQQFELIDNEFN EVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLADSEMD KLYERVKRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNTYDHSK YREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLV FICVKNNGNMRCT	79
AGU02233 A/Zhejiang/DTI D-ZJU08/2013 2013/04/ HA 532808788	FALIAIIPTNADKICLGHHAVSNGTKVNTLTERGGGEVVNATETVE RTNFPRICSKGKRTVDLGQCGLRGTTITGPPQCDQFLEFSADLIIE RREGSDVCYPGKFVNEEALRQILRESGGIDKEAMGFTYSGIRTNG ATSACRRSGSSFYAEMKWLLSNTDNAAFPQMTKSYKNTRKSPALI VWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPSPGARPQV NGLSGRIDFHWLMLNPNDTVTFSFNGAFIAPDRASFLRGKSMGIQ SGVQVDANCEGDCYHSGGTIISNLPFQNIIDSRVKGKCPRYVKQRS LLLATGMKNVPEIPKGRGLFGAIIAGFIENGWEGLIDGWYGFRHQ NAQGEFTAADYKSTQSAIDQITGKLNRLIEKTNQQFELIDNEFN EVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLADSEMDKL YERVKRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNTYDHSKYR EEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFI CVKNNGNMRCT	80
AGW82588 A/tree sparrow/Shangh ai/01/2013 2013/05/09 HA 546235348	MNTQILVFALIAIIPTNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKRTVDLGQCGLLGTITGPPQCDQFLEF SADLIIEERREGSDVCYPGKFVNEEALRQILRESGGIDKEAMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNTDNAAFPQMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDTVTFSFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTIISNLPFQNIIDSRVKGKCP RYVKQRSLLLATGMKNVPEIPKGRGLFGAIIAGFIENGWEGLIDGW YGFRHQNAQGEFTAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFN EVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFI CVKNNGNMRCTIGI	81
AGW82600 A/Shanghai/CN0 1/2013 2013/04/11 HA 546235368	ALIAIIPTNADKICLGHHAVSNGTKVNTLTERGVEVVNATETVER TNIPRICSKGKRTVDLGQCGLLGTITGPPQCDQFLEFSADLIIE REGSDVCYPGKFVNEEALRQILRESGGIDKEAMGFTYSGIRTNGA TSACRRSRSSFYAEMKWLLSNTDNAAFPQMTKSYKNTRKSPALIV WGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPSPGARPQVN GLSGRIDFHWLMLNPNDTVTFSFNGAFIAPDRASFLRGKSMGIQS GVQVDANCEGDCYHSGGTIISNLPFQNIIDSRVKGKCPRYVKQRS LLLATGMKNVPEIPKGRGLFGAIIAGFIENGWEGLIDGWYGFRHQ NAQGEFTAADYKSTQSAIDQITGKLNRLIEKTNQQFELIDNEFN EVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLADSEMDKLY ERVKRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNTYDHSKYRE EAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFI CVKNNGNMRCTICI	82

Accession No / Strain / Protein	Amino Acid Sequence	SEQ ID NO:
AGW82612 A/Shanghai/JS0 1/2013 2013/04/03 HA 546235388	MNTQILVFALIAIIPTNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKRTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDVCYPGKFVNEEALRQILRESGGIDKEAMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNTDNAAFPMTKSYKNT RKNPALIVWGIHHSGSTAEQTKLYGSGNKLVTVGSSNYQQSFAPS PGARTQVNGQSGRIDFHWLMLNPNDTVTFSTFNGAFIAPDRASFLR GKSMGIQSGVQVDADCEGDCYHSGGTIIISNLPFQNIIDSRVKGCP RYVKQRSLLLATGMKNVPEIPKGRGLFGAIIAGFIENGWEGLIDGW YGFRHQNAQGEETAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFTEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI AMGLVFICVKNMNRCTICI	83
AHA11472 A/turkey/Minne sota/31676/200 9 2009/12/08 HA 557478625	MNTQILALIAACMLIGAKGDKICLGHHAVANGTKVNTLTERGIEVV NATETVETANVKKICTQGKRPTDLGQCGLLGTLIGPPQCDQFLEF DADLIIERREGTDVCYPGKFTNEESLRQILRGSGGIDKESMGFTY SGIRTNGETSACRRSGSSFYAEMKWLLSNSNNAAFPMTKSYRNP RDKPALIIWGVHHSGSTAEQTKLYGSGNKLITVGSSKYQQSFTPS PGARPQVNGQSGRIDFHWLMLLDPNNDTVTFSTFNGAFIAPDRASFFR GESLGVQSDVPLDSGCEGDCFHSGGTIVSSLPFQNIINPRTVKGCP RYVKQTSLLLATGMRNVPEKPKTRGLFGAIIAGFIENGWEGLIDGW YGFRHQNAQGEETAADYKSTQSAIDQITNKLNLRLIDKTNQQFELI DNEFSEIEQQIGNVINWTRDSMTEVWSYNAELLVAMENQHTIDLA DSEMKNLYERVKRQLRENAEEDGTGCFEIFHKCDDQCMESIRNNT YDHTQYRKESLQNRIQIDPVKLSSGYKDIILWFSFGASCFLLLAII AMGLVFICIKNGMNRCTICI	84
AHA11483 A/turkey/Minne sota/14135- 2/2009 2009/08/07 HA 557478644	MNTQILALIAACMLIGAKGDKICLGHHAVANGTKVNTLTERGIEVV NATETVETANVKKICTQGKRPTDLGQCGLLGTLIGPPQCDQFLEF DADLIIERREGTDVCYPGKFTNEESLRQILRGSGGIDKESMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNSNNAAFPMTKSYRNP RDKPALIIWGVHHSGSTAEQTKLYGSGNKLITVGSSKYQQSFTPS PGARPQVNGQSGRIDFHWLMLLDPNNDTVTFSTFNGAFIAPDRASFFR GESLGVQSDVPLDSGCEGDCFHSGGTIVSSLPFQNIINPRTVKGCP RYVKQTSLLLATGMRNVPEKPKTRGLFGAIIAGFIENGWEGLIDGW YGFRHQNAQGEETAADYKSTQSAIDQITSKLNRLIDKTNQQFELI DNEFSEIEQQIGNVINWTRDSMTEVWSYNAELLVAMENQHTIDLA DSEMKNLYERVKRQLRENAEEDGTGCFEIFHKCDDQCMESIRNNT YDHTQYRKESLQNRIQIDPVKLSSGYKDIILWFSFGASCFLLLAII AMGLVFICIKNGMNRCTICI	85
AHA11500 A/Zhejiang/DII D-ZJU10/2013 2013/10/14 HA 557478676	TQILVFALIAIIPTNADKICLGHHAVSNGTKVNTLTERGVEVVNA TETVERTNIPRICSKGKRTVDLGQCGLLGTTITGPPQCDQFLEFSA DLIIERREGSDVCYPGKFVNEEALRQILRESGGIDKEAMGFTYSG IRTNGATSACRRSGSSFYAEMKWLLSNTDNAAFPMTKSYKNTRK SPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPSPG ARPPVNGLSGRIDFHWLMLNPNDTVTFSTFNGAFIAPDRASFLRGK SMGIQSGVQVDANCEGDCYHSGGTIIISNLPFQNIIDSRVKGCPRY VKQRSLLLATGMKNVPEIPKGRGLFGAIIAGFIENGWEGLIDGWYG FRHQNAQGEETAADYKSTQSAIDQITGKLNRLIEKTNQQFELIDN EFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLADS EMDKLYERVKRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNTYD HSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKN	86

Accession No / Strain / Protein	Amino Acid Sequence	SEQ ID NO:
AHA57050 A/turkey/Minne sota/14659/200 9 2009/08/12 HA 558484427	MNTQILALIALCMLIGAKGDKICLGHHAVANGTKVNTLTERGIEVV NATETVETANVKKICTQGKRPTDLGQCGLLGTLLIGPPQCDQFLEF DADLIIERREGTDVCYPGKFTNEESLRQILRGSGGIDKESMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNSNNAAFPQMTKSYRNP RDKPALIIWGVHHS GSATEQTKLYGSGNKLITVGSSKYQQSFTPS PGARPQVNGQSGRIDFHWLLLDPN DTVTFTFN GAFIAPDRASFFR GESLGVQSDVPLDSGCEGDCFHSGGTIVSSLPFQNI NPRTV GKCP RYVKQTSLLLATGMRNVPEKPKTRGLFGA IAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITSKLNRLIDKTNQQFELI DNEFSEIEQQIGNVINWTRDSMTEVWSYNAELLVAMENQHTIDLA DSEMKNLYERV RKQLRENAEEDGTGCFEIFHNCDDQCMESIRNNT YDHTQYRKESLQNRIQIDPVKLSSGYKDIILWFSFGASCFLLLAI AMGLVFICIKNGNMRCTICI	87
AHA57072 A/turkey/Minne sota/18421/200 9 2009/09/09 HA 558484465	MNTQILALIALCMLIGAKGDKICLGHHAVANGTKVNTLTERGIEVV NATETVETANVKKICTQGKRPTDLGQCGLLGTLLIGPPQCDQFLEF DADLIIERREGTDVCYPGKFTNEESLRQILRGSGGIDKESMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNSNDAAFPQMTKSYRNP RDKPALIIWGVHHS GSATEQTKLYGSGNKLITVGSSKYQQSFTPS PGARPQVNGQSGRIDFHWLLLDPN DTVTFTFN GAFIAPDRASFFR GESLGVQSDVPLDSGCEGDCFHSGGTIVSSLPFQNI NPRTV GKCP RYVKQTSLLLATGMRNVPEKPKTRGLFGA IAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRLIDKTNQQFELI DNEFSEIEQQIGNVINWTRDSMTEVWSYNAELLVAMENQHTIDLA DSEMKNLYERV RKQLRENAEEDGTGCFEIFHKCDDQCMESIRNNT YDHTQYRKESLQNRIQIDPVKLSSGYKDIILWFSFGASCFLLLAI AMGLVFICIKNGNMRCTICI	88
AHD25003 A/Guangdong/02 /2013 2013/10/ HA 568260567	MNTQILVFALIAIIP TNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKKTVDLGQCGLLGTITGPPQCDQFLEF SADLIIERREGSDVCYPGKFVN EEARLQILRESGGIDKEAMGFTY SGIRANGATSACRRSGSSFYAEMKWLLSNTDNAAFPQMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDTVTFSFN GAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTIIISNLPFQNI DSRVKGCP RYVKQRSLLLATGMKNVPEIPKGRGLFGA IAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERV KRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASC FILLAI VMGLVFICVKNGNM	89
AHF20528 A/Hong Kong/470129/20 13 2013/11/30 HA 570933555	MNTQILVFALIAIIP TNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKRTVDLGQCGLLGTITGPPQCDQFLEF SADLIIERREGSDVCYPGKFVN EEARLQILRESGGIDKEAMGFTY SGIRANGATSACRRSGSSFYAEMKWLLSNTDNAAFPQMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDTVTFSFN GAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTIIISL PFQNI DSRVKGCP RYVKQRSLLLATGMKNVPEIPKGRGLFGA IAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERV KRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASC FILLAI VMGLVFICVKNGNMRCTICI	90

Accession No / Strain / Protein	Amino Acid Sequence	SEQ ID NO:
AHF20568 A/Shanghai/CN0 2/2013 2013/04/02 HA 570933626	MNTQILVFALIAIIP TNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKRTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDVCYPGK FVN E EALRQILRESGGIDKEAMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNTDNAAFPMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTIMSNLPFQNI DSRVAGKCP RYVKQRSLLLATGMKNVPEIPKGRGLFGA IAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFE I FHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	91
AHH25185 A/Guangdong/04 /2013 2013/12/16 HA 576106234	MNTQILVFALIAIIP TNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKRTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDVCYPGK FVN E EALRQILRESGGIEKEAMGFTY SGIRANGATSACRRSGSSFYAEMKWLLSNTDNAAFPMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTII SNLPFQNI DSRVAGKCP RYVKQRSLLLATGMKNVPEIPKGRGLFGA IAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFE I FHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	92
AHJ57411 A/Shanghai/PD- 01/2014 2014/01/17 HA 585478041	MNTQILVFALIAIIP TNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKRTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDVCYPGK FVN E EALRQILRESGGIDKEAMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNTDNAAFPMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVSS PGARPQVNGLSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCKGDCYHSGGTII SNLPFQNI DSRVAGKCP RYVKQRSLLLATGMKNVPEIPKGRGLFGA IAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRIIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFE I FHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	93
AHJ57418 A/Shanghai/PD- 02/2014 2014/01/17 HA 585478256	MNTQILVFALIAIIP TNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKRTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDICYPGK FVN E EALRQILRESGGIDKEAMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNTDNAAFPMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLK GKSMGIQSGVQVDANCEGDCYHSGGTII SNLPFQNI DSRVAGKCP RYVKQRSLLLATGMKNVPEIPKGRGLFGA IAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRIIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFE I FHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	94

Accession No / Strain / Protein	Amino Acid Sequence	SEQ ID NO:
AHK10800 A/Shanghai/01/ 2014 2014/01/03 HA 587681014	MNTQILVFALIAIIP TNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKRTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDVCYPGKFVN E EALRQILRESGGIDKEAMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNTDNAAFPMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTII SNLPFQNI DSRVAGKCP RYVKQRSLLLATGMKNVPEIPKGRGLFGAIAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRIIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	95
AHM24224 A/Beijing/3/20 13 2013/04/16 HA 594704802	MNTQILVFALIAIIP TNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKRTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDVCYPGKFVKEEALRQILRESGGIDKEAMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNTDNAAFPMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTII SNLPFQNI DSRVAGKCP RYVKQRSLLLATGMKNVPEIPKGRGLFGAIAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	96
AHN96472 A/chicken/Shan ghai/PD-CN- 02/2014 2014/01/21 HA 602701641	MNTQILVFALIAIIP TNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKKTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDVCYPGKFVN E EALRQILRESGGIDKEAMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNTDNAAFPMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTII SNLPFQNI DSRVAGKCP RYVKQKSLLLATGMKNVPEIPKGRGLFGAIAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	97
AHZ39686 A/Anhui/DEWH72 -01/2013 2013// HA 632807036	MNTQILVFALIAIIP TNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKRTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDVCYPGKFVN E EALRQILRESGGIDKEAMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNTDDAAFPMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTII SNLPFQNI DSRVAGKCP RYVKQRSLLLATGMKNVPEIPKGRGLFGAIAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	98

Accession No / Strain / Protein	Amino Acid Sequence	SEQ ID NO:
AHZ39710 A/Anhui/DEWH72 -03/2013 2013// HA 632807076	MNTQILVFALIAIIP TNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKRTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDVCYPGK FVNEEALRQILRESGGIDKEAMGFTY SGIRTDGATSACRRSGSSFYAEMKWLLSNTDDAAFPQMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTII SNLPFQNI DSRVKGCP RYVKQRSLLLATGMKNVPEIPKGRGLFGA IAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFE IFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	99
AHZ39746 A/Anhui/DEWH72 -06/2013 2013// HA 632807136	MNTQILVFALIAIIP TNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKRTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDVCYPGK FVNEEALRQILRESGGIDKEAMGFTY SGIRTN GATSACRRSGSSFYAEMKWLLSNTDNAAFPQMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGERPQVNGLSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTII SNLPFQNI DSRVKGCP RYVKQRSLLLATGMKNVPEIPKGRGLFGA IAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFE IFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	100
AHZ41929 A/mallard/Swed en/1621/2002 2002/12/12 HA 632810949	MNTQILVFALVAIIP INADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNVPRICSRGKRTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDVCYPGK FVNEEALRQILRESGGIDKETMGFTY SGIRTN GATSACRRSGSSFYAEMKWLLSNTDNAAFPQMTKSYKNT RNDPALIIWGIHHSGSTTEQTKLYGSGNKLITVGSSNYQQSFVPS PGARPQVNGQSGRIDFHWLILNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQIDANCEGDCYHSGGTII SNLPFQNI NSRAVKGCP RYVKQESLLLATGMKNVPEIPKGRGLFGA IAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFTEVEKQIGNVINWTRDSMTEVWSYNAELLVAMENQHTIDLA DSEMKNLYERVRRQLRENAEEDGTGCFE IFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI AMGLVFM CVKNGNMRCTICI	101
AHZ42537 A/mallard/Minn esota/AI09- 3770/2009 2009/09/12 HA 632811964	MNTQILAFIACMLVGAKGDKICLGHHAVANGTKVNTLTERGIEVV NATETVETANIKKLCTQGKRPTDLGQCGLLGTLIGPPQCDQFLEF DADLIIERREGTDVCYPGKFTNEESLRQILRGSGGIDKESMGFTY SGIRTN GATSACRRSGSSFYAEMKWLLSNSDNAAFPQMTKSYRNP RNKPALIIWGVHHS GSATEQTKLYGSGNKLITVGSSKYQQSFTPS PGARPQVNGQSGRIDFHWL LLDPN DTVTF TFNGAFIAPDRASFFR GESLGVQSDVPLDSGCEGDCFHSGGTIVSSLPFQNI NPRTVKGCP RYVKQTSLLLATGM RNV PENPKTRGLFGA IAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRLIDKTNQQFELI DNEFSEIEQQIGNVINWTRDSMTELWSYNAELLVAMENQHTIDLA DSEMKNLYERVVRKQLRENAEEDGTGCFE IFHKCDDQCMESIRNNT YDHTQYRTESLQNRIQIDPVKLSSGYKDIILWFSFGASCFLLLAI AMGLVFICIKNGNMRCTICI	102

Accession No / Strain / Protein	Amino Acid Sequence	SEQ ID NO:
AHZ42549 A/ruddy turnstone/Dela ware/AI00- 1538/2000 2000/05/20 HA 632811984	MNTQILAFIACMLVGVRGDKICLGHHAVANGTKVNTLTEKGIEVV NATETVESANIKKICTQGKRPTDLGQCGLLGTITGPPQCDQFLEF DSDLIIERREGTDVCYPGKFTNEESLRQILRGSGGIDKESMGFTY SGIRTNGATSACRRLGSSSFYAEMKWLLSNSDNAAFPQMTKSYRN PRNKPALIIWGVHHSANEQTKLYGSGNKLITVGSSKYQQSFTP SPGARPQVNGQSGRIDFHWLLDPNDTVTFTFNAGFIAPDRASFF RGESLGIQSDVPLDSSCGGDCFHSGGTIVSSLPFQININPRTVGKC PRYVKQTSLLLATGMNRNVPENPKTRGLFGAIAAGFIENGWEGLIDG WYGFRHQNAQGEFTAADYKSTQSAIDQITGKLNRLIDKTNQQFEL MDNEFNEIEQQIGNVINWTRDSMTEVWSYNAELLVAMENQHTIDL ADSEMKNLYERVVKQLRENAEEDGTGCFEIFHKCDDQCMESIRNN TYDHTQYRTESLQNRIQIDPVKLSSGYKDIILWFSFGASCFLLLA IAMGLIFICIKNGNMRCITICI	103
AID70634 A/Shanghai/Mix 1/2014 2014/01/03 HA 660304650	MNTQILVFALIAIIPTNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKRTVDLGQCGLLGTITGPPQCDQFLEF SADLIIERREGSDVCYPGKFVNEEALRQILRESGGIDKEAMGFTY SGIRTNGATSACRRSGSSSFYAEMKWLLSNTDNAAFPQMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWMLNPNNDTVTFSFNAGFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTIISNLPFQONIDSRVKGCP RYVKQRSLLLATGMKNVPEIPKGRGLFGAIAAGFIENGWEGLIDGW YGFRHQNAQGEFTAADYKSTQSAIDQITGKLNRIIEKTNQQFELI DNEFNEVEKQISNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVVKRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCITICI	104
AIN76383 A/Zhejiang/LS0 1/2014 2014/02/08 HA 684694637	MNTQILVFALIAIIVPTNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKKTVDLGQCGLLGTITGPPQCDQFLEF SADLIIERREGSDVCYPGKFVNEEALRQILRESGGIDKEAMGFTY SGIRTNGTTSACRRSGSSSFYAEMKWLLSNTDNAAFPQMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWMLNPNNDTVTFSFNAGFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTIISNLPFQONIDSRVKGCP RYVKQKSLLLATGMKNVPEIPKGRGLFGAIAAGFIENGWEGLIDGW YGFRHQNAQGEFTAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVVKRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCITICI	105
AIU46619 A/chicken/Zhej iang/DTID- ZJU06/2013 2013/12/ HA 699978931	MNTQILVFALIAIIPTNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKRTVDLGQCGLLGTITGPPQCDQFLEF SADLIIERREGSDVCYPGKFVNEEALRQILRESGGIDKEAMGFTY SGIRTNGATSACRRSGSSSFYAEMKWLLSNTDNAAFPQMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWMLNPNNDTVTFSFNAGFIAPDRASFLR GKSMGIQSGVEVDANCEGDCYHSGGTIISNLPFQONIDSRVKGCP RYVKQRSLLLATGMKNVPEIPKGRGLFGAIAAGFIENGWEGLIDGW YGFRHQNAQGEFTAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVVKRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCITICI	106

Accession No / Strain / Protein	Amino Acid Sequence	SEQ ID NO:
AIU47013 A/chicken/Suzhou/040201H/2013 2013/04/ HA 699979673	MNTQILVFALIAIIP TNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKRTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDVCYPGK FVN E EALRQILRESGGIDKEAMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNTDNAAFPMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTII SNLPFQNI DSR AVGKCP RYVKQRSLLLATGMKNVPEIPKGRGLFGA IAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFE I FHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDMILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	107
AJJ90490 A/chicken/Shenzhen/742/2013 2013/12/10 HA 755178094	MNTQILVFALIAIIP TNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKKTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDVCYPGK FVN E EALRQILRESGGIDKEAMGFTY SGIRANGATSACRRSGSSFYAEMKWLLSNTDNAAFPMTKSYKNT RRSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTII SNLPFQNI DSR AVGKCP RYVKQRSLLLATGMKNVPEIPKGRGLFGA IAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFE I FHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	108
AJJ90526 A/chicken/Shenzhen/898/2013 2013/12/09 HA 755178154	MNTQILVFALIAIIP TNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKKTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDICYPGK FVN E EALRQILRESGGIDKEAMGFTY SGIRANGATSACKRSGSSFYAEMKWLLSNTDNAAFPMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTII SSLPFQNI DSR AVGKCP RYVKQRSLLLATGMKNVPEIPKGRGLFGA IAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFE I FHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKL S RGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	109
AJJ90538 A/silkie chicken/Shenzhen/918/2013 2013/12/09 HA 755178174	MNTQILVFALIAIIP TNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKKTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDVCYPGK FVN E EALRQILRESGGIDKEAMGFTY SGIRANGATSACRRSGSSFYAEMKWLLSNTDNAAFPMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTII SNLPFQNI DSR AVGKCP RYVKQRSLLLATGMKNVPEIPKGRGLFGA IAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFE I FHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	110

