Title: COMPOSITION AND METHOD TO TREAT VIRAL, BACTERIAL AND PARASITIC INFECTIONS AND INFESTATIONS

Abstract: A composition for nasal administration to animals, including humans. Applicants’ composition includes lysozyme in combination with zinc. In certain embodiments, the composition further includes one or more anthelmintic compounds. A method to treat animals, including humans, having a pulmonary bacterial infection by delivering a therapeutically effective amount of lysozyme to the animal’s nasal pharynx. A method to treat animals, including humans, having a viral infection by delivering a therapeutically effective amount of zinc to the animal’s nasal pharynx. In certain embodiments, the method further includes delivering lysozyme to the animal’s nasal pharynx.
COMPOSITION AND METHOD TO TREAT VIRAL, BACTERIAL AND 
PARASITIC INFECTIONS AND INFESTATIONS

Field Of The Invention

Applicants' invention includes composition and method to treat animals, 
including humans, having viral, bacterial, and/or parasitic infections / infestations. In 
certain embodiments, Applicants' composition comprises zinc and a carrier. In 
certain embodiments, Applicants' composition includes lysozyme. In certain 
embodiments, Applicants' composition further includes one or more polymeric 
materials, one or more anthelmentics, copper, silver, Vitamin A, Vitamin E, and/or 
aloevera.

Background Of The Invention

Foot and Mouth Disease ("FMD"), caused by Aphthovirus, is known to be 
highly contagious, and therefore, one of the most feared diseases. FMD is endemic to 
Asia, Africa, parts of Europe and South America. Because the disease is easily 
transmitted and spreads rapidly, outbreaks cause enormous financial losses in terms of 
production and export revenue, costs of eradication, and vaccination programs. 
Cloven hoofed livestock such as cattle, pigs, sheep and goats as well as species of 
wild animals (deer, water buffaloes, bears, antelopes, llamas, camels, giraffes, 
elephants, rats, hedgehogs) of all ages and sexes are susceptible to infection. Humans 
in very rare cases may develop very mild forms of disease.

FMD is resistant to cold temperatures and survives even freezing, but it is 
susceptible to pH less than 5, sunlight, heat and dryness. Transmission typically 
occurs either by aerosol from animal to animal, or through contact with contaminated 
personnel, equipment or feed. Wind may spread the virus over long distances.

Occasionally, it is imported to FMD-free countries by contaminated frozen meat or 
garbage. Several outbreaks have been traced to consumption of uncooked waste 
(swill feeding) from ships or airplanes originating from FMD-infected countries. 
Historically, even contaminated biologicals (modified live vaccines against hog 
cholera, Rinderpest or insufficiently inactivated FMD vaccines) have been a source of 
infection. In cattle, the primary site of infection are mainly the nostrils, following 
inhalation.
Secondary bacterial infections are caused by certain species of bacteria that wait around for an accident to occur. They are commonly found in the environment or in the animal, cause no problems, and only become a problem if certain tissues or functions in the animal become damaged or stressed.

Bovine respiratory disease complex ("BRDC") is a complex involving environmental, viral, and bacterial factors. Pneumonia typically starts to appear soon after a significant environmental, physiological, or psychological stress and/or exposure to new disease organisms. Production examples include weaning, commingling at points-of-sale followed by shipping, increasing dietary energy-density in the feedlot, parturition and lactation in dairy cattle, and heat or cold stress in pasture cattle.

Several different pathogens play a role in BRDC. *Pasteurella haemolytica*, biotype A, serotype 1 (A1) is the primary, but not sole, bacterial pathogen in BRDC in the United States. *Pasteurella haemolytica* occurs in the nasopharynx of healthy cattle, and is pathogenic only in ruminants, presumably because of the ability of a heat-labile leukotoxin that is active only against ruminant leukocytes. *Pasteurella haemolytica* A2 seems to be the primary serotype colonizing the nasopharynx in cattle on the farm, whereas *P. haemolytica* A1 proliferates during shipping and becomes the primary isolate in feedlots. Infection with bovine respiratory viruses enhances nasopharynx colonization by *P. haemolytica* A1, even in the face of active immunity.

Pasteurellosis disease occurs when the animal's normal defenses are compromised. In this case the lining of the upper respiratory tract could be damaged by IBR, PI-3, or BRSV viruses, the clearing mechanism could be depressed by BVD virus, or the production of local antibodies against *Pasteurella* may be interrupted by environmental or nutritional stress. When the defenses are compromised, the bacteria become attached to the lining of the respiratory tract (colonize), reproduce rapidly, and spread throughout the lungs. The severity of the disease depends upon which *Pasteurella* organism is involved and, at least in calves, with the nature of associated infections, such as Infectious Bovine Rhinotracheitis Virus ("IBRV"), bovine viral diarrhea virus ("BVDV"), Bovine Rhino Syncytial Virus ("BRSV"), parainfluenza type 3 virus ("PI3V"), and/or other bacteria. *P. haemolytica* causes a more rapid and
more severe disease course than *P. multocida*; however, depending upon associated infections, both can result in death of the animal.

The first clinical signs seen in calves affected by pasteurellosis are vague, often limited to a slight depression and lack of interest in eating. As the disease progresses, the calf refuses to eat, the depression worsens and is exhibited by a lowered head and ears, discharges from the nose increase and change in consistency from being thin-clear to thick-yellow, body temperatures rise to as high as 107°F, and breathing becomes rapid and labored. A cough may be noted early in the disease; however, as the lung damage increases, coughing and breathing may become very painful for the animal. The calf may likely try to suppress a cough. The calf, however, cannot suppress breathing. The labored breathing and associated pain make the calf reluctant to move, and cause the calf to stand and extend its neck and tongue to suck in air. If the disease process is not stopped, the lungs become irreversibly damaged, the body temperature drops to below normal, and the animal usually dies.

If it survives, the irreversible lung damage results in a poor-doing calf that will never be able to perform; these calves are referred to as chronic in the stocker and feedyard industries.

*Pasteurella* pneumonia develops very rapidly; if the first sign of the disease (lack of interest in food) goes unnoticed and the start of treatment is delayed, the outcome of the disease becomes much poorer. This delay in detection and treatment becomes a major factor in the severity and duration of sickness in calves.

