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(54) Titre : PROCEDE DE PRODUCTION D'UN CONJUGUE STAPHYLOCOCCIQUE
(54) Title: PROCESS FOR PRODUCING A STAPHYLOCOCCAL CONJUGATE

(57) **Abrégé/Abstract:**

The present application relates to immunogenic compositions comprising staphylococcal PNAG which is less than 40% N-acetylated and is conjugated to a carrier protein by a linker bonded to an amine group on PNAG to form a PNAG conjugate. Vaccines, methods of treatment using and processes to make an immunogenic composition comprising PNAG and Type 5 and/or 8 capsular polysaccharides are also described.

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(57) Abstract: The present application relates to immunogenic compositions comprising staphylococcal PNAG which is less than 40% N-acetylated and is conjugated to a carrier protein by a linker bonded to an amine group on PNAG to form a PNAG conjugate. Vaccines, methods of treatment using and processes to make an immunogenic composition comprising PNAG and Type 5 and/or 8 capsular polysaccharides are also described.

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PROCESS FOR PRODUCING A STAPHYLOCOCCAL CONJUGATE

Technical Field

The present invention relates to the field of Staphylococcal immunogenic compositions and vaccines, their manufacture and the use of such compositions in medicine. More particularly, it relates to vaccine compositions comprising a PNAG polysaccharide or oligosaccharide conjugate made by particular conjugation methods, optionally combined with type 5 and/or 8 polysaccharides or oligosaccharides from *S. aureus*. Methods for the treatment or prevention of staphylococcal infections using such vaccines are also provided.

Background

The number of both community acquired and hospital acquired infections have increased over recent years with the increased use of intravascular devices. Hospital acquired (nosocomial) infections are a major cause of morbidity and mortality, more particularly in the US, where they affect more than 2 million patients annually. Following various studies, about 6 percent of the US patients will acquire an infection during their stay in hospital. The economic burden in the USA was estimated to be more than \$4.5 billion in 1992 (Emori and Gaynes, 1993, Clin. Microbiol. Rev. 6; 428). The most frequent infections are urinary tract infections (UTI-33% of the infections), followed by pneumonia (15.5%), surgical site infections (14.8%) and primary bloodstream infections (13%) Emori and Gaynes, 1993, Clin. Microbiol. Rev. 6; 428).

Staphylococcus aureus, Coagulase-negative Staphylococci (mostly *Staphylococcus epidermidis*), *enterococcus* spp, *Escherichia coli* and *Pseudomonas aeruginosa* are the major nosocomial pathogens. Although those pathogens almost cause the same number of infections, the severity of the disorders they can produce combined with the frequency of antibiotic resistant isolates balance this ranking towards *S. aureus* and *S. epidermidis* as being the most significant nosocomial pathogens.

Staphylococcus aureus is the most common cause of nosocomial infections with a significant morbidity and mortality (Romero-Vivas et al 1995, Infect. Dis. 21; 1417). It is

the cause of some cases of osteomyelitis, endocarditis, septic arthritis, pneumonia, abscesses and toxic shock syndrome.

5 *S. epidermidis* is a normal skin commensal which is also an important opportunistic pathogen responsible for infections of implanted medical devices and infections at sites of surgery. Medical devices infected by *S. epidermidis* include cardiac pacemakers, cerebrospinal fluid shunts, continuous ambulatory peritoneal dialysis catheters, orthopaedic devices and prosthetic heart valves.

10 *S. aureus* and *S. epidermidis* infections are treated with antibiotics, with pericillin being the drug of choice whereas vancomycin is used for methicillin resistant isolates. The percentage of staphylococcal strains exhibiting wide-spectrum resistance to antibiotics has become increasingly prevalent since the 1980's (Panlilo et al 1992, Infect.Control. Hosp. Epidemiol. 13; 582), posing a threat for effective antimicrobial therapy. In addition,
15 the recent emergence of vancomycin resistant *S. aureus* strain has aroused fear that methicillin resistant *S.aureus* strains will emerge and spread for which no effective therapy is available.

An alternative approach of using antibodies against staphylococcal antigens in passive
20 immunotherapy has been investigated. Therapy involving administration of polyclonal antisera are under development (WO 00/15238, WO 00/12132) as well as treatment with a monoclonal antibody against lipoteichoic acid (WO 98/57994).

An alternative approach would be use of active vaccination to generate an immune
25 response against staphylococci. Several candidates for inclusion as vaccine components have been identified. These include Fibronectin binding protein (US5840846), MHC II analogue (US5648240), fibrinogen binding protein (US6008341), GehD (US 2002/0169288), collagen binding protein (US6288214), SdrF, SdrG and SdrH (WO 00/12689), mutant SEA and SEB exotoxins (WO 00/02523) and 52kDa vitronectin binding
30 protein (WO 01/60852).

The *S. aureus* genome has been sequenced and many of the coding sequences have been identified (EP786519, WO02/094868). The same is true for *S. epidermidis* (WO 01/34809). As a refinement of this approach, others have identified proteins that are

recognised by hyperimmune sera from patients who have suffered staphylococcal infection (WO01/98499, WO 02/059148).

5 The first generation of vaccines targeted against *S. aureus* or against the exoproteins it produces have met with limited success (Lee 1996 Trends Microbiol. 4; 162). There remains a need to develop effective vaccines against staphylococcal infections.

Description of Figures

10 Figure 1 – Polypeptide sequences of preferred proteins. Table 1 provides information on which protein is represented by each SEQ ID.

Figure 2 – Nucleotide sequences encoding preferred proteins. Table 1 provides information on which protein is encoded by each SEQ ID.

15 Figure 3 – Purification of alpha toxin under native conditions. Panel A shows a coomassie stained SDS-PAGE of samples prepared during the purification of alpha toxin. Lane 1 – molecular weight markers, lane 2 – soluble fraction containing over-expressed alpha toxin, lane 3 – flow through from the Ni-NTA column, lane 4 – fractions eluted with 10% buffer B, lane 5 – fractions eluted with 20% buffer B, lane 6 – fractions
20 eluted with 30% buffer B, lane 7 – fractions eluted with 50% buffer B, lane 8 – fractions eluted with 75% buffer B, lane 9 and 10 fractions eluted with 100% buffer B, lane 11 bacteria at T=0 before induction, lane 12 – bacteria at T=4 hours after induction, lane 13 – cell lysate, lane 14 – soluble fraction, lane 15 – insoluble fraction.

Panel B shows a coomassie stained SDS-PAGE of 10, 5, 2 and 1µl of the purified alpha
25 toxin.

Figure 4 – Purification of SdrC under denaturing conditions. Panel A shows a coomassie stained SDS-PAGE of samples prepared during the purification of alpha toxin. Lane M – molecular weight markers, lane Start – supernatant from the insoluble fraction
30 containing over-expressed SdrC, lane FT1 – flow through from the Ni-NTA column, lane C – fractions eluted with wash buffer C, lane D – fractions eluted with buffer D, lane E – fractions eluted with buffer E.

Panel B shows a coomassie stained SDS-PAGE of 1, 2, 5 and 10µl of the purified SdrC.

Figure 5 – ELISA results for antisera against staphylococcal proteins in plates coated with purified proteins.

Pool mice pre – result using pooled sera extracted from mice pre-innoculation. Pool mice
 5 Post III – result using pooled mouse sera extracted post-immunisation. Pool rabbit pre –
 result using pooled sera extracted from rabbits pre-innoculation. Pool rabbit Post III –
 result using pooled rabbit sera extracted post-immunisation. Blc- negative control.

Figure 6 – ELISA results for mouse antisera raised against staphylococcal proteins in
 10 plates coated with killed staphylococci.

Panel A uses plates coated with *S. aureus* serotype 5 killed whole cells. Panel B uses
 plates coated with *S. aureus* serotype 8 killed whole cells. Panel C uses plates coated
 with *S. epidermidis* killed whole cells.

15

The line marked with square signs shows the ELISA result using antisera from mice
 immunised three times with the indicated staphylococcal protein. The line marked with
 diamond signs shows the ELISA result for pre-immune mouse sera.

20 Figure 7 - ELISA results for rabbit antisera raised against staphylococcal proteins in
 plates coated with killed staphylococci.

Panel A uses plates coated with *S. aureus* serotype 5 killed whole cells. Panel B uses
 plates coated with *S. aureus* serotype 8 killed whole cells. Panel C uses plates coated
 25 with *S. epidermidis* killed whole cells.

The line marked with square signs shows the ELISA result using antisera from rabbits
 immunised three times with the indicated staphylococcal protein (except for HarA where
 only one immunisation was given). The line marked with diamond signs shows the ELISA
 30 result for pre-immune rabbit sera.

Detailed description

The present invention discloses an immunogenic composition comprising staphylococcal
 PNAG which is less than 40%, 35%, 30 %, 25%, 20%, 15%, 10% or 5% N-acetylated
 35 wherein the PNAG is conjugated to a carrier protein by a linker bonded to an amine

group on PNAG to form a PNAG conjugate. Such immunogenic compositions optionally comprise Type 5 and/or 8 capsular polysaccharide or oligosaccharide from *S. aureus*.

5 This combination of antigens is capable of eliciting an immune response against a range of staphylococcal infections. PNAG is highly conserved among Gram positive bacteria and provides protection against a broad range of bacteria whereas Type 5 and 8 polysaccharides are potent immunogens that elicit an immune response against most strains of *S. aureus* which is the most common cause of nosocomial infection.

Polysaccharides

10

Poly N-acetylated glucosamine (PNAG)

PNAG is a polysaccharide intercellular adhesin and is composed of a polymer of β -(1 $\rightarrow$ 6)-linked glucosamine, optionally substituted with N-acetyl groups. This polysaccharide is present in both *S. aureus* and *S. epidermidis* and can be isolated from either source (Joyce et al 2003, Carbohydrate Research 338; 903; Maira-Litran et al 2002, Infect. Immun. 70; 4433). For example, PNAG may be isolated from *S. aureus* strain MN8m (WO 04/43407).

20 The polysaccharide previously known as poly-N-succinyl- β -(1 $\rightarrow$ 6)-glucosamine (PNSG) was recently shown not to have the expected structure since the identification of N-succinylation was incorrect (Maira-Litran et al 2002, Infect. Immun. 70; 4433). Therefore the polysaccharide formally known as PNSG and now found to be PNAG is also encompassed by the term PNAG.

25

PNAG may be of different sizes varying from over 400kDa to between 75 and 400kDa to between 10 and 75kDa to oligosaccharides composed of up to 30 repeat units (of β -(1 $\rightarrow$ 6)-linked glucosamine substituted with N-acetyl and O-succinyl constituents). Any size of PNAG polysaccharide or oligosaccharide may be use in an immunogenic composition of the invention, for example a size of over 40kDa. Sizing may be achieved by any method known in the art, for instance by microfluidisation, ultrasonic irradiation or by chemical cleavage (WO 03/53462, EP497524, EP497525).

30

Examples of size ranges of PNAG are 40-400kDa, 50-350kDa, 40-300kDa, 60-300kDa, 50-250kDa and 60-200kDa.

The term PNAG comprises both dPNAG and PNAG. The PNAG is less than 40, 35, 30, 25, 20, 15, 10, 5, 2 or 1% N-acetylated so that it is predominantly in the deacetylated form. De-acetylated epitopes of PNAG can elicit antibodies that are capable of mediating opsonic killing of Gram positive bacteria, for example *S. aureus* and/or *S. epidermidis*. In an embodiment, the PNAG is not O-succinylated or is O-succinylated on less than 25, 20, 15, 10, 5, 2, 1 or 0.1% of residues.

10

In an embodiment, the PNAG has a size between 40kDa and 300kDa (or between 75KDa and 150KDa) and is deacetylated so that less than 40%, 35%, 30%, 25%, 20%, 15% or 10% of amino groups are acetylated.

15 In an embodiment, the PNAG is not O-succinylated or is O-succinylated on less than 25, 20, 15, 10, 5, 2, 1 or 0.1% of residues.

The term deacetylated PNAG (dPNAG) refers to a PNAG polysaccharide or oligosaccharide in which less than 60%, 50%, 40%, 30%, 20%, 10% or 5% of the amino groups are acetylated.

20

As used herein, the term PNAG encompasses both acetylated and deacetylated forms of the saccharide.

25 In an embodiment, PNAG is deacetylated to form dPNAG by chemically treating the native polysaccharide. For example, the native PNAG is treated with a basic solution such that the pH rises to above 10. For instance the PNAG is treated with 0.1-5M, 0.2-4M, 0.3-3M, 0.5-2M, 0.75-1.5M or 1M NaOH, KOH or NH₄OH. Treatment is for at least 10 or 30 minutes, or 1, 2, 3, 4, 5, 10, 15 or 20 hours at a temperature of 20-100, 25-80, 30-60 or 30-50 or 35-45 °C. dPNAG may be prepared as described in WO 04/43405.

30

In an embodiment, the polysaccharide(s) included in the immunogenic composition of the invention are conjugated to a carrier protein as described below.

Type 5 and Type 8 polysaccharides from *S.aureus*

Most strains of *S.aureus* that cause infection in man contain either Type 5 or Type 8 polysaccharides. Approximately 60% of human strains are Type 8 and approximately 30% are Type 5. The structures of Type 5 and Type 8 capsular polysaccharide antigens are described in Moreau et al Carbohydrate Res. 201; 285 (1990) and Fournier et al Infect. Immun. 45; 87 (1984). Both have FucNAcp in their repeat unit as well as ManNAcA which can be used to introduce a sulfhydryl group.

Recently (Jones Carbohydrate Research 340, 1097-1106 (2005)) NMR spectroscopy revised the structures of the capsular polysaccharides to :

Type 5

→4)-β-D-ManNAcA-(1 →4)-α-L-FucNAc(3OAc)-(1 →3)-β-D-FucNAc-(1 →

Type 8

→3)-β-D-ManNAcA(4OAc)-(1 →3)-α-L-FucNAc(1 →3)-α-D-FucNAc(1 →

20

Polysaccharides may be extracted from the appropriate strain of *S. aureus* using methods well known to the skilled man, for instance as described in US6294177. For example, ATCC 12902 is a Type 5 *S. aureus* strain and ATCC 12605 is a Type 8 *S. aureus* strain. Type 5 and type 8 polysaccharides may be extracted from *S.aureus* as described in Infection and Immunity (1990) 58(7); 2367.

25

Polysaccharides are of native size or alternatively may be sized, for instance by microfluidisation, ultrasonic irradiation or by chemical treatment. The invention also covers oligosaccharides derived from the type 5 and 8 polysaccharides from *S. aureus*.

30

The type 5 and 8 capsular polysaccharide or oligosaccharides included in the immunogenic composition of the invention are O-acetylated. In an embodiment, the degree of O-acetylation of type 5 capsular polysaccharide or oligosaccharide is 10-100%, 20-100%, 30-100%, 40-100%, 50-100%, 60-100%, 70-100%, 80-100%, 90-100%, 50-90%, 60-90%, 70-90% or 80-90%. In an embodiment, the degree of O-acetylation of type

35

8 capsular polysaccharide or oligosaccharide is 10-100%, 20-100%, 30-100%, 40-100%, 50-100%, 60-100%, 70-100%, 80-100%, 90-100%, 50-90%, 60-90%, 70-90% or 80-90%. In an embodiment, the degree of O-acetylation of type 5 and type 8 capsular polysaccharides or oligosaccharides is 10-100%, 20-100%, 30-100%, 40-100%, 50-100%, 60-100%, 70-100%, 80-100%, 90-100%, 50-90%, 60-90%, 70-90% or 80-90%.

The type 5 and 8 polysaccharides included in the immunogenic composition of the invention are optionally conjugated to a carrier protein as described below or are alternatively unconjugated.

The immunogenic compositions of the invention optionally contains either type 5 or type 8 polysaccharide or both of these.

S. aureus 336 antigen

In an embodiment, the immunogenic composition of the invention comprises the *S. aureus* 336 antigen described in US6294177.

The 336 antigen comprises β -linked hexosamine, contains no O-acetyl groups and specifically binds to antibodies to *S. aureus* Type 336 deposited under ATCC 55804.

In an embodiment, the 336 antigen is a polysaccharide which is of native size or alternatively may be sized, for instance by microfluidisation, ultrasonic irradiation or by chemical treatment. The invention also covers oligosaccharides derived from the 336 antigen.

The 336 antigen, where included in the immunogenic composition of the invention is optionally conjugated to a carrier protein as described below or are alternatively unconjugated.

Type I, II and III polysaccharides from *S. epidermidis*

Strains ATCC-31432, SE-360 and SE-10 of *S. epidermidis* are characteristic of three different capsular types, I, II and III respectively (Ichiman and Yoshida 1981, J. Appl.

Bacteriol. 51; 229). Capsular polysaccharides extracted from each serotype of *S. epidermidis* constitute Type I, II and III polysaccharides. Polysaccharides may be extracted by several methods including the method described in US4197290 or as described in Ichiman et al 1991, J. Appl. Bacteriol. 71; 176.

5

In one embodiment of the invention, the immunogenic composition comprises type I and/or II and/or III polysaccharides or oligosaccharides from *S. epidermidis*.

Polysaccharides are of native size or alternatively may be sized, for instance by microfluidisation, ultrasonic irradiation or chemical cleavage. The invention also covers oligosaccharides extracted from *S. epidermidis* strains.

These polysaccharides are unconjugated or are optionally conjugated as described below.

15 **Conjugation of polysaccharides**

Amongst the problems associated with the use of polysaccharides in vaccination, is the fact that polysaccharides *per se* are poor immunogens. Strategies, which have been designed to overcome this lack of immunogenicity, include the linking of the polysaccharide to large protein carriers, which provide bystander T-cell help. It is preferred that the polysaccharides utilised in the invention are linked to a protein carrier which provide bystander T –cell help. Examples of these carriers which are currently used for coupling to polysaccharide or oligosaccharide immunogens include the Diphtheria and Tetanus toxoids (DT, DT CRM197 and TT), Keyhole Limpet Haemocyanin (KLH), *Pseudomonas aeruginosa* exoprotein A (rEPA) and the purified protein derivative of Tuberculin (PPD), protein D from *Haemophilus influenzae*, pneumolysin or fragments of any of the above. Fragments suitable for use include fragments encompassing T-helper epitopes. In particular protein D fragment will preferably contain the N-terminal 1/3 of the protein. Protein D is an IgD-binding protein from *Haemophilus influenzae* (EP 0 594 610 B1).

The immunogenic compositions of the invention comprise staphylococcal PNAG which is at least 60%, 70%, 75%, 80%, 85%, 90% or 95% de-N-acetylated (or N-acetylated on no more than 40%, 30%, 25%, 20%, 15%, 10% or 5% of residues) wherein the PNAG is

conjugated to a carrier protein by a linker bonded to an amine group on PNAG to form a PNAG conjugate.

5 The term linker refers to the molecule which covalently links the PNAG and the carrier protein in the completed conjugate. The linker may originate from the covalent bonding of two molecules which were used in the conjugation reaction. Alternatively, the linker may derive from a single molecule used in the conjugation reaction or from three molecules used in the conjugation reaction. In an embodiment, the linker may be a single peptide bond with the NH derived from the amine of PNAG and the CO derived from a carboxylic acid group on the carrier protein.

The amine group on PNAG is the primary amine on the glucosamine ring and becomes a secondary amine after bonding to the linker.

15 In an embodiment, the linker is bonded to an amine group on the carrier protein. For example, the amine group on the carrier protein is a lysine residue or the amino terminus of the carrier protein.

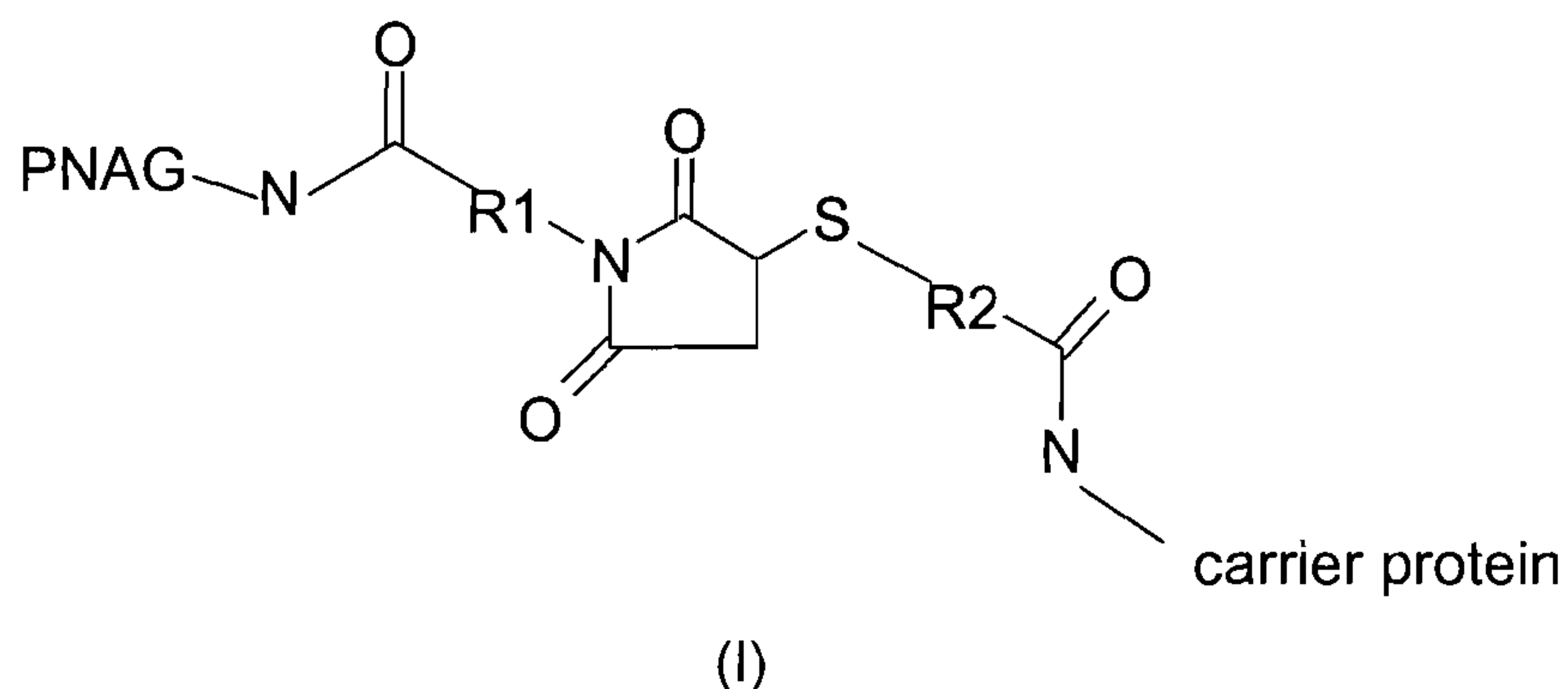
Alternatively, the linker is bonded to a carboxylic acid group on the carrier protein. For example a glutamic acid or aspartic acid residue or the carboxyl terminus of the carrier protein.

In an embodiment, the linker contains a peptide bond at the position at which the linker is covalently bonded to either or both of PNAG and the carrier protein. In an embodiment the linker contains two peptide bonds, the first at the position at which the linker is covalently bonded to PNAG and the second at the position at which the linker is covalently bonded to the carrier protein.

In an embodiment, the linker is between 1-40, 5-30, 5-20, 10-20, 12-18, 14-16 or 1-5 Angstroms in length.

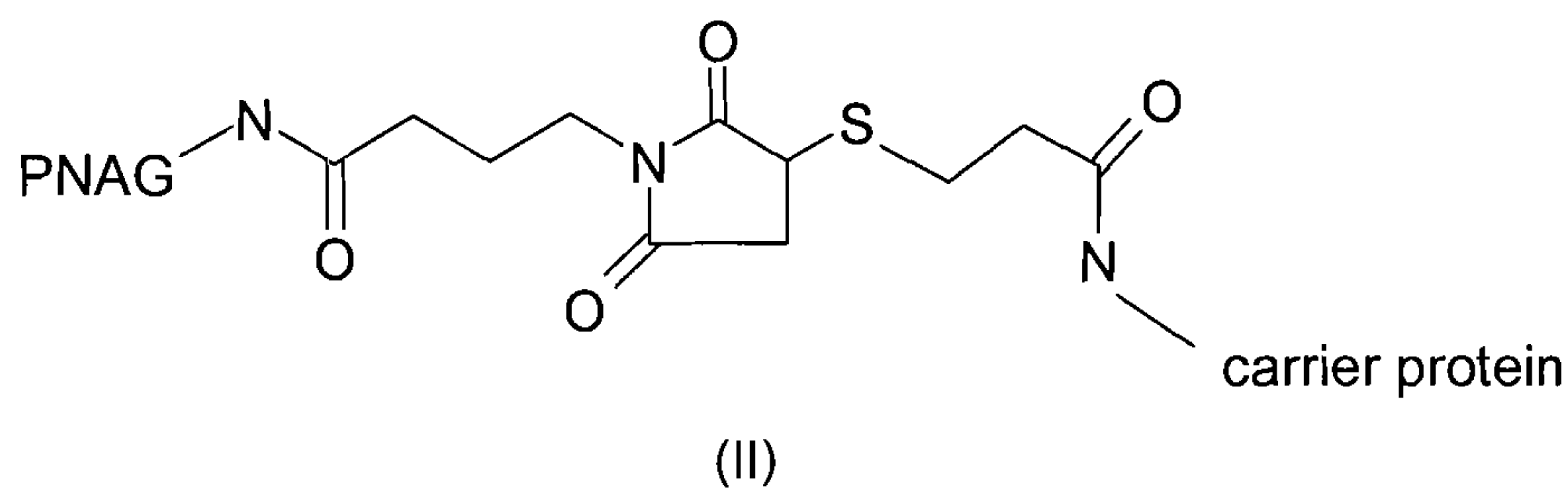
In an embodiment the linker contains a maleimide group. Optionally the maleimide group is linked (i.e. covalently bonded) to a sulphur atom.

35 In an embodiment the PNAG conjugate is of formula (I):

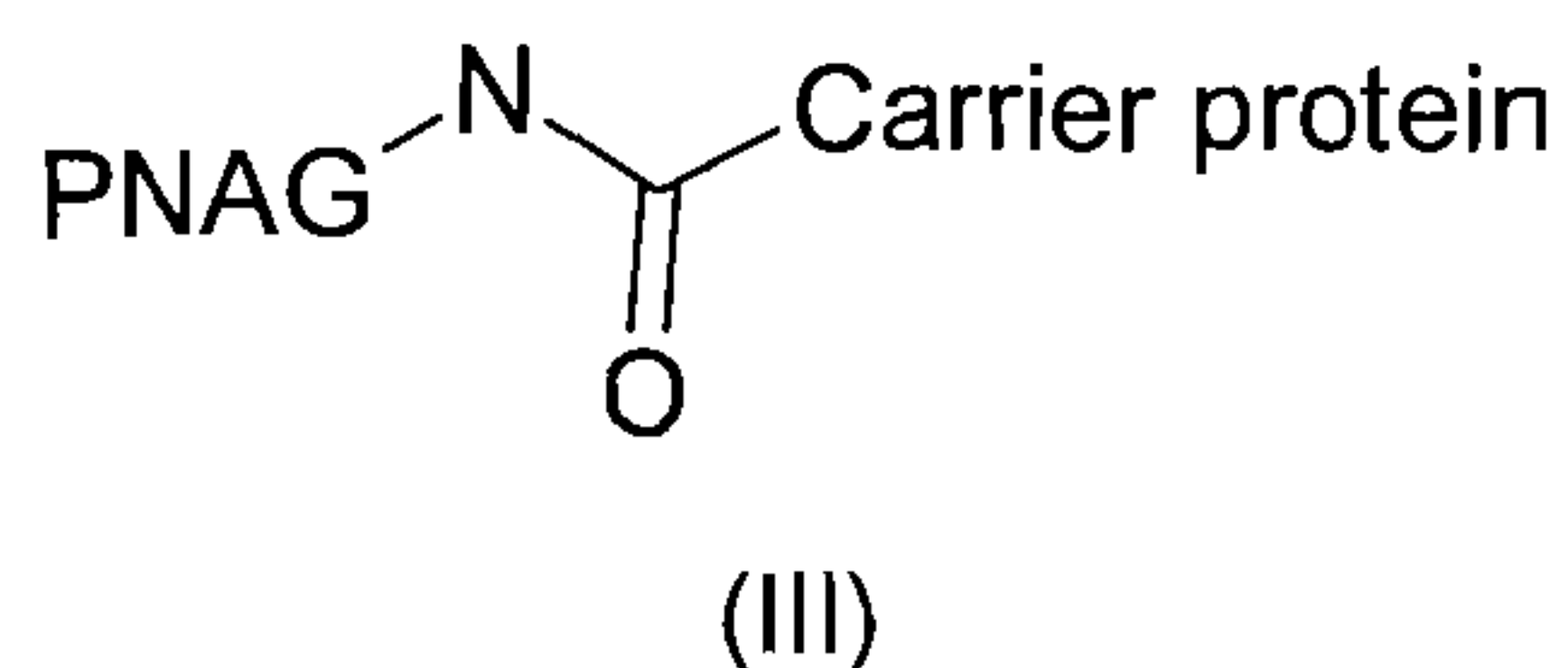


5 wherein R1 and R2 are independently selected from an aromatic or aliphatic chain, optionally substituted, or a bond. For example R1 is C1-C6 alkyl, C2-C5 alkyl, C3-C4 alkyl, C2 alkyl, C3 alkyl, C4 alkyl or C5 alkyl. For example R2 is C1-C6 alkyl, C2-C5 alkyl, C3-C4 alkyl, C2 alkyl, C3 alkyl, C4 alkyl or C5 alkyl.

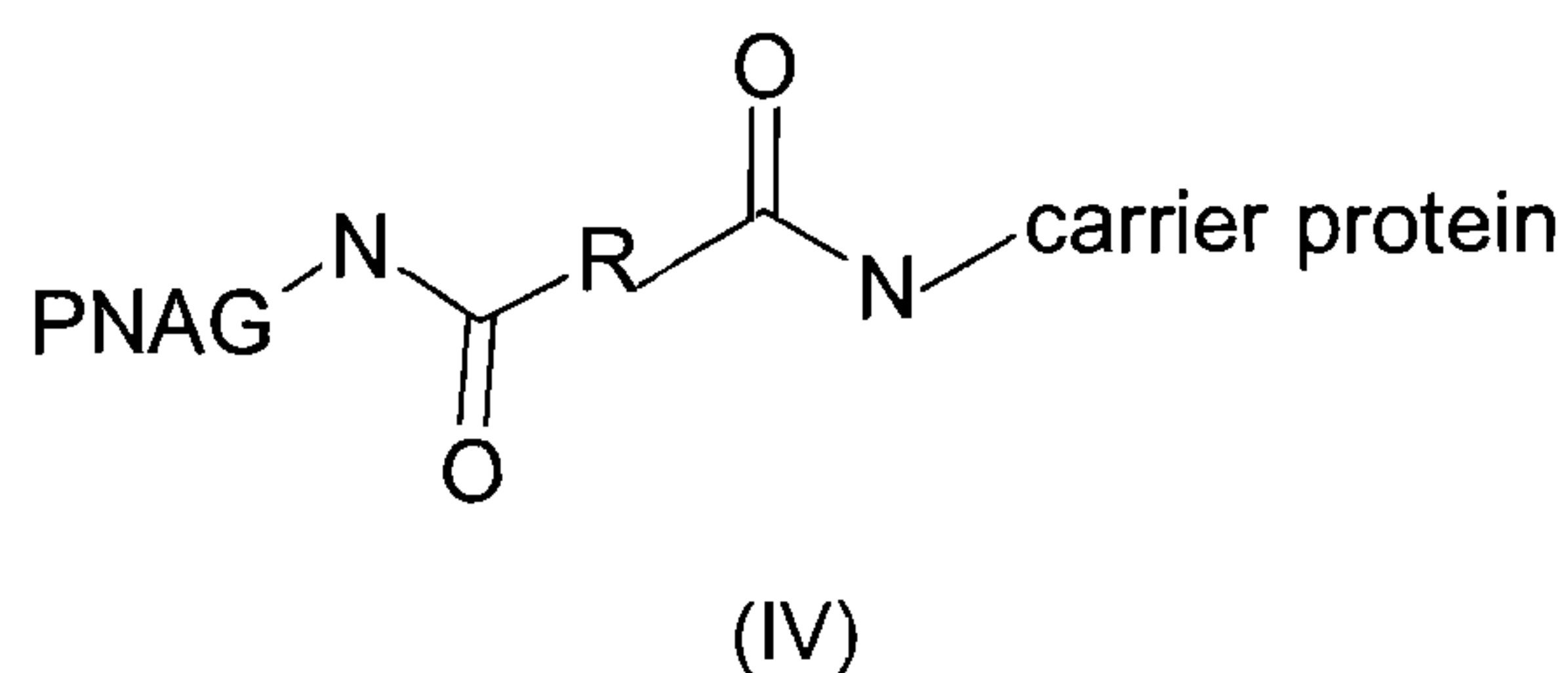
10 In an embodiment, the PNAG conjugate has the structure of formula II:



In an embodiment, the PNAG conjugate has the structure of formula III:

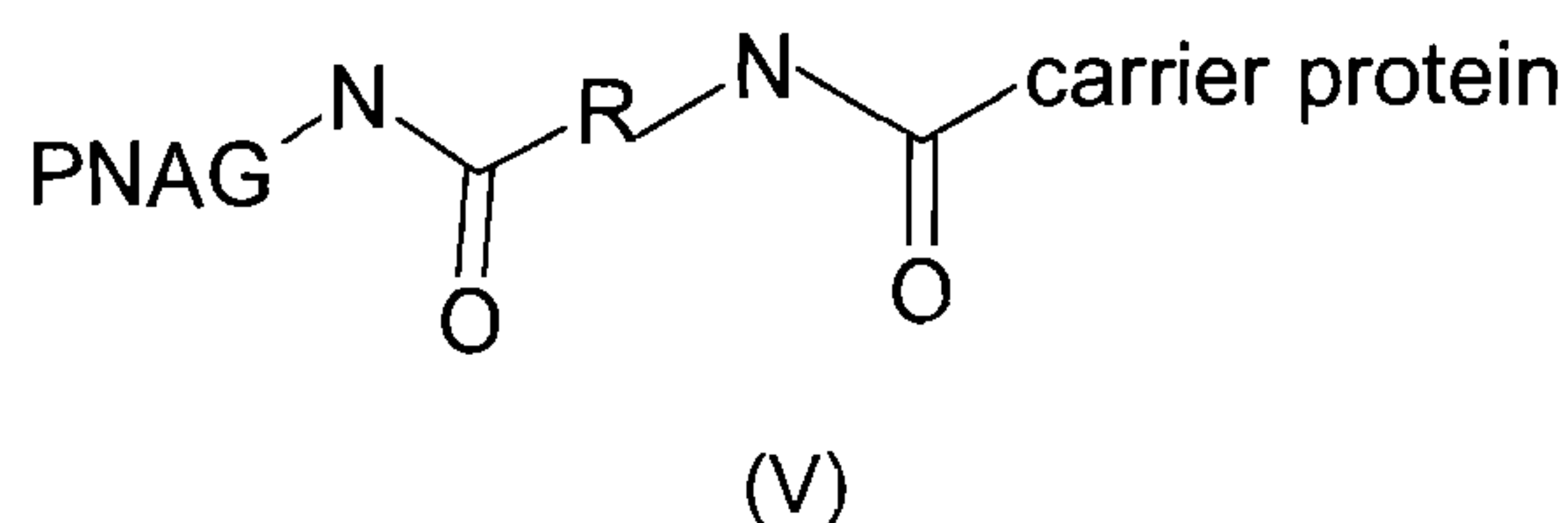


In an embodiment, the PNAG conjugate has the structure of formula IV:



wherein R is an aromatic or aliphatic chain, optionally substituted, or a bond. For example
 5 R is C1-C12 alkyl, C3-C10 alkyl, C4-C8 alkyl or C6 alkyl.

In an embodiment, the PNAG conjugate has the structure of formula V:

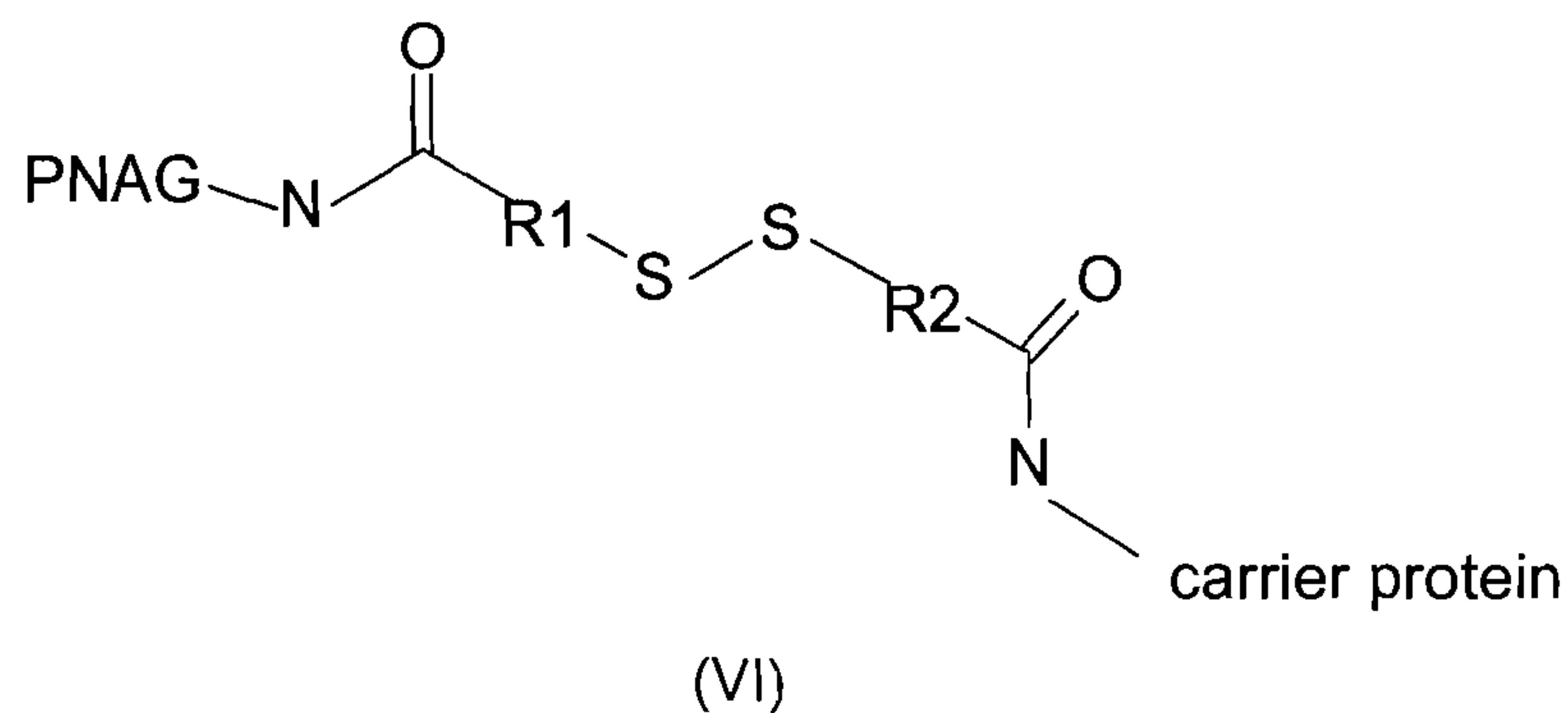


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wherein R is an aromatic or aliphatic chain, optionally substituted, or a bond. For example
 R is C1-C12 alkyl, C3-C10 alkyl, C4-C8 alkyl or C6 alkyl.

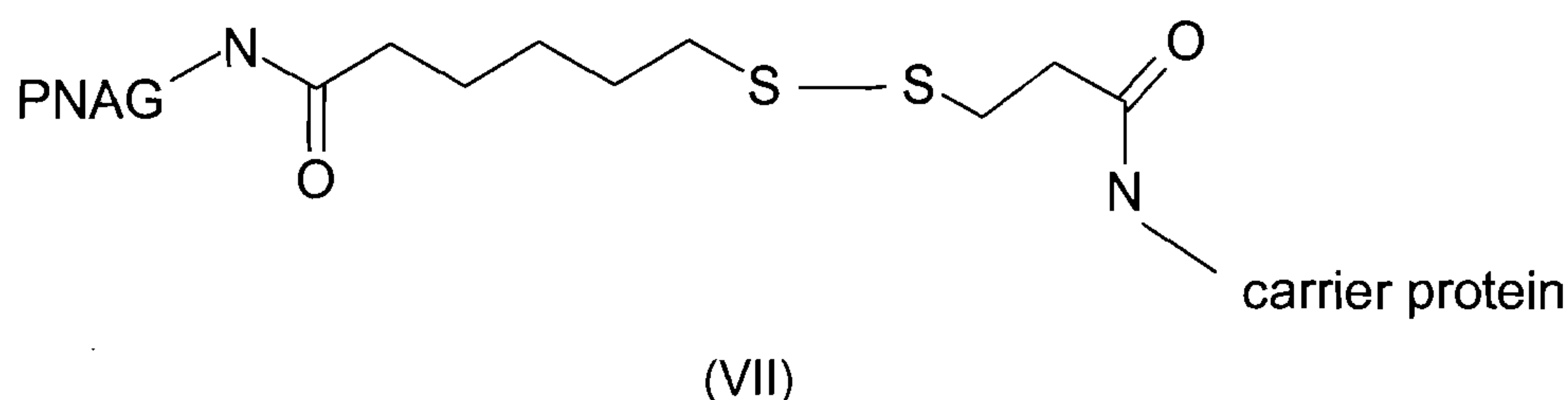
In an embodiment the PNAG conjugate is of formula (VI):

15



wherein R1 and R2 are independently selected from an aromatic or aliphatic chain,
 20 optionally substituted, or a bond. For example R1 is C1-C6 alkyl, C2-C5 alkyl, C3-C4
 alkyl, C2 alkyl, C3 alkyl, C4 alkyl or C5 alkyl. For example R2 is C1-C6 alkyl, C2-C5
 alkyl, C3-C4 alkyl, C2 alkyl, C3 alkyl, C4 alkyl or C5 alkyl. For example R1 and R2 are
 C2 and C2; C2 and C3; C2 and C4; C2 and C5; C3 and C2; C3 and C3; C3 and C4;
 C3 and C5; C4 and C2; C4 and C3; C4 and C5; C5 and C2; C5 and C4; C5 and C3;
 25 C5 and C4 or C5 and C5 respectively.

In an embodiment the PNAG conjugate is of formula (VII):



10

In an embodiment the carrier protein is selected from the group consisting of tetanus toxoid, diphtheria toxoid, CRM197, *Haemophilus influenzae* protein D, *Pseudomonas aeruginosa* exoprotein A, pneumococcal pneumolysin and alpha toxoid.

15

In an embodiment, the carrier protein comprises a staphylococcal protein or fragment thereof selected from the group consisting of laminin receptor, SitC/MntC/saliva binding protein, EbhA, EbhB, Elastin binding protein (EbpS), EFB (FIB), SBI, autolysin, ClfA, SdrC, SdrD, SdrE, SdrG, SdrH, Lipase GehD, SasA, SasB, SasC, SasD, SasF, SasK, FnbA, FnbB, Cna, ClfB, FbpA, Npase, IsaA/PisA, SsaA, EPB, SSP-1, SSP-2, HBP, Vitronectin binding protein, fibrinogen binding protein, coagulase, Fig, MAP, Immunodominant ABC transporter, IsdA, IsdB, HarA, Mg²⁺ transporter, SitC and Ni ABC transporter, alpha toxin (Hla), alpha toxin H35R mutant and RNA III activating protein (RAP).

20

25

An alternative carrier protein to use in the immunogenic composition of the invention is a single staphylococcal protein or fragment thereof or a fusion protein comprising at least or exactly 1, 2, 3 or 4 or more of the staphylococcal proteins listed in the section below or fragments thereof.

30

A new carrier protein that would be particularly advantageous to use in the context of a staphylococcal vaccine is staphylococcal alpha toxoid. The native form may be conjugated to a polysaccharide since the process of conjugation reduces toxicity.

Preferably a genetically detoxified alpha toxin such as the His35Leu or His 35 Arg variants are used as carriers since residual toxicity is lower. Alternatively the alpha toxin is chemically detoxified by treatment with a cross-linking reagent, formaldehyde or glutaraldehyde. A genetically detoxified alpha toxin is optionally chemically detoxified, preferably by treatment with a cross-linking reagent, formaldehyde or glutaraldehyde to further reduce toxicity. Other staphylococcal proteins or fragments thereof, particularly those listed above may be used as a carrier protein for the polysaccharides listed above. The carrier protein may be a fusion protein comprising at least or exactly 1, 2, 3, 4 or 5 of the staphylococcal proteins listed above.

The PNAG or polysaccharides may be linked to the carrier protein(s) by known methods (for example, by Marburg U.S. Patent 4830852, by Likhite, U.S. Patent 4,372,945 by Armor et al., U.S. Patent 4,474,757, Jennings et al., U.S. Patent 4,356,170 or Kossaczka and Szu Glycoconjugates Journal 17, 425-433. 2000). Alternatively, CDAP conjugation chemistry is carried out (see WO95/08348).

In CDAP, the cyanylating reagent 1-cyano-dimethylaminopyridinium tetrafluoroborate (CDAP) is preferably used for the synthesis of polysaccharide-protein conjugates. The cyanilation reaction can be performed under relatively mild conditions, which avoids hydrolysis of the alkaline sensitive polysaccharides. This synthesis allows direct coupling to a carrier protein.

The polysaccharide may be solubilized in water or a saline solution. CDAP may be dissolved in acetonitrile and added immediately to the polysaccharide solution. The CDAP reacts with the hydroxyl groups of the polysaccharide to form a cyanate ester. After the activation step, the carrier protein is added. Amino groups of lysine react with the activated polysaccharide to form an isourea covalent link. After the coupling reaction, a large excess of glycine is then added to quench residual activated functional groups. The product is then passed through a gel permeation column to remove unreacted carrier protein and residual reagents.

In an embodiment, the PNAG is conjugated by a method involving the conjugation of an amine group on the PNAG to a carboxyl group on the carrier protein, for example using carbodiimide chemistry, for example using EDAC (Kossaczka and Szu Glycoconjugates Journal 17; 425-433, 2000). In an embodiment, the PNAG is conjugated to the carrier

protein via a spacer, for instance a bifunctional spacer. The spacer is optionally heterobifunctional or homobifunctional, having for example a reactive amino group and a reactive carboxylic acid group, 2 reactive amino groups or two reactive carboxylic acid groups. The spacer has for example between 4 and 20, 4 and 12, 5 and 10 carbon atoms.

5 A possible spacer is ADH. Other spacers include B-propionamido (WO 00/10599), nitrophenyl-ethylamine (Gever et al (1979) Med. Microbiol. Immunol. 165; 171-288), haloalkyl halides (US4057685) glycosidic linkages (US4673574, US4808700) and 6-aminocaproic acid (US4459286).

10 **Conjugation of *S. aureus* capsular polysaccharides or oligosaccharides using CDAP**

In a further embodiment of the invention, there is provided a process for producing a conjugate comprising a bacterial saccharide (for example *S. aureus* type 5 or 8 polysaccharide or oligosaccharide) and a carrier protein comprising the steps of:

- 15 a) activating the bacterial saccharide (for example *S. aureus* type 5 or 8 polysaccharide or oligosaccharide) with a cyanylating reagent to form an activated bacterial (for example *S. aureus* type 5 or 8) polysaccharide or oligosaccharide; and
- 20 b) covalently linking the activated bacterial (for example *S. aureus* type 5 or 8) polysaccharide or oligosaccharide to a carrier protein to form a bacterial (for example *S. aureus* type 5 or 8) polysaccharide or oligosaccharide conjugate.

25 The cyanylating reagent conjugation process of the invention may be used for conjugating a carbohydrate containing moiety to a protein. For example, the bacterial capsular saccharide, optionally selected from Neisserial capsular saccharides from serogroups A, B, C, W or Y, pneumococcal saccharides from serotypes 1, 2, 3, 4, 5, 6A, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F, staphylococcal capsular saccharides from type 5 or 8 strains, *S. epidermidis*, GBS, GAS or *Haemophilus influenzae* PRP.

30 The *S. aureus* or *S. epidermidis* saccharides may have any of the attributes described above.

35 For example, the *S. aureus* type 5 or 8 saccharide is of native size or is sized, for example by microfluidisation, ultrasonic irradiation or chemical treatment. Type 5 or 8 saccharide optionally has a molecular weight of between 100kDa-1000kDa, 100-300kDa, 300-1000kDa, 30-300kDa, 10-100kDa or 5-50kDa as measured by MALLS. Type 5 or 8 saccharide is optionally sized to give a viscosity of 1-3, 2.0-3.0, 2.5-2.9 or 2.6-2.8cp.

The Type 5 or 8 polysaccharide or oligosaccharide optionally has a degree of O-acetylation of 10-100, 20-100, 30-100, 40-100, 50-100 60-100, 70-100 or 80-100%.

5 The carrier protein used in the process of the invention may be as described above. In an embodiment, the carrier protein is selected from the group consisting of diphtheria toxoid, Crm197, tetanus toxoid, keyhole limpet haemocyanin, *Pseudomonas aeruginosa* exoprotein A, *Haemophilus influenzae* protein D, pneumococcal pneumolysin and a staphylococcal protein or fragment thereof. The staphylococcal protein or fragment thereof is optionally selected from the group consisting of laminin receptor, 10 SitC/MntC/saliva binding protein, EbhA, EbhB, Elastin binding protein (EbpS), EFB (FIB), SBI, Protein A, autolysin, ClfA, SdrC, SdrG, SdrH, Lipase GehD, SasA, SasB, SasC, SasD, SasF, SasK, FnbA, FnbB, Cna, ClfB, FbpA, Npase, IsaA/PisA, SsaA, EPB, SSP-1, SSP-2, HBP, Vitronectin binding protein, fibrinogen binding protein, coagulase, Fig, MAP, Immunodominant ABC transporter, IsdA, IsdB, HarA, MRPII, Mg²⁺ transporter, proteinA, 15 Aaa, Ant, SdrD, SdrE, SitC and Ni ABC transporter, alpha toxin (Hla), alpha toxin H35R mutant and RNA III activating protein (RAP).

In an embodiment, the cyanylating reagent is 1-cyano-dimethylaminopyridinium tetraborate (CDAP).

20

In an embodiment, the type 5 or 8 polysaccharide or oligosaccharide is directly linked to the carrier protein for example via a isourea covalent link.

25 In an embodiment the type 5 or 8 polysaccharide or oligosaccharide is linked to the carrier protein via a spacer. In order to conjugate a *S. aureus* polysaccharide to a carrier protein via a spacer, the following method was used. The covalent binding of the polysaccharide and the spacer (for example ADH) is carried out by a coupling chemistry by which the polysaccharide is activated under controlled conditions by a cyanylating agent, 1-cyano-4-dimethylamino-pyridinium tetrafluoroborate (CDAP). The spacer reacts with the 30 cyanylated PS through its hydrazino groups, to form a stable isourea link between the spacer and the polysaccharide.

35 In an embodiment, the spacer is bifunctional and/or contains a C4-12 alkyl group and/or contains two amino group and/or contains two carboxylic acid groups. In an embodiment the spacer is ADH.

40 In an embodiment, the ratio of cyanylating reagent to polysaccharide or oligosaccharide in step a) is between 0.25/1 and 1/1 (w/w) or between 0.3/1 and 0.7/1 (w/w), 0.5-0.75, or around 0.5/1 or around 0.75/1.