Accession No / Strain / Protein	Amino Acid Sequence	SEQ ID NO:
AJJ90576 A/chicken/Shen zhen/1665/2013 2013/12/12 HA 755178238	MNTQILVFALIAIPTNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKKTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDICYPGKFFVNEEALRQILRESGGIDKEAMGFTY SGIRANGATSACKRSGSSFYAEMKWLLSNTDNAAFPMQTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWMLNPNNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTII SNLPFQNI DSRVKGCP RYVKQRSLLLATGMKNVPEIPKGRGLFGAIAAGFIENGWEGLIDGW YGFRHQNAQGEETAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSRGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	111
AJJ90588 A/chicken/Shen zhen/2110/2013 2013/12/13 HA 755178258	MNTQILVFALIAIPTNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKKTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDVCYPGKFFVNEEALRQILRESGGIDKEAMGFTY SGIRANGATSACRRSGSSFYAEMKWLLSNTDNAAFPMQTKSYKNT RRSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWMLNPNNDTVTF SFNGAFIAPDRASFLR GKSIQGIQSGVQVDANCEGDCYHSGGTII SNLPFQNI DSRVKGCP RYVKQRSLLLATGMKNVPEIPKGRGLFGAIAAGFIENGWEGLIDGW YGFRHQNAQGEETAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	112
AJJ90661 A/chicken/Dong guan/2912/2013 2013/12/18 HA 755178380	MNTQILVFALIAIPTNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKKTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDVCYPGKFFVNEEALRQILRESGGIDKEAMGFTY SGIRANGATSACRRSGSSFYAEMKWLLSNTDNAAFPMQTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWMLNPNNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTII SNLPFQNI DSRVKGCP RYVKQRSLLLATGMKNVPEIPKGRGLFGAIAAGFIENGWEGLIDGW YGFRHQNAQGEETAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFEIFHKCDNDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	113
AJJ90673 A/silkie chicken/Donggu an/3049/2013 2013/12/18 HA 755178400	MNTQILVFALTAIPTNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKKTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDVCYPGKFFVNEEALRQILRESGGIDKEAMGFTY SGIRANGATSACRRSGSSFYAEMKWLLSNTDNAAFPMQTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWMLNPNNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTII SNLPFQNI DSRVKGCP RYVKQRSLLLATGMKNVPEIPKGRGLFGAIAAGFIENGWEGLIDGW YGFRHQNAQGEETAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFEIFHKCDNDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	114

Accession No / Strain / Protein	Amino Acid Sequence	SEQ ID NO:
AJJ90795 A/silkie chicken/Donggu an/3281/2013 2013/12/18 HA 755178604	MNTQILVFALIAIIPTNADKICLGHHAVPNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKKTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDVCYPGKFFVNEEALRQILRESGGIDKEAMGFTY SGIRANGATSACRRSGSSFYAEMKWLLSNTDNAAFPMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWMLNPNNDTVTFSFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTIIISNLPFQNIIDRAVKGCP RYVKQRSLLLATGMKNVPEIPKGRGLFGAIIAGFIENGWEGLIDGW YGFRHQNAQGEETAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	115
AJJ90891 A/silkie chicken/Donggu an/3520/2013 2013/12/19 HA 755178764	MNTQILVFALIAIIPTNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKKTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDVCYPGKFFVNEEALRQILRESGGIDKEAMGFTY SGIRANGATSACRRSGSSFYAEMKWLLSNTDNAAFPMTKSYKNT RKXPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWMLNPNNDTVTFSFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTIIISNLPFQNIIDRAVKGCP RYVKQRSLLLATGMKNVPEIPKGRGLFGAIIAGFIENGWEGLIDGW YGFRHQNAQGEETAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFEIFHKCDNDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	116
AJJ90951 A/chicken/Dong guan/3544/2013 2013/12/19 HA 755178864	MNTQILVFALIAIIPTNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKKTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDVCYPGKFFVNEEALRQILRESGGIDKEAMGFTY SGIRANGATSACRRSGSSFYAEMKWLLSNTDNAAFPMTKSYRNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWMLNPNNDTVTFSFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTIIISNLPFQNIIDRAVKGCP RYVKQRSLLLATGMKNVPEIPKGRGLFGAIIAGFIENGWEGLIDGW YGFRHQNAQGEETAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	117
AJJ91035 A/chicken/Shen zhen/3780/2013 2013/12/19 HA 755179004	MNTQILVFALIAIIPTNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKKTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDVCYPGKFFVNEEALRQILRESGGIDKEAMGFTY SGIRANGATSACRRSGSSFYAEMKWLLSNTDNAAFPMTKSYKNT RRSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWMLNPNNDTVTFSFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTIIISNLPFQNIIDRAVKGCP RYVKQRSLLLATGMKNVPEIPKGRGLFGAIIAGFIENGWEGLIDGW YGFRHQNAQGEETAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	118

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AJJ91155 A/chicken/Dong guan/4037/2013 2013/12/19 HA 755179204	MNTQILVFALIAIIP TNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKKTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDVCYPGK FVN E EALRQILRESGGIDKEAMGFTY SGIRANGATSACRRSGSSFYAEMKWLLSNTDNAAFPMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTII SNLPFQNI DSRVKGCP RYVKQRSLLLATGMKNVPEIPKGRGLFGA IAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMNKLYERVKRQLRENAEEDGTGCFE I FHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	119
AJJ92005 A/chicken/Shen zhen/801/2013 2013/12/09 HA 755180629	MNTQILVFALIAIIP TNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKKTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDVCYPGK FVN E EALRQILRESGGIDKEAMGFTY SGIRANGATSACRRSGSSFYAEMKWLLSNTDNAAFPMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTII SNLPFQNI DSRVKGCP RYVKQRSLLLATGMKNVPEIPKGRGLFGA IAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFE I FHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKL S RGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	120
AJJ94254 A/chicken/Dong guan/1374/2014 2014/02/21 HA 755184382	MNTQILVFALIAIIP TNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKKTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDVCYPGK FVN E EALRQILRESGGIDKEAMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNTDNAAFPMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDTVTF SFNGAFIAPERASFLR GKSMGIQSGVQVDANCEGDCYHSGGTII SNLPFQNI DSRVKGCP RYVKQRSLLLATGMKNVPEIPKGRGLFGA IAGFIENGWEGLIDGW YGFKHQNAQGE GTAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVETQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFE I FHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	121
AJJ94606 A/chicken/Dong guan/191/2014 2014/02/20 HA 755184968	MNTQILVFALIAIIP TNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKKTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDVCYPGK FVN E EALRQILRKSGGIDKEAMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNTDNAAFPMTKSYKNT RKSPAII V WGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDADCEGDCYHSGGTII SNLPFQNI DSRVKGCP RYVKQRSLLLATGMKNVPEIPKGRGLFGA IAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFE I FHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	122

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AJJ96552 A/chicken/Jiangxi/12206/2014 2014/03/16 HA 755188219	MNTQILVFALIAIIP TNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKKTIDLGQCGLLGTTITGPPQCDQFLEF SADLI IERREGSDVCYPGK FVNEEALRQILRESGGIDKEAMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNTDNAAFPMQTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTII SNLPFQNI DSRVAGKCP RYVKQKSLLLATGMKNVPEIPKGRGLFGA IAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFE IFHKCDDDCMASIRNNT YDHNKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	123
AJJ96684 A/chicken/Jiangxi/13207/2014 2014/03/30 HA 755188439	MNTQILVFALIAIIP TNADKICLGHHAVSNGTKINTLTERGVEVV NATETVERTNIPRICSKGKKTVDLGQCGLLGTTITGPPQCDQFLEF SADLI IERREGSDVCYPGK FVNEEALRQILRESGGIDKEAMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNTDNAAFPMQTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTII SNLPFQNI DSRVAGKCP RYVKQKSLLLATGMKNVPEIPKGRGLFGA IAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITELWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFE IFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	124
AJJ96732 A/chicken/Jiangxi/13223/2014 2014/03/30 HA 755188519	MNTQILVFALIAIIP TNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKKTVDLGQCGLLGTTITGPPQCDQFLEF SADLI IERREGSDVCYPGK FVNEEALRQILRESGGIDKEAMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNTDNAAFPMQTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTII SNLPFQNI DSRVAGKCP RYVKQKSLLLATGMKNVPEIPKGRGLFGA IAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITELWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFE IFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	125
AJK00354 A/duck/Zhejiang/LS02/2014 2014/01/12 HA 755194469	MNTQILVFALVAIIP TNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKKTVDLGQCGLLGTTITGPPQCDQFLEF SADLIVERREGSDVCYPGK FVNEEALRQILRESGGIDKEAMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNTDNAAFPMQTKSYKNT RKDPALIIWGIHHSGSTTEQTKLYGSGNKLITVGSSNYQQSFVPS PGARPLVNGQSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTII SNLPFQNI NSRAVAGKCP RYVKQESLLLATGMKNVPEVPKGRGLFGA IAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQVTGKLNRLIEKTNQQFELI DHEFTEVEKQIGNVINWTRDSMTEVWSYNAELLVAMENQHTIDLA DSEMKNLYERVKRQLRENAEEDGTGCFE IFHKCDNDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	126

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AJJ91264 A/silkie chicken/Dongguan/4129/2013 2013/12/19 HA 755179386	MNTQILVFALIAIIP TNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKKTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDVCYPGK FVN E EALRQILRESGGIDKEAMGFTY SGIRANGATSACRRSGSSFYAEMKWLLSNTDNAAFPMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTII SNLPFQNI DSRVAGKCP RYVKQRSLLLATGMKNVPEIPKGRGLFGA IAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRLMEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFE I FHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	127
AJJ91314 A/chicken/Shaoxing/2417/2013 2013/10/20 HA 755179470	MNTQILVFALIAIIP TNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKRTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDVCYPGK FVN E EALRQILRESGGIDKEAMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNTDNAAFPMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPPVNGLSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTII SNLPFQNI DSRVAGKCP RYVKQRSLLLATGMKNVPEIPKGRGLFGA IAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFE I FHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	128
AJJ91402 A/chicken/Huzhou/4045/2013 2013/10/24 HA 755179618	MNTQILVFALIAIIP TNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKRTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDVCYPGK FVN E EALRQILRESGGIDKEAMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNTDNAAFPMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTII SNLPFQNI DSRVAGKCP RYVKQRSLLLATGMKNVPEIPKGRGLFGA IAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITELWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFE I FHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKEVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	129
AJJ91476 A/chicken/Huzhou/4076/2013 2013/10/24 HA 755179743	MNTQILVFALIAIIP TNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKRTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDVCYPGK FVN E EALRQILRKSGGIDKEAMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNTDNAAFPMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSRGTII SNLPFQNI DSRVAGKCP RYVKQRSLLLATGMKNVPEIPKGRGLFGA IAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFE I FHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	130

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AJJ91725 A/chicken/Shao xing/5201/2013 2013/10/28 HA 755180161	MNTQILVFALIAIIP TNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKRTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDVCYPGK FVN E EALRQILRESGGIDKEAMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNTDNAAFPMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTII SNLPFQNI DSRVKGCP RYVKQRSLLLATGMKNVPEIPKGRGLFGA IAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITELWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	131
AJJ91885 A/Shenzhen/SP4 /2014 2014/01/16 HA 755180429	MNTQILVFALIAIIP TNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKKTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDVCYPGK FVN E EALRQILRESGGIDKEAMGFTY SGIRANGVTSACRRSGSSFYAEMKWLLSNTDNAAFPMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTII SNLPFQNI DSRVKGCP RYVKQRSLLLATGMKNVPEIPKGRGLFGA IAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKL S RGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	132
AJJ91909 A/Shenzhen/SP2 6/2014 2014/01/20 HA 755180469	MNTQILVFALIAIIP TNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKKTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDICYPGK FVN E EALRQILRESGGIDKEAMGFTY SGIRANGATSACKRSGSSFYAEMKWLLSNTDNAAFPMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTII SSLPFQNI DSRVKGCP RYVKQRSLLLATGMKNVPEIPKGRGLFGA IAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFEIFHKCDDGCMASIRNNT YDHSKYREEAMQNRIQIDPVKL S RGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	133
AJJ91945 A/Shenzhen/SP3 8/2014 2014/01/22 HA 755180529	MNTQILAFALIAIIP TNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKKTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDVCYPGK FVN E EALRQILRESGGIDKEAMGFTY SGIRANGATSACRRSGSSFYAEMKWLLSNTDNAAFPMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTII SNLPFQNI DSRVKGCP RYVKQRSLLLATGMKNVPEIPKGRGLFGA IAGFIENGWEGLIGGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	134

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AJJ91957 A/Shenzhen/SP4 4/2014 2014/01/23 HA 755180549	MNTQILVFALIAIIP TNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKRTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDVCYPGK FVN E EALRQILRESGGIDKEAMGFTY SGIRANGTTSACRRSGSSFYAEMKWLLSNTDNAAFPMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTIISSLPFQNI DSRAVGKCP RYVKQRSLLLATGMKNVPEIPKGRGLFGA IAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFE I FHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	135
AJJ91969 A/Shenzhen/SP4 8/2014 2014/01/23 HA 755180569	MNTQILVFALIAIIP TNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKKTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDVCYPGK FVN E EALRQILRESGGIDKEAMGFTY SGIRTNGATSACRRSGSSFYAEMKWLLSNTDNAAFPMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTII SNLPFQNI DSRAVGKCP RYVKQRSLLLATGMKNVPEIPKGRGLFGA IAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVETQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFE I FHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	136
AJJ91993 A/chicken/Dong guan/4119/2013 2013/12/19 HA 755180609	MNTQILVFALIAIIP TNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKKTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDVCYPGK FVN E EALRQILRESGGIDKEAMGFTY SGIRANGATSACRRSGSSFYAEMKWLLSNTDNAAFPMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTII SNLPFQNI DSRAVGKCP RYVKQRSLLLATGMKNVPEIPKGRGLLGA IAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFE I FHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFTLLAI VMGLVFICVKNGNMRCTICI	137
AJJ92031 A/chicken/Dong guan/4064/2013 2013/12/19 HA 755180672	MNTQILVFALIAIIP TNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKKTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDVCYPGK FVN E EALRQILRESGGIDKEAMGFTY SGIRANGATSACRRSGSSFYAEMKWLLSNTDNAAFPMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVESSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTII SNLPFQNI DSRAVGKCP RYVKQRSLLLATGMKNVPEIPKGRGLFGA IAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFE I FHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	138

Accession No / Strain / Protein	Amino Acid Sequence	SEQ ID NO:
AJJ92967 A/silkie chicken/Jiangxi/9469/2014 2014/02/16 HA 755182232	MNTQILVFALIAIVPTNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKKTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDVCYPGKFFVNEEALRQILRESGGIDKEAMGFTY SGIRTNGVTSACRRSGSSFYAEMKWLLSNTDNAAFPQMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTII SNLPFQNI DSRVKGCP RYVKQKSLLLATGMKNVPEIPKGRGLFGAIAAGFIENGWEGLIDGW YGFRHQNAQGEETAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	139
AJJ93027 A/chicken/Jiangxi/9558/2014 2014/02/16 HA 755182332	MNTQILVFALIAIVPTNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKKTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDVCYPGKFFVKEEALRQILRESGGIDKEAMGFTY SGIRTNGVTSACRRSGSSFYAEMKWLLSNTDNAAFPQMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTII SNLPFQNI DSRVKGCP RYVKQKSLLLATGMKNVPEIPKGRGLFGAIAAGFIENGWEGLIDGW YGFRHQNAQGEETAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	140
AJJ93051 A/chicken/Jiangxi/10573/2014 2014/02/18 HA 755182372	MNTQILVFALIAIVPTNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKKTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDVCYPGKFFVNEEALRQILRESGGIDKEAMGFTY SGIRTNGVTSACRRSGSSFYAEMKWLLSNTDDAAFPQMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTII SNLPFQNI DSRVKGCP RYVKQKSLLLATGMKNVPEIPKGRGLFGAIAAGFIENGWEGLIDGW YGFRHQNAQGEETAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	141
AJJ93845 A/silkie chicken/Dongguan/157/2014 2014/02/20 HA 755183695	MNTQILVFALIAIIPNTNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKKTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDVCYPGKFFVNEEALRQILRESGGIDKEAMGFTY SGIRANGATSACRRSGSSFYAEMKWLLSNTDNAAFPQMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTII SNLPFQNI DSRVKGCP RYVKQKSLLLATGMKNVPEIPKGRGLFGAIAAGFIENGWEGLIDGW YGFRHQNAQGEETAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFEIFHKCDNDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	142

Accession No / Strain / Protein	Amino Acid Sequence	SEQ ID NO:
AJJ93857 A/chicken/Dong guan/169/2014 2014/02/20 HA 755183715	MNTQILVFALIAIIP TNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKKTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDVCYPGK FVN E EALRQILRKSGGIDKEAMGFTY SGIRTNGATSACMRSGSSFYAEMKWLLSNTDNAAFPMTKSYKNT RKSPAIIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDADCEGDCYHSGGTII SNLPFQNI DSRVKGCP RYVKQRSLLLATGMKNVPEIPKGRGLFGAIAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	143
AJJ93869 A/chicken/Dong guan/173/2014 2014/02/20 HA 755183735	MNTQILVFALIAIIP TNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKKTVDLGQCGLLGTVTGPPQCDQFLEF SADLIIERREGSDVCYPGK FVN E EALRQILRESGGIDKEAMGFTY SGIRANGATSACRRSGSSFYAEMKWLLSNTDNAAFPMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTII SNLPFQNI DSRVKGCP RYVKQKSLLLATGMKNVPEIPKGRGLFGAIAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFEIFHKCDNDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	144
AJJ93881 A/chicken/Dong guan/189/2014 2014/02/20 HA 755183755	MNTQILVFALIAIIP TNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKKTVDLGQCGLLGTVTGPPQCDQFLEF SADLIIERREGSDVCYPGK FVN E EALRQILRESGGIDKEAMGFTY SGIRANGATSACRRSGSSFYAEMKWLLSNTDNAAFPMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDTVTF SFNGAFIAPDRASFLR GKSMGIQSGVQVDANCEGDCYHSGGTII SNLPFQNI DSRVKGCP KYVKQKSLLLATGMKNVPEIPKGRGLFGAIAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFEIFHKCDNDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	145
AJJ93907 A/chicken/Dong guan/449/2014 2014/02/20 HA 755183799	MNTQILVFALIAIIP TNADKICLGHHAVSNGTKVNTLTERGVEVV NATETVERTNIPRICSKGKKTVDLGQCGLLGTTITGPPQCDQFLEF SADLIIERREGSDVCYPGK FVN E EALRQILRESGGIDKEAMGFTY SGIRANGATSACRRSGSSFYAEMKWLLSNTDNAAFPMTKSYKNT RKSPALIVWGIHHSVSTAEQTKLYGSGNKLVTVGSSNYQQSFVPS PGARPQVNGLSGRIDFHWLMLNPNDTVTF SFNGAFIAPERASFLR GKSMGIQSGVQVDANCEGDCYHSGGTII SNLPFQNI DSRVKGCP RYVKQRSLLLATGMKNVPEIPKGRGLFGAIAGFIENGWEGLIDGW YGFRHQNAQGE GTAADYKSTQSAIDQITGKLNRLIEKTNQQFELI DNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLA DSEMDKLYERVKRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNT YDHSKYREEAMQNRIQIDPVKLSSGYKDVILWFSFGASCFILLAI VMGLVFICVKNGNMRCTICI	146

DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

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NOTE : Pour les tomes additionels, veuillez contacter le Bureau canadien des brevets

JUMBO APPLICATIONS/PATENTS

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NOM DU FICHER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

What is claimed is:

CLAIMS

1. An influenza virus vaccine, comprising:
5 at least one ribonucleic acid (RNA) polynucleotide having an open reading frame encoding at least one influenza virus antigenic polypeptide or an immunogenic fragment thereof, formulated in a lipid nanoparticle.
2. The influenza vaccine of claim 1, wherein the at least one antigenic polypeptide is
10 influenza hemagglutinin 1 (HA1), hemagglutinin 2 (HA2), an immunogenic fragment of HA1 or HA2, or a combination of any two or more of the foregoing.
3. The influenza vaccine of claim 1, wherein at least one antigenic polypeptide is HA1, HA2, or a combination of HA1 and HA2, and at least one antigenic polypeptide is selected
15 from the group consisting of neuraminidase (NA), nucleoprotein (NP), matrix protein 1 (M1), matrix protein 2 (M2), non-structural protein 1 (NS1) and non-structural protein 2 (NS2).
4. The influenza vaccine of claim 3, wherein at least one antigenic polypeptide is HA2 and at least one antigenic polypeptide is selected from the group consisting of NA, NP, M1,
20 M2, NS1 and NS2.
5. The influenza vaccine of claim 4, wherein at least one antigenic polypeptide is HA2 and at least one antigenic polypeptides is selected from the group consisting of NA, NP, M1, M2, NS1 and NS2.
25
6. The influenza vaccine of any one of claims 1-5, wherein the at least one antigenic polypeptide is from influenza virus strain H1/PuertoRico/8/1934, H1/New Caledonia/20/1999, H1/California/04/2009, H5/Vietnam/1194/2004, H2/Japan/305/1957, H9/Hong Kong/1073/99, H3/Aichi/2/1968, H3/Brisbane/10/2007, H7/Anhui/1/2013,
30 H10/Jiangxi-Donghu/346/2013, H3/Wisconsin/67/2005, H1/Vietnam/850/2009, or a combination thereof.
7. The vaccine of any one of claims 1-6, wherein the at least one antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 1-444, 458, 460,
35 462-479.

8. The vaccine of any one of claims 1-7, wherein the at least one RNA polypeptide is encoded by a nucleic acid sequence identified by any one of SEQ ID NO: 447-457, 459, 461, and/or wherein the at least one RNA polypeptide comprises a nucleic acid sequence identified by any one of SEQ ID NO: 491-503.

9. The vaccine of any one of claims 1-8, wherein the at least one antigenic polypeptide has an amino acid sequence that has at least 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 1-444, 458, 460, 462-479.

10. The vaccine of any one of claims 1-9, wherein the at least one antigenic polypeptide has an amino acid sequence that has 95%-99% identity to an amino acid sequence identified by any one of SEQ ID NO: 1-444, 458, 460, 462-479.

11. The vaccine of any one of claims 1-10, wherein the at least one antigenic polypeptide has an amino acid sequence that has at least 90% identity to an amino acid sequence of SEQ ID NO: 1-444, 458, 460, 462-479 and wherein the antigenic polypeptide or immunogenic fragment thereof has membrane fusion activity, attaches to cell receptors, causes fusion of viral and cellular membranes, and/or is responsible for binding of the virus to a cell being infected.

