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Tiakitanga Pūtaiao Aotearoa

Import Risk Analysis: Bovine Serum from Australia and the United States of America

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Import Risk Analysis: Bovine Serum from Australia and the United States of America

Version 1.0

25 June 2021

Approved for IHS development

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New Zealand is a member of the World Trade Organization and a signatory to the Agreement on the Application of Sanitary and Phytosanitary Measures ("the Agreement"). Under the Agreement, countries must base their measures on an international standard or an assessment of the biological risks to plant, animal or human health.

This document provides a scientific analysis of the biosecurity risks associated with bovine, fetal and calf serum (processed and unprocessed) from Australia and the United States of America. It assesses the likelihood of entry and exposure of organisms and the consequences the organisms would have if they entered and became established and/or spread in New Zealand. The document has been internally and externally peer reviewed and is now released publicly.

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Contents

Index of Tables and Figures

Acronyms and abbreviations

Term/Acronym	Definition
AGID	agar gel immunodiffusion
AHAW	Animal Health and Welfare, European Union
AINOV	Aino virus
AKAV	Akabane virus
APHIS	Animal and Plant Health Inspection Service
BEFV	*Bovine ephemeral fever virus*
BoHV	Bovine herpesvirus
BRD complex	bovine respiratory disease complex
BSA	bovine serum albumin
BTV	*Bluetongue virus*
BVDV	*Bovine viral diarrhoea virus*
CDC	Centers for Disease Control and Prevention, United States of America
C-ELISA	Competitive ELISA
CFT	complement fixation test
CVV	Cache Valley virus
DAWR	Department of Agriculture and Water Resources, Australia
EFSA	European Food Safety Authority
EHDV	*Epizootic haemorrhagic disease virus*
ELISA	enzyme linked immunosorbent assay
ESR	Environmental Science and Research Limited, New Zealand
FAO	Food and Agriculture Organization
FBS	fetal bovine serum
FPA	fluorescence polarisation assay
GMP	good manufacturing practices
HI	haemagglutination inhibition
HTST	high-temperature short-time
IBR	infectious bovine rhinotracheitis
ICTV	International Committee on Taxonomy of Viruses
IDV	Influenza D virus
IETS	International Embryo Transfer Society
IFAT	indirect fluorescent antibody test
IHA	indirect haemagglutination
IHC	immunohistochemistry
IHS	import health standard
IPB	infectious pustular balanoposthitis
IPV	infectious pustular vulvovaginitis
IRA	import risk analysis
ISIA	International Serum Industry Association
kGy	kilogray
MAb	monoclonal antibody
M. bovis	*Mycoplasma bovis*
MPI	Ministry for Primary Industries
mrad	megarad
NAMP	National Arbovirus Monitoring Program
nm	nanometre
OIE	The World Organisation for Animal Health

Term/Acronym	Definition
OIE Code	Terrestrial Animal Health Code of the OIE
OSPRI	Operational Solutions for Primary Industries, New Zealand
PCR	polymerase chain reaction
PI	persistently infected
PRNT	plaque reduction neutralisation test
RMP	risk management proposal
RT-PCR	reverse transcription polymerase chain reaction
SPS	sanitary and phytosanitary
TB	tuberculosis
The Code	The OIE Terrestrial Animal Health Code
USDA	United States Department of Agriculture
UV	ultraviolet
VI	virus isolation
VN	virus neutralisation
WAHIS	World Animal Health Information System database
WHO	World Health Organization
WTO	World Trade Organization
µm	micrometre

1. Executive summary

This import risk analysis (IRA) assesses the biosecurity risks associated with the importation of bovine serum from Australia and the United States of America to New Zealand. This IRA also assesses the effectiveness of the current risk mitigation measures for processed (tested, filtered and irradiated) fetal bovine serum, calf serum and bovine serum of Australian origin.

For the purposes of this IRA, the term "bovine serum" refers to the following commodities: fetal bovine serum, newborn calf serum, calf serum, adult bovine serum and donor bovine serum. Each commodity is further defined in the "Commodity definition" section.

The methodology for this risk assessment follows the guidelines in the Terrestrial Animal Health Code (hereafter referred to as the Code) of the World Organisation for Animal Health (OIE) and the OIE handbook on import risk analysis for animals and animal products.

Hazard identification was conducted on bovine diseases and infections caused by viral, bacterial, protozoal and rickettsial agents, as well as mollicutes and prions. Out of 52 infectious agents considered for this IRA, 11 viruses, nine bacteria, mollicutes including *Mycoplasma bovis*, one protozoan, and one rickettsial agent were identified as hazards in bovine serum, and further risk assessment was conducted.

The following are the pathogens identified as hazards in bovine serum:

Viruses

- Aino virus
- Akabane virus
- *Bluetongue virus*
- *Bovine ephemeral fever virus*
- Bovine herpesvirus 1
- Bovine herpesvirus 5
- *Bovine influenza D virus*
- *Bovine viral diarrhoea virus*
- Cache Valley virus
- *Epizootic haemorrhagic disease virus* including Ibaraki
- *Palyam virus*

Bacteria

- *Bacillus anthracis*
- *Borrelia burgdorferi*
- *Brucella abortus*
- *Burkholderia pseudomallei*
- *Chlamydia abortus*
- *Coxiella burnetii*
- *Leptospira* spp.
- *Mycobacterium bovis*

- *Salmonella* spp.

Mollicutes
- *Mycoplasma bovis* and other mollicutes

Protozoa
- *Babesia* spp.

Rickettsia
- *Anaplasma* spp.

Four hazards (*Palyam virus*, *Bacillus anthracis*, *Babesia* spp. and *Anaplasma* spp.) were assessed to be posing a negligible risk, and no risk management measures are proposed.

The remaining 19 hazards were assessed to pose a non-negligible risk to New Zealand through the importation of bovine serum. Appropriate risk management options are described for these organisms based on the OIE Terrestrial Animal Health Code recommendations for the importation of animals and animal products.

Following collection, defibrination/clotting and centrifugation, bovine serum may undergo processing to mitigate the risk of any adventitious agents[1] it may contain. The post-collection processing methods can be applied individually or in combination to achieve the desired level of risk mitigation.

The commonly used post-collection processing methods for risk reduction/mitigation of bovine serum are sterile filtration and gamma irradiation. Validated sterile filtration methods are highly effective in reducing bacterial contamination of bovine serum. Filtration through a 0.1-µm filter can remove all bacteria and mollicutes present in the serum but cannot render the serum free of all viruses (Hanson *et al*., 2019). Triple 0.1-µm filtration has become the standard method of aseptic processing for serum and has been shown to result in a high degree of mycoplasma removal.

Further reduction/mitigation of risks (i.e. viruses) from filtered bovine serum can be obtained by gamma irradiation. Gamma irradiation is an effective method for pathogen inactivation of animal serum to reduce the microbial and viral burden in the serum. The primary assurances against contamination by any adventitious agents are good manufacturing practices involving effective post-collection processing and extensive testing of the serum for any specific risk organisms of concern.

[1] Contaminating microorganisms including bacteria, fungi, mycoplasmas/spiroplasmas, rickettsia, protozoa, parasites, transmissible spongiform encephalopathies agents and viruses that have been unintentionally introduced into the manufacturing process of a biological agent (WHO, 2010).

2. Introduction

Purpose of the risk analysis

The Animal Imports team asked the Animal Risk Assessment team to assess the risks associated with importing fetal bovine serum, calf serum and bovine serum originating from Australia and the United States. Risk management options identified in this import risk analysis (IRA) may be used, as appropriate, in the revised import health standard (IHS).

This risk assessment also assesses the effectiveness of the current risk mitigation measures for processed (tested, filtered and irradiated) fetal bovine serum, calf serum and bovine serum of Australian origin.

The import risk analysis *Non-viable biological products, micro-organisms and other viable cells into New Zealand* (IRA 2005), provides the basis for the IHS for biological products (including samples) (BIOPRODIC.ALL). IRA 2005 does not address specific risks that may be present in the imported fetal, calf and bovine serum.

Current import health standards

Currently, bovine serum imported into New Zealand is regulated under the Biosecurity Act 1993, and must meet the requirements set under the following import health standards (IHS):

- BIOPRODIC.ALL – importation of non-viable biological products (including animal product samples) into New Zealand. This standard is currently under review, and additional import health standards are expected to be consolidated under the revised import health standard for biological products.
- BOVFBSIC.AUS – importation of tested, filtered and irradiated fetal bovine serum, calf serum and bovine serum from Australia into New Zealand. Bovine serum imported into New Zealand under this standard does not require a permit and is eligible for clearance when the consignment is accompanied by appropriate health certification from a representative of the Australian competent authority, which certifies that the consignment meets the requirements set in the standard.
- BOVSFPIC.AUS – importation of fetal bovine serum, calf serum and bovine serum for further processing from Australia into New Zealand.

Bovine serum imported into New Zealand under the standards BIOPRODIC.ALL and BOVSFPIC.AUS requires an import permit that directs the serum to an MPI-registered transitional facility. While in the transitional facility, the consignment is subjected to testing, treatments or procedures required under the relevant IHS.

3. Scope

This qualitative risk analysis assesses the biosecurity risks to animal health that may be associated with the importation of bovine serum from Australia and the United States. It also assesses the effectiveness of the current risk mitigation measures for processed

(tested, filtered and irradiated) fetal bovine serum, calf serum and bovine serum of Australian origin. Thus, the scope of this risk analysis is limited to bovine serum imported from these two countries for use as raw materials for end products (such as vaccines, cell culture media).

Contamination during collection of blood and processing of serum pre-export is out of scope. Moreover, processes and procedures for manufacturing end products (such as vaccines[2]) are also out of scope. Other characteristics of bovine serum such as sterility, endotoxin content, total protein concentration, haemoglobin content, pH and osmolality also are out of scope for this assessment.

Impacts on human health from the use of end products such as vaccines produced from fetal, calf and bovine serum are not considered in this risk analysis.

Assumptions:

(1) The freedom from microorganisms in the fetal, calf and bovine serum is prerequisite for all end uses.
(2) Any viruses, microorganisms and/or blood parasites found in blood can also be found in bovine serum, if no evidence is available to prove otherwise.
(3) Imported serum complies with the current ISO 9001 standard.
(4) The serum is to be packaged, stored and transported according to the serum industry's good manufacturing practice (GMP) guidelines or equivalent.
(5) The likelihood of exposure to pathogens varies according to the mode of administration of the finished product (e.g. parenteral vs intrauterine administration), and it is assumed that parenteral administration of products contaminated with pathogens presents the highest risk.
(6) For the purposes of this IRA, an assumption is made that if the serum is contaminated with pathogens, then the end products may also be contaminated.

4. Commodity definition

The commodity considered in this risk analysis is bovine (*Bos taurus* and *Bos indicus*) serum imported only from Australia and the United States. Bovine serum is the liquid fraction of blood, obtained from cattle (*Bos taurus* and *Bos indicus),* and from which cells, fibrin and clotting factors have been removed.

Bovine serum is either processed in the exporting country and is ready for use or is imported unprocessed. Unprocessed serum must be further processed in the transitional facility in New Zealand before biosecurity clearance. Processed bovine serum refers to the commodity that has undergone testing, filtration or gamma irradiation prior to export. Unprocessed bovine serum refers to a commodity that has not undergone any testing or post-collection processing prior to export.

[2] Bovine serum imported for vaccine production is not captured within the scope of an agricultural compound under the Agricultural Compounds and Veterinary Medicines Act 1997 (ACVM Act). Biosecurity requirements preceeds the ACVM requirements for bovine serum imported for vaccine production. ACVM rely on an assessment by Biosecurity New Zealand to ensure freedom from any extraneous agents in the bovine serum that is used as an ingredient in vaccine production (ACVM, 2021).

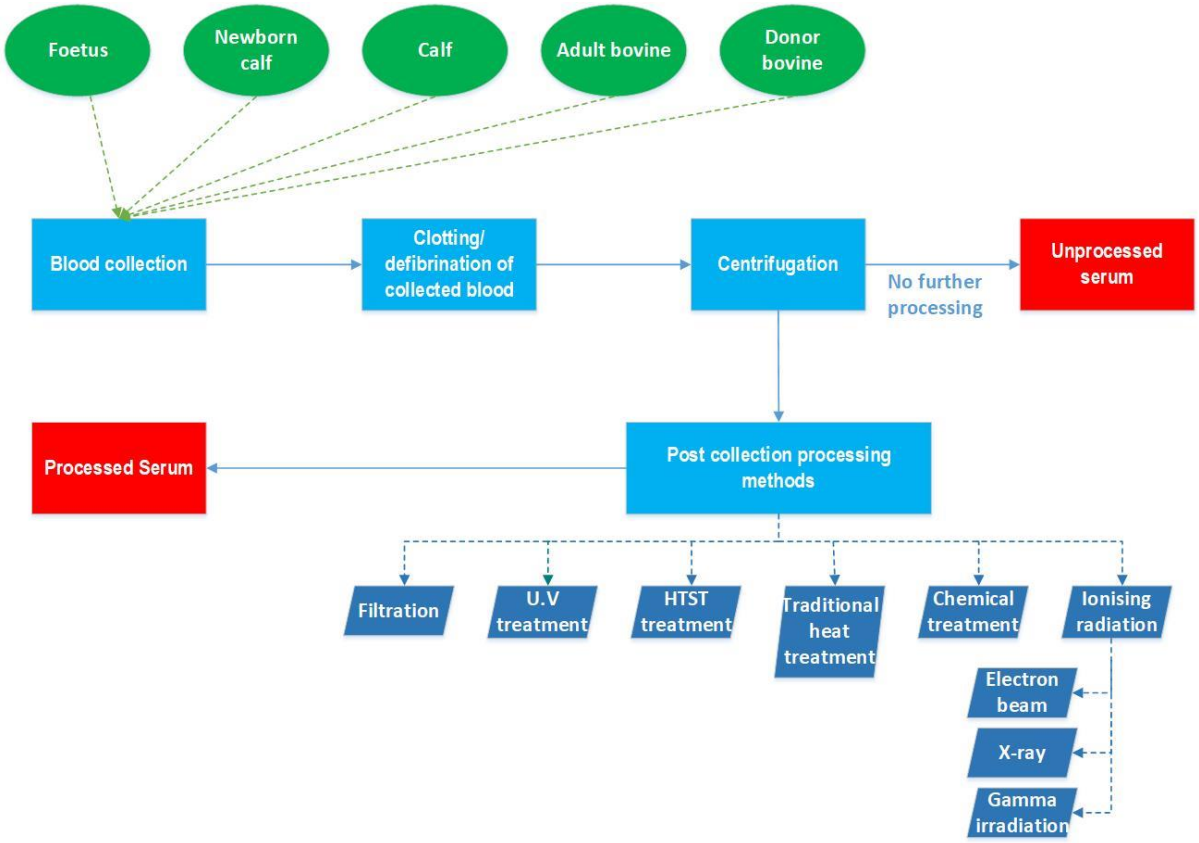
For the purposes of this IRA, the term "bovine serum" refers to the commodities defined in Table 1.