The pneumonia caused by *Pasteurella* alone has been commonly referred to as shipping fever; the respiratory illness caused by the association of *Pasteurella* and other diseases has been called Bovine Respiratory Disease Complex (BRD or BRDC). Presently, in the scientific world, shipping fever is not talked about much; BRDC is the subject of interest; the true "shipping fever" losses are minimal compared to the BRDC losses in the cattle industry. *Pasteurella* pneumonia is present in nearly 75% of all diagnosed cases of BRD.

Viral isolates from bovine respiratory disease cases include IBRV, BVDV, BRSV, PI3V, malignant catarrhal fever virus, reovirus, calicivirus, and bovine adenovirus, parvovirus, herpesvirus type 4, rhinovirus, reovirus, enterovirus, and
respiratory coronavirus. Of these, IBRV, BVDV, and BRSV are of major importance in field cases of bovine respiratory disease in the United States.

Colonization of the nasopharynx allows inspiration of Pasteurella sp. organisms, which are cleared from the lungs if a competent immune system is present.

High-stress environments, viral immunosuppression, or inadequate nutrition in the form of energy, protein, and trace elements may allow inspired Pasteurella sp. to colonize the lungs.

_Pasteurella multocida_ is secondary in importance to _P. haemolytica_ in bovine pneumonia except in veal and dairy calves, where prevalence of _P. multocida_ infection may be higher than _P. haemolytica_. _Haemophilus somnus_ is a major cause of respiratory disease in fall-weaned calves shipped to feedlots in Canada. _Mycoplasma_ organisms play a secondary, but perhaps important, role in bovine respiratory disease.

Prior art methods attempt to keep the _Pasteurella_ growth in animals under control (reduce the challenge) by administering antibacterial drugs in the feed, in the water, by injection, or in bolus form. Applicants' method administers one or more antibacterial medicaments to the animal's nasal cavity / nasopharynx (collectively the "nasal pharynx").

An infection of the lower respiratory tract, usually resulting in bronchitis or pneumonia, can be caused by any of several parasitic nematodes, including _Dictyocaulus viviparus_ in cattle. _Dictyocaulus viviparus_ belongs to the superfamily Trichostrongyloidea and has direct life-cycles. It is common in northwest Europe and is the cause of severe outbreaks of "husk" or "hoose" in young grazing cattle.

With regard to the _Dictyocaulus_ spp., adult females in the bronchi lay larvated eggs that hatch in the bronchi after being coughed up and swallowed. The larvae can become infective in feces on pasture after a minimum of 1 week in warm, moist conditions, but typically in summer in temperate northern climates will require 2-3 weeks. Once infective, the larvae can be further dispersed from fecal pats mechanically or by the sporangia of the fungus _Pilobolus_. A proportion of infective larvae will survive on pasture throughout the winter until the following year but, in very cold conditions, most will become nonviable. The principal source of new infections each year is from infected carrier animals with overwintered larvae.
providing a secondary but not unimportant contribution in some countries. Clinical disease usually develops on first exposure to sufficient infective larvae. Because D. viviparur infection in cattle is the most economically important, it has been most investigated and many of the observations from it are applicable to other species.

The pathogenic effect of lungworms depends on their location within the respiratory tract, the number of infective larvae ingested, and animal's immune state. During the prepatent phase of D. viviparur infection, the main lesion is blockage of bronchioles by an infiltrate of eosinophils in response to the developing larvae; this results in obstruction of the airways and collapse of alveoli distal to the block.

The clinical signs are moderate unless large number of larvae are present, in which case the animals may expire in the prepatent phase with severe interstitial emphysema. In the patent phase, the adults in the segmental and lobar bronchi cause a bronchitis, with eosinophils, plasma cells, and lymphocytes in the bronchial wall, a cellular exudate, frothy mucus, and adult nematodes are found in the lumen. The bronchial irritation causes marked coughing, and the entire reaction leads to increased airway resistance. A major component of the patent state is development of a chronic, nonsuppurative, eosinophilic, granulomatous pneumonia in response to eggs and first-state larvae spirated into alveoli and bronchioles. This usually occurs in the caudal lobes of the lungs and is severe when widespread; in combination with the bronchitis, death may result. Interstitial emphysema, pulmonary edema, and secondary bacterial infection are complications that increase the likelihood of death. Survivors may suffer considerable weight loss. If the animal survives until the end of patency, which is 2-3 months for D. viviparur, most or even all of the adult worms are expelled, and the cellular exudate resolves over the ensuing 4 weeks. Most recover unless secondary infection develops in the damaged lungs during the postpatent phase. In a few animals, clinical signs are exacerbated in the postpatent phase. This is due to development of a diffuse, proliferative alveolitis characterized by hyperplasia of the type II alveolar epithelial cells; the cause is unknown. One or more benzimidazoles, and/or invermectin are frequently used in cattle and are effective against all stages of D. viviparur. Applicants' method administers to the nasal cavity / nasopharynx (collectively hereinafter the "nasal pharynx") of animals, including humans, one or more parasiticides in combination with one or more antibacterial compositions.
Summary Of The Invention

Applicants’ invention includes a composition for nasal administration to animals, including humans. Applicants’ composition includes lysozyme in combination with zinc. In certain embodiments, Applicants’ composition further includes one or more anthelmintic compounds. In certain embodiments, those one or more anthelmintic compounds include ivermectin and/or one or more benzimidazoles. In certain embodiments, Applicants’ composition further includes one or more water soluble polymeric materials. In certain embodiments, such polymeric materials include one or more carbopol homopolymers, and/or one or more carbopol copolymers, and/or one or more water soluble polymers.

Applicants’ invention further includes a method to treat animals, including humans, having a pulmonary bacterial infection by delivering a therapeutically effective amount of lysozyme to the animal’s nasal pharynx. In certain embodiments, Applicants’ method further includes delivering zinc to the animal’s nasal pharynx.

Applicants’ invention further includes a method to treat animals, including humans, having a viral infection by delivering a therapeutically effective amount of zinc to the animal’s nasal pharynx. In certain embodiments, Applicants’ method further includes delivering lysozyme to the animal’s nasal pharynx.

In certain embodiments, Applicants’ methods further includes delivering a carbopol to the animal’s nasal pharynx. In certain embodiments, Applicants’ methods further includes delivering one or more anthelmintic compounds to the animal’s nasal pharynx.

