and only 10.5% were infected with BVDV-2a. Unfortunately, while these data *clearly* demonstrated that BVDV-1b is the predominate subtype of PI cattle entering domestic feedlots, there are currently no USDA-licensed vaccines that are specific for BVDV-1b infection.

Thus, for these and other reasons inherent in the prior art, there is a need for BVDV vaccine formulations that elicit a vigorous and multi-faceted immune response, and particularly those that elicit an immune response against the Type 1b form of BVDV. Because of the potential for great economic loss in unvaccinated herds, there is a need for cost-effective (and preferably, single-dose) vaccines containing modified, live BVDV-1b viruses that induce prophylaxis against BVDV infections in mammalian livestock populations.

Likewise, because contemporary polyvalent vaccines against multifactorial diseases such as BRDC and related shipping fever diseases are largely ineffective at preventing infection by BVDV-1b, there is also a need for improved vaccination modalities to better effect prophylaxis and control of disease outbreak in BVDV-1b-susceptible livestock.

BRIEF SUMMARY

The present disclosure encompasses new and useful compositions, as well as methods of employing them that may advantageously improve delivery of prophylactic and/or therapeutic agents to an animal in need thereof. The present disclosure provides vaccine compositions that offer advantages over conventional formulations, and specifically provide ways of preventing or controlling diseases caused by one or more pestiviruses, and in particular, those caused by BVDV viruses including those of the Type 1b subgenotype (*i.e.,* BVDV-1b).

In an overall and general sense, the present disclosure encompasses compositions, methods of making such compositions, and methods for their use in the prevention, treatment, and/or management, of viral and/or microbial infection, pathogenesis, and disease. The immunogenic compositions disclosed herein, as well as methods employing them, find particular use in the prevention, treatment, and/or amelioration of one or more symptoms of shipping fever/BRDC in susceptible mammals using the inventive vaccine

compositions and methods employing them that are superior to conventional shipping fever preventatives/treatments currently available in the veterinary medical arts.
In particular embodiments, the present disclosure provides immunogenic compositions comprising modified, live BVDV-1b viruses, as well as pharmaceutical formulations containing them, and methods for making such vaccines in a variety of prophylactic and/or therapeutic regimens. Such compositions and methods find particular use in the prevention of viral and multifactorial diseases in animals such as mammalian livestock that are susceptible to BVDV infection.

In one aspect of the present disclosure, there is provided an immunogenic composition comprising: a modified, live, attenuated bovine viral diarrhea virus type 1b (BVDV-1b) and a veterinary-acceptable carrier;
wherein the modified, live BVDV-1b is ATCC PTA-11553.

In another aspect of the present disclosure, there is provided a vaccine comprising a prophylactically-effective amount of the immunogenic composition as defined herein, and an adjuvant.

In a further aspect of the present disclosure, there is provided a prophylactically-effective amount of a composition as defined herein, for use in preventing shipping fever in an animal.

In another aspect of the present disclosure, there is provided a prophylactically- or therapeutically-effective amount of a composition as defined herein for use in preventing, treating, managing, or ameliorating one or more symptoms of a disease caused by a pestivirus in an animal susceptible to pestivirus infection.

In a further aspect of the present disclosure, there is provided a prophylactically-effective amount of a composition as defined herein for use in protecting an animal against shipping fever, bovine respiratory disease complex, or bovine viral diarrhea.

In another aspect of the present disclosure, there is provided the use of a composition as defined herein in the manufacture of a medicament for the induction of a bovine viral diarrhea virus Type 1b (BVBV-1b)-specific immune response in a mammal.

In a further aspect of the present disclosure, there is provided the use of a composition as defined herein in the manufacture of a medicament for the prevention of shipping fever.

In another aspect of the present disclosure, there is provided the use of a composition as defined herein in the manufacture of a medicament for the prevention, treatment, management or amelioration of one or more symptoms of a disease caused by a pestivirus in an animal susceptible to pestivirus infection.

In a further aspect of the present disclosure, there is provided the use of a composition as defined herein in the manufacture of a medicament for the prevention of an animal against a disease caused by BVBV-1b.

In related embodiments, the present disclosure also provides methods for using the disclosed vaccine compositions for eliciting a viral-specific immunological response in an animal. In an overall and general sense, such methods generally involve providing to a selected animal one or more of the immunogenic compositions disclosed herein in amount(s) and for a time effective to elicit a viral-specific immunological response in an animal, and in particular, a BVDV-specific immunological response. In such embodiments, the animal is preferably a cloven-hoofed mammal, and more preferably, a member of the family *Bovidae*.

The present disclosure also provides a method of preventing or controlling an outbreak of viral and/or microbial infection(s) (and pestiviral infections caused by BVDV and related species in particular) in one or more selected mammalian populations. The method generally involves providing to a susceptible or an at-risk member of such a population an effective amount of one or more of the disclosed immunogenic or vaccine compositions, for a time sufficient to delay, lessen, reduce, inhibit, and/or prevent the outbreak of such an infection in the general population. Exemplary mammalian populations include, without limitation, members of the *Bovinae* and *Caprinae,* and particularly those of the genera *Bison*, *Bos*, *Bubalus*, *Capra*, *Oreamnos*, *Ovibos*, *Ovis*, *Syncerus,* and such like. In illustrative embodiments, these methods are particularly desirable in the treatment of commercial livestock in the genera Bison, Bos, Capra, and Ovis, including, without limitation, *Bison bison*, *Bos taurus*, *Capra hircus* and *Ovis aries*.