Table 1. Bovine serum types

Bovine serum type	Definition*
Fetal bovine serum (FBS)	FBS is derived from blood collected at the slaughterhouse from fetuses of healthy, pre-partum dams that have been deemed fit for human consumption through antemortem and/or postmortem inspection. It is collected aseptically within specifically designated rooms in slaughter premises.
Newborn calf serum	Newborn calf serum is obtained at the time of slaughtering from healthy calves less than 20 days old deemed fit for human consumption through antemortem and/or postmortem veterinary inspection.
Calf serum	Calf serum is collected from healthy calves at the time of slaughtering between ages, 20 days to 12 months deemed fit for human consumption through antemortem and/or postmortem veterinary inspection.
Adult bovine serum	Adult bovine serum is obtained at the time of slaughtering from healthy cattle 12 months of age or older, deemed fit for human consumption through antemortem and/or postmortem veterinary inspection.
Donor bovine serum	Donor bovine serum is the non-slaughterhouse derived blood collected from live healthy cattle 12 months of age or older, from controlled donor herds whose health status is confirmed by regular inspection by a competent veterinary authority.

* Types of bovine serum (ISIA, 2019; Versteegen *et al*., 2016).

Figure 1. Bovine serum production



UV – ultraviolet
HTST – high-temperature short-time

Various uses of bovine serum

Serum and animal blood-derived products are widely used in biotechnology. Bovine serum, especially fetal bovine serum (FBS), is used extensively as a growth medium supplement in cell cultures. Serum provides growth factors and nutrition within the growth medium of cell cultures and can contribute up to 10% of the composition of the culture media. Bovine serum is commonly used in vaccine manufacturing, both for human and animal use (Versteegen *et al*., 2016). Bovine serum is also used as a component in diluents, controls and buffer solutions in various laboratory-based procedures. Bovine serum albumin (BSA), which is a natural subcomponent of the bovine serum, can be used in embryo culture media and as a constituent in semen extender.

The presence of infectious agents within the serum can adversely affect the quality of end products such as vaccines. There is also a risk to human and animal health.

Post-collection processing methods for bovine serum

Following collection, defibrination/clotting and centrifugation of blood, several treatments can be applied to mitigate the risk of any pathogens, especially if they are present at levels below the limit of detection of analytical methods. These post-collection processing methods can be applied individually or in combination to mitigate risks. The most commonly used post-collection processing methods are filtration, heat treatment,

ultraviolet treatment, chemical treatment and ionising radiation. Filtration and gamma irradiation are the most effective and safe post-collection processing methods.

Filtration

Filtration removes bacteria and mollicutes present in the serum but cannot render serum free of viruses (Hanson *et al*., 2019).

The pooled serum is passed through filters with pore sizes appropriate for the intended application. Filtration using 0.2-µm or smaller pore size filters are usually used for removing bacterial contaminants. Mycoplasma removal is commonly performed using 0.1-µm rated membrane filters (Akers *et al*., 2009; Jornitz, 2009). Triple 0.1-µm filtration is the standard method of aseptic processing for serum. According to the United States Pharmacopoeia, triple 0.1-µm filtration has been shown to result in a high degree of mycoplasma removal.

Nanofiltration using filters with a pore size of 0.02 µm can be effective for removal of small viruses. However, scalability and flux decay with serum materials are disadvantages of this method. Therefore, nanofiltration method is not suitable for large-scale processing of serum products (Versteegen *et al*., 2016).

Gamma irradiation

Ionising radiation capable of reducing the microbial and viral burden in serum includes electron beam, X irradiation, and gamma irradiation. Gamma irradiation is the most employed and one of the most effective methods of pathogen inactivation treatment for animal serum. It is also convenient, safe and effective and does not leave any residual molecules in the final product (Merten, 2002). The main reason for its widespread usage is that serum can be irradiated in the final container. Also, the serum is irradiated at extremely low temperatures; thus, the performance capabilities of the serum are mostly unaffected (Versteegen *et al*., 2016).

Gamma irradiation dose generally used for inactivation of pathogens in animal sera ranges from 25 – 40 kGy (Nims et al., 2011; Plavsic et al., 2016; Purtle et al., 2006). Even though most of the bacteria, mollicutes and viruses are inactivated at this dose range, to reduce the viral burden of some viruses such as circovirus, parvovirus and polyomavirus to a significant level, a higher dose of 50 kGy or more is needed (Nims et al., 2011; Plavsic et al., 2016). For bacteria, a general dose of 10 kGy can inactivate vegetative forms of the bacteria; higher doses above 25 kGy are required to achieve greater levels of bacterial freedom or 'bacterial sterility' (Department of Agriculture, 2014). Purtle and others (2006) reported that gamma irradiation doses above 15 kGy could achieve a bacterial inactivation of greater than 5 $\log_{10}$ in animal sera.

The gamma irradiation dose required to inactivate the viruses and mollicutes considered for this IRA are enumerated in Table 2.

Table 2. Pathogen inactivation using gamma irradiation

Pathogen	Family	Gamma irradiation dose for inactivation (kGy)	Log_{10} reduction in titre achieved[3]	Reference
Aino virus	*Bunyaviridae*	30	8.7	(Plavsic et al., 2016)
Akabane virus	*Bunyaviridae*	30	12	(Plavsic et al., 2016)
Bluetongue virus	*Reoviridae*	25–35	3.5–4.0	(Nims et al., 2011; Plavsic et al., 2016; Purtle et al., 2006)
Bovine ephemeral fever virus	*Rhabdoviridae*	30	10	(House et al., 1990; Nims et al., 2011; Plavsic et al., 2016)
Bovine herpesvirus 1	*Herpesviridae*	25–35	≥ 4.7	(Plavsic et al., 2016; Purtle et al., 2006)
Bovine herpesvirus 5	*Herpesviridae*	25–35	≥ 4.7	(Plavsic et al., 2016; Purtle et al., 2006)
*Bovine influenza D virus**	*Orthomyxoviridae*	30	*	(Plavsic et al., 2016)
Bovine viral diarrhoea virus	*Flaviviridae*	25–35	≥ 4.3	(Nims et al., 2011; Plavsic et al., 2016; Purtle et al., 2006)
Cache Valley virus	*Bunyaviridae*	26–34	≥ 5.4	(Nims et al., 2011; Plavsic et al., 2016)
Epizootic haemorrhagic disease virus including Ibaraki**	*Reoviridae*	25–35	≥ 7.1	(Plavsic et al., 2016)
Mollicutes	*Mycoplasmatacea*	26–34	≥ 6.3	(Nims et al., 2011; Plavsic et al., 2016)

* Literature on gamma irradiation of *Bovine influenza D virus* (IDV) is not available. Since Orthomyxoviridae and Bunyaviridae are both negative-sense RNA viruses with similar structure and size, gamma irradiation parameters for Bunyaviridae are used for IDV.

** Based on other species in the same family

Gamma irradiation always inactivates pathogens and reduces the pathogen burden of the bovine serum, but the inactivation rate varies with the dose applied. Although 25 kGy can achieve a log_{10} reduction of greater than four for some pathogens, others would require an average dose of more than 35 kGy to achieve a significant pathogen load reduction. A combination of pathogens could be present in the bovine serum, and therefore, the irradiation dose to inactivate the most resistant organism should be used. Therefore, a

[3] The pathogen reduction potential: ≤ 1 log_{10} = not significant, 1 – 2 log_{10} = low/not effective, 2 – 4 log_{10} = Moderate, > 4 log_{10} = High (EMA, 1996; Ruppach, 2014).

minimum of 35 kGy is required to reduce the pathogen load of bovine serum imported from Australia and the United States.

The European Pharmacopoeia (monograph 2262) states, "For bovine serum intended for use in immunological veterinary medicinal products, for inactivation by gamma irradiation, a minimum dose of 30 kGy is applied unless otherwise justified and authorised."

According to the United States Pharmacopoeia, chapter 1024 (Bovine Serum), "Serum treatment by gamma irradiation is very common and one of the most effective methods of virus inactivation. The most frequently used minimum dose is 25 kilograys (kGy)." Chapter 90 (Foetal bovine serum – quality attributes and functionality tests) states that, "Gamma irradiation doses of 25–40 kGy provide significant log reduction of viral and other adventitious agents while preserving cellular growth performance."

The policy review document *Gamma irradiation as a treatment to address pathogens of animal biosecurity concern*, by Department of Agriculture, Australia, states, "Where the risk assessment considers irradiation is necessary, a dose of 50 kGy should continue to be used as a routine animal biosecurity treatment unless otherwise determined by the biosecurity assessment of the import application." (Department of Agriculture, 2014).

For New Zealand, the current requirements are as follows:

1. This product has been filtered to 0.22 μm or less and has been irradiated with a single or multiple irradiation dose totalling 5 mrad (50 kGy).

   OR

2. This product has been subject to triple 0.1 μm membrane filtration and has been irradiated with a single or multiple irradiation dose totalling 2.5 mrad (25 kGy),

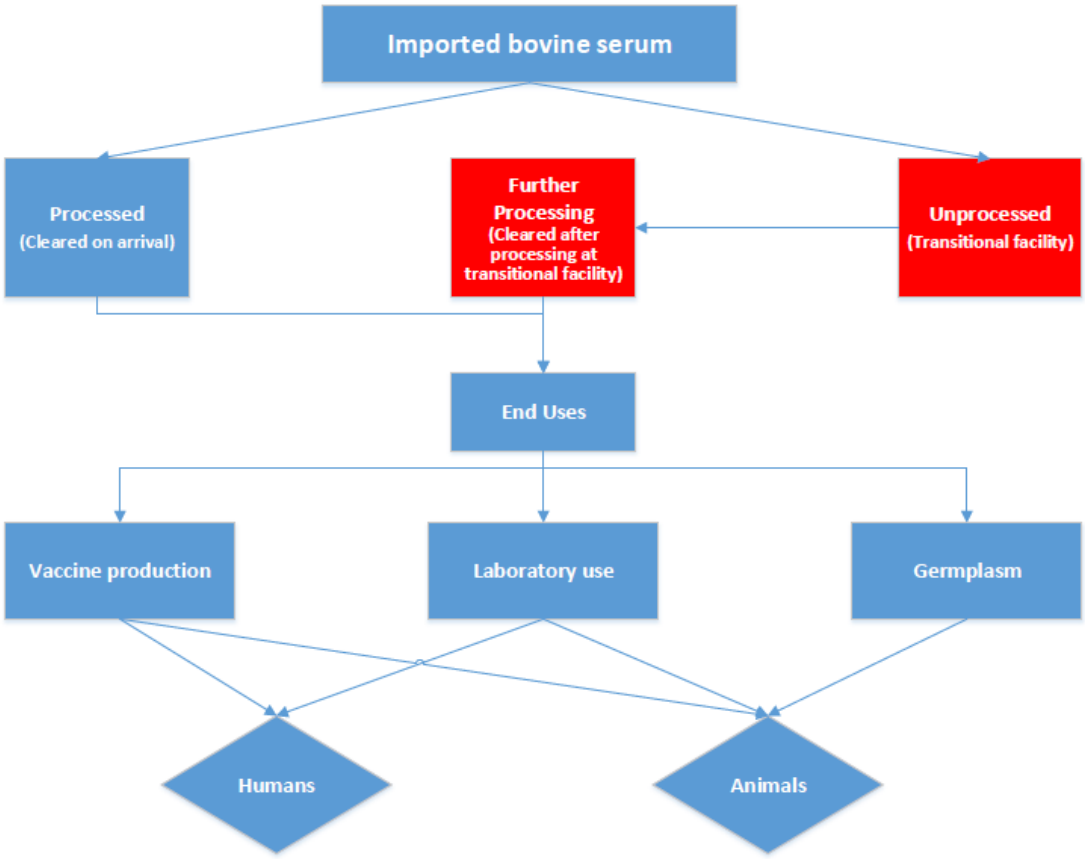
   AND

   The product has been tested and found free from mycoplasma. It has also been tested and found free from bovine virus diarrhoea, infectious bovine rhinotracheitis, bluetongue and parainfluenza-3 using the methods described in 'Australian Standard Diagnostic Techniques for Animal Diseases'.

Distribution pathway diagram

The potential distribution pathways for both processed and unprocessed bovine serum imported from Australia and the United States are shown in Figure 2.

Figure 2. Potential distribution pathways for the commodity



Pathway 1 – Exposure through the use of bovine serum in vaccines: The production process and quality control measures for vaccines and its components are out of scope for this IRA. Therefore, this IRA is based on the premise that if an organism enters New Zealand through contaminated bovine serum, it could contaminate the vaccines, and there would be likely exposure through inoculation in animals.

Pathway 2 – Exposure through the use of bovine serum in laboratories: This is not a significant exposure pathway as the bovine serum used in labs are used for research and analytical purposes only (as growth media in cell cultures, as a component in diluents, controls and buffer solutions). These products are not used in/on animals and waste materials generated during lab procedures will be inactivated. The only possible exposure in this distribution pathway is through people handling raw bovine serum without any safety procedures in place, which is unlikely.