In an embodiment step a) is carried out at pH 5.0-7.0, pH 5.5-6.5 or around pH 6.0.

In an embodiment step a) is carried out for between 30 seconds and 10 minutes, 1 minute and 5 minutes or 2-5 minutes.

- 5 In an embodiment step a) is terminated by raising the pH to between 8.0-10.0 or to around pH 9.0.

In an embodiment the ratio of carrier protein to type 5 or 8 polysaccharide or oligosaccharide in step b) is between 1/1 and 10/1, between 1.1/1 and 5/1 or between
10 1.2/1 and 2.5/1 (w/w).

In an embodiment step b) is carried out at pH 8.0-10.0 or at around pH 9.0.

15 In an embodiment step b) is carried out for between 10 minutes and 12 hours, 25 minutes and 4 hours, 30 minutes and 2 hours or for around 1 hour.

In an embodiment, the process comprises a further step of combining the type 5 or 8 polysaccharide or oligosaccharide conjugate with at least one additional staphylococcal antigen. For example, any of the staphylococcal antigens (including saccharides and
20 proteins) described above.

In an embodiment, the process of the invention comprises a further step of combining the type 5 or 8 polysaccharide or oligosaccharide conjugate with a pharmaceutically acceptable excipient or diluent to form a vaccine. In an embodiment, the conjugate is
25 combined with an adjuvant. Any of the excipients or adjuvants described below may be combined with the conjugate.

A further aspect of the invention is a conjugate comprising a *S. aureus* type 5 or 8 polysaccharide or oligosaccharide and a carrier protein bonded by a linker comprising an isourea covalent link.
30

In an embodiment the *S. aureus* type 5 or 8 polysaccharide has any of the attributes described above. For example, it is optionally of native size or is sized as described above.
35

A further aspect of the invention is a conjugate obtainable by the process of the invention.

A further aspect of the invention is a vaccine comprising the conjugate of the invention and a pharmaceutically acceptable excipient or diluent, optionally comprising an adjuvant.
40 The excipient and adjuvants are optionally as described below.

A further aspect of the invention is a method of making a vaccine comprising the steps of mixing the conjugate of in the invention and adding a pharmaceutically acceptable excipient.

- 5 A further aspect of the invention is a method of preventing or treating staphylococcal infection comprising the step of administering the vaccine of the invention to a patient in need thereof. In an embodiment, this method is as described below.

10 A further aspect of the invention is a use of the conjugate of the invention in the manufacture of a vaccine for treatment or prevention of staphylococcal infection.

Proteins

The immunogenic composition of the invention optionally further comprises a staphylococcal protein, for example a protein from *S. aureus* or *S. epidermidis*. Some
15 embodiments of the invention contain proteins from both *S. aureus* and *S. epidermidis*. Immunogenic compositions of the invention comprise an isolated protein which comprises an amino acid sequence which has at least 85% identity, optionally at least 90% identity, at least 95% identity, at least 97-99% or exact identity, to that of any sequence of figure 1.

20 Where a protein is specifically mentioned herein, it is optionally a reference to a native or recombinant, full-length protein or optionally a mature protein in which any signal sequence has been removed. The protein may be isolated directly from the staphylococcal strain or produced by recombinant DNA techniques. Immunogenic fragments of the protein may be
25 incorporated into the immunogenic composition of the invention. These are fragments comprising at least 10 amino acids, at least 20 amino acids, at least 30 amino acids, at least 40 amino acids, at least 50 amino acids or at least 100 amino acids, taken contiguously from the amino acid sequence of the protein. In addition, such immunogenic fragments are typically immunologically reactive with antibodies generated against the Staphylococcal
30 proteins or with antibodies generated by infection of a mammalian host with Staphylococci or contain T cell epitopes. In an embodiment, immunogenic fragments also includes fragments that when administered at an effective dose, (either alone or as a hapten bound to a carrier), elicit a protective immune response against Staphylococcal infection, optionally it is protective against *S. aureus* and/or *S. epidermidis* infection. Such an immunogenic
35 fragment may include, for example, the protein lacking an N-terminal leader sequence, and/or a transmembrane domain and/or a C-terminal anchor domain. In an embodiment,

the immunogenic fragment according to the invention comprises substantially all of the extracellular domain of a protein which has at least 85%, 90%, 95%, 97% or 99% identity, to that a sequence selected from Figure 1 over the entire length of the fragment sequence.

5 In an embodiment, immunogenic compositions of the invention may contain fusion proteins of Staphylococcal proteins, or fragments of staphylococcal proteins. Such fusion proteins may be made recombinantly and may comprise one portion of at least 2, 3, 4, 5 or 6 staphylococcal proteins, for example the combinations of staphylococcal proteins listed below. Alternatively, a fusion protein may comprise multiple portions of at least 2, 3,
10 4 or 5 staphylococcal proteins. These may combine different Staphylococcal proteins or fragments thereof in the same protein. Alternatively, the invention also includes individual fusion proteins of Staphylococcal proteins or fragments thereof, as a fusion protein with heterologous sequences such as a provider of T-cell epitopes or purification tags, for example: β -galactosidase, glutathione-S-transferase, green fluorescent proteins (GFP),
15 epitope tags such as FLAG, myc tag, poly histidine, or viral surface proteins such as influenza virus haemagglutinin, or bacterial proteins such as tetanus toxoid, diphtheria toxoid, CRM197. The fusion protein may be present in the immunogenic composition of the invention as a free protein or it may be a carrier protein linked to a saccharide.

Proteins

20 In an embodiment, the immunogenic composition of the invention further comprises one or more of the proteins mentioned below or immunogenic fragments thereof. Many of the proteins fall into the categories of extracellular component binding proteins, transporter proteins or toxins and regulators of virulence. The immunogenic composition of the
25 invention optionally further comprises a staphylococcal extracellular component binding protein or a staphylococcal transporter protein or a staphylococcal toxin or regulator of virulence. The immunogenic composition of the invention optionally comprises at least or exactly 1, 2, 3, 4, 5 or 6 staphylococcal proteins.

Table 1

The following table sets out the SEQ ID numbers of preferred protein sequences and DNA sequences that are found in Figure 1 and Figure 2 respectively. SA indicates a sequence from *S. aureus* and SE indicates a sequence from *S. epidermidis*.

Name	Protein sequence	DNA sequence
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Immunodominant ABC transporter		
SA	SEQ ID 1	SEQ ID 34
SE	SEQ ID 2	SEQ ID 35
Laminin receptor		
SA	SEQ ID 3	SEQ ID 36
SE	SEQ ID 4	SEQ ID 37
Secretory Antigen A SsaA		
SA 1	SEQ ID 5	SEQ ID 38
SA 2	SEQ ID 6	SEQ ID 39
SE	SEQ ID 7	SEQ ID 40
SitC		
SA	SEQ ID 8	SEQ ID 41
SE	SEQ ID 9	SEQ ID 42
IsaA / PisA (IssA)		
SA	SEQ ID 10	SEQ ID 43
SE	SEQ ID 11	SEQ ID 44

EbhA / B		
SA EbhA	SEQ ID 12	SEQ ID 45
SA EbhB	SEQ ID 13	SEQ ID 46
SE EbhA	SEQ ID 14	SEQ ID 47
SE EbhB	SEQ ID 15	SEQ ID 48
Accumulation-assoc pro Aap		
SA	SEQ ID 16	SEQ ID 49
SE	SEQ ID 17	SEQ ID 50
RNA III activating protein RAP		
SA	SEQ ID 18	SEQ ID 51
SE	SEQ ID 19	SEQ ID 52
FIG / SdrG		
SA	SEQ ID 20	SEQ ID 53
SE	SEQ ID 21	SEQ ID 54
Elastin binding protein EbpS		
SA	SEQ ID 22	SEQ ID 55
SE	SEQ ID 23	SEQ ID 56
Extracellular protein EFB SA	SEQ ID 24	SEQ ID 57
alpha toxin SA	SEQ ID 25	SEQ ID 58
SBI SA	SEQ ID 26	SEQ ID 59
IsdA SA	SEQ ID 27	SEQ ID 60
IsdB SA	SEQ ID 28	SEQ ID 61
SdrC SA	SEQ ID 29	SEQ ID 62
ClfA SA	SEQ ID 30	SEQ ID 63

FnbA SA	SEQ ID 31	SEQ ID 64
ClfB SA	SEQ ID 32	SEQ ID 65
Coagulase SA	SEQ ID 33	SEQ ID 66
FnbB SA	SEQ ID 67	SEQ ID 77
MAP SA	SEQ ID 68	SEQ ID 78
HarA SA	SEQ ID 69	SEQ ID 79
Autolysin glucosaminidase SA	SEQ ID 70	SEQ ID 80
Autolysin amidase SA	SEQ ID 71	SEQ ID 81
Ebh fragment SA	SEQ ID 72	SEQ ID 82
Autolysin Ant SA	SEQ ID 73	SEQ ID 83
SdrC SA	SEQ ID 74	SEQ ID 84
MRPII SA	SEQ ID 75	SEQ ID 85
SdrG SA	SEQ ID 76	SEQ ID 86
SdrE SA	SEQ ID 87	SEQ ID 88
SdrD SA	SEQ ID 89	SEQ ID 90
SasF SA	SEQ ID 91	SEQ ID 92
SasD SA	SEQ ID 93	SEQ ID 94

Extracellular component binding proteins

5 Extracellular component binding proteins are proteins that bind to host extracellular components. The term includes, but is not limited to adhesins.

Examples of extracellular component binding proteins include laminin receptor (Naidu et al J. Med. Microbiol. 1992, 36; 177), SitC/MntC/saliva binding protein (US5801234, Wiltshire and Foster Infec. Immun. 2001, 69; 5198), EbhA (Williams et al Infect. Immun. 10 2002, 70; 6805), EbhB, Elastin binding protein (EbpS) (Park et al 1999, J. Biol. Chem. 274; 2845), EFB (FIB) (Wastfelt and Flock 1995, J. Clin. Microbiol. 33; 2347), SBI (Zhang et al FEMS Immun. Med. Microbiol. 2000, 28; 211), autolysin (Rupp et al 2001, J. Infect. Dis. 183; 1038), ClfA (US6008341, McDevitt et al Mol. Microbiol. 1994, 11; 237), SdrC, SdrG (McCrea et al Microbiology 2000, 146; 1535), SdrH (McCrea et al Microbiology 15 2000, 146; 1535), Lipase GehD (US2002/0169288), SasA (Roche et al Microbiology 2003, 149 ; 643), SasC (Roche et al Microbiology 2003, 149 ; 643), SasK (Roche et al Microbiology 2003, 149 ; 643), FnbA (Flock et al Mol Microbiol. 1994, 12; 599, US6054572), FnbB (WO 97/14799, Booth et al 2001 Infec. Immun. 69; 345), collagen binding protein Cna (Visai et al 2000, J. Biol. Chem. 275; 39837), ClfB (WO 99/27109), 20 SdrD (WO 99/27109), SdrE (WO 99/27109), FbpA (Phonimdaeng et al 1988 J. Gen Microbiol.134; 75), Npase (Flock 2001 J. Bacteriol. 183; 3999), IsaA/PisA (Lonenz et al FEMS Immuno. Med. Microbiol. 2000, 29; 145), SsaA (Lang et al FEMS Immunol. Med. Microbiol. 2000, 29; 213), EPB (Hussain and Hermann symposium on Staph Denmark 14-

17th 2000), SSP-1 (Veenstra et al 1996, J. Bacteriol. 178; 537), SSP-2 (Veenstra et al 1996, J. Bacteriol. 178; 537), 17 kDa heparin binding protein HBP (Fallgren et al 2001, J. Med. Microbiol. 50; 547), Vitronectin binding protein (Li et al 2001, Curr. Microbiol. 42; 361), fibrinogen binding protein, coagulase, Fig (WO 97/48727) and MAP (US5648240)

5

SitC/MntC/saliva binding protein

This is an ABC transporter protein which is a homologue of adhesin PsaA in *S. pneumoniae*. It is a highly immunogenic 32kDa lipoprotein which is distributed through the bacterial cell wall (Cockayne et al Infect. Immun. 1998 66; 3767). It is expressed in *S. aureus* and *S. epidermidis* as a 32kDa lipoprotein and a 40kDa homologue is present in *S. hominis*. In *S. epidermidis*, it is a component of an iron-regulated operon. It shows considerable homology to both adhesins including FimA of *Streptococcus parasanguis*, and with lipoproteins of a family of ABC transporters with proven or putative metal ion transport functions. Therefore SitC is included as an extracellular binding protein and as a metal ion transporter.

20

The saliva binding protein disclosed in US5,801,234 is also a form of SitC and can be included in an immunogenic composition of the invention.

ClfA and ClfB

25

Both these proteins have fibrinogen binding activity and trigger *S. aureus* to form clumps in the presence of plasma. They contain a LPXTG motif common to wall associated proteins.

ClfA is described in US6008341 and ClfB is described in WO 99/27109.

Coagulase (FbpA)

30

This is a fibrinogen binding protein which triggers *S. aureus* to form clumps in the presence of plasma. It is described in references related to Coagulase : Phonimdaeng et al (J. Gen. Microbio. 1988, 134:75-83), Phonimdaeng et al. (Mol Microbiol 1990; 4:393-404), Cheung et al. (Infect Immun 1995; 63:1914-1920) and Shopsin et al. (J. Clin. Microbiol. 2000; 38:3453-3456).

35

Preferred fragments for inclusion in the immunogenic composition of the invention include the mature protein in which the signal peptide has been removed (amino acids 27 to the C-terminus).

40

Coagulase has three distinct domains. Amino acids 59-297 which is a coiled coil region, amino acids 326-505 which is a proline and glycine rich region and the C-terminal domain from amino acid 506 to 645 which has a beta sheet conformation. Each of these domains is a fragment which may be incorporated into the immunogenic composition of the invention.

SdrG

This protein is described in WO 00/12689. SdrG is found in coagulase negative staphylococci and is a cell wall associated protein containing a LPXTG sequence.

SdrG contains a signal peptide (amino acids 1-51), a region containing fibrinogen binding sites and collagen binding sites (amino acids 51-825), two CnaB domains (amino acids 627-698 and 738-809), a SD repeat region (amino acids 825-1000) and an anchor domain (amino acids 1009-1056).

Preferred fragments of SdrG include polypeptides in which the signal peptide and/or the SD repeats and the anchor domain have been removed. These include polypeptides comprising or consisting of amino acids 50-825, amino acids 50-633, amino acids 50-597 (SEQ ID NO 2 of WO 03/76470), amino acids 273-597 (SEQ ID NO 4 of WO 03/76470), amino acids 273-577 (SEQ ID NO 6 of WO 03/76470) amino acids 1-549, amino acids 219-549, amino acids 225-549, amino acids 219-528, amino acids 225-528 of SEQ ID NO: 70 or 20 or 21.

Preferably, an SdrG polypeptide having a sequence at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or 100% homologous to the sequence of SEQ ID NO: 70, 20 or 21 is incorporated into the immunogenic composition of the invention.

The compositions of the invention optionally comprise a fragment of the SdrG polypeptides described above.

In an embodiment fragments have the signal peptide and/or the SD repeat domain and/or the anchoring domain deleted. For example sequences corresponding to amino acids 1-713, 1-549, 225-549, 225-529, 24-717, 1-707, 1-690, 1-680, 1-670, 1-660, 1-650, 1-640, 1-630, 1-620, 1-610, 1-600, 34-707, 44-697, 36-689 of SEQ ID 70 or sequences having 85%, 90%, 92%, 95%, 97%, 98%, 99% or 100% identity to SEQ ID 70 or 20 or 21.

In an embodiment, fragments with the signal peptide deleted have a methionine residue at the N-terminus of the fragment to ensure correct translation.

In an embodiment, the fragment has the following sequence:-

5

MEENSVQDVKDSNTDDELSDSNDQSSDEEKNDVINNNQSINTDDNNQIIKKEETNNYDGLIEKRSEDRTESTTN
VDENEATFLQKTPQDNTHLTEEEVKESSSVESSNSSIDTAQQPSHTTINREESVQTSNVEDSHVSDFANSKI
KESNTESGKEENTIEQPNKVKEDSTTSQPSGYTNIDEKISNQDE

10

LLNLPINEYENKARPLSTTSAQPSIKRVTVNQLAAEQGSNVNHLIKVTDQSITEGYDDSEGVKAHDAENLIY
DVTFEVDDKVKSGDTMTVDIDKNTVPSDLTDSFTIPKIKDNSGEIIATGTYNKNKQITYTFTDYVDKYENIK
AHLKLTSYIDKSKVPNNNTKLDVEYKTALSSVNKTITVEYQRPENRTANLQSMFTNIDTKNHTVEQTIYINP
LRYSAKETNVNISGNGDEGST

15

IIDDSTIIKVYKVGDNQNLPSNRIYDYSEYEDVTNDDYAQLGNNNDVNINFGNIDSPYIIKVISKYDPNKDD
YTTIQQTVTMQTTINEYTGEFRTASYDNTIAFSTSSGQGQGDLPPEKTYKIGDYVWEDVDKDGIQNTNDNEKP
LSNVLVTLTYPDGTSKSVRTDEDGKYQFDGLKNGLTYKITFETPEGYTPTLKHSGTNPALDSEGNSVWVTING
QDDMTIDSGFYQTPKYSLGNY
VWYDTNKDGIQGDDEKGISGVKVTCLKDENGNIISTTTTDENGKYQFDNLNSGNYIVHFDKPSGMTQTTTDSGD
DDEQDADGEEVHVTITDHDDFSIDNGYYDDE

20

EbhA and EbhB

EbhA and EbhB are proteins that are expressed in both *S. aureus* and *S. epidermidis* (Clarke and Foster Infect. Immun. 2002, 70; 6680 , Williams et al Infect. Immun. 2002, 20; 6805) and
25 which bind to fibronectin. Since fibronectin is an important component of extracellular matrix, EbhA and EbhB have an important function in adhering staphylococci to host extracellular matrix.

The Ebh proteins are large, having a molecular weight of 1.1 megadaltons. It is advantageous
30 to use a fragment of the Ebh protein rather than the complete sequence due to ease of production and formulation. The central region of the protein contains imperfect repeats which contain fibronectin binding sites. Fragments containing one or more of the repeat domains described below are preferred fragments for incorporation into the immunogenic composition of the invention.

35

Ebh proteins contain imperfect repeats units of 127 amino acids in length which are characterised by containing the consensus sequence:-

L.G.{10}A.{13}Q.{26}L...M..L.{33}A

or

.{19}L.G.{10}A.{13}Q.{26}L...M..L.{33}A.{12}

or

5 I/V..A...I/V..AK.ALN/DG..NL..AK..A.{6}L..LN.AQK..L..QI/V..A..V..
V.{6}A..LN/D.AM..L...I/V.D/E...TK.S.NY/F.N/DAD..K..AY/F..AV..A..I/V.N
/D.....

10 Where '.' means any amino acid and '{10}' means any 10 amino acids
and I/V indicates alternative choices of amino acid.

By reference to the sequence disclosed in Kuroda et al (2001) Lancet 357; 1225-1240, and Table 2, the repeat sequences within Ebh proteins are readily deduced.

15 In an embodiment, fragments to be included in the immunogenic composition of the invention include proteins containing of one, two, three, four, five, six, seven, eight, nine, ten or more than 10 of the 127 amino acid repeat units. Such fragments may consist of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more repeats of the 127 amino acid repeat region or may consist of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more repeats with additional amino acid residues present at either or both ends of
20 the fragment. Optionally the fragment is the H2 polypeptide of about 44kDa spanning three repeats (amino acids 3202-3595) as described in Clarke et al Infection and Immunity 70, 6680-6687, 2002. Such fragments will preferably be able to bind fibronectin and/or to elicit antibodies that are reactive against the whole Ebh protein.

25 The Ebh proteins are capable of binding to fibronectin. Preferred fragments of these polypeptides sequences retain the ability to bind to fibronectin. Binding to fibronectin can be assessed by ELISA as described by Clarke et al (Infection and Immunity 70; 6680-6687 2002).

30 In an embodiment, the fragment is one which comprises a B-cell or T-helper epitope, for example those fragments/peptides described in Tables 3 and 4.

TABLE 2 Repeat sequences in the full-length sequence of Ebh.

The full-length sequence of Ebh is disclosed in Kuroda et al (2001) Lancet 357; 1225-1240. The following table shows the amino acid residues at which the 127 amino acid repeats begin and end within the full length sequence.

	Begin	End
1	3204	3330
2	3331	3457
3	3457	3583
4	3583	3709
5	3709	3835
6	3835	3961
7	3961	4087
8	4200	4326
9	4326	4452
10	4452	4578
11	4578	4704
12	4704	4830
13	4830	4956
14	4956	5082
15	5082	5208
16	5208	5334
17	5334	5460
18	5460	5586
19	5585	5711
20	5711	5837
21	5837	5963
22	5963	6089
23	6089	6215
24	6215	6341
25	6341	6467
26	6467	6593
27	6593	6719
28	6719	6845
29	6845	6971
30	6971	7097
31	7097	7223
32	7223	7349
33	7349	7475
34	7475	7601
35	7601	7727
36	7727	7853

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37	7852	7978
38	7978	8104
39	8104	8230
40	8230	8356
41	8356	8482
42	8482	8608
43	8604	8730
44	8858	8984

Table 3 B-cell epitope prediction for a 127 amino acid repeat :

The full-length sequence is disclosed in Kuroda et al (2001) Lancet 357; 1225-1240. One of these repeats, encoded by amino acids 3204-3331 of the full-length sequence was chosen to carry out an epitope prediction:-

MDVNTVNQKAASVKSTKDALDGQQNLQRAKTEATNAITHASDLNQAQKNALTQQVN
SAQNVHAVNDIKQTTQSLNTAMTGLKRGVANHNQVVQSDNYVNADTNKKNDYNNAY
NHANDIINGNAQHPVI

10

Begin	End	Epitope sequence	Start	Stop
5	10	TVNQKA	3208	3213
14	19	KSTKDA	3217	3222
21	33	DGQQNLQRAKTEA	3224	3236
42	51	DLNQAQKNAL	3245	3254
66	74	DIKQTTQSL	3269	3277
100	112	ADTNKKNDYNNAY	3303	3315
117	123	DIINGNA	3320	3326

- The "Begin" and "End" columns present the position of the predicted B-cell epitopes in the 127 amino acid repeat
- The "Start" and "Stop" columns present the position of the predicted B-cell epitopes in the Ebh full length sequence

15

Table 4 T-helper cell epitope prediction in Ebh :

The full-length sequence is disclosed in TrEMBL database, sequence reference Q8NWQ6. One of these repeats, encoded by amino acids 3204-3331 of the full-length sequence was chosen to carry out an epitope prediction:-

MDVNTVNQKAASVKSTKDALDGQQNLQRAKTEATNAITHASDLNQAQKNALTQQVN
SAQNVHAVNDIKQTTQSLNTAMTGLKRGVANHNQVVQSDNYVNADTNKKNDYNNAY
NHANDIINGNAQHPVI

Position repeat	Epitope sequence	Position sequence
1	MDVNTVNQK	3204
3	VNTVNQKAA	3206
6	VNQKAASVK	3209
26	LQRAKTEAT	3229
37	ITHASDLNQ	3240
43	LNQAQKNAL	3246
51	LTQQVNSAQ	3254
55	VNSAQNVHA	3258
61	VHAVNDIKQ	3264
64	VNDIKQTTQ	3267
67	IKQTTQSLN	3270
74	LNTAMTGLK	3277
78	MTGLKRGVA	3281
81	LKRGVANHN	3284
85	VANHNQVVQ	3288
91	VVQSDNYVN	3294
92	VQSDNYVNA	3295
97	YVNADTNKK	3301
98	VNADTNKKN	3302
108	YNNAYNHAN	3311
112	YNHANDIIN	3315
118	IINGNAQHP	3321
119	INGNAQHPV	3322

- The "Position repeat" column presents the position of the predicted T-cell epitopes in the repeat
- The "Position sequence" column presents the position of the predicted T-cell epitopes in the Ebh full length sequence

Fragments of the proteins of the invention may be employed for producing the corresponding full-length polypeptide by peptide synthesis; therefore, these fragments may be employed as intermediates for producing the full-length proteins of the invention.

- 5 In an embodiment, variants are used in which several, 5-10, 1-5, 1-3, 1-2 or 1 amino acids are substituted, deleted, or added in any combination.

Elastin binding protein (EbpS)

- 10 EbpS is a protein containing 486 amino acids with a molecular weight of 83kDa. It is associated with the cytoplasmic membrane of *S. aureus* and has three hydrophobic regions which hold the protein in the membrane (Downer et al 2002, J. Biol. Chem. 277; 243; Park et al 1996, J. Biol. Chem. 271; 15803).

- 15 Two regions between amino acids 1-205 and 343-486 are surface exposed on the outer face of the cytoplasmic membrane. The ligand binding domain of EbpS is located between residues 14-34 at the N-terminus (Park et al 1999, J. Biol. Chem. 274; 2845).

- 20 In an embodiment, the fragment to be incorporated into the immunogenic composition of the invention is the surface exposed fragment containing the elastin binding region (amino acids 1-205). Optionally the fragments do not contain the entire exposed loop but should contain the elastin binding region (amino acids 14-34). An alternative fragment which could be used consists of amino acids forming the second surface exposed loop (amino acids 343-486). Alternative fragments containing up to 1, 2, 5, 10, 20, 50 amino acids less
25 at one or both ends are also possible.

Laminin receptors

- 30 The laminin receptor of *S. aureus* plays an important role in pathogenicity. A characteristic feature of infection is bloodstream invasion which allows widespread metastatic abscess formation. Bloodstream invasion requires the ability to extravasate across the vascular basement membrane. This is achieved through binding to laminin through the laminin receptor (Lopes et al Science 1985, 229; 275).

- 35 Laminin receptors are surface exposed and are present in many strains of staphylococci including *S. aureus* and *S. epidermidis*.

SBI

Sbi is a second IgG binding protein in addition to protein A and it is expressed in most strains of *S.aureus* (Zhang et al 1998, Microbiology 144; 985).

5

The N-terminus of the sequence of Sbi has a typical signal sequence with a cleavage site after amino acid 29. Therefore a fragment of Sbi which could be used in an immunogenic composition of the invention starts at amino acid residue 30, 31, 32 or 33 and continues to the C-terminus of Sbi, for example of SEQ ID NO: 26.

10

The IgG binding domain of Sbi has been identified as a region towards the N-terminus of the protein from amino acids 41-92. This domain is homologous to the IgG binding domains of protein A.

15 The minimal IgG binding domain of Sbi contains the following sequence:-

```

QTTQNNYVTDQQKAFYQVLHLKGITEEQRNQYIKTLREHPERAQEVFSESLK
      **  ***   *           ***   *   *   *           *   *

```

20 * - denotes amino acids which are similar between IgG binding domains

In an embodiment, a fragment of Sbi to be included in the immunogenic composition of the invention contains an IgG binding domain. This fragment contains the consensus sequence for an IgG binding domain as designated by * as shown in the above sequence. Optionally the fragment contains or consists of the complete sequence shown above. Optionally, the fragment contains or consists of amino acids 30-92, 33-92, 30-94, 33-94, 30-146, 33-146, 30-150, 33-150, 30-160, 33-160, 33-170, 33-180, 33-190, 33-200, 33-205 or 33-210 of Sbi, for example of SEQ ID NO:26.

30

A fragment may contain 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 amino acid substitutions from the sequences indicated.

A fragments may contain multiple repeats (2, 3, 4, 5, 6, 7,8, 9 or 10) of the IgG binding domain.

35

EFB - FIB

Fib is a 19kDa fibrinogen binding protein which is secreted into the extracellular medium by *S. aureus*. It is produced by all *S. aureus* isolates tested (Wastfelt and Flock 1995, J. Clin. Microbiol. 33; 2347).

- 5 *S. aureus* clumps in the presence of fibrinogen and binds to fibrinogen coated surfaces. This ability facilitates staphylococcal colonisation of catheters and endothelial cells.

10 Fib contains a signal sequence at the N-terminus of the protein with a putative cleavage site at about amino acid 30. In an embodiment, the immunogenic composition of the invention comprises or consists of the sequence of the mature protein (from about amino acid 30 to the C-terminus of the protein).

Fbe – EfB/FIG

- 15 Fbe is a fibrinogen binding protein that is found in many isolates of *S. epidermidis* and has a deduced molecular weight of 119 kDa (Nilsson et al 1998. Infect. Immun. 66; 2666). Its sequence is related to that of clumping factor from *S. aureus* (ClfA). Antibodies against Fbe can block the binding of *S. epidermidis* to fibrinogen coated plates and to catheters (Pei and Flock 2001, J. Infect. Dis. 184; 52).

20

Fbe has a putative signal sequence with a cleavage site between amino acids 51 and 52. Therefore a preferred fragment of Fbe contains the mature form of Fbe extending from amino acid 52 to the C-terminus (amino acid 1,092).

- 25 The domain of Fbe from amino acid 52 to amino acid 825 is responsible for fibrinogen binding. In an embodiment, the fragment of Fbe consists of or contains amino acids 52-825.

30 The region between amino acid 373 and 516 of Fbe shows the most conservation between Fbe and ClfA. In an embodiment, the fragment contains amino acids 373-516 of Fbe.

Amino acids 825 – 1041 of Fbe contains a highly repetitive region composed of tandemly repeated aspartic acid and serine residues.

35

IsaA/PisA

IsaA is a 29kDa protein, also known as PisA has been shown to be a immunodominant staphylococcal protein during sepsis in hospital patients (Lorenz et al 2000, FEMS Immunol. Med. Microb. 29; 145).

- 5 The first 29 amino acids of the IsaA sequence are thought to be a signal sequence. In an embodiment, the fragment of IsaA to be included in an immunogenic composition of the invention contains amino acid residues 30 onwards, to the end of the coded sequence.

Fibronectin binding protein

10

Fibronectin binding protein A contains several domains that are involved in binding to fibronectin (WO 94/18327). These are called D1, D2, D3 and D4. In an embodiment fragments of fibronectin binding protein A or B comprise or consist of D1, D2, D3, D4, D1-D2, D2-D3, D3-D4, D1-D3, D2-D4 or D1-D4.

15

Fibronectin binding protein contains a 36 amino acid signal sequence. For example:

VKNNLRYGIRKHKLGAA SVFLGTMIVVG MGQDKEAA

- 20 Optionally, the mature protein omitting this signal sequence is included in the immunogenic composition of the invention.

Transporter proteins

25 The cell wall of Gram positive bacteria acts as a barrier preventing free diffusion of metabolites into the bacterium. A family of proteins orchestrates the passage of essential nutrients into the bacterium and are therefore essential for the viability of the bacterium. The term transporter protein covers proteins involved in the initial step of binding to metabolites such as iron as well as those involved in actually transporting the metabolite into the bacterium.

30

Molecular iron is an essential co-factor for bacterial growth. Siderophores are secreted that bind free iron and then are captured by bacterial surface receptors that deliver iron for transport across the cytoplasmic membrane. Iron acquisition is critical for the establishment of human infections so that the generation of an immune response against this class of proteins leads to a loss of staphylococcal viability.

35

Examples of transporter proteins include Immunodominant ABC transporter (Burnie et al 2000 Infect. Immun. 68; 3200), IsdA (Mazmanian et al 2002 PNAS 99; 2293), IsdB (Mazmanian et al 2002 PNAS 99; 2293), IsdC (WO 06/59247), Mg²⁺ transporter, SitC
 5 (Wiltshire and Foster 2001 Infect. Immun. 69; 5198) and Ni ABC transporter.

Immunodominant ABC transporter

Immunodominant ABC transporter is a well conserved protein which may be capable of
 10 generating an immune response that is cross-protective against different staphylococcal strains (Mei et al 1997, Mol. Microbiol. 26; 399). Antibodies against this protein have been found in patients with septicaemia (Burnie et al 2000, Infect. Immun. 68; 3200).

Optional fragments of immunodominant ABC transporter will include the peptides DRHFLN,
 15 GNYD, RRYPF, KTTLLK, GVTTSLS, VDWLR, RGFL, more preferably KIKVYVGNYDFWYQS, TVIVVSHDRHFLYNNV and/or TETFLRGFLGRMLFS since these sequences contain epitopes that are recognised by the human immune system.

IsdA-IsdB

20 The *isd* genes (iron-regulated surface determinant) of *S. aureus* encode proteins responsible for haemoglobin binding and passage of haem iron to the cytoplasm, where it acts as an essential nutrient. IsdA and IsdB are located in the cell wall of staphylococci. IsdA appear to be exposed on the surface of bacterium since it is susceptible to proteinase K digestion. IsdB was partially digested suggesting that it is partially exposed
 25 on the surface of the bacterium (Mazmanian et al 2003 Science 299; 906).

IsdA and IsdB are both 29kDa proteins which bind heme. Their expression is regulated by the availability of iron via the Fur repressor. Their expression will be high during infection in a host where the concentration of iron will be low.

30

They are also known as FrpA and FrpB (Morrissey et al 2002, Infect. Immun. 70; 2399). FrpA and FrpB are major surface proteins with a high charge. They have been shown to provide a major contribution to adhesion to plastic.

In an embodiment, the immunogenic composition of the invention comprises a fragment of IsdA and/or IsdB which is described in WO 01/98499 or WO 03/11899.

5 **Toxins and regulators of virulence**

Members of this family of proteins include toxin such as alpha toxin, hemolysin, enterotoxin B and TSST-1 as well as proteins that regulate the production of toxins such as RAP.

10

Alpha toxin (Hla)

15

Alpha toxin is an important virulence determinant produced by most strains of *S.aureus*. It is a pore forming toxin with haemolytic activity. Antibodies against alpha toxin have been shown to neutralise the detrimental and lethal effects of alpha toxin in animal models (Adlam et al 1977 Infect. Immun. 17; 250). Human platelets, endothelial cells and mononuclear cells are susceptible to the effects of alpha toxin.

20

The high toxicity of alpha toxin requires that it should be detoxified before being used as an immunogen. This can be achieved by chemical treatment, for instance by treating with formaldehyde, glutaraldehyde or other cross-linking reagents or by chemically conjugating it to bacterial polysaccharides as described below.

25

A further way of removing toxicity is to introduce point mutations that remove toxicity while retaining the antigenicity of the toxin. The introduction of a point mutation at amino acid 35 of alpha toxin where a histidine residue is replaced with a leucine residue results in the removal of toxicity whilst retaining immunogenicity (Menzies and Kernodle 1996; Infect. Immun. 64; 1839). Histidine 35 appears to be critical for the proper oligomerization required for pore formation and mutation of this residue leads to loss of toxicity.

30

When incorporated into immunogenic compositions of the invention, alpha toxin is optionally detoxified by mutation of His 35, for example by replacing His 35 with Leu or Arg. In an alternative embodiment, alpha toxin is detoxified by conjugation to other components of the immunogenic composition, for example capsular polysaccharides or

PNAG, most preferably to *S. aureus* type 5 polysaccharide and/or *S.aureus* Type 8 polysaccharide and/or PNAG.

RNA III activating protein (RAP)

5

RAP is not itself a toxin, but is a regulator of the expression of virulence factors. RAP is produced and secreted by staphylococci. It activates the agr regulatory system of other staphylococci and activates the expression and subsequent release of virulence factors such as hemolysin, enterotoxin B and TSST-1.

10 **Other immunodominant proteins**

Accumulation-associated protein (Aap)

15

Aap is a 140kDa protein which is essential for the accumulation of *S. epidermidis* strains on surfaces (Hussain et al Infect. Immun. 1997, 65; 519). Strains expressing this protein produced significantly larger amounts of biofilm and Aap appear to be involved in biofilm formation. Antibodies against Aap are able to inhibit biofilm formation and inhibit the accumulation of *S. epidermidis*.

Staphylococcal Secretory antigen SsaA

20

SsaA is a strongly immunogenic protein of 30kDa found in both *S. aureus* and *S. epidermidis* (Lang et al 2000 FEMS Immunol. Med. Microbiol. 29; 213). Its expression during endocarditis suggested a virulence role specific to the pathogenesis of the infectious disease.

25

SsaA contains an N-terminal leader sequence and a signal peptidase cleavage site. The leader peptide is followed by a hydrophilic region of approximately 100 amino acids from residue 30 to residue 130.

30

An optional fragment of SsaA to be incorporated into the immunogenic composition of the invention is made up of the mature protein (amino acids 27 to the C-terminus or amino acids 30 to the C-terminus).

A further optional fragments contains the hydrophilic area of SsaA from amino acid 30 to amino acid 130.

Combinations

5 Staphylococcal infections progress through several different stages. For example, the staphylococcal life cycle involves commensal colonisation, initiation of infection by accessing adjoining tissues or the bloodstream, anaerobic multiplication in the blood, interplay between *S. aureus* virulence determinants and the host defence mechanisms and induction of complications including endocarditis, metastatic abscess formation and
10 sepsis syndrome. Different molecules on the surface of the bacterium will be involved in different steps of the infection cycle. By targeting the immune response against a combination of particular antigens involved in different processes of Staphylococcal infection, multiple aspects of staphylococcal function are affected and this can result in good vaccine efficacy.

15 In particular, combinations of certain antigens from different classes, some of which are involved in adhesion to host cells, some of which are involved in iron acquisition or other transporter functions, some of which are toxins or regulators of virulence and immunodominant antigens can elicit an immune response which protects against multiple
20 stages of infection.

Some combinations of antigens are particularly effective at inducing an immune response. This can be measured either in animal model assays as described in the examples and/or using an opsonophagocytic assay as described in the examples. Without wishing
25 to be bound by theory, such effective combinations of antigens are thought to be enabled by a number of characteristics of the immune response to the antigen combination. The antigens themselves are usually exposed on the surface of Staphylococcal cells, they tend to be conserved but also tend not to be present in sufficient quantity on the surface cell for an optimal bactericidal response to take place using antibodies elicited against the
30 single antigen. Combining the antigens of the invention can result in a formulation eliciting an advantageous combination of antibodies which interact with the Staphylococcal cell beyond a critical threshold. At this critical level, sufficient antibodies of sufficient quality bind to the surface of the bacterium to allow either efficient killing by complement or

neutralisation of the bacterium. This can be measured in either an animal challenge model or an opsonisation assay as described in the examples.

Preferred immunogenic compositions of the invention comprise a plurality of proteins selected from at least two different categories of protein, having different functions within Staphylococci. Examples of such categories of proteins are extracellular binding proteins, transporter proteins such as Fe acquisition proteins, toxins or regulators of virulence and other immunodominant proteins.

- 10 In a preferred embodiment, immunogenic composition of the invention further comprises a number of proteins equal to or greater than 2, 3, 4, 5 or 6 selected from 2, 3 or 4 different groups selected from;
- Group a) extracellular component binding proteins;
 - Group b) transporter proteins;
 - 15 • Group c) toxins or regulators of virulence
 - Group d) structural proteins.

In a preferred embodiment, immunogenic composition of the invention further comprises a number of proteins equal to or greater than 2, 3, 4, 5 or 6 selected from 2, 3 or 4 of the following groups:

- 20 • group a) - at least one staphylococcal extracellular component binding protein or fragment thereof selected from the group consisting of laminin receptor, SitC/MntC/saliva binding protein, EbhA, EbhB, Elastin binding protein (EbpS), EFB (FIB), SBI, ClfA, SdrC, SdrD, SdrE, SdrG, SdrH, SasF, lipase GehD, SasA, , SasB, SasC, SasD, SasK, FnbA, FnbB, Cna, ClfB, FbpA, Npase, IsaA/PisA, SsaA, EPB, SSP-1, SSP-2, HBP, Vitronectin binding protein, fibrinogen binding protein, coagulase, Fig and MAP;
- 25 • group b) - at least one staphylococcal transporter protein or fragment thereof selected from the group consisting of Immunodominant ABC transporter, IsdA, IsdB, IsdC, Mg²⁺ transporter, HarA, SitC and Ni ABC transporter;
- 30 • group c) - at least one staphylococcal regulator of virulence, toxin or fragment thereof selected from the group consisting of alpha toxin (Hla), alpha toxin H35R mutant, RNA III activating protein (RAP);
- 35 • group d) - at least one staphylococcal structural protein or immunogenic fragment thereof selected from the group consisting of MRPII and autolysin.

In a preferred embodiment, the immunogenic composition of the invention comprises a number of proteins equal to or greater than 2, 3, 4, 5 or 6 selected from 2 or 3 of the following groups:

- group a) - at least one staphylococcal extracellular component binding protein or immunogenic fragment thereof selected from the group consisting of laminin receptor, SitC/MntC/saliva binding protein, EbhA, EbhB, Elastin binding protein (EbpS), EFB (FIB), SBI, autolysin, ClfA, SdrC, SdrD, SdrE, SdrG, SdrH, SasF, Lipase GehD, SasA, FnbA, FnbB, Cna, ClfB, FbpA, Npase, IsaA/PisA, SsaA, EPB, SSP-1, SSP-2, HBP, Vitronectin binding protein, fibrinogen binding protein, coagulase, Fig and MAP;
- group b) - at least one staphylococcal transporter protein or immunogenic fragment thereof selected from the group consisting of Immunodominant ABC transporter, IsdA, IsdB, IsdC, HarA, Mg²⁺ transporter, SitC and Ni ABC transporter;
- group c) - at least one staphylococcal regulator of virulence, toxin or immunogenic fragment thereof selected from the group consisting of alpha toxin (Hla), alpha toxin H35R mutant, RNA III activating protein (RAP).

In a preferred embodiment, the immunogenic composition of the invention contains at least one protein selected from group a) and an additional protein selected from group b) and/or group c).

In a further embodiment, the immunogenic composition of the invention contains at least one antigen selected from group b) and an additional protein selected from group c) and/or group a).

In a further embodiment, the immunogenic composition of the invention contains at least one antigen selected from group c) and an additional protein selected from group a) and/or group b).

An optional combination of proteins in the immunogenic composition of the invention comprises laminin receptor and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, IsdC, HarA, Mg²⁺ transporter, SitC, Ni ABC transporter, alpha toxin, alpha toxin H35L or H35R mutant, RAP, Aap and SsaA.

A further combination of proteins in the immunogenic composition of the invention comprises SitC and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, IsdC, HarA, Mg²⁺ transporter, SitC, Ni ABC transporter, alpha toxin, alpha toxin H35L or H35R mutant, RAP, Aap and SsaA.

A further combination of proteins in the immunogenic composition of the invention comprises EbhA and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of

immunodominant ABC transporter, IsdA, IsdB, IsdC, HarA, Mg²⁺ transporter, SitC, Ni ABC transporter, alpha toxin, alpha toxin H35L or H35R mutant, RAP, Aap and SsaA.

5 A further combination of proteins in the immunogenic composition of the invention comprises EbhB and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, IsdC, HarA, Mg²⁺ transporter, SitC, Ni ABC transporter, alpha toxin, alpha toxin H35L or H35R mutant, RAP, Aap and SsaA.

10 A further combination of proteins in the immunogenic composition of the invention comprises EbpS and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, IsdA, HarA, Mg²⁺ transporter, SitC, Ni ABC transporter, alpha toxin, alpha toxin H35L or H35R mutant, RAP, Aap and SsaA.

15 A further combination of proteins in the immunogenic composition of the invention comprises EFB(FIB) and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, IsdC, HarA, Mg²⁺ transporter, SitC, Ni ABC transporter, alpha toxin, alpha toxin H35L or H35R mutant, RAP, Aap and SsaA.

20 A further combination of proteins in the immunogenic composition of the invention comprises SBI and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, IsdC, HarA, Mg²⁺ transporter, SitC, Ni ABC transporter, alpha toxin, alpha toxin H35L or H35R mutant, RAP, Aap and SsaA.

25 A further combination of proteins in the immunogenic composition of the invention comprises autolysin and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, IsdC, HarA, Mg²⁺ transporter, SitC, Ni ABC transporter, alpha toxin, alpha toxin H35L or H35R mutant, RAP, Aap and SsaA.

30 A further combination of proteins in the immunogenic composition of the invention comprises ClfA and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, IsdC, HarA, Mg²⁺ transporter, SitC, Ni ABC transporter, alpha toxin, alpha toxin H35L or H35R mutant, RAP, Aap and SsaA.

35

A further combination of proteins in the immunogenic composition of the invention comprises SdrC and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, IsdC, HarA, Mg²⁺ transporter, SitC, Ni ABC transporter, alpha toxin, alpha toxin H35L or H35R mutant, RAP, Aap and SsaA.

5

A further combination of proteins in the immunogenic composition of the invention comprises SdrD and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, IsdC, HarA, Mg²⁺ transporter, SitC, Ni ABC transporter, alpha toxin, alpha toxin H35L or H35R mutant, RAP, Aap and SsaA.

10

A further combination of proteins in the immunogenic composition of the invention comprises SdrE and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, IsdC, HarA, Mg²⁺ transporter, SitC, Ni ABC transporter, alpha toxin, alpha toxin H35L or H35R mutant, RAP, Aap and SsaA.

15

A further combination of proteins in the immunogenic composition of the invention comprises SdrG and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, IsdC, HarA, Mg²⁺ transporter, SitC, Ni ABC transporter, alpha toxin, alpha toxin H35L or H35R mutant and RAP.

20

A further combination of proteins in the immunogenic composition of the invention comprises SdrH and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, IsdC, HarA, Mg²⁺ transporter, SitC, Ni ABC transporter, alpha toxin, alpha toxin H35L or H35R mutant, RAP, Aap and SsaA.

25

A further combination of proteins in the immunogenic composition of the invention comprises SasF and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, IsdC, HarA, Mg²⁺ transporter, SitC, Ni ABC transporter, alpha toxin, alpha toxin H35L or H35R mutant, RAP, Aap and SsaA.

30

A further combination of proteins in the immunogenic composition of the invention comprises Lipase GehD and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, IsdC, HarA, Mg²⁺ transporter, SitC, Ni ABC transporter, alpha toxin, alpha toxin H35L or H35R mutant, RAP, Aap and SsaA.

35

A further combination of proteins in the immunogenic composition of the invention comprises SasA and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, IsdC, HarA, Mg²⁺ transporter, SitC, Ni
5 ABC transporter, alpha toxin, alpha toxin H35L or H35R mutant, RAP, Aap and SsaA.

A further combination of proteins in the immunogenic composition of the invention comprises FnbA and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, IsdC, HarA, Mg²⁺ transporter, SitC, Ni
10 ABC transporter, alpha toxin, alpha toxin H35L or H35R mutant, RAP, Aap and SsaA.

A further combination of proteins in the immunogenic composition of the invention comprises FnbB and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, IsdC, HarA, Mg²⁺ transporter, SitC, Ni
15 ABC transporter, alpha toxin, alpha toxin H35L or H35R mutant, RAP, Aap and SsaA.

A further combination of proteins in the immunogenic composition of the invention comprises Cna and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, IsdC, HarA, Mg²⁺ transporter, SitC, Ni
20 ABC transporter, alpha toxin, alpha toxin H35L or H35R mutant, RAP, Aap and SsaA.

A further combination of proteins in the immunogenic composition of the invention comprises ClfB and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, IsdC, HarA, Mg²⁺ transporter, SitC, Ni
25 ABC transporter, alpha toxin, alpha toxin H35L or H35R mutant, RAP, Aap and SsaA.

A further combination of proteins in the immunogenic composition of the invention comprises FbpA and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, IsdC, HarA, Mg²⁺ transporter, SitC, Ni
30 ABC transporter, alpha toxin, alpha toxin H35L or H35R mutant, RAP, Aap and SsaA.

A further combination of proteins in the immunogenic composition of the invention comprises Npase and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, IsdC, HarA, Mg²⁺ transporter, SitC, Ni
35 ABC transporter, alpha toxin, alpha toxin H35L or H35R mutant, RAP, Aap and SsaA.

A further combination of proteins in the immunogenic composition of the invention comprises IsaA/PisA and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, IsdC, HarA, Mg²⁺ transporter, SitC, Ni ABC transporter, alpha toxin, alpha toxin H35L or H35R mutant, RAP, Aap and SsaA.

A further combination of proteins in the immunogenic composition of the invention comprises SsaA and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, IsdC, HarA, Mg²⁺ transporter, SitC, Ni ABC transporter, alpha toxin, alpha toxin H35L or H35R mutant, RAP, Aap and SsaA.

A further combination of proteins in the immunogenic composition of the invention comprises EPB and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, IsdC, HarA, Mg²⁺ transporter, SitC, Ni ABC transporter, alpha toxin, alpha toxin H35L or H35R mutant, RAP, Aap and SsaA.

A further combination of proteins in the immunogenic composition of the invention comprises SSP-1 and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, IsdC, HarA, Mg²⁺ transporter, SitC, Ni ABC transporter, alpha toxin, alpha toxin H35L or H35R mutant, RAP, Aap and SsaA.

A further combination of proteins in the immunogenic composition of the invention comprises SSP-2 and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, IsdC, HarA, Mg²⁺ transporter, SitC, Ni ABC transporter, alpha toxin, alpha toxin H35L or H35R mutant, RAP, Aap and SsaA.

A further combination of proteins in the immunogenic composition of the invention comprises HPB and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, IsdC, HarA, Mg²⁺ transporter, SitC, Ni ABC transporter, alpha toxin, alpha toxin H35L or H35R mutant, RAP, Aap and SsaA.

A further combination of proteins in the immunogenic composition of the invention comprises vitronectin binding protein and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, IsdC, HarA, Mg²⁺

transporter, SitC, Ni ABC transporter, alpha toxin, alpha toxin H35L or H35R mutant, RAP, Aap and SsaA.

5 A further combination of proteins in the immunogenic composition of the invention comprises fibrinogen binding protein and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, IsdC, HarA, Mg²⁺ transporter, SitC, Ni ABC transporter, alpha toxin, alpha toxin H35L or H35R mutant, RAP, Aap and SsaA.

10 A further combination of proteins in the immunogenic composition of the invention comprises coagulase and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, IsdC, HarA, Mg²⁺ transporter, SitC, Ni ABC transporter, alpha toxin, alpha toxin H35L or H35R mutant, RAP, Aap and SsaA.

15

A further combination of proteins in the immunogenic composition of the invention comprises Fig and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, IsdC, HarA, Mg²⁺ transporter, SitC, Ni ABC transporter, alpha toxin, alpha toxin H35L or H35R mutant, RAP, Aap and SsaA.

20

A further combination of proteins in the immunogenic composition of the invention comprises MAP and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of immunodominant ABC transporter, IsdA, IsdB, IsdC, HarA, Mg²⁺ transporter, SitC, Ni ABC transporter, alpha toxin, alpha toxin H35L or H35R mutant, RAP, Aap and SsaA.

25

A further combination of protein in the immunogenic composition of the invention comprises immunodominant ABC transporter and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of laminin receptor, SitC/MntC/saliva binding protein, EbhA, EbhB, Elastin binding protein (EbpS), EFB (FIB), SBI, autolysin, ClfA, SdrC, SdrD, SdrE, SdrG, SdrH, Lipase GehD, SasA, FnbA, FnbB, Cna, ClfA, ClfB, FbpA, Npase, IsaA/PisA, SsaA, EPB, SSP-1, SSP-2, HBP, Vitronectin binding protein, fibrinogen binding protein, coagulase, Fig, MAP, alpha toxin, alpha toxin H35L or H35R mutant, RAP, Aap and SsaA.

30

A further combination of protein in the immunogenic composition of the invention comprises IsdA and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of

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laminin receptor, SitC/MntC/saliva binding protein, EbhA, EbhB, Elastin binding protein (EbpS), EFB (FIB), SBI, autolysin, ClfA, SdrC, SdrC, SdrE, SdrG, SdrH, SasF, Lipase GehD, SasA, FnbA, FnbB, Cna, ClfA, ClfB, FbpA, Npase, IsaA/PisA, SsaA, EPB, SSP-1, SSP-2, HBP, Vitronectin binding protein, fibrinogen binding protein, coagulase, Fig, MAP, 5 alpha toxin, alpha toxin H35L or H35R mutant, RAP, Aap and SsaA.