Brief Description Of The Drawings

The invention will be better understood from a reading of the following detailed description taken in conjunction with the drawings in which like reference designators are used to designate like elements, and in which:

FIG. 1 is a table showing embodiments of Applicants’ composition which include zinc, lysozyme, and a polymeric component;

FIG. 2 is a table showing embodiments of Applicants’ composition which include one or more anthelmintics, lysozyme, and a polymeric component;
FIG. 3 is a table showing embodiments of Applicants’ composition which include zinc, lysozyme, and one or more anthelmentic compounds.

**Detailed Description Of The Preferred Embodiments**

“Lysozyme” comprises a group of enzymes that catalyze the hydrolysis of specific glycosidic bonds in mucopolysaccharides that constitute some bacterial cell walls. Bacteria build a tough skin of carbohydrate chains, interlocked by short peptide strands, that braces their delicate membrane against the cell’s high osmotic pressure. Lysozyme breaks these carbohydrate chains, destroying the structural integrity of the cell wall. The bacteria burst under their own internal pressure.

Many mammals, including humans, have moderate to high levels of lysozyme in certain secretions, white blood cells and tissue macrophages. Because the molecular weight is relatively large it is thought that lysozyme cannot affect systemic action. Administration of lysozyme via the nasal pharynx of animals, including humans, can assist treatment of pulmonary bacterial infections.

In certain embodiments, Applicants’ composition includes lysozyme. In certain embodiments, Applicants’ composition includes lysozyme in combination with one or more carriers. In certain embodiments, Applicants’ composition includes lysozyme in combination with zinc. In certain embodiments, Applicants’ composition includes lysozyme in combination with one or more parasiticides. In certain embodiments, Applicants’ composition includes lysozyme at a level between about 0.01 weight percent and about 10 weight percent.

The following Example I is presented to further illustrate to persons skilled in the art how to make and use the invention and to identify presently preferred embodiments thereof. This Example I is not intended, however, as a limitation upon the scope of the invention, which is defined only by the appended claims.

Table I recites *in vitro* data comprising the concentration of lysozyme needed to inhibit growth of different bacteria cultures.
TABLE I

<table>
<thead>
<tr>
<th>ORGANISM</th>
<th>Concentration Of Lysozyme, ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Pasteurella haemolytica</em> 127-13</td>
<td>200</td>
</tr>
<tr>
<td><em>Pasteurella haemolytica</em> 128-94</td>
<td>200</td>
</tr>
<tr>
<td><em>Pasteurella multocida</em> 127-4-283</td>
<td>25,000</td>
</tr>
<tr>
<td><em>Pasteurella multocida</em> 127-4-30118</td>
<td>25,000</td>
</tr>
</tbody>
</table>

Lysozyme was obtained from Fondras S.A., Via Molinazzo, 2, 6906 Lugano, Switzerland. The in vitro studies of Table I were performed in water.

Lactoferrin comprises a protein found naturally within biological fluids, such as milk and saliva, at mucosal surfaces and within white blood cells. It is thought that lactoferrin can kill many disease causing bacteria, whilst protecting the body's natural flora. In addition, lactoferrin appears effective to kill a range of fungi and yeasts, including the causative agent of thrush, *Candida albicans*. Moreover, research has shown that lactoferrin can prevent viruses, such as HIV, hepatitis and CMV, from binding to the body's cells and therefore prevents viral infection. In addition, lactoferrin helps to mature a regulate a number of immune cells throughout the body.

It is further thought postulated that the strong binding of iron by lactoferrin, prevents "free iron" from forming free-radicals. Free radicals have been implicated for many diseases and cancers. Because lactoferrin binds very tightly to iron, lactoferrin is thought to allow efficient uptake of iron into the body. This is thought to beneficial for anemia.

Lactoferrin is one of the principle proteins responsible for providing protection to infant mammals before their immune systems begin to function. It is a minor protein in cow's milk (0.3% by weight) and is extracted from skim milk or whey through protein separation. Apart from milk, lactoferrin is generally produced and released in the body in the digestive, respiratory and reproductive systems through saliva, tears, nasal secretions, etc. Lactoferrin is also produced by a special group of white blood cells known as neutrophils

Lactoferrin occurs naturally in three forms: (i) iron-saturated, (ii) iron-free, and (iii) immobilized (Activated). It is thought that the iron-free and immobilized forms of lactoferrin have the highest antimicrobial abilities through the binding of
iron required by bacteria for growth and the ability for lactoferrin to detach bacteria from surfaces and eliminate bacterial attachment structures. Most of the biological activity of lactoferrin is believed to be related to its excellent iron binding properties, but many non-iron binding related effects have been described as well. With respect to its role as a primary pathogen defense protein, research supports the following important functionalities:

The antimicrobial activity of lactoferrin is believed to include several working mechanisms. Firstly, because Lactoferrin binds iron which is an essential element for bacterial growth, bacterial cells become iron deprived and stop growing. Lactoferrin also binds to bacteria and, as a consequence, the microbial cell membrane loses its integrity and the bacteria is killed. Further, Lactoferrin stimulates phagocytosis or microbial destruction by the macrophages and monocytes. Lactoferrin also eliminates and prevents bacteria from forming essential attachment structures making them incapable of colonizing and multiplying.

Although the antiviral activity of lactoferrin is known, the mechanism of action is unclear. The mechanism of action appears to be the inhibition of the absorption process of the virus particle to the mammalian host cell, either through binding to the host cell or to the virus itself.

It is known that neutrophils, monocytes and macrophages are cells of the immune system that kill invading pathogens by oxidation reactions. Free iron is often present in areas of inflammation or infection. Oxidation reactions are accelerated by the catalytic effect of iron on free radical production. Lactoferrin binds the free iron with extremely high affinity and thus functions as a powerful local antioxidant protecting the immune cells against the free radicals produced during the inflammatory response. Although only the neutrophils produce and deliver lactoferrin, monocytes and macrophages have lactoferrin receptors on their cell surfaces.

One of the most potent stimulants of cytokine activity, (compounds produced by immune cells during infection and inflammation to coordinate the defense against pathogens), is the endotoxin LPS. This microbial membrane derived lipopolysaccharide (LPS) is bound and neutralized by lactoferrin and down regulates the immune response before it can get out of control as is the case with autoimmune
disease. Both in vitro and in vivo studies have shown this protective and stimulatory effects of lactoferrin.