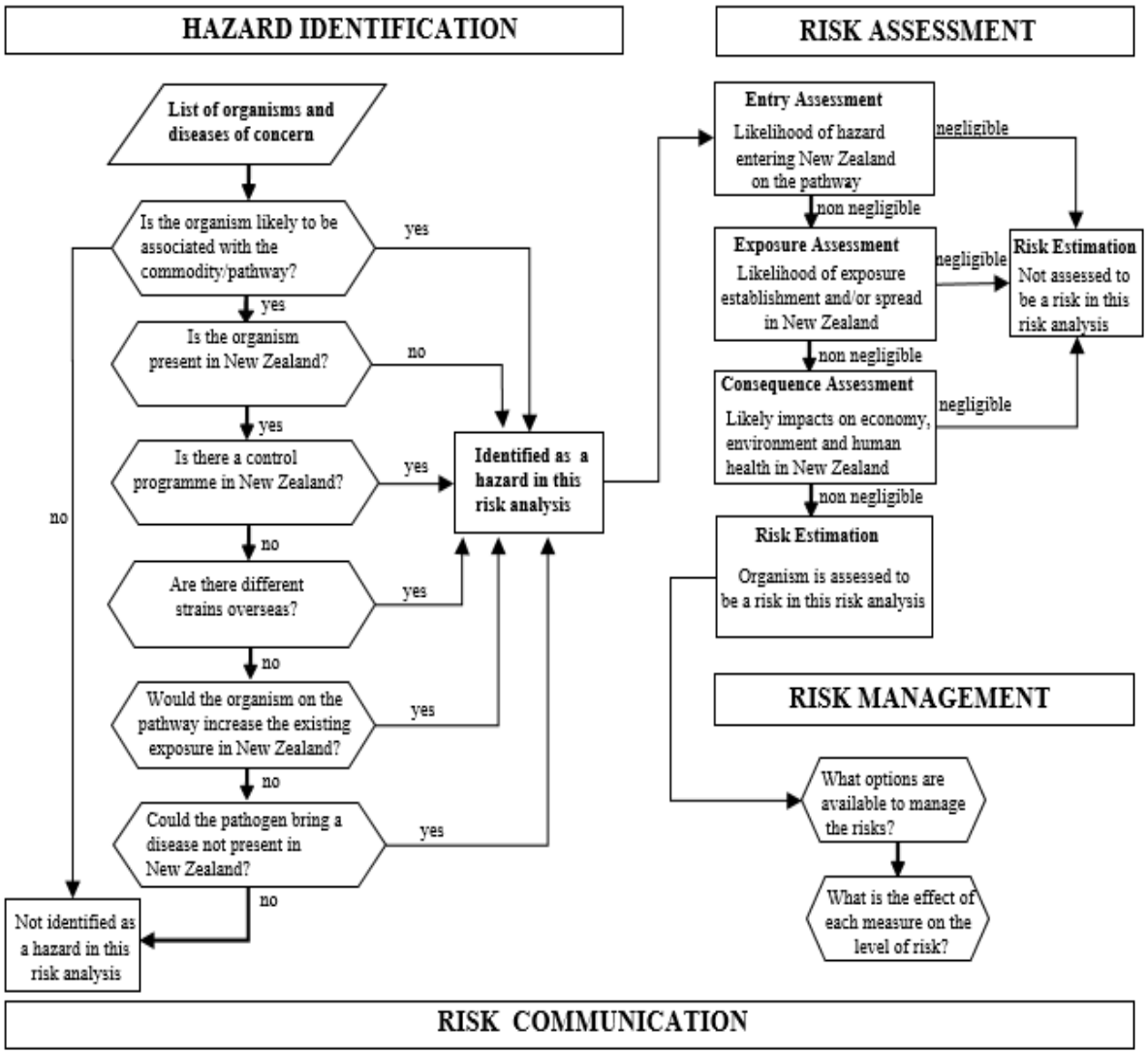
Pathway 3 – Exposure through the use of bovine serum in germplasm production: Bovine serum can be used as a component in germplasm and could have additional quality control requirements to safeguard contamination. For this IRA, production of germplasm and associated quality control measures for its components are out of scope. Therefore, if an organism is transmitted through germplasm, it is assumed that that the organism is

likely to be transmitted through contaminated bovine serum used as a media/diluent in germplasm.

5. Risk analysis methodology

The methodology used in this risk analysis follows the guidelines in Section 2 of the *Terrestrial Animal Health Code* of the World Organisation for Animal Health (OIE, 2019e) and the OIE handbook on import risk analysis for animals and animal products: Volume 1 – *Introduction and qualitative risk analysis* (OIE, 2010). The process followed is shown in Figure 3.

Figure 3. The risk analysis process



5.1. Hazard identification

From consulting authoritative texts, electronic databases and previous MPI risk analyses, a preliminary list of potential hazards has been collated. This list was subjected to a hazard identification step. This includes formal identification of the organism, whether it is an OIE-listed disease, its status in Australia, the United States and New Zealand, and a

discussion on the relevant aspects of the epidemiology and characteristics of the organism. The hazard identification section is concluded by an assessment of whether the organism is a hazard or not. The results of the hazard identification are commonly summarised as a table. All hazards identified are subjected to risk assessment.

5.2. Risk assessment

The risk assessment will define risk as either negligible or non-negligible (see below) and proposes risk descriptors to describe the comparative levels of these risk attributes.

Table 3. Risk attributes and descriptors

Risk Attributes	
Negligible	Not worth considering; insignificant
Non-negligible	Worth considering; significant
Risk Descriptors	
Very Low	Close to insignificant
Low	Less than average, coming below the normal level
Medium/Moderate	Around the normal or average level
High	Extending above the normal or average level
Very High	Well above the normal or average level

The risk assessment consists of:

Entry assessment: The likelihood of a hazard being imported with the commodity per consignment.

Exposure assessment: Describes the biological pathways necessary for exposure of susceptible animals or humans in New Zealand to the hazard. In general, a description of the pathways necessary for the establishment and/or spread of the disease agent following exposure is included within the exposure assessment. In the case of end products such as vaccines contaminated with pathogens, the exposure is certain as every vaccinated animal will be exposed to the pathogen. However, establishment will be limited to the vaccinated animals. In the case of vector-borne diseases, if there is no competent vector, there will be no further spread, and therefore, the likelihood of exposure assessment would be non-negligible but very low.

Consequence assessment: Describes the likely consequences of entry, exposure, establishment and/or spread of an imported hazard.

Risk estimation: An estimation of the risk posed by the hazard associated with importing bovine serum products. This is based on the entry, exposure and consequence assessments. If the risk estimate is assessed to be non-negligible, then the hazard is assessed to be a risk and risk management measures may be justified to reduce the level of risk to an acceptable level.

Not all the above steps may be necessary in all risk assessments. The OIE methodology makes it clear that if the likelihood of entry is negligible, then the risk estimate is automatically negligible, and the remaining steps of the risk assessment need not be carried out. The same situation arises when the likelihood of entry is non-negligible, but the exposure assessment concludes that the likelihood of susceptible species being

exposed is negligible, or when both entry and exposure are non-negligible, but the consequences of introduction are assessed to be negligible.

5.3. Risk management

For each organism assessed to be a risk, a risk management step is carried out, which identifies the options available for managing that risk. Where the OIE *Code* lists recommendations for the management of a risk, these are described alongside options of equivalent, lesser or greater stringency, where available. In addition to the options presented, unrestricted entry or prohibition may also be considered. Recommendations for the appropriate sanitary measures to achieve the effective management of risks are not made in this document. These will be determined when an IHS is drafted.

As obliged under Article 3.1 of the WTO SPS Agreement, the measures adopted in IHSs are to be based on international standards, guidelines and recommendations where they exist except as otherwise provided for under Article 3.3. That is, measures providing a higher level of protection than international standards can be applied where there is scientific justification, or if there is a level of protection that the member country considers more appropriate that are based on a scientific risk assessment.

5.4. Risk communication

After an import risk analysis has been written, the Animal Imports Team of MPI analyses the options available and proposes draft measures for the effective management of identified risks. These are then presented in a draft import health standard (IHS) that is released for public comment, together with a risk management proposal (RMP). The RMP summarises the options analysis and the rationale for the proposed measures and provides a link to the draft risk analysis. The package of documents (draft IHS, RMP and draft risk analysis) is released for stakeholder consultation. Stakeholder submissions in relation to these documents are reviewed and published, including any supplementary risk analyses that may be required, before a final IHS is issued.

6. Hazard identification

The preliminary list of hazards was compiled using the following published sources:

- OIE-listed diseases affecting multiple species and cattle (OIE, 2020).
- Import risk analysis: Cattle from Australia, Canada, the European Union, and the United States of America (2009). Ministry for Primary Industries, Wellington, New Zealand. http://www.mpi.govt.nz/importing/overview/import-health-standards/risk-analysis/
- Import risk analysis: Cattle germplasm from all countries (2009). Ministry for Primary Industries, Wellington, New Zealand. http://www.mpi.govt.nz/importing/overview/import-health-standards/risk-analysis/
- Biosecurity import risk analysis: Meat and meat products from ruminants and pigs, *Draft for public consultation* (2014). Ministry for Primary Industries, Wellington, New Zealand. http://www.mpi.govt.nz/importing/overview/import-health-standards/risk-analysis/

- Other sources such as ProMED, emerging risk system of Ministry for Primary Industries

Diseases of cattle that are absent from all three countries (the United States, Australia and New Zealand) are not included in the Hazard Identification table. Diseases of cattle that are confirmed to be present in New Zealand and not under any disease control programmes are also not included in the Hazard Identification table. Diseases caused by external and intestinal parasites are excluded because these parasites cannot normally be transmitted by blood products.

Table 4. Hazard identification table

Disease agent	OIE-listed	Present in Australia	Present in USA	Present in New Zealand	Zoonotic	Susceptible animals	Present in bovine blood	Hazard	References
Viruses[4]									
Aino virus (Simbu virus group)	No	Yes	No	No	No	Cattle, sheep, goats	Yes	**Yes**	(Spickler, 2018f; Weir, 2003)
Akabane virus (Simbu virus group)	No	Yes	No	No	No	Cattle, sheep, goats, pigs	Yes	**Yes**	(Spickler, 2018e; USDA, 2015)
Aujeszky's disease virus	Yes	No	Yes	No	No	Pigs – domestic, feral and wild All mammals except tailless apes and humans are dead-end hosts	No	**No**[5]	(Spickler, 2017; Van Oirschot, 2004)
Bluetongue virus	Yes	Yes	Yes	No	No	Domestic and wild ruminants, camels	Yes	**Yes**	(Di Gialleonardo *et al*., 2011; Spickler, 2015)
Border disease virus	No	Yes	Yes	Yes	No	Sheep, goats, pig, cattle	Yes	**No**	(McFadden *et al*., 2012; OIE, 2018b)

[4] The majority of viruses have a viraemic stage, and most viruses spread among cells extracellularly (Goldman & Prabhakar, 1996). Hence, virus can be present in serum.
[5] No sufficient evidence was found to show the presence of *Aujeszky's disease virus* in bovine blood.

Disease agent	OIE-listed	Present in Australia	Present in USA	Present in New Zealand	Zoonotic	Susceptible animals	Present in bovine blood	Hazard	References
Bovine adenovirus	No	Yes	Yes	Yes	No	Cattle	Yes	**No**	(Hawkes, 2015; MPI, 2009a)
Bovine calicivirus	No	No	Yes	Unknown - Probable	No	Cattle (calves)	No	**No**[6]	(MPI, 2009a)
Bovine ephemeral fever virus	No	Yes	No	No	No	Cattle, water buffaloes, camels, yaks,	Yes	**Yes**	(St George, 2004; Walker and Klement, 2015)
Bovine herpesvirus 1	Yes	Only BoHV-1.2b is present	Yes	Only BoHV-1.2b present	No	Cattle, sheep, goats, water buffaloes	Yes	**Yes**	(d'Offay *et al*., 1995; Nandi *et al*., 2009; OGTR, 2005; Wang *et al*., 2006)
Bovine herpesvirus 4	No	Yes	Yes	Yes	No	Cattle, bison, buffaloes, sheep	No	**No**	(de Boer *et al*., 2014)
Bovine herpesvirus 5	No	Yes	Yes	No	No	Young cattle, sheep	Yes	**Yes**	(Cascio *et al*., 1999; Delhon *et al*., 2003; d'Offay *et al*., 1995; Favier *et al*., 2012; Thiry *et al*., 2006; Zajac *et al*., 2010)

[6] Viraemia has not been reported. Hence it is considered as a virus not found in bovine blood.

Disease agent	OIE-listed	Present in Australia	Present in USA	Present in New Zealand	Zoonotic	Susceptible animals	Present in bovine blood	Hazard	References
Bovine immunodeficiency virus	No	Yes	Yes	Yes	No	Cattle, buffaloes	No	**No**	(Bhatia *et al*., 2013; Horner, 1991)
Bovine influenza D virus	No	No	Yes	No	Yes	Cattle, pigs, camelids, horses, sheep, goats	Yes	**Yes**	(Asha & Kumar, 2019; Ferguson *et al*., 2016; Zhang *et al*., 2019)
Bovine leukaemia virus (BLV) causing enzootic bovine leukosis (EBL)	Yes	Dairy herds free, low prevalence in beef	Yes	No	No	Cattle, buffaloes, capybaras	Yes	**No**[7]	(MPI, 2019a)
Bovine parvovirus	No	Yes	Yes	Yes	No	Cattle	Yes	**No**	(Sandals *et al*., 1995; Tana, 2020a., Thomson, 2004; Wosu *et al*., 1979)
Bovine polyomavirus	No	Yes	Yes	Yes	Yes	Cattle	Yes	**No**	(Wang, 2005)
Bovine respiratory syncytial virus	No	Yes	Yes	Yes	No	Cattle	No	**No**	(Motha and Hansen, 1997)

[7] BLV infects only lymphocytes, and serum does not have lymphocytes (MPI, 2019a). Cell contact is required for efficient transmission; cell-free infection by these viruses is believed to be very inefficient (Aida et al., 2013). Hence, EBL is not considered a hazard in the commodity.

Disease agent	OIE-listed	Present in Australia	Present in USA	Present in New Zealand	Zoonotic	Susceptible animals	Present in bovine blood	Hazard	References
Bovine viral diarrhoea virus (BVDV)	Yes	BVDV-1 present, BVDV-2 not reported, BVDV-3 Unknown	BVDV-1 present, BVDV-2 present, BVDV-3 not reported	BVDV-1 present, BVDV-2 and BVDV-3 not reported	No	Cattle, sheep, goats, pig, camelids	Yes	**Yes**	(Horner, 2000; Potgieter, 2004; Xia *et al*., 2011)
Cache Valley virus and other Bunyamwera viruses	No	No	Yes	No	Yes	All ruminants	Yes	**Yes**	(Edwards, 1994; Noronha and Wilson, 2017; OIE, 2018d)
Crimean Congo haemorrhagic fever virus	Yes	No	No	No	Yes	Cattle, sheep, goats, water buffaloes, hares, hedgehogs	Yes	**No**	(WAHIS, 2019a)
Epizootic haemorrhagic disease virus including Ibaraki	Yes	Yes (strains of EHDV-2)	Yes (strains of EHDV-2)	No	No	Domestic and wild ruminants	Yes	**Yes**	(Spickler, 2006; Uren, 1986; Weir, 2003; Weir and Agnihotri, 2014);
Equine encephalomyelitis viruses	Yes	No	Yes	No	Yes	Cattle, pigs, sheep, deer, dogs, poultry, game birds, ratites, horses	No	**No**[8]	(Radostits *et al*., 2007)

[8] Cattle are incidental/dead end hosts not known to be involved in the maintenance or amplification of the virus and do not develop sufficient viraemia for transmission (Radostits et al., 2007).

Disease agent	OIE-listed	Present in Australia	Present in USA	Present in New Zealand	Zoonotic	Susceptible animals	Present in bovine blood	Hazard	References
Foot-and-mouth disease virus	Yes	No	No	No	Yes (minor)	All cloven-hoofed animals	Yes	**No**	(WAHIS, 2019a)
Japanese encephalitis virus	Yes	Yes (in areas)	No	No	Yes	Equids, pigs, cows (rare); other species are susceptible	No	**No**[9]	Ilkal *et al*., 1988; Mansfield *et al*., 2017; OIE, 2019d
Palyam virus group (Orbiviruses)	No	Yes	No	No	No	Cattle	Yes	**Yes**	(Gard and Melville, 1992; Harasawa *et al*., 1988; Miura *et al*., 1991; Swanepoel, 2004; Whistler and Swanepoel, 1990)
Parainfluenza 3 virus	No	Yes	Yes	Yes	No	Cattle, sheep, goats, wild ruminants	No	**No**	(MPI, 2009a)

[9] Cattle are not known to be involved in the maintenance or amplification of the virus. They are considered dead-end hosts, and do not develop sufficient viraemia for transmission (Ilkal et al., 1988; Mansfield et al., 2017; OIE, 2019d). Hence it is not considered as a hazard in the commodity.