12. The vaccine of any one of claims 1-11, wherein the at least one antigenic polypeptide has an amino acid sequence that has 90%-99% identity to an amino acid sequence of SEQ ID NO: 1-444, 458, 460, 462-479 and wherein the antigenic polypeptide or immunogenic fragment thereof has membrane fusion activity, attaches to cell receptors, causes fusion of viral and cellular membranes, and/or is responsible for binding of the virus to a cell being infected.

13. The vaccine of any one of claims 1-2, wherein the open reading frame is codon-optimized.

14. The vaccine of any one of claims 1-3, wherein the vaccine is multivalent.

15. The vaccine of any one of claims 1-4 formulated in an effective amount to produce an antigen-specific immune response.

16. A method of inducing an immune response in a subject, the method comprising administering to the subject the vaccine of any one of claims 1-15 in an amount effective to produce an antigen-specific immune response in the subject.

5

17. The method of claim 16, wherein the antigen specific immune response comprises a T cell response or a B cell response.

10

18. The method of claim 16 or 17, wherein the subject is administered a single dose of the vaccine.

19. The method of claim 16 or 17, wherein the subject is administered a booster dose of the vaccine.

15

20. The method of any one of claims 16-19, wherein the vaccine is administered to the subject by intradermal injection or intramuscular injection.

20

21. The method of any one of claims 16-20, wherein an anti-antigenic polypeptide antibody titer produced in the subject is increased by at least 1 log relative to a control.

22. The method of any one of claims 16-21, wherein an anti-antigenic polypeptide antibody titer produced in the subject is increased by 1-3 log relative to a control.

25

23. The method of any one of claims 16-22, wherein the anti-antigenic polypeptide antibody titer produced in the subject is increased at least 2 times relative to a control.

24. The method of any one of claims 16-23, wherein the anti-antigenic polypeptide antibody titer produced in the subject is increased 2-10 times relative to a control.

30

25. The method of any one of claims 21-24, wherein the control is an anti-antigenic polypeptide antibody titer produced in a subject who has not been administered a vaccine against the virus.

26. The method of any one of claims 21-24, wherein the control is an anti-antigenic polypeptide antibody titer produced in a subject who has been administered a live attenuated vaccine or an inactivated vaccine against the virus.

5 27. The method of any one of claims 21-24, wherein the control is an anti-antigenic polypeptide antibody titer produced in a subject who has been administered a recombinant protein vaccine or purified protein vaccine against the virus.

10 28. The method of any one of claims 21-24, wherein the control is an anti-antigenic polypeptide antibody titer produced in a subject who has been administered a VLP vaccine against the virus.

15 29. The method of any one of claims 16-28, wherein the effective amount is a dose equivalent to an at least 2-fold reduction in the standard of care dose of a recombinant protein vaccine or a purified protein vaccine against the virus, and wherein an anti-antigenic polypeptide antibody titer produced in the subject is equivalent to an anti-antigenic polypeptide antibody titer produced in a control subject administered the standard of care dose of a recombinant protein vaccine or a purified protein vaccine against the virus, respectively.

20

30. The method of any one of claims 16-28, wherein the effective amount is a dose equivalent to an at least 2-fold reduction in the standard of care dose of a live attenuated vaccine or an inactivated vaccine against the virus, and wherein an anti-antigenic polypeptide antibody titer produced in the subject is equivalent to an anti-antigenic polypeptide antibody titer produced in a control subject administered the standard of care dose of a live attenuated vaccine or an inactivated vaccine against the virus, respectively.

25

31. The method of any one of claims 16-28, wherein the effective amount is a dose equivalent to an at least 2-fold reduction in the standard of care dose of a VLP vaccine against the virus, and wherein an anti-antigenic polypeptide antibody titer produced in the subject is equivalent to an anti-antigenic polypeptide antibody titer produced in a control subject administered the standard of care dose of a VLP vaccine against the virus.

30

32. The method of any one of claims 16-31, wherein the effective amount is a total dose of 50 μ g-1000 μ g.

35

33. The method of claim 32, wherein the effective amount is a dose of 25 μ g, 100 μ g, 400 μ g, or 500 μ g administered to the subject a total of two times.

5 34. The method of any one of claims 16-33, wherein the efficacy of the vaccine against the virus is greater than 65%.

35. The method of any one of claims 16-34, wherein the vaccine immunizes the subject against the virus for up to 2 years.

10

36. The method of any one of claims 16-34, wherein the vaccine immunizes the subject against the virus for more than 2 years.

15

37. The method of any one of claims 16-36, wherein the subject has been exposed to the virus, wherein the subject is infected with the virus, or wherein the subject is at risk of infection by the virus.

38. The method of any one of claims 16-37, wherein the subject is immunocompromised.

20

39. The vaccine of any one of claims 1-15 for use in a method of inducing an antigen specific immune response in a subject, the method comprising administering to the subject the vaccine in an amount effective to produce an antigen specific immune response in the subject.

25

40. Use of the vaccine of any one of claims 1-15 in the manufacture of a medicament for use in a method of inducing an antigen specific immune response in a subject, the method comprising administering to the subject the vaccine in an amount effective to produce an antigen specific immune response in the subject.

30

41. An engineered nucleic acid encoding at least one RNA polynucleotide of a vaccine of any one of claims 1-15.

42. An expression vector comprising engineered nucleic acid encoding at least one RNA polynucleotide of a vaccine of any one of claims 1-15.

35

43. A host cell comprising an engineered nucleic acid encoding at least one RNA polynucleotide of a vaccine of any one of claims 1-16.

44. A method of producing a polypeptide, comprising culturing the host cell of claim 43 in a medium under conditions permitting expression of a polypeptide encoded by the nucleic acid, and purifying the polypeptide from the cultured cell or the medium of the cell.

45. A multiple consensus subtype vaccine comprising at least one ribonucleic acid (RNA) polynucleotide having an open reading frame encoding at least one influenza virus antigenic polypeptide or an immunogenic fragment thereof, wherein the vaccine provides cross-reactivity against a variety of influenza strains, the vaccine comprising at least one consensus hemagglutinin antigen.

46. The vaccine of claim 45, wherein the consensus hemagglutinin antigen is selected from the group consisting of influenza hemagglutinin 1 (HA1), hemagglutinin 2 (HA2), an immunogenic fragment of HA1 or HA2, or a combination of any two or more of the foregoing.

47. The vaccine of claim 45, wherein at least one antigenic polypeptide is HA1, HA2, or a combination of HA1 and HA2, and at least one antigenic polypeptide is selected from the group consisting of neuraminidase (NA), nucleoprotein (NP), matrix protein 1 (M1), matrix protein 2 (M2), non-structural protein 1 (NS1) and non-structural protein 2 (NS2).

48. The vaccine of claim 47, wherein at least one antigenic polypeptide is HA2 and at least one antigenic polypeptide is selected from the group consisting of NA, NP, M1, M2, NS1 and NS2.

49. The vaccine of claim 48, wherein at least one antigenic polypeptide is HA2 and at least one antigenic polypeptides is selected from the group consisting of NA, NP, M1, M2, NS1 and NS2.

50. The vaccine of any one of claims 45-49, wherein the at least one antigenic polypeptide is from influenza virus strain H1/PuertoRico/8/1934, H1/New Caledonia/20/1999, H1/California/04/2009, H5/Vietnam/1194/2004, H2/Japan/305/1957, H9/Hong Kong/1073/99, H3/Aichi/2/1968, H3/Brisbane/10/2007, H7/Anhui/1/2013,

H10/Jiangxi-Donghu/346/2013, H3/Wisconsin/67/2005, H1/Vietnam/850/2009, or a combination thereof.

51. The vaccine of any one of claims 45-49, formulated in a lipid nanoparticle.

5

52. The vaccine of claim 51 or any one of claims 1-15, wherein the nanoparticle has a mean diameter of 50-200 nm.

53. The vaccine of claim 51 or any one of claims 1-15, wherein the lipid nanoparticle
10 comprises a cationic lipid, a PEG-modified lipid, a sterol and a non-cationic lipid.

54. The vaccine of claim 53, wherein the lipid nanoparticle carrier comprises a molar ratio of about 20-60% cationic lipid, 0.5- 15% PEG-modified lipid, 25-55% sterol, and 25% non-cationic lipid.

15

55. The vaccine of claim 54, wherein the cationic lipid is an ionizable cationic lipid and the non-cationic lipid is a neutral lipid, and the sterol is a cholesterol.

56. The vaccine of claim 54, wherein the cationic lipid is selected from 2,2-dilinoleyl-4-
20 dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319).

57. The vaccine of any one of claims 51-56, wherein the nanoparticle has a polydispersity
25 value of less than 0.4.

58. The vaccine of any one of claims 51-57, wherein the nanoparticle has a net neutral charge at a neutral pH value.

30 59. The vaccine of any one of claims 1-15 or 45-58, wherein the at least one RNA polynucleotide comprises at least one chemical modification.

60. The vaccine of claim 59, wherein the chemical modification is selected from pseudouridine, N1-methylpseudouridine, N1-ethylpseudouridine, 2-thiouridine, 4'-
35 thiouridine, 5-methylcytosine, 5-methyluridine, 2-thio-1-methyl-1-deaza-pseudouridine, 2-

thio-1-methyl-pseudouridine, 2-thio-5-aza-uridine, 2-thio-dihydropseudouridine, 2-thio-dihydrouridine, 2-thio-pseudouridine, 4-methoxy-2-thio-pseudouridine, 4-methoxy-pseudouridine, 4-thio-1-methyl-pseudouridine, 4-thio-pseudouridine, 5-aza-uridine, dihydropseudouridine, 5-methoxyuridine and 2'-O-methyl uridine.

5

61. A method of inducing cross-reactivity against a variety of influenza strains in a mammal, the method comprising administering to the mammal in need thereof the vaccine of any one of claims 1-15 or 45-60.

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62. The method of claim 61, wherein at least two ribonucleic acid (RNA) polynucleotides having an open reading frame each encoding a consensus hemagglutinin antigen are administered to the mammal separately.

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63. The method of claim 61, wherein at least two ribonucleic acid (RNA) polynucleotides having an open reading frame each encoding a consensus hemagglutinin antigen are administered to the mammal simultaneously.

20

64. A pharmaceutical composition for use in vaccination of a subject comprising an effective dose of mRNA encoding an influenza virus antigen,
wherein the effective dose is sufficient to produce detectable levels of antigen as measured in serum of the subject at 1-72 hours post administration.

25

65. The composition of claim 64, wherein the cut off index of the antigen is 1-2.

66. A pharmaceutical composition for use in vaccination of a subject comprising an effective dose of mRNA encoding an influenza virus antigen,
wherein the effective dose is sufficient to produce a 1,000- 10,000 neutralization titer produced by neutralizing antibody against said antigen as measured in serum of the subject at 1-72 hours post administration.