The present disclosure provides a method for stimulating the immune system of an animal to produce a protective immune response against a viral infection, and in particular, a *Bovidae*-virulent pestivirus infection. Such a method generally involves at

least administering to an animal in need thereof, an immunologically- and prophylactically-effective amount of one or more of the disclosed vaccine compositions in an amount and for a time sufficient to stimulate the immune system of the animal. In the conventional practice of this method in one embodiment, administration of one or more of the disclosed immunologically- and prophylactically-active vaccine compositions preferably induces at least a first detectable amount of anti-pestivirus antibodies in the animal, and more preferably still, induces at least a first detectable amount of anti-BVDV-1b antibodies in the animal. In preferred embodiments, administration of the composition preferably immunizes the animal against initial, subsequent, and/or recurrent infection by BVDV-1b virus, and in certain embodiments, also preferably immunizes the animal against initial, subsequent, and/or recurrent infection by one or more genetically-similar or epitopically-related viruses, including for example, one or more types, strains, and subtypes of BVDV virus (including, without limitation, BVDV-1a, BVDV-2, and other genetically-similar pestiviruses.

In yet another embodiment, the present disclosure provides a method for producing a protective immune response against pestivirus in an animal. Such a method generally includes providing to an animal in need thereof an immunologically- and prophylactically-effective amount of one or more of the disclosed BVDV-1b immunogenic compositions under conditions and for a time sufficient to produce such a protective immune response against one or more pestivirus species, subspecies, or strains, and preferably, against one or more BVDV species, strains, subtypes, or serotypes. Likewise, the present disclosure also provides a method of providing a prophylactic or therapeutic composition to a first cell in a mammalian host. This method generally involves providing to a mammal in need thereof a prophylactically- or therapeutically-effective amount of one or more of the BVDV-specific immunogenic compositions disclosed herein, under conditions and for a time effective to provide the composition to at least a first cell, tissue, organ, or organ system in such a mammal.

The present disclosure also provides a method for preventing, treating, and/or ameliorating one or more symptoms of BVDV infection in a mammal. Such a method generally includes providing to the mammal in need thereof an immunologically- and prophylactically-effective amount of one or more of the disclosed BVDV-1b

immunogenic compositions under conditions and for a time sufficient to prevent, treat, and/or ameliorate one or more symptoms of the BVDV infection in the mammal.

Likewise, the present disclosure also provides methods for preventing, treating, and/or ameliorating one or more symptoms of a multifactorial disease such as BRDC in a mammal, and particularly in those diseases in which infection by at least a first BVDV is implicated as a causal or contributory agent of the disease. Such methods generally involve administering to a selected mammal at least a first immunologically- or prophylactically-effective amount of at least a first anti-BVDV-1b vaccine composition under conditions and for a time sufficient to prevent, treat, and/or ameliorate one or more symptoms of the disease in the mammal.

In yet another embodiment, the present disclosure provides a method for preventing, treating, and/or ameliorating one or more symptoms of shipping fever in a member of the family *Bovidae*. Such a method generally includes providing to the bovid at least a first immunologically- or prophylactically-effective amount of a first composition comprising a population of modified, live BVDV-1b viruses under conditions and for a time sufficient to prevent, treat, and/or ameliorate one or more symptoms of shipping fever in the bovid.

IMMUNOGENIC COMPOSITIONS

In order to provide broader protection against one or more pestiviruses, and in particular, one or more of the viral agents implicated in BRDC and shipping fever in members of the family *Bovidae*, the inventors have developed safe and effective vaccine formulations that include one or more BVDV-1b-specific antigens. Both monovalent and polyvalent vaccine formulations have been described, including those that contain, in the case of monovalent vaccines, one or more antigens, epitopes, or modified live viruses that elicit an immune response specific for BVDV alone, or, in cases of polyvalent vaccines, one or more antigens, epitopes, or modified live viruses that elicit specific immune responses not only for BVDV, but also for one or more additional pathogens.

In illustrative embodiments, a monovalent immunogenic composition comprising modified, live BVDV-1b has been developed to protect livestock from BVDV-1b infection. Additionally, multivalent immunogenic compositions specific for BRDC and

Erysipelothrix, Escherichia, Histophilus, *Leptospira, Listeria*, *Mannheimia*, *Moraxella*, *Mycobacterium*, *Mycoplasma*, *Pasteurella, Salmonella*, and *Streptococcus,* or a combination thereof.

7. A prophylactically-effective amount of a composition according to any one of claims 1-4, for use in preventing shipping fever in an animal.

8. The composition of claim 7, wherein the animal is infected by, or susceptible to infection from, a pestivirus.

9. A prophylactically- or therapeutically-effective amount of a composition according to any one of claims 1-4 for use in preventing, treating, managing, or ameliorating one or more symptoms of a disease caused by a pestivirus in an animal susceptible to pestivirus infection.

10. The composition of claim 7 or 9, wherein the animal is a bovid.

11. A prophylactically-effective amount of a composition according to any one of claims 1-4 for use in protecting an animal against shipping fever, bovine respiratory disease complex, or bovine viral diarrhea.

12. Use of a composition according to any one of claims 1-4 in the manufacture of a medicament for the induction of a bovine viral diarrhea virus Type 1b (BVBV-1b)-specific immune response in a mammal.

13. Use of a composition according to any one of claims 1-4 in the manufacture of a medicament for the prevention of shipping fever.

14. Use of a composition according to any one of claims 1-4 in the manufacture of a medicament for the prevention, treatment, management or amelioration of one or more symptoms of a disease caused by a pestivirus in an animal susceptible to pestivirus infection.

15. Use of a composition according to any one of claims 1-4 in the manufacture of a medicament for the prevention of an animal against a disease caused by BVBV-1b.

16. The use of claim 15, wherein the disease is shipping fever, bovine respiratory disease complex, or bovine viral diarrhea.