Disease agent	OIE-listed	Present in Australia	Present in USA	Present in New Zealand	Zoonotic	Susceptible animals	Present in bovine blood	Hazard	References
Powassan virus (belonging to the group of flaviviruses that cause tickborne encephalitis)	No	No	Yes	No	Yes	Small- and medium-sized mammals; no evidence of infection in cattle	No	**No**[10]	(Hermance and Thangamani, 2017)
Rabies virus	Yes	No	Yes	No	Yes	All mammals	No	**No**[11]	(MPI, 2009a)
Reovirus 3	No	Yes	Yes	Yes	No	Cattle	Yes	**No**	(Hawkes, 2015)
Ross river virus and *Barmah forest virus*	No	Yes	No	No	Yes	Marsupials	No	**No**[12]	(Vale *et al*., 1991)
Schmallenberg virus	No	No	No	No	No	Cattle, sheep, goats	Yes	**No**[13]	(MPI, 2013)
Vesicular stomatitis virus	No	No	Yes	No	Yes	Equids, cattle, pigs, sheep, goats	No	**No**[14]	(Lubroth *et al*., 2006; MPI, 2016b)
West Nile fever virus	Yes	Kunjin strain present	Yes	No	Yes	Birds, bats, horses, cats, dogs, chipmunks, squirrels, rabbits	No	**No**[15]	(Ilkal *et al*., 1988)

[10] Powassan virus (POWV, Flaviviridae) is the only North American member of the tickborne encephalitis serogroup of flaviviruses. Compared to the other human pathogenic flaviviruses, POWV is not well studied (Hermance & Thangamani, 2017). No evidence of infection in cattle.
[11] No evidence of the virus in blood. *Rabies virus* almost exclusively infects neurons.
[12] Antibody against the virus has been demonstrated in cattle, but no isolation of virus have been reported (Vale *et al*., 1991). There have been no reports indicating that cattle are linked epidemiologically with the disease in humans.
[13] Australia and the United States are free of the virus.
[14] The virus has not been found in blood (Lubroth *et al*., 2006).
[15] Infections in cattle are subclinical. Cattle do not develop viraemia and are dead-end hosts (Ilkal *et al*., 1988).

Disease agent	OIE-listed	Present in Australia	Present in USA	Present in New Zealand	Zoonotic	Susceptible animals	Present in bovine blood	Hazard	References
Bacteria[16]									
Bacillus anthracis	Yes	Yes	Yes	No	Yes	All mammals	Yes	**Yes**	(Mabry *et al.*, 2006)
Borrelia burgdorferi	No	No	Yes	No	Yes	Dogs, horses, cattle, deer, mice, squirrels, chipmunks	Yes	**Yes**	(Parker and White, 1992; Sala and De Faveri, 2016)
Borrelia theileri	No	Yes	Yes	No	Yes	Cattle, sheep, horses	No	**No**[17]	(MPI, 2009a)
Brucella abortus	Yes	No	Yes	No	Yes	Cattle, yaks, water buffaloes, many other species including sheep, goats, pigs, horses	Yes	**Yes**	(DAWR, 2015; DAWR, 2017; Hellstrom, 1991; MacDiarmid, 1994; Olsen and Tatum, 2010; WAHIS, 2018)
Brucella melitensis	Yes	No	No	No	Yes	Sheep, goats, cattle, yak, water buffaloes, camels, alpacas, dogs, horses, pigs	Yes	**No**	(WAHIS, 2019a)

[16] The majority of bacterial agents listed can have a bacteraemic stage and can be maintained within the circulatory system. Bacteria can be present in serum.

[17] The spirochaete *Borrelia theileri* has been found in the blood of various mammalian hosts, including ruminants, in tropical and subtropical regions of Africa, America, Asia and Australia. *Borrelia theileri* causes a mild disease with a low mortality. Most infections are subclinical. Anaemia is occasionally seen in splenectomised calves. The organism cause infections that only rarely result in mild clinical disease. Therefore, *Borrelia theileri* is not considered a hazard in the commodity.

Disease agent	OIE-listed	Present in Australia	Present in USA	Present in New Zealand	Zoonotic	Susceptible animals	Present in bovine blood	Hazard	References
Brucella suis	Yes	Yes (among wild pigs)	Yes	No	Yes	Pigs, cattle, sheep, goats, horses, dogs, opossums	Yes	**Yes**	(OIE Terrestrial Manual, 2018h; WAHIS, 2018)
Burkholderia pseudomallei	No	Yes	No	No	Yes	Goats, sheep, pigs (primarily), many other species including cattle	Yes	**Yes**	(Beig *et al*., 2017; CDC., 2006; Choy *et al*., 2000; Limmathurotsakul *et al*., 2016; Sprague and Neubauer, 2004; Van Der Lugt, 2004)
Campylobacter fetus fetus (Cff) and *C. fetus venerealis*	Yes	Yes	Yes	Unknown (control program) *Cff* present in NZ	Yes	Cattle, sheep, goats	No	**No**	(Hum *et al*., 2009; Loveridge and Gardner, 1993; Michi *et al*., 2016; OIE, 2018c; Wagenaar *et al*., 2014)

Disease agent	OIE-listed	Present in Australia	Present in USA	Present in New Zealand	Zoonotic	Susceptible animals	Present in bovine blood	Hazard	References
Chlamydia abortus	Yes	No	Yes	No	Yes	Sheep, goats (primarily), many other species including cattle	Yes	**Yes**	(Longbottom and Coulter, 2003; WAHIS, 2019c; OIE, 2018; OIE, 2019)
Coxiella burnetii	Yes	Yes	Yes	No	Yes	Sheep, goats, cattle (primarily), many other species	Yes	**Yes**	(Guatteo *et al.*, 2011; Maurin and Raoult, 1999)
Leptospira spp.	No	Yes	Yes	Yes (8 endemic serovars)	Yes	Cattle, sheep, goats, pigs, horses, dogs	Yes	**Yes**	(Ellis, 2015; Marshall and Manktelow, 2002)
Mycobacterium bovis	Yes	No	Yes	Yes (control programme)	Yes	Mainly cattle but affects many domesticated and non-domesticated animals, including free or captive wildlife species	Yes	**Yes**	(Cousins *et al.*, 2004; OIE Terrestrial Manual, 2018f; Verteramo Chiu *et al.*, 2019)
Salmonella spp.	No	Yes	Yes	Yes (some strains not reported)	Yes	Poultry, pigs, reptiles, cattle, horses, amphibians	Yes	**Yes**	(Galanis *et al.*, 2006; Larson and Spickler, 2013; Tjaniadi *et al.*, 1988)

Disease agent	OIE-listed	Present in Australia	Present in USA	Present in New Zealand	Zoonotic	Susceptible animals	Present in bovine blood	Hazard	References
Mollicutes									
Mycoplasma bovis and other mollicutes that affect bovids	No	Yes	Yes	Controlled and unknown status	Yes	Cattle, sheep, goats	Yes	**Yes**	(Akers *et al*., 2009; Biosecurity New Zealand, 2018; Parker *et al*., 2018)
Protozoa									
Babesia bovis and *B. bigemina*	Yes	Yes	No	No	No	Cattle	Yes	**Yes**	(Bock *et al*., 2004; Bram *et al*., 2002; OIE, 2020; WAHIS, 2019c)
Theileria parva and *T. annulata*	Yes	No	No	No	No	Domestic and wild bovids	Yes	No	(WAHIS, 2019c)
Theileria orientalis	No	Yes	No	Yes	No	Domestic and wild bovids	Yes	No	(OIE Technical Disease Card, 2020)
Rickettsia									
Anaplasma marginale, *A. centrale*, *A. caudatum*, *A. phagocytophilum*	Yes	Yes	Yes	No	No	Many species of wild and domesticated animals	Yes	**Yes**	(Kocan *et al*., 2010; OIE, 2020; OIE Terrestrial Manual, 2018c; WAHIS, 2018; Woldehiwet, 2010)

Disease agent	OIE-listed	Present in Australia	Present in USA	Present in New Zealand	Zoonotic	Susceptible animals	Present in bovine blood	Hazard	References
Prions									
Bovine spongiform encephalopathy	Yes	No	No	No	Yes	Cattle, goats, zoo ruminants, felids, captive lemurs	No	**No**	(Anil *et al*., 1999; Dagleish *et al*., 2008; Dormont, 2002; Eloit *et al*., 2005; N. Hunter *et al*., 2012; Schmidt *et al*., 1999; WAHIS, 2019c)

From the hazard identification table, the following 23 hazards were identified for further risk assessment:

Viruses

Aino virus (Simbu virus group)

Akabane virus (Simbu virus group)

Bluetongue virus

Bovine ephemeral fever virus

Bovine herpesvirus 1

Bovine herpesvirus 5

Bovine influenza D virus

Bovine viral diarrhoea virus (BVDV)

Cache Valley virus

Epizootic haemorrhagic disease virus including Ibaraki

Palyam virus group (Orbiviruses)

Bacteria

Bacillus anthracis

Borrelia burgdorferi

Brucella abortus

Burkholderia pseudomallei

Chlamydia abortus

Coxiella burnetii

Leptospira spp.

Mycobacterium bovis

Salmonella spp.

Mollicutes

Mollicutes including *Mycoplasma bovis*

Protozoa

Babesia bovis and *B. bigemina*

Rickettsia

Anaplasma marginale, A. centrale, A. caudatum, A. phagocytophilum

7. Aino virus

7.1. TECHNICAL REVIEW

7.1.1. Aetiology

Family: *Peribunyaviridae*
Genus: *Orthobunyavirus*
Species: *Aino orthobunyavirus* (AINOV) (Abudurexiti *et al*., 2019)

7.1.2. OIE List

Infection with Aino virus (AINOV) is not an OIE-listed disease.

7.1.3. New Zealand status

There is no serological evidence and there are no published records indicating the presence of AINOV in New Zealand (Weir, 2003).

Vector surveillance for *Culicoides* spp., the vector transmitting AINOV, is part of the arbovirus surveillance programme in New Zealand. No *Culicoides* have been detected to date in New Zealand (Peacock *et al*., 2019a).

7.1.4. Zoonotic potential

Infection due to AINOV is not zoonotic. Antibodies to AINOV have been detected in humans, but there are no reports of human disease (EFSA Panel on Animal Health and Welfare, 2017; Spickler, 2018f).

7.1.5. Epidemiology

Host range

AINOV infection is an arthropod-borne viral infection mainly affecting cattle, sheep and goats (Tsuda *et al*., 2004). AINOV or specific neutralising antibodies for the virus were also found in buffaloes, camels and deer in the western Pacific region from Japan to Australia (Weir, 2003). Antibodies to AINOV have also been found in horses, pigs, wild boars, water buffaloes and wild ruminants, although there is currently no evidence that the virus can be pathogenic in these species. AINOV is teratogenic in chick embryos inoculated directly into the yolk sac; however, there are no reports demonstrating natural infection in birds outside this experimental setting (Weir, 2003).

Geographical distribution

AINOV was detected in Asia, Africa and Australia (EFSA Panel on Animal Health and Welfare, 2017). AINOV infection is present in Australia, especially in northern Australia and in New South Wales (NSW). Clinical disease in cattle has been reported from northern Queensland and the New England region of northern NSW (Weir, 2003). AINOV was first isolated in Australia from *Culicoides brevitarsis* collected at Samford in 1968 (Doherty *et al*., 1972; Weir, 2003). Cybinski and St George (1978) conducted a survey of antibodies to AINOV in Cattle in Australia over the period from August 1975 to May 1977. A herd prevalence of 74% (40 were tested positive out of 54 herds) was observed

during this study. Another study by Norton and others (1989) on abortion in dairy cattle in Atherton Tableland, Australia, during September 1984 indicated a prevalence of 62.1% (64 animals tested positive out of 103) for AINOV. No literature was found on the current seroprevalence rate of AINOV in Australia.

AINOV was first isolated from *Culex* species in Japan in 1964 (Takahashi *et al*., 1968). AINOV has been known to occur in Asia, and antibodies to AINOV have also been found in a few countries in the Middle East and Africa (Spickler, 2018f). AINOV infection is one of the significant bovine arboviral diseases in Korea and is a notifiable disease in Japan (MAFF Japan, 2019).

AINOV has never been reported in the United States (Hawkes, 2015) or New Zealand (Weir, 2003).

Pathogenesis

AINOV causes congenital disease in cattle, sheep and goats. AINOV infections are subclinical in most adult animals, and the virus can cross the placenta to infect the fetus (Weir, 2003). De Regge (2017) reported that the capacity of AINOV to cross the placenta is limited compared to similar viruses such as Akabane. Viraemia in cattle can last for less than one week, and the virus was isolated from transmitting insects for three to four weeks (Weir, 2003).

Adult animals infected with AINOV have been reported to either develop a subclinical infection or no clinical signs other than abortion (EFSA Panel on Animal Health and Welfare, 2017; Weir, 2003). Infection in pregnant cattle, sheep and goats can cause teratogenic effects in fetuses. Fetal infections do not become evident until the affected animals are born or aborted, which may not occur for several weeks or months. In naturally infected pregnant cattle and sheep, AINOV has been associated with stillbirths, premature births, and birth defects including arthrogryposis, scoliosis, sunken eyes, cataracts, maxillary retraction and dental irregularities. Some calves may have a domed head from hydranencephaly (Tsuda *et al*., 2004; Weir, 2003). The type of abnormality seen can be related to the time of infection of the fetus: early infection results in hydranencephaly, while later infection results in arthrogryposis. Surviving calves can be weak, have difficulty suckling or standing and have been reported not to survive more than a few days (Weir, 2003).

The mortality rate is high in calves with congenital defects. Clinical cases caused by AINOV have been generally thought to be uncommon compared to those caused by other related viruses. However, underdiagnosis may have contributed to the underreporting, specifically when it affects few animals (Spickler, 2018f).

Transmission

AINOV is transmitted primarily by biting midges in the genus *Culicoides*, mainly *C. punctatus, C. oxystoma* and *C. brevitarsis* (Weir, 2003; Yanase *et al*., 2005). *C. brevitarsis* has been reported to be the primary vector transmitting the disease in Australia (Weir, 2003).

AINOV has also been detected in *Culex pipens*, *C. pseudovishnui* and *C. tritaeniorhynchus* (EFSA Panel on Animal Health and Welfare, 2017; Heath, 2019).

In addition to vector-borne transmission, transplacental fetal infection with AINOV has been reported (Weir, 2003).

Diagnosis

There are no OIE-recommended diagnostic tests for the detection and confirmation of AINOV. Diagnosis of AINOV is by virus isolation, antigen detection or antibody detection.

Virus isolation can be attempted on a variety of postmortem tissues, including the brain, spleen, liver, lymph nodes, and placenta, and/or fluids, such as cerebrospinal fluid or clotted blood (Weir, 2003).