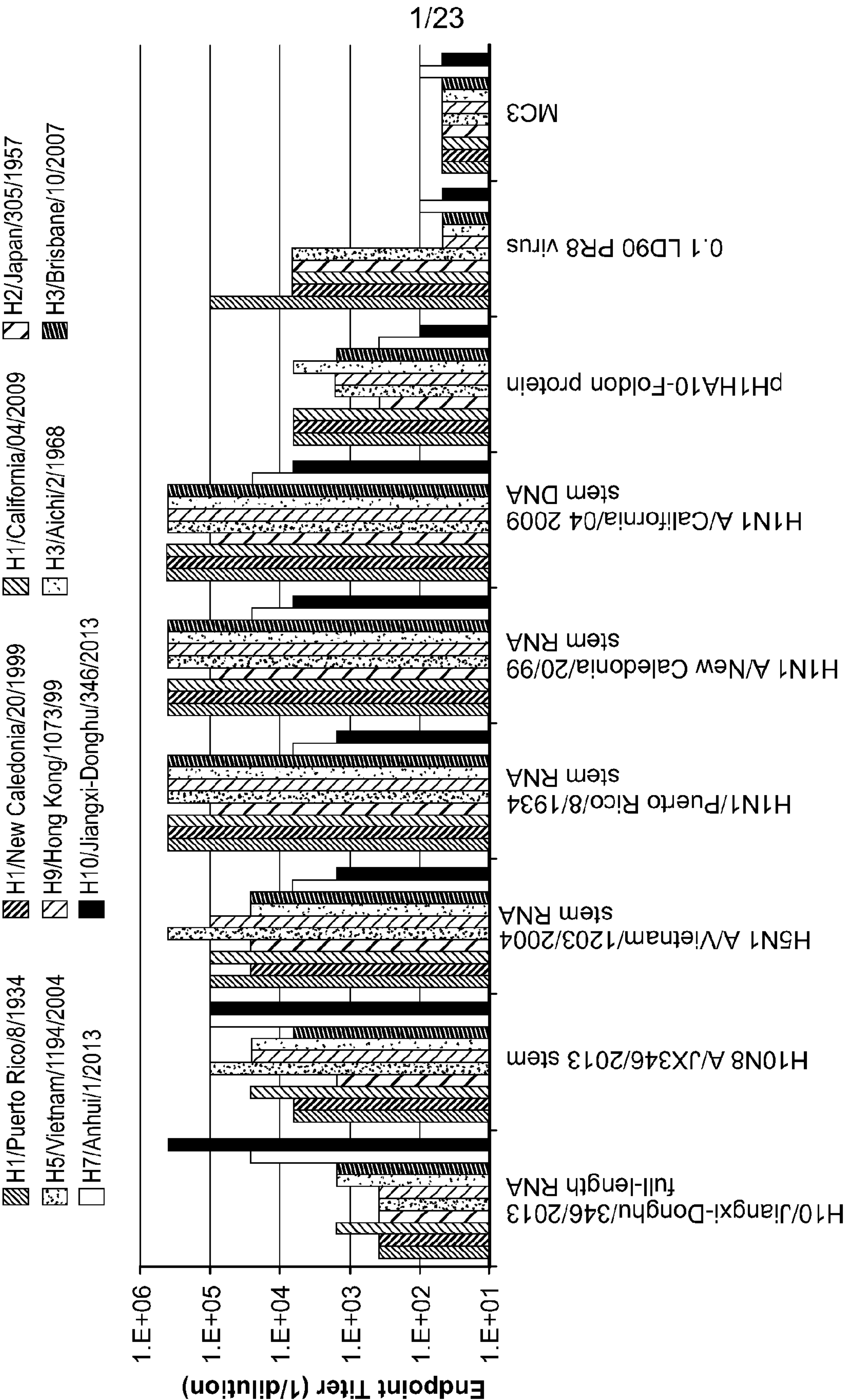


Fig. 1

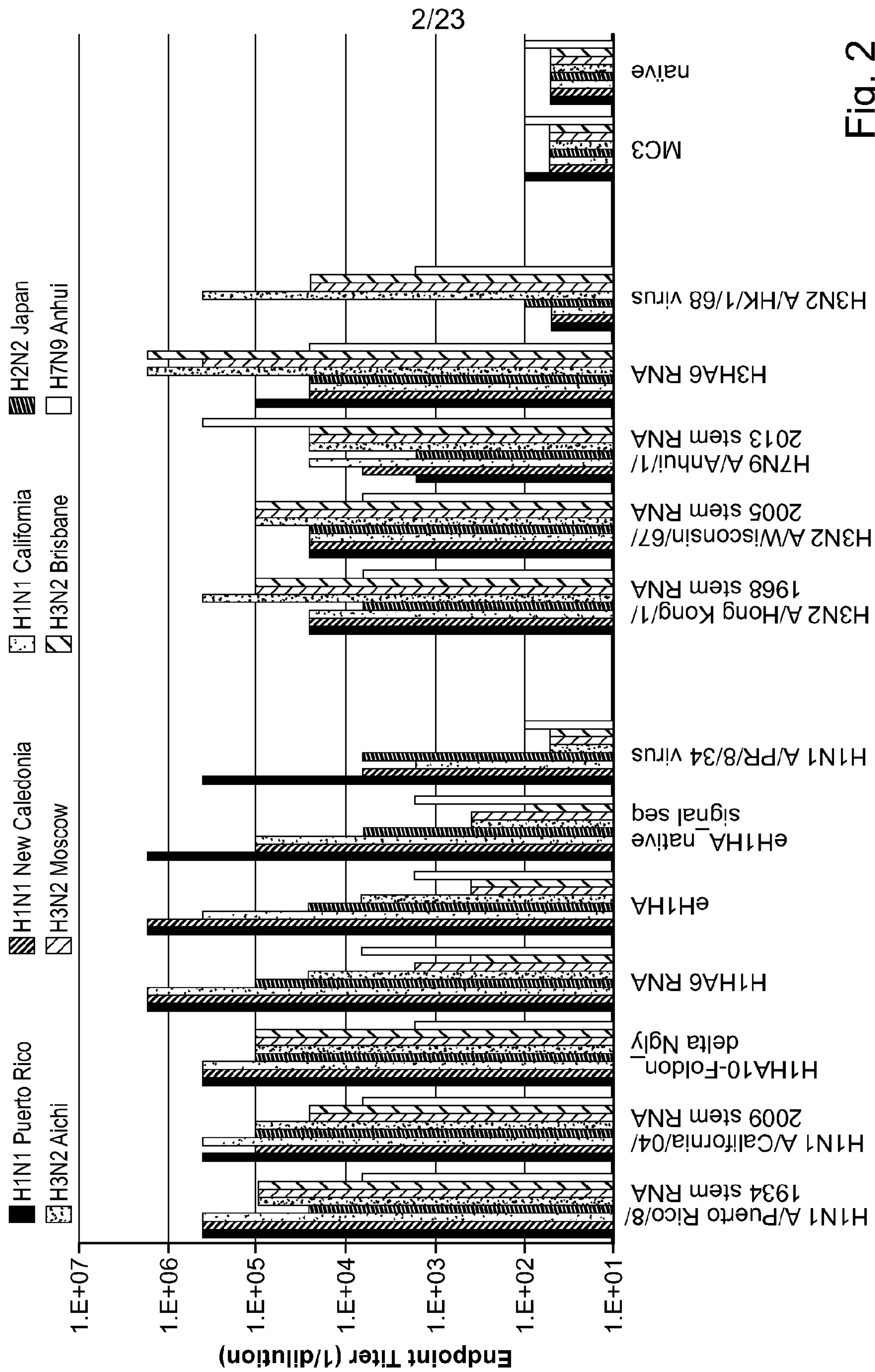


Fig. 2

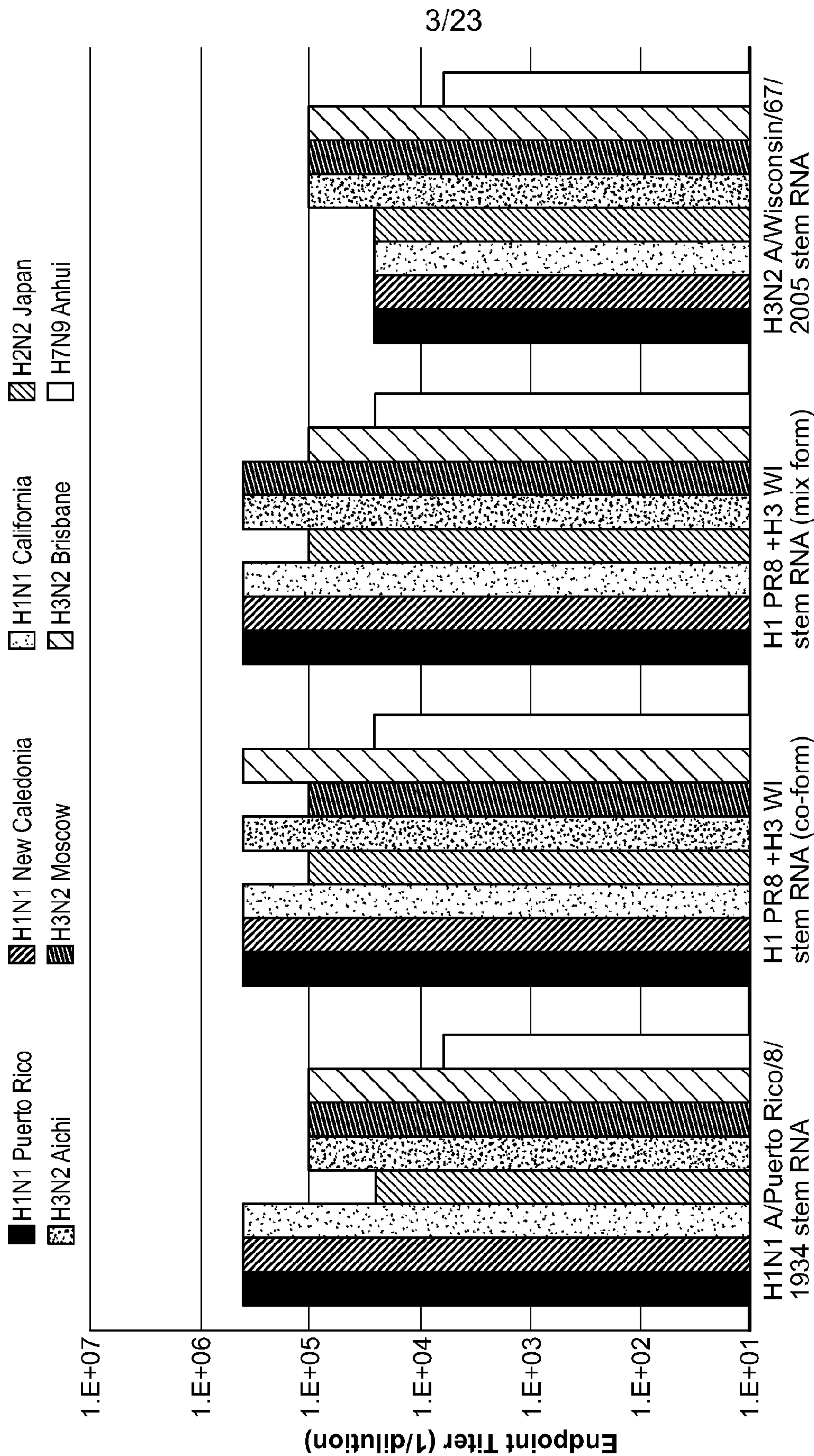


Fig. 3

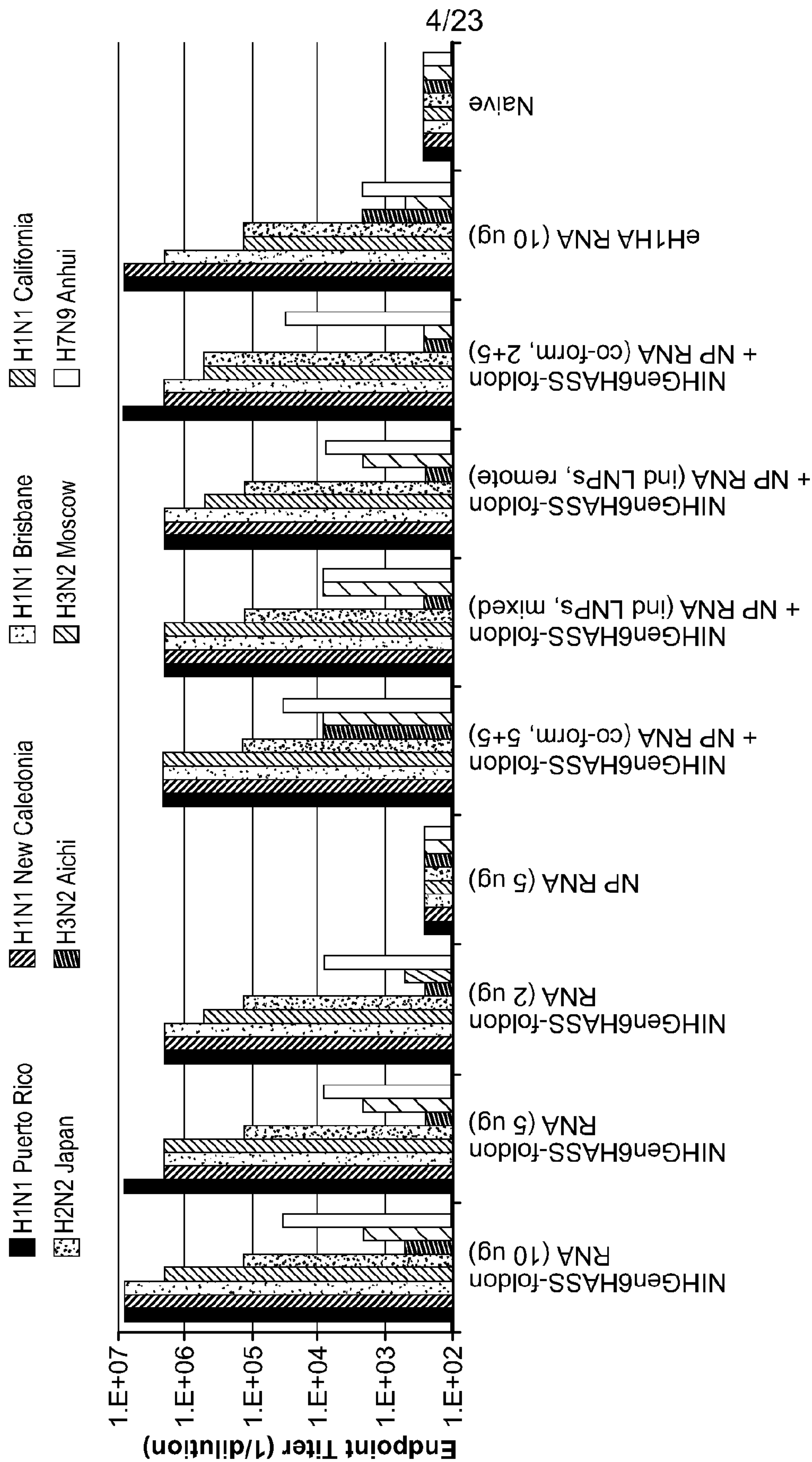


Fig. 4A

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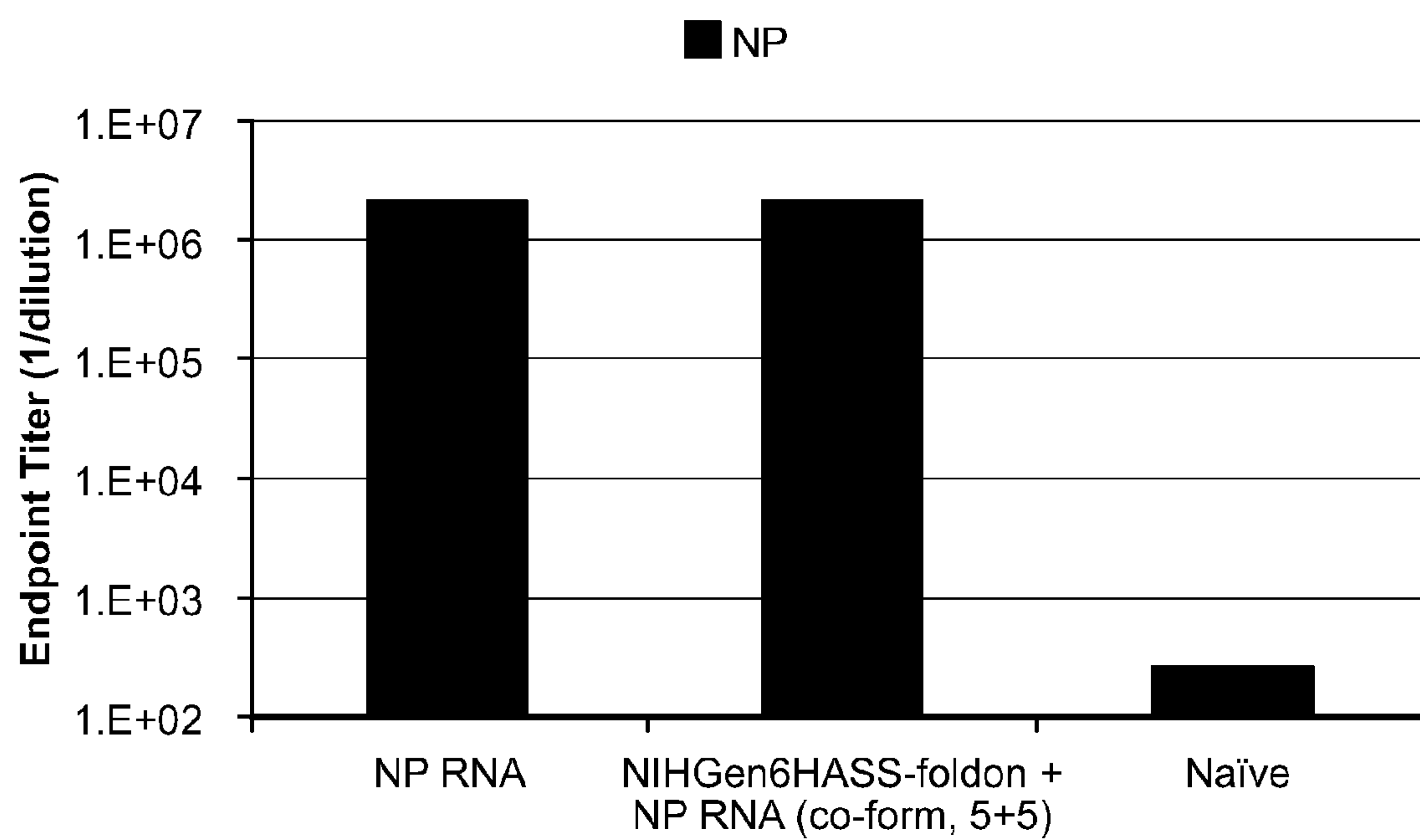


Fig. 4B

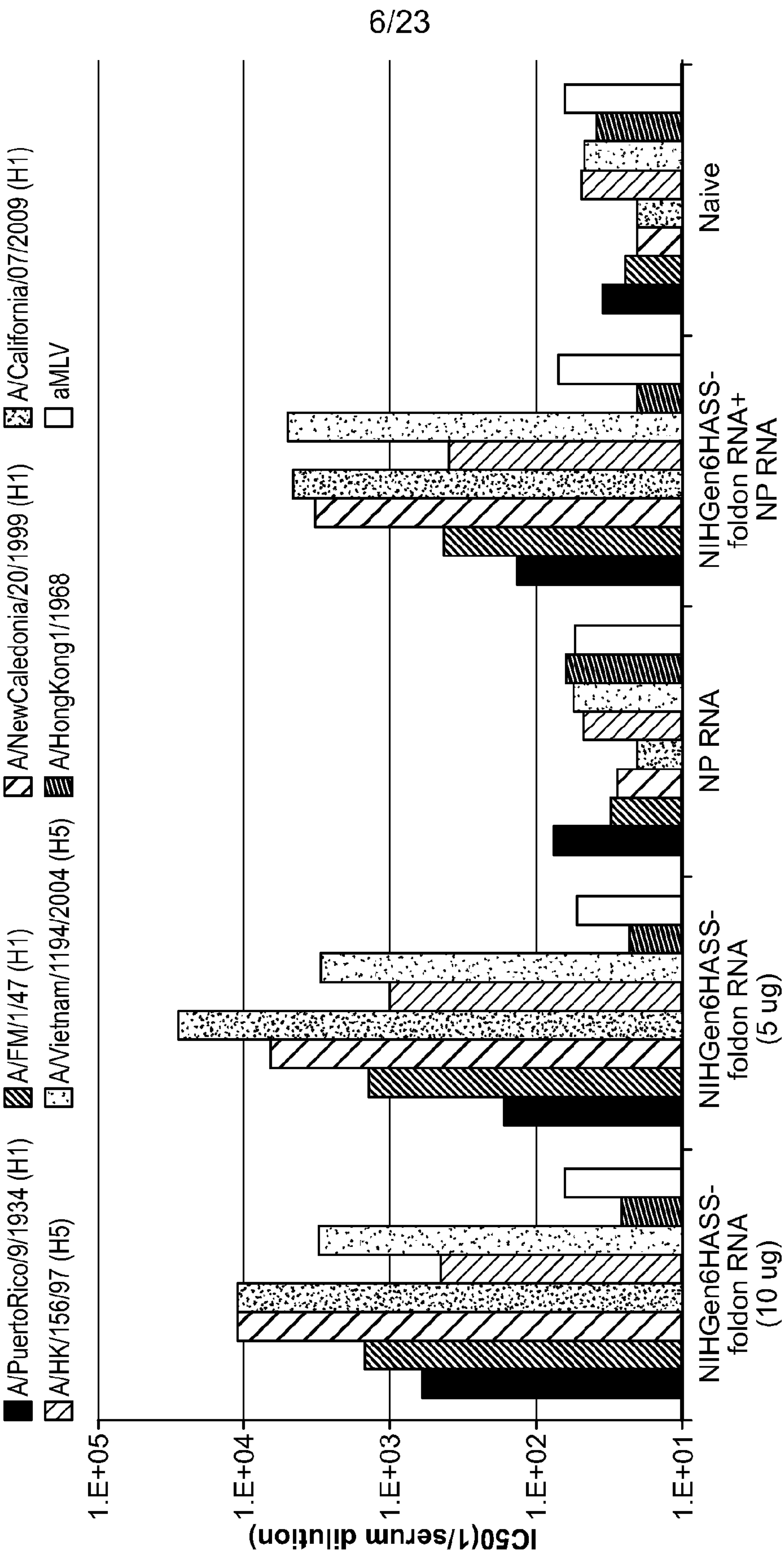
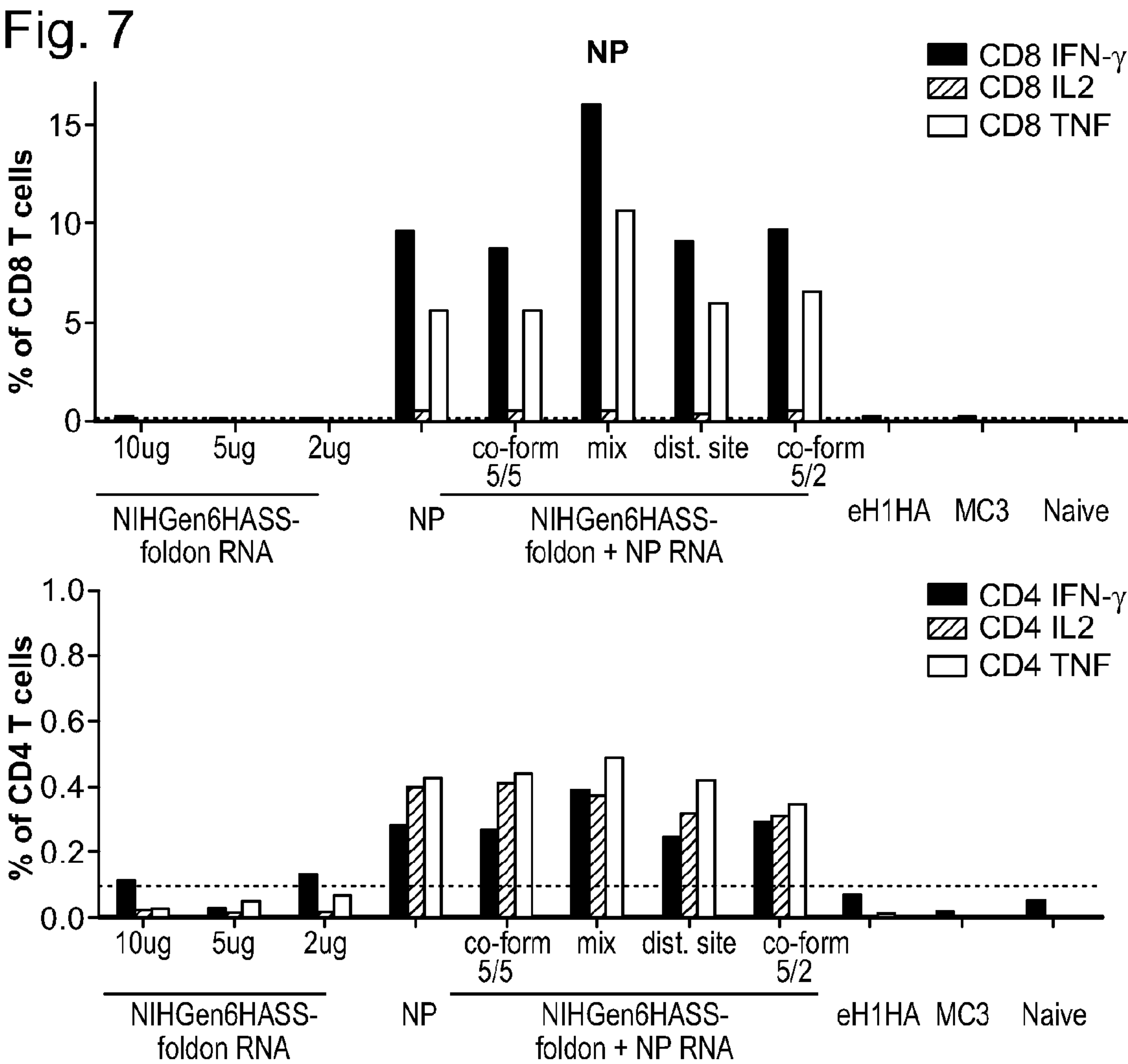
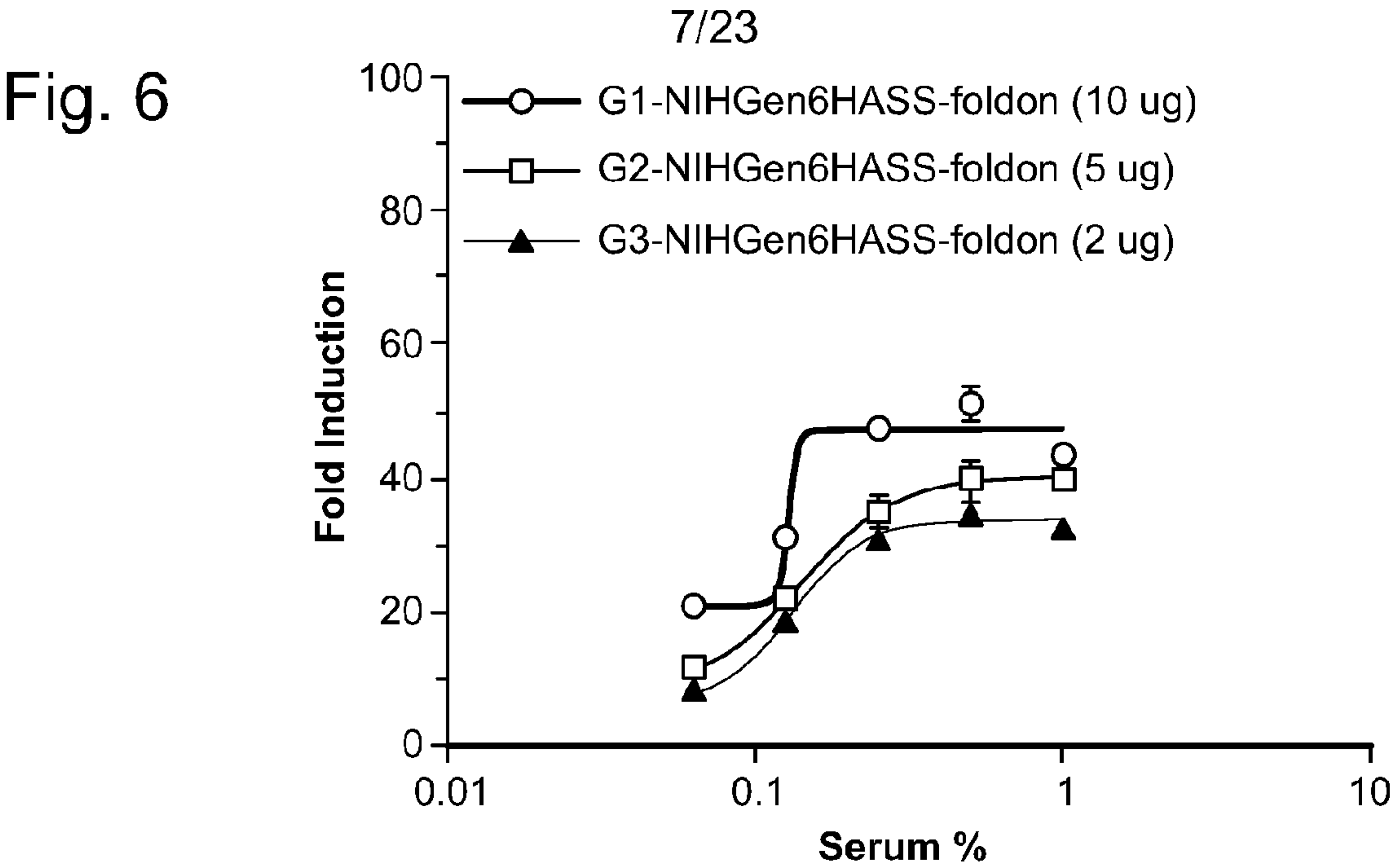