A further combination of protein in the immunogenic composition of the invention comprises IsdB and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of laminin receptor, SitC/MntC/saliva binding protein, EbhA, EbhB, Elastin binding protein 10 (EbpS), EFB (FIB), SBI, autolysin, ClfA, SdrC, SdrG, SdrH, SasF, Lipase GehD, SasA, FnbA, FnbB, Cna, ClfA, ClfB, FbpA, Npase, IsaA/PisA, SsaA, EPB, SSP-1, SSP-2, HBP, Vitronectin binding protein, fibrinogen binding protein, coagulase, Fig, MAP, alpha toxin, alpha toxin H35L or H35R mutant, RAP, Aap and SsaA.

15 A further combination of protein in the immunogenic composition of the invention comprises SitC and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of laminin receptor, SitC/MntC/saliva binding protein, EbhA, EbhB, Elastin binding protein (EbpS), EFB (FIB), SBI, autolysin, ClfA, SdrC, SdrD, SdrE, SdrG, SdrH, SasF, Lipase GehD, SasA, FnbA, FnbB, Cna, ClfA, ClfB, FbpA, Npase, IsaA/PisA, SsaA, EPB, SSP-1, 20 SSP-2, HBP, Vitronectin binding protein, fibrinogen binding protein, coagulase, Fig, MAP, alpha toxin, alpha toxin H35L or H35R mutant, RAP, Aap and SsaA.

A further combination of protein in the immunogenic composition of the invention comprises alpha toxin and 1, 2, 3, 4 or 5 further antigens selected from the group 25 consisting of laminin receptor, SitC/MntC/saliva binding protein, EbhA, EbhB, Elastin binding protein (EbpS), EFB (FIB), SBI, autolysin, ClfA, SdrC, SdrD, SdrE, SdrG, SdrH, SasF, Lipase GehD, SasA, FnbA, FnbB, Cna, ClfB, FbpA, Npase, IsaA/PisA, SsaA, EPB, SSP-1, SSP-2, HBP, Vitronectin binding protein, fibrinogen binding protein, coagulase, Fig, MAP, immunodominant ABC transporter, IsdA, IsdB, IsdC, HarA, Mg²⁺ transporter, 30 SitC, Ni ABC transporter, Aap and SsaA.

A further combination of protein in the immunogenic composition of the invention comprises alpha toxin H35L OR H35R variant and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of laminin receptor, SitC/MntC/saliva binding protein, EbhA, 35 EbhB, Elastin binding protein (EbpS), EFB (FIB), SBI, autolysin, ClfA, SdrC, SdrD, SdrE,

SdrG, SdrH, SasF, Lipase GehD, SasA, FnbA, FnbB, Cna, ClfB, FbpA, Npase, IsaA/PisA, SsaA, EPB, SSP-1, SSP-2, HBP, Vitronectin binding protein, fibrinogen binding protein, coagulase, Fig, MAP, immunodominant ABC transporter, IsdA, IsdB, IsdC, HarA, Mg²⁺ transporter, SitC, Ni ABC transporter, Aap and SsaA.

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A further combination of protein in the immunogenic composition of the invention comprises RAP and 1, 2, 3, 4 or 5 further antigens selected from the group consisting of laminin receptor, SitC/MntC/saliva binding protein, EbhA, EbhB, Elastin binding protein (EbpS), EFB (FIB), SBI, autolysin, ClfA, SdrC, SdrD, SdrE, SdrG, SdrH, SasF, Lipase
 10 GehD, SasA, FnbA, FnbB, Cna, ClfB, FbpA, Npase, IsaA/PisA, SsaA, EPB, SSP-1, SSP-2, HBP, Vitronectin binding protein, fibrinogen binding protein, coagulase, Fig, MAP, immunodominant ABC transporter, IsdA, IsdB, IsdC, HarA, Mg²⁺ transporter, SitC, Ni ABC transporter, Aap and SsaA.

15 A further combinations of protein in the immunogenic composition of the invention comprises IsdA and IsdB; IsdA and ClfA; IsdA and ClfB; IsdA and SdrC; IsdA and SdrD; IsdA and SdrE; IsdA and SdrG; IsdA and SasF; IsdB and ClfA; IsdB and ClfB; IsdB and SdrC; IsdB and SdrD; IsdB and SdrE; IsdB and SdrG; IsdB and SasF; ClfA and ClfB; ClfA and SdrC; ClfA and SdrD; ClfA and SdrE; ClfA and SasF; ClfB and SdrC; ClfB and SdrD;
 20 ClfB and SdrE; ClfB and SasF; SdrC and SdrD; SdrC and SdrE; SdrC and SasF; SdrD and SdrE; SdrD and SasF; SdrE and SasF.

In the above and below combinations, the specified proteins may optionally be present in the immunogenic composition of the invention as a fragment or fusion protein as
 25 described above.

Combinations of three proteins

In an embodiment, the immunogenic composition of the invention further comprises three protein components in a combination of alpha-toxin, an extracellular component binding
 30 protein (for example an adhesin) and a transporter protein (for example an iron-binding protein).

In such a combination, the alpha toxin may be chemically detoxified or genetically detoxified by introduction of point mutation(s), for example the His35Leu point mutation.
 35 The alpha toxin is present as a free protein or alternatively is conjugated to a polysaccharide or PNAG component of the immunogenic composition.

Examples of combinations include:-

5 An immunogenic composition comprising alpha toxin, IsdA and an extracellular component binding protein selected from the group consisting of laminin receptor, SitC/MntC/saliva binding protein, EbhA, EbhB, Elastin binding protein (EbpS), EFB (FIB), SBI, autolysin, ClfA, SdrC, SdrG, SdrH, Lipase GehD, SasA, FnbA, FnbB, Cna, ClfB, FbpA, Npase, IsaA/PisA, SsaA, EPB, SSP-1, SSP-2, HBP, Vitronectin binding protein, fibrinogen binding protein, coagulase, Fig and MAP.

10

An immunogenic composition comprising alpha toxin, IsdB and an extracellular component binding protein selected from the group consisting of laminin receptor, SitC/MntC/saliva binding protein, EbhA, EbhB, Elastin binding protein (EbpS), EFB (FIB), SBI, autolysin, ClfA, SdrC, SdrD, SdrE, SdrG, SdrH, Lipase GehD, SasA, FnbA, FnbB, 15 Cna, ClfB, FbpA, Npase, IsaA/PisA, SsaA, EPB, SSP-1, SSP-2, HBP, Vitronectin binding protein, fibrinogen binding protein, coagulase, Fig and MAP.

20 An immunogenic composition comprising alpha toxin, IsdA and an adhesin selected from the group consisting of laminin receptor, EbhA, EbhB, Elastin binding protein (EbpS), EFB (FIB), ClfA, SdrC, SdrD, SdrE, SdrG, SdrH, autolysin, FnbA, FnbB, Cna, ClfB, FbpA, Npase, SSP-1, SSP-2, Vitronectin binding protein, fibrinogen binding protein, coagulase, Fig and MAP.

25 An immunogenic composition comprising alpha toxin, IsdB and an adhesin selected from the group consisting of laminin receptor, EbhA, EbhB, Elastin binding protein (EbpS), EFB (FIB), autolysin, ClfA, SdrC, SdrD, SdrE, SdrG, SdrH, FnbA, FnbB, Cna, ClfB, FbpA, Npase, SSP-1, SSP-2, Vitronectin binding protein, fibrinogen binding protein, coagulase, Fig and MAP.

30 An immunogenic composition comprising alpha toxin, IsdA and laminin receptor.

An immunogenic composition comprising alpha toxin, IsdA and EbhA.

An immunogenic composition comprising alpha toxin, IsdA and EbhB.

35

An immunogenic composition comprising alpha toxin, IsdA and EbpS.

An immunogenic composition comprising alpha toxin, IsdA and EFB (FIB).

40 An immunogenic composition comprising alpha toxin, IsdA and SdrG.

An immunogenic composition comprising alpha toxin, IsdA and ClfA.

An immunogenic composition comprising alpha toxin, IsdA and ClfB.

5 An immunogenic composition comprising alpha toxin, IsdA and FnbA.

An immunogenic composition comprising alpha toxin, IsdA and coagulase.

An immunogenic composition comprising alpha toxin, IsdA and Fig.

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An immunogenic composition comprising alpha toxin, IsdA and SdrH.

An immunogenic composition comprising alpha toxin, IsdA and SdrC.

15

An immunogenic composition comprising alpha toxin, IsdA and SdrD.

An immunogenic composition comprising alpha toxin, IsdA and SdrE.

An immunogenic composition comprising alpha toxin, IsdA and MAP.

20

An immunogenic composition comprising IsaA and Sbi.

An immunogenic composition comprising IsaA and IsdB.

25

An immunogenic composition comprising IsaA and IsdA.

An immunogenic composition comprising IsaA and SdrC.

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An immunogenic composition comprising IsaA and Ebh or fragment thereof as described above.

An immunogenic composition comprising Sbi and SdrC.

35

An immunogenic composition comprising Sbi and Ebh or fragment thereof as described above.

An immunogenic composition of the invention comprising IsaA, Sbi or SdrC

Selection of antigens expressed in different clonal lineages

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Analysis of the occurrence of virulence factors in relation with the population structure of *Staphylococcus aureus* showed variable presence of virulence genes in natural populations of *S. aureus*.

- 5 Among clinical isolates of *Staphylococcus aureus*, at least five clonal lineages were shown to be highly prevalent (Booth *et al.*, 2001 Infect Immun. 69(1):345-52). Alpha-hemolysin (*hla*), fibronectin-binding protein A (*fnbA*) and clumping factor A (*clfA*) were shown to be present in most of the isolates, regardless of lineage identity, suggesting an important role of these proteins in the survival of *S. aureus* (Booth *et al.*, 2001 Infect
- 10 Immun. 69(1):345-52). Moreover, according to Peacock *et al.* 2002 (Infect Immun. 70(9):4987-96), the distributions of *fnbA*, *clfA*, coagulase, *spa*, *map*, *pvl* (Panton-Valentine leukocidin), *hlg* (gamma-toxin), alpha-toxin and *ica* appeared to be unrelated to the underlying clonal structure suggesting considerable horizontal transfer of these genes.
- 15 In contrary, other virulence genes such as fibronectin binding protein B (*fnbB*), beta-hemolysin (*hly*), collagen binding protein (*cna*), TSST-1 (*tst*) and methicillin resistance gene (*mecA*) are strongly associated with specific lineages (Booth *et al.*, 2001 Infect Immun. 69(1):345-52). Similarly, Peacock *et al.* 2002 (Infect Immun. 70(9):4987-96) showed that the distributions of the enterotoxins, *tst*, the exfolatins (*eta* and *etb*), beta-
- 20 and delta-toxins, the *sdr* genes (*sdrD*, *sdrE* and *bbp*), *cna*, *ebpS* and *efb* within the population are all highly significantly related to MLST-derived clonal complexes.

- MLST data provide no evidence that strains responsible for nosocomial disease represent a distinct subpopulation from strains causing community-acquired disease or strains
- 25 recovered from asymptomatic carriers (Feil *et al.*, 2003 J Bacteriol. 185(11):3307-16).

In an embodiment, immunogenic compositions of the invention are effective against staphylococci from different clonal lineages.

- 30 In an embodiment, the immunogenic composition comprises 1, 2, 3, 4, or at least 1 protein that is expressed in most isolates of staphylococci. Examples of such proteins include alpha-hemolysin (*hla*), fibronectin-binding protein A (*fnbA*) and clumping factor A (*clfA*), coagulase, *spa*, *map*, *pvl* (Panton-Valentine leukocidin), *hlg* (gamma-toxin), *ica*, immunodominant ABC transporter, RAP, autolysin (Rupp *et al.* 2001, J. Infect. Dis. 183;
- 35 1038), laminin receptors, SitC, IsaA/PisA, SPOIIIE (), SsaA, EbpS, SasF (Roche *et al.*

2003, Microbiology 149; 643), EFB(FIB), SBI, ClfB, IsdA, IsdB, FnbB, Npase, EBP, Bone
sialo binding protein II, IsaB/PisB (Lorenz et al FEMS Immuno. Med. Microb. 2000, 29;
145), SasH (Roche et al 2003, Microbiology 149; 643), MRPI, SasD (Roche et al 2003,
Microbiology 149; 643), SasH (Roche et al 2003, Microbiology 149; 643), aureolysin
5 precursor (AUR)/Sepp1 and novel autolysin.

In an alternative embodiment, 2 or more proteins which are expressed in different sets of
clonal strains are included in the immunogenic composition of the invention. Optionally the
combination of antigens will allow an immune response to be generated that is effective
10 against multiple clonal strains, or against all clonal stains. For example combinations
include FnbB and betahemolysin, FnbB and Cna, FnbB and TSST-1, FnbB and mecA,
FnbB and SdrD, FnbB and SdrF, FnbB and EbpS, FnbB and Efb, beta-haemolysin and
Cna, beta-haemolysin and TSST-1, beta-haemolysin and mecA, beta-haemolysin and
SdrD, beta-haemolysin and SdrF, beta-haemolysin and EbpS, beta-haemolysin and Efb,
15 Cna and TSST-1, Cna and mecA, Cna and SdrD, Cna and SdrF, Cna and EbpS, Cna and
Efb, TSST-1 and mecA, TSST-1 and SdrD, TSST-1 and SdrF, TSST-1 and EbpS, TssT-1
and Efb, MecA and SdrD, MecA and SdrF, MecA and EbpS, MecA and Efb, SdrD and
SdrF, SdrD and EbpS, SdeD and Efb, SdrF and EbpS, SdrF and Efb, and, EbpS and Efb.

20 The combinations described above may be combined with additional components
described above.

Protection against *S.aureus* and *S. epidermidis*

In an embodiment of the invention the immunogenic composition provides an effective
25 immune response against more than one strain of staphylococci, for example against
strains from both *S.aureus* and *S. epidermidis*. For example, a protective immune
response is generated against type 5 and 8 serotypes of *S. aureus*.

One use of the immunogenic composition of the invention is to prevent nosocomial
30 infections, for instance in elective surgery patients, by inoculating prior to hospital
treatment. At this stage, it is difficult to accurately predict which staphylococcal strains the
patient will be exposed to. It is therefore advantageous to inoculate with a vaccine that is
capable of generating an effective immune response against various strains of
staphylococci.

An effective immune response is defined as an immune response that gives significant protection in a mouse challenge model or opsonophagocytosis assay as described in the examples. Significant protection in a mouse challenge model, for instance that of example 5, is defined as an increase in the LD50 in comparison with carrier inoculated mice of at least 10%, 20%, 50%, 100% or 200%. Significant protection in a cotton rat challenge model, for instance that of example 8, is defined as a decrease in the mean observed LogCFU/nose of at least 10%, 20%, 50%, 70% or 90%. The presence of opsonising antibodies is known to correlate with protection, therefore significant protection is indicated by a decrease in the bacterial count of at least 10%, 20%, 50%, 70% or 90% in an opsonophagocytosis assay, for instance that of example 7.

Several of the proteins including immunodominant ABC transporter, RNA III activating protein, Laminin receptors, SitC, IsaA/PisA, SsaA, EbhA/EbhB, EbpS and Aap are well conserved between *S. aureus* and *S. epidermidis* and example 8 shows that IsaA, ClfA, IsdB, SdrG, HarA, FnbpA and Sbi can generate a cross-reactive immune response (for example crossreactive between at least one *S. aureus* and at least one *S. epidermidis* strain). PIA is also well conserved between *S. aureus* and *S. epidermidis*.

Therefore in an embodiment, the immunogenic composition of the invention will comprise PNAG and type 5 and 8 polysaccharides and one, two, three or four of the above proteins.

Vaccines

In an embodiment, the immunogenic composition of the invention is mixed with a pharmaceutically acceptable excipient, and optionally with an adjuvant to form a vaccine.

Suitable adjuvants include an aluminum salt such as aluminum hydroxide gel (alum) or aluminium phosphate, but may also be a salt of calcium, magnesium, iron or zinc, or may be an insoluble suspension of acylated tyrosine, or acylated sugars, cationically or anionically derivatized polysaccharides, or polyphosphazenes.

In an embodiment, the adjuvant is a preferential inducer of either a TH1 or a TH2 type of response. High levels of Th1-type cytokines tend to favor the induction of cell mediated

immune responses to a given antigen, whilst high levels of Th2-type cytokines tend to favour the induction of humoral immune responses to the antigen.

- It is important to remember that the distinction of Th1 and Th2-type immune response is not absolute. In reality an individual will support an immune response which is described as being predominantly Th1 or predominantly Th2. However, it is often convenient to consider the families of cytokines in terms of that described in murine CD4 +ve T cell clones by Mosmann and Coffman (Mosmann, T.R. and Coffman, R.L. (1989) TH1 and TH2 cells: different patterns of lymphokine secretion lead to different functional properties. Annual Review of Immunology, 7, p145-173). Traditionally, Th1-type responses are associated with the production of the INF- γ and IL-2 cytokines by T-lymphocytes. Other cytokines often directly associated with the induction of Th1-type immune responses are not produced by T-cells, such as IL-12. In contrast, Th2-type responses are associated with the secretion of IL-4, IL-5, IL-6, IL-10. Suitable adjuvant systems which promote a predominantly Th1 response include: Monophosphoryl lipid A or a derivative thereof, particularly 3-de-O-acylated monophosphoryl lipid A (3D-MPL) (for its preparation see GB 2220211 A); and a combination of monophosphoryl lipid A, preferably 3-de-O-acylated monophosphoryl lipid A, together with either an aluminium salt (for instance aluminium phosphate or aluminium hydroxide) or an oil-in-water emulsion. In such combinations, antigen and 3D-MPL are contained in the same particulate structures, allowing for more efficient delivery of antigenic and immunostimulatory signals. Studies have shown that 3D-MPL is able to further enhance the immunogenicity of an alum-adsorbed antigen [Thoelen *et al.* Vaccine (1998) 16:708-14; EP 689454-B1].
- An enhanced system involves the combination of a monophosphoryl lipid A and a saponin derivative, particularly the combination of QS21 and 3D-MPL as disclosed in WO 94/00153, or a less reactogenic composition where the QS21 is quenched with cholesterol as disclosed in WO 96/33739. A possible adjuvant formulation involving QS21, 3D-MPL and tocopherol in an oil in water emulsion is described in WO 95/17210. Optionally the vaccine additionally comprises a saponin, for example QS21. The formulation may also comprise an oil in water emulsion and tocopherol (WO 95/17210). The present invention also provides a method for producing a vaccine formulation comprising mixing an immunogenic composition of the present invention together with a pharmaceutically acceptable excipient, such as 3D-MPL. Unmethylated CpG containing

oligonucleotides (WO 96/02555) are also preferential inducers of a TH1 response and are suitable for use in the present invention.

In an embodiment, the immunogenic compositions of the invention are those forming a liposome or ISCOM structure.

5

The ratio of QS21 : sterol will typically be in the order of 1 : 100 to 1 : 1 weight to weight. Preferably excess sterol is present, the ratio of QS21 : sterol being at least

1 : 2 w/w. Typically for human administration QS21 and sterol will be present in a vaccine in the range of about 1 µg to about 100 µg, preferably about 10 µg to about 50 µg per
10 dose.

The liposomes typically contain a neutral lipid, for example phosphatidylcholine, which is preferably non-crystalline at room temperature, for example egg yolk phosphatidylcholine, dioleoyl phosphatidylcholine or dilauryl phosphatidylcholine. The liposomes may also
15 contain a charged lipid which increases the stability of the liposome-QS21 structure for liposomes composed of saturated lipids. In these cases the amount of charged lipid is preferably 1-20% w/w, most preferably 5-10%. The ratio of sterol to phospholipid is 1-50% (mol/mol), typically 20-25%.

20 Optionally the compositions of the invention contain MPL (3-deacylated mono-phosphoryl lipid A, also known as 3D-MPL). 3D-MPL is known from GB 2 220 211 (Ribi) as a mixture of 3 types of De-O-acylated monophosphoryl lipid A with 4, 5 or 6 acylated chains and is manufactured by Ribi Immunochem, Montana. A possible form is disclosed in International Patent Application 92/116556.

25

Suitable compositions of the invention are those wherein liposomes are initially prepared without MPL, and MPL is then added, preferably as 100 nm particles. The MPL is therefore not contained within the vesicle membrane (known as MPL out). Compositions where the MPL is contained within the vesicle membrane (known as MPL in) also form an
30 aspect of the invention. The antigen can be contained within the vesicle membrane or contained outside the vesicle membrane. Optionally soluble antigens are outside and hydrophobic or lipidated antigens are either contained inside or outside the membrane.

The vaccine preparations of the present invention may be used to protect or treat a
35 mammal susceptible to infection, by means of administering said vaccine via systemic or mucosal route. These administrations may include injection *via* the intramuscular,

intraperitoneal, intradermal or subcutaneous routes; or *via* mucosal administration to the oral/alimentary, respiratory, genitourinary tracts. Intranasal administration of vaccines for the treatment of pneumonia or otitis media is preferred (as nasopharyngeal carriage of pneumococci can be more effectively prevented, thus attenuating infection at its earliest stage). Although the vaccine of the invention may be administered as a single dose, components thereof may also be co-administered together at the same time or at different times (for instance pneumococcal polysaccharides could be administered separately, at the same time or 1-2 weeks after the administration of any bacterial protein component of the vaccine for optimal coordination of the immune responses with respect to each other). For co-administration, the optional Th1 adjuvant may be present in any or all of the different administrations, for example, it may be present in combination with the bacterial protein component of the vaccine. In addition to a single route of administration, 2 different routes of administration may be used. For example, polysaccharides may be administered IM (or ID) and bacterial proteins may be administered IN (or ID). In addition, the vaccines of the invention may be administered IM for priming doses and IN for booster doses.

The amount of conjugate antigen in each vaccine dose is selected as an amount which induces an immunoprotective response without significant, adverse side effects in typical vaccines. Such amount will vary depending upon which specific immunogen is employed and how it is presented. Generally, it is expected that each dose will comprise 0.1-100 μ g of polysaccharide, typically 0.1-50 μ g, 0.1-10 μ g, 1-10 μ g or 1-5 μ g for polysaccharide conjugates.

The content of protein antigens in the vaccine will typically be in the range 1-100 μ g, 5-50 μ g or 5 - 25 μ g. Following an initial vaccination, subjects may receive one or several booster immunizations adequately spaced.

Vaccine preparation is generally described in Vaccine Design ("The subunit and adjuvant approach" (eds Powell M.F. & Newman M.J.) (1995) Plenum Press New York). Encapsulation within liposomes is described by Fullerton, US Patent 4,235,877.

The vaccines of the present invention may be stored in solution or lyophilized. Optionally the solution is lyophilized in the presence of a sugar such as sucrose, trehalose or

lactose. It is typical that they are lyophilized and extemporaneously reconstituted prior to use. Lyophilizing may result in a more stable composition (vaccine).

Methods

5 The invention also encompasses method of making the immunogenic compositions and vaccines of the invention.

10 In an embodiment, the process of the invention, is a method to make a vaccine comprising the steps of mixing antigens to make the immunogenic composition of the invention and adding a pharmaceutically acceptable excipient.

Methods of treatment

15 The invention also encompasses method of treatment or staphylococcal infection, particularly hospital acquired nosocomial infections.

20 This immunogenic composition or vaccine of the invention is particularly advantageous to use in cases of elective surgery. Such patients will know the date of surgery in advance and could be inoculated in advance. Since it is not known whether the patient will be exposed to *S. aureus* or *S. epidermidis* infection, it is preferred to inoculate with a vaccine of the invention that protects against both, as described above. Typically adults over 16 awaiting elective surgery are treated with the immunogenic compositions and vaccines of the invention. Alternatively children aged 3-16 awaiting elective surgery are treated with the immunogenic compositions and vaccines of the invention.

25 It is also possible to inoculate health care workers with the vaccine of the invention.

30 The vaccine preparations of the present invention may be used to protect or treat a mammal susceptible to infection, by means of administering said vaccine via systemic or mucosal route. These administrations may include injection *via* the intramuscular, intraperitoneal, intradermal or subcutaneous routes; or *via* mucosal administration to the oral/alimentary, respiratory, genitourinary tracts.

35 The amount of antigen in each vaccine dose is selected as an amount which induces an immunoprotective response without significant, adverse side effects in typical vaccines. Such amount will vary depending upon which specific immunogen is employed and how it

is presented. The protein content of the vaccine will typically be in the range 1 -100µg, 5-50µg, typically in the range 10 - 25µg. An optimal amount for a particular vaccine can be ascertained by standard studies involving observation of appropriate immune responses in subjects. Following an initial vaccination, subjects may receive one or several booster
5 immunisations adequately spaced.

Although the vaccines of the present invention may be administered by any route, administration of the described vaccines into the skin (ID) forms one embodiment of the present invention. Human skin comprises an outer “horny” cuticle, called the stratum
10 corneum, which overlays the epidermis. Underneath this epidermis is a layer called the dermis, which in turn overlays the subcutaneous tissue. Researchers have shown that injection of a vaccine into the skin, and in particular the dermis, stimulates an immune response, which may also be associated with a number of additional advantages.

Intradermal vaccination with the vaccines described herein forms a preferred feature of
15 the present invention.

The conventional technique of intradermal injection, the “mantoux procedure”, comprises steps of cleaning the skin, and then stretching with one hand, and with the bevel of a narrow gauge needle (26-31 gauge) facing upwards the needle is inserted at an angle of
20 between 10-15°. Once the bevel of the needle is inserted, the barrel of the needle is lowered and further advanced whilst providing a slight pressure to elevate it under the skin. The liquid is then injected very slowly thereby forming a bleb or bump on the skin surface, followed by slow withdrawal of the needle.

25 More recently, devices that are specifically designed to administer liquid agents into or across the skin have been described, for example the devices described in WO 99/34850 and EP 1092444, also the jet injection devices described for example in WO 01/13977; US 5,480,381, US 5,599,302, US 5,334,144, US 5,993,412, US 5,649,912, US 5,569,189, US 5,704,911, US 5,383,851, US 5,893,397, US 5,466,220, US 5,339,163, US 5,312,335,
30 US 5,503,627, US 5,064,413, US 5,520, 639, US 4,596,556, US 4,790,824, US 4,941,880, US 4,940,460, WO 97/37705 and WO 97/13537. Alternative methods of

intradermal administration of the vaccine preparations may include conventional syringes and needles, or devices designed for ballistic delivery of solid vaccines (WO 99/27961), or transdermal patches (WO 97/48440; WO 98/28037); or applied to the surface of the skin (transdermal or transcutaneous delivery WO 98/20734 ; WO 98/28037).

5

When the vaccines of the present invention are to be administered to the skin, or more specifically into the dermis, the vaccine is in a low liquid volume, particularly a volume of between about 0.05 ml and 0.2 ml.

- 10 The content of antigens in the skin or intradermal vaccines of the present invention may be similar to conventional doses as found in intramuscular vaccines (see above). However, it is a feature of skin or intradermal vaccines that the formulations may be “low dose”. Accordingly the protein antigens in “low dose” vaccines are preferably present in as little as 0.1 to 10 μ g, preferably 0.1 to 5 μ g per dose; and the polysaccharide (preferably
- 15 conjugated) antigens may be present in the range of 0.01-1 μ g, and preferably between 0.01 to 0.5 μ g of polysaccharide per dose.

- As used herein, the term “intradermal delivery” means delivery of the vaccine to the region of the dermis in the skin. However, the vaccine will not necessarily be located exclusively
- 20 in the dermis. The dermis is the layer in the skin located between about 1.0 and about 2.0 mm from the surface in human skin, but there is a certain amount of variation between individuals and in different parts of the body. In general, it can be expected to reach the dermis by going 1.5 mm below the surface of the skin. The dermis is located between the stratum corneum and the epidermis at the surface and the subcutaneous layer below.
- 25 Depending on the mode of delivery, the vaccine may ultimately be located solely or primarily within the dermis, or it may ultimately be distributed within the epidermis and the dermis.

- An embodiment of the invention is a method of preventing or treating staphylococcal
- 30 infection or disease comprising the step of administering the immunogenic composition or vaccine of the invention to a patient in need thereof.

- A further embodiment of the invention is a use of the immunogenic composition of the invention in the manufacture of a vaccine for treatment or prevention of staphylococcal
- 35 infection or disease, optionally post-surgery staphylococcal infection.

The term 'staphylococcal infection' encompasses infection caused by *S.aureus* and/or *S.epidermidis* and other staphylococcal strains capable of causing infection in a mammalina, preferably human host.

- 5 The terms "comprising", "comprise" and "comprises" herein are intended by the inventors to be optionally substitutable with the terms "consisting of", "consist of" and "consists of", respectively, in every instance.

10

In order that this invention may be better understood, the following examples are set forth. These examples are for purposes of illustration only, and are not to be construed as limiting the scope of the invention in any manner.

Examples

Example 1 Construction of Plasmid to Express Recombinant proteins

A: Cloning.

- 5 Appropriate restriction sites engineered into oligonucleotides specific for the staphylococcal gene permitted directional cloning of the PCR product into the *E.coli* expression plasmid pET24d or pQE-30 such that a protein could be expressed as a fusion protein containing a (His)₆ affinity chromatography tag at the N- or C-terminus.
- 10 The primers used were:
- Alpha toxin – 5'-CGCGGATCCGCAGATTCTGATATTAATATTAAC-3' and
5'CCCAAGCTTTTAATTTGTCATTTCTTCTTTTTC-3'
- EbpS – 5'-CGCGGATCCGCTGGGTCTAATAATTTTAAAGATG-3' and
5'CCCAAGCTTTTATGGAATAACGATTTGTTG-3'
- 15 ClfA – 5'-CGCGGATCCAGTGAAAATAGTGTTACGCAATC-3' and
5'CCCAAGCTTTTACTCTGGAATTGGTTCAATTTC-3'
- FnbpA – 5'-CGCGGATCCACACAAACAAGTCAACTAACG-3' and
5'CCCAAGCTTTTATGCTTTGTGATTCTTTTCAAAC-3'
- Sbi – 5'-CGCGGATCCAACACGCAACAAGTTC-3' and
20 5'GGAAGTGCAGTTATTTCCAGAATGATAATAATTAC-3'
- SdrC – 5'-CGCGGATCCGCAGAACATACGAATGGAG-3' and
5'CCCAAGCTTTTATGTTTCTTCTTCGTAGTAGC-3'
- SdrG – 5'-CGCGGATCCGAGGAGAATTCAGTACAAG-3' and
5'CCCAAGCTTTTATTCGTCATCATAGTATCCG-3'
- 25 Ebh – 5'-AAAAGTACTCACCACCACCACCACC-3' and
5'AAAAGTACTCACTTGATTCATCGCTTCAG-3'
- Aaa – 5'-GCGCGCCATGGCACAAGCTTCTACACAACATAC-3' and
5'GCGCGCTCGAGATGGATGAATGCATAGCTAGA-3'
- IsaA – 5'-GCATCCATGGCACCATCACCATCACCACGAAGTAAACGTTGATCAAGC-3'
30 and 5'-AGCACTCGAGTTAGAATCCCCAAGCACCTAAACC-3'
- HarA – 5'-GCACCCATGGCAGAAAATACAAATACTTC-3' and
5'TTTTCTCGAGCATTTTAGATTGACTAAGTTG-3'
- Autolysin glucosaminidase – 5'-CAAGTCCCATGGCTGAGACGACACAAGATCAAC-3'
and 5'-CAGTCTCGAGTTTTACAGCTGTTTTTGGTTG-3'

Autolysin amidase – 5'-AGCTCATATGGCTTATACTGTTACTAAACC-3' and
5'GCGCCTCGAGTTTATATTGTGGGATGTCG-3'

IsdA – 5'-CAAGTCCCATGGCAACAGAAGCTACGAACGCAAC-3' and
5'ACCAGTCTCGAGTAATTCTTTAGCTTTAGAGCTTG-3'

5 IsdB – 5'-TATTCTCGAGGCTTTGAGTGTGTCCATCATTTG-3' and 5'
GAAGCCATGGCAGCAGCTGAAGAAACAGGTGG-3'

MRPII – 5'-GATTACACCATGGTTAAACCTCAAGCGAAA-3' and
5'AGGTGTCTCGAGTGCGATTGTAGCTTCATT-3'

10 The PCR products were first introduced into the pGEM-T cloning vector (Novagen) using
Top10 bacterial cells, according to the manufacturer's instructions. This intermediate
construct was made to facilitate further cloning into an expression vector. Transformants
containing the DNA insert were selected by restriction enzyme analysis. Following
digestion, a ~20µl aliquot of the reaction was analyzed by agarose gel electrophoresis
15 (0.8 % agarose in a Tris-acetate-EDTA (TAE) buffer). DNA fragments were visualized by
UV illumination after gel electrophoresis and ethidium bromide staining. A DNA molecular
size standard (1 Kb ladder, Life Technologies) was electrophoresed in parallel with the
test samples and was used to estimate the size of the DNA fragments. Plasmid purified
from selected transformants for each cloning was then sequentially digested to completion
20 with appropriate restriction enzymes as recommended by the manufacturer (Life
Technologies). The digested DNA fragment was then purified using silica gel-based spin
columns prior to ligation with the pET24d or pQE-30 plasmid. Cloning of Ebh (H2
fragment), AaA, IsdA, IsdB, HarA, Atl-amidase, Atl-glucosamine, MRPII, IsaA was carried
out using the pET24d plasmid and cloning of ClfA, SdrC, SdrE, FnbpA, SdrG/Fbe, alpha
25 toxin and Sbi were carried out using the pQE-30 plasmid.

B: Production of expression vector.

To prepare the expression plasmid pET24d or pQE-30 for ligation, it was similarly
digested to completion with appropriate restriction enzymes. An approximately 5-fold
30 molar excess of the digested fragments to the prepared vector was used to program the
ligation reaction. A standard ~20 µl ligation reaction (~16°C, ~16 hours), using methods
well known in the art, was performed using T4 DNA ligase (~2.0 units / reaction, Life
Technologies). An aliquot of the ligation (~5 µl) was used to transform M15(pREP4) or
BT21::DE3 electro-competent cells according to methods well known in the art. Following
35 a ~2-3 hour outgrowth period at 37°C in ~1.0 ml of LB broth, transformed cells were

plated on LB agar plates containing ampicillin (100 µg/ml) and/or kanamycin (30µg/ml). Antibiotics were included in the selection. Plates were incubated overnight at 37°C for ~16 hours. Individual ApR/KanR colonies were picked with sterile toothpicks and used to “patch” inoculate fresh LB ApR/KanR plates as well as a ~1.0 ml LB Ap/ Kan broth culture.

5 Both the patch plates and the broth culture were incubated overnight at 37°C in either a standard incubator (plates) or a shaking water bath. A whole cell-based PCR analysis was employed to verify that transformants contained the DNA insert. Here, the ~1.0 ml overnight LB Ap/Kan broth culture was transferred to a 1.5 ml polypropylene tube and the cells collected by centrifugation in a Beckmann microcentrifuge (~3 min., room
10 temperature, ~12,000 X g). The cell pellet was suspended in ~200µl of sterile water and a ~10µl aliquot used to program a ~50µl final volume PCR reaction containing both forward and reverse amplification primers. The initial 95°C denaturation step was increased to 3 minutes to ensure thermal disruption of the bacterial cells and liberation of plasmid DNA. An ABI Model 9700 thermal cycler and a 32 cycle, three-step thermal amplification profile,
15 i.e. 95°C, 45sec; 55-58°C, 45sec, 72°C, 1min., were used to amplify the BASB203 fragment from the lysed transformant samples. Following thermal amplification, a ~20µl aliquot of the reaction was analyzed by agarose gel electrophoresis (0.8 % agarose in a Tris-acetate-EDTA (TAE) buffer). DNA fragments were visualised by UV illumination after gel electrophoresis and ethidium bromide staining. A DNA molecular size standard (1 Kb
20 ladder, Life Technologies) was electrophoresed in parallel with the test samples and was used to estimate the size of the PCR products. Transformants that produced the expected size PCR product were identified as strains containing a protein expression construct. Expression plasmid containing strains were then analyzed for the inducible expression of recombinant protein.

25

C: Expression Analysis of PCR-Positive Transformants.

An aliquot of the overnight seed culture (~1.0 ml) was inoculated into a 125 ml erlenmeyer flask containing ~25 ml of LB Ap/Kan broth and was grown at 37 °C with shaking (~250 rpm) until the culture turbidity reached O.D.600 of ~0.5, i.e. mid-log phase (usually about
30 1.5 - 2.0 hours). At this time approximately half of the culture (~12.5 ml) was transferred to a second 125 ml flask and expression of recombinant protein induced by the addition of IPTG (1.0 M stock prepared in sterile water, Sigma) to a final concentration of 1.0 mM. Incubation of both the IPTG-induced and non-induced cultures continued for an additional ~4 hours at 37 °C with shaking. Samples (~1.0 ml) of both induced and non-induced
35 cultures were removed after the induction period and the cells collected by centrifugation

in a microcentrifuge at room temperature for ~3 minutes. Individual cell pellets were suspended in ~50µl of sterile water, then mixed with an equal volume of 2X Laemmli SDS-PAGE sample buffer containing 2-mercaptoethanol, and placed in boiling water bath for ~3 min to denature protein. Equal volumes (~15µl) of both the crude IPTG-induced and the non-induced cell lysates were loaded onto duplicate 12% Tris/glycine polyacrylamide gel (1 mm thick Mini-gels, Novex). The induced and non-induced lysate samples were electrophoresed together with prestained molecular weight markers (SeeBlue, Novex) under conventional conditions using a standard SDS/Tris/glycine running buffer (BioRad). Following electrophoresis, one gel was stained with comassie brilliant blue R250 (BioRad) and then destained to visualize novel IPTG-inducible protein(s). The second gel was electroblotted onto a PVDF membrane (0.45 micron pore size, Novex) for ~2 hrs at 4 °C using a BioRad Mini-Protean II blotting apparatus and Towbin's methanol (20 %) transfer buffer. Blocking of the membrane and antibody incubations were performed according to methods well known in the art. A monoclonal anti-RGS (His)3 antibody, followed by a second rabbit anti-mouse antibody conjugated to HRP (QiaGen), were used to confirm the expression and identity of the recombinant protein. Visualization of the anti-His antibody reactive pattern was achieved using either an ABT insoluble substrate or using Hyperfilm with the Amersham ECL chemiluminescence system.

Example 2: Production of Recombinant Protein

Bacterial strain

A recombinant expression strain of *E. coli* M15(pREP4) containing a plasmid (pQE30) or BL21::DE3 containing plasmid pET24d encoding staphylococcal protein was used to produce cell mass for purification of recombinant protein.

Media

The fermentation medium used for the production of recombinant protein consisted of 2X YT broth (Difco) containing 100µg/ml Ap and/or 30 µg/ml Km. Antifoam was added to medium for the fermentor at 0.25 ml/L (Antifoam 204, Sigma). To induce expression of the recombinant protein, IPTG (Isopropyl β-D-Thiogalactopyranoside) was added to the fermentor (1 mM, final).

Production of recombinant proteins

Under native conditions

IPTG was added at a final concentration of 1mM and the culture was grown for 4 additional hours. The culture was then centrifuged at 6,000 rpm for 10 minutes and the
 5 pellet was resuspended in phosphate buffer (50mM K₂HPO₄, KH₂PO₄ pH 7) including a protease inhibitor cocktail. This sample was subjected to French pressure lysis using 1500 bar pressure (2 runs). After centrifugation for 30 minutes at 15,000 rpm, the supernatant was reserved for further purification and NaCl was added to 0.5M. The sample was then loaded on a Ni-NTA resin (XK 16 column Pharmacia, Ni-NTA resin Qiagen) conditioned in
 10 50mM K₂HPO₄, KH₂PO₄ pH 7. After loading the sample, the column was washed with Buffer A (0.2M NaH₂PO₄ pH7, 0.3M NaCl, 10% glycerol). To elute bound protein, a step gradient was used where different proportions of buffer B (0.2M NaH₂PO₄ pH7, 0.3M NaCl, 10% glycerol and 200mM imidazole) were added to buffer A. The proportion of buffer B was gradually increased from 10% to 100%. After purification, eluted fraction
 15 containing the protein were pooled, concentrated and dialysed against 0.002M KH₂PO₄/K₂HPO₄ pH7, 0.15M NaCl.

This method was used to purify ClfA, SdrG, IsdA, IsaB, HarA, Atl-glucosamine and alpha toxin.

20

Under denaturing conditions

IPTG was added at a final concentration of 1mM and the culture was grown for 4 additional hours. The culture was then centrifuged at 6,000 rpm for 10 minutes and the pellet was resuspended in phosphate buffer (50mM K₂HPO₄, KH₂PO₄ pH 7) including a
 25 protease inhibitor cocktail. This sample was subjected to French pressure lysis using 1500 bar pressure (2 runs). After centrifugation for 30 minutes at 15,000 rpm, the pellet was washed with phosphate buffer including 1M urea. The sample was centrifuged for 30 mins at 15000rpm and the pellet was resuspended in 8M urea, 0.1M NaH₂PO₄, 0.5M NaCl, 0.01M Tris-HCl pH8 and kept overnight at room temperature. The sample was centrifuged
 30 for 20 minutes at 15000rpm and the supernatant was collected for further purification. The sample was then loaded on a Ni-NTA resin (XK 16 column Pharmacia, Ni-NTA resin Qiagen) conditioned in 8M urea, 0.1M NaH₂PO₄, 0.5M NaCl, 0.01M Tris-HCl pH8. After passage of the flowthrough, the column was washed successively with buffer A (8M Urea, 0.1MNaH₂PO₄, 0,5M NaCl, 0.01M Tris, pH 8.0), buffer C (8M Urea, 0.1MNaH₂PO₄, 0.5M
 35 NaCl, 0.01M Tris, pH 6.3), buffer D (8M Urea, 0.1MNaH₂PO₄, 0.5M NaCl, 0.01M Tris, pH

5.9) and buffer E (8M Urea, 0.1MNaH₂PO₄, 0.5M NaCl, 0.01M Tris, pH 4.5). The recombinant protein was eluted from the column during washes with buffer D and E. The denatured, recombinant protein could be solubilized in a solution devoid of urea. For this purpose, denatured protein contained in 8M urea was successively dialyzed against 4M
 5 urea, 0.1MNa₂PO₄, 0.01M Tris-HCl, pH7.1, 2M urea, 0.1 M NaH₂PO₄, 0.01M Tris-HCl, pH 7.1, 0.5M arginine and 0.002M KH₂PO₄/K₂HPO₄ pH7.1, 0.15M NaCl, 0.5M arginine.

This method was used to purify Ebh (H2 fragment), AaA, SdrC, FnbpA, Sbi, Atl-amidase and IsaA.

10

The purified proteins were analysed by SDS-PAGE. The results for one protein purified under native conditions (alpha toxin) and one protein purified under denaturing conditions (SdrC) are shown in Figures 3 and 4.

15 **Example 3 Preparation of *S. aureus* Capsular Polysaccharide Conjugates using CDAP**

Activation and coupling chemistry for native PS8 using CDAP:

20

SA08-TT004

Activation and coupling were performed at room temperature under continuous stirring. 10 mg of native polysaccharide were dissolved to obtain a final PS concentration of 2.5
 25 mg/ml in 0.2M NaCl. The solution was then adjusted to pH 6.0+/-0.2 before the activation step.

At time 0, 50 µl of a CDAP solution (100 mg/ml freshly prepared in acetonitrile/WFI, 50/50) were added manually to reach the appropriate CDAP/PS (0.5/1) ratio.

30 After 1.5 minutes the pH was raised to pH 9.00+/-0.05 by addition of 0.5M NaOH. NaOH addition takes about 1 minutes and pH is stabilised at pH 9.00+/-0.05 up to carrier addition.

At time 4.5 minutes, 1.5 ml of TT (10 mg/ml in 0.2M NaCl) was added to reach the appropriate Protein/PS ratio (1.5/1); pH was immediately adjusted to coupling pH 9.00+/-
 35 0.05. The solution is left for one hour under manual pH regulation.

After the coupling step, 0.5 ml of 2M glycine (ratio gly/PS (w/w): 7.5/1) were added; pH was immediately adjusted to 9.00 $\pm$ 0.05. The solution was left for 30 minutes under manual pH regulation. Then the conjugate was clarified using a 5 μ m Minisart filter and injected on Sephacryl S400HR (XK16/100). The flow-rate was fixed at 30 ml/h, using
5 150mM NaCl.

The elution fractions were analysed by resorcinol and by μ BCA. Interesting fractions were pooled and filtered on 0.22 μ m Sterivex.

The resulting conjugate had a final TT/PS ratio (w/w) of 1.05 as assessed by resorcinol
10 and Lowry assays.

Example 4 Preparation of *S. aureus* Capsular Polysaccharide Conjugates using CDAP on sized polysaccharides

15 Activation and coupling chemistry for sized PS8 using CDAP

PS is weighted on the basis of 10% theoretical moisture content. 2 g of native, humid PS was dissolved overnight in WFI at an initial concentration of 10 mg/ml. Before the sizing, the solution of native PS was clarified on 5 μ m cut-off filter.

20 A EMULSIFLEX C-50 homogenizer apparatus, in which the homogenizing cell was replaced with a Microfluidics F20Y-0.75 μ m interaction chamber, was used to reduce the molecular weight and the viscosity of the polysaccharide before the activation step. The size reduction was realized at 10000 psi during the 10 first cycles and then at 15000 psi for the following 60 cycles. The progress of the size reduction was followed *in-process*
25 by measuring viscosity. The sizing was stopped after 70 cycles when the target of 2.74 $\pm$ 0.2 cp was reached.

Activation and coupling were performed at room temperature under continuous stirring. 50 mg of sized polysaccharide 8 were diluted to obtain a final PS concentration of 5 mg/ml
30 in 0.2M NaCl.

At time 0, 375 μ l of a CDAP solution (100 mg/ml freshly prepared in acetonitrile/WFI, 50/50) were added manually to reach the appropriate CDAP/PS (0.75/1) ratio.

After 1 minute the pH was raised to pH 9.00 $\pm$ 0.05 by addition of 0.5M NaOH.

At time 2.5 minutes, 10 ml of TT at 10 mg/ml in 0.2M NaCl were added to reach the appropriate Protein/PS ratio (2/1); pH was immediately adjusted to coupling pH 9.00+/-0.05. The solution was left for 55 minutes under manual pH regulation.

After the coupling step, 2.5 ml of 2M glycine (ratio gly/PS (w/w): 7.5/1) were added; pH was immediately adjusted to 9.00+/-0.05 by the regulator. The solution was left for 30 minutes under manual pH regulation.

Then the conjugate was clarified using a 5µm Minisart filter and injected on Sephacryl S400HR (XK26/100). The flow-rate was fixed at 60 ml/h.

The elution fractions were analysed by resorcinol and by protein dosage. Interesting fractions were pooled and filtered on 0.22 µm Millipack20.

The resulting conjugate has a final TT/PS ratio of 1.94.

Example 5 Preparation of *S. aureus* Capsular Polysaccharide Conjugates using EDAC

Activation and coupling chemistry using EDAC:

S. aureus capsular polysaccharide type 8-TT conjugate:

PS derivatization

Activation and coupling were performed at room temperature under continuous stirring. 30 mg of native polysaccharide were diluted to obtain a final polysaccharide concentration of 5 mg/ml in water. The solution was adjusted to pH 4.5-5.0 with 0.5N HCl and then 66 µg of ADH were added (2.2 mg/mg PS). After complete dissolution, 60 mg of EDAC were added (2 mg/mg PS). After 70 min the pH was raised to pH 7.5 with 1N NaOH to stop the reaction. Free ADH was removed by purification on Sephacryl S100HR (XK 16/40). The flow-rate was fixed at 60 ml/h using 0.2 M NaCl as elution buffer. A size reduction was done by sonication of 15 min allowing a sterile filtration on millex filter (0.22 µm).

Coupling

Tetanus toxoid was added to 5 to 10 mg of derivatized polysaccharide in 0.2M NaCl and the pH was adjusted to pH 5.0 or pH 6.0 by addition of 0.5N HCl. EDAC was dissolved in 0.1M Tris buffer pH 7.5 and then added over a period of 10 min (1/5 vol each 2 min). According to the conditions used (see Table 6), the reaction was stopped after between 30 and 180 minutes by addition of 1M Tris-HCl pH 7.5. Prior to purification on Sephacryl

S400HR, the conjugate was clarified using a 5µm Minisart filter. Alternatively, the conjugate was clarified by a 5 minute sonication step. The conjugate was then injected on Sephacryl S400HR (XK16/100). The flow-rate was fixed at 30 ml/h using 150 mM NaCl as elution buffer. The elution pool was selected on the basis of resorcinol and µBCA profiles (which measure polysaccharide and protein dosage respectively). The conjugate was filtered on a 0.22 µm sterilizing membrane (Millipack 20) at 10 ml/min.

Table 5

Conjugate	Coupling time	[PS (AH)] (mg/ml)	[TT (AH)] (mg/ml)	[reagent EDAC] (mg/mg PS)
SA08-TT011	40 min	3.58	6.45	0.5/1
SA08-TT015*	180 min	2	4.0	0.25/1
SA08-TT017	30 min	3.75	7.5	0.25/1
SA08-TT018	50 min	3.75	7.5	0.10/1

Table 5: * coupling done at pH 6.0

The resulting conjugates have the following characteristics shown in Table 6:

Table 6

Conjugate	In. TT/PS ratio(w/w)	F. TT/PS ratio (w/w)	Y. PS rec (%)	Filtr. Yield (%)
SA08-TT011	2/1	2.43/1	48	99
SA08-TT015	2/1	2.40/1	53	104
SA08-TT017	2/1	2.41/1	44	107
SA08-TT018	2/1	2.40/1	42	106

S. aureus polysaccharide type 8 was also treated by microfluidization before derivatization with ADH

PS derivatization

Activation and coupling are performed at room temperature under continuous stirring.

200 mg of sized polysaccharide are diluted to obtain a final PS concentration of 10 mg/ml in water. Then 440 mg of ADH were added (2.2 mg/mg PS). The solution was adjusted to pH 4.7 with 1N HCl before the addition of 400 mg of EDAC (2 mg/mg PS). After 60 min the pH was raised to pH 7.5 with 5M NaOH to stop the reaction. The mixture was concentrated on Amicon Ultra (cut-off 10.000 MWCO). Prior to purification on Sephacryl S200HR (XK16/100), the conjugate was clarified using a 5µm Minisart filter. The flow-rate was fixed at 30 ml/h using 0.150 M NaCl as elution buffer.

10

Coupling

100 mg of TT was added to 50 mg of derivatized polysaccharide in 0.2M NaCl. The pH was adjusted to pH 5.0 ± 0.02 by addition of 0.3N HCl. EDAC was dissolved in 0.1M Tris buffer pH 7.5 and then added over a period of 10 min (1/10 vol each minute). According to the conditions used (see Table 8), the reaction was stopped after between 30 and 180 minutes by addition of 1M Tris-HCl pH 7.5. Prior to purification on Sephacryl S400HR, the conjugate was clarified using a 5µm Minisart filter. The conjugate was then injected on Sephacryl S400HR (XK50/100). The flow-rate was fixed at 60 ml/h using 150 mM NaCl as elution buffer. The elution pool was selected on the basis of resorcinol and µBCA profiles (which measure polysaccharide and protein dosage respectively). Then, the conjugate was filtered on a 0.22 µm sterilizing membrane (Millipack 20) at 10 ml/min.