AINOV identification can be done by multiplex real-time reverse-transcription polymerase chain reaction (real-time RT-PCR). Real-time RT-PCR is used to differentiate AINOV and Akabane viruses (Stram *et al*., 2004).

Serological tests used for AINOV antibody detection include microneutralisation, plaque reduction neutralisation (PRNT), agarose gel immunodiffusion (AGID), indirect fluorescent antibody (IFA) and enzyme-linked immunosorbent assay (ELISA) (EFSA Panel on Animal Health and Welfare, 2017). The most reliable and specific test for the detection of AINOV antibodies is the virus neutralisation (VN) test, either in the microneutralisation or plaque reduction format (Weir, 2003).

Treatment, control and prevention

There is no effective treatment against AINOV infection. Vector control and herd management strategies (such as adjustment of reproductive timing) are the best preventive measures but can be difficult to implement. Vaccination before pregnancy is another control measure (St George and Kirkland, 2004).

Inactivated AINOV vaccines have been developed and are commercially available in Japan (OIE, 2018d). Kim and others (2011) developed an inactivated trivalent vaccine for the Aino, Akabane, and Chuzan viruses of the Palyam serogroup. Their in-vivo evaluation of the vaccine indicated that it could simultaneously produce antibodies against these viruses, thus preventing disease occurrence (Kim *et al*., 2011).

7.2. RISK ASSESSMENT

7.2.1. Entry assessment

AINOV is an arbovirus, transmitted mainly by *Culicoides* midges. It primarily affects cattle, sheep and goats. AINOV is present in Australia and is transmitted mainly by the vector *Culicoides brevitarsis* (Weir, 2003). A herd prevalence of 74% was observed in Australia from 1975 to 1977, and a seroprevalence of 62.1% was reported in dairy herds in Atherton Tableland in 1984. No literature on the current prevalence was found.

AINOV is absent from the United States. There are no reports or any other evidence to prove the presence of the virus in the United States (Hawkes, 2015).

Even though AINOV affects cattle of all ages, the clinical signs primarily manifest in young cattle, including fetuses. AINOV infection in the fetus causes malformations. Adult animals infected with AINOV may either develop only a subclinical infection or abort (EFSA Panel on Animal Health and Welfare, 2017; Weir, 2003). Viraemia in cattle usually lasts for less than one week, and the virus can persist in vectors for 3 to 4 weeks post-infection (Weir, 2003). Since AINOV can be isolated from the blood of viraemic cattle, it is assumed that unprocessed bovine serum can harbour AINOV and can act as a biological pathway for AINOV entry.

Compared to Akabane virus, transplacental transmission of AINOV is limited in occurrence (De Regge, 2017). Infections in fetuses are only detected at birth or following disease-induced abortion, so it is plausible that unprocessed FBS could harbour AINOV, even though the likelihood of it doing so is lower than with Akabane virus.

Therefore, the likelihood of entry of AINOV in bovine serum from the United States is, assessed as negligible, while the risk of entry through bovine serum imported from Australia is assessed as low.

7.2.2. Exposure assessment

Bovine serum imported from Australia is used for manufacturing vaccines intended for use in New Zealand animals and is also used to manufacture other products such as components of embryo culture and cell culture media. AINOV could be present as a contaminant in the serum, including FBS, imported from Australia. Biological products, including vaccines produced from the contaminated bovine serum could infect animals. Parenteral administration of the contaminated vaccines is the most likely pathway of transmission through vaccines. However, due to the lack of published literature, there is uncertainty around the infectious dose or proof of infection post-vaccination. Animals inoculated with the contaminated vaccine could potentially develop the disease. Therefore, a large number of animals could be exposed through a contaminated vaccine.

AINOV is transmitted through *Culicoides* midges and also, to a lesser extent, through several species of mosquitoes. *Culicoides* midges are absent from New Zealand, and the mosquito species present in New Zealand are not shown to be competent vectors for AINOV infection.

There are no references of AINOV being transmitted between animals by direct contact or through germplasm. Therefore, exposure may only be through animals receiving contaminated vaccine, and further establishment and/or spread to other animals are unlikely.

Since the AINOV transmission is dependent on geographic and seasonal vector distribution within New Zealand, especially the primary vector *Culicoides*, the likelihood of establishment and/or spread via the vector pathway is negligible.

Considering all the factors discussed above, the overall likelihood of exposure, establishment and/or spread of AINOV via bovine serum is assessed as very low.

7.2.3. Consequence assessment

AINOV infects cattle, sheep, and goats. The mortality rate is high in calves with congenital defects. Although only a small percentage of calves are affected, because bovine serum is used in the production of vaccines for multiple species, exposure to the contaminated vaccine could have significant consequences in animals. This could result in production losses, especially in dairy cattle.

AINOV has never been reported in New Zealand, and indirect consequences of the virus's introduction may involve surveillance, culling of the infected animals and control measures that may impact the New Zealand economy.

Because AINOV is not an OIE-listed disease, most countries are unlikely to enforce trade restrictions if the virus is discovered in New Zealand. However, limited trade impacts due to restrictions by some trading partner countries are still possible.

AINOV is not zoonotic, and therefore, the consequences for human health in New Zealand are negligible.

Even though AINOV can infect multiple other species of animals present in New Zealand, the absence of competent vectors negates the likelihood of further establishment and/or spread of the infection. Therefore, the consequences for the New Zealand environment are negligible.

The overall consequences of AINOV as a result of entry and exposure are, therefore, assessed as very low.

7.2.4. Risk estimation

The likelihood of entry of AINOV in bovine serum from the United States is negligible, and therefore, the risk estimate is negligible. Risk management measures are not required for AINOV in bovine serum imported from the United States.

The likelihood of entry of AINOV in bovine serum from Australia is assessed as low, while the overall likelihood of exposure, establishment and/or spread is assessed as very low. The consequences of AINOV are assessed as very low. Therefore, the overall risk is estimated as very low.

Since the likelihood of entry and exposure and the consequences are non-negligible for bovine serum imported from Australia, AINOV is a risk in the commodity. Therefore, risk management measures are justified for bovine serum imported from Australia.

7.3. RISK MANAGEMENT

The following points were considered when describing options for managing the risks:

- AINOV infection is not an OIE listed disease.
- AINOV is absent from New Zealand and the United States but present in Australia.
- AINOV infection is not zoonotic and does not constitute a threat to human health.
- AINOV is primarily transmitted by *Culicoides* midges.

- *Culex pipens, C. pseudovishnui and C. tritaeniorhynchus* are able to transmit AINOV.
- *Culicoides* midges and the specific mosquito species capable of transmitting AINOV are absent from New Zealand.
- Related mosquito species (in the genus *Culex*) are present in New Zealand, but their ability to transmit AINOV is not known.
- AINOV infects multiple species of animals, mainly cattle, sheep and goats.
- In infected cattle, a short period of viraemia has been demonstrated.
- There is no effective treatment for AINOV infection.

7.3.1. Options

The following options or a combination of these options can be considered to manage the risk associated with AINOV in bovine serum.

1. Bovine serum could be imported from countries free from AINOV.
2. The animals used for blood collection showed no clinical signs of the infection on the day of blood collection, and no other evidence of the infection were reported in the animal or herd during the last three months; and:
    a. For abattoir-sourced bovine serum, the serum was derived from animals kept since birth or for the last three months in a country or zone free from the disease or seasonally disease-free zone. The animals passed antemortem examination and postmortem inspection and were processed in premises under the oversight of the competent authority.
    b. For donor-animal-derived bovine serum, the serum was derived from herds that were under veterinary supervision in a country or zone free from the disease or seasonally disease-free zone, since birth or for the last three months, or the donor was tested with an MPI approved/recommended test, with negative results, at the time of blood collection.
3. Bovine serum could be either:
    a. tested with an MPI approved/recommended test, with negative results; OR
    b. subjected to gamma irradiation at a minimum dose of 35 kGy.

8. Akabane virus

8.1. TECHNICAL REVIEW

8.1.1. Aetiology

Family: *Peribunyaviridae*
Genus: *Orthobunyavirus*
Species: *Akabane orthobunyavirus (*AKAV*)* (Abudurexiti *et al*., 2019)

8.1.2. OIE List

Infection with Akabane virus (AKAV) is not an OIE-listed disease.

8.1.3. New Zealand status

AKAV is not present in New Zealand, and AKAV infection is listed as a disease absent from New Zealand (MPI, 2020).

In New Zealand, the Arbovirus Surveillance Programme was initiated in 1991 to ensure New Zealand's freedom from arboviruses. AKAV surveillance is a part of this programme, and AKAV has never been detected through this surveillance programme or any other disease monitoring programmes in New Zealand. Vector surveillance for *Culicoides* spp., the vector transmitting AKAV, is part of this surveillance programme. No *Culicoides* have been detected to date in New Zealand (Peacock *et al*., 2019a).

8.1.4. Zoonotic potential

AKAV infection is not zoonotic (Kirkland, 2015).

8.1.5. Epidemiology

Host range

AKAV predominantly infects domestic and wild ruminants (Kirkland, 2015). Among ruminants, AKAV mostly affects cattle, sheep and goats and is characterised by the birth of deformed progeny (Oliver, 1988; St George and Kirkland, 2004). Antibodies to AKAV have also been found in horses, donkeys, buffaloes, and camels (Kirkland, 2015; OIE, 2018d). Huang and others(2003) isolated AKAV from pigs, and their study demonstrated that pigs could be important in the infection cycle of the virus in endemic areas by playing a role in the maintenance of the virus, even though the disease has not been described in pigs.

Geographical distribution

AKAV is present in Australia and most countries in Africa, the Middle East and Southeast Asia. The distribution of the virus within each country is influenced by the distribution, abundance and seasonal activity of the insect vector capable of transmitting the virus (Kirkland, 2015; St George and Kirkland, 2004).

In Australia, the distribution of AKAV depends on the seasonal activity of the vector, *Culicoides brevitarsis.* Climatic factors such as rainfall, atmospheric temperature, wind speed and direction determine the distribution of the vector. The National Arbovirus Monitoring Program (NAMP) in Australia monitors the distribution of economically significant arboviruses and associated vectors and includes AKAV. The virus is endemic in the northern half of the country, but seasonal outbreaks occur in New South Wales and southern parts of Queensland when conditions are favourable for the vector to spread. AKAV has never been detected in South Australia, Tasmania or Victoria (Animal Health Australia, 2019).

The United States is free of AKAV (Hawkes, 2015), and AKAV is listed on the United States National List of Reportable Animal Diseases, 2017 (APHIS USDA, 2017).

Pathogenesis

AKAV infection causes congenital abnormalities in ruminants, especially cattle, sheep and goats. AKAV infections are subclinical in most adult animals or are associated with mild clinical signs (De Regge, 2017; OIE, 2018d) but can cause fatal defects in developing foetuses (OIE, 2018d). Even though AKAV infections are subclinical in most adult cattle, Lee and others (2002) reported encephalomyelitis associated with AKAV infection in adult cows between two and seven years old in Korea.

In most cases, viraemia develops soon after an infected vector has bitten the adult cattle. The virus then crosses the placenta to infect the fetus, and the virus multiplies in the brain and the spinal cord of the fetus. Viraemia can be very short. It usually commences one to six days after infection and can last for four to six days in naturally infected cattle (Kirkland, 2015; St George and Kirkland, 2004). Neutralising antibodies can be detected by serological tests approximately two to three weeks after the infection. The antibodies provide the animal with immunity from reinfection and have been shown to persist in cattle for at least two years (De Regge, 2017; Kirkland, 2015; St George and Kirkland, 2004).

Heifers in endemic areas are usually infected before they reach breeding age, and the antibodies produced due to this infection protect the fetus from contracting the disease. AKAV is a potent teratogen, and affected calves, lambs and kids usually show arthrogryposis and hydranencephaly (OIE, 2018d; Oliver, 1988). The type of abnormalities in the fetus depends on the stage of gestation at which the infection occurs in the dam. AKAV infection during the first two months of pregnancy in cattle do not produce any damage to the fetus. Hydranencephaly of the fetus has been reported at days 76–104 of gestation and arthrogryposis at days 103–174 of gestation in cattle (Kirkland, 2015; OIE, 2018d; St George and Kirkland, 2004). During this period of the gestation, up to 40% of the infected calves can have these congenital abnormalities (Spickler, 2018e). Stillbirth and abortion may follow these events or result from infections during late gestation. Usually, manifestations of infection at later stages of gestation are mild. Miyazato and others (1989) reported encephalomyelitis in calves experimentally infected with AKAV during late gestation. Infected fetuses are only identified at birth or in the event of disease-induced abortion (De Regge, 2017; USDA, 2015). Predilection sites for AKAV are the brain, spinal cord and skeletal muscles, where noninflammatory necrosis of cells interferes with the morphogenesis (OIE, 2018d).

Morbidity and mortality rates vary with the strain of the virus and in general, a morbidity rate of 5% to 50% can be observed in cattle. Highly virulent strains can affect as many as 50% of infected cattle, while other strains may cause clinical signs in fewer than 20%, even when the dam is infected at the most susceptible stage of the pregnancy. The mortality rate is very high in affected newborns. Most of the infected newborns die soon after birth or have to be euthanised (Spickler, 2018e; USDA, 2015).

Transmission

AKAV is an arbovirus transmitted primarily by biting midges of the genus *Culicoides*. The specific vectors differ between regions: *Culicoides oxystoma* in Japan, *C. brevitarsis*

and *C. wadai* in Australia, and *C. milnei* and *C. imicola* in Africa (Kurogi *et al*., 1987; Sick *et al*., 2019; St George and Kirkland, 2004).

AKAV has also been detected in various mosquitoes, such as *Aedes vexans, Culex tritaeniorhynchus, Anopheles funestu* and *Anopheles vagus*; however, their role in transmission (if any) is thought to be minor (Spickler, 2018e). None of these mosquitoes are present in New Zealand, but occasional detections at the New Zealand border have occurred (Heath, 2019).

In addition to vector-borne transmission, fetal infection with AKAV can also occur via transplacental transmission. This route of transmission can be of particular significance in the epidemiology of the disease, as AKAV is most damaging when infection of the fetus occurs (De Regge, 2017). This is because AKAV has a predilection for the brain, spinal cord and skeletal muscles, where noninflammatory necrosis of cells affects the morphogenesis.

AKAV is not known to spread through contact with infected animals or their tissues, sera, or excretions; accordingly, fomites and mechanical vectors are not considered relevant in transmission (USDA, 2015). AKAV has never been detected in the semen of infected bulls and in developing embryos from infected dams collected for embryo transfer. Therefore, transmission through germplasm is not considered a possible pathway for AKAV (Kirkland, 2015).

Diagnosis

Typically, diagnosis of AKAV is through serology and histopathology, and, rarely, by virus isolation. The reverse-transcription polymerase chain reaction (RT-PCR) method can be used for the identification of the virus. Other identification methods include virus neutralisation (VN) and immunofluorescence assays (OIE, 2018d). RT-PCR is also useful in differentiating Aino virus and AKAV (Stram *et al*., 2004). Isolation and identification of the virus can be done from the plasma of viraemic sentinel animals or buffy coat suspensions from engorged vector pools. Fetal material is occasionally used in virus identification (OIE, 2018d).