Applicants believe that lactoferrin improves the efficiency of antibiotic treatments in the fight against pathogenic microbes. Considering the out of control use of antibiotics and the rise in antibiotic resistant strains of “bad bugs,” this is very good news. In certain embodiments, Applicants’ composition comprises lactoferrin in combination with lysozyme. In certain embodiments, Applicants’ composition comprises lactoferrin in combination with zinc. In certain embodiments, Applicants’ composition comprises lactoferrin, lysozyme, and zinc. In certain embodiments, Applicants’ composition comprises lactoferrin, lysozyme, zinc, and one or more anthelmentics. In certain embodiments, Applicants’ composition comprises lactoferrin in an amount up to about ten weight percent.

Zinc and its compounds have long been recognized as possessing certain therapeutic functions. Particularly well recognized are benefits as astringents and wound healing agents. The latter use tends to be restricted to zinc chloride and zinc sulphate, zinc chloride being of use for application to foul-smelling wounds and ulcers, while zinc sulphate is given internally to promote healing.

Zinc has a number of in vitro and in vivo immunomodulatory effects. It is not clear if these effects are a consequence of direct effects of zinc or secondary effects mediated by zinc’s effects on immunologically active cells or blocking receptors needed by pathogens.

There have been several studies of the effects of orally administered zinc lozenges on naturally occurring colds and experimentally induced rhinovirus infections in humans. While results have been mixed, there are reports of reduction of clinical disease attributable to treatment with zinc lozenges. Zinc ions are antiviral to herpes simplex virus and there are reports of attenuation of herpes simplex infection following topical zinc treatment in humans. Zinc-containing dentifrices alter oral flora, reducing oral malodor, plaque, and gingivitis.

Approximately 40% of common colds are caused by rhinovirus infections. The precise mechanism of action is not known, although zinc has been shown to inhibit virion maturation by blocking cleavage of the large polypeptide which is the primary transcription product of the vital genome. This effect may be caused by zinc
acting as a protease inhibitor or by binding to and stabilizing regions of the precursor polypeptides. The latter possibility is supported by the observation that the polypeptides accumulating in the infected cell, in the presence of zinc, are primarily those containing coat protein sequences. Zinc has been shown to bind readily to purified rhinovirus, preventing normal crystallization.

In addition, rhinoviruses passaged in the presence of zinc (zinc resistant mutants) have been shown to display altered antigens. This suggests that zinc may affect the in vitro pathogenicity of the virus by making virions more susceptible to antibody attack as well as reducing the amounts of transmissible virus released.

BRDC is a disease complex involving both predisposing viruses and secondary bacterial proliferation and infection, with key pathogenesis steps occurring in the upper respiratory tract. As such, nasally administered zinc has the potential to block one or more essential steps in the pathogenesis and prevent or attenuate resultant disease.

Zinc prevents the formation of viral capsid proteins, thereby inhibiting in vitro replication of several viruses, including rhinovirus. Zinc combines with the carboxyl termini (negatively charged canyons) of rhinovirus coat proteins, which may prevent the virus from combining with the tissue-surface protein (intracellular adhesion molecule type 1) and entering the cell. This process stops further reproduction.

Extracellular zinc may exert antiviral effects by stabilizing and protecting cell membranes by uncertain means. In vitro studies have suggested that zinc may induce production of interferon. Zinc ions also have human prostaglandin metabolite-inhibiting properties at 0.01 to 0.1 mmol, which may also account for the ability of zinc to help relieve symptoms of the common cold.

While it is believed that the various embodiments of Applicants' compositions are actually virostatic or viricidal, it will be appreciated that this is not known for certain, and it is possible that only symptomatic relief is obtained. In general, best results seem to be obtained when treatment is commenced immediately upon manifestation of symptoms or immediately after exposure to pathogens. Several doses in rapid succession are frequently sufficient to overcome even the most severe onset. If symptoms persist after this initial period, it is generally recommended to reduce frequency of dosing to the levels described hereunder.
By "ionic zinc," Applicants mean any solution of zinc wherein a majority of the zinc is in free solution as the zinc ion. For this purpose, any compound may be used that releases zinc ion in solution. Applicants' composition differs from the prior art which teaches that solutions of free ionic zinc cannot be administered at all, and especially not in effective doses, without giving rise to substantial irritation and other adverse side effects. By "solution" is meant any solution of ionic zinc suitable to provide free zinc ions either upon administration or after being released from a carrier. Applicants' invention extends to solutions of zinc capable of yielding free zinc ion but which contain zinc in another form. Specifically, in polymeric release embodiments, Applicants' composition contains substantially chelated zinc ion.

Thus, despite the strong contraindications in the art, it has been found that it is possible to use ionic zinc solutions in high enough concentrations to be effective without causing irritation. In fact, zinc compounds, especially zinc sulphate, are only recommended for clinical use in concentrations of less than 0.25%. Nevertheless, certain embodiments of Applicants' composition include zinc concentrations of up to about 2.0% by weight zinc. In certain embodiments, Applicants' composition includes zinc between about 0.1 weight percent and about 2 weight percent. FIGs. 1 and 3 recite certain embodiments of Applicants' composition which include zinc. The formulations of FIGs. 1, 2, and 3, include the components shown in the weight percentages recited. The remainder of formulations 1A through 1X, 2A through 2X, and 3A through 3X, comprise carriers, such as water, propylene glycol, ethanol, and the like, with or without other components such as silver, copper, Vitamin A, Vitamin E, aloe vera, surfactants, buffering agents, fragrances, flavorings, dispersing agents, decongestants, and the like.

Relief of symptoms, such as nasal discharge, is often virtually instantaneous (frequently within minutes of administration), it frequently being possible to abort onset of BRDC altogether if caught early enough. A cure, or substantial relief of symptoms, may frequently be affected even during substantial attacks.

In treatment, it is generally preferred to administer the spray via the nasal cavity, although severe symptoms may benefit from application via both nasal and oral cavities. Efficacy is probably also enhanced by the affinity of zinc ions for mucous tissues. Thus, zinc ion is still present in the affected areas for periods of up to
several hours after administration. In another embodiment, to relieve eye infections, the solution is sprayed onto the eye.

A particular advantage of the invention is that considerably more zinc compound, in terms of orders of magnitude, can be used in combination with one or more water soluble polymers, and optionally in combination with Vitamin A, Vitamin E, and/or aloe vera, and no irritation or other undesirable side-effects are observed. Further, the solutions are remarkably effective, in contrast to the ambivalent art.