25 Table 7

Conjugate	Coupling time	[PS-AH] (mg/ml)	[TT] (mg/ml)	[EDAC] (mg/mg PS)
SA08-TT045	65 min	3.83	7.66	0.1
SA08-TT046	45 min	3.75	7.5	0.2
SA08-TT047	30 min	5.0	15.0	0.2
SA08-TT048	120 min	5.0	10.0	0.05
SA08-TT049*	50 min	5.0	10.0	0.1

* EDAC added in "one time"

Table 8

Conjugate	In. TT/PS ratio(w/w)	F. TT/PS ratio (w/w)	Y. PS rec (%)	Filtr. Yield (%)
SA08-TT045	2/1	2.20/1	57	101
SA08-TT046	2/1	2.80/1		
SA08-TT047	3/1	Gel- Not purified	-	-
SA08-TT048	2/1	3.35	30	101
SA08-TT049	2/1	3.5	24	106

Example 6 Preparation of *S. aureus* Capsular Polysaccharide Conjugates using EDAC on de-O-acetylated *S. aureus* polysaccharide 8

5

De-O-acetylation

0.1N NaOH was added to 16 ml of sized PS (10 mg/ml) to target a final PS concentration of 9 mg/ml and a final NaOH concentration of 0.1N. After a treatment of 1 or 2 h at 37°C, the PS had a level of O-acetylation of 35 and 12% (Hestrin dosage) respectively in comparison to the untreated PS.

0.1N NaOH was added to 19 ml of sized PS (10 mg/ml) to target a final PS concentration of 9.5 mg/ml and a final NaOH concentration of 0.05N. After a treatment of 1 or 2 h at 37°C, PS had a level of O-acetylation of 78 and 58% (Hestrin dosage) respectively in comparison to the untreated PS.

The derivatization step was done as shown previously for an untreated PS.

20 Table 9

Conjugate	O-acetyl level %	ADH/PS w/w* %
SA08-TT056	35	9.3
SA08-TT057	12	13.1
SA08-TT058	78	5.3
SA08-TT059	58	8.2

* TNBS assay

Removal of the O-acetyl groups resulted in an increased availability of reactive carboxylic groups. Indeed, the derivatization level of a PS having only 12% of O-acetyl groups was $\pm$ 2.5-fold superior to the one having 78% of O-acetyl groups.

Coupling was done as shown previously for a untreated PS

Table 10

Conjugate	O-acetyl level %	Coupling time	[PS-AH] (mg/ml)	[TT] (mg/ml)	[EDAC] (mg/mg PS)
SA08-TT056	35	45 min	2.87	5.74	0.5
SA08-TT057	12	30 min	2.62	5.24	0.5
SA08-TT058	78	50 min	3.16	6.32	0.5
SA08-TT059	58	40 min	2.53	5	0.5

Table 11

Conjugate	In. TT/PS ratio(w/w)	F. TT/PS ratio (w/w)	Y. PS rec (%)	Filtr. Yield (%)
SA08-TT056	2/1	1.70/1	51.3	100
SA08-TT057	2/1	1.78/1	63.0	105.4
SA08-TT058	2/1	2.08/1	46.3	99.6
SA08-TT059	2/1	1.86/1	50.8	99.2

Example 7 Conjugation of dPNAG

5 Activation and coupling of dPNAG:

dPNAG-TT conjugates

- 10 The following conjugates were produced using the approaches described herebelow:

dPNAG-TT010: dPNAG-S-GMBS + DTT treated TT-LC-SPDP

dPNAG-TT011: dPNAG-S-GMBS + DTT treated TT-LC-SPDP

- 15 dPNAG-TT012: dPNAG-S-GMBS + DTT treated TT-SPDP

dPNAG-TT014: dPNAG-SPDP + DTT treated TT-SPDP

dPNAG-TT017: DTT treated dPNAG-SPDP + TT-LC-SPDP

dPNAG-TT019: dPNAG-S-GMBS + DTT treated TT-SPDP

dPNAG-TT020: dPNAG-S-GMBS + DTT treated TT-SPDP

20

dPNAG

- 1g of PNAG was dissolved in 5N HCl at a concentration of 20mg/ml and was incubated for 1 hour. It was then neutralized with 5N NaOH. The solution was clarified on a 5µm membrane and purified on Sephacryl S400HR. Interesting fractions, corresponding to the "medium molecular size" (see Infection and Immunity, 70: 4433-4440 (2002)), were pooled and concentrated prior to de-N-acetylation treatment.
- 25

The solution was adjusted at 1M NaOH and left 24 hours at 37°C. After neutralization, the product was subjected to dialysis and concentration.

dPNAG Activation

5

S-GMBS (N-(γ-Maleimidobutyryloxy) sulfosuccinimide, Pierce) was added to dPNAG in 0.2M NaCl (ratio S-GMBS/PS (w/w):1/1) and incubated during 2h at room temperature at pH 7.0 (pH regulation using 1M NaOH). Excess GMBS and by-products were removed by purification on Toyopearl HW-40F using PBS,
10 10mM EDTA, 50 mM NaCl pH 7.2 as elution buffer with a flow-rate fixed at 60 ml/h. The elution pool was selected in function of the optical density (UV=206 nm) and then concentrated on Vivaspin tubes 3,000 MWCO or Amicon Ultra 10,000 MWCO.

15 Coupling

GMBS-activated dPNAG and DTT reduced TT-SPDP were mixed and stirred at room temperature. According to the conditions used the reaction was quenched after 20-120 min by the addition of cysteine (4 mg/ml in Na phosphate buffer pH
20 8.0) for 30 minutes. The conjugate was clarified on 5 µm filter and injected on Sephacryl S300HR resin (XK16/100) for purification. Elution was realized in 200 mM NaCl with a flow-rate fixed at 30 ml/h. The elution fractions were analysed by hexosamine and by protein dosage. Interesting fractions were pooled and filtered on 0.22 µm Sterivex. The final conjugate was tested for polysaccharide
25 (hexosamine dosage) and protein composition (Lowry dosage).

Table 12

Conjugate	N-acetylation level %	[dPNAG] mg/ml	[TT] mg/ml	PS scale (mg)	Coupl.time (min)
dPNAG-TT 010	10*	15	15	30	120
dPNAG-TT 011	10*	12	24	20	120
dPNAG-TT 012	10*	17.5	35	22	80
dPNAG-TT 019	34	5	10	10	20
dPNAG-TT 020	34	2	2	10	20

*Not done on the lot used in the conjugation but estimated on a previous lot by NMR using the same de-N-acetylation method.

Table 13

Conjugate	In.TT/PS ratio (w/w)	F.TT/PS ratio (w/w)	Yield PS rec (%)	Filtration yield (%)
dPNAG-TT010	1/1	1.86/1	43	99
dPNAG-TT011	2/1	2.86/1	56	99
dPNAG-TT012	2/1	2.29/1	61	108
dPNAG-TT019	2/1	1.45/1	81	97
dPNAG-TT020	1/1	0.89/1	82	109

5 dPNAG-SPDP:

A 5-fold molar excess of SPDP (N-Succinimidyl-3-(2-Pyridyldithio) Propionate, MW: 312.4, Pierce) dissolved in DMSO (dimethylsulfoxid, Merck) was added to 100 mg of dPNAG at 5mg/ml in 100 mM Na phosphate, pH 7.2) and incubated 1 h at room temperature. Before purification on Sephacryl S100HR (XK16/40) the reaction mixture was concentrated to $\pm$ 6 ml on Amicon Ultra 10,000 MWCO (centrifugation at 3000 rpm during 28 min). Elution was realized in phosphate buffer pH 7.4 with a flow-rate fixed at 60 ml/h. The interesting fractions (read at 206 nm) were pooled and concentrated to 1.1 ml on Amicon Ultra 10,000 MWCO (centrifugation at 3000 rpm during 30 min).

15

TT-SPDP:

A 15-fold molar excess of SPDP (Pierce) dissolved in DMSO (dimethylsulfoxid, Merck) was added to 1 g of TT (50 mg/ml) in 100 mM Na phosphate, pH 7.2 and incubated 80 min at room temperature. Then the product was injected on Sephacryl S100HR (XK16/40) and eluted in 100 mM Na acetate pH 5.6, 100 mM NaCl, 1mM EDTA with a flow-rate fixed at 60 ml/h. The elution pool was selected in function of the optical density (UV=280nm)

20

and then concentrated to 19.6 ml on Amicon Ultra 10,000 MWCO (centrifugation at 3000 rpm during 75 min).

TT-LC-SPDP was produced as TT-SPDP but using LC-SPDP (Succinimidyl 6-[3-(2-pyridyldithio)-propionamido]hexanoate, Pierce) and an incubation time of 60 min.

TT-SH or TT-LC-SH

DTT was added to TT-SPDP or TT-LC-SPDP in a DTT/TT ratio (mg/mg) of 0.7/1. After 2h at room temperature, the release of pyridine-2-thione was followed by its characteristic absorbance at 343 nm. The thiolated protein was purified from excess DTT by gel filtration (PD-10, Amersham). After concentration on Amicon Ultra 10,000 MWCO, protein content was estimated by Lowry dosage.

dPNAG-SPDP + TT-SH or TT-LC-SH (dPNAG-TT014 and 016)

Coupling was performed at room temperature under continuous stirring and with an initial TT/PS ratio (w/w) of 2/1.

dPNAG and TT-SH were mixed in order to obtain a final PS concentration of 20 mg/ml and a final protein concentration of 40 mg/ml. After 30 min, unreacted sulfhydryl groups were quenched by addition of 2-Iodoacetamide (Merck).

dPNAG and TT-LC-SH was mixed in order to obtain a final PS concentration of 10 mg/ml and a final protein concentration of 20 mg/ml. After 75 min, unreacted sulfhydryl groups were quenched by addition of 2-Iodoacetamide (Merck).

Then the conjugate is clarified using a 5 µm Minisart filter and injected on Sephacryl S300HR (XK16/100). Elution was realized in 200 mM NaCl with a flow-rate fixed at 30 ml/h.

The elution fractions were analysed by hexosamine and by protein dosage. Interesting fractions were pooled and filtered on 0.22 µm Sterivex.

The resulting conjugates have a final TT/PS ratio (w/w) of 2.18 (TT-SH) and 2.24 (TT-LC-SH).

Thiolation of dPNAG

11.6 mg of DTT (1, 4-Dithiothreitol, Boehringer Mannheim, MW: 154.24) were added to 16.5 mg of dPNAG-SPDP. After 2 h at room temperature, the release of pyridine-2-thione was followed by its characteristic absorbance at 343 nm. The thiolated PS was purified from excess DTT by gel filtration (Toyopearl HW40F) and then concentrated to 860 µl on
 5 Amicon Ultra 10,000 MWCO.

dPNAG-SH + TT-SPDP (dPNAG-TT017)

Coupling was performed at room temperature under continuous stirring and with an initial
 10 TT/PS ratio (w/w) of 1.7/1.

dPNAG-SH and TT-SPDP were mixed in order to obtain a final PS concentration of 7.73 mg/ml and a final protein concentration of 13.3 mg/ml. After 90 min, unreacted sulfhydryl groups were quenched by addition of 2-Iodoacetamide (Merck).

Then the conjugate was clarified using a 5 µm Minisart filter and injected on Sephacryl
 15 S300HR (XK16/100). Elution was realized in 200 mM NaCl with a flow-rate fixed at 30 ml/h.

The elution fractions are analysed by hexosamine and by protein dosage. Interesting fractions were pooled and filtered on 0.22 µm Sterivex.

The resulting conjugate has a final TT/PS ratio (w/w) of 2.74.

20 **Example 8 Formulation**

Adjuvant compositions

The conjugates were inoculated either unadjuvanted or adjuvanted with adjuvant A, having the following composition:

25

Composition of Adjuvant A

Qualitative Quantitative (per 0.5 mL dose)

Liposomes:

30 - DOPC 1 mg
 - cholesterol 0.25 mg

3DMPL 50 µg

QS21 50 µg

KH₂PO₄ 1 3.124 mg Buffer

Na₂HPO₄ 1 0.290 mg Buffer

35 NaCl 2.922 mg
 (100 mM)

WFI q.s. ad 0.5 ml Solvent

pH 6.1

1. Total PO₄ concentration = 50 mM

Example 9

Animal experiments.

Female CD-1 mice, 8 to 10 weeks old, are obtained from Charles River Laboratories, Kingston, Mass. For lethality studies, five groups of 9 to 11 CD-1 mice are challenged intraperitoneally (i.p.) with serial dilutions of *S. aureus* grown on CSA plates. The inocular sizes range from $\sim 10^{10}$ to 10^8 CFU/mouse. Mortality is assessed on a daily basis for 3 days. The 50% lethal doses (LD_{50} s) is estimated by using a probit model of the dose-response relationship. The null hypothesis of common LD_{50} s was tested by the likelihood ratio test. Sublethal bacteremia is initiated by challenging groups of 8 to 20 mice by the intravenous (i.v.) route with $\sim 2 \times 10^6$ CFU/mouse or by the i.p. route with $\sim 2 \times 10^7$ CFU/mouse. After inoculation separate groups of animals are bled from the tail at specified times, and the bacteremia levels are estimated by quantitative plate counts performed in duplicate on tryptic soy agar plates with 5% sheep blood (Becton Dickinson Microbiology Systems). Statistical significance is determined with the Welch modification of the unpaired Student's *t* test.

Example 10

Immunogenicity of *S. aureus* PS8-TT and dPNAG-TT conjugates

Groups of 30 mice were inoculated subcutaneously with *S. aureus* PS8-TT conjugate at a saccharide dose of $3\mu\text{g}$, either unadjuvanted or combined with adjuvant A, on days 0, 14, 28 and 42. On day 0, the mice received a first saccharide dose including between 0.001 and $0.013\mu\text{g}$. The further three immunisations were done with a dose of $0.3\mu\text{g}$ in saline. On day 55 serum was collected from the mice and each serum sample was tested by ELISA to assess the immune response against PS8. Groups of 10 mice were used in the control groups and these were inoculated with either saline or saline containing adjuvant A.

The purified PS8 was coated at $2\mu\text{g/ml}$ in phosphate buffered saline (PBS) on high binding microtitre plates (Nunc Maxisorp) overnight at 4°C . The plates were blocked with PBS-BSA 1% for 30 min at room temperature with agitation. The mice antisera were prediluted 1/100, then further twofold dilutions were made in microplates which were incubated at 37°C for 1 hour. After washing, bound murine antibody was detected using

Jackson ImmunoLaboratories Inc. peroxidase-conjugated affiniPure Goat Anti-Mouse IgG (H+L) (ref: 115-035-003) diluted 1:5000 in PBS-tween 0.05%. The detection antibodies were incubated for 30 minutes at room temperature with agitation. The color was developed using 4 mg OPD (Sigma) + 5 µl H₂O₂ per 10 ml pH 4.5 0.1M citrate buffer for 15 minutes in the dark at room temperature. The reaction was stopped with 50 µl HCl, and the optical density was read at 490 nm relative to 650 nm.

The results were expressed in mid-point titers and the GMT was calculated for the 30 samples (10 for controls). The results are shown in Table 14 below.

Table 14

Conjugate	Anti-PS8 titre (GMT) nonadsorbed	Anti-PS8 titre (GMT) Adjuvant A
SA08-TT011	4714	2109
SA08-TT015	2806	5631
SA08-TT017	3770	4396
SA08-TT018	5349	4748
Control	50	50

Groups of 30 mice were inoculated subcutaneously with *S. aureus* dPNAG-TT conjugates (containing dPNAG which was between 10% and 30% N-acetylated) at a saccharide dose of 0.3µg in 200mM NaCl, either unadjuvanted or combined with adjuvant A. The mice received three inoculations on days 0, 14 and 28. On day 41 or 42 serum was collected from the mice and each serum sample was tested by ELISA to assess the immune response against PNAG. Groups of 10 mice were used in the control groups and these were inoculated with saline or with adjuvant alone.

Anti-PNAG ELISA:

Purified PNAG (2.5 µg/ml) mixed with methylated HSA (2.5 µg/ml) diluted in phosphate buffered saline (PBS) was coated on high binding microtitre plates (Nunc Maxisorp) overnight at 4° C.

The plates were blocked with PBS-BSA 1%, 30 min at RT with agitation. The mice antisera were prediluted 1/100, then further twofold dilutions were made in microplates and incubated at room temperature with agitation for 1 hour. After washing, bound murine antibody was detected using Jackson ImmunoLaboratories Inc. peroxidase-conjugated
5 affiniPure Goat Anti-Mouse IgG (H+L) (ref: 115-035-003) diluted 1:5000 in PBS-BSA 0.2%-tween 0.05%. The detection antibodies were incubated for 30 min. at room temperature with agitation. The color was developed using 4 mg OPD (Sigma) + 5 µl H₂O₂ per 10 ml pH 4.5 0.1M citrate buffer for 15 minutes in the dark at room temperature. The reaction was stopped with 50 µl HCl, and the optical density was read at 490 nm
10 relative to 650 nm.

A GMT was calculated on the mid-point titers of the 30 samples (10 for the controls).

Table 15

Conjugate	Anti-PNAG GMT Non-adsorbed	Anti-PNAG GMT Adjuvant A
dPNAG-TT010	1371	28465
dPNAG-TT011	1133	40899
dPNAG-TT019	425	13429
dPNAG-TT020	656	10080
dPNAG-TT014	342	9806
dPNAG-TT017	203	8094
dPNAG-TT012	398	40509
dPNAG-TT016	719	7937
Control	50	50

15

Example 11 Immunogenicity of PS*-TT conjugates made by the CDAP method

Results

Table 16

Conjugate	Anti PS8 GMT post three inoculations in mice	Anti-PS8 GMT post two inoculations in mice
SAPS8-TT-04 Specol	207068	41326

SAPS8-TT-04 Adjuvant A	47405	15577
SAPS8-TT-04 AIPO4	7380	4510
Specol	50	
Adjuvant A	50	
AIPO4	50	

Example 12**Opsonophagocytosis assay.**

5

The in vitro opsonophagocytotic killing of *S.aureus* by human polymorphonuclear leukocytes (PMNs) is performed as described in Xu et al 1992 Infect. Immun. 60; 1358. Human PMNs are prepared from heparinized blood by sedimentation in 3% dextran T-250. The opsonic reaction mixture (1 ml) contains $\sim 10^6$ PMNs in RPMI 1640 medium supplemented with 10% heat-inactivated fetal calf serum, $\sim 10^8$ CFU of *S-aureus*, and 0.1 ml of the test serum or IgG preparation. Hyperimmunized rabbit serum is used as a positive control, and 0.1 ml of nonimmune rabbit serum was used as a complete source for the IgG samples. The reaction mixtures are incubated at 37°C, and bacterial samples are transferred at 0, 60, and 120 min into water and subsequently diluted, spread on tryptic soy agar plates, and incubated at 37°C for bacterial count after overnight incubation.

10

15

Example 1320 **Immunogenicity of staphylococcal proteins in mice and rabbits**

Animals were immunized with purified staphylococcal proteins in order to generate hyper-immune sera. Mice were immunized three times (days 0, 14 and 28) with 10 µg of each proteins adjuvanted in Specol. Rabbits were immunized three times (days 0, 21 and 42) with 20 µg of each proteins adjuvanted in Specol. Immune sera were collected and evaluated in anti-protein and anti-killed whole cells ELISA.

25

Anti-Protein ELISA:

The purified protein was coated at 1 µg/ml in phosphate buffered saline (PBS) on high binding microtitre plates (Nunc Maxisorp) overnight at 4° C. The plates were blocked with PBS-BSA 1%, for 30 min at RT with agitation. The test samples were then diluted 1/1000 and incubated at room temperature for 1 hour with agitation. After washing, bound murine or rabbit antibody was detected using Jackson ImmunoLaboratories Inc. peroxidase-conjugated affiniPure Goat Anti-Mouse IgG (H+L) (ref: 115-035-003) or AffiniPure Goat Anti-Rabbit IgG (H+L) (ref: 11-035-003) diluted 1:5000 in PBS-tween 0.05%. The detection antibodies were incubated for 30 min. at room temperature with agitation. The color was developed using 4 mg OPD (Sigma) + 5 µl H₂O₂ per 10 ml pH 4.5 0.1M citrate buffer for 15 minutes in the dark at room temperature. The reaction was stopped with 50 µl HCl, and the optical density was read at 490 nm relative to 650 nm.

The O.D. for a 1/1000 dilution of Post III was compared to the O.D. obtained with the same dilution of Pre-immune sera.

Results generated with mice and rabbit sera are presented in Figure 5. A good seroconversion against each antigen was observed. Evaluation of sera directed against SBI was impaired due to the Ig binding activity of this protein.

Anti-killed whole cells ELISA:

Killed whole cells (heat or formaldehyde inactivated) from *S. aureus* type 5 and 8 or *S. epidermidis* strain Hay were coated at 20 µg/ml in phosphate buffered saline (PBS) on high binding microtitre plates (Nunc Maxisorp) overnight at 4° C with evaporation. The plates were blocked with PBS-BSA 1% 30 min at room temperature with agitation. Protein A was neutralised by addition of 10µg/ml of Affinity Purified Chickedn anti-ProteinA (ICL ref: CPA-65A-2) diluted in PBS-tween 0.05% followed by incubation for 1 hour at room temperature. The test samples were then diluted two-fold on the microplate in PBS-0.05% from a starting dilution at 1/10 and incubated 1 hour at room temperature with agitation. After washing, bound murine or rabbit antibody was detected using Jackson ImmunoLaboratories Inc. peroxidase-conjugated affiniPure Goat Anti-Mouse IgG (H+L) (ref: 115-035-003) or AffiniPure Goat Anti-Rabbit IgG (H+L) (ref: 11-035-003) diluted 1:5000 in PBS-tween 0.05%. This detection antibodies were incubated for 30 min. at room temperature with agitation. The color was developed using 4 mg OPD (Sigma) + 5 µl H₂O₂ per 10 ml pH 4.5 0.1M citrate buffer for 15 minutes in the dark, at room

temperature. The reaction was stopped with 50 μ l HCl, and the optical density was read at 490 nm relative to 650 nm.

It should be noted that expression levels of proteins in staphylococci will vary depending on culture conditions. Therefore a negative result may reflect the choice of incorrect culture conditions rather than a lack of immunogenicity.

The results using mice sera are shown in Table 17 and some of the graphs are shown in figure 6. A weak recognition of *S. aureus* strain 5 is observed with sera directed against SdrC, FnbpA, Ebh, Sbi and IsaA. Recognition of *S. aureus* strain 8 is only observed with the serum directed against Sbi. Weak recognition of *S. epidermidis* Hay is observed with sera directed against Atl amidase, MRPII, IsdA, IsaA, Ebh, Aaa and Sbi.

A selection of results generated using rabbit sera are shown in figure 7 and summarized in Table 18. Very good recognition of the three strains was observed with IsaA and IsdB. A weak recognition of the three stains was observed with HarA although animals only received one injection rather than the three injections used for the other proteins.

Table 17

Protein name	React on SA5	React on SA8	React on SE Hay
IsaA	(+)	(+)	(+)
ClfA	-	(+)	(+)
Atl amidase	-	-	++
SdrG	-	-	-
Glucosamidase	-	-	-
IsdA	-	-	++
Alpha toxin	-	-	-
SrdC	++	(+)	-
Ebh	+	-	+
AaA	-	-	++
MRPII	-	-	++
Sbi	++	++	+++
FnbpA	+	+	(+)

Table 18

Protein name	React on SA5	React on SA8	React on SE Hay
IsaA	+++	+++	+++
ClfA	+	++	++
Atl amidase	-	++	+
IsdB	+++	+++	+++
SdrG	+	+	+
Glucosamidase	-	-	-
HarA (1 inject.)	+	+	+
IsdA	-	-	-
Alpha toxin	-	-	+
SrdC	-	-	-
Ebh	-	+	-
AaA	-	-	-
MRPII	-	-	++
Sbi	-	+++	-
FnbpA	-	++	++

Example 14

5

Efficacy of combinations of staphylococcal proteins in a nasal colonization model.

Fifteen groups of three cotton rats were inoculated with combinations of eight staphylococcal antigens and five cotton rats which acted as controls were treated with no antigen. These sixteen groups are as follows:

- Group 1 – Atl-glucosamine, Atl-amidase, AAA, alpha toxin, SdrC, SdrG, Ebh, Sbi
Group 2 - Atl-glucosamine, Atl-amidase , IsdA, IsdB, ClfA, SdrC, Ebh, FnbpA
Group 3 - Atl-glucosamine, Atl-amidase, HarA, IsdA, MRPII, IsdB, AAA, alpha toxin
15 Group 4 - Atl-glucosamine, HarA, IsdA, AAA, ClfA, IsaA, Ebh, Sbi
Group 5 – HarA, MRPII, AAA, alpha toxin, ClfA, SdrC, Ebh, FnbpA
Group 6 – IsdA, IsdB, AAA, alpha toxin, ClfA, SdrG, Sbi, FnbpA
Group 7 – Atl-aminidase, IsdA, MRPII, AAA, IsaA, SdrG, Ebh, FnbpA
Group 8 – Control
20 Group 9 – Atl-glucosamine, IsdA, MRPII, alpha toxin, IsaA, SdrC, Sbi, FnbpA
Group 10 – Atl-glucosamine, MRPII, IsdB, AAA, ClfA, IsaA, SdrC, SdrG

Group 11- Atl-amindase, MRPII, IsdB, alpha toxin, ClfA, IsaA, Ebh, Sbi

Group 12 – Atl-glucosamine, HarA, IsdB, alpha toxin, IsaA, SdrG, Ebh, FnbpA

Group 13 – Atl-amidase, HarA, IsdB, AAA, IsaA, SdrC, Sbi, FnbpA

Group 14 – Atl-glucosamine, Atl-amidase, HarA, MRPII, ClfA, SdrG, Sbi, FnbpA

5 Group 15 – Atl-amidase, HarA, IsdA, alpha toxin, ClfA, IsaA, SdrC, SdrG

Group 16 – HarA, IsdA, MRPII, IsdB, SdrC, SdrG, Ebh, Sbi

Each mix of antigens contained 3µg of each antigen mixed with an adjuvant made of liposomes containing MPL and QS21. The cotton rats were inoculated three times on
10 days 1, 14 and 28 of the experiment. Two weeks after inoculation, the efficacy of the immunisations were assessed using a nasal colonisation assay as described in Kokai-Kun et al (2003) Antimicrob.Agents.Chemother. 47; 1589-1597.

Classical multiple linear regression analysis was carried out on the data using “Design
15 Expert 6” software. The presence of an antigen was coded as +1 and the absence of an antigen by -1. Using the equation of the model it was possible to determine which antigens were the key antigens which produced a large decrease in the number of colonies per nose.

20 Results

The results of the nasal colonisation assay are shown in Table 19. The control group had a mean logCFU/nose of 3.51335 and a decrease in nasal colonisation could be see for all the groups of cotton rats inoculated with staphylococcal proteins. Groups 4, 9 and 13
25 showed the greatest decrease in nasal colonisation with a decrease of over 2 logs in CFU/nose. Groups 12 and 16 also gave good results, showing a decrease of about 2 logs in CFU/nose.

Table 19

30

Group	Mean observed LogCFU/nose	Predicted LogCFU/nose
1	1.77527	2.03560
2	2.90435	2.52684
3	1.96556	2.23033
4	1.27748	1.21872
5	1.67304	1.93128
6	2.79745	2.98193
7	2.21481	2.30705
8	3.51355	3.47317
9	1.22480	1.44080

10	2.03085	1.93204
11	2.02522	1.81581
12	1.53402	1.70996
13	1.36063	1.49100
14	2.31201	1.73909
15	2.22979	1.98223
16	1.58109	1.44004

5 The contribution of specific antigens within the antigen mix was calculated using multiple regression analysis of the nasal colonisation data. The final model contains the seven best antigens. Results for these antigens are shown in Table 20. Within the context of the protein mix, the inclusion of HarA gave the greatest decrease in nasal colonisation, followed by IsaA, Sbi, SdrC, autolysin-glucosamine, MRPII and Ebh.

10 Table 20 Effects in difference of logCFU/nose and ratio of CFU/nose for the seven best antigens in the model and corresponding p-values.

antigen	prob >F	Effect estimate	Reduction ratio	Cumulative effect	Cumulative ratio
HarA	0.033	-0.596	3.9	-0.596	3.9
IsaA	0.046	-0.558	3.6	-1.154	14.3
Sbi	0.077	-0.491	3.1	-1.645	44.2
SdrC	0.22	-0.337	2.2	-1.982	96.0
Atl-glucos	0.238	-0.324	2.1	-2.306	202.2
MRPII	0.239	-0.323	2.1	-2.629	425.3
Ebh	0.297	-0.286	1.9	-2.914	821.0

CLAIMS

1. A process for producing a conjugate comprising a *S. aureus* type 5 or 8 polysaccharide or oligosaccharide and a carrier protein comprising the steps of:
 - a) activating the *S. aureus* type 5 or 8 polysaccharide or oligosaccharide with a cyanylating reagent to form an activated *S. aureus* type 5 or 8 polysaccharide or oligosaccharide; and
 - b) covalently linking the activated *S. aureus* type 5 or 8 polysaccharide or oligosaccharide to a carrier protein to form a type 5 or 8 polysaccharide or oligosaccharide conjugate.
2. The process of claim 1, wherein the Type 5 or 8 polysaccharide is of native size.
3. The process of claim 1, wherein the Type 5 or 8 polysaccharide or oligosaccharide is sized.
4. The process of claim 3, wherein the Type 5 or 8 polysaccharide or oligosaccharide is sized by microfluidisation, ultrasonic irradiation or chemical treatment.
5. The process of any one of claims 1-4, wherein the Type 5 or 8 polysaccharide or oligosaccharide has a degree of O-acetylation of 50-100%.
6. The process of any one of claims 1-5, wherein the carrier protein is selected from the group consisting of diphtheria toxoid, Crm197, tetanus toxoid, keyhole limpet haemocyanin, *Pseudomonas aeruginosa* exoprotein A, *Haemophilus influenzae* protein D, pneumococcal pneumolysin and a staphylococcal protein.
7. The process of any one of claims 1-5, wherein the carrier protein is a staphylococcal protein or fragment thereof selected from the group consisting of laminin receptor, SitC/MntC/saliva binding protein, EbhA, EbhB, Elastin binding protein (EbpS), EFB (FIB), SBI, Protein A, autolysin, ClfA, SdrC, SdrD, SdrE, SdrG, SdrH, Lipase GehD, SasA, SasB, SasC, SasD, SasF, SasK, FnbA, FnbB, Cna, ClfB, FbpA, Npase, IsaA/PisA, SsaA, EPB, SSP-1, SSP-2, HBP, Vitronectin binding protein, fibrinogen binding protein, coagulase, Fig, MAP, Immunodominant ABC transporter, IsdA, IsdB, IsdC, HarA, Mg²⁺ transporter, SitC and Ni ABC transporter, alpha toxin (Hla), alpha toxin H35R mutant and RNA III activating protein (RAP).
8. The process of any one of claims 1-7, wherein the cyanylating reagent is 1-cyano-dimethylaminopyridinium tetraborate (CDAP).
9. The process of any one of claims 1-8, wherein the type 5 or 8 polysaccharide or oligosaccharide is directly linked to the carrier protein.
10. The process of any one of claims 1-9, wherein the type 5 or 8 polysaccharide or oligosaccharide is linked to the carrier protein via a spacer.

11. The process of claim 10, wherein the spacer is ADH.
12. The process of any one of claims 1-11, wherein the ratio of cyanylating reagent to polysaccharide or oligosaccharide in step a) is between 0.25/1 and 1/1 w/w or between 0.3/1 and 0.7/1 w/w.
13. The process of any one of claims 1-12, wherein step a) is carried out at pH 5.0-7.0.
14. The process of any one of claims 1-13, wherein step a) is carried out for between 1 minute and 5 minutes.
15. The process of any one of claims 1-14, wherein step a) is terminated by raising the pH to between 8.0-10.0.
16. The process of any one of claims 1-15, wherein the ratio of carrier protein to type 5 or 8 polysaccharide or oligosaccharide in step b) is between 1.1/1 and 4/1 or between 1.2/1 and 2/1 w/w.
17. The process of any one of claims 1-16, wherein step b) is carried out at pH 8.0-10.0.
18. The process of any one of claims 1-17, wherein step b) is carried out for between 25 minutes and 4 hours.
19. The process of any one of claims 1-18, comprising a further step of combining the type 5 or 8 polysaccharide or oligosaccharide conjugate with at least one additional staphylococcal antigen.
20. The process of any one of claims 1-19, comprising a further step of combining the type 5 or 8 polysaccharide or oligosaccharide conjugate with a pharmaceutically acceptable diluent to form a vaccine
21. A conjugate comprising a *S. aureus* type 5 or 8 polysaccharide or oligosaccharide and a carrier protein bonded by a linker comprising an isourea covalent link.
22. The conjugate of claim 21, wherein the *S. aureus* type 5 or 8 polysaccharide is of native size.
23. The conjugate of claim 22, wherein the *S. aureus* type 5 or 8 polysaccharide is sized.
24. The conjugate of any one of claims 21-23, wherein the *S. aureus* type 5 or 8 polysaccharide has a degree of O-acetylation of 50-100%.
25. The conjugate of any one of claims 21-24, wherein the carrier protein is selected from the group consisting of diphtheria toxoid, Crm197, tetanus toxoid, keyhole limpet haemocyanin, *Pseudomonas aeruginosa* exoprotein A, *Haemophilus influenzae* protein D, pneumococcal pneumolysin and a staphylococcal protein.

26. The conjugate of claim 21-24, wherein the carrier protein is a staphylococcal protein or fragment thereof selected from the group consisting of laminin receptor, SitC/MntC/saliva binding protein, EbhA, EbhB, Elastin binding protein (EbpS), EFB (FIB), SBI, Protein A, autolysin, ClfA, SdrC, SdrG, SdrH, Lipase GehD, SasA, SasB, SasC, SasD, SasF, SasK, FnbA, FnbB, Cna, ClfB, FbpA, Npase, IsaA/PisA, SsaA, EPB, SSP-1, SSP-2, HBP, Vitronectin binding protein, fibrinogen binding protein, coagulase, Fig, MAP, Immunodominant ABC transporter, IsdA, IsdB, Mg²⁺ transporter, SitC and Ni ABC transporter, alpha toxin (Hla), alpha toxin H35R mutant and RNA III activating protein (RAP).
27. A vaccine comprising the conjugate of any one of claims 21-26 and a pharmaceutically acceptable excipient.
28. A method of making a vaccine comprising the steps of mixing the conjugate of any one of claims 21-26 and adding a pharmaceutically acceptable excipient.
29. Use of the conjugate as defined in any one of claims 21-26 for the treatment or prevention of staphylococcal infection.
30. Use of the conjugate as defined in any one of claims 21-26 in the manufacture of a vaccine for the treatment or prevention of staphylococcal infection.
31. Use of a vaccine as defined in claim 27 for preventing or treating a staphylococcal infection.

Figure 1

SEQ ID NO:1 polypeptide sequence

MLQVTDVSLRFGDRKLFEDVNIKFTEGNCYGLIGANGAGKSTFLKILSGELDSQTGHVSLGKNERLAVLKQDHYAYEDER
 VLDVVIKGHERLYEVMKEKDEIYMKPDFSDEDGIRAAELEGEFAEMNGWNAEADAANLLSGLGIDPTLHDKKMAELENNO
 KIKVLLAQSLFGEPDVLLLDDEPTNGLDIPAISWLEDFLINFNTVIIVSHDRHFLNNVCTHIADLDFGKIKVYVGNVDFW
 YQSSQLAQKMAQEONKKKEEKMKELODFIARFSANASKSKQATSRKKQLEKIELDDIQSSRRYPFVKFTPHEREIGNDLL
 IVQNLSKTIDGKVLNDVNSFTMNPNDKAILIGDSEIAKTTLKILAGEMEPDEGSFKWGVTTSLSYFPKDNSEFFEGVNM
 NLVDWLRQYAPEDEQTETFLRGFLGRMLFSGEEVKKKASVLSGGEKVRCLMSKMMLSSANVLLLDDEPTNHLDESITAVN
 DGLKSFKGSIIFTSYDFEFINTIANRVIDLNKQGGVSKEIPYEEYLQEIGVLK

SEQ ID NO:2 polypeptide sequence

MLQVTDVSLRFGDRKLFEDVNIKFTEGNCYGLIGANGAGKSTFLKILSGEIDSQTGHVSLGKDERLAVLKQDHFAYEDER
 VLDVVIKGHERLYQVMKEKDEIYMKPDFSDEDGIRAAELEGEFAEMNGWNAEADAANLLSGLGIEPDLHDKNMSELENNO
 KVKVLLAQSLFGDPDVLLLDDEPTNGLDIPAISWLEDFLINFNTVIIVSHDRHFLNNVCTHIADLDFGKIKLYVGNVDFW
 YQSSQLAQKMAQEONKKKEEKMKELODFIARFSANASKSKQATSRKKQLEKIELDDIQSSRRYPYVKFTPHEREIGNDLL
 TVENLSKTIDGKVLNDVNSFTMNPNDKAILVGDSEIAKTTLKILAGEMEPDEGTFKWGVTTSLSYFPKDNSEFFDGVDM
 NLVEWLRQYAPEDEQTETFLRGFLGRMLFSGEEVKKKASVLSGGEKVRCLMSKMMLSSANVLLLDDEPTNHLDESITAVN
 DGLKSFKGSIIFTSYDFEFINTIANRVIDLNQAGALSKEVPYEEYLQEIGVLQNN

SEQ ID NO:3 polypeptide sequence

MPIIITDVYAREVLDSRGNPTVEVEVLTESGAFGRALVPSGASTGEHEAVELRDGDKSRYLGKGVTKAVENVNEIIAPEII
 EGEFSVLDQVSIDKMMIALDGTPNKGKLGANAILGVSI AVARAAADLLGQPLYKYLGGFNGKQLPVPMMNIVNGGSHSDA
 PIAFQEFMILPVGATTFKESLRWGTEIFHNLKSILSKRGLETAVGDEGGFAPKFEGTEDAVETIIQAIEAAGYKPGEEVF
 LGFDCASSEFYENGVDYDYSKFEGEHGAKRTAAEQVDYLEQLVDKYPIITIEDGMDENDWDGWKQLTERIGDRVQLVGDDL
 FVTNTEILAKGIENGIGNSILIKVNQIGTLTETFDAIEMAQKAGYTAVVSHRSGETEDTTIADIAVATNAGQIKTGSLSR
 TDRIAKYNQLLRIEDEL FET
 AKYDGIKSFYNLDK

SEQ ID NO:4 polypeptide sequence

MPIIITDVYAREVLDSRGNPTVEVEVLTESGAFGRALVPSGASTGEHEAVELRDGDKSRYLGKGVTKAVENVNEMIAPEIV
 EGEFSVLDQVSIDKMMIQLDGTHNKGKLGANAILGVSI AVARAAADLLGQPLYKYLGGFNGKQLPVPMMNIVNGGSHSDA
 PIAFQEFMILPVGAESFKESLRWGAEIFHNLKSILSERGLETAVGDEGGFAPRFEGTEDAVETIIKAIEKAGYKPGEDVF
 LGFDCASSEFYENGVDYTKFEGEHGAKRSAAEQVDYLEELIGKYPIITIEDGMDENDWEGWKQLTDRIGDKVQLVGDDL
 FVTNTEILSKGIEQGIGNSILIKVNQIGTLTETFDAIEMAQKAGYTAVVSHRSGETEDTTIADIAVATNAGQIKTGSLSR
 TDRIAKYNQLLRIEDEL YETAKFEGIKSFYNLDK

SEQ ID NO:5 polypeptide sequence

MKKIVTATIATAGLATIAFAGHDAQAAEQNNNGYNSNDAQSYSYTYTIDAQGNHYHTWTGNWNPSQLTQNNTYYNNYNT
 YSYNNASYNNYNHSYQNNYTNNSTATNNYYTGGSGASYSTTSNNVHVTTTAAPSSNGRSISNGYASGSNLYTSGQCT
 YYVFDRVGGKIGSTWGNASNWANAASSGYTVNNTPKVGAIMQTTQGYGHVAYVEGVNSNGSVRVSEMNHYGHGAGVVS
 RTISANQAGSYNFIH

SEQ ID NO:6 polypeptide sequence

MKKIATATIATAGFATIAIASGNQAHASEQDNYGYNPNDPYSYSYTYTIDAQGNHYHTWKGNWHPSQLNQDNGYYSYYYY
 NGYNNYNNYNNGYSYNNYSRYNNYSNNNQSYNNYNNYSYNTNSYRTGGLGASYSTSSNNVQVTTTMAPSSNGRSISSGYT
 SGRNLYTSGQCTYYVFDRVGGKIGSTWGNASNWANAARAGYTVNNTPKAGAIMQTTQGAYGHVAYVESVNSNGSVRVSE
 MNHYGYGPGVVTSRTISASQAAGYNFIH

SEQ ID NO:7 polypeptide sequence

MKKIATATIATAGIATFAFAHDAQAAEQNNDGYNPNDPYSYSYTYTIDAEGNYHYTWKGNWSPDRVNTSYNNYNNYNNY
 YGYNNYSYNNYNNYNNYNNYQSNNTQSQRRTTQPTGGLGASYSTSSSNVHVTTTTSAPSSNGVSLSNARSASGNLYTSGQ
 CTYYVFDRVGGKIGSTWGNANNWANAARSYTVNNSPAKGAILQTSQGAYGHVAYVEGVNSNGSIRVSEMNHYGHGAGVV

TSRTISASQAASNYIH

SEQ ID NO:8 polypeptide sequence

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DNDKKHKADYEKQGNKYIAQLEKLNNSDKDKFNDIPKEQRAMITSEGAFKYFSKQYGITPGYIWEINTEKQGTPEQMRQA
IEFVKHKLKHLLEVTSVDKKAMESLSEETKKDIFGEVYTD SIGKEGTKGDSYYKMMKSNIETVHGSMK

SEQ ID NO:9 polypeptide sequence

MKKILALAI AFLII LAACGNHSNHEHHSHEGKLVVTTNSILYDMVKRVGGNKVDVHSIVPVGQDPHEYEYVKKPKDIKALT
DADVVFYNGLNLETGNGWFEKALDQAGKSTKDKNVIAASNNVKPIYLNAGEEGNKDKQDPHAWLSLENGIKYVKTIQKSLE
HHDKKDKSTYEKQGNAYISKLEELNKDSKNKFDDIPKNQRAMMTSEGAFKYFAQQFDVKPGYIWEINTEKQGTGQMKQA
IKFVKDNHLKHLLEVTSVDKKAMQSLSEETKKDIYGEVFTD SIGKEGTKGDSYYKMMKSNIETVHGSMK

SEQ ID NO:10 polypeptide sequence

MKKTIMASSLAVALGVTGYAAGTGHQAHA AEVNVDQ AHLVDLAHNHQDQLNAAPIKDGAYDIHFVKDGFQYNFTSNGTTW
SWSYEAANGQTAGFSNVAGADYTTSYNQGSVDQSVSYNAQSSNSNVEAVSAPTYHNYSTSTTSSSVRLSNGNTAGATGSS
AAQIMAQRTGVSASTWAAIIARESNGQVNAYNPSGASGLFQTMPGWGPTNTVDQQINA AVKAYKAQGLGAWGF

SEQ ID NO:11 polypeptide sequence

MKKTVIASTLAVSLGIAGYGLSGHEAHASETTNVDKAHLVDLAQHNPEELNAKPVQAGAYDIHFVDNGYQYNFTSNGSEW
SWSYAVAGSDADYTESSSNQEVSANTQSSNTNVQAVSAPTSSESRSYSTSTTSYSAPSHNYSSHSSSVRLSNGNTAGSVG
SYAAAQMAARTGVSASTWEHIIARESNGQLHARNASGAAGLFQTMPGWGSTGSVNDQINAAYKAYKAQGLSAWGM

SEQ ID NO:12 polypeptide sequence

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QAVALI RTMPQRQQT SRRSNRIQTRSVESRAAEPRSVSDYQANANSSYYVENANDGSGYPVGTYINASSKGAPYNLPTTPW
NTLKASDSKEIALMTAKQTGDGYQWVIKFNKGHAPHQNMIFWFALPADQVPVGR TDFVTVNSDGTNVQWSHGAGAGANKP
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DEKQSIITAFMNKNQNIRGYLASTDPVTVDNNGNVTLHYRDGSSTTL DATNVMTYEPVVKSEYQTANA AKTATVTIAKGQ
SFNIGDIKQYFTLSNGQAI PNGTFTNITS DRTIPTAQEVSQM NAGTQLYHIVASNAYHKDTEDFYISLKIVDVKQPEGDQ
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 SIQAYENAKRAGQTETTTNAQNVINNGDATDQQIAAEKTKVEEKYNSLKQAIAGLTPDLAPLQTAKTQLQNDIDQPTSTTG
 MTSASVAAFNDKLSAARTKIQEIDRVLASHPDVATIRQNVTAANAATAKDQARNGLTVDKAPLENAKNQLQHSIDTQTS
 TTGMTQDSINAYNAKLTAARNKVQQINQVLGASPTVDQINTNTSAANQAKSDDLHARQALTPDKAPLQNAKTQLEQSINQ
 PTDTTGMTTASLNAYNQKLQARQKLTEINQVLNGNPTVQNINDKVAEANQAKDQLNTARQGLTLDRQPALTTLHGASNL
 NQAQQNNFTQQINAAQNHAALETIKSNITALNTAMTKLKDSVADNNTIKSGQNYTDATPANKQAYDNAVNAAKGVIGETT
 NPTMDVNTVNQKAASVKSTKDALDGQONLQRAKTEATNAITHASDLNQAQKNALTTQQVNSAQNVQAVNDIKQTTQSLNTA
 MTGLKRGVANHNQVVQSDNYVNADTNKKNDYNNAYNHANDIINGNAQHPVITPSDVNNALSNVTSKEHALNGEAKLNAAK
 QEANTALGHLNLLNNVQRQNLQSQINGAHQIDAVNTIKQONATNLNSAMGNLRQAVADKQVVKRTEDYADADTAKQNAYS
 AVSSAETIINQNTANPTMSVDDVNRATSAVTTNKNALNGDEKLVSQSKTDAARAIDALPHLNNAQKADVSKINAASNIAGV
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 EAALQRVNTAKDALNGDAKLIAAQNAAKQHLGTLTHITTAQRNDLTNQIS

SEQ ID NO:13 polypeptide sequence

MGNLQTAINDKSGTLASQNFDADEQKRNAVNAQISAAETILNKQTPNTAKTAVEQALNNVNSAKHALNGTQNLNNAKQ
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 VTNAEHIISGTPTVVTPSEVTAAANQVNSAKQELNGDERLRVAKQNANTAIDALTQLNTPQKAKLKEQVGQANRLEDVQ
 SVQTNQSLNNAMKGLRDSIANETTVKASQNYTDASPNQSTYNSAVSNAKGIINQTNPTMDTSAITQATTQVNNAKNG
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 SLNNAMDQLKQAIQGDHDTIVAGGNYTNASPDQKQAYTDAYNAAKNIVNGSPNVITNAADVTAATQRVNNAETSLNGDTNL
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 AYNTAVTSAENIINATSQPTLDPASVTQAANQVNTNKTALNGAQNLANKKQETTANINRLSHLNNAAQKQDLNTQVTNAPN
 ISTVNQVKTKAEQLDQAMERLINGIQDKDQVKQSVNFTDADPEKQTAYNNAVTAAENIINQANGTNANQSQVEAALSTVT
 TTKQALNGDRKVTDAKNNANQTLSTLDNLNNAQKGAVTGNINQAHTVAEVTQAIQTAQELNTAMGNLKNLSLNDKDTTLGS
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 TANHPFNSSTIGHKKKLDEDDIDPLHMRHFSNNFGNVKNAIGVVGISGLLASFWFFIAKRRRKEDEEELEIRDNNKD
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SEQ ID NO:14 polypeptide sequence

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 TENVLAESRASKNDKEKENLQEKDKSQQVHPPLDKNALQAFDASYHNYRMIDRDRADATEYQKVKSTFDYVNDLLGNNQ
 NIPSEQLVSAQQLEKALELARTLPQQSTTEKRGRSTRSVVENRSSRSDYLDARTEYYVSKDDDDSGFPPGTFFFHASNR
 RWPYNLPRSRNILRASDVQGNAYITTKRLKDGQWDILFNSNHKGHEMYWYFGLPSDQTPPTGPVTFITINRDGSSTSTG
 GVGFGSGAPLPQFWRSGAINSSVANDFKHGSATNYAFYDGVNNFSDFARGGELYFDREGATQTNKYYGDENFALLNSEK
 PDQIRGLDTIYSFKGSGDVSYRISFKTQGAPTARLYYAAGARSGEYKQATNYNQLYVEPYKNYRNRVQSNVQVKNRTLHL
 KRTIRQFDPTLQRTTDVPILDSGSGSIDSVYDPLSYVKNVTGTVLGIYPSYLPYNQERWQGANAMNAYQIEELFSQENL
 QNAARSGRPIQFLVGFDVEDSHHNPETLLPVNLYVKPELKHTIELYHDNEKQDRKEFSVSK

SEQ ID NO:15 polypeptide sequence

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 GSGSLRDVNVNLPQGWTKTFTINPNNTTEGTLKLIGNIPSNEAYNTTYHFNITATDNSGNTTNPAKTFILNVGKLADDLN
 PVGLSRDQLQLVTDPSLSNSEREVEVKRKISEANANIRSYLLQNNPILAGVNGDVTFYYRDGSDVIDAENVITYEPERK
 SIFSENGNTNKKEAVITTIARGQNYTIGPNLRKYFSLNGSDLPNRDFTSISAIGSLPSSSEISRLNVGNYNRYVNAKNAY
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 GAHTVQDVHKALLQGIEQILKVNVSIIINQSFNDSLHNFNYLH SKFDARLREKDVANHIVQTETFEVLKGTGVEPGKINK
 ETQQPKLHKNDNDSL FKH LVDNFGKTVGVITLTGLLSSFWLV LAKRRKKEEEEKQSIKNH HKDIRLSDTDKIDPIVITKR
 KIDKEEQIQNDDKHSIPVAKHKKSKEKQLSEEDIHSIPVVKRKQNSDNKDTKQKKVTSKKKKTPQSTKKVVKTKKRSK

SEQ ID NO:16 polypeptide sequence

MRDKKGPVNKRVDFLSNKLNKYSIRKFTVGTASILIGSLMYLGTQQEAEAAENNIENPTTLKDNVQSKEVKIEEVTNKDT
 APQGVEAKSEVTSNKDTIEHEASVKAEDISKKEDTPKEVANVAEVQPKSSVTHNAEAPKVRKARSVDEGSFDITRDSKNV
 VESTPITIQQKEHFEGYGSVDIQKNPTDLGVSEVTRFNVGNESNGLIGALQLKNKIDFSKDFNFKVRVANNHQSNTTGAD
 GWGFLFSKGNAAEYLTNGGILGDKGLVNSGGFKIDTGYIYTSSMDKTEKQAGQGYRGYGA FVKNDSSGNSQMVGENIDKS
 KTNFLNYADNSTNTSDGKFHGQRLNDVILTYVASTGKMRAEYAGKTWETSITDLGLSKNQAYNFLTSSQRWGLNQGINA
 NGWMRTDLKGSEFTFTPEAPKTITELEKKVEEIPFKKERKFNPDLAPGTEKVTREGQKGEKTITPTLKNPLTGEIISKG
 ESKEEITKDPINELTEYGPETIAPGHRDEFDPKLPTGEKEEVPKPGIKNPETGDVVRPPVDSVTKYGPVKGDSIVEKEE
 IPFEKERKFNPDLAPGTEKVTREGQKGEKTITPTLKNPLTGEIISKGESKEEITKDPINELTEYGPETIAPGHRDEFDP
 KLPTGEKEEVPKPGIKNPETGDVVRPPVDSVTKYGPVKGDSIVEKEEIPFKKERKFNPDLAPGTEKVTREGQKGEKTIT