Fig. 5



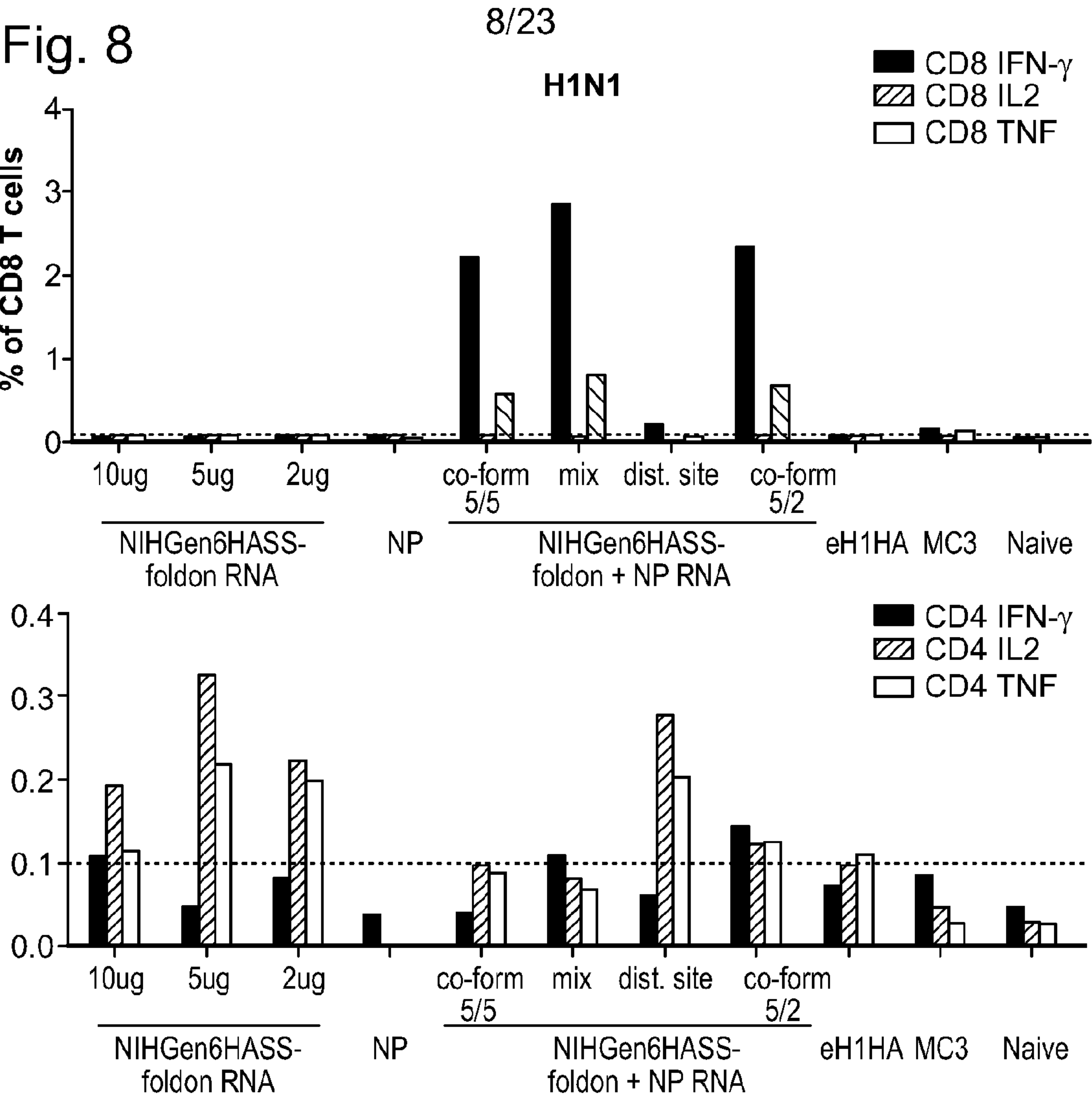
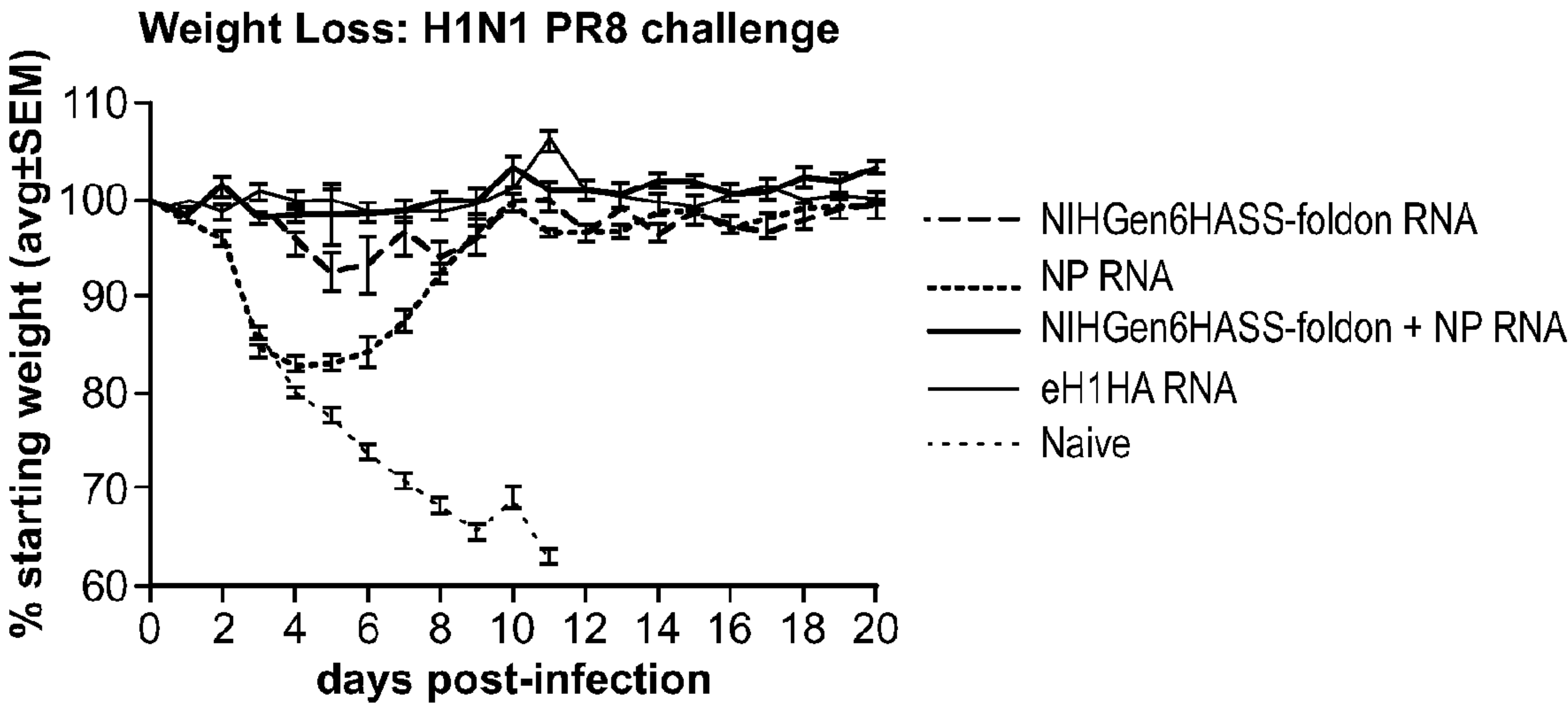
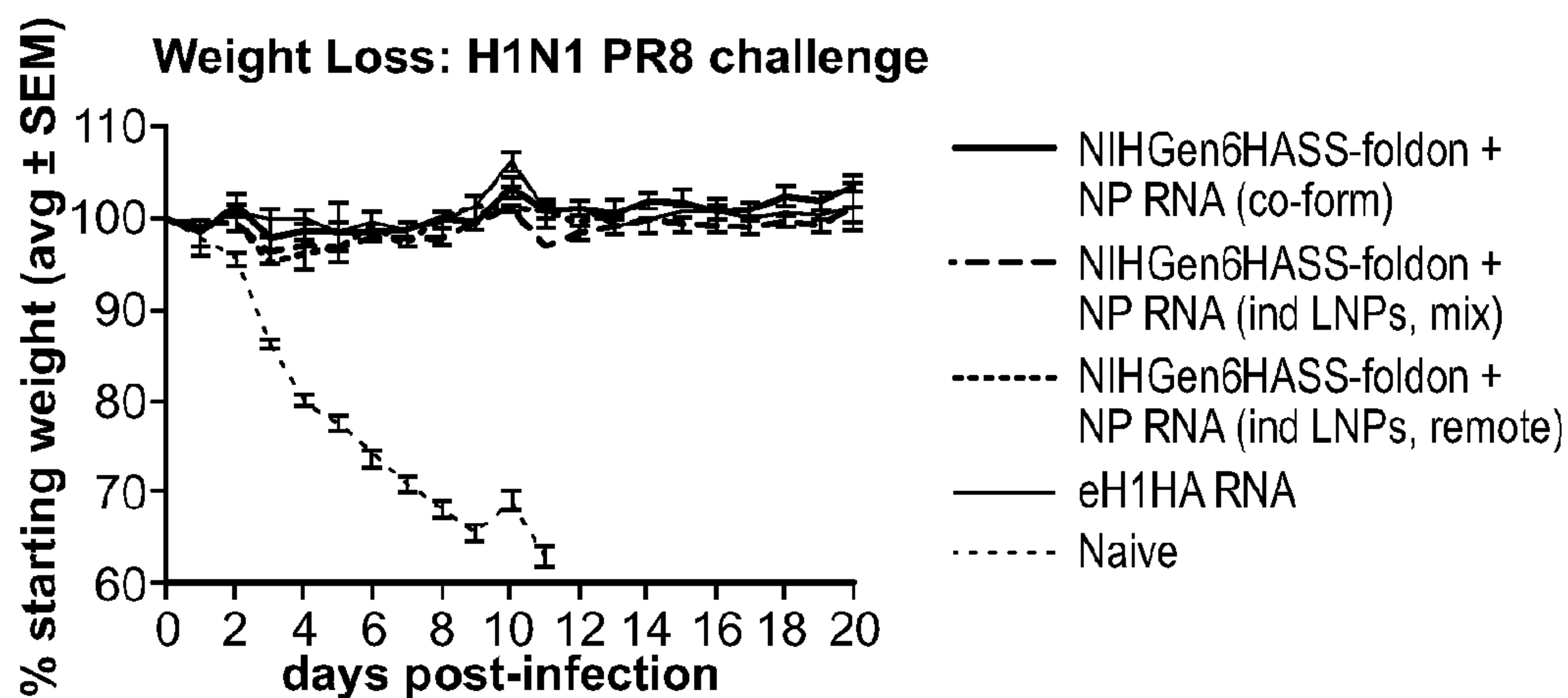
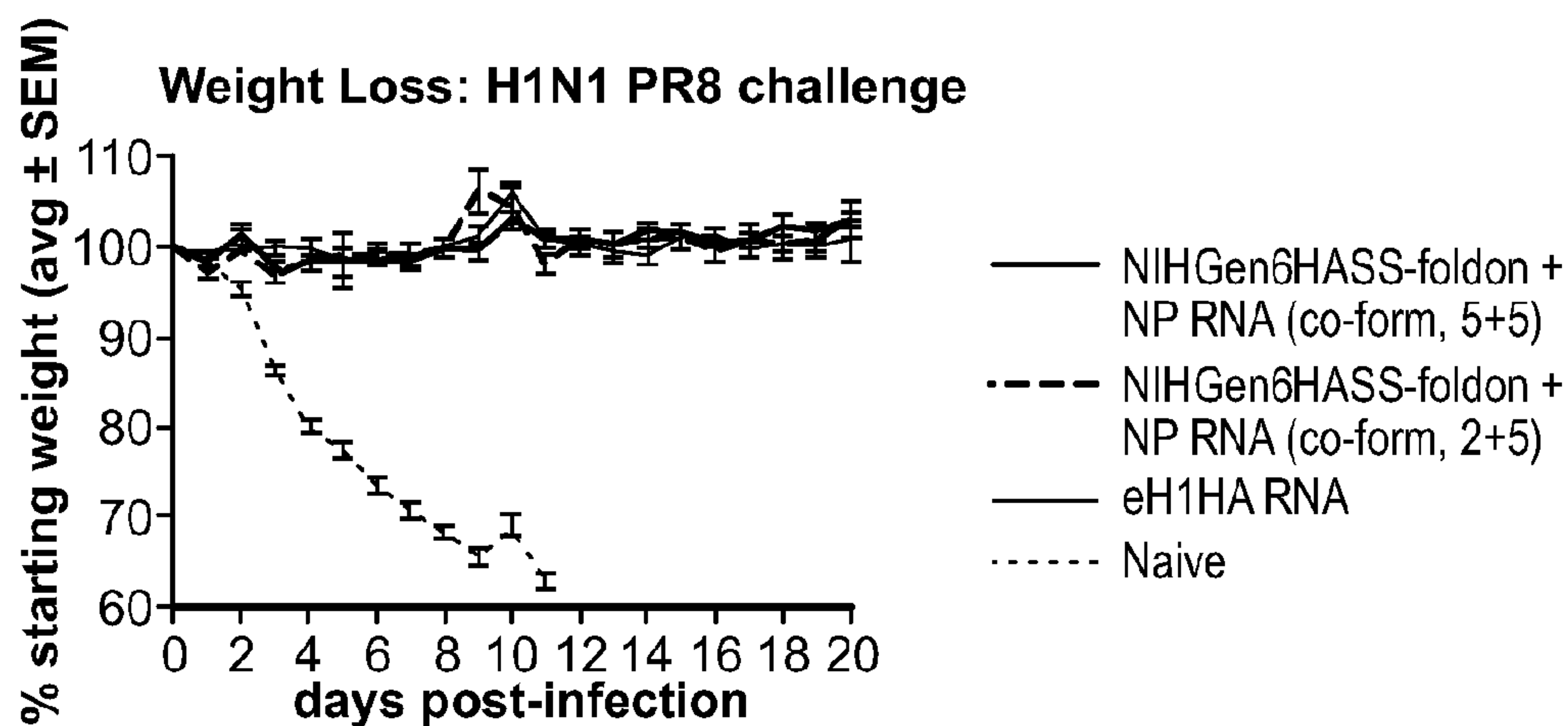
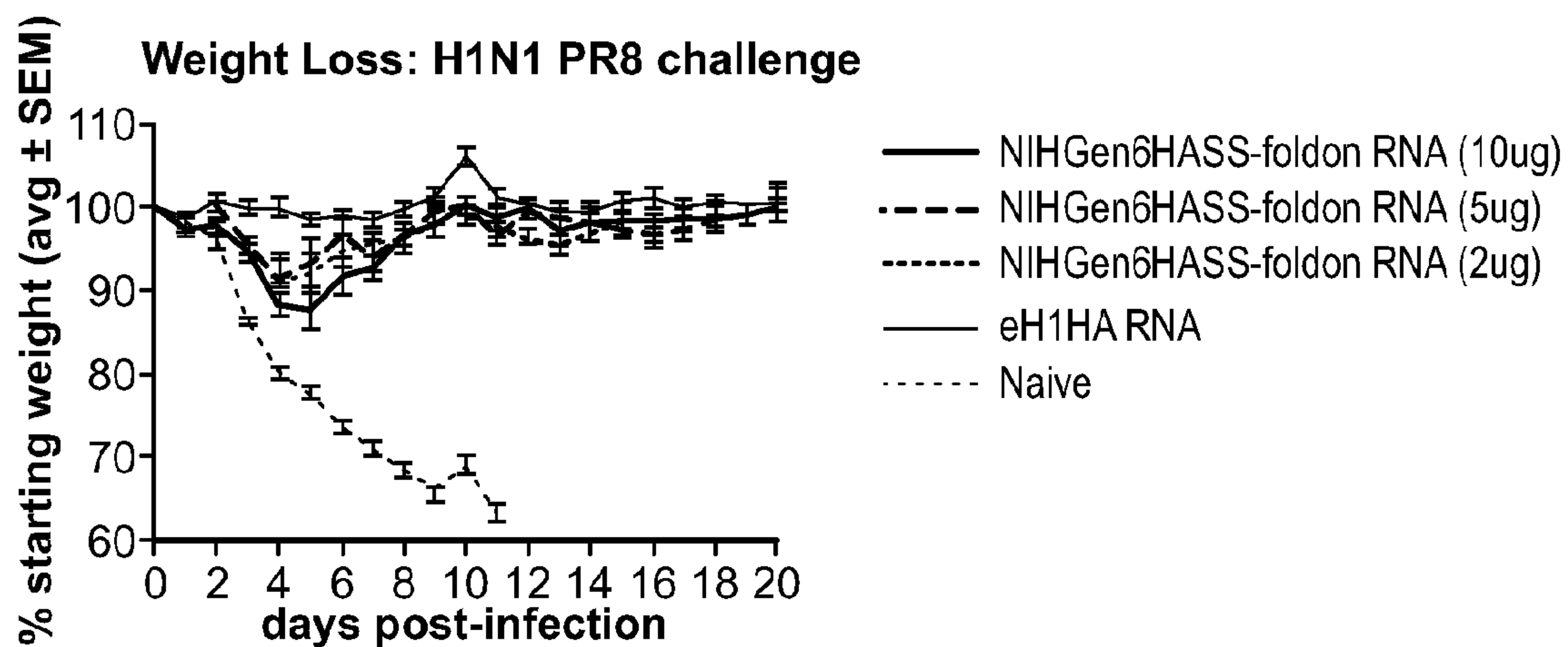


Fig. 9



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Fig. 10



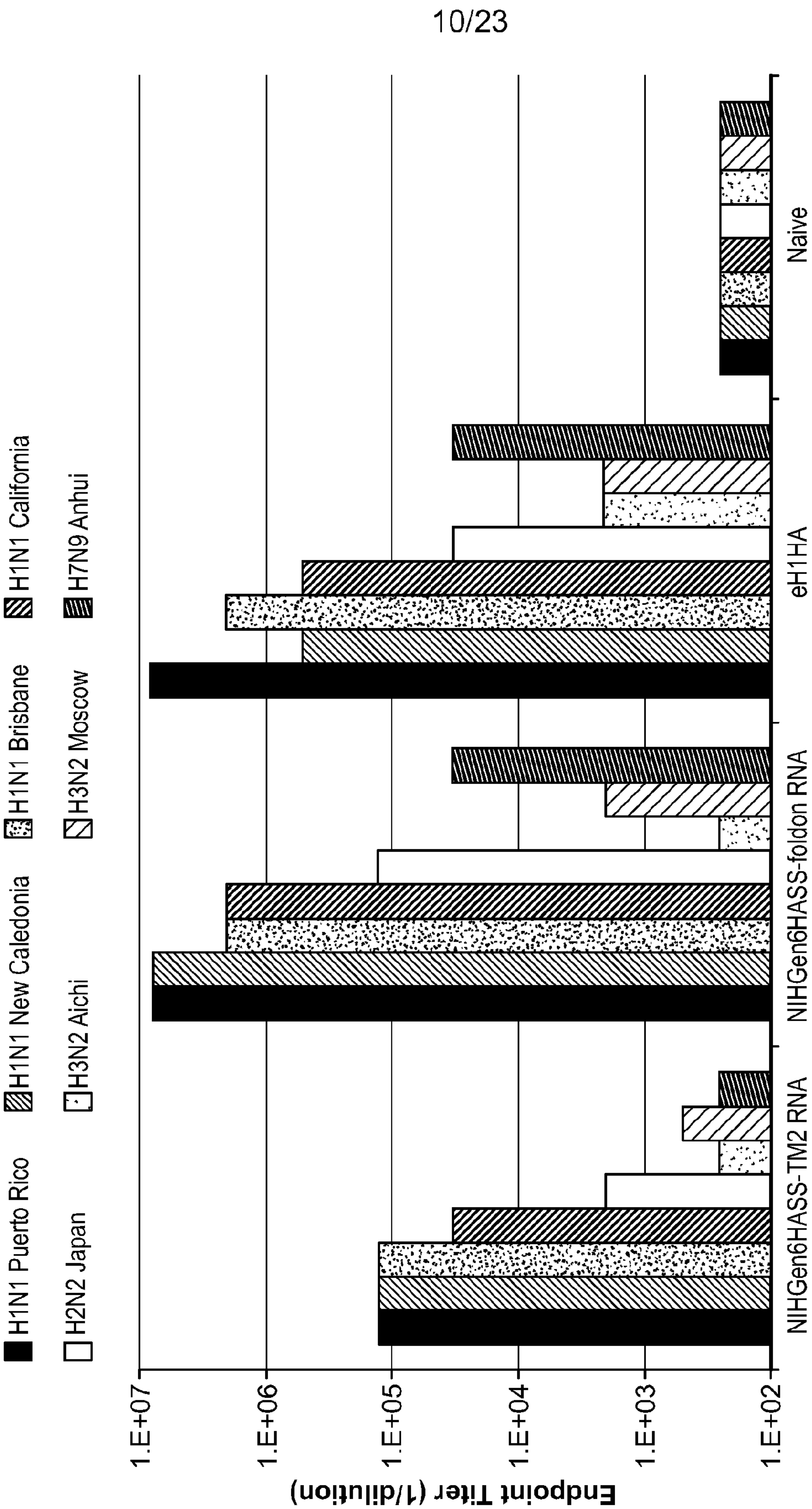


Fig. 11A

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Fig. 11B

Weight Loss: H1N1 PR8 challenge

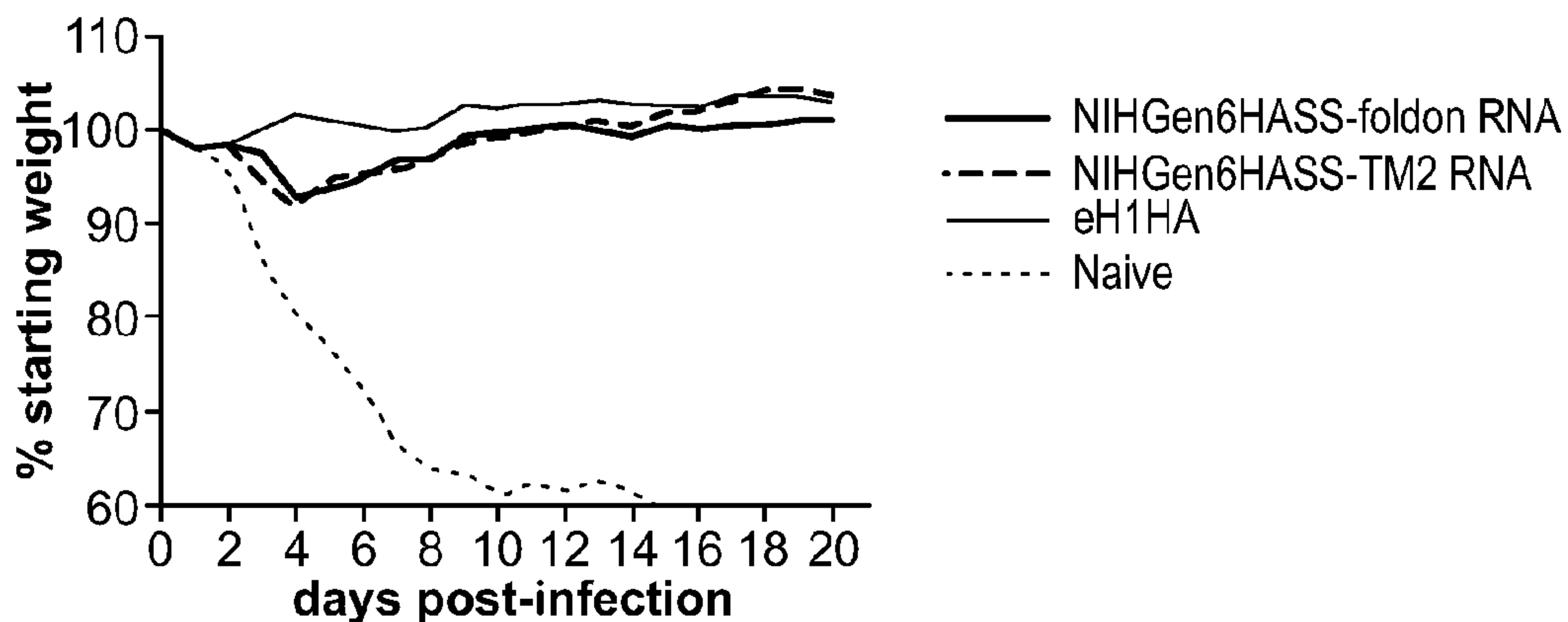


Fig. 12A

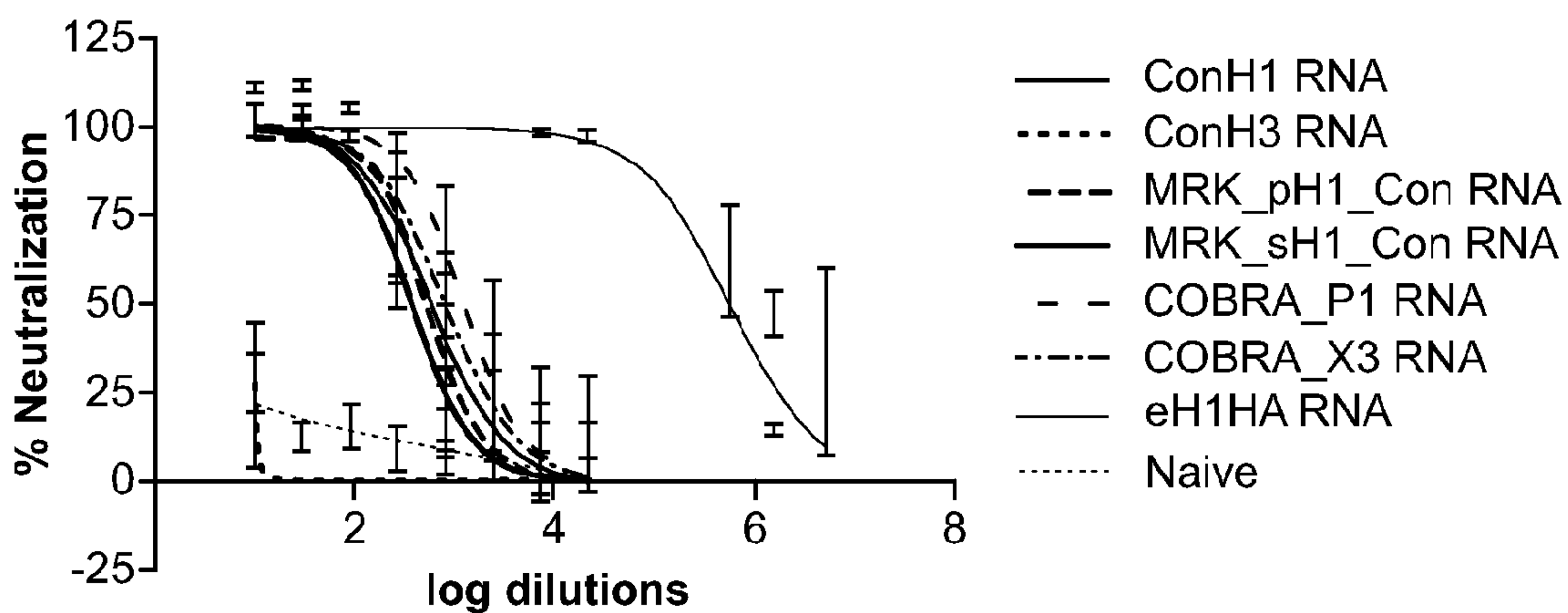
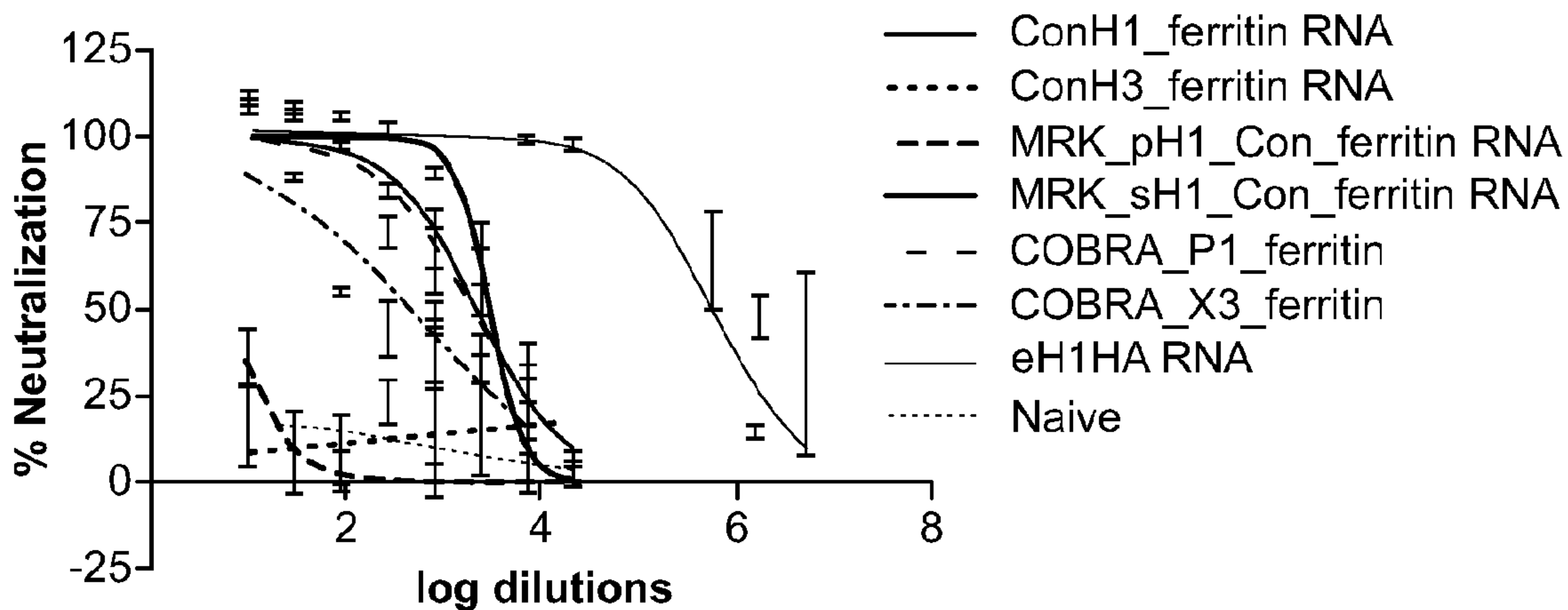