Particularly good results have been obtained with zinc acetate, although other ionic zinc compounds can be used, especially the chloride. In general, suitable anions are those allowing free dissociation in solution, that is, which do not chelate the zinc ion. Those compounds of low solubility, or which are only soluble with difficulty, may be less convenient for use, but are not excluded from the invention provided that an effective concentration of zinc may be obtained. Inorganic or simple organic compounds, such as zinc acetate, are generally preferable.

The solvent used to dissolve the ionic zinc compound may be selected from any that is physiologically acceptable. Zinc sulphate, for example, is virtually insoluble in alcohol, but freely soluble in water, while zinc chloride is soluble in either. Indeed, a direct aqueous solution of the compound forms a preferred embodiment. However, other solutions are equally preferred, such as those based on saline and/or aqueous glycerol, or other mixtures suitable for nasal administration.

Applicants have found an aqueous solution of zinc acetate particularly effective. In particular, the stage of the viral/bacterial infection appears to be of significance with regard to efficacy, with infections only treated at later stages responding less well. However, this tallies well with zinc affecting the virus directly, as the virus will be wider spread at later stages of infection while, at earlier stages, there is a good chance of the virus still being localized in the nasal mucosae, with treatment effectively pre-emptying further replication. The malady is thereby caught early, and subsequent treatment of symptoms is unnecessary, as the subject is no longer infected.

Although solutions are preferred, zinc-containing emulsions are also effective. In certain embodiments, the zinc compound is dissolved in an aqueous-based solvent system which is dispersed in a larger amount of a second, non-aqueous solvent.
The following Example II is presented to further illustrate to persons skilled in the art how to make and use the invention and to identify presently preferred embodiments thereof. This Example II is not intended, however, as a limitation upon the scope of the invention, which is defined only by the appended claims.

Table II recites one embodiment of Applicants' composition that has shown in vitro efficacy in killing Pasteurella haemolytica bacteria.

<table>
<thead>
<tr>
<th>COMPONENT</th>
<th>AMOUNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>LYSOZYME</td>
<td>0.04 GRAM</td>
</tr>
<tr>
<td>ZINC ACETATE</td>
<td>2.0 GRAM</td>
</tr>
<tr>
<td>CARBOPOL 940</td>
<td>1.25 GRAM</td>
</tr>
<tr>
<td>GLYCERIN</td>
<td>75 MILLILITER</td>
</tr>
<tr>
<td>TRIETHANOLAMINE</td>
<td>6.0 MILLILITER</td>
</tr>
</tbody>
</table>

Triethanolamine is added in an amount to adjust the pH of the composition to about 7.4. The embodiment of Table I includes about 6 milliliters of triethanolamine.

Lysozyme was obtained from Fondras S.A., Via Molinazzo, 2, 6906 Lugano, Switzerland. Carbopol® is a trademark of Noveon, Inc. (formerly The B. F. GOODRICH COMPANY).

Water was added to the composition of Table II to bring the total weight of the formulation to about 100 grams. That aqueous formulation Table I killed a culture of Pasteurella haemolytica bacteria when used at a level of 400 ppm.

In certain embodiments, Applicants' composition includes one or more water soluble polymers, such as polyethylene oxide, polyvinyl alcohol, poly-2-ethyl-2-oxazoline, and the like. Molecular weights for such water soluble polymers range from about 5,000 daltons to about 5,000,000 daltons. Applicants' have found that inclusion of such one or more water soluble polymers facilitates use of up to about 2% zinc by weight in Applicants' composition. It is thought that these one or more water soluble polymers solvate, i.e. chelate, with the Zn ions and permit use of higher zinc levels than is taught in the prior art.

As those skilled in the art will appreciate, the higher the molecular weight of the polymer used, and/or the greater the amount of polymer used, the higher the
viscosity of the resulting zinc-containing composition. The one or more water soluble polymers are present in Applicants' composition at a level up to about 20 weight percent.

FIGs. 1 and 2 recite certain embodiments of Applicants' composition which include one or more polymeric materials. In certain embodiments, the polymer components of formulations 1A through 1X, and 2A through 2X, comprise one or more water soluble polymers and/or one or more carbopols. The formulations of FIGs. 1 and 2 include the components shown in the weight percentages recited. The remainder of formulations 1A through 1X, and 2A through 2X, comprise carriers, such as water, propylene glycol, ethanol, and the like, with or without other components such as silver, copper, Vitamin A, Vitamin E, aloe vera, surfactants, buffering agents, fragrances, flavorings, dispersing agents, decongestants, and the like.

Additionally, other metals and metal ions can be used with Zinc, including, but not limited to, ions of Cu, Al, Ag, Au, K, Mn, and B in their various valence states. For example, Cu can form salts as Cu⁺, Cu++, and Cu+++.

A multitude of tests have shown the effectiveness of silver in killing E. Coli bacteria. Silver is effective because of its capabilities of interfering with DNA production and accelerating the death phase. Many other tests have shown that silver also kills viruses and other types of bacteria. It has been reported that herpes simplex virus (HSV) type I is quite sensitive to silver. Other published reports suggest that only 3 ug/l silver was necessary to prevent the growth of pseudomonas. It is known that silver kills salmonella and E. Coli, and can kill bacteria highly resistant to antibiotics.

Examples of silver salts useful in the present invention include silver acetate, silver borate, silver bromide, silver butyrate, silver carbonate, silver chlorate, silver chloride, silver chromate, silver citrate, silver formate, silver glycinate, silver hydroxide, silver iodide, silver nitrate, silver oleate, silver oxalate, silver oxide, silver perchlorate, silver phosphate, silver salicylate, silver selenate, silver stearate, silver sulfide, and silver tartrate. In certain embodiments, silver is present in Applicants' composition in an amount up to about 10 weight percent.
Copper has the ability to pierce the protective outer membrane of a cell and disrupt enzyme balance. Preliminary research indicates the disease-causing bacterium, E. coli O157, is killed within hours of its contact with copper surfaces. The bacteria-killing properties of copper have been known for many thousands of years and are mentioned in the records of early civilizations. More recent research has shown that pathogens such as the Polio virus, opportunistic Legionella pneumophila, Pseudomonas florescens, Bacillus subtilis and the Bateriophage M2 are inhibited by passage through copper plumbing tube.