TPTLKNPLTGEIISKGESKEEITKDPINELTEYGPETITPGHRDEFDPKLPKTGEKEEVPKGPGIKNPETGDVVRPPVDSV
TKYGPVKGDSIVEKEEIPFEKERKFNPDLAPGTEKVTREGQKGEKTITPTLKNPLTGEIISKGESKEEITKDPVNELTE
FGGEKIPQGHKIDFDPNLPTDQTEKVPKGPGIKNPDTGKVIEEPVDDVIKHGPKTGTPETKTVEIPFETKREFNPKLQPG
EERVKQEGQPGSKTITTPITVNPILTGEKVGEGQPTTEEITKQPVDKIVEFGGEKPKDPKGPENPEKPSRPTHPSGPVNPNN
PGLSKDRAKPNPGPVHSMKDNDKVKKSKIAKESVANQEKKRAELPKTGLESTQKGLIFSSIIGIAGLMLLARRRKN

SEQ ID NO:17 polypeptide sequence

MGKRRQGPINKKVDFLPNKLNKYSIRKFTVGTASILLGSTLIFGSSSHEAKAAEEKQVDPITQANQNDSSERSLENTNQPTVNNEAPQMSSTLQAEEGSNAEAPNVPTIKANSNDNDTQTQFSEAPTRNDLARKEDIPAVSKNEELQSSSQPNTDSKIEPTTSEPVLNLNYSSPFFMSLLSMPADSSSNNTKNTIDIPPTTVKGRDNYDFYGRVDIQSNPTDLNATNLTRYNYGQPPGTTTAGAVQFKNQVSFDKDFDFNIRVANNRQSNTTGADGWGFMFSKKDGGDFLKNGGILREKGTPSAAGFRIDTGYNNNDPLDKIQKQAGQGYRGYGTFFVKNDSSQGNTSKVGSSTPSTDFLNYADNTTNDLDGKFHGGQKLNNVNLKYNASNQTFATYAGKTWTATLSELGLSPTDSYNFLVTSSQYGNNGNSGTYADGVMRADLDGATLTYTPKAVDGDPITSTKEIPFNKKREFDPNLAPGTEKVVQKGEPGIETTTTPTYVNPNTGEKVGEGTPTTKITKQPVDEIVHYGGEEIKPGHKDEFDPNAPKGSQTTQPGKPGVKNPDTGEVVTTPPVDDVTKYGPVDGDPITSTEEIPFDKKREFNPDLKPGEERVVKQKGEPGTKTITPTTKNPLTGEKVGEGEPTTEKITKQPVDEITEYGGEEIKPGHKDEFDPNAPKGSQEDVPGKPGVKNPDTGEVVTTPPVDDVTKYGPVDGDPITSTEEIPFDKKREFDPNLAPGTEKVVQKGEPGTKTITPTTKNPLTGEKVGEGEPTTEKITKQPVDEIVHYGGEEIKPGHKDEFDPNAPKGSQEDVPGKPGVKNPDTGEVVTTPPVDDVTKYGPVDGDPITSTEEIPFDKKREFNPDLKPGEERVVKQKGEPGTKTITPTTKNPLTGEKVGEGEPTTEKVTKQPVDEIVHYGGEEIKPGHKDEFDPNAPKGSQEDVPGKPGVKNPDTGEVVTTPPVDDVTKYGPVDGDPITSTEEIPFDKKREFDPNLAPGTEKVVQKGEPGTKTITPTTKNPLTGEKVGEGEPTTEKITKQPVDEIVHYGGEEIKPGHKDEFDPNAPKGSQTTQPGKPGVKNPDTGEVVTTPPVDDVTKYGPVDGDPITSTEEIPFDKKREFDPNLAPGTEKVVQKGEPGTKTITPTTKNPLTGEKVGEGEPTTEKITKQPVDEIVHYGGEEIQPGHKDEFDPNAPVDSKTEVPGKPGVKNPDTGEVVTTPPVDDVTKYGPVKGNPITSTEEIPFDKKRVFNPDLPKGEERVVKQKGEPGTKTITPTILVNPITGEKVGEGKSTEVTKQPVDEIVEYGPTKAEPGKPAEPGKPAEPGKPAEPGTPAEPGKPAEPGKPAEPGKPAEPGKPAEPGTPAEPGKPAEPGKPAEPGTPAEPGKPAEPGTPQSGAPEQPNRSMHSTDNKNQLPDTGENRQANEGTLVGSLLAIVGSLFIFGRRKKGNEK

SEQ ID NO:18 polypeptide sequence

MKKLYTSYGTYGFLHQIKINNP¹THQLFQFSASDTSVIFEETDGETVLKSPSIYEVIKEIGEFSEHHFYCAIFIPSTEDHAYQLEKKLISVDDNFRNFGGFKSYRLLRPAKGTTYKIYFGFADRHAYEDFKQSDAFNDHFSKDALSHYFGSSGQHSSYFER
YLYPIKE

SEQ ID NO:19 polypeptide sequence

MYLYTSYGTQFLNQIKLNHQERSLQFSTNDSSIILEESEGKSILKHPSAYQVIDSTGEFNEHHFYSAIFVPTSEDHRQ
QLEKKLLLVDPVPLRNFGGFKSYRLLKPTEGSTYKIYFGFANRTAYEDFKASDIFNENFSKDALSQYFGASGQHSSYFERY
LYPIEDH

SEQ ID NO:20 polypeptide sequence

MINRDNKKAITKKGMISNRLNKF SIRKYTVGTASILVGTTLIFGLGNQEA KAAENTSTENAKQDDATTS DNKEVVSETEN
NSTTENDSTNPIKKETNTDSQPEAKEESTTSSTQQQQNNVTATTETKPQNI EKENVKPSTDKTATEDTSVILEEKKAPNY
TNNDVTTK PSTSEIQTKPTTPQESTNIENSQPQPTPSKVDNQVTDATNPKEPVNVSKEELKNNPEKLKELVRNDNNTDRS
TKPVATAPTSVAPKRLNAKMRFAVAQPAAVASNNVNDLITVTKQTIKVG DGKDNVAAAHDGKDIEYDTEFTIDNKVKKGD
TMTINYDKNVIPSDLTDKNDPIDITDPSGEVIAKGTFDKATKQITYTFTDYVDKYEDIKARLTLYSYIDKQAVPNETSLN
LTFATAGKETSQNVSVDYQDPMVHGDSNIQSIFTKL DENKQTI EQQIYVNPLKKTATNTKVDIAGSQVDDYGNIKLGNGS
TII DQNT EIKVYKVNPNQQLPQSNRIYDFSQYEDVTSQFDNKKSF SNNVATLDFGDINSAYIIKVVSKYTP TSDGELDIA
QGTSMR TTDKYGYNYAGYSNFIVTSNDTGGGDGT VKPEEKLYKIGDYVWEDVDKDG VQG TDSKEKPMANVLVTLTYPDG
TTKSVRTDANGHYEFGGLKDGETYTVKFETPAGYLP TKVNGTTDGEKDSNGSSITV KINGKDDMSLDTGFYKEPKYNLGD
YVWEDTNKDGIQDANEPGIKDVKVTLKDSTGKVI GTTTTTDASGKYKFTDL DNGNYTVEFETPAGYTPTVKNTTAEDKDSN
GLTTTGVIKDADNMTLDSGFYKTPKYS LGDYVWYDSNKGKQDSTEKGIKDVKVTL LNEKGEVIGTTKTDENGKYRFDNL
DSGKYKVI FEKPAGLTQTVTNTTEDDKDADGGEVDVTITDHDDFILDNGYFEEDTSDSDSDSDSDSDSDSDSDSDSDSDSDS
SDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDS
SDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDAGKHTPVKPMSTTKDHHNKAKALPETGSENNGSNNATLFGGLFAALGSLLLFGRRKKONK

SEQ ID NO:21 polypeptide sequence

MINKKNNLLTKKKPIANKSNKYAIRKFTVGTASIVIGATLLFGLGHNEAKAEENSVQDVKDSNTDDELSDSNDQSSDEEK
NDVINNNQSINTDDNNQIIKKEETNNYDGIKRSERTESTTNVDENEATFLQKTPQDNTHLTEEEVKESSSVSSNSSI
DTAQQPSHTTINREESVQTSNVEDSHVSDFANSKIKESNTESGKEENTIEQPNKVKEDSTTSQPSGYTNIDEKISNQDE
LLNLPINEYENKARPLSTTSAOPSIKRVTVNOLAAEOGSNVNHLIKVTDOSITEGYDDSEGVIIKAHDAENLIYDVTFEVD

[illegible]

SEQ ID NO:22 polypeptide sequence

MSNNFKDDFEKNRQS IDTNSHQDHTEDVEKDQSELEHQDTIENTEQQFPFPRNAQRRKRRRDLATNHNKQVHNESQTSEDN
VQNEAGTIDDRQVESSHSTESQEPHQDSTPQHEEEYYNKNFAFAMDKSHPEPIEDNDKHETIKDAENNTEHSTVSDKSIA
EQSQQPKPYFATGANQANTSKDKHDDVTVKQDKDESKDHHSGKKGAAGAGTAGVAGAAGAMGVSKAKKHSNDAQNKSNS
DKSNNSTEDKASQDKSKDHHNGKKGAAGAGTAGLAGGAASKSASASASKPHASNNASQNHDEHDNHDRDKERKKGGMAKV
LLPLIAAVLIIGALAI FGGMALNNHNNGTKENKIAN TNKNNADESKDKDTSKDASKDKSKSTDSKSKEDQDKATKDESD
NDQNNANQANNQAQNNQNQQQANQNQQQQQQQRQGGGQRHTVNGQENLYRIAIQYYGSGSPENVEKIRRANGLSGNNIRNG
QQIVIP

SEQ ID NO:23 polypeptide sequence

MIELIKMEGMIVVSNNNFKDDFEKNRQSINPDEQQTELKEDDKTNENKKEADSQNSLSNNSNQQFPPRNAQRRKRRRETA
TNQSKQQDDKHQKNSDAKTTEGSLDDRYDEAQLQQQHDKSQQQNKTEKQSQDNRMKDGDAAIVNGTSESPEHKSSTQN
RPGPKAQQQRKSESTQSKPSTNKDKKAATGAGIAGAAGVAGAAETSKRHHNKKDKQDSKHSNHENDEKSVKNDDQKQSK
KGKKA AVGAGAAAGVGAAGVAHHNNQNKHHNEEKNSNQNNQYNDQSEGKKKGGFMKILLPLIAAILILGAI AIFGGMALN
NHNDSSDDQKIANQSKKDSKDKDGAQSEDNKDKKSDSNKDKKSDSDKNADDDSDNSSSNPNATSTNNNDNVANNNSNYT
NQNQQDNANQNSNNOQATQGQQSHTVYGQENLYRIA IQYYGEGTQANVDKI KRANGLSSNNIHNQTLV I PQ

SEQ ID NO:24 polypeptide sequence

MKNKLIAKSLLTIAAIGITTTTIASTADASEGYGPREKKPVSINHNIVEYNDGTFKYQSRPKFNSTPKYIKFKHDYNILE
FNDGTFEYGARPQFNKPAAKTDATIKKEQKLIQAQNLVREFEKTHTVSAHRKAQKAVNLVSFEYKVKMVLQERIDNVLK
OGLVR

SEQ ID NO:25 polypeptide sequence

MKTRIVSSVTTLLLSILMNPVANAADSDINIKTGTDIGSNTTVKTGDLVITYDKENGMHKKVFYFSFIDDKNHNKKLLV
 IRTKGTIAGQYRVYSEEGANKSGLAWPSAFKVQLQLPDNEVAQISDYYPNSIDTKEYMSTLTYGFNGNVTGDDTGKIGG
 LIGANVSIGHTLK YVQPDFKTILESP TDKKVGWKVIFNNMVNQNWGPYDRDSWNPVYGNQLFMKTRNGSMKAAENFLDPN
 KASSLLSSGFS PDFATVITMDRKASKOQTNI DVIYERVRDDYQLHWTSTNWKGTNTKDKWTD RSSERYKIDWEKEEMTN

SEQ ID NO:26 polypeptide sequence

MMHKNKYISKLLVGAATITLATMISNGEAKASENTQQTSTKHQTTQNNYVTDQQKAFYQVLHLKGITEEQRNQYIKTLRE
HPERAQEVFSESLKDSKNPDRRVAQQNAFYNVLKNDNLTEQEKNNYIAQIKENPDRSQQVWVESVQSSKAKERQNIENAD
KAIKDFQDNKAPHDKSAAYEANSKLPKDLRDKNNRFVEKVSIEKAIVRHDERVKSANDAI SKLNEKDSIENRRLAQREVN
KAPMDVKEHLQKQLDALVAQKDAEKKVAPKVEAPQIQSPQIEKPKAESPKVEVPQSKLLGYYQSLKDSFNYYGYKYLTDTY
KSYKEKYDTAKYYYNTYYKYKGAIDQTVLTVLGS GSKSYIQPLKVDDKNGYLAKSYAQVRNYVTESINTGKVLTYTFYQNP
TLVKTAIKAQETASSIKNTLSNLLSFWK

SEQ ID NO:27 polypeptide sequence

MTKHYLNSKYQSEQRSSAMKKITMGTAIIILGSLVYIGADSQQVNAATEATNATNNQSTQVSOATSQPINFQVQKDGSSSE
KSHMDDYMQHPGKVIKQNNKYYFQTVLNNASFWKEYKFYNANNQELATTVVNDNKKADTRTINVAVEPGYKSLTTKVHIV
VPQINYNHRYTTTHLEFEKAIPTLADAAKPNNVKPVQPKPAQPKTPTEQTKPVQPKVEKVKPTVTTTTSKVEDNHSTKVVST
DTTKDQTKTQTAHTVKTAQTAQEONKVQTPVKDVATAKSESNNQAVSDNKSQQTNKVTKHNETPKQASKAKELPKTGLTS
VDNFISTVAFATLALLGSLSLLLFKRKESK

SEQ ID NO:28 polypeptide sequence

MNKQQKEFKSFYSIRKSSLGVASVAISTLLLLMSNGEAQAAAEETGGTNTEAQPKTEAVASPTTTSEKAPETKPVANAVS
VSNKEVEAPTSETKEAKEVKVKAPKETKAVKPAAKATNNTYPILNQELREAIKNPAIKDKDHSAPNSRPIDFEMKKENG
EQQFYHYASSVKPARVIFTDSKPEIELGLOSGOFWRKFVYEGDKKLPIKLVSYDTVKDYAYIRFSVSNNGTKAVKIVSST

HFNNKEEKYDYTLMEFAQPIYNSADKFKTEEDYKA EKLLAPYKAKT LERQVYELNKIQDKLPEKLKAEYKKKLEDTKKALDEQVKS AITEFQNVQPTNEKMTDLQDTKYVVYESVENNESMMDTFVKHPIKTGMLNGKKYMMETTND D YWKDFMVEGQ RVRTISKDAKNNTRTII FPYVEGKTLYDAIVKVHVKTIDYDGYHVRIVDKEAFTKANTDKSNKKEQQDNSAKKEATPATPSKPTPSPVEKESQKQDSQKDDNKQLPSVEKENDASSESGKDKTPATKPTKGEVESSTTPTKVVSTTQNVAKPTTASSKTTKD VVQTSAGSSEAKDSAPLQKANIKN TNDGHTQSQNKN TQENKAKSLPQTGEESNKDMTLPLMALLALSSIVAFVLP RKRKN

SEQ ID NO:29 polypeptide sequence

[illegible]

SEQ ID NO:30 polypeptide sequence

[illegible]

SEQ ID NO:31 polypeptide sequence

MKNNLRYGIRKHKLGAA SVFLGTMIVVGMGQDKEAAASEQKTTTVEENGNSATDNKTSETQTTATNVNHI EETQSYNATV
 TEQPSNATQVTTTEEAPKAVQAPQTAQPANVETVKEEEKPQVKETTQPDNSGNQRQVDLTPKKVTQNOGTETQVEVAQPR
 TASESKPRVTRSADVAEAKEASDVSEVKGTDVTSKVTVESGSI EAPQGNKVEPHAGQRVVLKYKLFADGLKRGDYFDFT
 LSNNVNTYGVSTARKVPEIKNGSVVMATGEILGNGNIRYFTTNEIEHKVEVTANLEINL FIDPKTVQSNGEQKITSKLNG
 EETEKTI PVVYNPGVSN SYTNVNGS IETFNKESNKFTHIAYIKPMNGNQSN TVSVTGTLTEGSNLAGGQPTVKVYEYL GK
 KDEL PQSVYANTSDTNKFKDVT KEMNGKLSVQDN GSYSLNLDKLDKTYVIHYTGEY LQGS DQVNFRT ELYGYPERAYKSY
 YVYGGYRLTWDNGLVLVYSNKADGNGKNGQIIQDNDFEYKEDTAKGTMSGQYDAKQII ETEENQDNTPLDIDYHTAIDGEG
 GYVDGYIETIEETDSSAIDIDYHTAVDSEVGHVGGYTESSES ESNPIDFEESTHENS KHHADVVEYEEDTNPGGGQVTTES
 NLVEFDEESTKGIVTGAVSDHTTIEDTKEYTTESNLIELVDELPEEHGQAQGPIEEITENNNHHISHSGLGTENGHGNYGV
 IEEIEENSHVDIKSELGYEGGQNSGNQSFEEDTEEDKPKYEQGGNIVDIDFDSVPQI HGQNKGDQSFEEDTEKD KPKYEH
 GGNIIDIDFDSVPQI HGFNKHNEIIEEDTNKD KPNYQFGGHNSVD FEEDTLPKVSGQNEGQQTIEEDTTPPTPPTPEVPS
 EPETPMPPTPEVPSEPETPTPPTPEVPSEPETPTPPTPEVPSEPETPTPPTPEVPSEPETPTPPTPEVPAEPGKVP PPAK
 EEPKKPSKPVEOGKV VTPVIEINEKV KAVAPT KKAOSKKSEL PETGGEESTNKGMLFGGLFSILGLALLRRNKKNNKA

SEQ ID NO:32 polypeptide sequence

MKKRIDYLSNKQNKYSIRRFTVGTTSVIVGATILFGIGNHQAQASEQSNDDTTQSSKNNASADSEKNNMIETPQLNTTAND
 TSDISANTNSANVDSTTKPMSTQTSNTTTTTEPASTNETPQPTAIKNQATAAKMQDQTPVQEQANSQVDNKTNDANSIATN
 SELKNSQTLDPQSSPQTISSNAQGTSKPSVRTRAVRSLAVAEPVVNAADAKGTNVNDKVTASNFKLEKTTTFDPNQSGNTF
 MAANFTVTDKVKSGDYFTAKLPDSLTTGNGDGDYSSNSNNTMPIADIKSTNGDVVAKATYDILTCKTYTFVFTDYVNNKENIN
 GQFSLPLFTDRAKAPKSGTYDANINIADEMFNNKITYNYSSPIAGIDKPNGANISSQIIGVDTASGQNTYKQTVFVNPQKQ
 RVLGNTWVYIKGYQDKIEESSGKVSATDTKLRIFEVNDTSKLSDSYADPNDSNLKEVTDQFKNRIYYEHPNVAISIKFGD
 ITKTYVVLVEGHYDNTGKNLKTQVIQENVDPVTNRDYSIFGWNNENVVRYGGGSADGDSAVNPKDPTPGPPVDPEPSDP
 EPEPTPDPEPSDPPEPEPSDPDPDSDSDSDSGSDSDSGSDSDSESDSDSDSDSDSDSDSDSDSESDSDSESDSDSDSDSDSDS
 DSDSDSESDSDSDSDSDSDSDSDSESDSDSESDSESDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSESDSDSDS

MNKHHPKLRSFY S IRKSTLGVASVIVSTLFLITSQHQAQAAENTNTSDKISENQNNNATT
TQPPKDTNQTPATQPANTAKNYPAADESLKDAIKDPALENKEHDIGPREQVNFQLLDKN
NETQYYHFFS I KDPADVYYTKKKA EVELDINTASTWKKKFEVYENNQKLPVRLVSYSPVPE
DHAYIRFPVSDGTQELKIVSSTQIDDGEETNYDYTKLVFAKPIYNDPSLVKSDTNDVVT
NDQSSSVASNQTNTNTSNQNISTINNANNQPQATTNMSQPAQPKSSTNADQASSQPAHET
NSNGTNDKTNNESSNQSDVNQQYPPADESLQDAIKNPAIIDKEHTADNWRPIDFQMKNDK
GERQFYHYASTVEPATVIFTKTGP I IELGLKTASTWKKKFEVYEGDKKLPVELVSYDSDKD

YAYIRFPVSNGTREVKIVSSIEYGENIHEDYDYTLMVFAQPITNNPDDYVDEETYNLQKL
LAPYHKAKTLERQVYELEKLQEKLPEKYKA EYKKKLDQTRVELADQVKS AVTEFENVTP
NDQLTDLQEAHFVVFES EENSESVM DGFVEHPFYTATLNGQKYVVMKTKDDSYWKDLIVE
GKRVTTVSKDPKNNSRTLIFPYIPDKAVYNAIVKV VVANIGYEGQYHVRIINQDINTKDD
DTSQNN TSEPLNVQ TGQEGKVADTDVAENSSTATNPKDASDKADVIEPESDVVKDADNNI
DKDVQHDVDHLS DMSDNNHFDKYDLKEMDTQIAKDTDRNVDKDADNSVGMSSNVDTDKDS
NKNKDKVIQLNHIADKNNHTGKAAKLDVVKQNYNNTDKVTDKKTTEHLPSDIHKTVDKTV
KTKEKAGTPSKENKLSQSKMLPKTGETTSSQSWWGLYALLGMLALFIPKFRKESK

SEQ ID NO:70 polypeptide sequence

MAETTQDQTTNKNVLD SNKVKATTEQAKAEVKNPTQNI SGTQVYQDPAIVQPKTANNKTG
NAQVSQKVDTAQVNGDTRANQSATTNNTQPVAKSTSTTAPKTNTNVTNAGYSLVDDDDN
SENQINPELIKSAAKPAALETQYKTAAPKAATTSAPKAKTEATPKVTTFSASAQPRSVAA
TPKTS LPKYKPQVNSSINDYICKNNLKAPKIEEDYTSYFPKYAYRNGVGRPEGIVVHDTA
NDRSTINGEISYMKNNYQNAFVHAFVDGDR I IETAPTDYLSWGVGAVGNPRFINVEIVHT
HDYASFARSMNNYADYAATQLQYYGLKPD SAEYDGN GTVWTHYAVSKYLGGTDHADPHGY
LRSHNYSYDQLYDLIN EKYL IKMGKVAPWGTQSTTTPTTPSKPTTPSKPSTGKLTVAANN
GVAQIKPTNSGLYTTVYDKTGKATNEVQKTFAVSKTATLGNQKFYLVQDYN SGNKFGWVK
EGDVVYNTAKSPVNVNQSY SIKPGTKLYTVPWGTSKQVAGSVSGSGNQTFKASKQQQIDK
SIYLYG SVNGKSGWVSKAYLVDTAKPTPTPTPKPSTPTTNNKLTVSSLNGVAQINAKNNG
LFTTVYDKTGKPTKEVQKTFAVTK EASLGGNKFYLVKDYN SPTLIGWVKQGDVIYNNAKS
PVNVMQTYTVKPGTKLYSVPWGTYKQEAGAVSGTGNQTFKATKQQQIDKSIYLF GTVNGK
SGWVSKAYLAVPAAPKKAVAQPKTAVK

SEQ ID NO: 71 polypeptide sequence

MAYTVTKPQTTQT VSKIAQVKPNNTGIRASVYEKTAKNGAKYADRTFYVTKERAHGNETY
VLLNNTSHNIP LGWFNVKDLNVQNLGKEVKTTQKYTVNKSNNGLSMVPWGTKNQVILTGN
NIAQGT FNATKQVSVGKD VYLYGTINNRTGWN AKDLTAPTAVKPTTSAAKDYN TYVIK
NGNGYYYVTPNSDTAKYSLKAFNEQPF AVVKEQVINGQ TWYYGKLSNGKLAWIKSTD LAK
ELIKYNQTGMTLNQVAQIQAGLQYKPQVQRVPGK WTDAKFNDVKHAMDTKRLAQDPALKY
QFLRLDQPQNISIDKINQFLKGKGVLENQGAAFNKAAQMYGINEVYLISHALLETGNGTS
QLAKGADV VNNKVV TNSNTKYHNVFGIAAYDNDPLREGIKYAKQAGWDTVSKAIVGGAKF
IGNSYVKAGQNTLYKMRWNP AHPGTHQYATDVDWANINAKIIKGY YDKIGE V GK YFDIPQ
YK

SEQ ID NO:72 polypeptide sequence

DRVLASHPDVATIRQNVTAANA AKSALDQARNGLTVDKAPLEN AKNQLQHSIDTQTSTTG
MTQDSINAYNAKLTAARNKIQQINQVL AGSPTVEQINTNTSTANQAKSDLDHARQALTPD
KAPLQTAKTQLEQSINQPTD TTGMTTASLNAYNQKLQAARQKLTEINQVLNGNPTVQNIN
DKVTEANQAKDQLNTARQGLTLDRQPALTTLHGASNLNQAQQNNFTQQINAAQNHA ALET
IKSNITALNTAMTKLKDSVADNNTIKSDQNYTDATPANKQAYDNAVNAAKGVIGETTNP
MDVNTVNQKAASVKSTKDALDGQQLQRAKTEATNAITHASDLNQAQKNALTQQVNSAQN
VQAVNDIKQTTQSLNTAMTGLKRGVANHNQVVQSDNYVNADTNKKNDYNNAYNHANDIIN
GNAQHPVITPSDVNNALSNVTSKEHALNGEAKLNAAKQEANTALGHLNNLNNAQRQNLQS
QINGAHQIDAVNTIKQNATNLNSAMGNLRQAVADKDQVKRTEDYADADTAKQNAYNSAVS
SAETIINQTTNP TMSVDDVNRATS AVTSNKNALNGYEKLAQSKTDAARAIDALPHLNNAQ
KADV KSKINAASNIAGVNTVKQQGTDLNTAMGNLQGA INDEQTTLNSQNYQDATPSKKTA
YTNAVQAAKDILNKSNGQNKT KDQVTEAMNQVNSAKNNLDGTRLLD

SEQ ID NO: 73 polypeptide sequence

ASTQHTVQSGESLWSIAQKYNTSVESIKQNNQLDNNLVFPGQVISVGGSDAQNTSNTSPQ
AGSASSHTVQAGESLNI IASRYGVSV DQLMAANNLRGYLIMP NQTLQIPNGGSGGTTPTA
TTGSNGNASSFNHQNL YTAGQCTWYVFD RRAQAGSPISTYWSDAKYWAGNAANDGYQVNN
TPSVGSIMQSTPGPYGHVAYVERVNGDGSILISEMNYTYGPYNNMNYRTIPASEVSSYAFI
H

SEO ID NO: 74 polypeptide sequence

[illegible]

SEQ ID NO: 75 polypeptide sequence

MNLLKKNKYSIRKYKVGIFSTLIGTVLLLSNPNGAQALTTDNNVQSDTNQATPVNSQDKD
 VANNRGLANSAQNTPNQSATTNQATNQALVNHNGSIVNQATPTSVQSSTPSAQNNNHTD
 GNTTATETVSNANNNDVVSNN TALNVPTKTNENGSGGHLTLKEIQEDVRHSSNKPELVAI
 AEPASNRPKKRSRAAPADPNATPADPAAAAVGNNGGAPVAITAPYTPTTDPNANNAGQNA
 PNEVLSFDDNGIRPSTNRSVPTVNVVNNLPGFTLINGGKVGVF SHAMVRTSMFDSGDNKN
 YQAQGNVIALGRIHGTDTNDHGDFNGIEKALTVNPNSELIFEFNTMTTKNGQGATNVI I K
 NADTNDTIAEKTVEGGPTLRLFKVPDNVRNLKIQFVPKNDAITDARGIYQLKDGYKYYSF
 VDSIGLHSGSHVFVERRTMDPTATNNKEFTVTTSLKNNGNSGASLDTNDFVYQVQLPEGV
 EYVNNSLTKDFPSNNSGVDVNDMNVTYDAANRVITIKSTGGGTANS PARLMPDKI LD LRY
 KLRVNNVPTPRTVTFNETLTYKTYTQDFINSAAESHTVSTNPYTI DIIMNKDALQAEVDR
 RIQQADYTFASLDIFNGLKRRRAQTILDENRNNVPLNKRVSQAYIDS LTNQM QHTLIRSVD
 AENAVNKKVDQMEDLVNQND ELTDEEKQAAIQVIEEHKNEIIGNIGDQTTDDGVTRIKDQ
 GIQTLSGDTATPVVKPNAKKAIRD KATKQREIINATPDATEDEIQDALNQLATDETDAID
 NVTNATTNADVETAKNNGINTIGAVVPQVTHKKAARDAINQATATKRQQINSNREATQEE
 KNAALNELTQATNHALEQINQATTNANVDNAKGDGLNAINPIAPVTVVKQAARDAVSHDA
 QQHIAEINANPDATQEERQAAIDKVNAAVTAANTNILNANTNADVEQVKTNAIQGIQAIT
 PATKVKTDAKNAIDKSAETQHNTIFNNNDATLEEQQAAQQLLDQAVATAKQNI NAADTNQ
 EVAQAKDQGTQNI VVIQPATQVKTDTRNVVNDKAREAITNINATTGATREEKQEA INRVN
 TLKNRALTDIGVTSTTAMVNSIRDDAVNQIGAVQPHVTKKQTATGVLNDLATAKKQEINQ
 NTNATTEEKQVALNQVDQELATAINNINQADTNAEVDQAQQLGTKAINAIQPNIVKKPAA
 LAQINQHYNAKLAEINATPDATNDEKNAAINTLNQDRQQAIESIKQANTNAEVDQAATVA
 ENNIDAVQVDVVKKQAARDKITA EVAKRIEAVKQTPNATDEEEKQAAVNQINQLKDQAINQ
 INQNQTNDQVDTTTNQAVNAIDNVEAEVVIKTKAIADIEKAVKEKQQQIDNSLDSTDNEK
 EVASQALAKEKEKALAAIDQAQTNSQVNQAATNGVSAIKIIQPETKVKPAAREKINQKAN
 ELRAKINQDKEATAEERQVALDKINEFVNQAMTDITNNRTNQVDDTTSQALDSIALVTP
 DHIVRAAARDAVKQQYEAKKREIEQAEHATDEEEKQVALNQLANNEKRALQNIDQAIANND
 VKRVETNGIATLKG VQPHIVIKPEAQQA IKASAENQVESIKDTPHATVDELDEANQLISD
 TLKQAQQEIENTNQDAAVTDVRNQTIKAIIEQIKPKVRRKRAALDSIEENNKNQLDAIRNT
 LDTTQDERDVAIDTLNKIVNTIKNDIAQNKTNAEVDRTETDGNDNIKVILPKVQVKPAAR
 QSVGVKAEAQNALIDQSDLSTEEERLAAKHLVEQALNQ AIDQINHADKTAQVNQDSINAQ
 NIISKIKPATTVKATALQQIQNIATNKINLIKANNEATDEEQNIAIAQVEKELIKAKQQI
 ASAVTNADVAYLLHDEKNEIREIEPVINRKASAREQLTTLFNDKKQAIEANIQATVEERN
 SILAQLQNIYDTAIGQIDQDRSNAQVDKTASLNLQTIHDL DVHPIKKPDAEKTINDDLAR
 VTALVQNYRKVSNRNKADALKAITALKLQMD EELKTARTNADVDAVLKRFNVALSDIEAV
 ITEKENSLLRIDNIAQQTYAKFKAIATPEQLAKVKVLIDQYVADGNRMIDEDATLNDIKQ
 HTQFIVDEILAIKLPAEATKVPSPKEIQPAPKVCTPIKKEETHESRKVEKELPNTGSEGMD
 LPLKEFALITGAALLARRRTKNEKES

SEQ ID NO: 76 polypeptide sequence

EENSVQDVKDSNTDDELSDSNDQSSDEEKNDVINNNOSINTDDNNOIIKKEETNNYDIE

KRSEDRTTESTTNVDENEATFLQKTPQDNTHLTEEEVKESSSVESNSSIDTAQQPSHTTI
 NREESVQTSNDVEDSHVSDFANSKIKESNTESGKEENTIEQPNKVKEDSTTSQPSGYTNI
 DEKISNQDELLNLPINEYENKARPLSTTSAQPSIKRVTVNQLAAEQGSNVNHLIKVTDQS
 ITEGYDDSEGVKAHDAENLIYDVTFEVDKVKSGDTMTVDIDKNTVPSDLTDSFTIPKI
 KDNSGEIIATGTYDNKNKQITYTFTDYVDKYENIKAHLKLTSYIDKSKVPNNNTKLDVEY
 KTALSSVNKTITVEYQRPENRTANLQSMFTNIDTKNHTVEQTIYINPLRYSAKETNVNI
 SGNNGDEGSTIIDDSTIIKVYKVGDNQNLPDSNRIYDYSEYEDVTNDDYAQLGNNNDVNIN
 FGNIDSPYIIKVISKYDPNKDDYTTIIQQTVTMQTTINEYTGFEFRTASYDNTIAFSTSSGQ
 GQGDLPPEKTYKIGDYVWEDVDKDGIQNTNDNEKPLSNVLVTLTYPDGTSKSVRTDEDGK
 YQFDGLKNGLTYSKITFETPEGYTPTLKHSNTPALDSEGNVWVTINGQDDMTIDSGFYQ
 TPKYSLGNYVWYDTNKGDIQGDDEKGISGVKVTLDENGNIISTTTTDENGKYQFDNLNS
 GNYIVHFDKPSGMTQTTTDSGDDDEQDADGEEVHVTITDHDDFSIDNGYYDDE

SEQ ID NO: 87 polypeptide sequence

MINRDNKKAITKKGMISNRLNKF SIRKYTVGTASILVGTTLIFGLGNQEAKAAENTSTEN
 AKQDDATTSNDKEVVSETENNSTTENDSTNPIKKETNTDSQPEAKEESTTSSTQQQQNNV
 TATTETKPQNIKENVKPSTDKTATEDTSVILEEKKAPNYTNNDVTTKPSTSEIQTTPPT
 PQESTNIENSQPQPTPSKVDNQVTDATNPKEPVNVSKEELKNNPEKLKELVRNDNNTDRS
 TKPVATAPTSVAPKRLNAKMRFAVAQPAVASNNVNDLITVTKQTIKVGDKDNVAAAH
 GKDI EYDTEFTIDNKVKKGDTMTINYDKNVIPSDLTDKNPIDITDPSGEVIAKGTFDKA
 TKQITYTFTDYVDKYEDIKARLTLYSYIDKQAVPNETSLNLT FATAGKETSQNVSVDYQD
 PMVHGDSNIQSIFTKLDENKQTI EQQIYVNPLKKTATNTKVDIAGSQVDDYGNIKLGNGS
 TIIDQNT EIKVYKVNPNQQLPQSNRIYDFSQYEDVTSQFDNKKSFNNVATLDFGDINSA
 YIIKVVS KYTPTSDGELDIAQGTSMRTTDKYGYNYAGYSNFIVTSNDTGGGDGTVKPEE
 KLYKIGDYVWEDVDKGVQGTDSKEKPMANVLVTLTYPDGTTKSVRTDANGHYEFGGLKD
 GETYTVKFETPAGYLP TKVNGTTDGEKDSNGSSITVKINGKDDMSLDTGFYKEPKYNLGD
 YVWEDTNKDG IQDANE PGIKDVKVTLLKDS TGKVI GTTTT DASGKYKFTDL DNGNYTVEFE
 TPAGYTPTVKNTTAEDKDSNGLTTTGVIKDADNMTLDSGFYKTPKYS LGDYVWYDSNKDG
 KQDSTEKG IKDVKVTLLNEKGEVIGTTKTDENGKYRFDNLDSGKYKVI FEKPAGLTQTVT
 NTTEDDKDADGGEVDVTITDHDDFIL DNGYFEEDTSDSDSDSDSDSDSDSDSDSDSDSDS
 DSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDS
 DSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDS
 DAGKHTPVKPMSTTKDHHNKAKALPETGSENNGSNNATLFGGLFAALGSLLLFGRRKKQN
 K

SEQ ID NO: 89 polypeptide sequence

MLNRENKTAITRKG MVSNRLNKF SIRKYTVGTASILVGTTLIFGLGNQEAKAAESTNKEL
 NEATTSASDNQSSDKVDMQQLNQEDNTKNDNQKEMVSSQGNETTSNGNKLIEKESVQSTT
 GNKVEVSTAKSDEQASPKSTNEDLNTKQ TISNQEALQPD LQENKSVVNVQPTNEENKKVD
 AKTESTTLNVKSDAIKSND ETLVDNNSNSNNENNADIILPKSTAPKRLNTRMRIA AVQPS
 STEAKNVNDLITSNTTLTVVDADKNNKIVPAQDYLSLKSQITVDDKVKSGDYFTIKYSDT
 VQVYGLNPEDIKNIGDIKDPNNGETIATAKHDTANNLITYTFTDYVDRFNSVQMGINYSI
 YMDADTIPVSKNDVEFNVTIGNTTTKTTANI QYPDYVVNEKNSIGSAFTETVSHVGNKEN
 PGYYKQTIYVNPSENSLTNAKLKVQAYHSSYPNNIGQINKDVTDIKIYQVPKGYTLNKG
 YDVNTKELTDVTNQYLQKIT YGDNNSAVIDFGNADSAYVVMVNTKFQYTNSESPTLVQMAT
 LSSTGNKSVSTGNALGFTNNQSGGAGQEVYKIGNYVWEDTNKNGVQELGEKGVGNVTVTV
 FDNNTNTKVGEAVTKEDGSYLIPNL PNGDYRVEFSNLPKGYEVTSPSKQGNNEELDSNGLS
 SVITVNGKDNLSADLGIYKPKYNLGDYVWEDTNKNGIQDQDEKGISGVTVTLKDENG NVL
 KTVTTDADGKYKFTDL DNGNYKVEFTTPEGYTPTTVTSGSDIEKDSNGLTTTGVI NGADN
 MTLDSGFYKTPKYNLGN YVWEDTNKDGKQDSTEKGISGVTVTLKNENGEVLQTTKTDKDG
 KYQFTGLENGTYKVEFETPSGYTPTQVGSGTDEGIDSNGTSTTGVIKDKDNDTIDSGFYK
 PTYNLGDYVWEDTNKNGVQDKDEKGISGVTVTLKDENDKVLKTVTTDENGKYQFTDLNNG
 TYKVEFETPSGYTPTSVTSGNDTEKDSNGLTTTGVIKDADNMTLDSGFYKTPKYS LGDYV
 WYDSNKDGKQDSTEKG IKDVKVTLLNEKGEVIGTTKTDENGKYCFDNLDSGKYKVI FEKP
 AGLTQTVTNTTEDDKDADGGEVDVTITDHDDFTLDNGYFEEDTSDSDSDSDSDSDSDSDSDS
 DSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDS
 DSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDS
 DSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDSDS
 GSNNTLFGGLFAALGSLLLFGRRKKQNK

SEQ ID NO: 91 polypeptide sequence

MAKYRGKPFQLYVKLSCSTMATSIIILTNILPYDAQASNDIEIIEIIEISRQDELDKVDKAIHQIEQLKQLSASSKEHY
KAQLNEAKTASQIDEIIEKRANELDSKDNKSSHEMNGQSDIDSKLDQLLKDLNEVSSNVDRGQQSGEDDLNAMKNDMSQT
ATTKHGEKDDKNDEAMVNKALEDLDHLNQQIHKSKDASKDTSSEDPVSTTDNNHEVAKTPNNDGSGHVVLNKFLSNEENQ
SHSNRLTDKIQGSDKINHAMI EKLAASNASTQHYYTHKLNTLQSLDQRIANTQLPKNQKSDLMSEVNKTKERIKSQRNII
LEELARTDDKKYATQSILESIFNKDEAVKILKDIRVDGKTDQQIADQITRHIDQLSLTTSDDLTLTSLIDQSQDKSLLISQ
ILQTKLGKAEADKLAKDWTNKGLSNRQIVDQLKKHFASTGDTSSDDILKAILNNAKDKKQAIETILATRIERQKAKLLAD
LITKIETDQNKIFNLVKSALNGKADDLLNLQKRLNQTKKDIDYILSPIVNRPSLLDRLNKNGKTTDLNKLANLMNQSDL
LDSIPDIPTPKPEKTLTLGKGNGLLSGLLNADGNVSLPKAGETIKEHWLPISVIVGAMGVLMIWLSRRNKLKNKA

SEQ ID NO: 93 polypeptide sequence

MKKLATVGSILIVTSTLVFSSMPFQNAHADTTSMNVS NKQSQNVQNH RPYGGVVPQGM
TQAQYTELEKALPQLSAGSNMQDYNMKLYDATQNIADKYNV IITTNVGVFKPHAVRD
MNGHALPLTKDGNFYQTNVDANGVNHGGSEMVQNKTGHMSQQGHMNQNT HMNQPPHM
QQGHMQSSNHQMMSPKANMHSSNHQMNQSNKKVLPAAGESMTSSILTASIAALLLVS
GLFLAFRRRSTNK

Figure 2

SEQ ID NO:34 polynucleotide sequence

ATGTTACAAGTAACTGATGTGAGTTTACGTTTTTGGAGATCGTAAACTATTTGAAGATGTAAATATTAAATTTACAGAAGG
TAATTGTTATGGATTAATTGGTGCGAATGGTGACAGGTAAATCAACATTCTTAAAAATATTATCTGGTGAATTAGATTCTC
AAACAGGACATGTTTCATTAGGTAAAAATGAACGTCTAGCTGTTTTTAAACAGGACCACTATGCTTATGAAGATGAACGC
GTGCTTGATGTTGTAATTAAAGGTCACGAACGTCTTTATGAGGTTATGAAAGAAAAAGATGAAATCTATATGAAGCCAGA
TTTCAGTGATGAAGATGGTATCCGTGCTGCTGAACCTTGAAGGTGAATTTGCAGAAATGAATGGTTGGAATGCTGAAGCTG
ATGCTGCTAACCTTTTTATCTGGTTTAGGTATCGATCCAACCTTTACACGATAAAAAAATGGCTGAATTAGAAAACAACCAA
AAAATTAAAGTATTATTAGCGCAAAGTTTATTCGGTGAACCAGACGTACTATTACTGGATGAGCCTACTAACGGTCTCGA
TATTCAGCAATCAGTTGGTTAGAAGATTTCTTAATTAACCTTTGATAATACTGTTATCGTAGTATCGCATGACCGTCATT
TCTTAAATAATGTATGTACTCATATCGCTGATTTAGACTTCGGTAAAATTAAAGTTTATGTTGGTAACTATGATTTTTGG
TATCAATCTAGTCAGTTAGCTCAAAAGATGGCTCAAGAACAAAACAAGAAAAAAGAAGAAAAAATGAAAGAGTTACAGGA
CTTTATTGCACGTTTCTCAGCTAACGCTTCTAAATCTAAACAAGCAACAAGTCGTAAAAAACAACCTTGAGAAAATTGAAT
TAGATGATATTCAACCATCATCAAGAAGATATCCTTTCGTTAAATTCACGCCTGAGCGTGAGATTGGTAACGACTTATTA
ATCGTTCAAAATCTTTCTAAAACAATTGACGGCGAAAAAGTATTAGATAATGTATCATTCACAATGAATCCAAATGATAA
AGCGATTTTAATTGGAGATAGTGAAATTGCAAAAACAACATTACTTAAATATTAGCTGGCGAAATGGAACCAGACGAAG
GTTCATTTTAAATGGGGTGTTACTACATCATTAAAGTTACTTCCCTAAAGATAACTCAGAGTTCTTTGAGGGTGTAATATG
AATCTCGTTGATTGGTTAAGACAATATGCTCCTGAAGATGAACAAACAGAAACATTTTTTACGTGGTTTCTTAGGTCGTAT
GTTATTTAGTGGTGAAGAAGTTAAGAAAAAAGCTAGTGTGCTTTCAGGTGGAGAAAAAGTACGTTGTATGCTAAGTAAAA
TGATGTTATCAAGTGCGAATGTACTTTTACTTGACGAACCTACTAACCCTTAGACTTAGAAAGTATTACTGCTGTCAAT
GATGGTCTTAAATCATTAAAGGTTCTATCATCTTTACTTCTTATGACTTCGAATTTATCAACACGATTGCAAACCGTGT
TATCGATTTAAATAAACAAGGCGGCGTTTCAAAGAAATTCCATATGAAGAATACTTGCAAGAAATCGGCGTTTTAAAT
AA

SEQ ID NO:35 polynucleotide sequence

ATGTTACAAGTAACTGATGTAAGTTTACGTTTTTGGTGATCGTAAACTATTTGAAGATGTAAATATAAAATTTACAGAGGG
TAATTGTTATGGATTAATTGGTGCAAATGGTGCTGGGAAATCTACATTCTTGAAGATTTTATCAGGCGAAATTGATTAC
AGACTGGTCATGTATCTCTAGGTAAAGATGAGCGTTTGGCTGTGTTAAACAAGATCATTTTGCTTATGAAGATGAACGT
GTTTTAGATGTTGTGATTAAAGGACATGAACGTTTGTATCAAGTGATGAAAGAGAAAGATGAAATTTATATGAAACCTGA
TTTCAGCGATGAGGACGGTATTCGCGCTGCAGAACTTGAAGGAGAATTTGCAGAAATGAACGGTTGGAATGCTGAAGCTG
ATGCTGCTAACCTTATTATCAGGATTAGGCATAGAACCTGACTTACATGATAAAAAATATGCTCTGAACCTTGAAAATAATCAA
AAAGTTAAGGTATTGTTAGCTCAAAGTTTATTTGGTGATCCTGACGTTCTTTTACTAGATGAGCCTACCAATGGTTTAGA
TATACCAGCAATAAGTTGGTTAGAAGACTTTTTTAATTAATTTTGAAAATACTGTCATTGTCGTTTCGCATGACCGTCACT
TCTTAAATAATGTTTGTACTCATATTGCTGATTTAGACTTTGGCAAATTAACCTTTATGTTGGTAACTATGATTTTTGG
TATCAATCAAGTCAATTAGCACAAAAAATGGCACAGAACAATAAGAAAAAAGAAGAAAAAATGAAAGAGTTACAGGA
TTTCATCGCACGCTTCTCAGCAAATGCTTCTAAATCTAAACAGGCAACAAGTCGTAAAGAAACAATTAGAAAAAATGAAT
TAGATGATATCCAGCCATCATCTCGTAGATACCCTTACGTGAAATTTACTCCTGAACGTGAAATTGGAATGATTTACTT
ACAGTAGAAAATCTTTCTAAAACAATTGACGGCGAAAAAGTACTAGACAATGTTTCATTCACTATGAATCCTAATGATAA
AGCTATTTTAGTTGGTGATAGCGAAATTGCTAAAACAACATTGTTAAAAATTTTAGCTGGAGAAATGGAACCAGATGAAG
GTACATTTAAATGGGGTGTAACGACATCTTTAAGTTACTTCCCTAAAGATAACTCTGAGTTCTTTGATGGTGTGATATG
AATTTAGTTGAATGGTTACGTCAATACGCTCCAGAAGATGAACAACTGAAACATTTTTTACGTGGTTTCTTAGGTCGCAT
GTTATTTAGTGGTGAGGAAGTTAAGAAAAAAGCAAGCGTGCTTTCAGGTGGAGAAAAAGTACGTTGCATGTTAAGTAAAA
TGATGTTATCAAGTGCTAACGTACTTTTACTTGATGAGCCAACAAACCATTTAGATTTGGAAGTATCACTGCTGTAAAT
GACGGATTAAAATCATTAAAGGTTCTATCATCTTCACTTCTTATGATTTTGAATTTATTAATACAATCGCAAATCGAGT
GATTGACTTGAATCAAGCTGGTGCCCTTTCTAAAGAAGTACCTTATGAGGAATACTTACAAGAAATGGTGTATTACAAA
ATAATTAA

SEQ ID NO:36 polynucleotide sequence

ATGCCAATTATTACAGATGTTTACGCTCGCGAAGTCTTAGACTCTCGTGGTAACCCAACTGTTGAAGTAGAAGTATTAAC
TGAAAGTGGCGCATTTGGTCGTGCATTAGTACCATCAGGTGCTTCAACTGGTGAACACGAAGCTGTTGAATTACGTGATG
GAGACAAATCACGTTATTTAGGTAAAGGTGTTACTAAAGCAGTTGAAAACGTTAATGAAATCATCGCACCAGAAATTATT
GAAGGTGAATTTTCAGTATTAGATCAAGTATCTATTGATAAAATGATGATCGCATTAGACGGTACTCCAAACAAAGGTAA
ATTAGGTGCAAATGCTATTTTAGGTGTATCTATCGCAGTAGCACGTGCAGCAGCTGACTTATTAGGTCAACCACTTTACA
AATATTTAGGTGGATTTAATGGTAAGCAGTTACCAGTACCAATGATGAACATCGTTAATGGTGGTTCTCACTCAGATGCT
CCAATTGCATTCCAAGAATTCATGATTTTACCTGTAGGTGCTACAACGTTCAAAGAATCATTACGTTGGGGTACTGAAAT
TTTCCACAACCTTAAATCAATTTTAAGCAAACGTGGTTTAGAACTGCAGTAGGTGACGAAGGTGGTTTCGCTCCTAAAT
TTGAAGGTACTGAAGATGCTGTTGAAACAATTATCCAAGCAATCGAAGCAGCTGGTTACAAACCAGGTGAAGAAGTATTC

TTAGGATTTGACTGTGCATCATCAGAATTCTATGAAAATGGTGTATATGACTACAGTAAGTTCGAAGGCGAACACGGTGC
AAAACGTACAGCTGCAGAACAAGTTGACTACTTAGAACAATTAGTAGACAAATATCCTATCATTACAATTGAAGACGGTA
TGGACGAAAACGACTGGGATGGTTGGAAACAACTTACAGAACGTATCGGTGACCGTGTACAATTAGTAGGTGACGATTTA
TTCGTAACAAACACTGAAATTTTAGCAAAAGGTATTGAAAACGGAATTGGTAACTCAATCTTAATTAAAGTTAACC
CGGTACATTAACCTGAAACATTTGATGCAATCGAAATGGCTCAAAAAGCTGGTTACACAGCAGTAGTTTCTCACC
GTGAAACAGAAGATACAACAATTGCTGATATTGCTGTTGCTACAAACGCTGGTCAAATTTAAACTGGTTCATTATC
ACTGACCGTATTGCTAAATACAATCAATTATTACGTATCGAAGATGAATTATTTGAACTGCTAAATATGACGGTATCAA
ATCATTCTATAACTTAGATAAATAA