Fig. 12B



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Fig. 13A

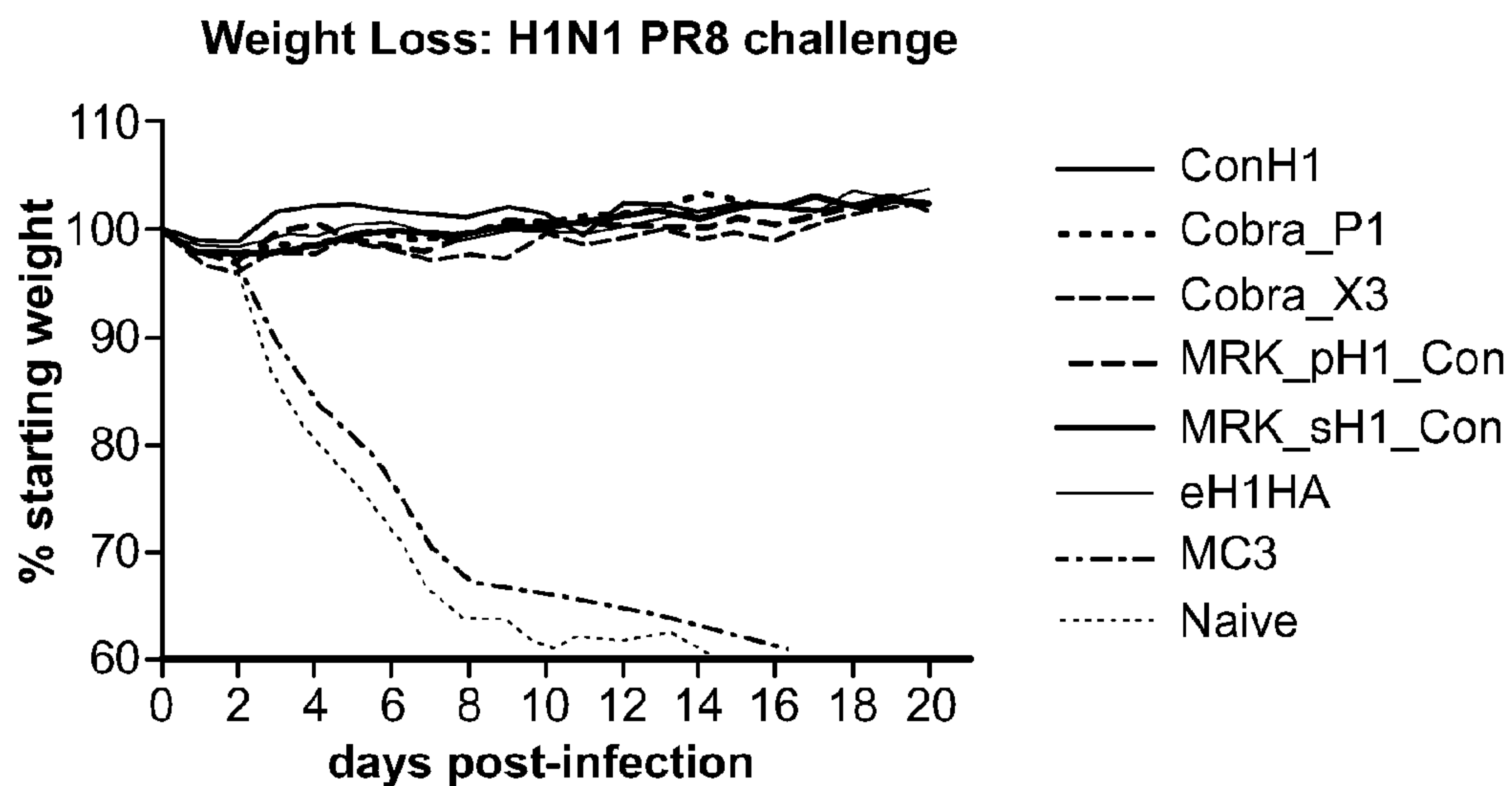


Fig. 13B

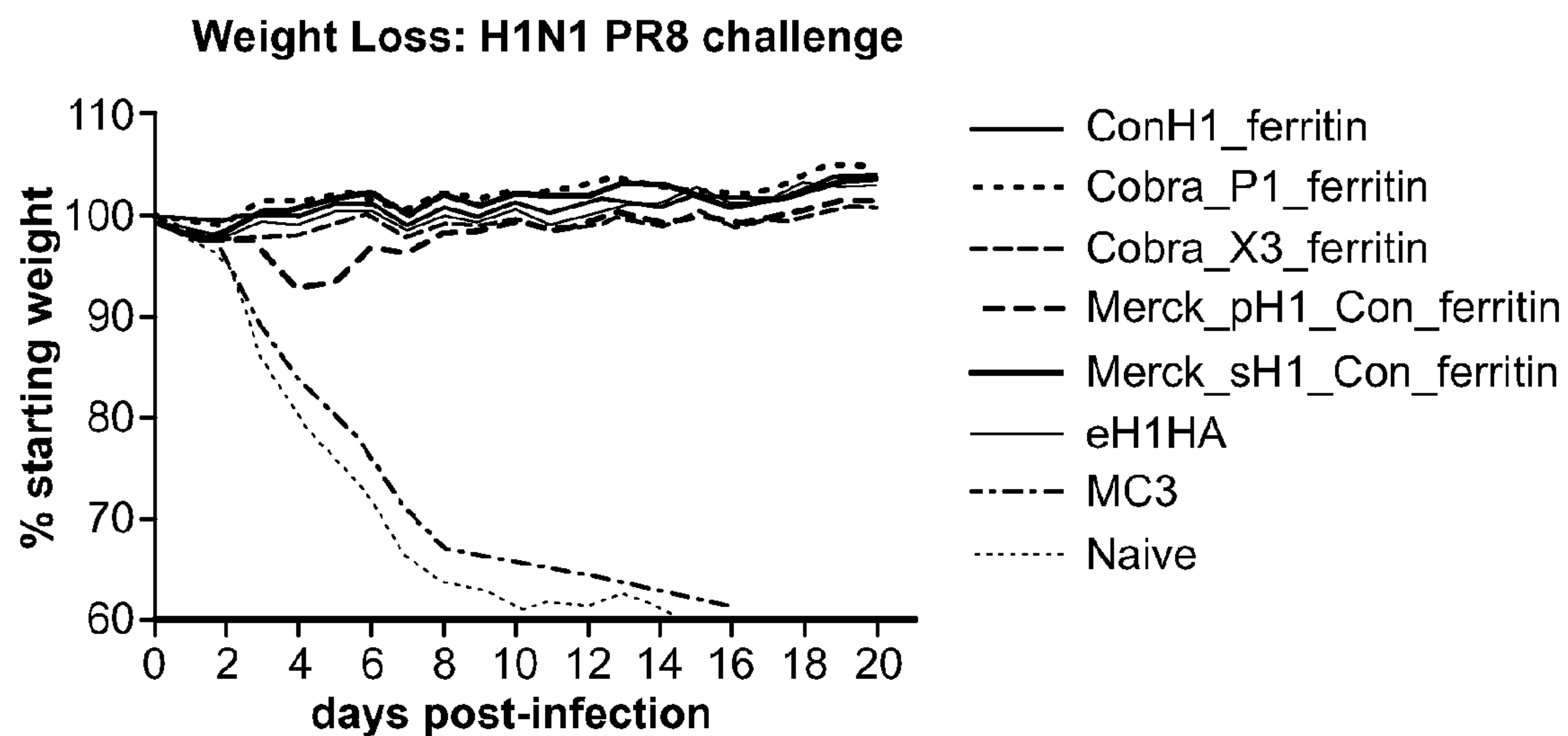


Fig. 14

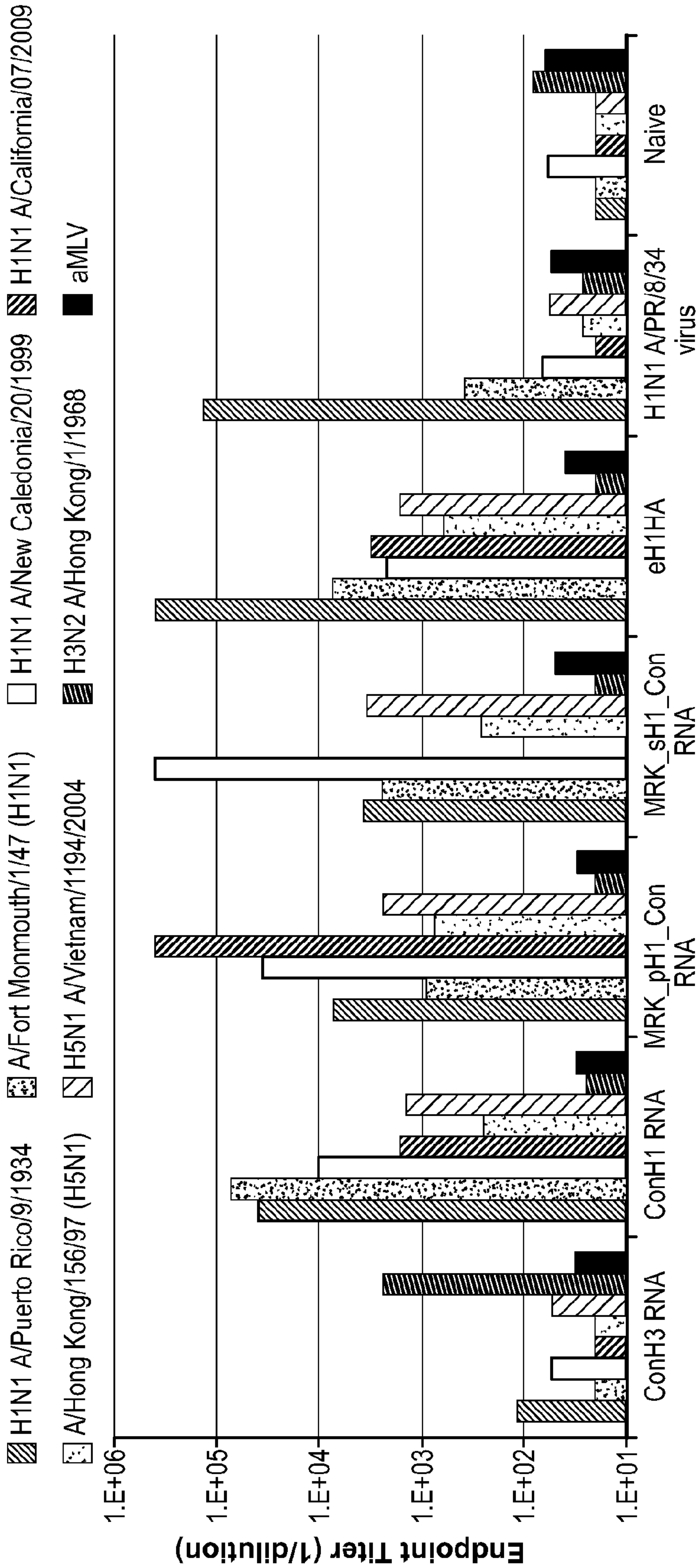
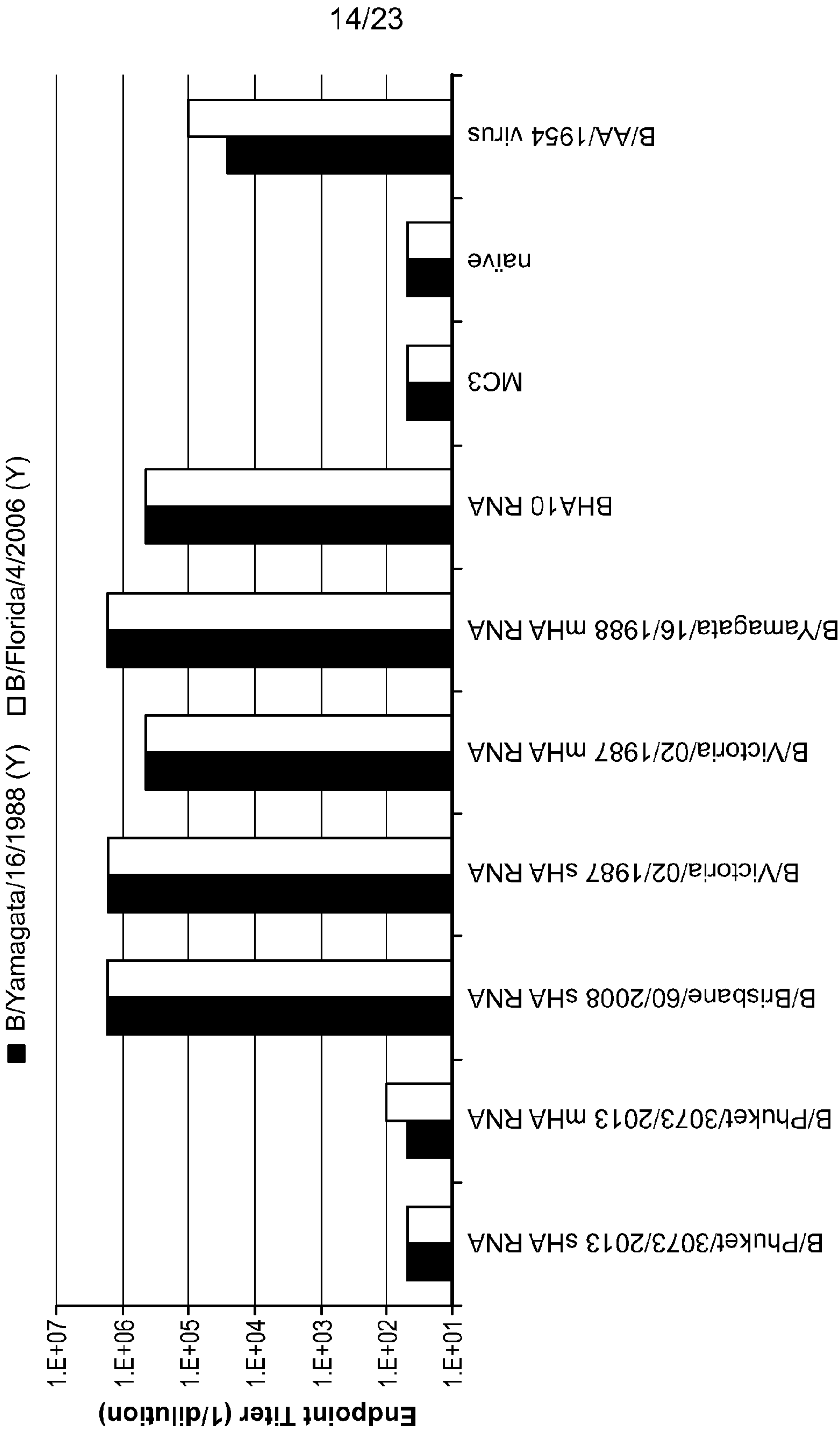


Fig. 15A



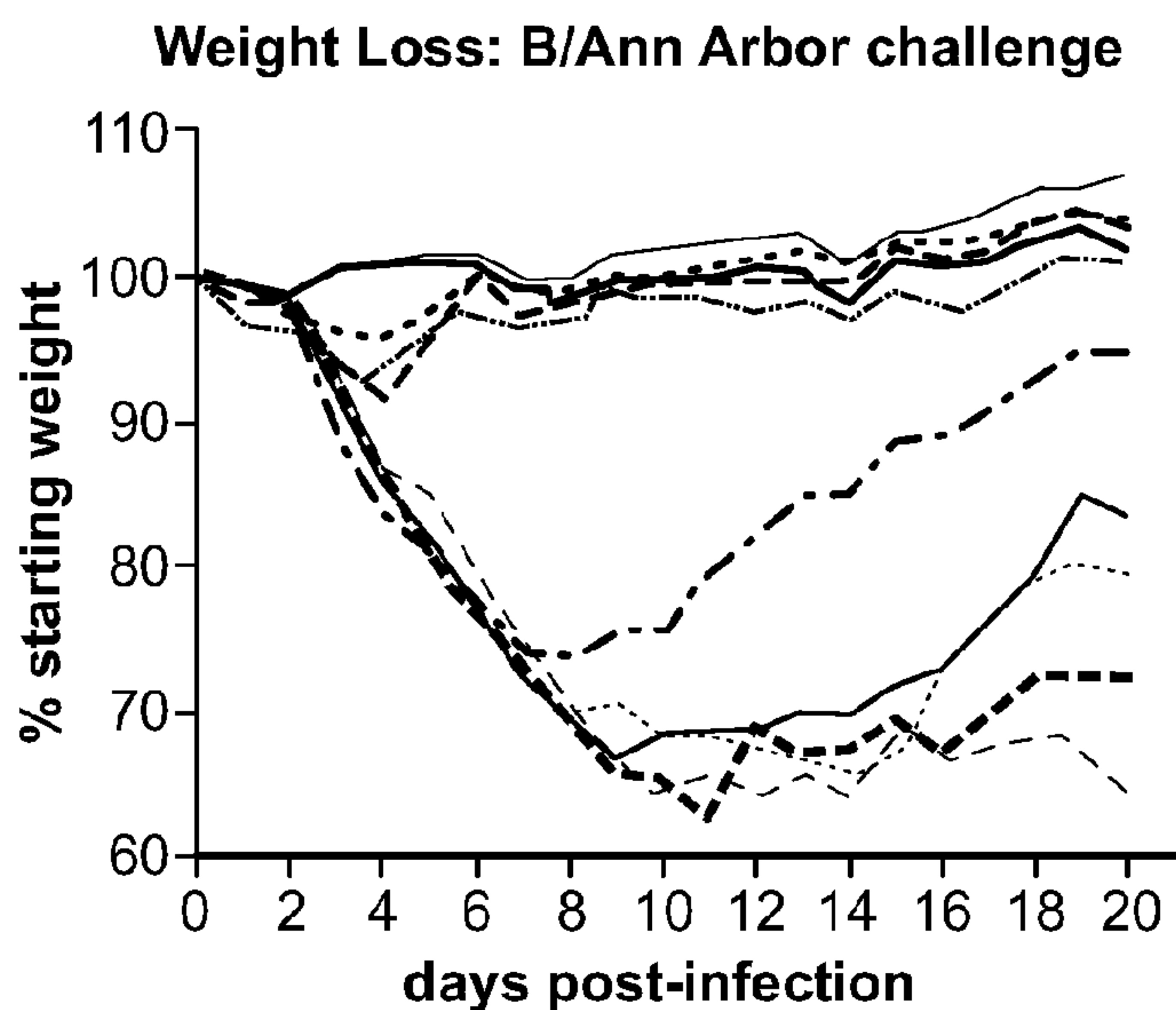
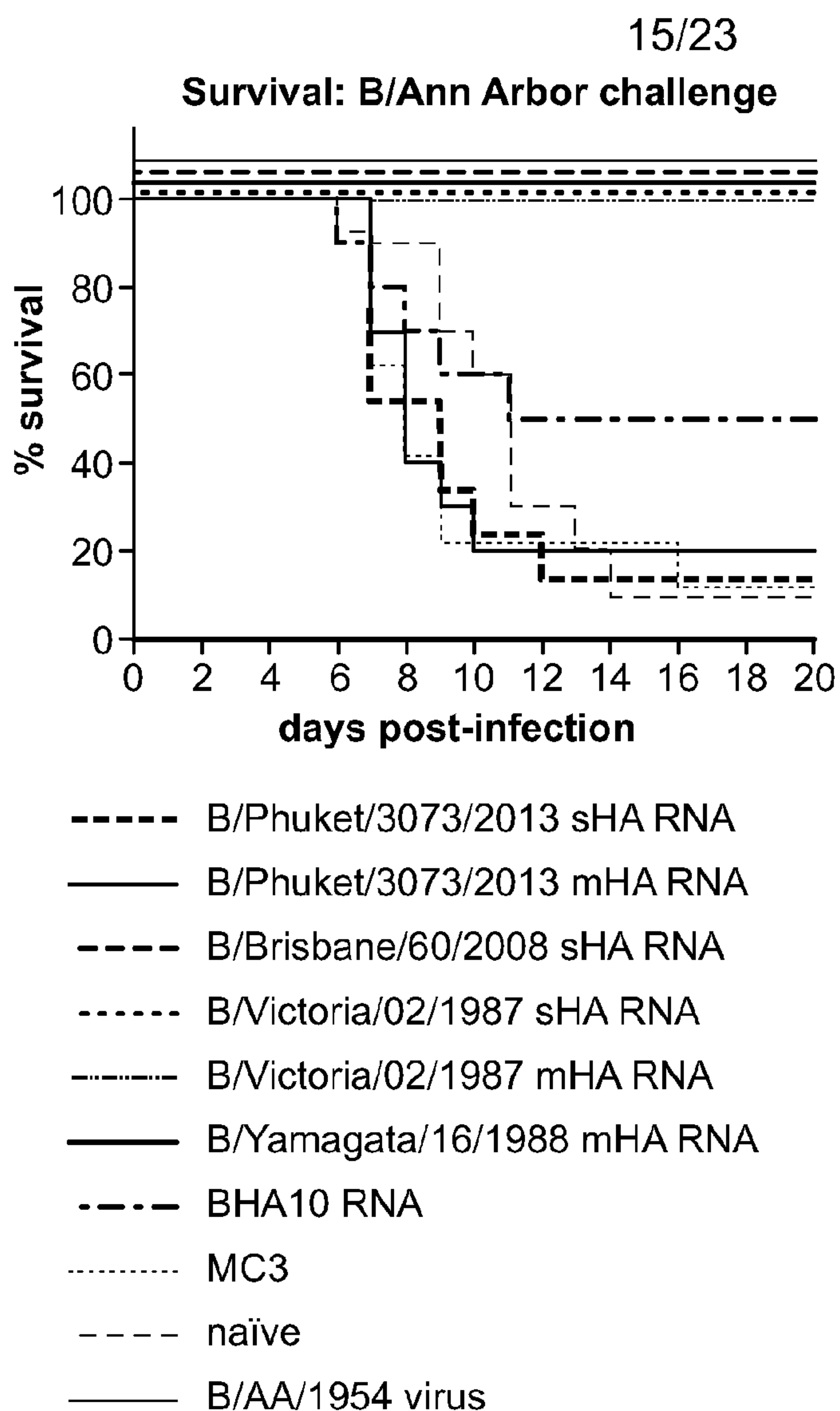