Examples of copper salts useful in the present invention include copper sulfate (cupric sulfate), copper nitrate, copper phosphate, copper fluoride, copper gluconate, copper chelate, copper histadyl chelate, copper peptide chelate, copper EDTA, copper EGTA, cupric acetate, cupric borate, cupric bromide, cupric butyrate, cupric carbonate, cupric chloride, cupric chloride, cupric chromate, cupric citrate, cupric formate, cupric glycinate, cupric hydroxide, cupric nitrate, cupric oleate, cupric oxalate, cupric oxide, cupric perchlorate, cupric phosphate, cupric salicylate, cupric selenate, cupric stearate, cupric sulfide, cupric tartrate, cuprous acetate, cuprous borate, cuprous bromide, cuprous butyrate, cuprous carbonate, cuprous chloride, cuprous chloride, cuprous chromate, cuprous citrate, cuprous formate, cuprous glycinate, cuprous hydroxide, cuprous iodide, cuprous nitrate, cuprous oleate, cuprous oxalate, cuprous oxide, cuprous perchlorate, cuprous phosphate, cuprous salicylate, cuprous selenate, cuprous stearate, cuprous sulfide, and cuprous tartrate. In certain embodiments, copper is present in Applicants’ composition in an amount up to about ten weight percent.

In certain embodiments, Applicants’ composition also includes additional components, including Vitamin A, Vitamin E, and/or aloe vera. In certain embodiments, ingredients such as Vitamin A, Vitamin E, aloe vera, and the like, are dissolved in a non-aqueous solvent and dispersed in a water or water/alcohol system which also contains the zinc-containing compound.

Vitamin A is required for the normal maintenance of epithelial cells that form the protective lining of the body. The mucosal membranes are the first line of defense against penetration by exterior invaders. As such, Vitamin A comprises an effective
component of Applicants' nasal spray composition. Vitamin A is present in Applicants' composition in an amount up to about ten weight percent.

Alpha-tocopherol, also known as Vitamin E, is involved in the structure of biological membranes. Vitamin E is a powerful antioxidant in both intracellular and extracellular membranes and prevents the oxidation of unsaturated lipid materials within the cells. As such, Vitamin E is an effective component of Applicants' aerosol spray composition. In certain embodiments Vitamin E is present in Applicants' composition in an amount up to about ten weight percent.

As used herein, "Aloe Vera" is the plant Aloe vera Linne, sometimes referred to as Aloe barbadensis Miller, which is known to those skilled in the art to be the variety of the Aloe vera plant used in the cosmetic industry. As used herein, "aloe vera extract" means either the liquid extract or gel obtained directly from the inner central zones of the leaves of the aloe vera plant, or the gel reconstituted from powdered aloe vera extract.

Aloe vera extract is used to moisturize and enhance the healing of membranes. In addition, aloe vera extract is also reported to have anti-bacterial and anti-viral properties. It has been shown in United States patent number 5,587,364 that acemannan is the active ingredient of the aloe vera plant and is an important immunoenhancer in that it increased lymphocyte response to alloantigen. It is suggested that the mechanism involves enhancement of monocyte release of IL-1 under the aegis of alloantigen. This mechanism may explain in part the capacity of acemannan to abrogate viral infections experimentally induced in animals and man. In certain embodiments, Applicants' composition includes aloe vera in an amount up to about fifteen weight percent.

Applicants' composition may also contain other ingredients. Such ingredients include, for example, buffering agents, flavor and odor enhancing agents, surface active agents, dispersing agents, decongestants and the like. The solutions for use in accordance with the invention may also contain, or be combined with, other medications suitable for administration by nasal spray, such as antimicrobial agents and antihistamines.

Carbopol has some indications of stimulating the immune system. By "carbopol," Applicants mean crosslinked homo- and co-polymeric materials.
comprising acrylic acid-based polymers. In certain embodiments, carbopol homopolymers are polymers of acrylic acid I crosslinked with allyl sucrose or allylpentaerythritol. In certain embodiments, carbopol copolymers include both acrylic acid repeat units I, and long chain alkyl acrylate repeat units II wherein R1 includes alkyl groups with between about ten carbons atoms and about 30 carbon atoms, crosslinked with allylpentaerythritol.

As those skilled in the art will appreciate, such carbopol homopolymers / copolymers are generally insoluble in water.

In certain embodiments, Applicant’s formulation includes carbopol in combination with ionic zinc. Such formulations may be affective by allowing zinc to move into the surface layer of the nasal mucosa for a secondary line of defense. In certain embodiments, the carbopol component of Applicants’ composition is present up to about 5 weight percent.

FIGS. 1 and 2 recite certain embodiments of Applicants’ composition which include one or more polymers. In certain embodiments, the polymer components of formulations 1A through 1X, and 2A through 2X, comprises one or more carbopols. In certain embodiments, the polymer components of formulations 1A through 1X, and 2A through 2X, comprise one or more water soluble polymers. The formulations of FIGs. 1 and 2 include the components shown in the weight percentages recited. The remainder of formulations 1A through 1X, and 2A through 2X, comprise carriers, such as water, propylene glycol, ethanol, and the like, with or without other components such as silver, copper, Vitamin A, Vitamin E, aloe vera, surfactants, buffering agents, fragrances, flavorings, dispersing agents, decongestants, and the like.

One embodiment of Applicants’ invention relates to polymeric controlled release compositions specifically targeted to the organs that contain mucus membranes at the interface. In one embodiment, the polymeric resin component of
this invention comprises a resin containing pendent carboxylic acid groups. Such a carboxy polymer could be linear polyacrylic acid resin or crosslinked resins with average molecular weight between about 100,000 daltons to about 10,000,000 daltons for linear polymers and could run into several billion daltons for crosslinked polymers. The polymer could be derived from carboxylic acid containing monomers like acrylic, alkyl acrylate, lactic, maleic, itaconic and citraconic acids and their combinations. Crosslinking agent could be polyalkenyl polyethers like allyl sucrose, allyl pentaerythritol and divinylglycol in 0.05 to 2.0 weight percent.

In certain embodiments, Applicant’s formulation includes polymeric materials which comprise pendent receptor sites specific to certain bacteria and/or viruses. In certain embodiments, such a pendent group comprises a crown ether moiety disposed on a pendent group attached to the polymer chain. Such crown ethers include materials sometimes called a 12-crown-6 ring which comprises a cyclic structure having six oxygen atoms and twelve carbon atoms symmetrically disposed in a ring structure. Applicant’s formulation also includes a polymeric material comprising a plurality of pendent groups each of which includes an 8-crown-4 cyclic ether moiety. Applicant’s formulation also includes a polymeric material comprising a plurality of pendent groups each of which includes an 16-crown-8 cyclic ether moiety.