Serological tests are commonly used in the diagnosis of AKAV in laboratories and tests to identify the antibodies produced by the virus include enzyme-linked immunosorbent assay (ELISA), haemagglutination inhibition (HI) and VN tests. A competitive ELISA with 98% specificity has also been developed (Kittelberger *et al*., 2013; OIE, 2018d). Serological testing of dams can be of value only in non-endemic regions, and negative serological results in these areas can convincingly exclude the disease (Kirkland, 2015).

Treatment, control and prevention

There is no effective treatment against AKAV infection. Vector control and herd management strategies such as reproductive timing are the best preventive measures but can be challenging to implement (EFSA AHAW Panel, 2017; Kirkland, 2015). Vaccination before pregnancy is another possible control measure (St George and Kirkland, 2004).

A live attenuated vaccine is used in cattle in Japan (OIE, 2018d). Inactivated vaccines have been used in Australia, Japan and Korea, and they are suitable for use in pregnant animals (Kirkland, 2015; St George and Kirkland, 2004). An inactivated trivalent vaccine (Aino, Akabane and Chuzan viruses) has been tested successfully in cattle (Kim *et al.*, 2011). Vaccination of animals prior to the increased seasonal vector distribution is considered as one of the successful control measures for the disease (Kirkland, 2015).

Other control measures include vector control and herd and flock management, especially in seasons where vector activity is high. Herd and flock management such as limiting animal movement, especially pregnant animals, delaying mating and introduction of new stock into the herd can also be used as control measures (Kirkland, 2015; Parsonson *et al.*, 1981; Singh *et al.*, 1982).

8.2. RISK ASSESSMENT

8.2.1. Entry assessment

AKAV is an arbovirus transmitted predominantly by *Culicoides* midges. It affects wild and domestic bovids, primarily cattle. AKAV is present in Australia and distribution of AKAV in Australia depends on the seasonal activity of the vector, *Culicoides brevitarsis*.

There are no reports or any other evidence that indicate the presence of the virus in the United States.

AKAV infects cattle of all ages. Transplacental transmission of AKAV infection in the fetus causes fetal malformations. Although AKAV infections are subclinical in most adult animals, it is demonstrated that viraemia usually occurs one to six days after infection and lasts four to six days in naturally infected cattle. Since AKAV can be isolated from the blood of viraemic animals, it is hypothesised that bovine serum can harbour AKAV.

As AKAV can be transmitted across the placenta to the fetus, blood collected from the fetus of an infected dam may also harbour the virus. Infected fetuses are only identified at birth or in the event of a disease-induced abortion. However, fetal blood is collected from the fetus still in the uterus of the slaughtered cow. Fetuses can be infected without any signs of viral infection, and these fetuses may not be rejected for blood collection. Therefore, it is likely that unprocessed FBS can harbour AKAV.

According to the National Arbovirus Monitoring Programme (NAMP) in Australia, the virus is endemic in the northern half of the country where the vector is present throughout the year, but AKAV is present only seasonally in New South Wales and southern parts of Queensland. Morbidity in cattle ranges from 5% to 50%, and a high mortality rate is reported in the newborns. Blood collected from cattle sourced from these areas is likely to contain AKAV.

The likelihood of AKAV entry through bovine serum imported from parts of Australia where the disease is endemic or seasonally present is assessed as low. The likelihood of entry of AKAV through bovine serum from the United States and parts of Australia where the disease is absent is assessed as negligible.

8.2.2. Exposure assessment

AKAV could be present as a contaminant in bovine serum, including FBS, sourced from endemic regions of Australia. Biological products, such as vaccines, produced from contaminated bovine serum could act as a mechanical vector for the virus. Parenteral administration of contaminated vaccines is the most likely pathway of transmission. Animals inoculated with contaminated vaccines could potentially develop the disease. Multiple animals could be exposed through the same vaccine. There is uncertainty around the infectious dose in contaminated products and the potential for infection post-vaccination. The assessment of these factors leads to the inference that there is a likelihood of exposure to the AKAV through contaminated vaccines.

AKAV is primarily transmitted through *Culicoides* midges and also, to a lesser extent, through some species of mosquitoes. *Culicoides* midges are absent from New Zealand, and the mosquito species present in New Zealand are not shown to be competent vectors for AKAV infection. Therefore, the risk of establishment and/or spread via vectors is negligible.

AKAV is not known to spread through direct contact with infected animals, and transmission through germplasm is not considered a possible pathway for AKAV. Therefore, exposure would be limited to animals that receive contaminated vaccines, and further establishment and/or spread to other animals are unlikely in the absence of the competent vector.

Considering all the factors discussed above, the overall likelihood of exposure, establishment and/or spread of AKAV via bovine serum is assessed as very low.

8.2.3. Consequence assessment

AKAV is known to infect a wide range of animal species, especially cattle, sheep, and goats. Since bovine serum is used in the production of vaccines for multiple species of animals, exposure to contaminated vaccine could have significant consequences in animals. The disease, especially in cattle, could lead to more fetal abnormalities and mortalities than Aino virus. Most newborns infected with AKAV die soon after birth or have to be euthanised.

Considering that AKAV has never been reported in New Zealand, in the event of a disease outbreak, a New Zealand response is most likely to be aimed at surveillance and culling of infected animals. The economic and social impacts of such a programme could be significant.

Infection with AKAV is not an OIE-listed disease. There are unlikely to be any wide-ranging trade impacts related to AKAV infection, but it is possible there will be limited impacts on trade with some trading countries.

AKAV infection is not zoonotic; therefore, the consequences for human health in New Zealand are negligible.

Even though AKAV could infect multiple species of wild animals present in New Zealand, the absence of competent vectors in New Zealand negates the likelihood of

further establishment and/or spread of the infection. Therefore, the consequences for the New Zealand environment are negligible.

Therefore, the overall consequences of AKAV as a result of the entry and exposure are assessed as very low.

8.2.4. Risk estimation

The likelihood of entry of AKAV in bovine serum from the United States is negligible, and therefore, the overall risk estimate is negligible. Risk management measures are not required for AKAV in bovine serum imported from the United States.

The likelihood of entry of AKAV in bovine serum from Australia is assessed as low, the likelihood of exposure, establishment and/or spread is assessed as very low, and the consequences of AKAV are assessed as very low. Therefore, the overall risk is estimated as very low.

Since the entry, exposure, and consequence assessments are non-negligible for bovine serum imported from Australia, AKAV is a risk in the commodity. Therefore, risk management measures are justified for bovine serum imported from Australia.

8.3. RISK MANAGEMENT

The following points were considered when formulating options for managing the risks:

- AKAV infection is not an OIE-listed disease.
- *Culicoides* midges transmit AKAV.
- AKAV is absent from New Zealand and the United States but present in Australia.
- In Australia, AKAV is limited to certain zones, depending on the seasonal activity of the vector, *Culicoides brevitarsis.*
- AKAV is a pathogen surveyed under the Australian NAMP.
- AKAV infection is not zoonotic.
- *Culicoides* midges are absent from New Zealand.
- AKAV infects multiple species of animals, mainly bovids.
- In infected cattle, a short period of viraemia has been demonstrated.
- There is no effective treatment for AKAV infection.

8.3.1. Options

The following options can be considered individually or in combination to manage the risk associated with AKAV in bovine serum.

1. Bovine serum could be imported from countries that are free from AKAV.
2. The animals used for blood collection showed no clinical signs of AKAV infection on the day of blood collection, and no other evidence of the infection was reported in the animal or herd during the last three months; and:
    a. For abattoir-sourced bovine serum, the serum was derived from animals kept since birth or for the last three months in a country or zone free from the disease or in a seasonally disease-free zone. The animals passed antemortem

examination and postmortem inspection and were processed in premises under the oversight of the competent authority.

b. For donor-animal-derived bovine serum, the serum was derived from herds that were under veterinary supervision in a country or zone free from the disease or in a seasonally disease-free zone, since birth or for the last three months, or the donor was tested with an MPI-approved/recommended test, with negative results, at the time of blood collection.

3. Bovine serum could be either:

   a. tested with an MPI-approved/recommended test, with negative results; OR

   b. subjected to gamma irradiation at a minimum dose of 35 kGy.

9. Bluetongue virus

9.1. TECHNICAL REVIEW

9.1.1. Aetiology

Family: *Reoviridae*
Genus: *Orbivirus*
Species: *Bluetongue virus* (BTV) (OIE Terrestrial Manual, 2018b)

BTV is a non-enveloped RNA virus, approximately 60–80 nm in diameter (Mertens *et al*., 2004; Plavsic *et al*., 2016). It has a complex, multiprotein-layered capsid structure (Celma and Roy, 2009). There are 27 known serotypes of BTV (Rojas *et al*., 2019).

9.1.2. OIE List

Bluetongue is an OIE-listed disease (OIE, 2020).

9.1.3. New Zealand status

Bluetongue is absent from New Zealand (MPI, 2020), and both BTV and *Culicoides* midges, the vector transmitting the disease, are monitored in New Zealand under the Arbovirus Surveillance Programme (Peacock *et al*., 2019a). To date, BTV and *Culicoides* have never been detected through the surveillance programme in New Zealand. BTV is listed as a notifiable organism in the Biosecurity (Notifiable Organisms) Order 2016 (MPI, 2016a).

9.1.4. Zoonotic potential

Bluetongue is not a zoonotic disease (OIE Terrestrial Manual, 2018b).

9.1.5. Epidemiology

Host range

Bluetongue is one of the most significant vector-borne viral diseases affecting all domestic and wild ruminants. The vertebrate hosts for BTV include sheep, goats, cattle, buffaloes, deer, African antelopes and other cloven-hooved animals such as camels (OIE Technical

Disease Card, 2013; OIE Terrestrial Manual, 2018b). The disease can be fatal in sheep, goats and deer, but cattle, camels and wild ruminants generally show inapparent infection (OIE Technical Disease Card, 2013). Even though live virus or antibodies were detected in some carnivores, rhinoceroses and elephants, the role of non-ruminants in the disease is minimal or not fully known (OIE Technical Disease Card, 2013; OIE Terrestrial Manual, 2018b).

Geographical distribution

BTV has a wide distribution within tropical and subtropical climates, owing to the presence of its competent vector (Tabachnick, 2004; Verwoerd and Erasmus, 2004). Endemic areas exist in Africa, Europe, the Middle East, North and South America, Australia and Asia.

Culicoides brevitarsis is the primary vector for BTV transmission in Australia, and other midges that can transmit the virus in Australia include *C. actoni*, *C. dumdumi*, *C. fulvus* and *C. wadai*. In Australia, the distribution of BTV depends on the seasonal activity and prevalence of the vector, which is influenced by climatic factors such as rainfall, temperature, wind speed and direction. BTV surveillance is a part of the Australian National Arbovirus Monitoring Program (NAMP) (Animal Health Australia, 2019). BTV is endemic in northern Australia (Northern Territory, Queensland and Western Australia) and its distribution can extend down the east coast into New South Wales, south of Sydney (Queensland Government, 2016). BTV has never been detected in South Australia, Tasmania or Victoria (Animal Health Australia, 2019).

To date, 27 serotypes of BTV have been recognised worldwide, with 12 serotypes isolated in Australia (Agriculture Victoria, 2017; Animal Health Australia, 2015). To minimise the disruption to trade and to manage the risks associated with the presence of BTVs, Australia has established a BTV-free zone and a zone of possible transmission (Kirkland, 2004).

BTV distribution in the United States is limited by the range of the *Culicoides* spp. vectors (Ostlund *et al*., 2004). To date, 15 serotypes of BTV have been found in the country (Maan *et al*., 2012). The United States does not conduct any active surveillance of circulating BTV serotypes in the whole country. Because of this, virus isolations are only made during an outbreak of bluetongue disease or when testing for export purposes. Virus isolation during a disease outbreak more often identifies only the serotypes that caused the disease outbreak (Schirtzinger *et al*., 2018).

Bluetongue is widely distributed throughout the world. BTV is a virus of regulatory concern when importing and exporting FBS, because BTV crosses the placental barrier and different serotypes exist in different countries (Hawkes, 2016).

Pathogenesis

Bluetongue is an infectious, non-contagious disease affecting all domestic and wild ruminants, transmitted mainly by *Culicoides* spp. midges. *Culicoides* spp. are much more attracted to cattle, and cattle serve as the primary reservoir and amplifying host for the virus, as they develop a high level of viraemia (Berrier, 2005). Cattle and buffaloes can be subclinically affected and act as carriers of BTV (Maan *et al*., 2017). The incubation

period is usually 5–10 days (OIE, 2013). The virus can persist in the blood of some animals for relatively long periods, facilitating transmission to *Culicoides* (MacLachlan, 2004). The live virus has been isolated from some cattle for as long as five to nine weeks, and viral RNA has been found for much longer (Spickler, 2015). BTV in the blood is associated mostly with erythrocytes and to a lesser extent with the buffy coat fraction and plasma (Verwoerd and Erasmus, 2004). In the early phase of infection, a more substantial part of viral RNA detected in the blood can be likely to derive from live virions. During the later phases, most of the viral RNA are probably derived from degraded virions. The RNA derived from these degraded virions is not capable of infecting vectors (Di Gialleonardo *et al*., 2011). The impact of virus dose on the outcome of infection is poorly understood (Di Gialleonardo *et al*., 2011).

The severity of the disease varies among different species. The occurrence and severity of the clinical disease in cattle has been reported to be much lower than in sheep. In cattle, mortality is negligible. Infected cattle remain viraemic for about 50 days (Verwoerd and Erasmus, 2004) and can act as a source of infection for *Culicoides* spp. Cattle rarely show clinical signs, which are limited to a transient febrile response, increased respiratory rate, increased lachrymation and salivation, stiffness and inflammatory changes in the skin (Maclachlan *et al*., 2015a; Verwoerd and Erasmus, 2004). During the BTV-8 epidemic in 2006 in northwestern Europe, there were reports of cattle showing clinical signs similar to sheep (Elbers *et al*., 2008). A study conducted to determine the risk factors for BTV in cattle in Sudan has indicated older cattle (>2 years of age) are four times more likely to be infected with BTV than young cattle (Adam *et al*., 2014).

Clinical signs are most severe in sheep, resulting in deaths, weight loss and disruption of wool growth. Other clinical signs in sheep include acute febrile response characterised by hyperaemia and congestion; oedema of the face, eyelids, lips and ears; ulceration and necrosis of the mucosae of mouth, nose, lips and tongue; hyperaemic and oedematous tongue which become cyanotic in severe cases; and laboured breathing and dyspnoea. Hyperaemia can also extend to other parts of the body, such as the coronary band of the hoof, the groin, axilla and perineum, which can result in lameness and stiffness (Hawkes, 2016; OIE Technical Disease Card, 2013; OIE Terrestrial Manual, 2018b). Fetal abnormalities and abortions are also reported in sheep. In highly susceptible sheep, morbidity can be as high as 100%. Mortality averages from 2–30% but can be as high as 70% in sheep (OIE Technical Disease Card, 2013; Verwoerd and Erasmus, 2004).