SEQ ID NO:37 polynucleotide sequence

ATGCCAATTATTACAGATGTTTACGCTCGCGAAGTCTTAGACTCACGTGGTAACCCAACAGTTGAAGTTGAAGTATTAAC
TGAAAGCGGTGCTTTTCGGACGTGCATTAGTACCTTCTGGTGCTTCTACTGGTGAACATGAAGCAGTTGAATTACGTGATG
GAGATAAATCACGTTATTTAGGTAAAGGTGTGACTAAAGCGGTAGAAAATGTTAACGAAATGATCGCACCAGAAATCGTT
GAAGGTGAATTTTCAGTTTATAGATCAAGTATCTATTGATAAAATGATGATTCAATTAGACGGTACACACAACAAAGGTAA
ATTAGGTGCAAATGCCATTTTAGGTGTTTCTATTGCCGTAGCTCGTGCAGCTGCTGACTTATTAGGTCAACCATTATATA
AATATTTAGGTGGATTTAATGGTAAACAATTGCCAGTACCTATGATGAATATTGTTAATGGTGGTTCTCACTCAGATGCA
CCAATTGCTTTCCAAGAGTTCATGATTTTACCTGTAGGTGCTGAGTCATTCAAAGAATCATTACGTTGGGGTGCAGAAAT
CTTCCATAACCTTAAATCAATCTTAAGTGAACGTGGTTTAGAACTGCAGTAGGTGATGAAGGTGGTTTCGCTCCTAGAT
TTGAAGGCACTGAAGACGCTGTAGAACTATTATTAAAGCTATCGAAAAAGCAGGATACAAACCAGGTGAAGATGTATTC
TTAGGATTTGACTGTGCTTCTTCTGAATTCTATGAAAATGGTGTATTATGATTACACTAAATTCGAAGGTGAACACGGTGC
TAAACGTAGTGCAGCAGAGCAAGTTGACTACTTAGAAGAATTAATTGGTAAATATCCAATCATCACTATTGAAGATGGTA
TGGATGAAAACGATTGGGAAGGTGGAAACAATTAAGTATCGTATCGGTGATAAAGTTCAATTAGTTGGTGTGATTTA
TTCGTAACAACTGAAATTTTATCTAAAGGTATCGAACAAGGTATTGGTAACTCAATCTTAATCAAAGTAAACCAAT
CGGTACATTAACCTGAAACATTCGATGCTATTGAAATGGCTCAAAAAGCTGGATATACTGCGGTTGTATCTCACC
GTGAACTGAAGATACTACAATTGCTGATATCGCAGTTGCTACAAATGCAGGCCAAATTTAAACAGGTTCATTATCTAGA
ACTGACCGTATTGCTAAATACAATCAATTATTACGTATTGAAGATGAATTATACGAAACAGCTAAATTTGAAGGAATTAA
ATCTTTCTACAATTTAGATAAATAA

SEQ ID NO:38 polynucleotide sequence

ATGAAAAAATCGTTACAGCTACAATCGCTACAGCAGGACTTGCCACTATCGCATTTGCAGGACATGATGCACAAGCCGC
AGAACAAAATAACAATGGATATAATTCTAATGACGCTCAATCATAACAGCTATACGTATACAATTGATGCACAAGGTAATT
ATCATTACACTTGGACAGGAAATTGGAATCCAAGTCAATTAACGCAAAACAACACATACTACTACAACAACACTACAATACT
TATAGTTATAACAATGCATCTTACAATACTACTATAATCATTATCATATCAATACAATACTATAACAACAATAGCCAAAC
AGCAACAAATAACTATTATACTGGTGGTTCAGGTGCAAGTTATAGCACAACAAGTAATAATGTTTCATGTGACTACA
CAGCGCCATCTTCAAATGGTCGTTCAATTTCTAATGGTTATGCATCAGGAAGTAACCTTATACTTCAGGACAATGTACT
TATTATGTATTTGATCGTGTGGTGGGAAAATTGGTTCAACATGGGGTAACGCAAGTAATTGGGCTAACGCAGCTGCATC
ATCTGGCTATACAGTGAACAATACACCAAAAGTTGGTGCTATCATGCAACAACAAGGCTATTACGGTCATGTTGCTT
ACGTTGAAGGCGTTAACAGCAACGGTTCTGTTCTGTTTCAGAAATGAACATATGGACATGGTGCTGGTGTGGTTACGTCT
CGTACAATTTACAGCAAAACCAAGCAGGTTTCATATAATTTCAATTCATTAA

SEQ ID NO:39 polynucleotide sequence

ATGAAGAAAATCGCTACAGCTACTATCGCAACTGCAGGATTCGCTACAATCGCAATTGCATCAGGAAATCAAGCTCATGC
TTCTGAGCAAGATAACTACGGTTATAATCCAAACGACCCAACATCATATAGCTATACTTACACTATTGATGCACAAGGTA
ACTACCATTACACATGGAAAGGTAACCTGGCATCCAAGTCAATTAACCAAGATAATGGCTACTACAGCTATTACTACTAC
AATGGCTACAATAACTACAACAATTACAACAATGGTTATAGCTACAATAATTACAGCCGTTACAACAACACTACTCAAATAA
TAATCAATCATATAACTACAATACTATAATAGTTACAACACAAACAGCTACCGTACTGGTGGTTTAGGTGCAAGCTACA
GCACTTCAAGCAACAATGTTCAAGTAACCTACAACCTATGGCTCCATCATCAAATGGCCGTTCAATCTCAAGTGGTTATACT
TCAGGACGTAACCTTATACTTCTGGTCAATGTACATACTACGTATTTGATCGTGTAGGTGGTAAATCGGTTCAACTTG
GGGCAATGCAAGTAACCTGGGCTAACGCAGCTGCAAGAGCTGGTTACACAGTGAACAATACACCAAAAGCTGGTGCATTA
TGCAACAACCTCAAGGTGCATACGGTCACGTTGCATACGTTGAAAGTGTTAACAGCAATGGTTCAGTAAGAGTTTCAGAA
ATGAACATATGGTTATGGCCCAGGTGTTGTAACCTTCACGTACAATCTCAGCTAGCCAAGCTGCTGGTTATACTTCATTCA
CTAA

SEQ ID NO:40 polynucleotide sequence

ATGAAAAAATCGCTACAGCTACAATTGCAACTGCAGGAATCGCTACTTTTCGCATTTGCACACCATGACGCACAAGCAGC
AGAACAAAATAATGATGGGTACAATCCAAACGACCCCTTATTCATATAGCTACACTTACACAATCGATGCTGAAGGTAAC
ACCACTACACTTGGAAAGGTAACCTGGAGTCCAGATCGTGTAATACTTCATATACTATAATAATTATAATACTACAAC
TACTATGGTTACAATACTATAGCAACTACAATACTACAGTAATTACAACAATTACAACAACCTATCAATCAAACAACAC
GCAATCACAAAGAACAACCTCAACCGACTGGTGGTTTAGGCGCAAGCTATTCAACATCAAGTAGTAATGTTACAGTTACAA

CAACTTCTGCGCCATCATCAAACGGTGTATCTTTATCAAACGCTCGCTCAGCATCTGGTAACTTATACACTTCAGGTCAA
TGTACATATTATGTATTTGACAGAGTAGGTGGCAAATCGGTTCAACGTGGGGTAACGCAAACAACCTGGGCAAACGCTGC
AGCACGTTCTGGTTACACAGTAAACAATTTCGCCTGCTAAAGGTGCAATCTTACAAACGTCACAAGGTGCATACGGACACG
TAGCATA CGTTGAAGGTGTAAACAGCAATGGTTCAATCAGAGTTTCAGAAATGAACTACGGTCACGGTGCAGGTGTTGTC
ACTTCACGTACAATCTCTGCGAGCCAAGCTGCTTCATATAACTATATTCACTAA

SEQ ID NO:41 polynucleotide sequence

ATGAAAAAATTAGTACCTTTATTATTAGCCTTATTACTTCTAGTTGCTGCATGTGGTACTGGTGGTAAACAAAGCAGTGA
TAAGTCAAATGGCAAATTAAAAGTAGTAACGACGAATTCAATTTTATATGATATGGCTAAAAATGTTGGTGGAGACAACG
TCGATATTCATAGTATTGTACCTGTTGGTCAAGATCCTCATGAATATGAAGTTAAACCTAAAGATATTAAAAAGTTAACT
GACGCTGACGTTATTTTATACAACGGATTAAATTTAGAGACTGGTAAACGGTTGGTTTGAAAAAGCCTTAGAACAGGCTGG
TAAATCATTA AAAAGATAAAAAAGTTATCGCAGTATCAAAGATGTTAAACCTATCTATTTAAACGGTGAAGAAGGCAACA
AAGATAAACAAGATCCACACGCATGGTTAAGTTTAGATAATGGTATTAAATACGTAAAAACAATTCAACAAACATTTATC
GATAACGACAAAAAACATAAAGCAGATTATGAAAAGCAAGGTAACAAATACATTGCTCAATTGGAAAAATTAAATAATGA
CAGTAAAGACAAATTTAATGACATTCCAAAGAACAACGTGCCATGATTACAAGTGAAGGTGCCTTCAAGTACTTCTCAA
AACAAATACGGTATTACACCAGGTTATATTTGGGAAATTAACACTGAAAAACAAGGTACACCTGAACAAATGAGACAAGCT
ATTGAGTTTGTTAAAAAGCACAAATTA AACACTTATTAGTAGAAACAAGTGTGATAAGAAAGCAATGGAAAGTTTATC
TGAAGAAACGAAGAAAGATATCTTTGGTGAAGGTACACAGATTCAATCGGTAAAGAAGGCACTAAAGGTGACTCTTACT
ACAAAATGATGAAATCAAATATTGAAACTGTACACGGAAGCATGAAATAA

SEQ ID NO:42 polynucleotide sequence

GTGAAAAAATTCTCGCTTTAGCAATAGCATTTTTTAATTATCCTTGCCGCATGTGGGAATCACAGTAACCATGAACATCA
CTCACATGAAGGAAAATTAAAAGTTGTAAC TACAACTCTATTCTCTATGACATGGTTAAACGTGTCGGTGGAAATAAGG
TCGATGTT CATAGCATCGTTCCAGTAGGACAAGACCCACATGAATATGAGGTTAAACCTAAAGATATTAAAGCATTAACA
GATGCTGACGTTGTATTTTATAACGGTTTAAACCTAGAACTGGAAATGGTTGGTTTGAAAAAGCACTTGACCAAGCAGG
AAAATCAACAAAAGATAAAAAATGTGATAGCAGCATCAAATAATGTTAAACCAATATACTTAAATGGTGAGGAAGGTAACA
AAAACAAACAAGATCCACATGCATGGTTAAGTTTAGAGAATGGAATTAAATACGTAAAAACAATACAAAAATCACTAGAA
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SEQ ID NO:43 polynucleotide sequence

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SEQ ID NO:44 polynucleotide sequence

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SEQ ID NO:45 polynucleotide sequence

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SEQ ID NO:47 polynucleotide sequence

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SEQ ID NO:48 polynucleotide sequence

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SEQ ID NO:49 polynucleotide sequence

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SEQ ID NO:50 polynucleotide sequence

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SEQ ID NO:51 polynucleotide sequence

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SEQ ID NO:52 polynucleotide sequence

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SEQ ID NO:53 polynucleotide sequence

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SEQ ID NO:54 polynucleotide sequence

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SEQ ID NO:55 polynucleotide sequence

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SEQ ID NO:56 polynucleotide sequence

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SEQ ID NO:57 polynucleotide sequence

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SEQ ID NO:58 polynucleotide sequence

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SEQ ID NO:60 polynucleotide sequence

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SEQ ID NO:61 polynucleotide sequence

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SEQ ID NO:62 polynucleotide sequence

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SEQ ID NO:63 polynucleotide sequence

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SEQ ID NO:64 polynucleotide sequence

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SEQ ID NO:65 polynucleotide sequence

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SEQ ID NO:66 polynucleotide sequence

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SEQ ID NO:77 polynucleotide sequence

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SEQ ID NO:78 polynucleotide sequence

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SEQ ID NO:79 polynucleotide sequence

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SEQ ID NO:80 polynucleotide sequence

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SEQ ID NO: 81 polynucleotide sequence

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SEQ ID NO: 82 polynucleotide sequence

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SEQ ID NO: 83 polynucleotide sequence

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SEQ ID NO:84 polynucleotide sequence

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SEQ ID NO: 85 polynucleotide sequence

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SEQ ID NO: 86 polynucleotide sequence

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SEQ ID NO: 88 polynucleotide sequence

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SEQ ID NO: 92 polynucleotide sequence

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Figure 3

Purification of alpha toxin

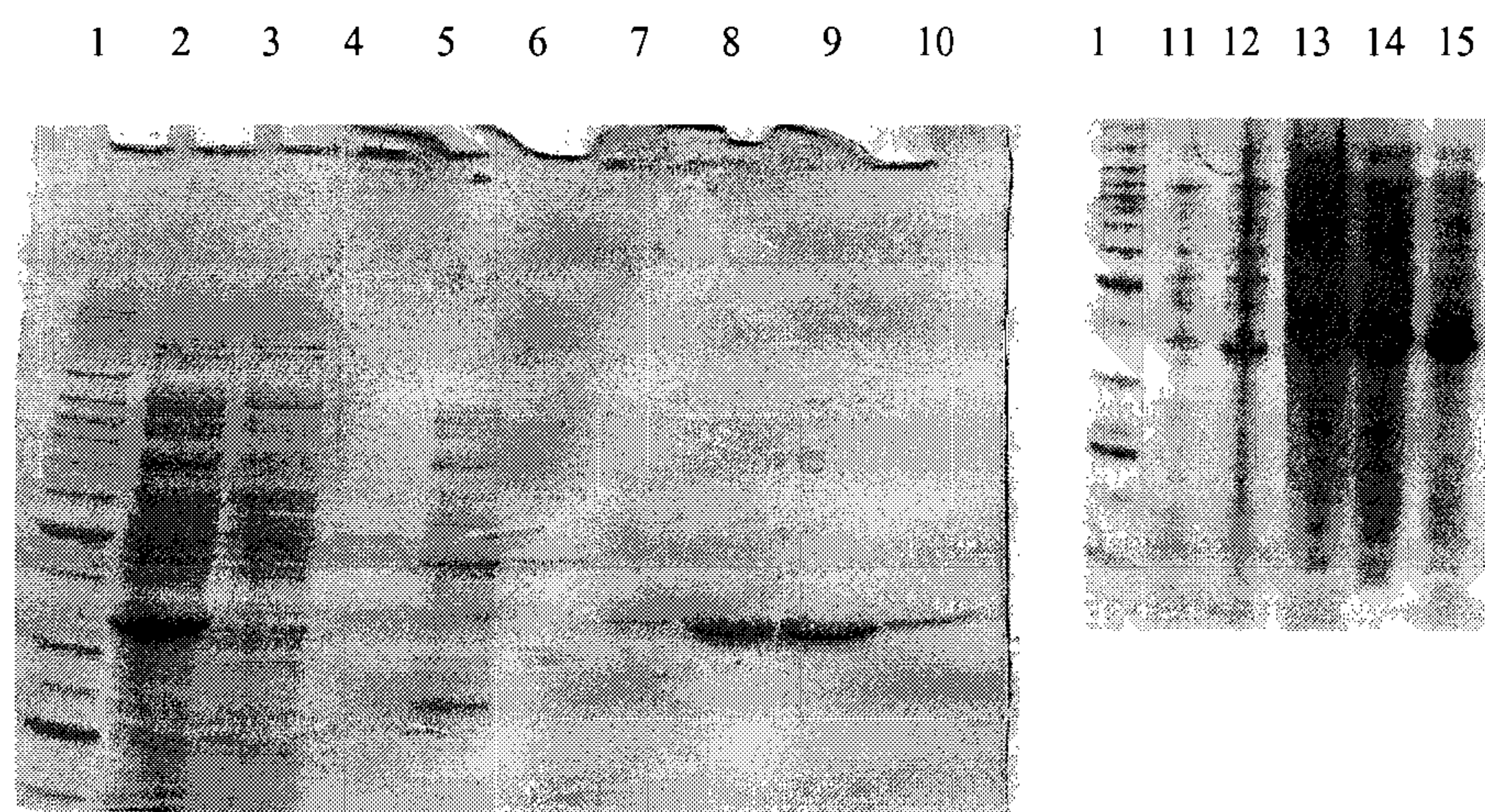
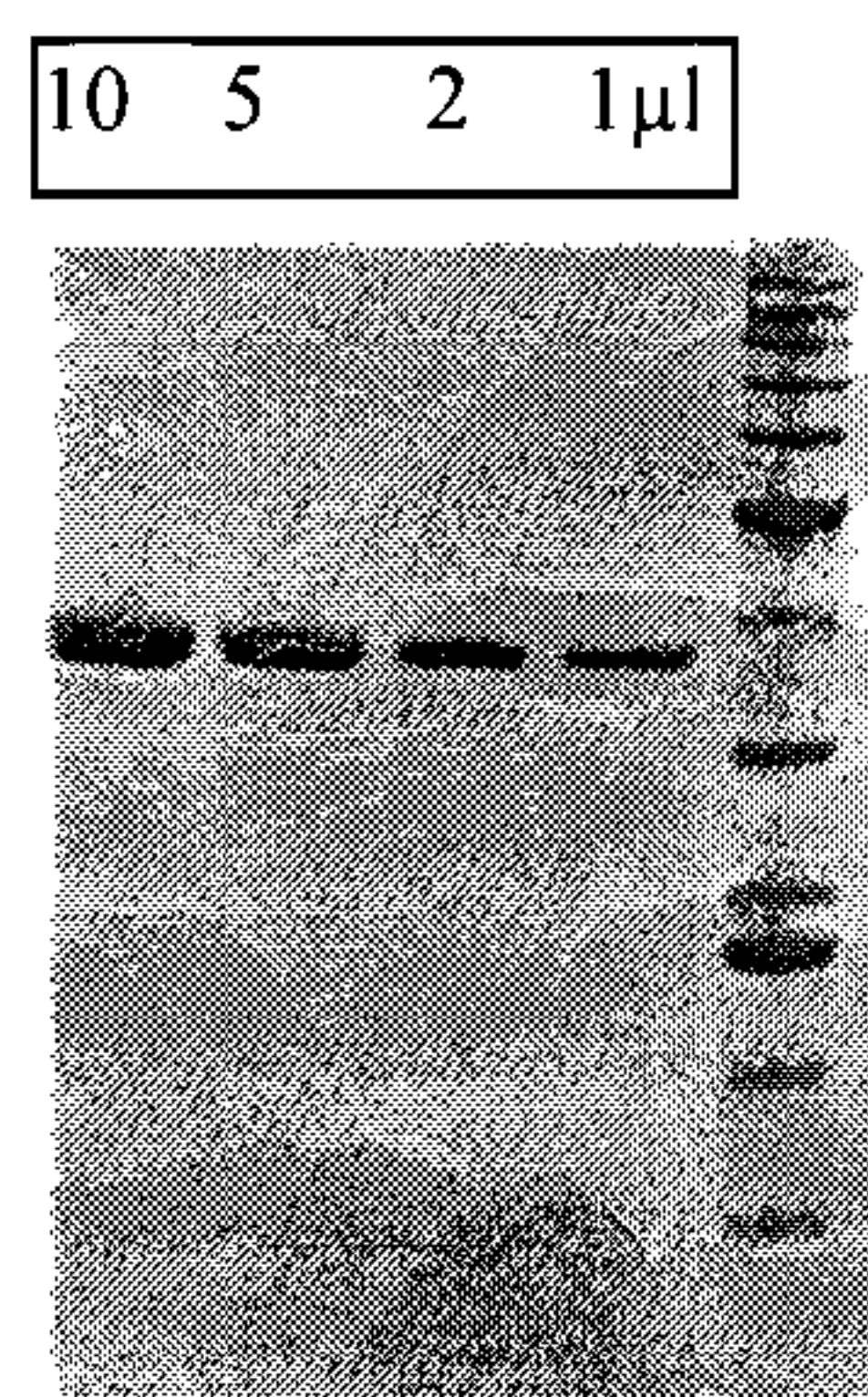
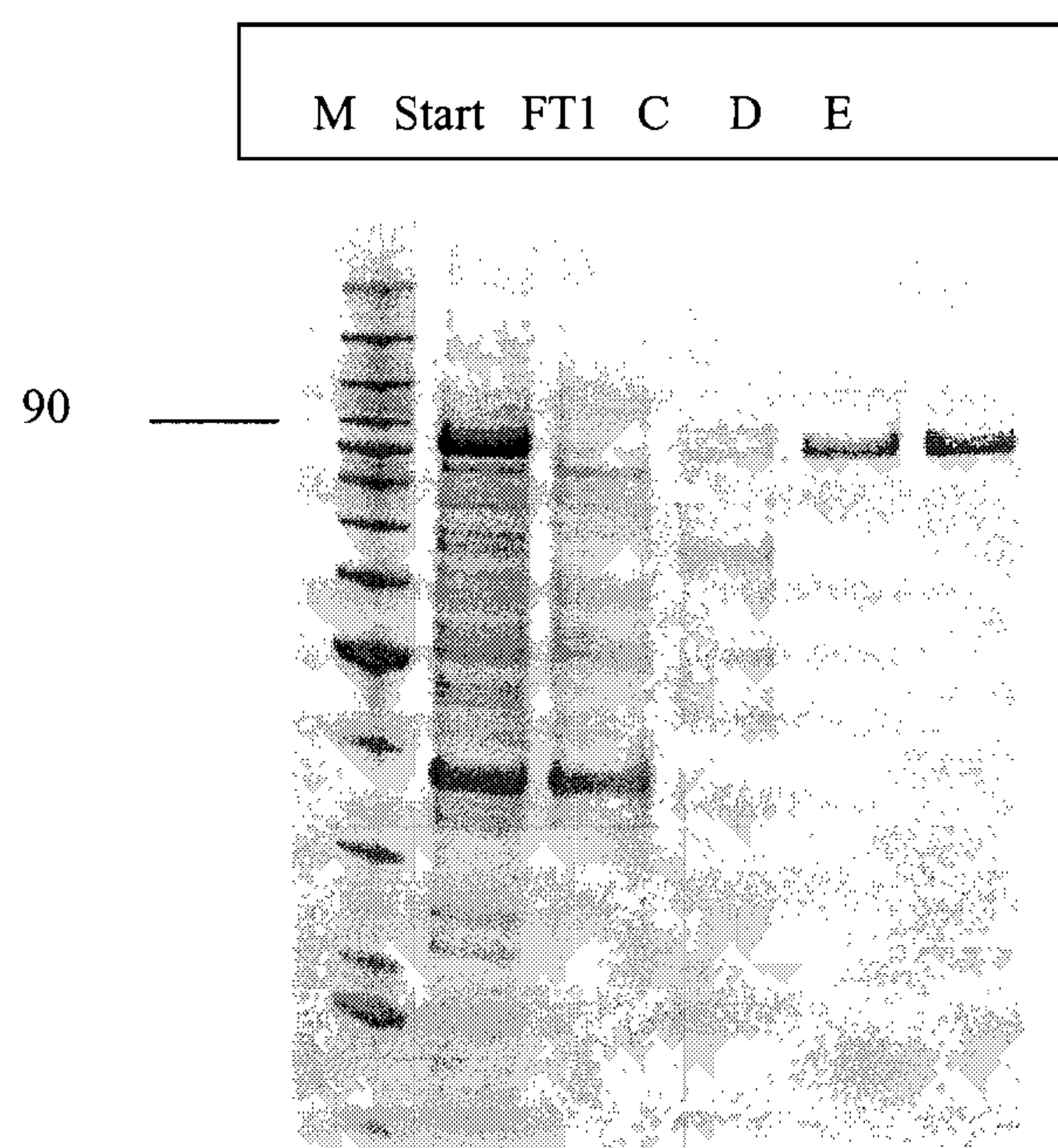
A**B**

Figure 4

Purification of SdrC

A



B

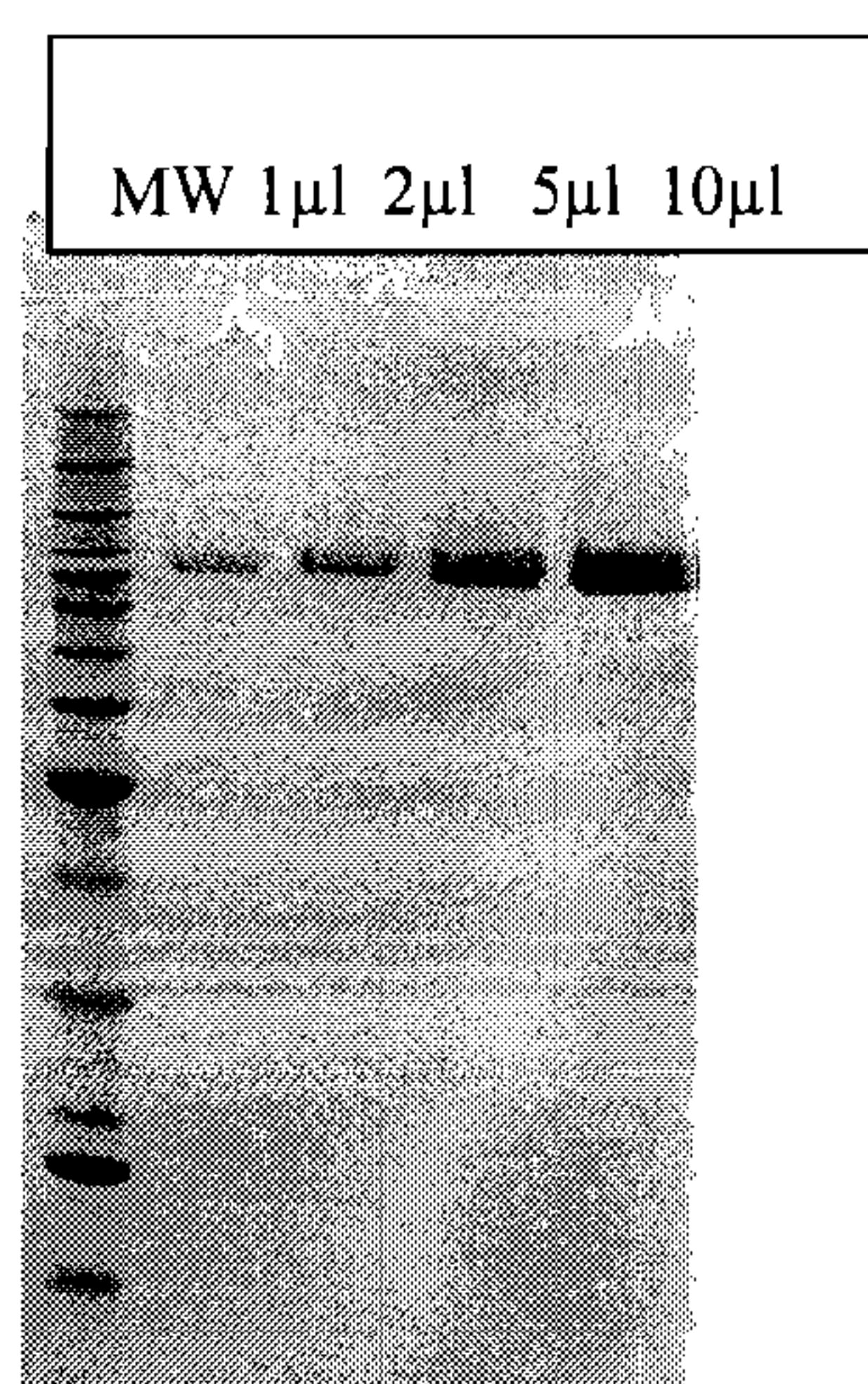


Figure 5

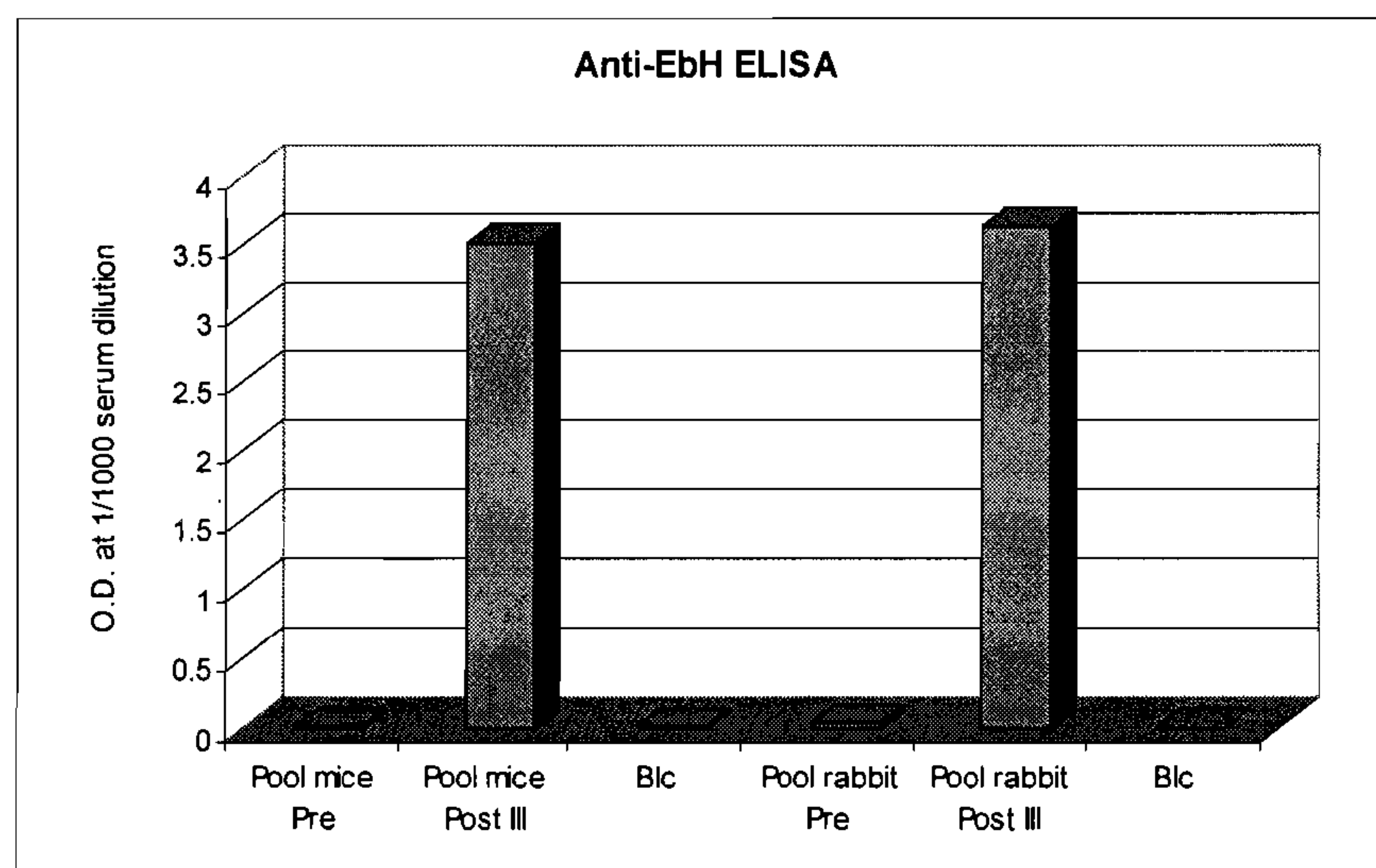
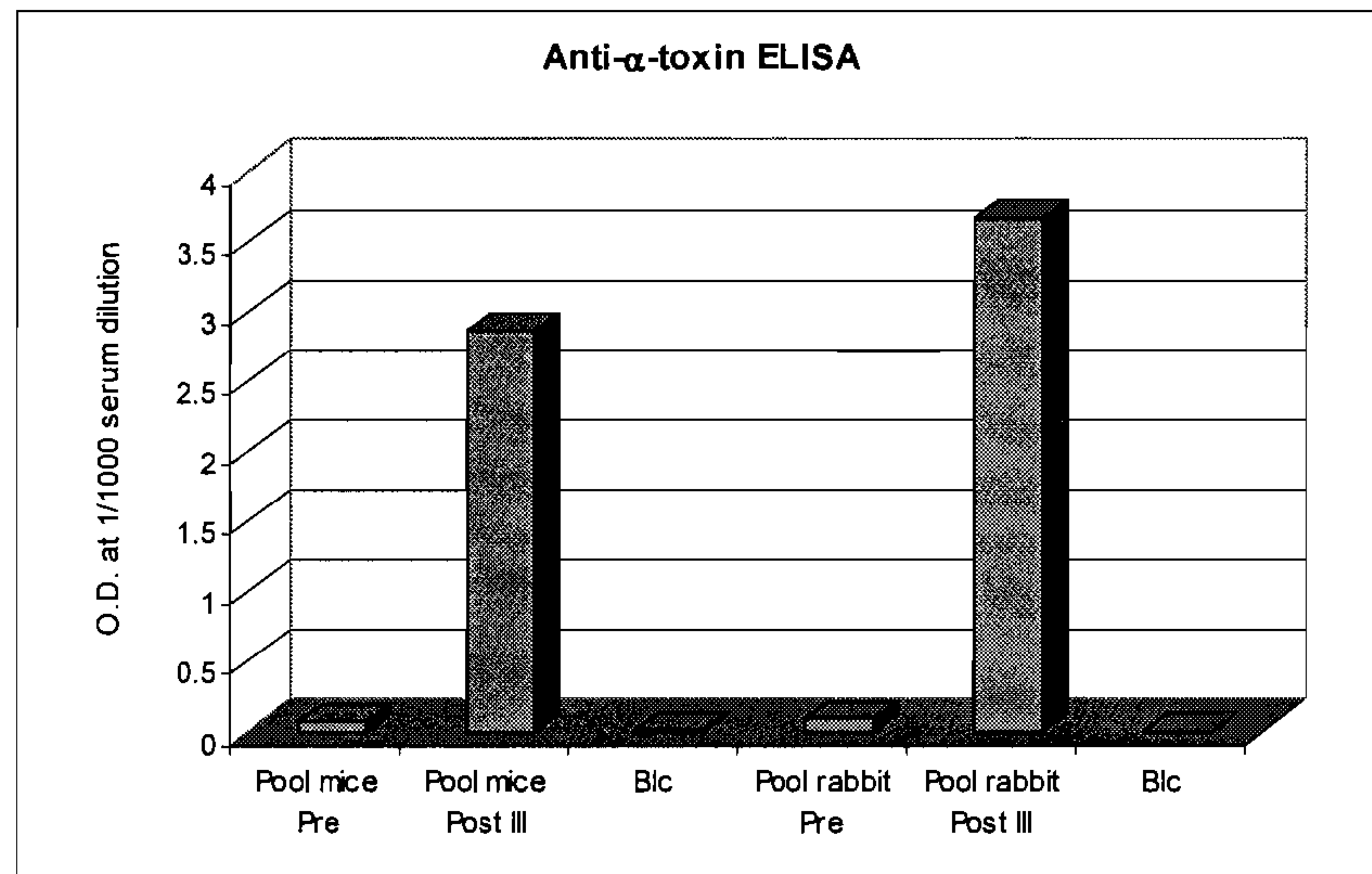
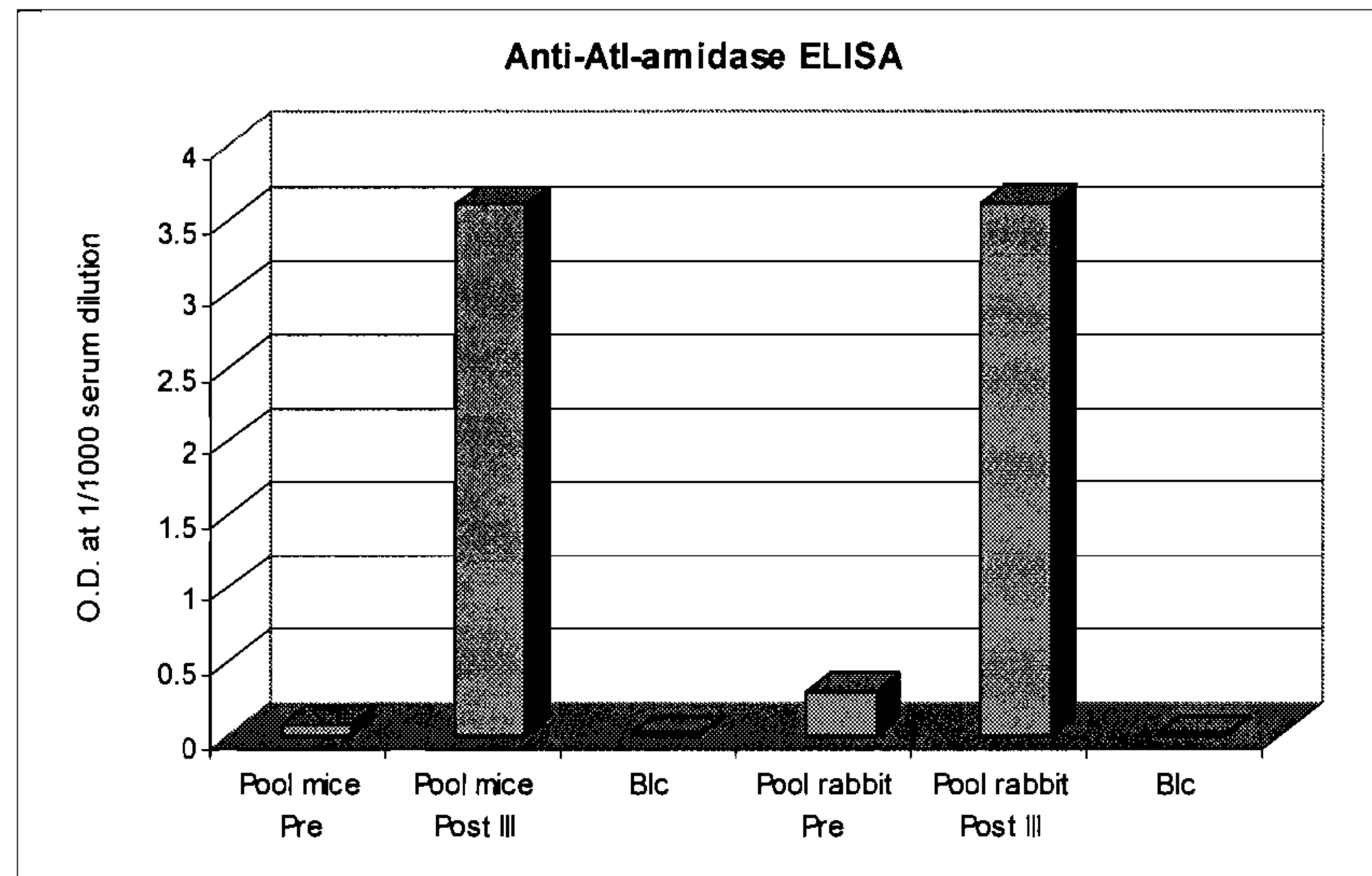
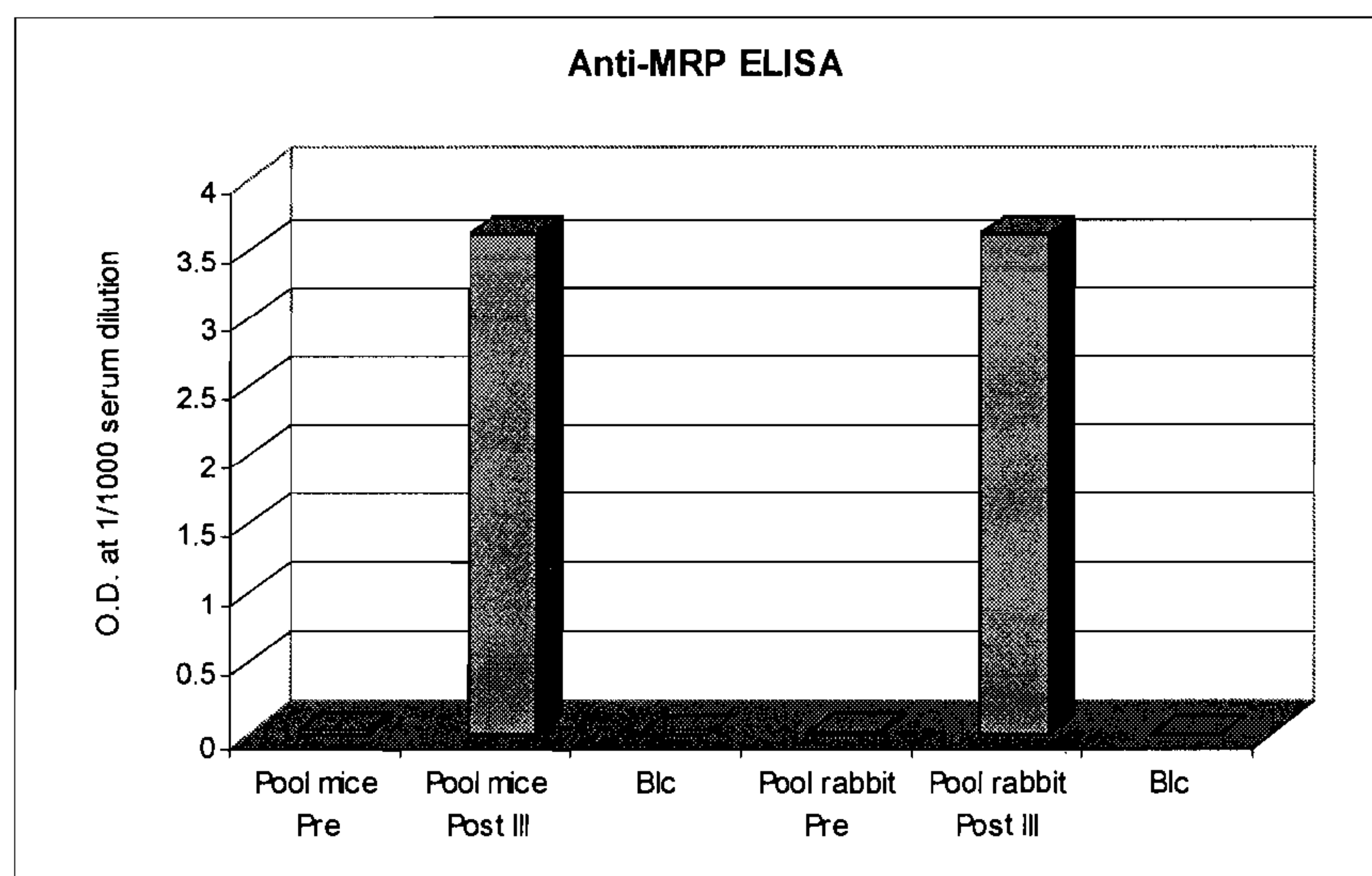
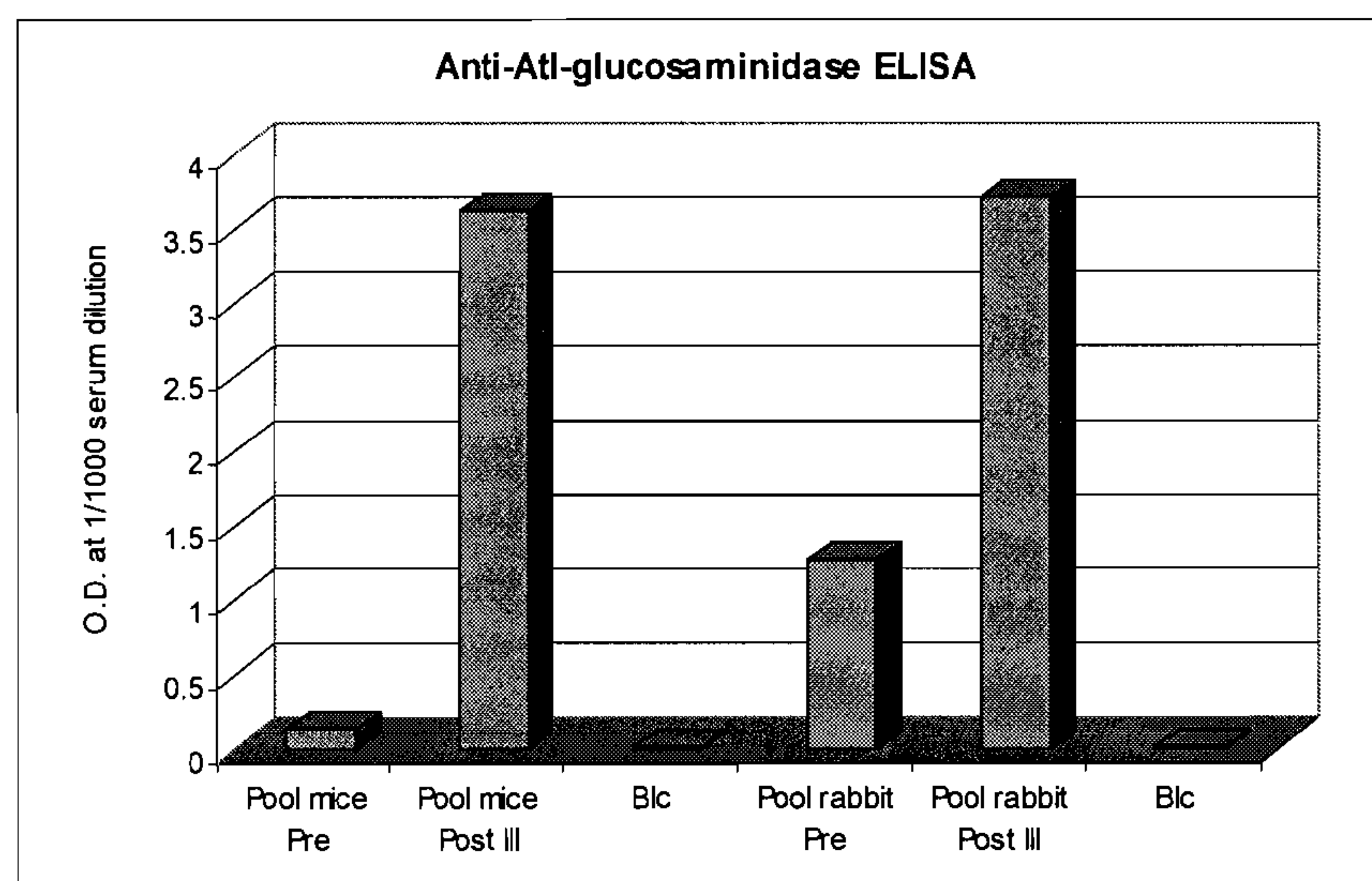
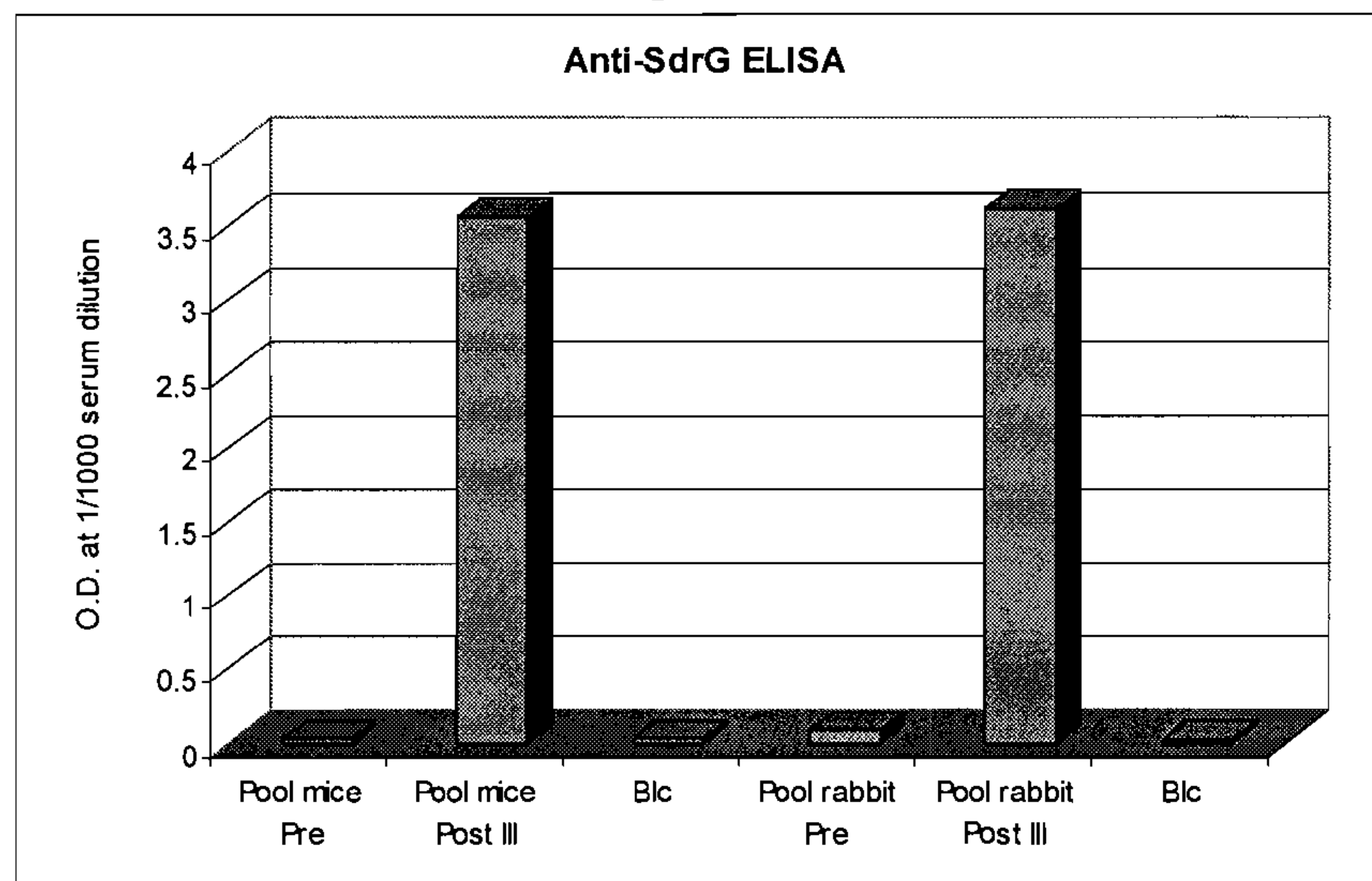