Fig. 15B

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Fig. 16A

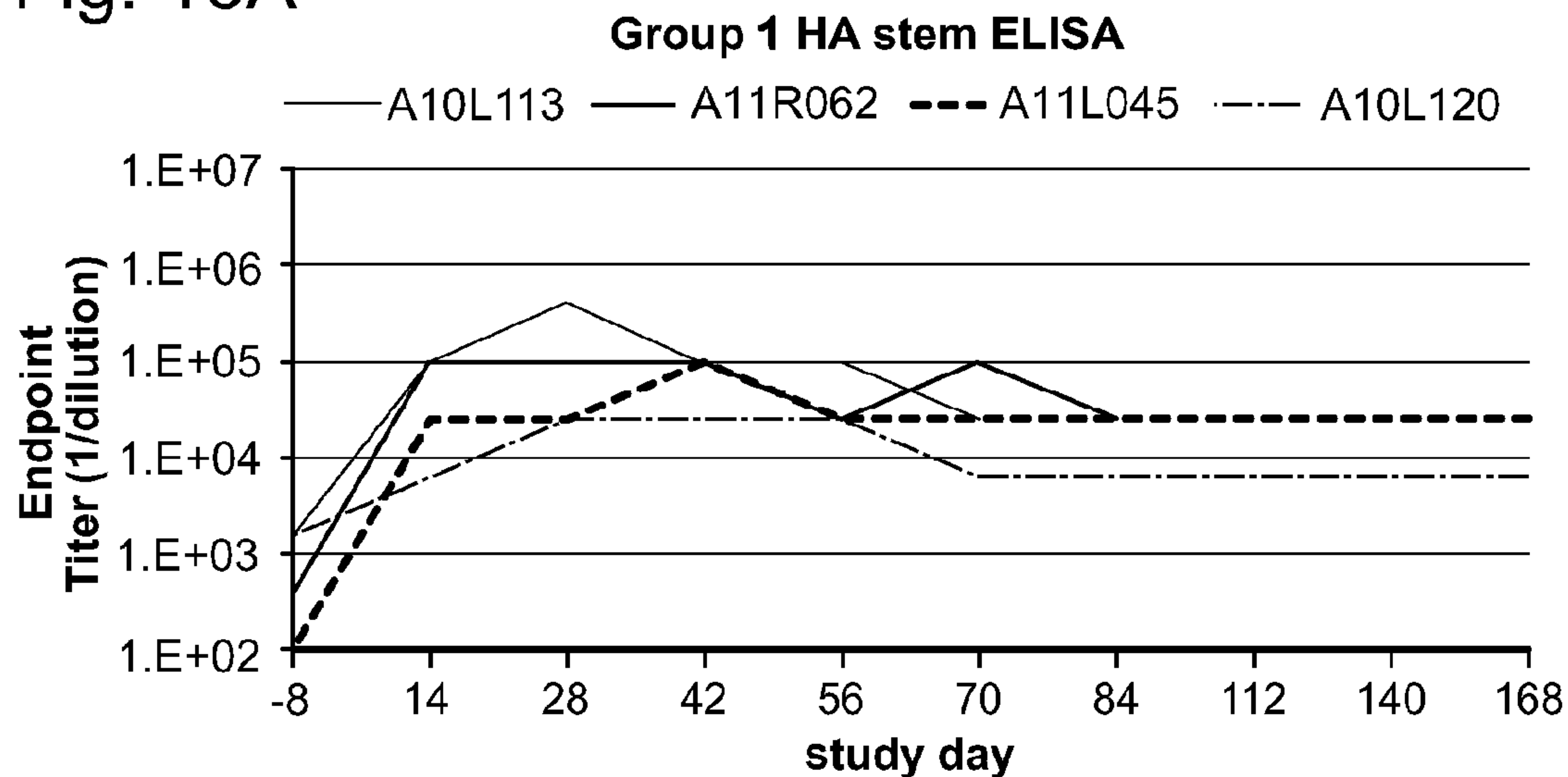


Fig. 16B

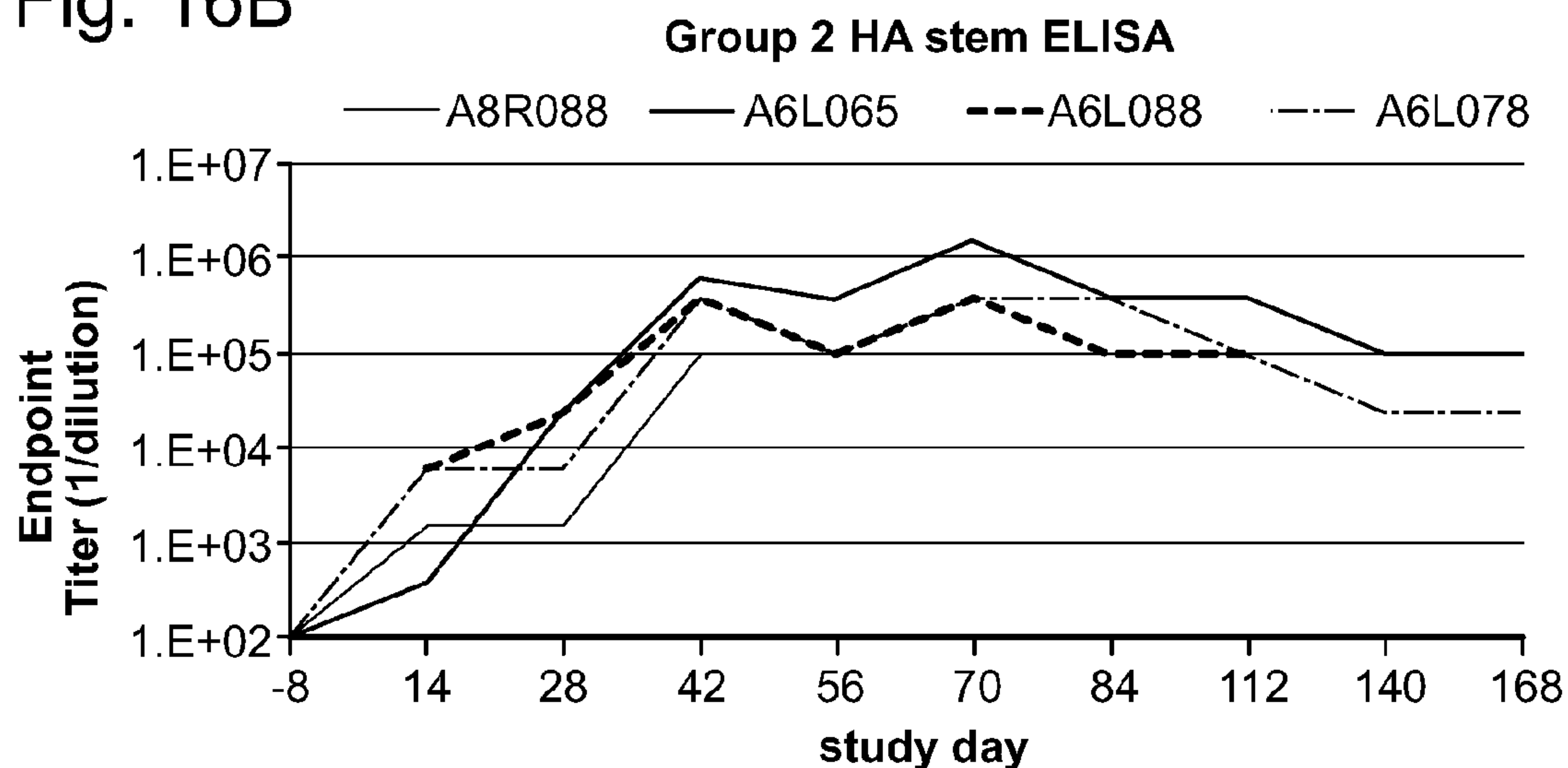
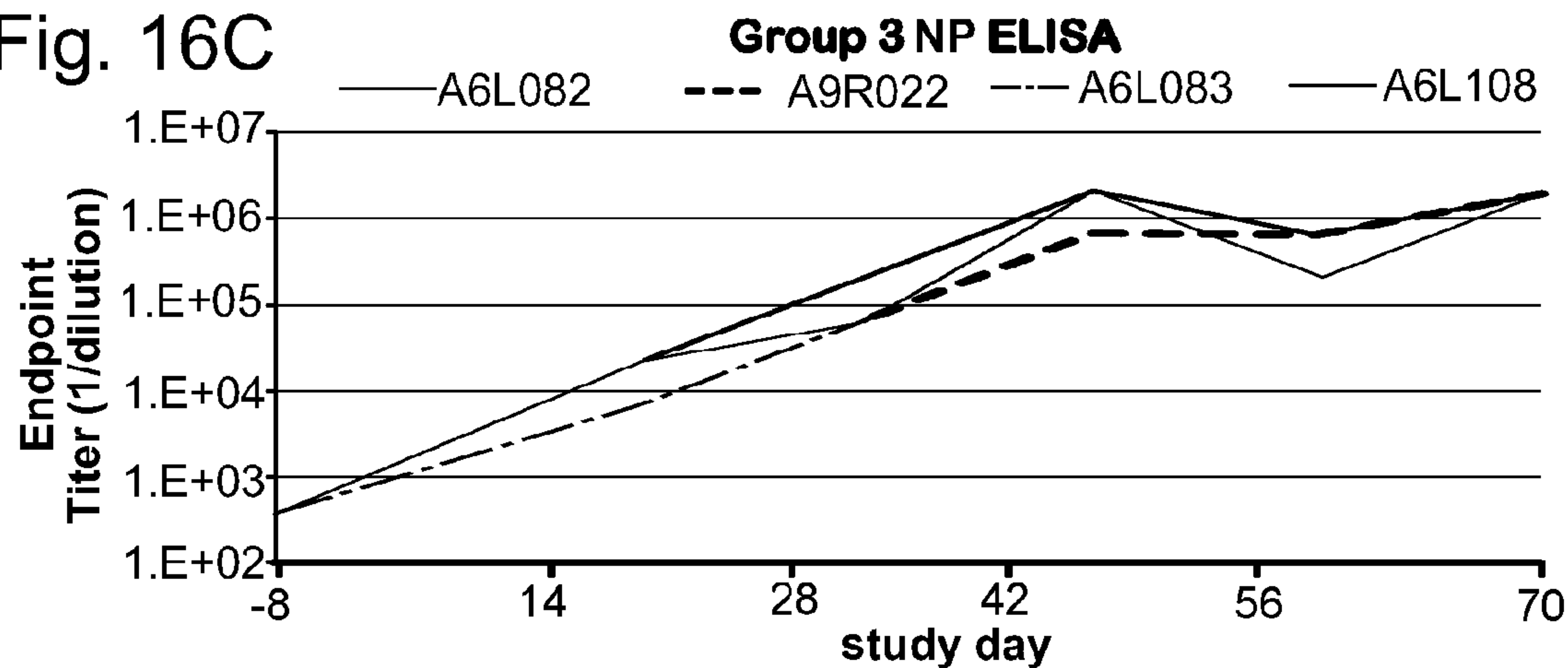


Fig. 16C



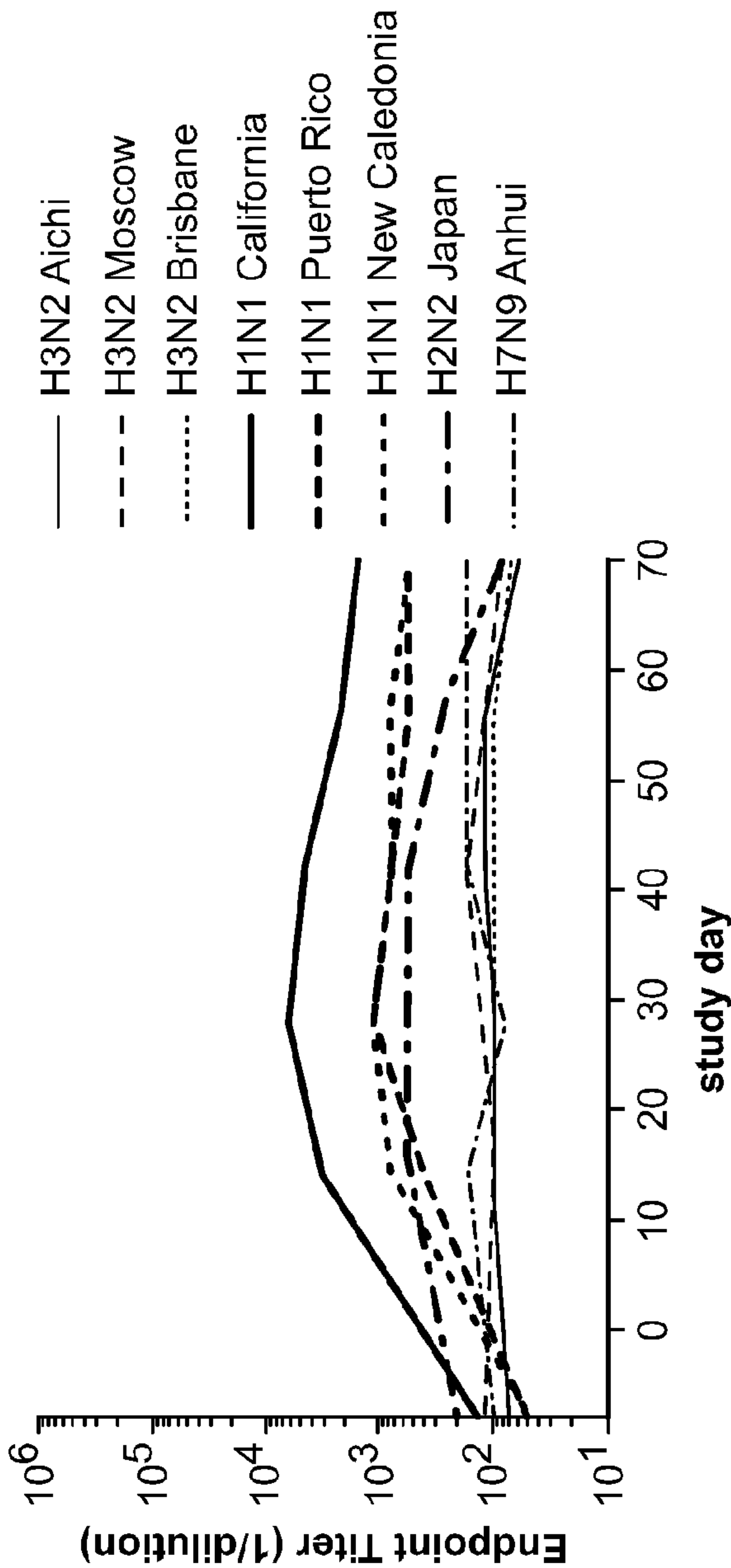


Fig. 17A

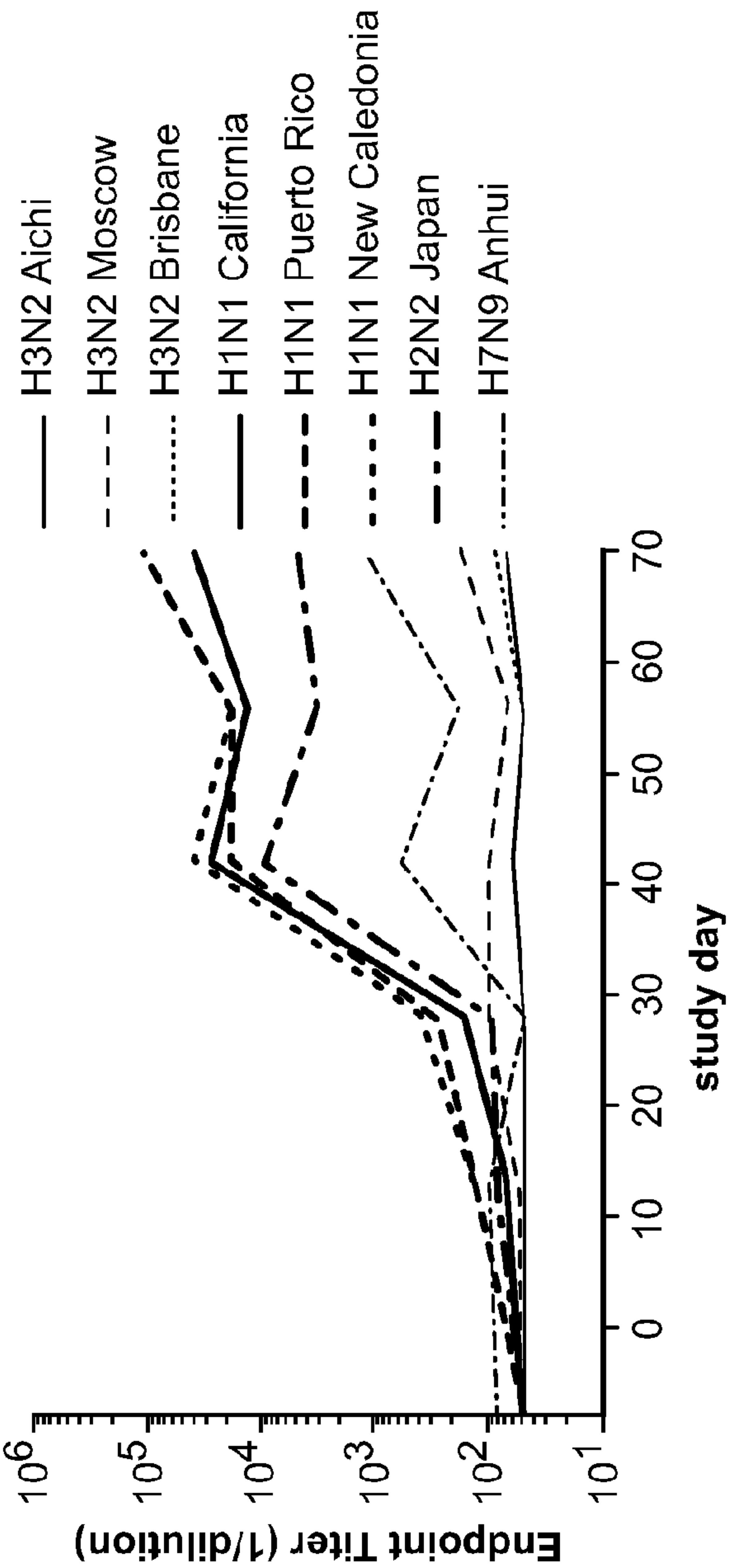
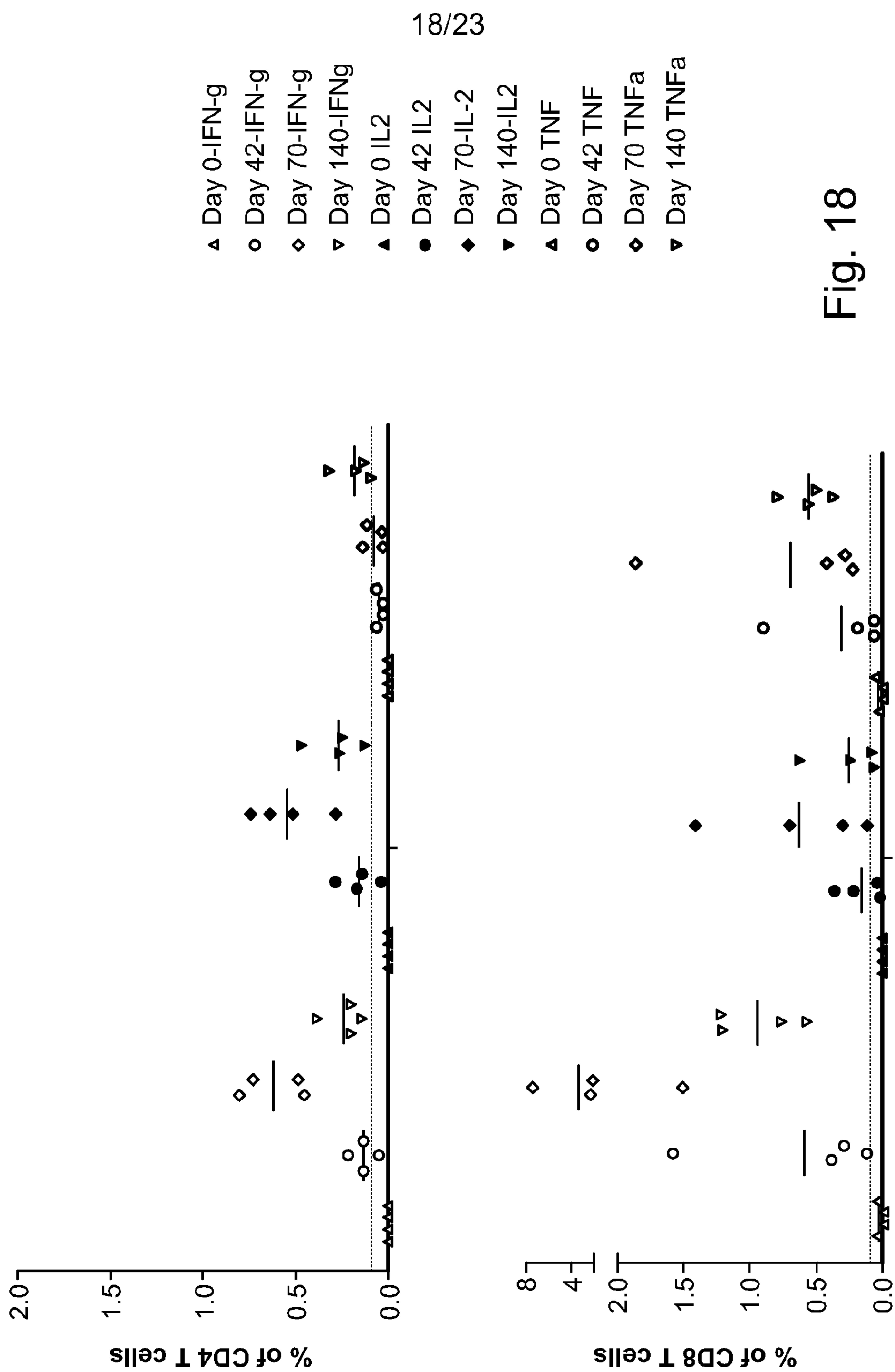