Transmission

BTV is mainly transmitted by midges of the genus *Culicoides*. Sheep keds (*Melophagus ovinus*), ticks and biting flies can also act as mechanical vectors, even though BTV transmission through them is considered very limited (Spickler, 2015). Vectors are infected with BTV after ingesting blood from infected animals (Maclachlan *et al*., 2015a; OIE Terrestrial Manual, 2018b; Verwoerd and Erasmus, 2004).

Mechanical transmission can also occur through contaminated surgical equipment and needles (Morley and Rawdon, 2009). BTV is not naturally transmitted through contact with animals, wool or consumption of milk.

Only laboratory-adapted strains of BTV and BTV-8 have been found in semen from infected bulls and rams at the time of peak viraemia (Kirkland *et al.*, 2004; OIE Terrestrial Manual, 2018b).

Transmission of BTV by bovine embryos is generally considered negligible as long as the embryos are washed according to the International Embryo Transfer Society (IETS) protocol (Venter *et al.*, 2011). However, it was recently found that the IETS washing protocol was not successful in removing BTV-8 from bovine embryos (Haegeman *et al.*, 2019).

Menzies and others (2008) described overwintering mechanisms of BTV in their study conducted on the BTV-8, which was endemic in northwestern Europe in 2006. This study presented evidence for the possibility of transplacental transmission and contact transmission through ingestion of infected placenta.

Diagnosis

BTV can be found in blood from viraemic live animals and in spleen, liver, heart blood, lymph node or bone marrow samples collected at necropsy. Blood collected from aborted or congenitally infected newborn animals and pre-colostrum serum can also be used for diagnosis (OIE Technical Disease Card, 2013).

Clinical diagnosis of BTV can be achieved based on clinical signs in infected animals and necropsy findings in aborted fetuses. Clinical diagnosis should be confirmed through laboratory diagnostic methods, which include BTV isolation, antigen /or antibody identification (Sperlova and Zendulkova, 2011).

The reverse transcription polymerase chain reaction (RT-PCR) method is widely used to identify viral RNA in clinical samples, as well as identify the serotype. RT-PCR, real-time RT-PCR and classical virus isolation by inoculation of embryonated chicken eggs are the OIE-recommended virus identification tests for BTV (OIE Terrestrial Manual, 2018b). These tests could be used to substantiate claims of individual animal freedom from BTV prior to movement.

Serological tests for antibodies to BTV include competitive ELISA (C-ELISA), the complement fixation test (CFT), agar gel immunodiffusion (AGID), indirect ELISA and virus neutralisation (VN) tests. Among these tests, the C-ELISA and VN tests are the OIE-recommended tests for claiming individual animal freedom from BTV prior to movement (OIE Terrestrial Manual, 2018b). The C-ELISA test has high sensitivity and specificity and can detect antibodies for all serotypes and strains of BTV (Maclachlan *et al.*, 2015a).

The OIE *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals* details the various laboratory procedures for diagnosing BTV (OIE Terrestrial Manual, 2018b).

Treatment, control and prevention

No specific treatment is available for bluetongue disease, other than supportive care. Hence, treatment is limited to antibiotic therapy to control secondary bacterial infections.

Control of BTV is problematic because of the large number of potential hosts and virus serotypes (Scott and Tarlinton, 2017). BTV control becomes complicated once it has been

transmitted to vectors. While control is aimed at keeping susceptible animals isolated from the vector, it is not always practical, particularly in extensive pastoral settings (Maclachlan *et al*., 2015a). An immediate ban on animal imports from countries with BTV, followed by the monitoring of domestic ruminants through clinical examinations, serological and virological testing are some control options (Sperlova and Zendulkova, 2011). Movement restrictions imposed on affected animals can help to reduce the spread to disease-free regions (Scott and Tarlinton, 2017).

Vaccines are available for animals deemed to be at high risk of contracting BTV. Currently, inactivated and live attenuated vaccines are commercially available and have been successfully used to control bluetongue. (Maclachlan *et al*., 2015a; OIE Technical Disease Card, 2013). Attenuated vaccines are more effective than killed vaccines but have been reported to cause reduced milk production in sheep, abortion, embryonic death and fetal malformations in pregnant ewes vaccinated during the first half of gestation. Also, the live attenuated vaccine has the potential to be spread by vectors (OIE Terrestrial Manual, 2018b).

However, the potential benefits of attenuated BTV vaccines are manifold. They are inexpensive to produce in large quantities, they generate protective immunity after a single inoculation, and they have proven effective in preventing clinical disease.

Vaccination is vital to the prevention of the disease in endemic areas (Maclachlan *et al*., 2015a; Verwoerd and Erasmus, 2004) and has been used in several countries to limit direct losses, minimise the circulation of BTV and allow safe movement of animals (OIE Terrestrial Manual, 2018b). Vaccination is usually carried out prior to the seasonal period of virus transmission (vector distribution) and breeding season. Safer new-generation vaccines, such as vectored recombinant vaccines, have been developed for BTV. These vaccines will potentially allow differentiation between infected and vaccinated animals (DIVA) (Maclachlan *et al*., 2015a).

9.2. RISK ASSESSMENT

9.2.1. Entry assessment

Bluetongue is one of the most significant vector-borne viral diseases affecting all domestic and wild ruminants. In cattle, the disease is usually subclinical, and the virus can persist in bovine blood for long periods. The live virus can be isolated from some cattle for as long as nine weeks. Hence, bovine blood can play a role in the biological entry pathway for BTV. Even though BTV is mainly associated with erythrocytes during viraemia, the virus has also been reported to be associated with buffy coat fraction and plasma (Verwoerd and Erasmus, 2004). Since BTV can be isolated from plasma in the viraemic animals, and given the possibility of BTV being released from infected erythrocytes and white blood cells into extracellular medium (Celma and Roy, 2009), it is likely that bovine serum can act as a biological pathway for BTV entry.

BTV is present in both Australia and the United States, and multiple serotypes of BTV have been reported from these countries. Information about the prevalence of BTV in Australia and the United States is not available. According to the NAMP, BTV is endemic in northern Australia (Northern Territory, Queensland and Western Australia), and its distribution can extend down the east coast into New South Wales, south of Sydney.

Assuming donors will be subject to antemortem examination, this assessment considers only subclinically infected donors. Bovine serum collected from subclinically infected animals can be contaminated with BTV and may act as a pathway for BTV entry into New Zealand.

The likelihood of entry of BTV in bovine serum from endemic regions of Australia and the United States is assessed as moderate.

9.2.2. Exposure assessment

In mid-1993, BTV infection was reported in two Australian Shepherd dogs that were linked to a commercial multivalent modified-live canine distemper virus, adenovirus and parvovirus vaccine contaminated with BTV (Akita *et al*., 1994). Both dogs aborted seven to nine days after vaccination and died after 48 to 72 hours with signs of heart failure and respiratory distress. This case demonstrated the transmission of BTV through parenteral administration of biological commodities.

BTV could be present as a contaminant in bovine serum, including FBS, imported from Australia and the United States. Biological products like vaccines produced from the contaminated bovine serum could harbour BTV, and parenteral administration of the contaminated vaccines could potentially infect the vaccine recipients leading to the development of viraemia and disease. Vaccination is generally implemented as a herd management tool, and therefore, many animals could be exposed through the contaminated vaccine. Therefore, there could be exposure to BTV infection resulting from inoculation of contaminated end products such as vaccines.

BTV is mainly transmitted by midges of the genus *Culicoides*. To date, the New Zealand vector surveillance programme for *Culicoides* spp. has not detected any *Culicoides* spp. (Peacock *et al*., 2019a).

Sheep keds (*Melophagus ovinus*), ticks and biting flies can act as mechanical vectors, although this mode of transmission is considered very limited (Spickler, 2015). Although rare, the sheep ked is present in New Zealand (Heath, 2019; Tenquist and Charleston, 2001). The ticks and flies present in New Zealand are not proven to be competent vectors for BTV.

Transmission of BTV by direct contact is considered negligible. Therefore, exposure would be limited to animals receiving a contaminated vaccine, and further establishment and spread to other animals in New Zealand is unlikely.

Since BTV transmission is dependant on the geographic and seasonal vector distribution within New Zealand, and the primary competent vector *Culicoides* is not present in the country, the likelihood of establishment and/or spread through live vectors is negligible.

Considering all the factors mentioned above, the overall likelihood of exposure, establishment and/or spread of BTV via bovine serum from Australia and the United States is assessed as low.

9.2.3. Consequence assessment

BTV affects all domestic and wild ruminants and can be fatal in infected sheep, goats and deer. Cattle usually show inapparent infection. Production losses can be a direct consequence, sheep being the worst affected domestic species. In susceptible sheep, morbidity can be as high as 100%. Mortality averages from 2–30% but can be as high as 70% (Verwoerd and Erasmus, 2004). Hence, even without the vector, the consequences of acquiring BTV from contaminated end products such as vaccines may be more serious for sheep than for other animals. Goats and cattle usually have mild, self-limiting cases, and thus, the consequences may not be as significant for goats and cattle as they are for sheep (Hawkes, 2016).

Indirect consequences include costs incurred for biosecurity response, increased surveillance and other biosecurity services, trade losses (embargoes, sanctions, lost market opportunities) and compensation.

Bluetongue is an OIE-listed disease, and there could be trade impacts related to bluetongue infection.

BTV is a disease of ruminants, and there is no threat to indigenous non-ruminant animals, birds or humans (MPI, 2009a). Some species of deer are susceptible to the infection. However, the lack of competent vectors in New Zealand negates the likelihood of further spread of the infection. Therefore, the consequences for the New Zealand environment are negligible.

BTV is not zoonotic; therefore, the consequences for human health in New Zealand are negligible.

The overall consequences of BTV as a result of entry and exposure are assessed as moderate.

9.2.4. Risk estimation

The likelihood of entry of BTV in bovine serum from endemic regions of Australia and the United States is assessed as moderate; the likelihood of exposure, establishment and/or spread is assessed as low; and the consequences of BTV are assessed as moderate. Therefore, the overall risk is estimated as moderate.

Since the entry, exposure, and consequence assessments are non-negligible for bovine serum imported from endemic regions of Australia and the United States, BTV is a risk in the commodity. Therefore, risk management measures are justified for bovine serum imported from Australia and the United States.

9.3. RISK MANAGEMENT

The following points were considered when describing options for managing the risks:

- Infection with BTV is an OIE-listed disease.
- BTV is absent from New Zealand but present in Australia and the United States.
- In Australia, BTV is only present in certain zones and is monitored as a part of NAMP.
- Bluetongue is not a zoonotic disease.

- BTV infection in cattle is usually subclinical, and mortality is negligible.
- Viraemia is reported in cattle infected with BTV, and infected cattle remain viraemic for about 50 days.
- BTV is mainly transmitted by *Culicoides* midges.
- The BTV vector, *Culicoides*, is not present in New Zealand.
- BTV is a virus of regulatory concern when importing and exporting FBS, because BTV crosses the placental barrier.
- Different serotypes exist in different countries.

9.3.1. Options

The following options individually or in a combination can be used to manage the risk associated with BTV in bovine serum. These options have been adopted based on some of the OIE recommendations for infection with BTV (OIE Terrestrial Code, 2018).

1. Bovine serum could be imported from countries free from BTV as per the relevant OIE Code chapter.

2. The animals used for blood collection showed no clinical sign of BTV infection on the day of collection, and no other evidence of the infection was reported in the animal or herd; and:

    a. For abattoir-sourced bovine serum, the serum was derived from animals kept in a country or zone free from BTV infection or a seasonally free country or zone during the free season in accordance with the requirements of the OIE Code. The animals passed antemortem examination and declared fit for human consumption in abattoirs and were processed in premises under the oversight of the competent authority.

    b. For donor-animal-derived bovine serum, the animals were under veterinary supervision in a country or zone free from BTV infection or in a seasonally free country or zone during the free season in accordance with the requirements of the OIE Code, or the donor was tested with an MPI-approved/recommended test, with negative results, at the time of blood collection.

3. Bovine serum could either be:

    a. tested with an MPI-approved/recommended test, with negative results; or

    b. subjected to gamma irradiation at a minimum dose of 35 kGy.

10. Bovine ephemeral fever virus

10.1. TECHNICAL REVIEW

10.1.1. Aetiology

Family: *Rhabdoviridae*
Genus: *Ephemerovirus*
Species: *Bovine fever ephemerovirus* (ICTV 2018) / *Bovine ephemeral fever virus* (BEFV)

10.1.2. OIE List

Bovine ephemeral fever (BEF) is not an OIE-listed disease.

10.1.3. New Zealand status

BEFV is not reported in New Zealand to date, and there is no serological evidence indicating its presence in the country. BEFV surveillance is part of the Arbovirus Surveillance Programme in New Zealand. BEFV has never been detected through this surveillance programme or any other disease monitoring programmes in New Zealand (Peacock *et al*., 2019a).

10.1.4. Zoonotic potential

Bovine ephemeral fever is not a zoonotic disease.

10.1.5. Epidemiology

Host range

Cattle, yaks (both members of the genus *Bos*) and water buffalo are known to be clinically affected by BEFV (Walker and Klement, 2015). Antibodies to BEFV have also been found in sheep, goats and pigs with no clinical signs of the disease (Walker and Klement, 2015). There is no evidence of clinical disease in sheep or evidence that this species plays any role in the epidemiology of BEF (Walker and Klement, 2015).

Antibodies have also been detected in many wild animals including African buffaloes, hartebeests, waterbucks, wildebeests, kudus, giraffes, elephants, hippopotamuses, warthogs and various species of deer and antelope (Aziz-Boaron *et al*., 2015). Seroprevalence can be high in certain African wildlife, with some species acting as reservoir hosts (Anderson and Rowe, 1998).

Geographical distribution

BEFV is present in tropical, subtropical and warm temperate regions of Africa, Australia (St George, 2004), the Middle East and Asia (Aziz-Boaron *et al*., 2015). BEFV is not present in Europe (other than in the western regions of Turkey), North America, South America (Kirkland, 2002; Walker and Klement, 2015) or the Pacific islands (Walker and Klement, 2015).

BEFV has not been reported in the United States.

Since the first report of BEFV in Australia in 1936 in the Northern Territory, it has spread to the eastern and western regions of Australia (Trinidad *et al*., 2014). Seroconversion rates of up to 90% were reported in cattle in eastern Australia during these epizootics, but in the intervening periods, only sporadic seasonal outbreaks were reported (George *et al*., 1977).

BEFV surveillance is a part of the National Arbovirus Monitoring Program (NAMP) in Australia (Animal Health Australia, 2019). According to NAMP, BEFV is endemic in northern Australia. During 2018–2019, BEFV distribution in the Northern Territory was limited and was detected only in a few NAMP sites. In New South Wales and Queensland,

BEFV occurrence is weather dependent, limited by cold weather. BEFV distribution is restricted to the Kimberley region in Western Australia. BEFV or clinical cases of BEF has never been detected in South Australia, Victoria or Tasmania (Animal Health Australia, 2019).