Figure 5



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Figure 5

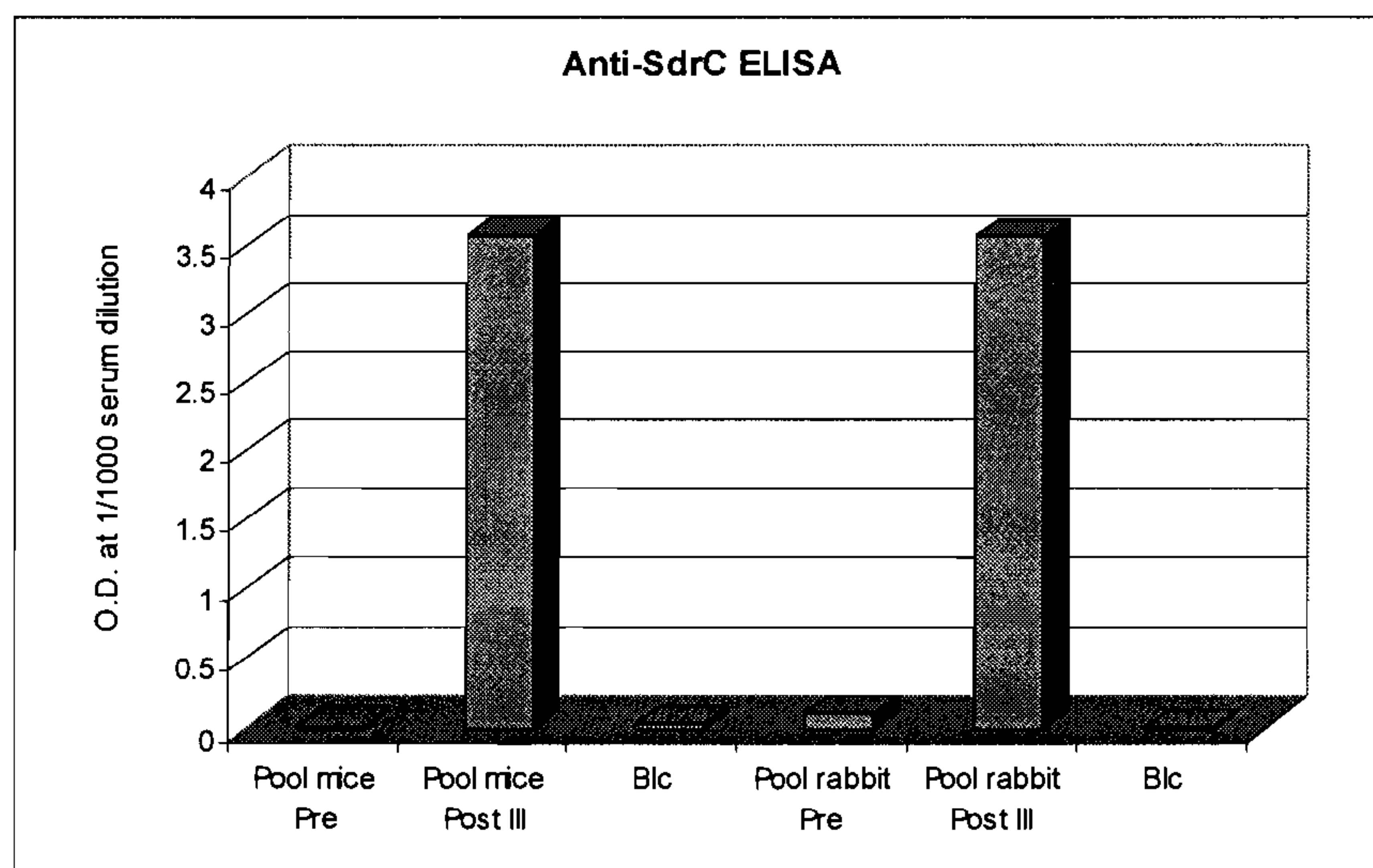
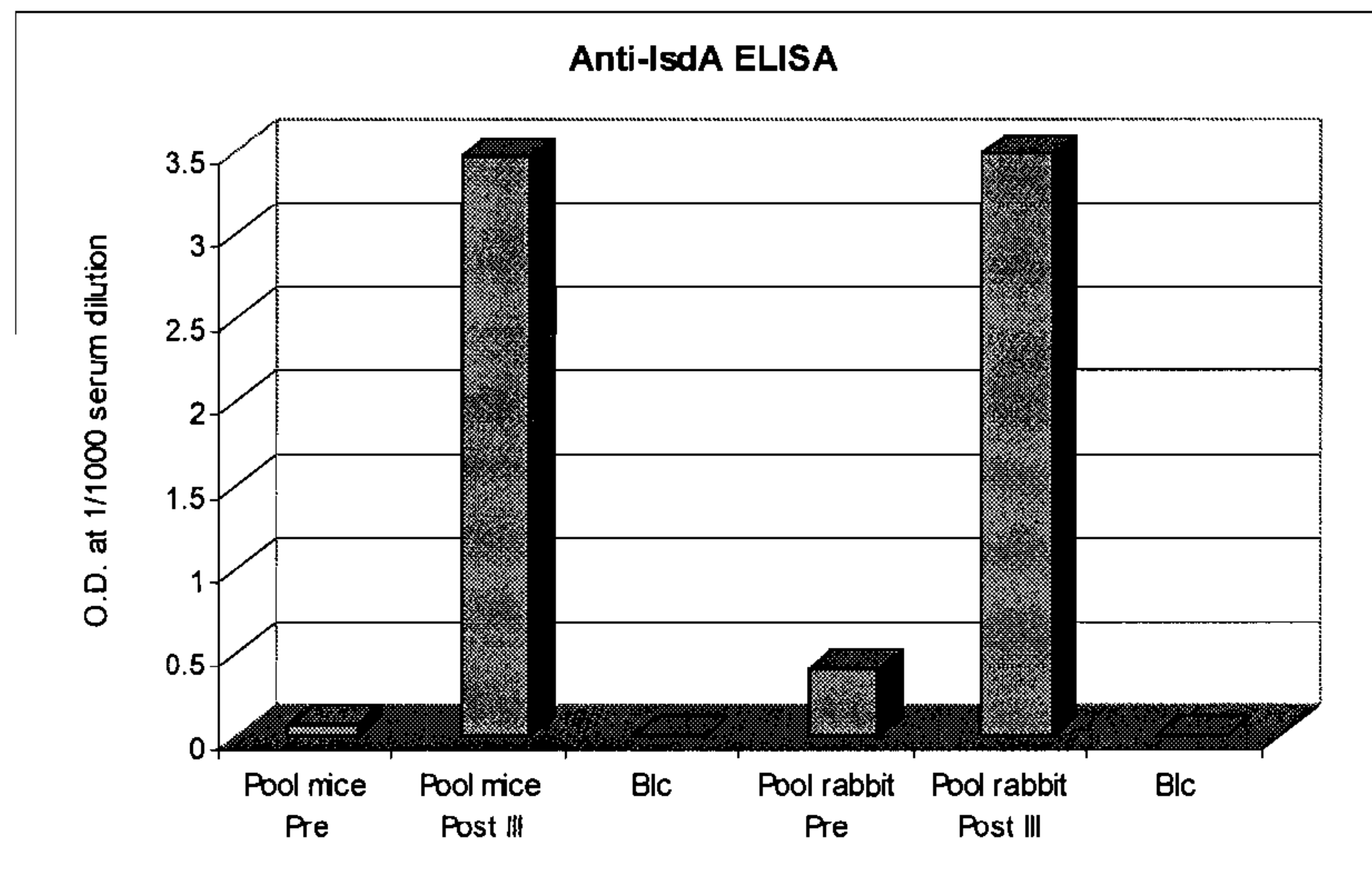
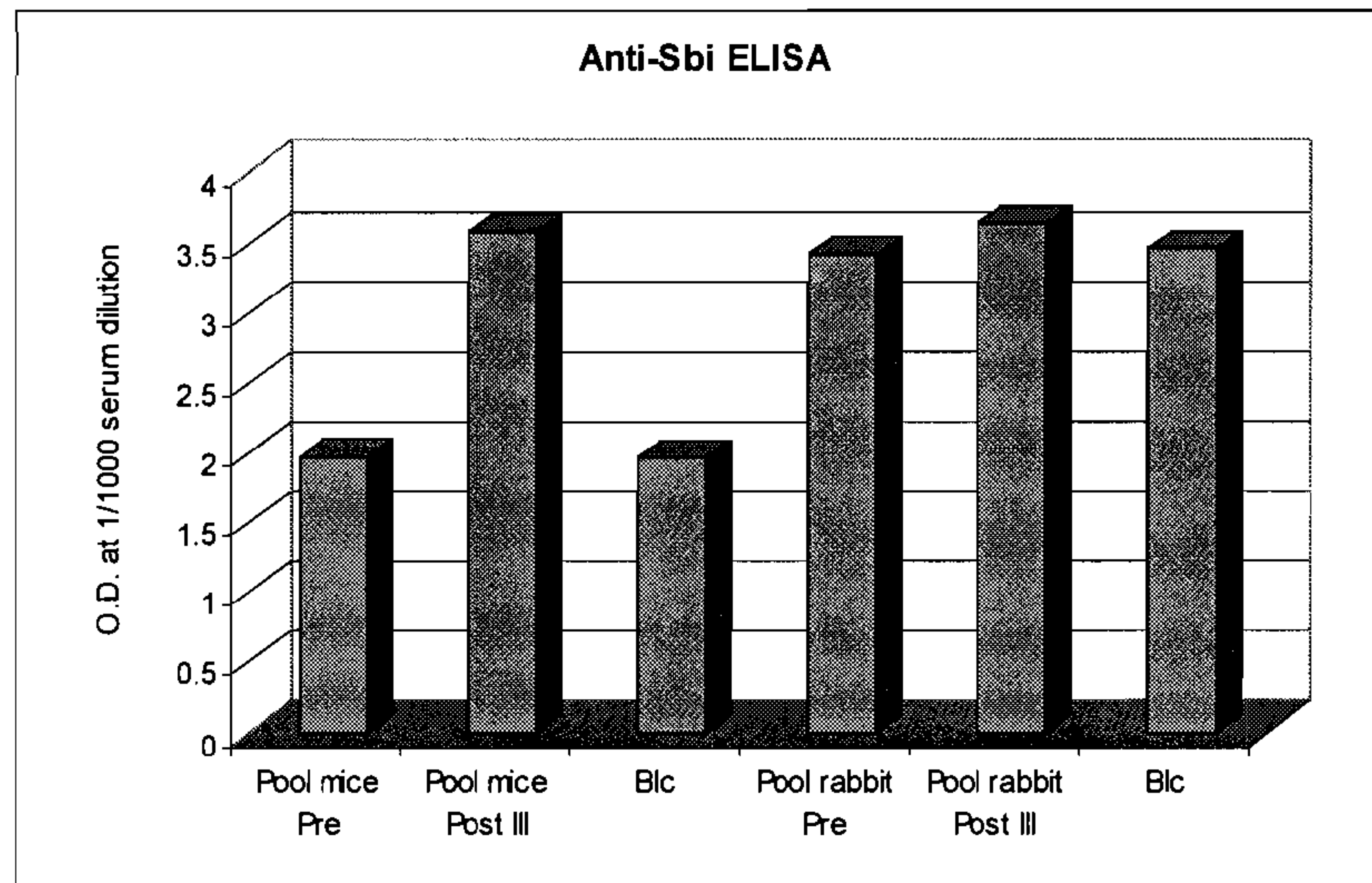


Figure 5

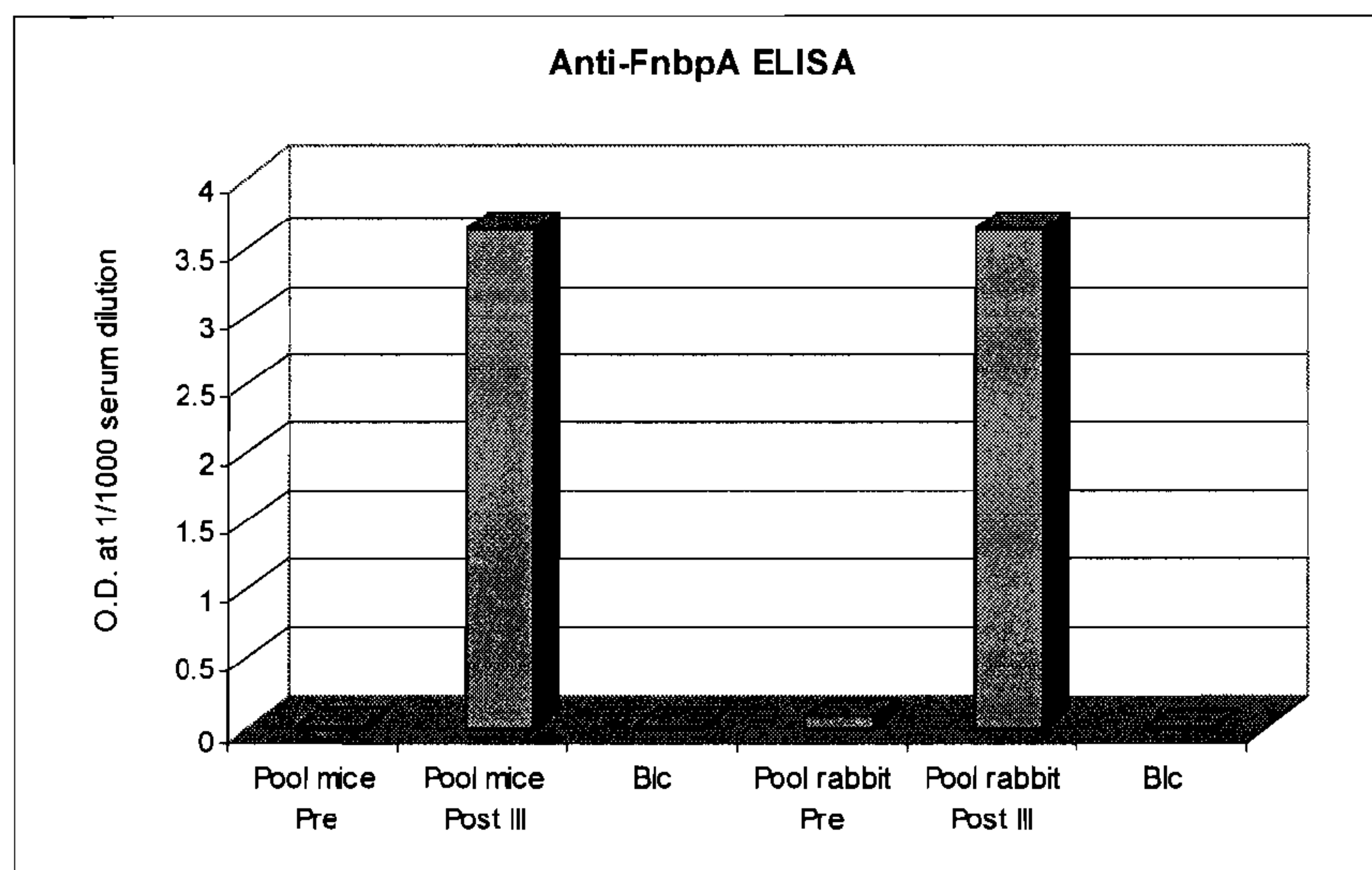
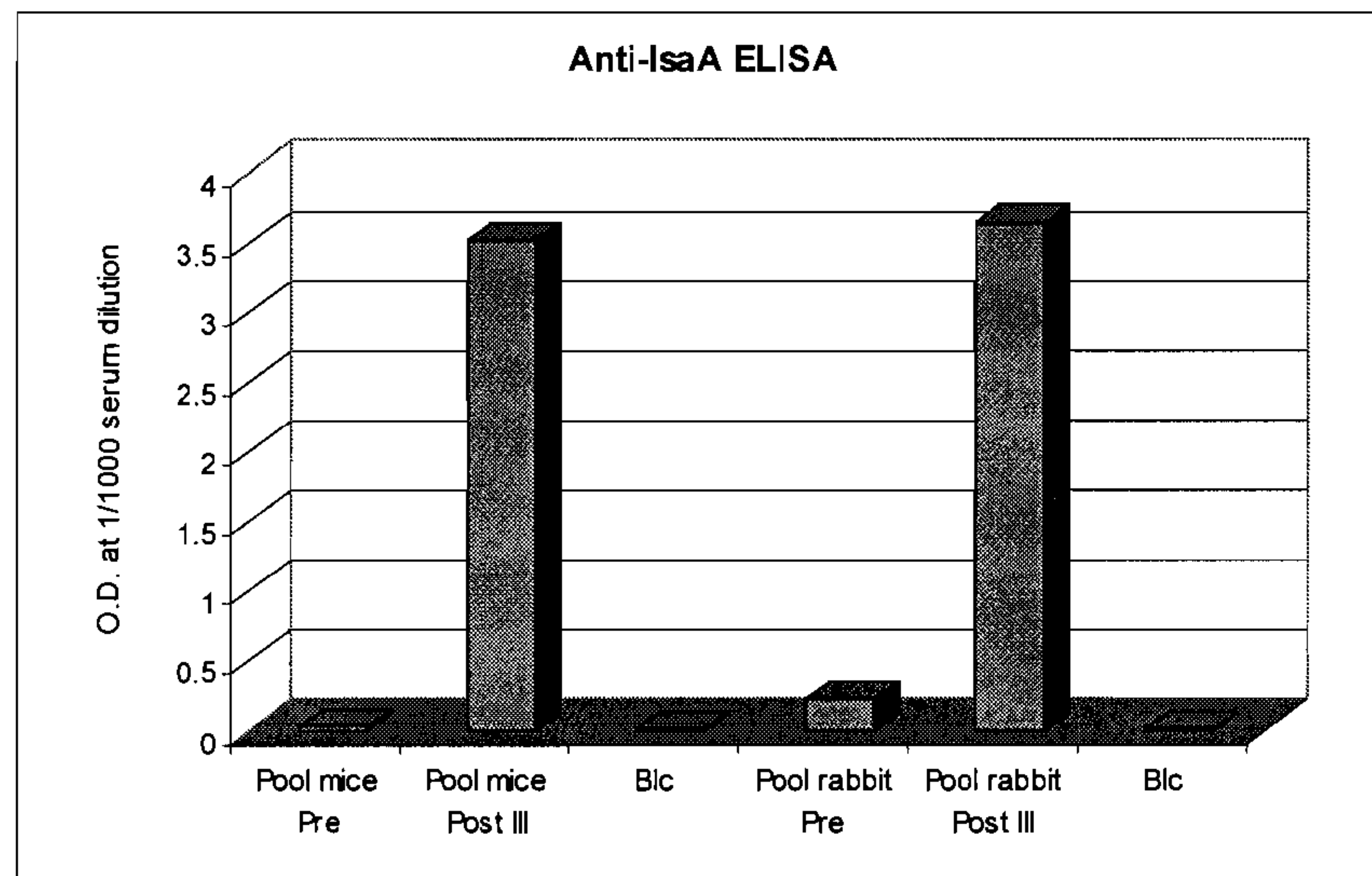
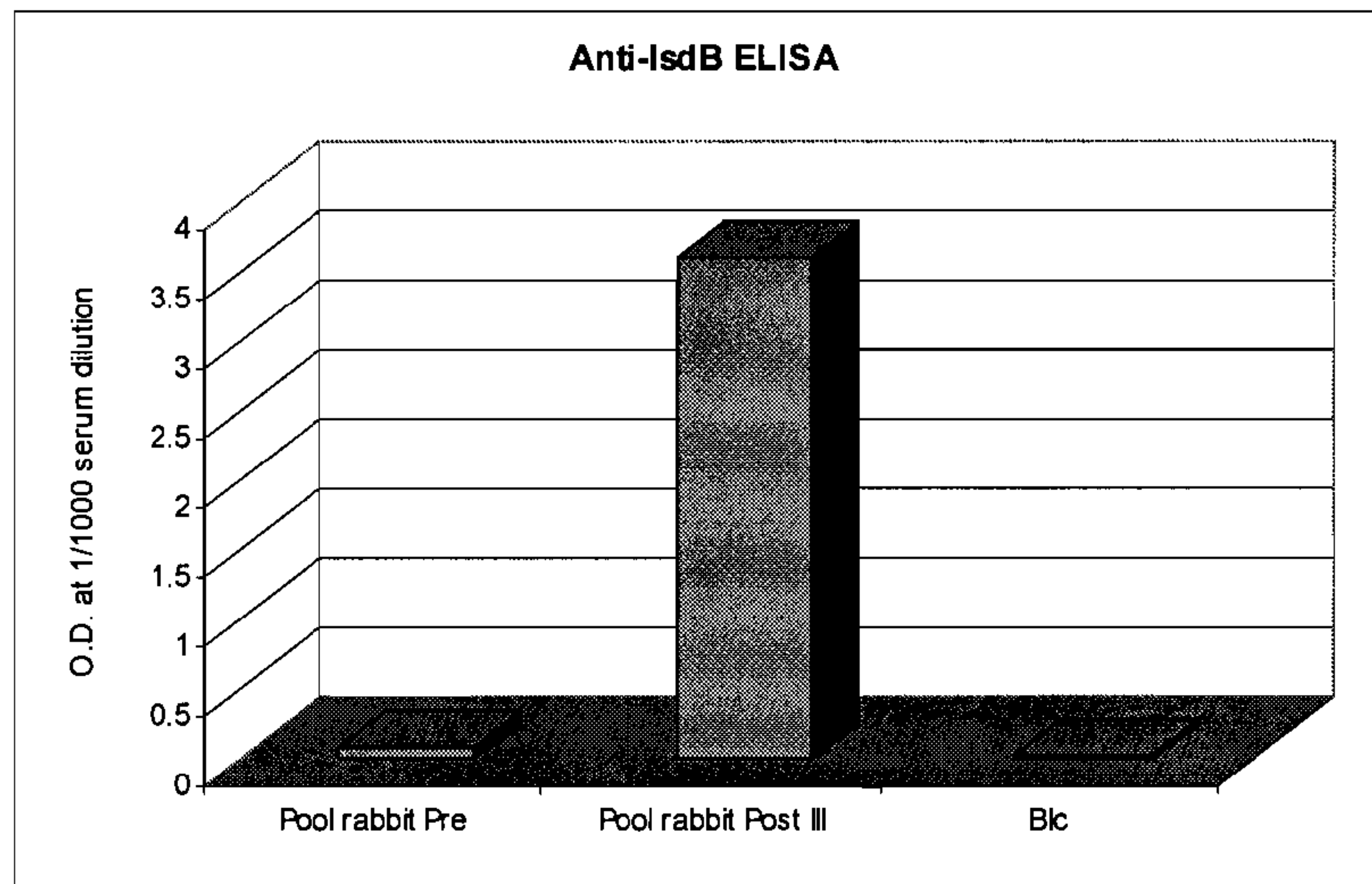


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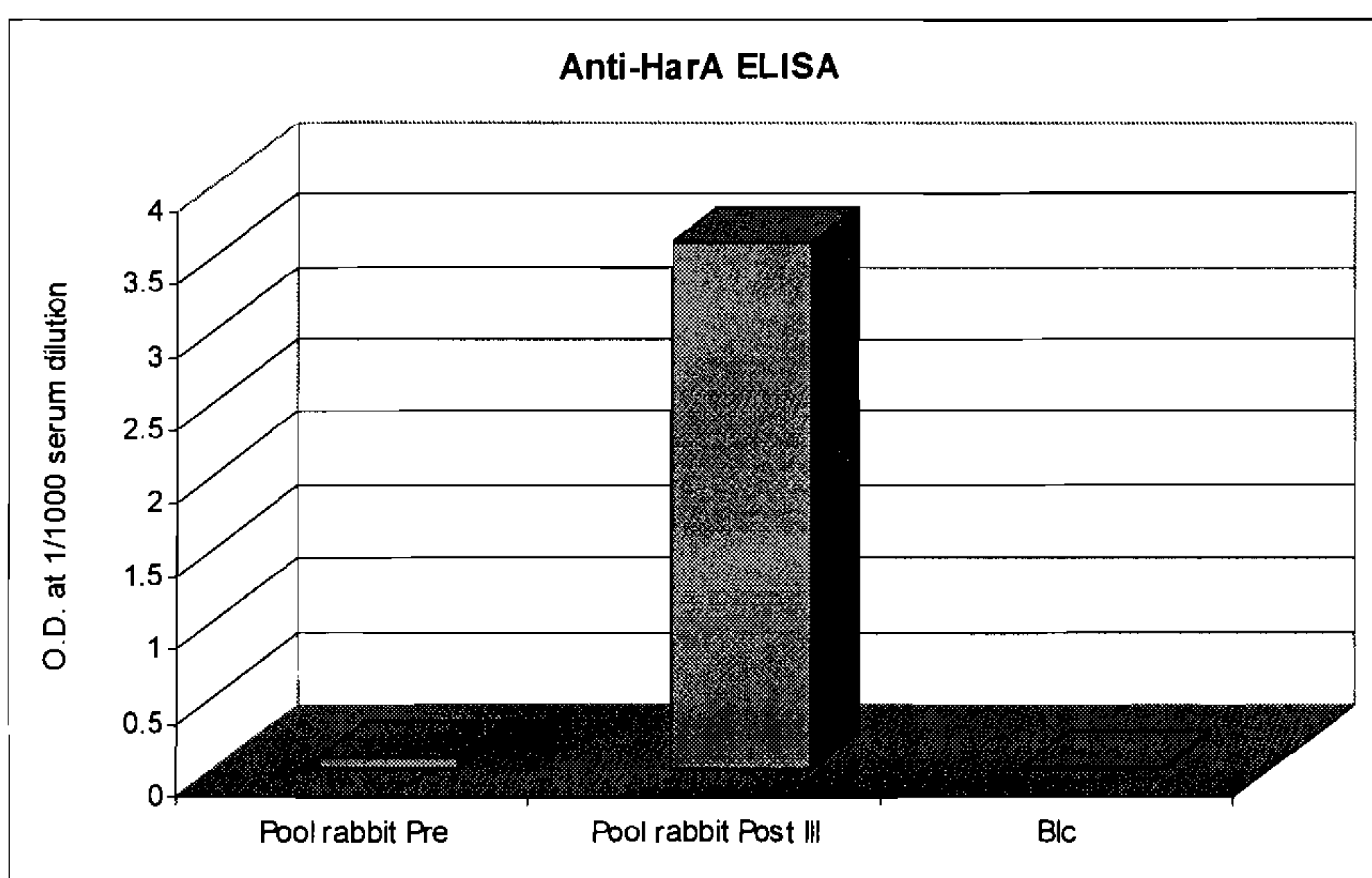
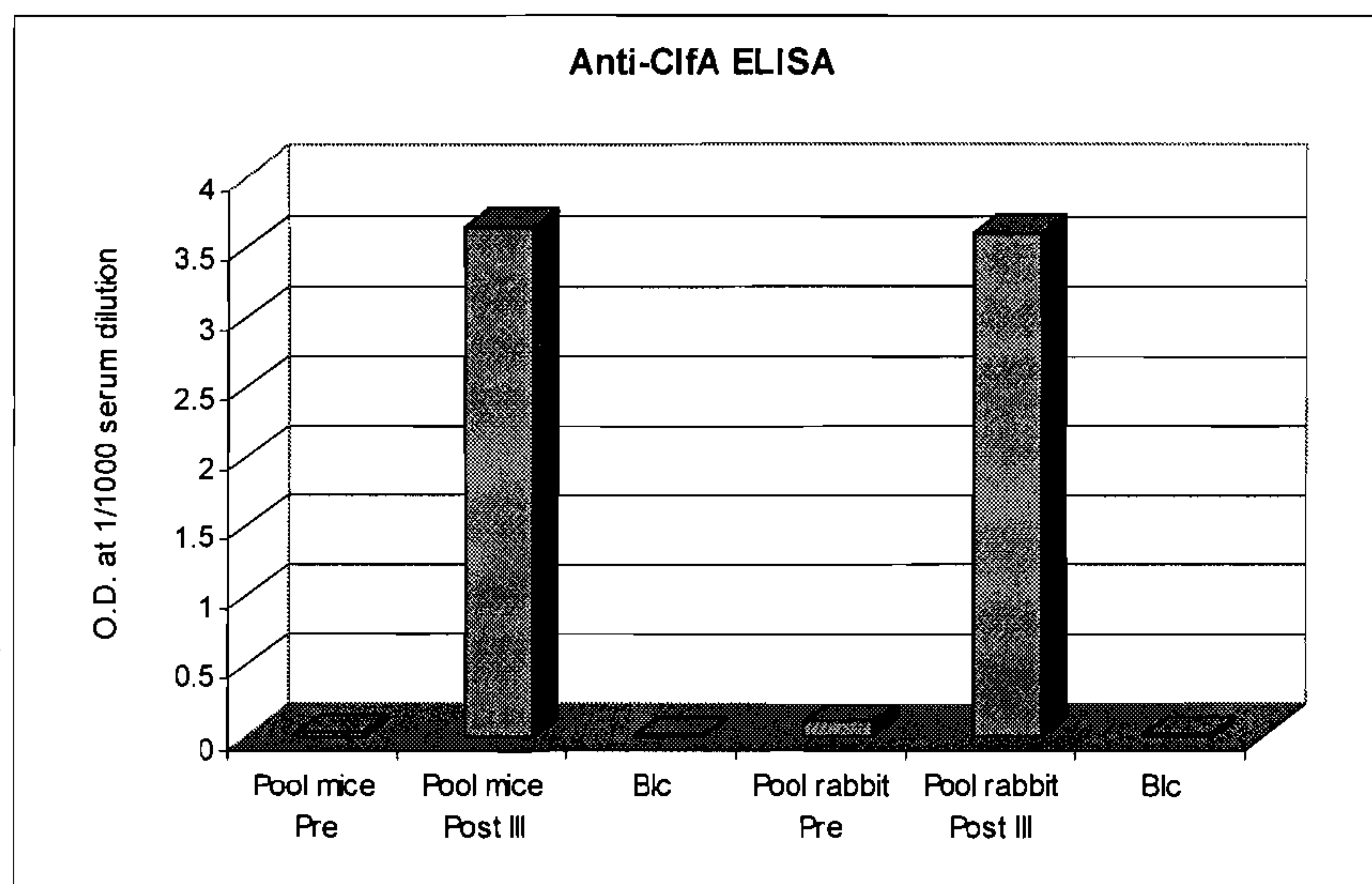
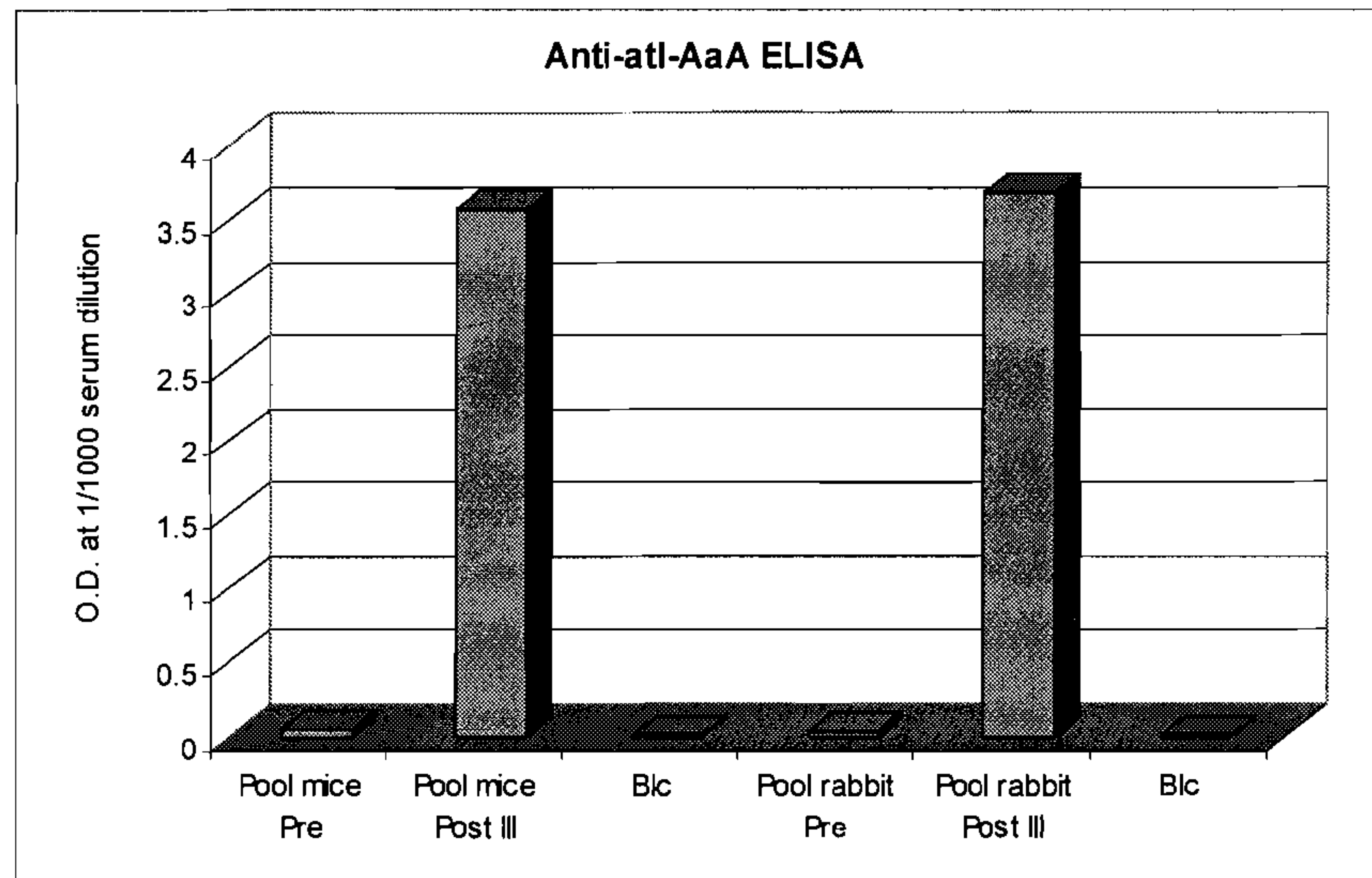


Figure 6

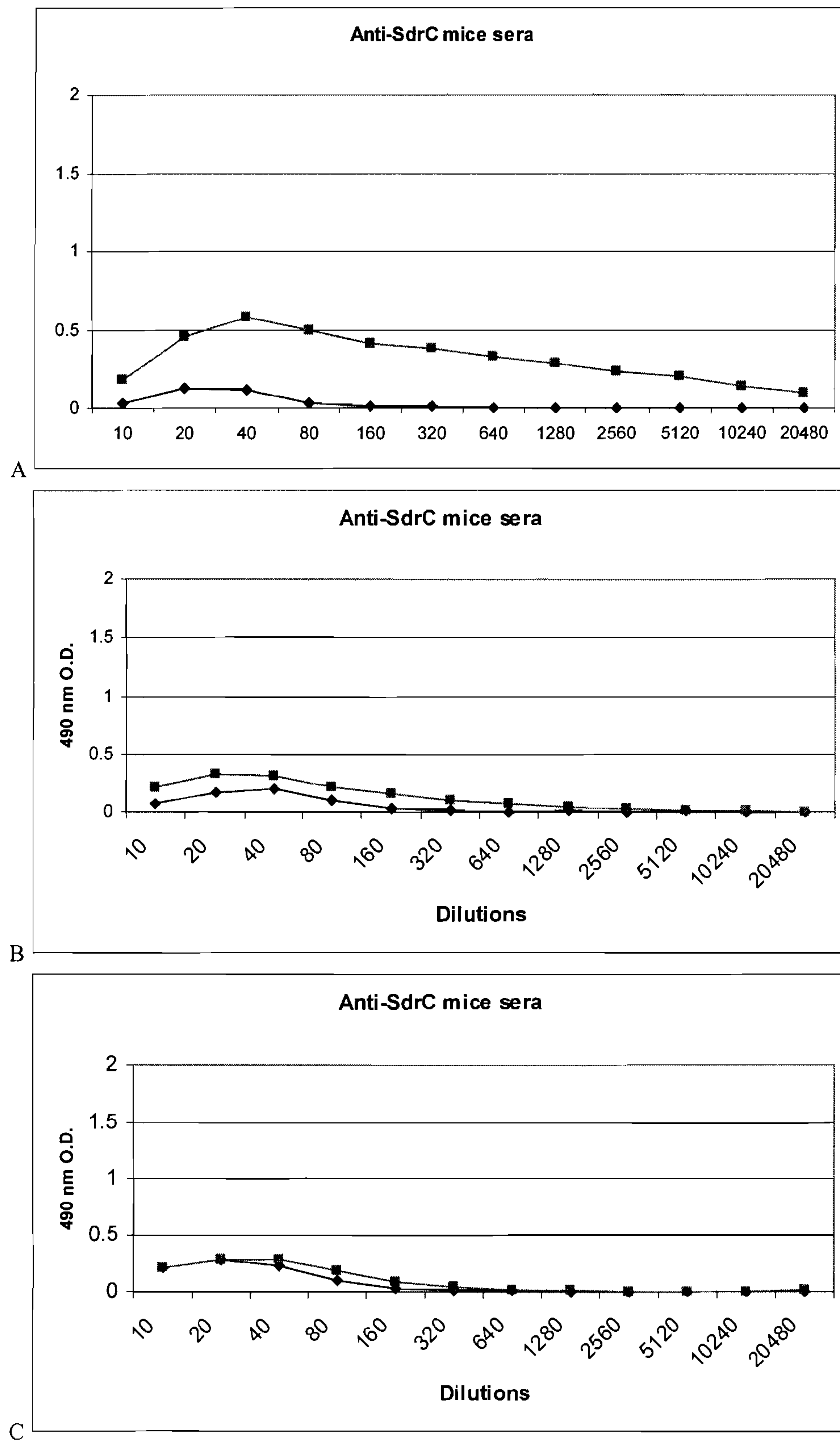


Figure 6

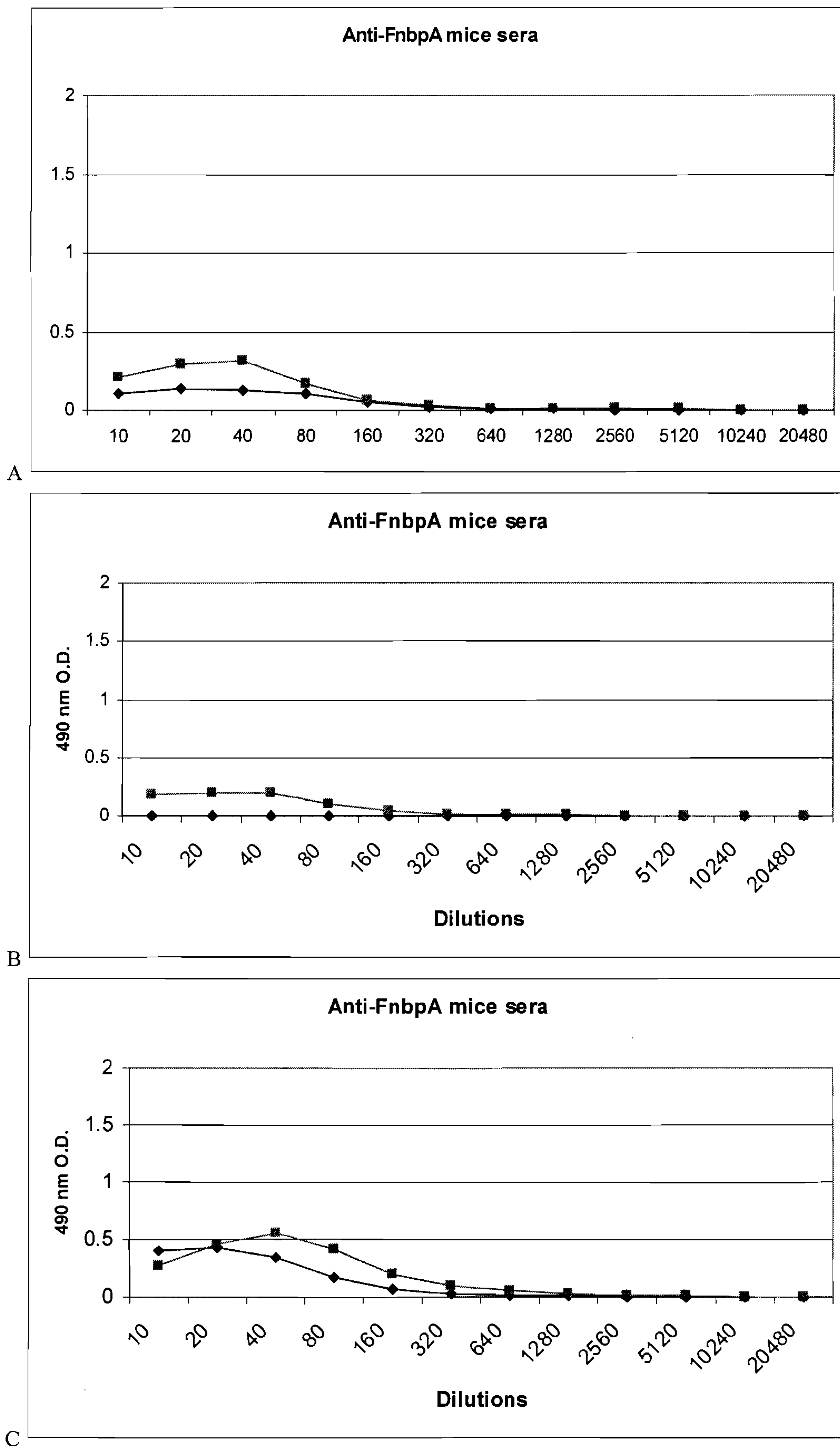


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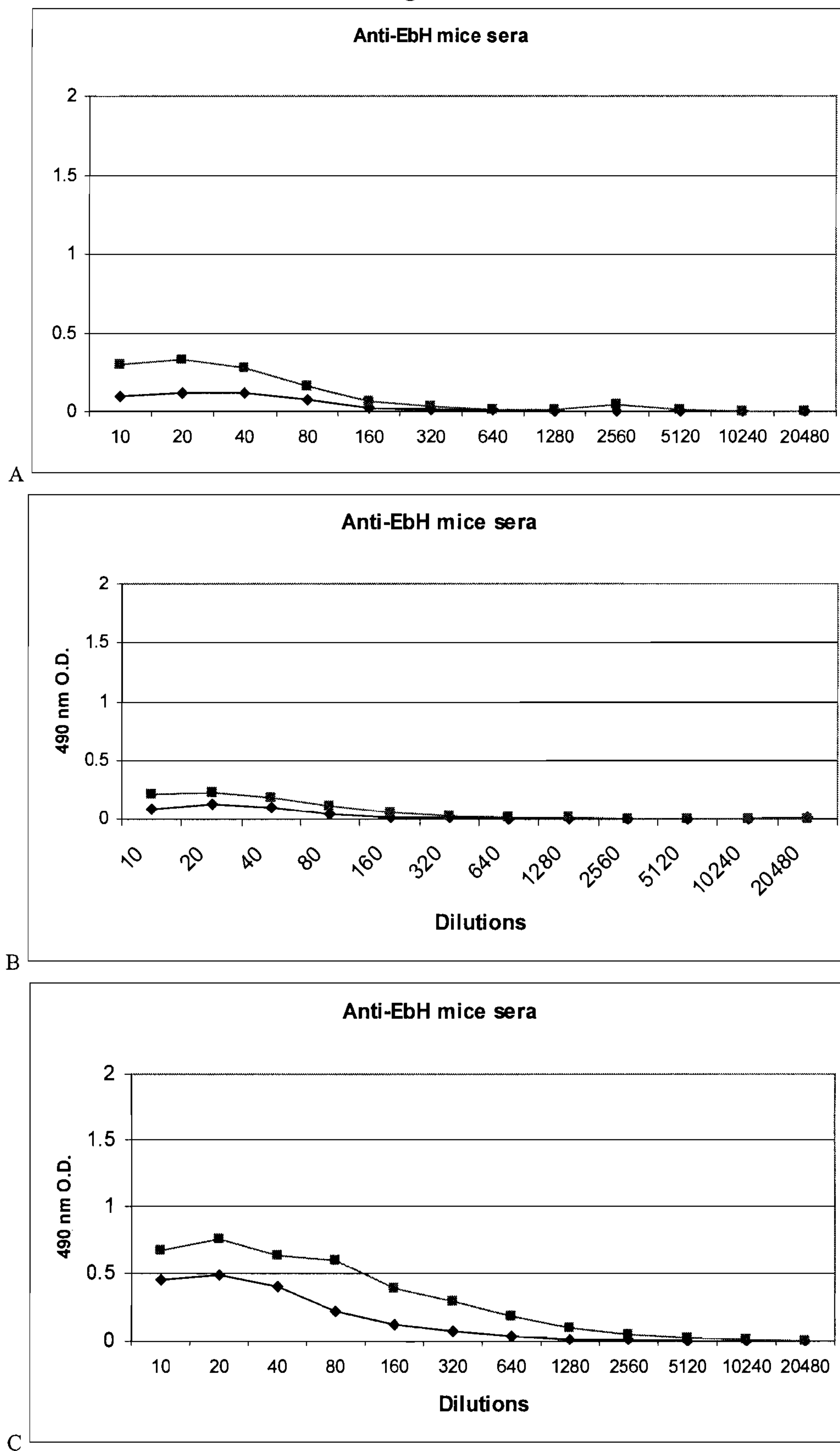


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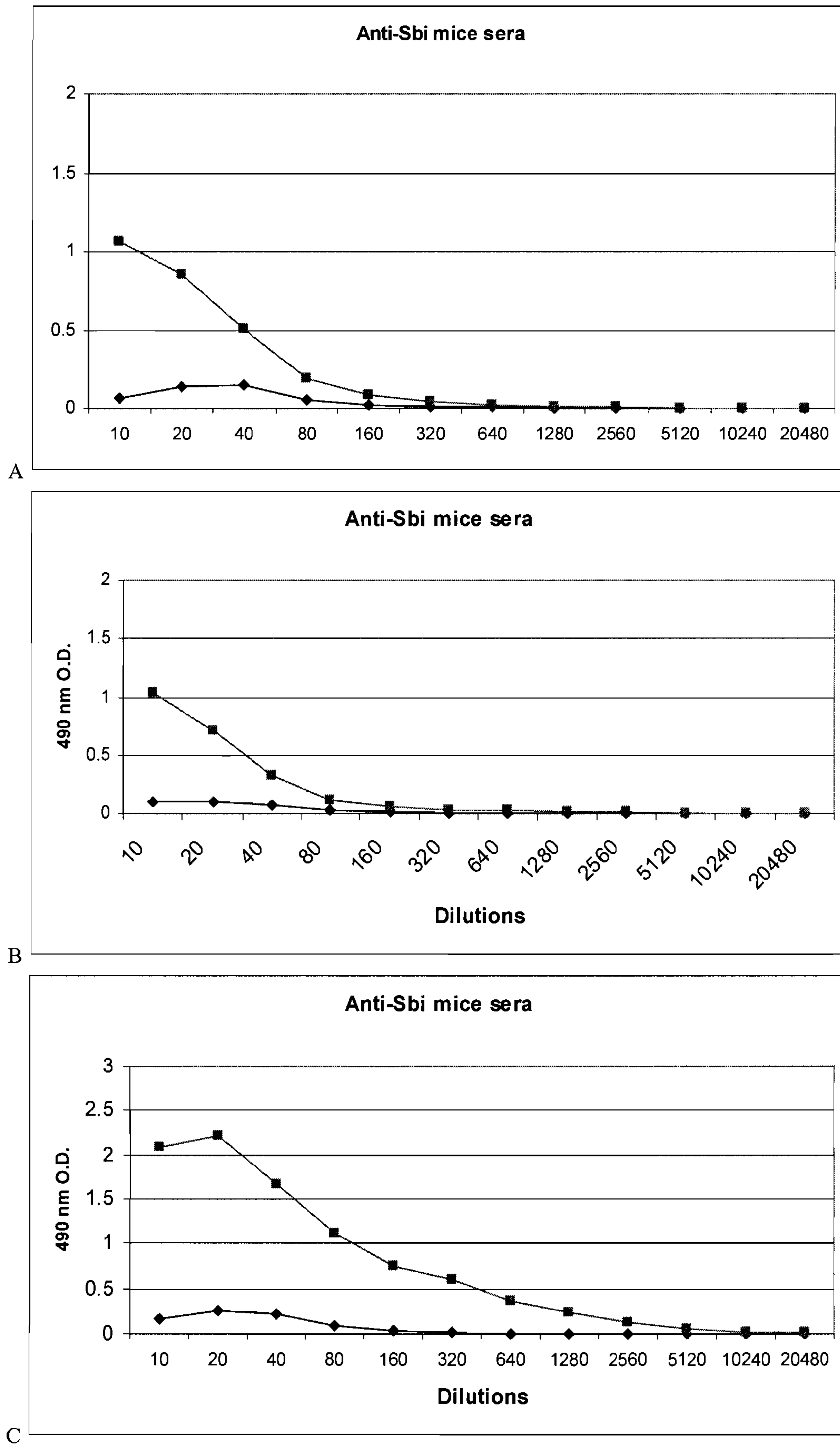