Fig. 17B



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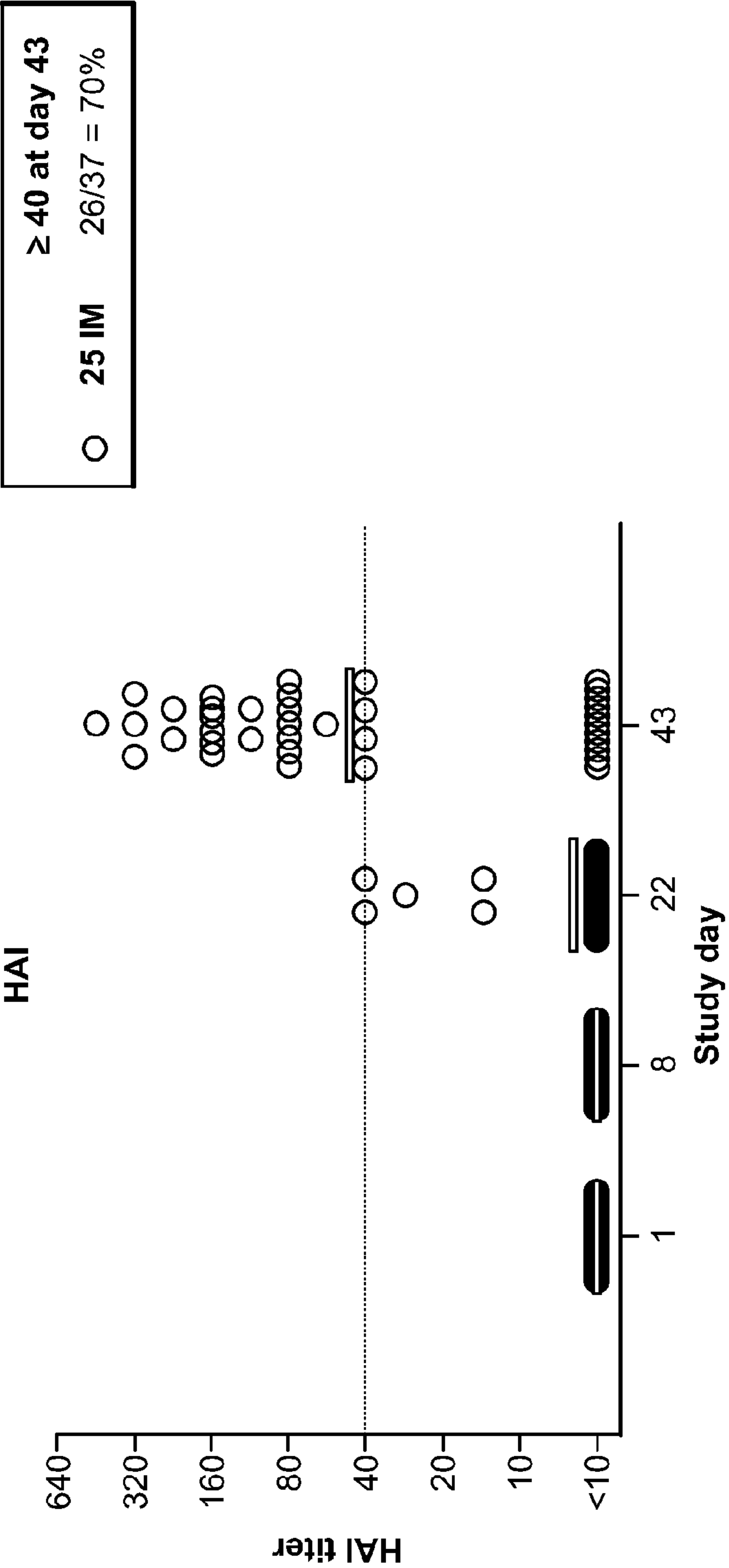


Fig. 19

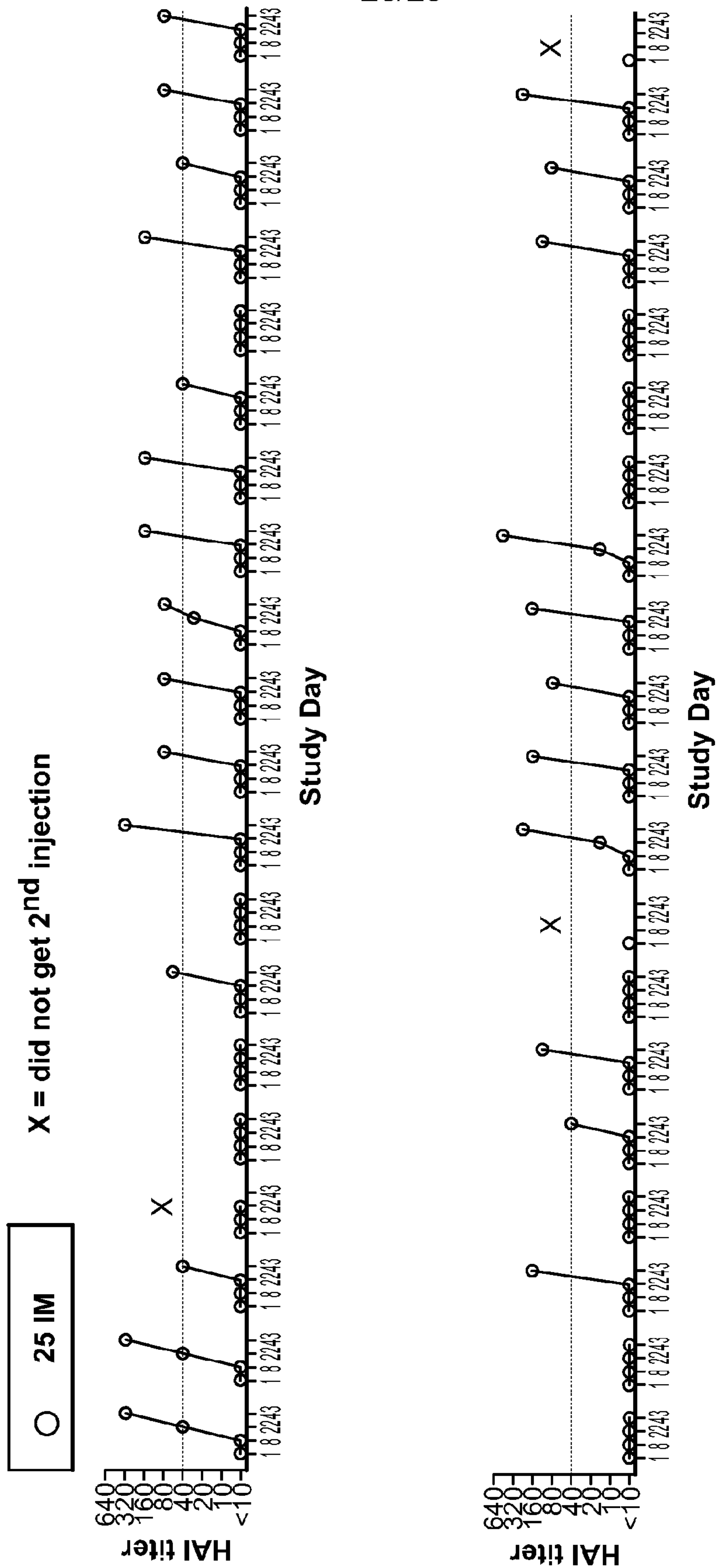


Fig. 20

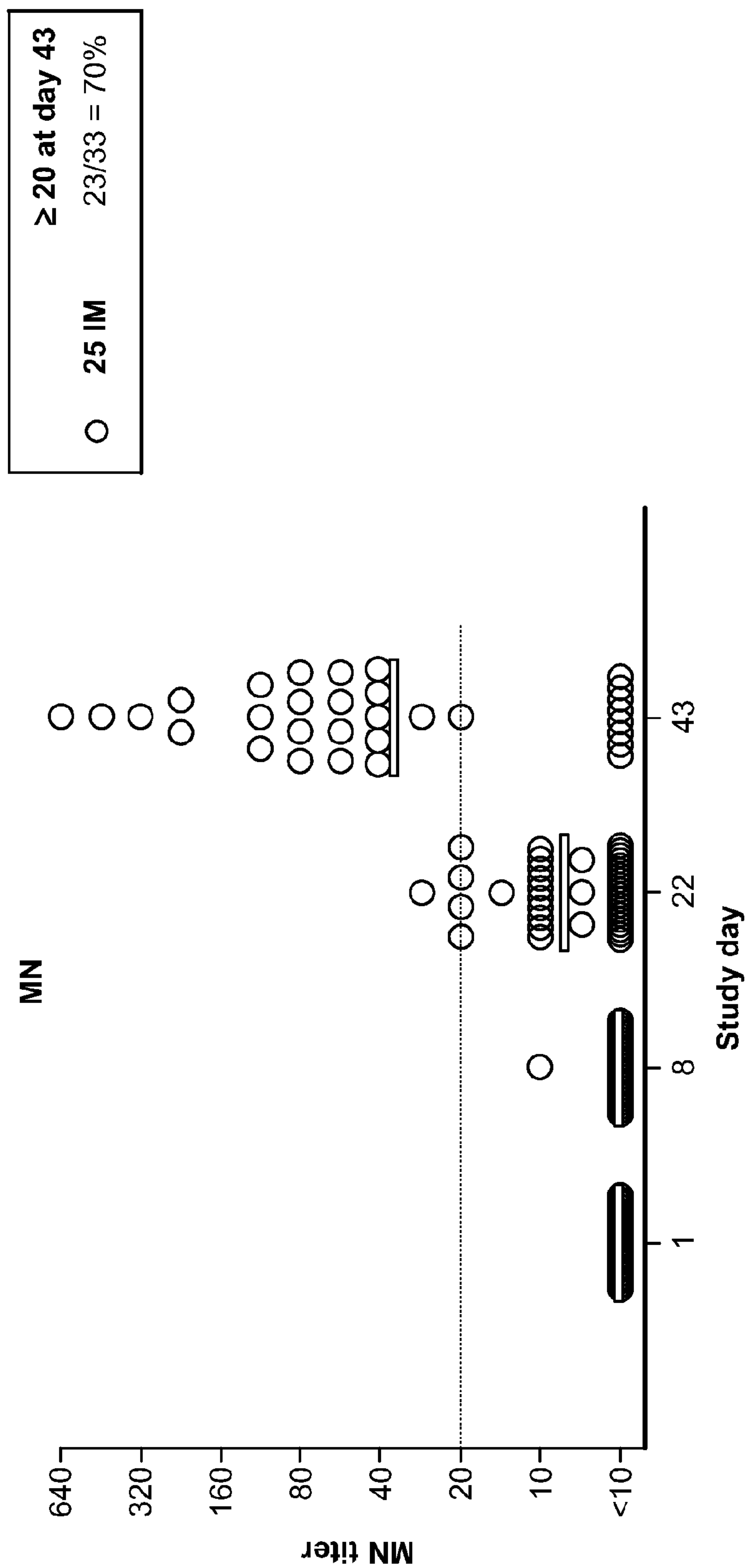
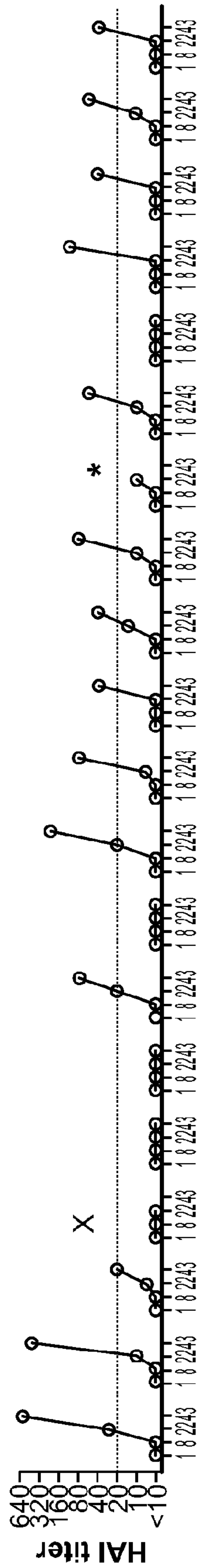


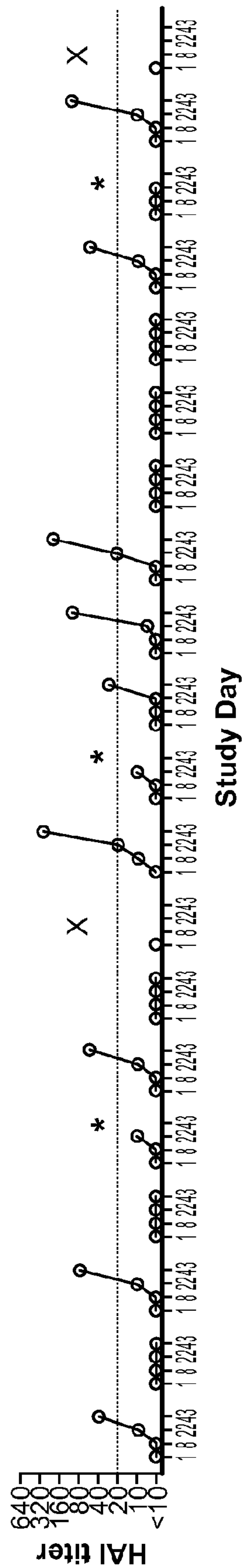
Fig. 21

X = did not get 2nd injection

○ 25 IM



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Study Day

Fig. 22

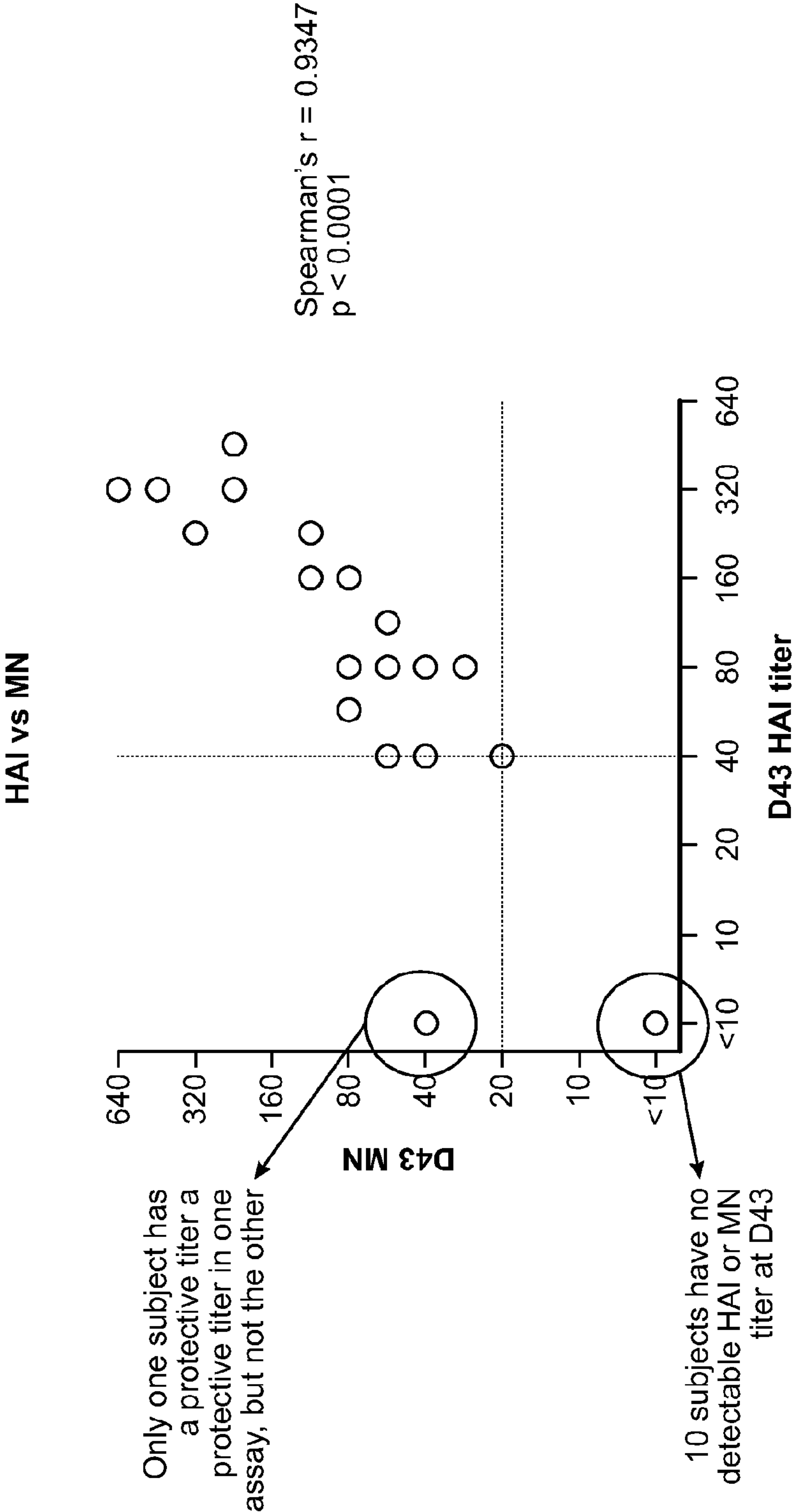


Fig. 23

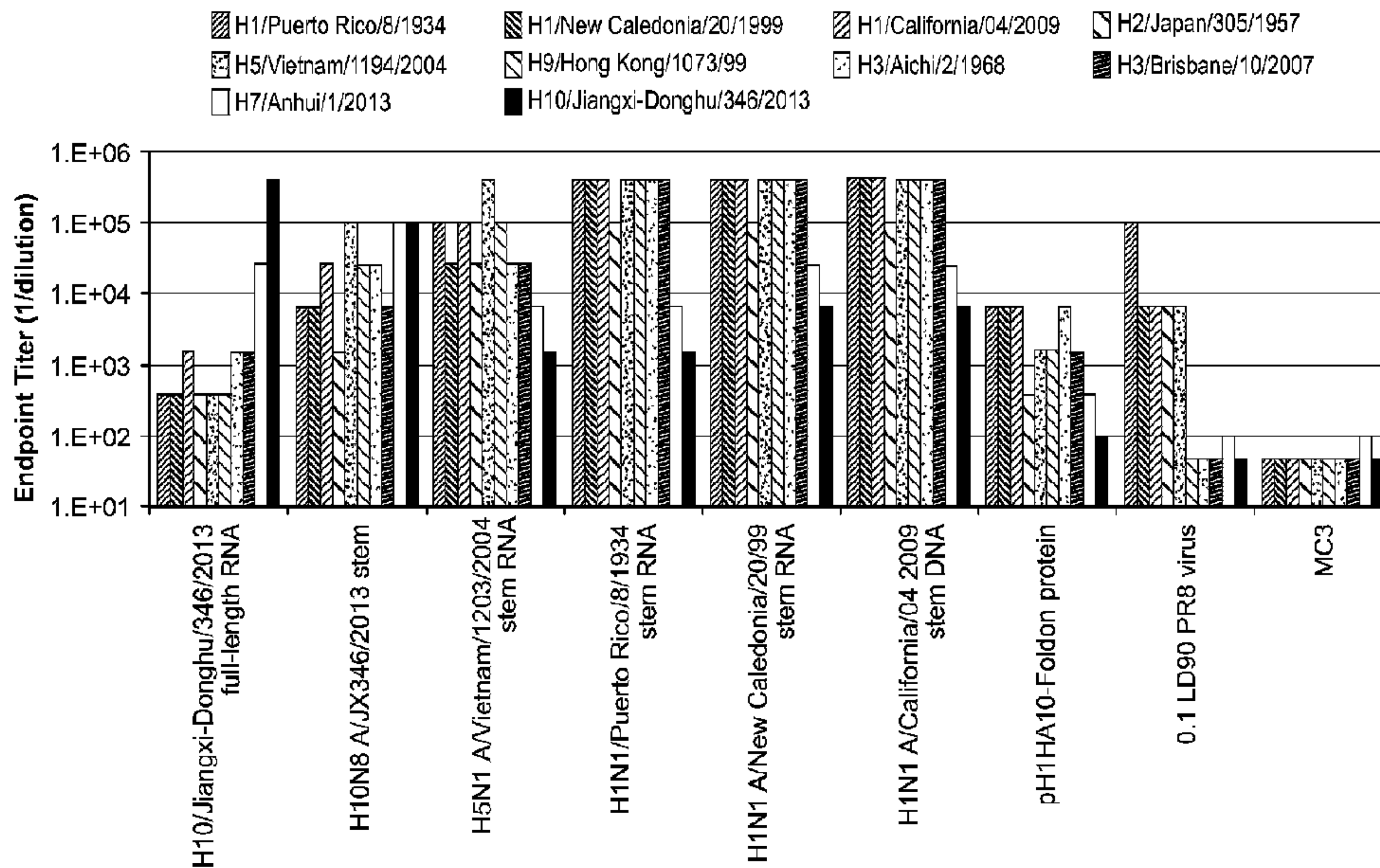


Fig. 1