In certain embodiments, Applicants’ composition includes one or more anthelmentic components. Applicants have found that the combination of zinc and one or more anthelments useful. It is thought that the zinc aids in the prevention / treatment of a secondary viral attack in the parasite-damaged respiratory system. Applicants have further found that the combination of zinc and one or more anthelments and in combination with lysozyme is useful in the prevention / treatment of secondary viral and/or bacterial attacks in the parasite-damaged respiratory system.

Certain macrocyclic lactones are natural fermentation products of soil-dwelling Streptomyces bacteria. They consist of two sub groups, the avermectins and the milbemycins. Their basic chemical structure consists of a macrocyclic lactone, a spiroketal addition fused from C-17 to C-25 and a hexahydrobenzofuran unit fused from C-2 to C-8. The avermectins also include an oxy disaccharide substituted at position C-13 whereas this position is not substituted in the
milbemycins. Several different alkyl groups can be substituted at position C-25 in both sub groups. The basic structures of the two can be superimposed on each other. As a result the avermectins may be described as glycosylated milbemycins. Conversely the milbemycins may be described as deglycosylated avermectins.

The macrocyclic lactones have broad spectrum activities against a wide range of nematodes and arthropods and their effectiveness against both endo- and ectoparasites has given rise to the name endectocides. They are highly effective at low doses (micrograms per kilogram of body weight) against most of the economically important nematodes of food-producing livestock and have a wide margin of safety. Some of them have zero meat and milk withdrawal times.

In the United States, there are, currently, six commercially available macrocyclic lactones: Ivermectin, Eprinomectin, Moxidectin, Selamectin, Doramectin and Milbemycin. The macrocyclic lactones are not effective against trematodes and cestodes. To compensate for this, Applicants' method includes administering to the nasal pharynx of animals, including humans, one or more avermectins / milbemycins in combination with one or more other anthelmintic drugs. In certain embodiments,
Applicants' method includes administering via the nasal pharynx ivermectin in combination with Clorsulon.

Production of avermectins from natural fermentation of *Streptomyces avermitilis* results in a mixture of eight slightly different components. They are designated A1a, A1b, A2a, A2b, B1a, B1b, B2a and B2b. Of these, only A2a, B1a and B2a are produced in significant amounts during fermentation. The B1 homologs are the most potent and also have the broadest spectrum of activity, at least among the nematodes.

The a and b homologs have almost identical activities and because a is produced in much greater amounts than b, the terminology used to describe the avermectins is often shortened to omit separate reference to the a and b homologs and the more abundant a component is the only one shown in structural drawings. This is illustrated below in reference to ivermectin.

<table>
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<th>Ivermectin terminology</th>
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<td>Common description</td>
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<td>22,23 dihydro(xy) avermectin B1</td>
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Milbemycins result from fermentation of *Streptomyces hygroscopicus* and *Streptomyces cyaneogriseus*. They are also produced as mixtures of slightly different components similar to the avermectins.

The macrocyclic lactones appear to act by interacting with glutamate-gated chlorine channels in muscle membranes. This interaction opens these chloride channels allowing chlorine ions to pass through and alter muscle function resulting in paralysis. The specific sites of action may include not only somatic muscles but also pharyngeal muscles since experiments with ivermectin using *Haemonchus contortus* and *Trichostrongylus colubriformis* have shown more potent inhibition of pharyngeal pumping than motility. Although most of the experiments have been done with ivermectin, it is generally believed that all macrocyclic lactones will share the same mode of action.
The macrocyclic lactones are expensive. Nevertheless, these macrocyclic lactones have gained wide acceptance by veterinarians, horse owners, farmers and the dog and cat owning public. Prior art methods of administering ivermectin vary considerably with respect to effective delivery and ease of use. Comparing subcutaneous injection of ivermectin with topical application of ivermectin, administration by injection realizes a cost efficiency with a lower time efficiency.

The following Example III is presented to further illustrate to persons skilled in the art how to make and use the invention and to identify presently preferred embodiments thereof. This Example III is not intended, however, as a limitation upon the scope of the invention, which is defined only by the appended claims.

**EXAMPLE III**

To study the dose/response efficacy of nasal administration of macrocyclic lactone parasiticides, three (3) beef steers of mixed breeding were used to evaluate three treatments. These three treatments were:

- **Treatment 1**: 500 milligrams of ivermectin in 5 ml propylene glycol; 1 ml of mixture administered to nasal pharynx at level of about 248 μg / kg body weight;
- **Treatment 2**: 1,000 milligrams of ivermectin in 5 ml propylene glycol; 1 ml of mixture administered to nasal pharynx at level of about 409 μg / kg body weight;
- **Treatment 3**: 1,500 milligrams of ivermectin in 5 ml propylene glycol; 1 ml of mixture administered to nasal pharynx at level of about 872 μg / kg body weight;

Treatments were applied and cattle were bled via jugular venipuncture at 0, 6, 24, 48, and 96 hours post-dosing.

**TABLE III**

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<th>48 Hours</th>
<th>96 Hours</th>
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22
Table III recites serum levels of ivermectin, in nanograms per milliliter, for the three treatments recited above at 0, 6, 24, 48, and 96 hours post dosing by nasal administration. Each treatment included delivering a 1 ml mixture comprising ivermectin and propylene glycol to the nasal pharynx of the animal.

Applicant’s invention includes compositions comprising one or more ivermectins in combination with ionic zinc. The zinc component is useful to treat secondary viral infections in a parasite-damaged respiratory tract. Applicant’s invention includes compositions comprising one or more ivermectins in combination with lysozyme. The lysozyme component is useful to treat secondary bacterial infections in a parasite-damaged respiratory tract. Applicant’s invention includes compositions comprising one or more ivermectins, zinc, and lysozyme. In these embodiments, the zinc component in combination with the lysozyme component is useful to secondary viral and/or bacterial infections in a parasite-damaged respiratory tract. In certain embodiments, the one or more ivermectins are present, in the aggregate, at a level up to about 50 weight percent.

In certain embodiments, Applicants’ composition includes other anthelmentic compounds. For example, the benzimidazoles are very safe drugs even at 10X the recommended dosage. Nematode resistance to anthelmentics is most commonly associated with repeated use of these drugs against nematodes of sheep and horses. These drugs, the benzimidazoles, interfere with energy metabolism, essentially starving the parasite.