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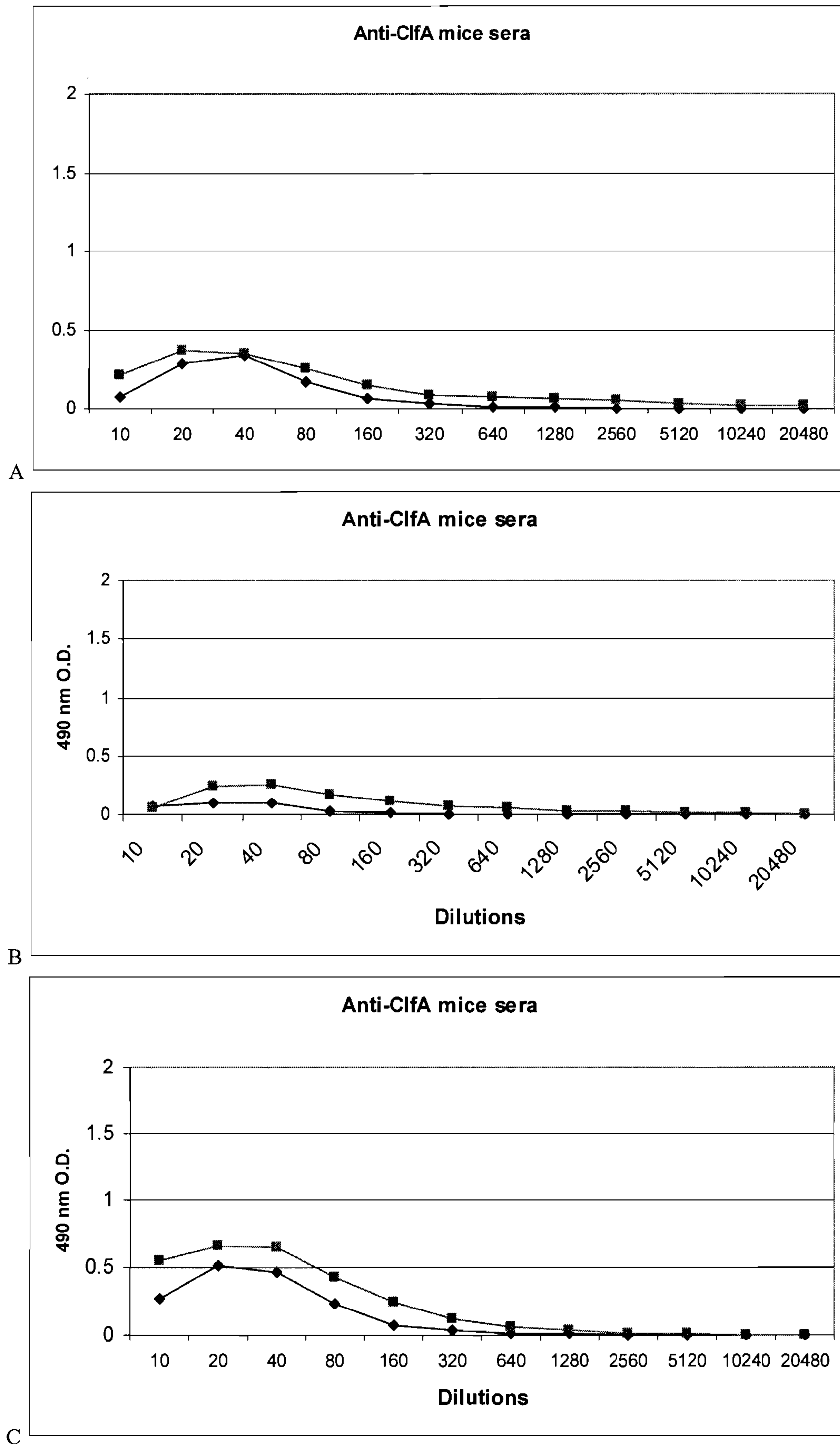
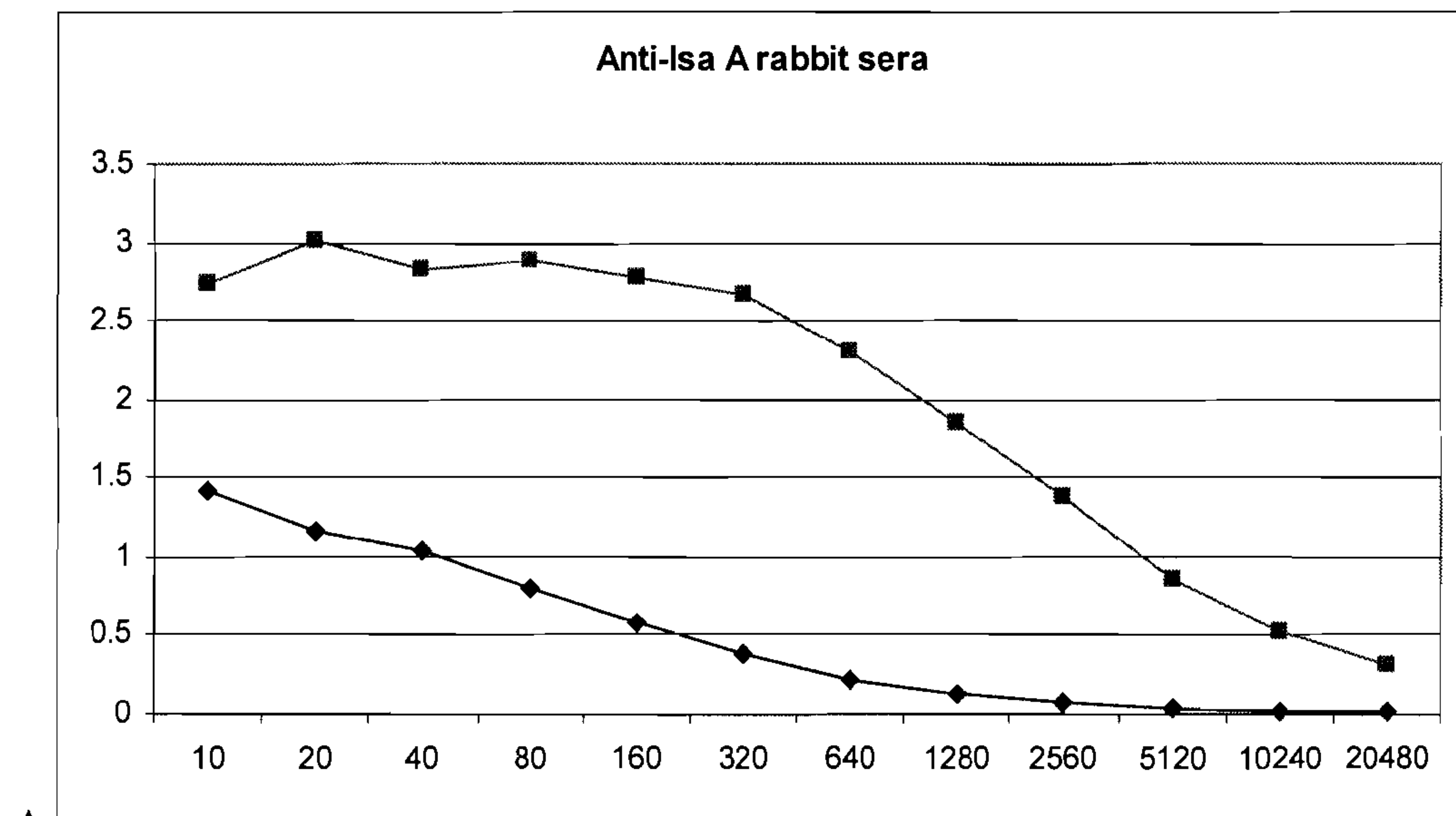
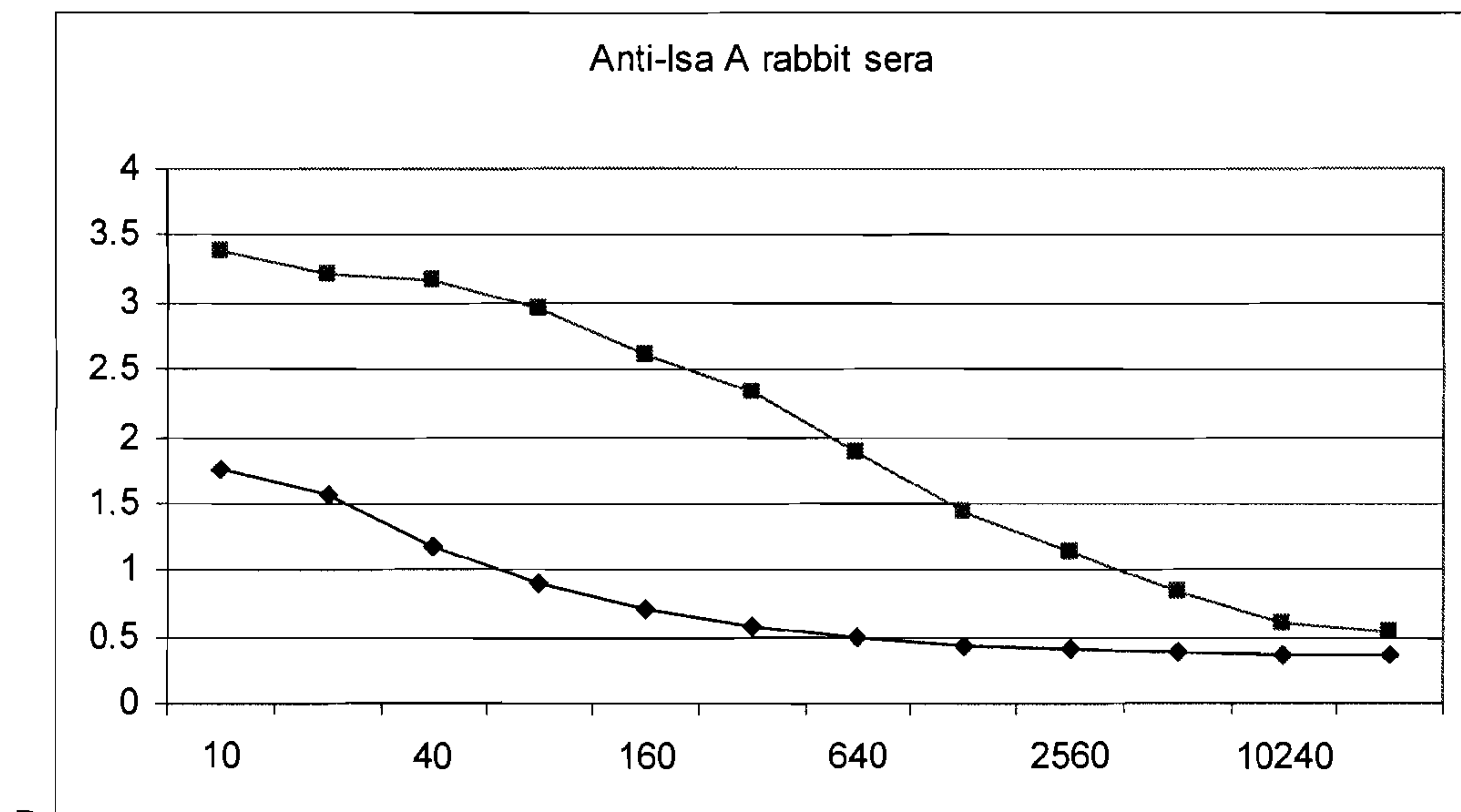


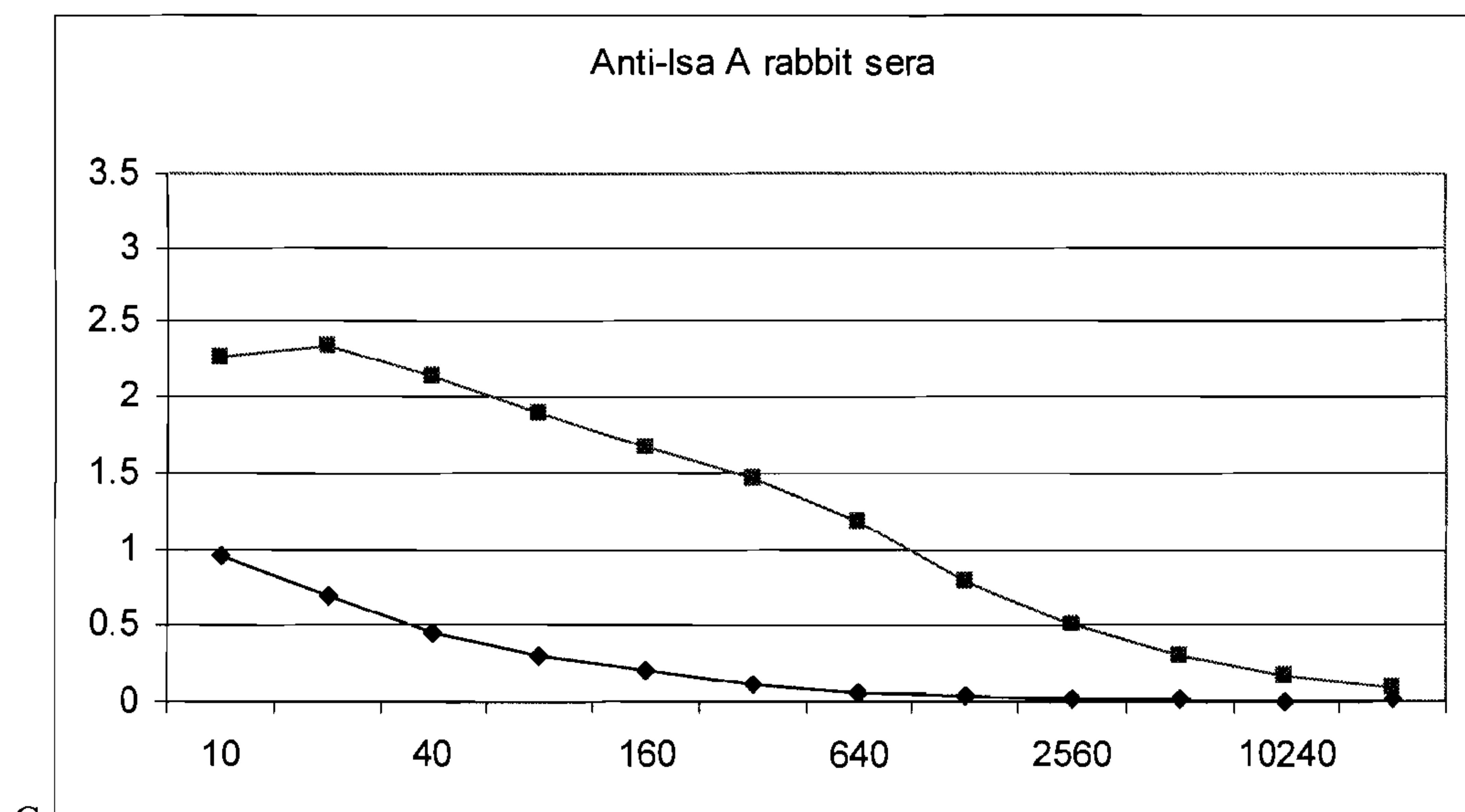
Figure 7



A

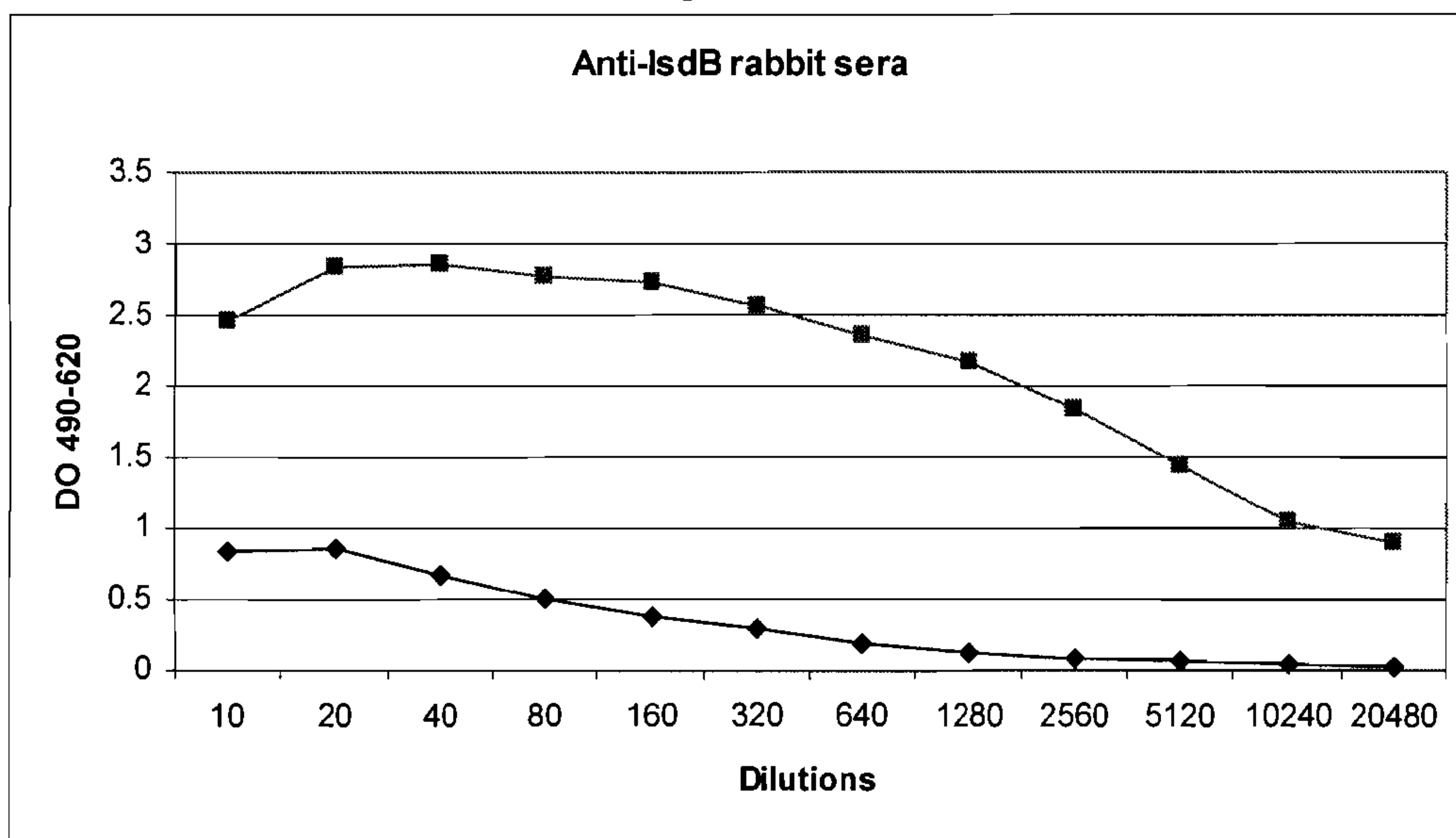


B

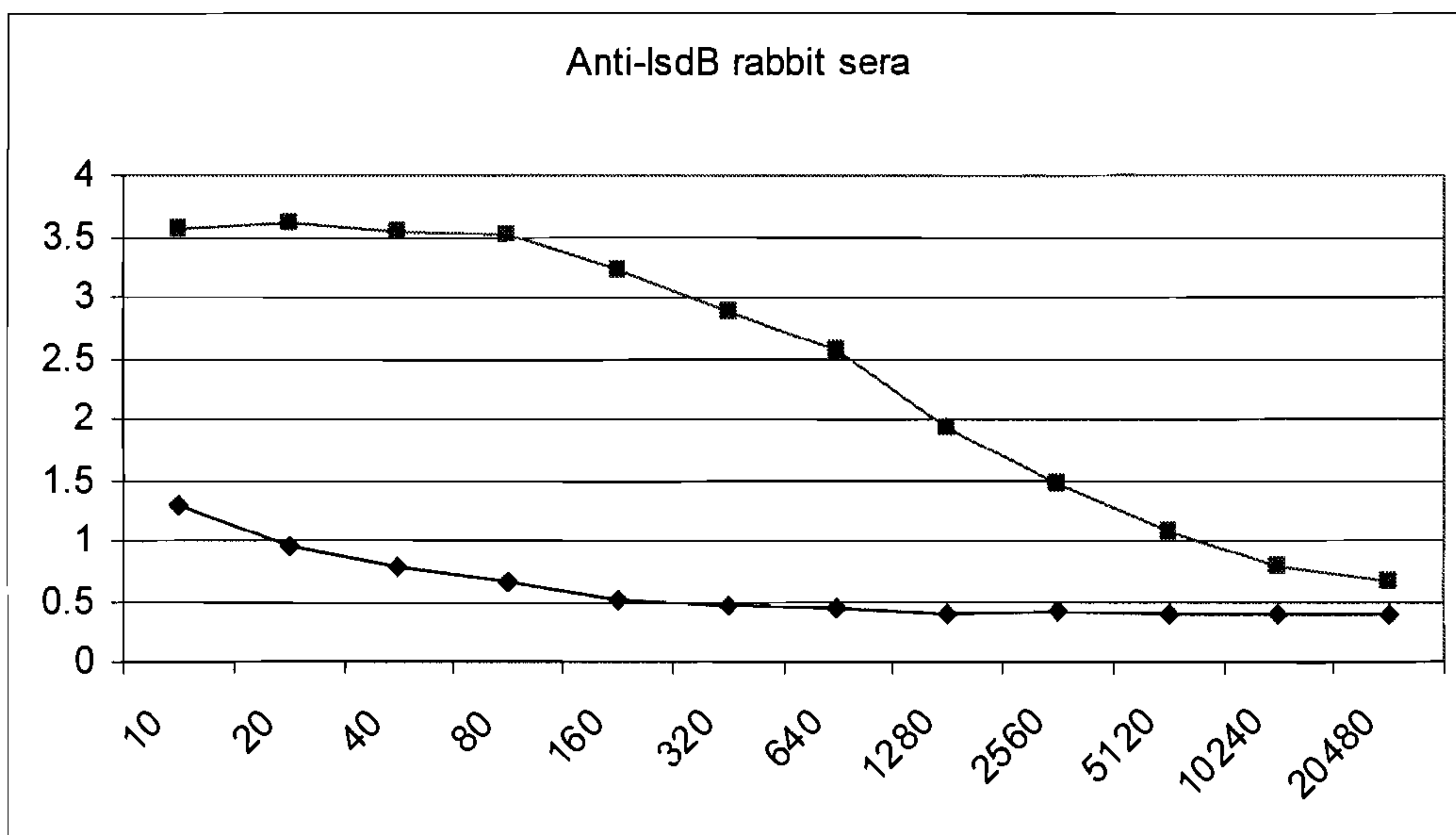


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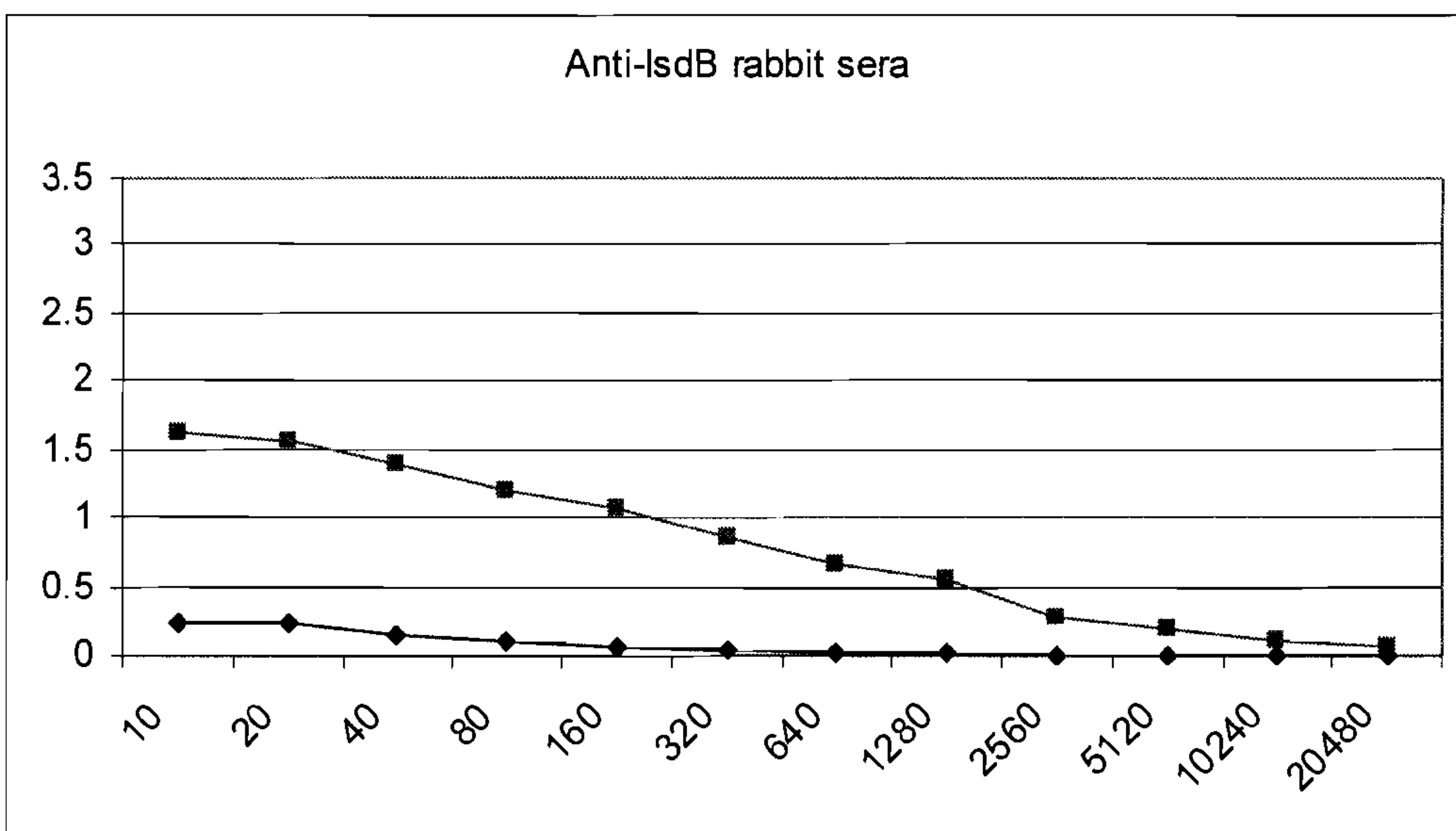
Figure 7



A



B



C

Figure 7

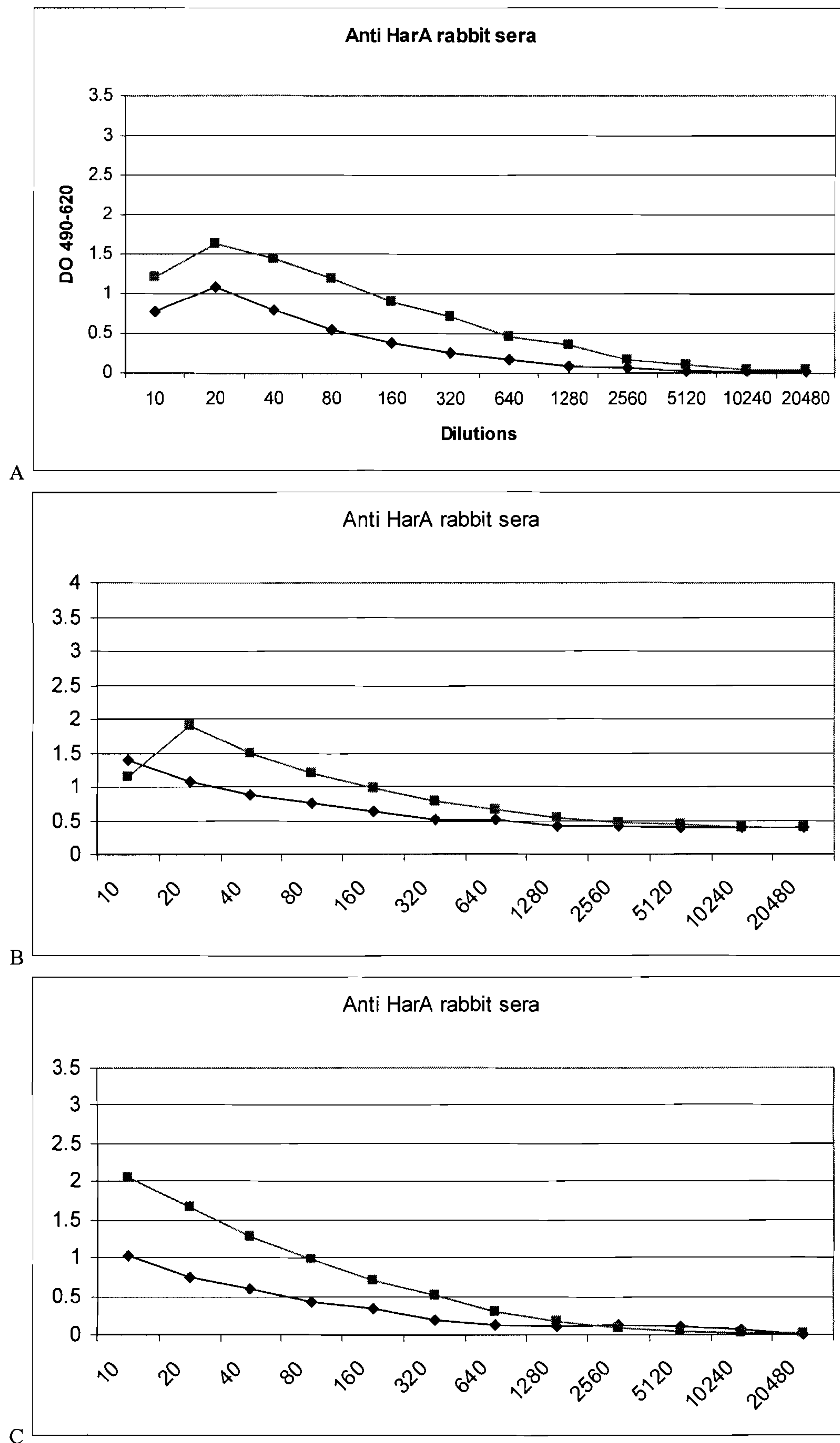


Figure 7

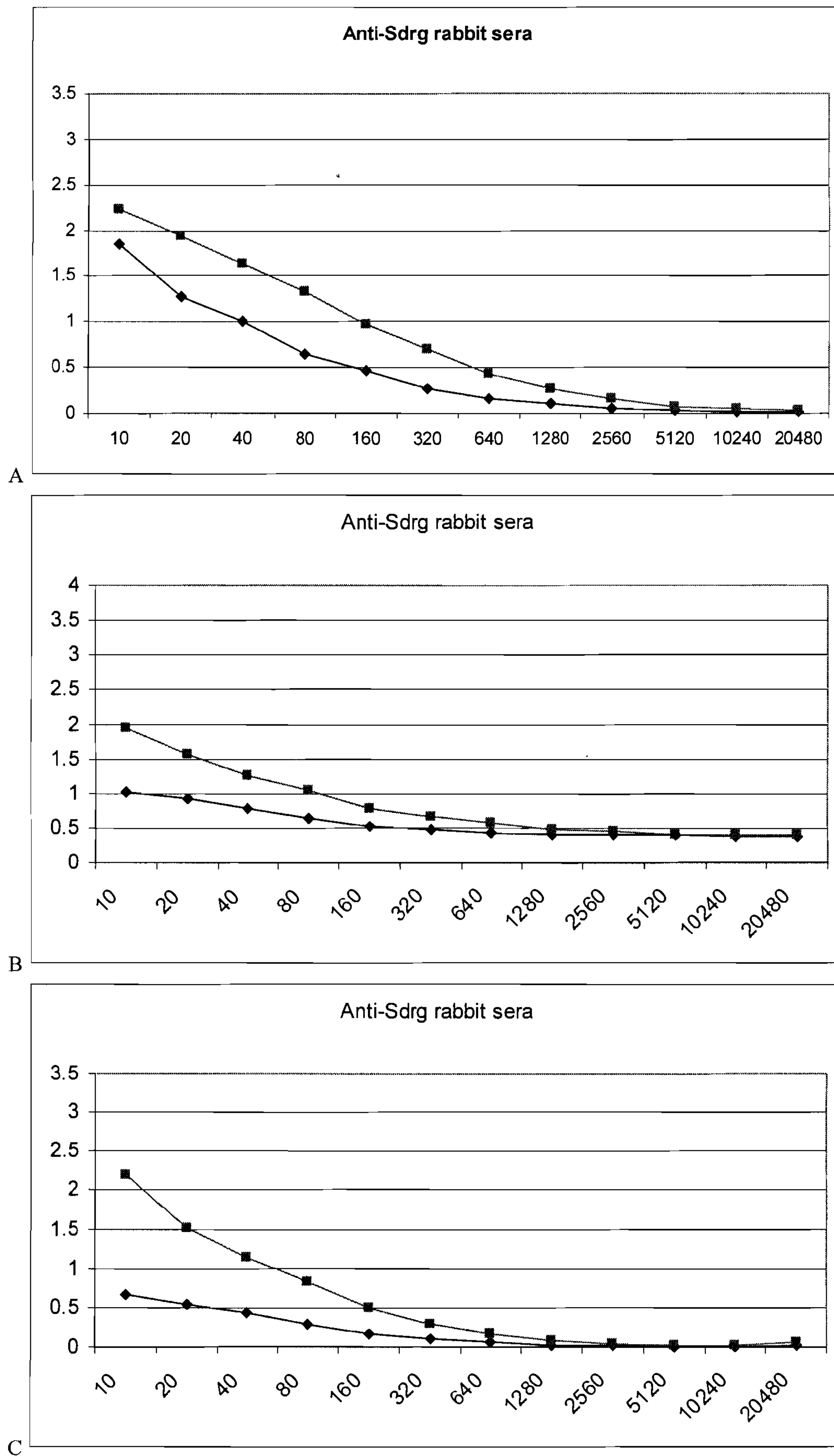


Figure 7

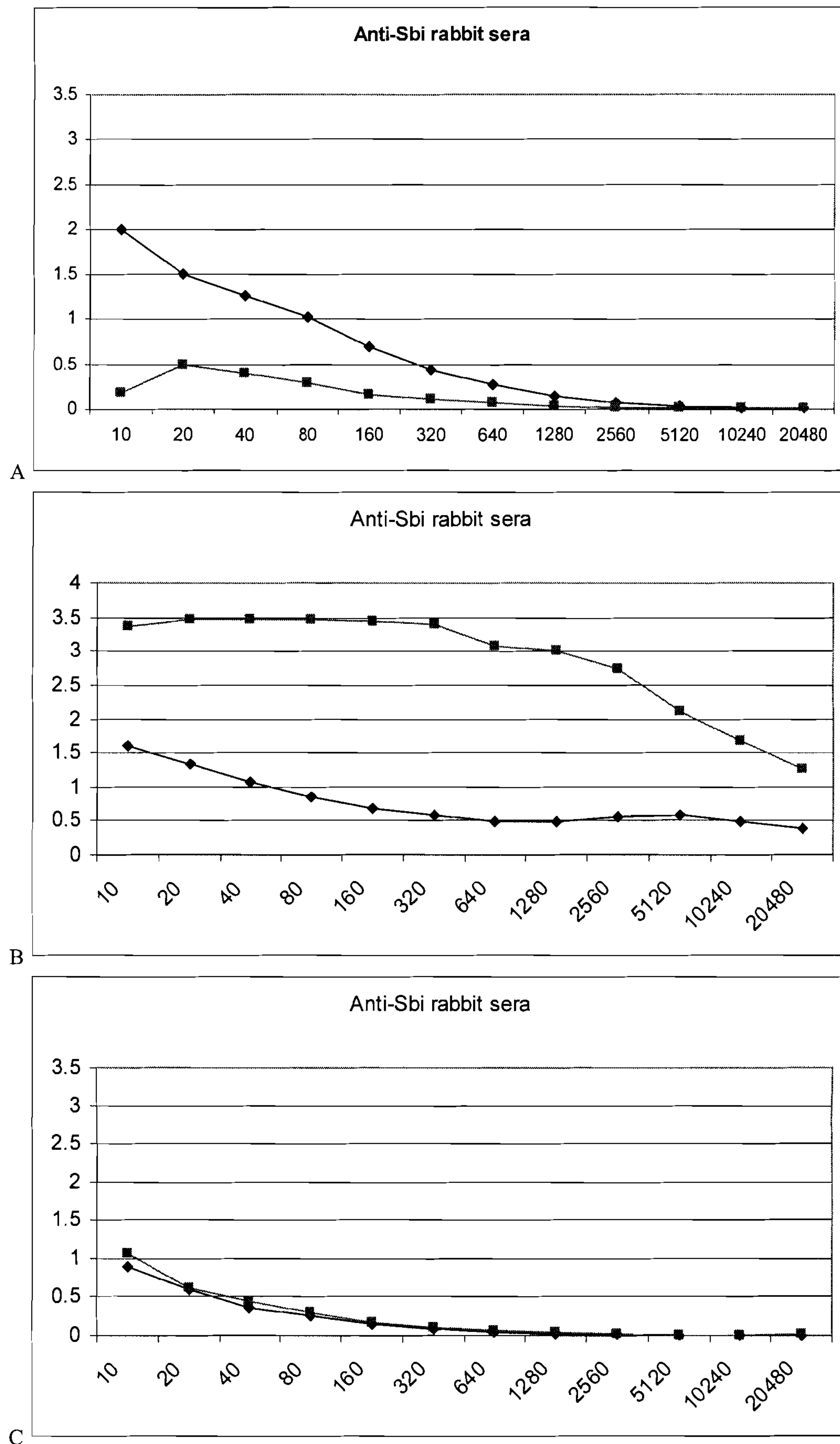


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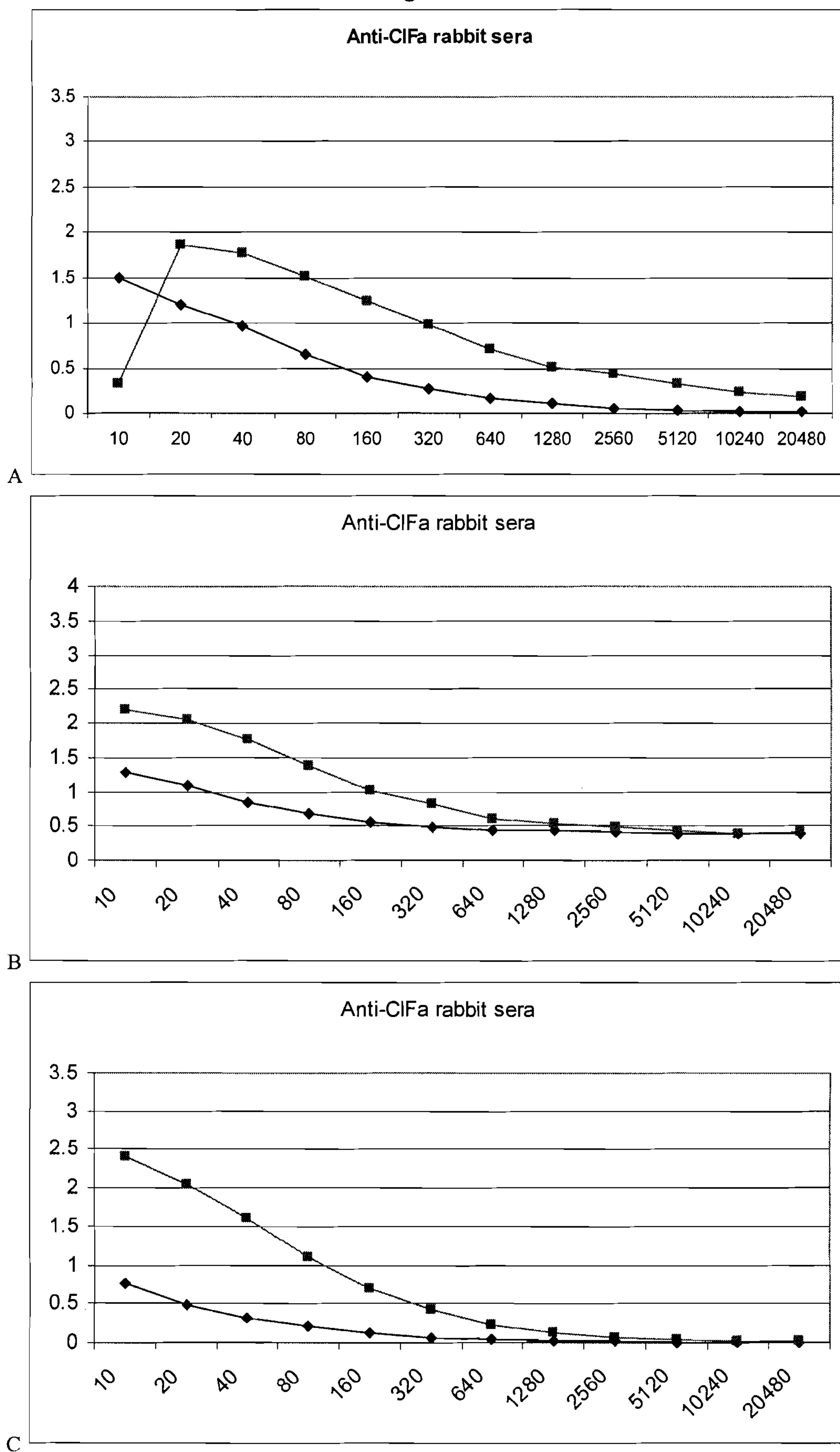


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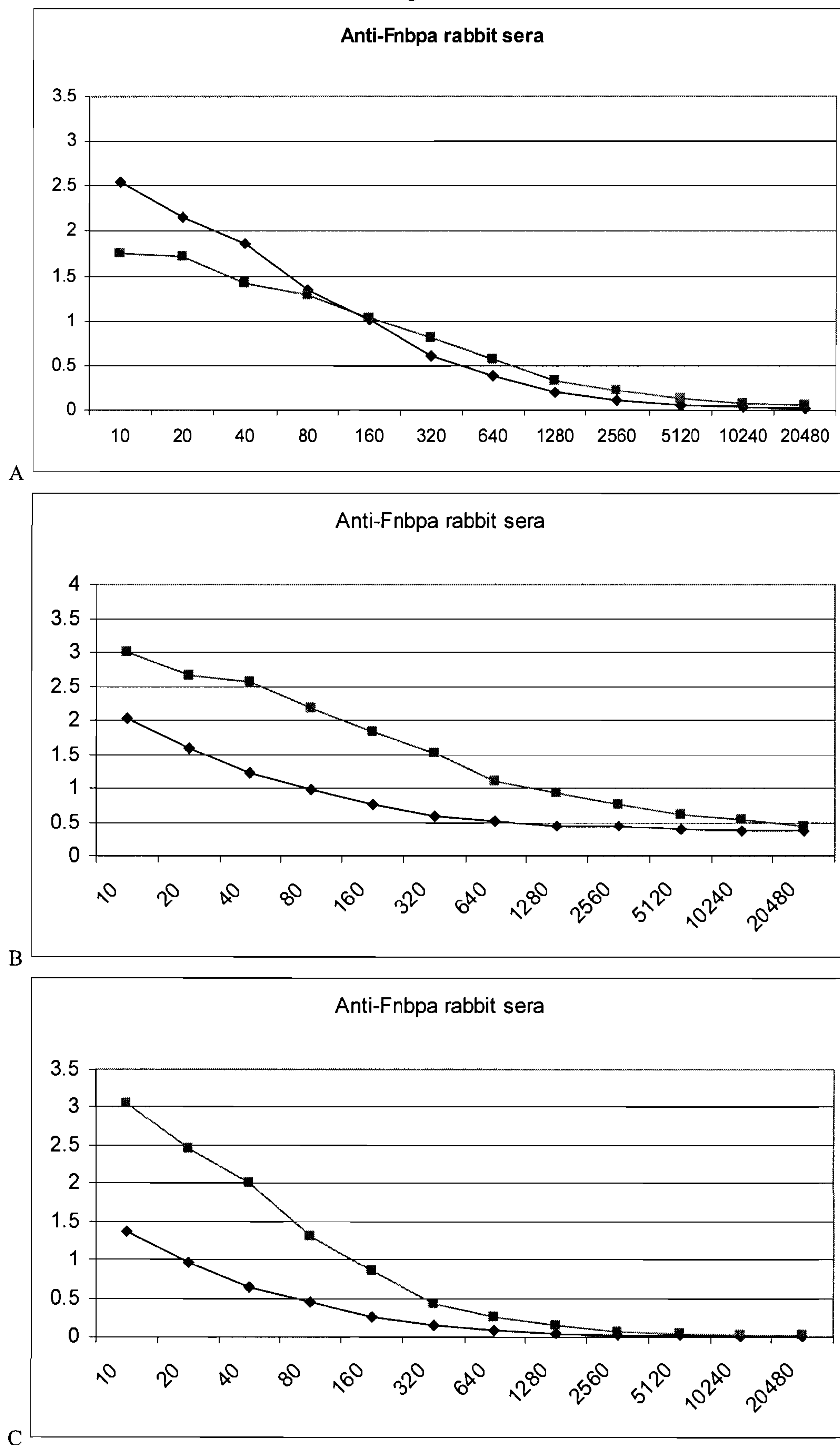
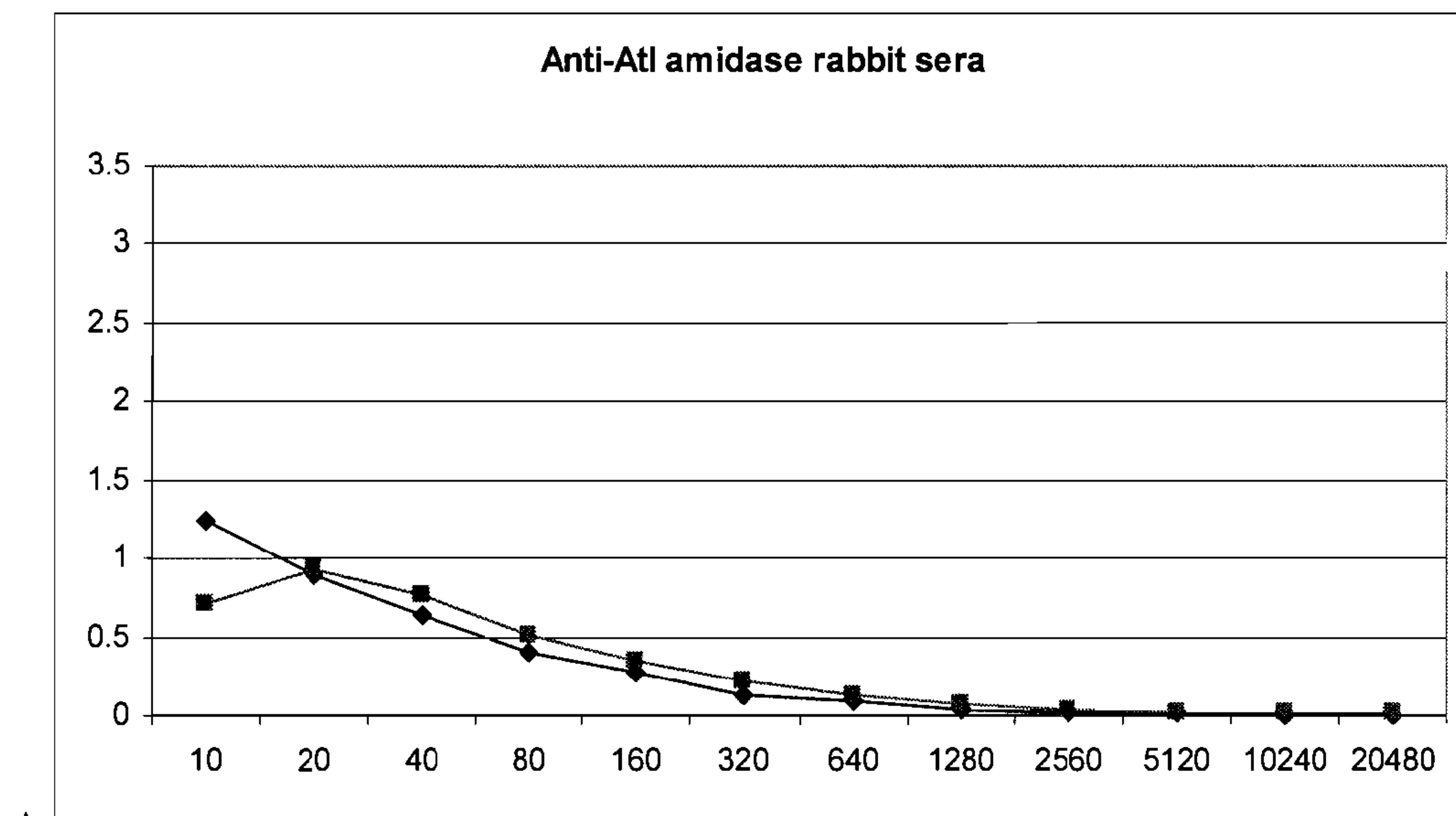
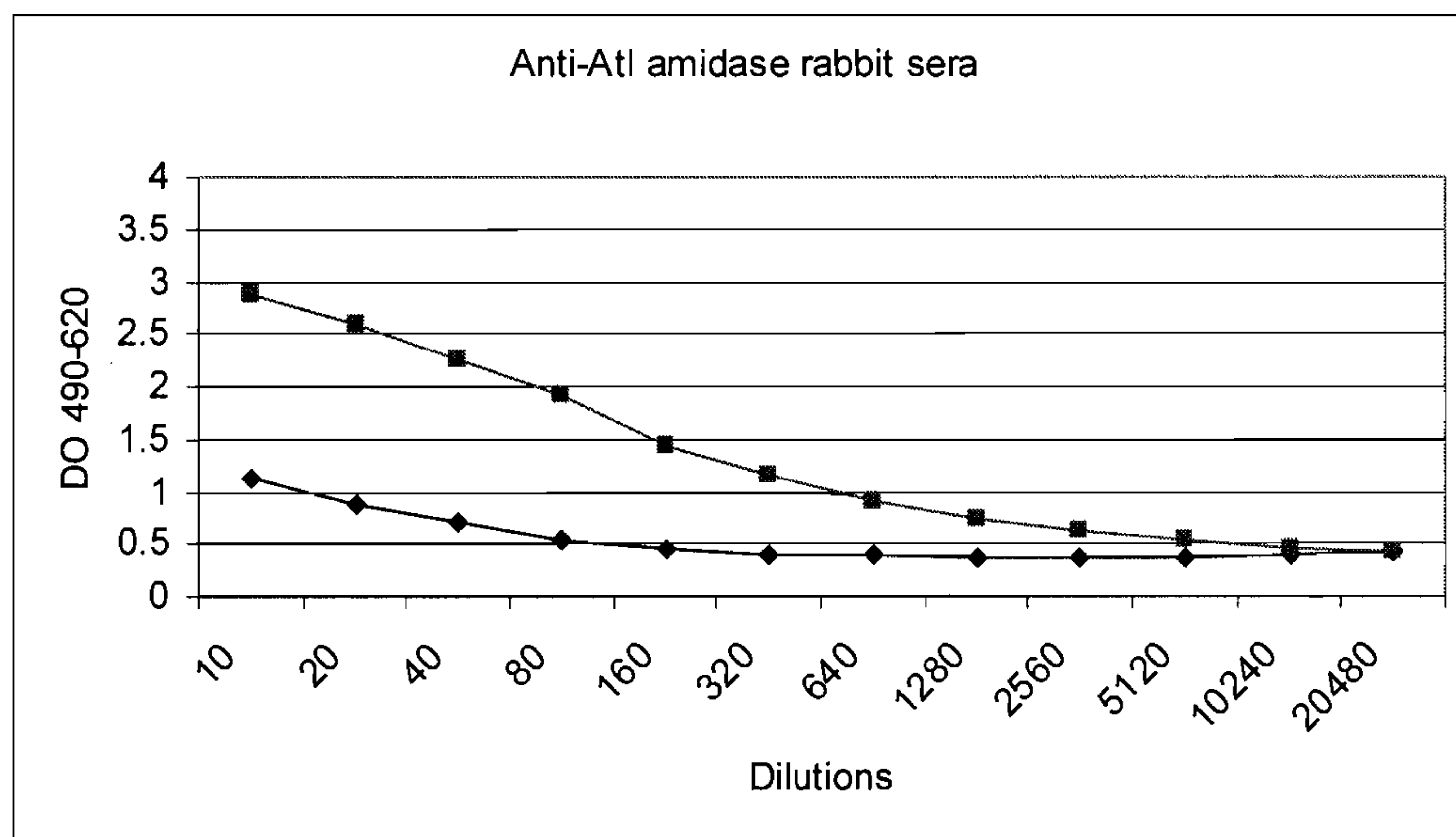


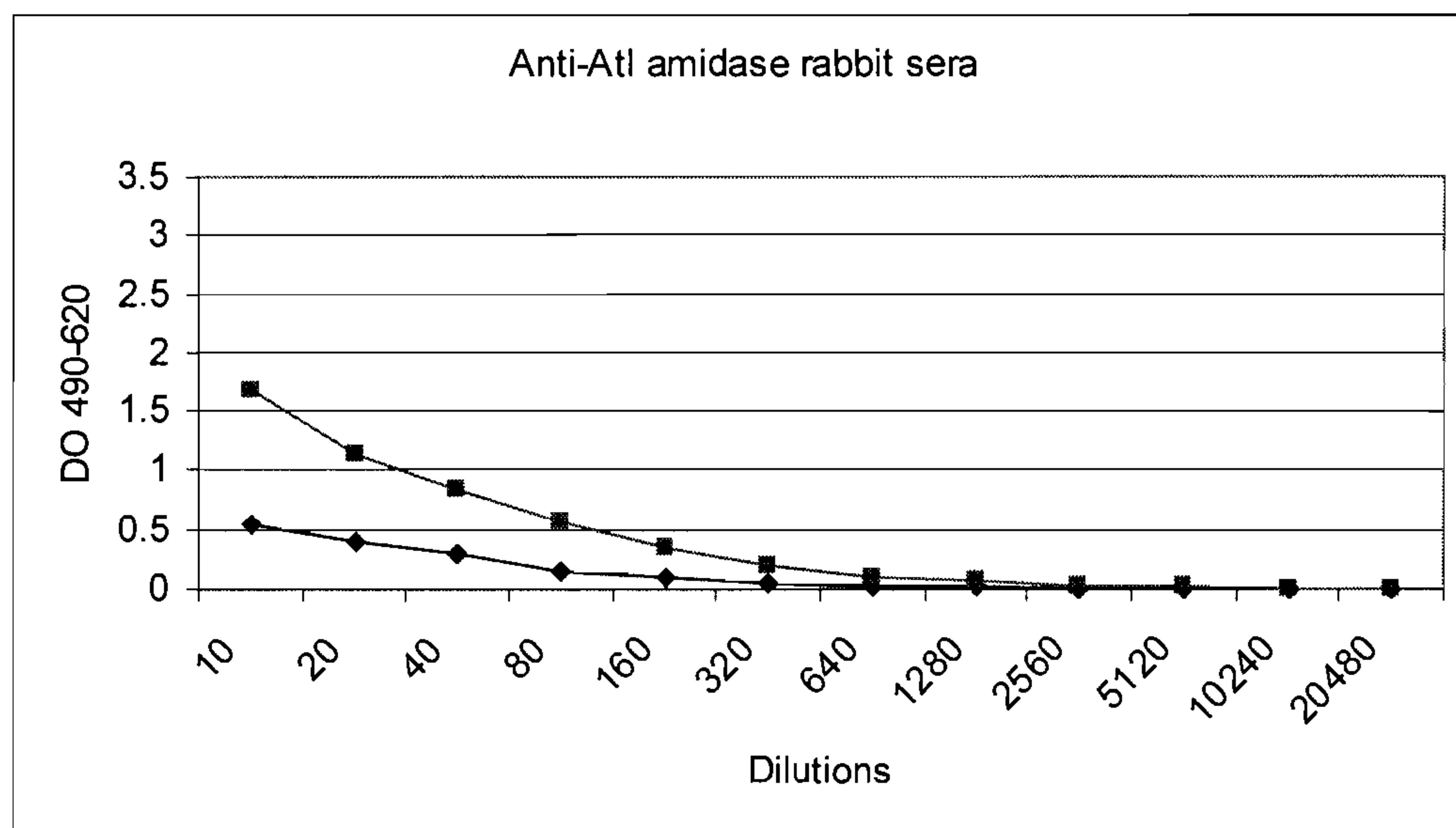
Figure 7



A



B



C