Applicant’s invention includes compositions comprising one or more benzimidazoles / pro-benzimidazoles in combination with lysozyme. Applicant’s invention includes compositions comprising one or more benzimidazoles / pro-benzimidazoles in combination with ionic zinc. In certain embodiments, the one or
more benzimidazoles / pro-benzimidazoles are present, in the aggregate, at a level up
to about 95 weight percent.

Applicant’s invention includes a method to administer to the nasal pharynx of
animals, including humans, a composition comprising one or more benzimidazoles /
pro-benzimidazoles in combination with lysozyme. Applicant’s invention includes a
method to administer to the nasal pharynx of animals, including humans, a
composition comprising one or more benzimidazoles / pro-benzimidazoles in
combination with ionic zinc.

The imidathiazoles are widely used in cattle and sheep to treat parasite
infestations. An advantage is that the imidathiazoles are active against g.i nematodes
and lungworms. On the other hand, the imidathiazoles are not widely used in horses
because they are rather toxic and not particularly effective against horse strongyles. It
is thought imidathiazoles act as cholinergic agonists which bind to acetylcholine
binding sites, cause an acetylcholine-like response and cannot be inactivated by
cholinesterase resulting in spastic paralysis.

The tetrazydropirimidines also act as cholinergic agonists. They are widely
used in ruminants and horses. The action of organophosphates is related to their
ability to inhibit cholinesterase. Since cholinesterase is required by nematodes to
inactivate acetylcholine, and since excitatory neuromuscular transmission is
cholinergic in action, the inhibition of cholinesterase by the organophosphates will
cause a spastic paralysis.

Applicant’s invention includes compositions comprising one or more
imidathiazoles, tetrazydropirimidines and/or organophosphates in combination with
ionic zinc. In certain embodiments, the one or more imidathiazoles,
tetrazydropirimidines and/or organophosphates are present, in the aggregate, at a
level up to about 50 weight percent.

Solutions of Applicants’ composition may be prepared in any suitable manner.
In general, this will involve no more than the dissolution of the compound in the
solvent. This will usually be at ambient or elevated temperature, and under aseptic
conditions. If the animal has a runny or blocked nose, it is generally recommended
that the nose be cleared prior to administration, to facilitate access of the solution to
the mucosae. Inhaling during spraying is also recommended.
Suitable aerosol dispensers for use in accordance with the invention will be apparent to those skilled in the art, and may vary from simple devices analogous to perfume dispensers to pressurized spray cans and even complex apparatus such as might be used in hospitals.

Applicants' method includes administering Applicants' composition to the nasal pharynx of animals, including humans. In certain embodiments, Applicants' composition is administered via a syringe advanced into the animal's nose. In certain embodiments, Applicants' composition is administered via a spray device. Suitable means for dispersing the spray, preferably in aerosol form, include devices employing pressurized gas forced across the opening of a tube leading into the reservoir to create an aerosol, and press-button type devices wherein the button, when pressed, creates pressure on the surface of the liquid in the reservoir, forcing it up through a tube and through a fine nozzle to disperse the solution into an aerosol spray. It is generally preferable that air forms the aerosol propellant, but any suitable propellant may be used.

Whichever device is used it is generally preferable that it comprises some kind of dosimeter to control the amount of solution administered in one dose. A preferred device, comprising a dispenser with a nozzle, effectively incorporates such a dosimeter without any specialized adaptation being necessary. In such a device, the limit stop of the depressible spray head determines the maximum single amount of solution dispensable at once. Specially developed spray devices may be made, but it is generally preferable to provide a simple hand-held device comprising a reservoir of Applicants' composition.

While the preferred embodiments of the present invention have been illustrated in detail, it should be apparent that modifications and adaptations to those embodiments may occur to one skilled in the art without departing from the scope of the present invention as set forth in the following claims.
We claim:

1. A method to treat animals, including humans, having a pulmonary bacterial infection by delivering a therapeutically effective amount of lysozyme to the animal’s nasal pharynx.

2. The method of claim 1, further comprising delivering zinc to the animal’s nasal pharynx.

3. The methods of claims 1 or 2, further comprising delivering lactoferrin to the animal’s nasal pharynx.

4. A method to treat animals, including humans, having a viral infection by delivering a therapeutically effective amount of zinc to the animal’s nasal pharynx.

5. The method of claim 3, further comprising delivering lysozyme to the animal’s nasal pharynx.

6. The methods of claims 4 or 5, further comprising delivering lactoferrin to the animal’s nasal pharynx.

7. The methods of claims 1, 2, 3, 4, or 5, further comprising delivering a carbopol to the animal’s nasal pharynx.

8. A method to treat animals, including humans, in need thereof with a parasiticide by delivering a therapeutically effective amount of said parasiticide to the animal’s nasal pharynx.

9. The method of claim 8, further comprising delivering zinc to the animal’s nasal pharynx.

10. The method of claims 8 or 9, further comprising delivering lysozyme to the animal’s nasal pharynx.

11. The method of claims 8, 9, or 10, further comprising delivering lactoferrin to the animal’s nasal pharynx.

12. The methods of claims 8, 9, 10, or 11, further comprising delivering one or more water soluble polymers to the animal’s nasal pharynx.

13. The method of claim 12, wherein said one or more water soluble polymers are selected from the group consisting of polyethylene oxide, polyvinyl alcohol, and poly-2-ethyl-2-oxazoline.
14. The methods of claims 8, 9, 10, or 11, further comprising delivering one or more carbopols to the animal's nasal pharynx.

15. A composition for nasal administration to animals, including humans, comprising:
   lysozyme; and
   zinc.

16. The composition of claim 15, further comprising one or more anthelmintic compounds.

17. The composition of claim 16, wherein said one or more anthelmintic compounds comprises ivermectin.

18. The composition of claim 17, wherein said one or more anthelmintic compounds further comprises one or more benzimidazoles.

19. The composition of claims 15 or 16, further comprising lactoferrin.

20. The composition of claims 15, 16, or 19, further comprising one or more water soluble polymers.

21. The composition of claim 20, wherein said one or more water soluble polymers is selected from the group consisting of polyethylene oxide, polyvinyl alcohol, and poly-2-ethyl-2-oxazoline.

22. The composition of claims 15, 16, 19, or 20, further comprising one or more carbopols.
FIG. 1

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