Pathogenesis

The incubation period in experimental infections of cattle is three to five days, with 10 days being the longest (Spickler, 2016b; Zheng *et al*., 2016). Viraemia could last for four to five days (St George, 2004; Walker and Klement, 2015). Zheng and others (2016) experimentally demonstrated a positive correlation between the duration of clinical signs and the inoculated viral dose. In this experiment, BEFV was isolated from blood samples of infected cattle, and the virus was present for a longer period when a higher viral dose was given.

The initial site of replication following transmission of BEFV is not known. However, the virus was detected circulating in the blood in high titre one day prior to the onset of the clinical signs, especially fever (St George 2004). After the replication in the initial site of infection, BEFV can be detected primarily in the leucocytes and blood plasma (Walker, 2005).

There is no evidence of carrier status of BEFV in cattle (Zheng *et al*., 2016).

Outbreaks of the disease result in production losses, particularly in dairy cattle. Infection may be clinically inapparent or may result in mild to severe clinical signs, including a biphasic fever, salivation, ocular and nasal discharge, recumbency, muscle stiffness, lameness and anorexia (Walker and Klement, 2015). Postmortem lesions include fibrin-rich fluid accumulation in pleural, pericardial and peritoneal surfaces. Oedema in lungs and lymph nodes may be apparent in some cases (Spickler, 2016b).

The acute clinical signs usually only last for one to three days (Spickler, 2016b; Walker and Klement, 2015) but can extend up to seven to eight days (Zheng *et al*., 2016). A minority of cases may be fatal if animals become recumbent.

Morbidity rates can be very high (approaching 100%), and mortality rates are low (<1%). However, there have been reports from several countries of high case-fatality rates, sometimes exceeding 20% (Hsieh *et al*., 2005; Spickler, 2016b).

Transmission

Transmission of the virus is predominantly through mosquitoes (Murray, 1997). This virus was isolated from various genera of mosquitoes such as *Culex*, *Aedes* and *Anopheles* (St George *et al*., 1976; Walker, 2005) and several *Culicoides* species (biting midges) (Blackburn *et al*., 1985; Spickler, 2016b; Walker and Klement, 2015). In Australia, the primary vector for the transmission of BEFV is the mosquito *Culex annulirostris* (Animal Health Australia, 2019). Other mosquitoes from which BEFV has been isolated include *Anopheles bancroftii, Uranotaenia* spp. and *Aedes* spp. (Walker and Klement, 2015). *Culicoides* spp. may not be the primary vector of the disease (St George, 2004). Six *Aedes* spp. of mosquitoes are reported to be present in New Zealand, but none of the other

mosquitoes known to be capable of transmitting the disease are present in New Zealand (Heath, 2019).

There is no evidence that BEFV can be transmitted directly between animals; in nature, BEFV is not spread by close contact, body secretions or aerosol droplets (St George, 2004). However, animals can be infected experimentally by intravenous inoculation of small amounts of blood (St George, 2004; Zheng *et al*., 2016). There is no evidence that this virus can be transmitted through semen or embryos.

Diagnosis

In most cases, BEFV is confirmed by serology of paired serum samples showing a rising titre. Virus neutralisation (VN) or enzyme-linked immunosorbent assays (ELISAs) are the most commonly used serological tests (Anderson and Rowe, 1998; Aziz-Boaron *et al*., 2015; Walker and Klement, 2015).

Reverse transcription polymerase chain reaction (RT-PCR) assays are used for routine diagnosis in some countries. These assays can be used to detect viral RNA in the blood (Zheng *et al*., 2016). Virus isolation (VI) has been successful, especially during the first 24–48 hours of clinical signs (Zheng *et al*., 2016).

Treatment, control and prevention

Treatment may be unnecessary in milder cases, but more severely affected animals are often treated, particularly when they have become recumbent (Spickler, 2016b; Walker and Klement, 2015).

Short quarantine periods in vector-free facilities should manage the risks associated with the introduction of BEFV in imported animals because illness and viraemia are brief, and carriers are not known (Zheng *et al*., 2016).

In endemic areas, vaccination is used to prevent disease, particularly in dairy and feedlot herds. Valuable breeding stock is also vaccinated in endemic areas to prevent production losses (Walker and Klement, 2015). Four types of BEF vaccines have been developed to date. They are live-attenuated vaccines, inactivated vaccines, subunit G protein-based vaccines, and recombinant vaccines. Live-attenuated, inactivated, and subunit vaccines are used in the field (Walker and Klement, 2015).

10.2. RISK ASSESSMENT

10.2.1. Entry assessment

Infected animals develop a viraemia that lasts four to five days. If the infection is clinically inapparent or results in mild signs, it may go undiagnosed during clinical examination of donors or antemortem examination at slaughter plants. Therefore, contaminated blood may be collected from infected donor animals for bovine serum production. Although there is no evidence of BEFV in serum, evidence of virus isolation from blood has been demonstrated. After the replication in the initial site of infection, BEFV can be detected primarily in the leucocytes and plasma (Walker, 2005). It is likely that virus remains in the serum of infected animals.

BEFV is absent from the United States; therefore, the likelihood of entry of BEFV in bovine serum from the United States is assessed as negligible and is not considered further in this assessment.

Australia experiences epizootics and sporadic seasonal outbreaks in the intervening periods. According to NAMP, BEFV is endemic in northern Australia, and is present in New South Wales and Queensland where it is weather dependent. Therefore, the occurrence of outbreaks of BEFV is dependent on the extent of the seasonal multiplication of vectors.

Thus, the likelihood of entry of BEFV in bovine serum from Australia is variable and is assessed as very low to low. The likelihood of entry of BEFV through bovine serum from the United States is assessed as negligible.

10.2.2. Exposure assessment

Animal vaccines produced from contaminated bovine serum could contain viable BEFV. Parenteral administration of these contaminated vaccines is the primary pathway for transmission through vaccines. There is evidence that animals can be experimentally infected by inoculation of small amounts of blood intravenously (St George, 2004; Zheng *et al*., 2016). However, the infectious dose for BEFV is not known; therefore, there is uncertainty in relation to a vaccine causing infection in an animal following parenteral administration. During natural transmission, mosquitoes inoculate the virus into sub-cutaneous capillaries. It is also likely that during vaccination, needles may rupture subcutaneous capillaries and virus may spread into the vessels.

Therefore, it is reasonable to assume that there is the likelihood of exposure to infection with BEFV after vaccination with a contaminated vaccine.

BEFV was isolated from mosquitoes and biting midges (*Culicoides* spp.) in Australia and Africa (Trinidad *et al*., 2014), but most data suggest that mosquitoes are the primary vector. The mosquito species that are present in New Zealand are not proven to be competent vectors of the disease. The vector surveillance programme operating in New Zealand includes *Culicoides* spp., and no *Culicoides* midges have been detected to date (Peacock *et al*., 2019a). Since the BEFV transmission is dependent on the capability of vectors present in New Zealand, the risk of establishment and/or spread is negligible.

There is no evidence of BEFV being transmitted directly between animals; in nature, BEFV is not spread by close contact, body secretions, or aerosol droplets (St George, 2004). Also, transmission through germplasm is not considered a possible pathway for BEFV. Therefore, exposure may only be limited to animals receiving contaminated vaccines and further establishment and/or spread to other animals are unlikely in the absence of any competent vectors.

Thus, the overall likelihood of exposure, establishment and/or spread of BEFV based on all the factors discussed above is assessed as very low.

10.2.3. Consequence assessment

BEFV is not known to cause clinical disease in animal species other than cattle, yaks and water buffaloes. Vaccinated naive animals (cattle, yaks and water buffaloes) could

potentially become infected and could develop clinical disease. Considering the livestock industry and its contribution to the New Zealand economy, it is reasonable to assume that there could be significant consequences to New Zealand due to economic losses from animal infection, disease and production loss.

BEF is not an OIE-listed disease, and there are no trade restrictions related to BEF. The economic impacts of BEFV can be considerable and are due primarily to the cessation of lactation in dairy cattle and loss of condition in beef cattle (Davis *et al*., 1984; Walker and Klement, 2015). BEFV would impact trade in live cattle from infected zones in New Zealand if the disease became established in New Zealand (Walker and Klement, 2015). The disease is exotic to New Zealand. If a control (including culling of infected animals) or containment programme were to be implemented following the establishment of BEFV, there would be economic impacts to New Zealand.

BEFV is not zoonotic; therefore, the consequences to human health are negligible.

The overall consequences of BEFV as a result of entry and exposure are assessed as very low.

10.2.4. Risk estimation

The likelihood of entry of BEFV in bovine serum from the United States is negligible, and therefore, the risk estimate is negligible. No risk management measures are required for BEFV in bovine serum imported from the United States.

The likelihood of entry of BEFV in bovine serum from endemic regions in Australia is assessed as very low to low; exposure, establishment and/or spread are assessed as very low, and consequences of BEFV are assessed as very low. Therefore, the overall risk is estimated as very low.

Since the likelihood of entry, exposure and the consequences are non-negligible for bovine serum imported from Australia, BEFV is a risk in the commodity. Therefore, risk management measures are scientifically justified.

10.3. RISK MANAGEMENT

The following points were considered when presenting options for managing the risks:

- BEF is not an OIE-listed disease.
- BEF is not a zoonotic disease.
- BEFV occurs in Australia but is absent from the United States.
- In Australia, BEFV is only present in certain zones and is monitored as a part of NAMP.
- BEFV is not known to cause clinical disease in animal species other than cattle, yaks and water buffaloes.
- The incubation period in experimental infections is usually three to five days with an extreme of 10 days, with viraemia lasting four to five days.
- Transmission of the virus is mainly associated with mosquitoes and *Culicoides* midges.

- New Zealand does not have *Culicoides* midges, and mosquitoes in New Zealand are not proven vectors of BEFV.
- Animals can be infected experimentally by inoculation of small amounts of blood.
- Diagnostic tests include ELISAs, RT-PCR, VI and VN.

10.3.1. Options

The following options, either individually or in combination can manage the risk associated with BEFV in bovine serum.

1. Bovine serum could be imported from countries free from BEFV.
2. The animals used for blood collection showed no clinical signs of the infection on the day of blood collection, and no other evidence of the infection were reported in the animal or herd during the last three months; and:
    a. For abattoir-sourced bovine serum, the serum was derived from animals kept since birth or for the last three months in a country or zone free from the disease or seasonally disease-free zone. The animals passed antemortem examination and postmortem inspection and were processed in premises under the oversight of the competent authority.
    b. For donor-animal-derived bovine serum, the serum was derived from herds that were under veterinary supervision in a country or zone free from the disease or seasonally disease-free zone, since birth or for the last three months, or tested with an MPI approved/recommended test, with negative results, at the time of blood collection.
3. Bovine serum could be either:
    a. tested with an MPI approved/recommended test, with negative results; OR
    b. subjected to gamma irradiation at a minimum dose of 35 kGy.

11. Bovine herpesvirus 1

11.1. TECHNICAL REVIEW

11.1.1. Aetiology

Family: *Herpesviridae*
Genus: *Varicellovirus*
Species: *Bovine herpesvirus 1* (BoHV-1)

BoHV-1 causes different diseases in cattle, including infectious bovine rhinotracheitis (IBR), infectious pustular vulvovaginitis (IPV) and infectious pustular balanoposthitis (IPB).

There are three subtypes of BoHV-1 species: BoHV-1.1, BoHV-1.2a and BoHV-1.2b. Although there is no definite association between subtypes and clinical infections, BoHV-1 subtype 1 is mainly associated with the respiratory form of the disease and BoHV-1

subtypes 2a and 2b with the genital form of the disease (Muylkens *et al*., 2007). Subtypes 1.1 and 1.2a are abortifacient and virulent strains of BoHV-1 (Wentink *et al*., 1993).

11.1.2. OIE List

Infectious bovine rhinotracheitis and infectious pustular vulvovaginitis (IBR/IPV) caused by BoHV-1 are OIE-listed diseases (OIE, 2020). Infectious pustular balanoposthitis (IPB) is not an OIE-listed disease.

11.1.3. New Zealand status

BoHV-1.2b is prevalent in the cattle population in New Zealand (Durham, 1974; Fastier, 1967; Horner, 1990; Wang *et al*., 2006). According to Wang and others (2006), abortifacient and virulent strains of subtypes, BoHV-1.1 and 1.2a, do not appear to be present in New Zealand. In New Zealand, BoHV1.2b infection causes subclinical disease or respiratory disease with mild clinical signs (Lawrence, 2012; Vermunt and Parkinson, 2000).

BoHV-1 (abortifacient strains) causing abortion is listed as a notifiable organism on the Biosecurity (Notifiable Organisms) Order 2016 (MPI, 2016a). According to the OIE, IBR/IPV is present in New Zealand (WAHIS, 2018), and available literature suggests that the strain present in New Zealand is BoHV-1.2b. Therefore, only abortifacient and virulent strains of BoHV-1 are further considered in this assessment.

11.1.4. Zoonotic potential

Infectious bovine rhinotracheitis (IBR), infectious pustular vulvovaginitis (IPV) and infectious pustular balanoposthitis (IPB) are not zoonotic diseases.

11.1.5. Epidemiology

Host range

IBR/IPV/IPB, caused by BoHV-1, is a disease primarily affecting domestic and wild cattle. Other hosts susceptible to the infection include goats, sheep, water buffaloes and camelids (Babiuk *et al*., 2008; Borujeni *et al*., 2020; OIE Terrestrial Manual, 2018k). Red deer and reindeer have been experimentally infected with BoHV-1 (Thiry *et al*., 2006). All these susceptible hosts may act as potential reservoirs for the virus (Babiuk *et al*., 2008).

Geographical distribution

BoHV-1 is distributed worldwide but has been eradicated from several European countries (OIE Terrestrial Manual, 2018k).

In Australia, only BoHV-1.2b strains have been isolated from cattle, and BoHV-1.1 and 1.2a have never occurred (Animal Health Australia, 2018; OGTR, 2005). The OIE reports IBR/IPV as a disease present in Australia and not an officially notifiable disease (WAHIS, 2018).

According to the OIE, IBR/IPV is present in the United States and is notifiable (WAHIS, 2018). All subtypes of BoHV-1 are found in the United States (d'Offay *et al*., 1995).

Pathogenesis

BoHV-1 infection causes an acute, contagious disease, which is clinically manifested as either a respiratory or genital infection. The most common clinical signs of the disease include rhinotracheitis, pustular vulvovaginitis and pustular balanoposthitis (Babiuk *et al*., 2008). Other clinical signs of the disease include conjunctivitis, infertility, abortion and encephalitis (Nandi *et al*., 2009).

BoHV-1 subtypes 1.1 and 1.2a are associated with severe diseases and can involve fever, drop in milk yield, abortion, and a lethal outcome (Wentink *et al*., 1993). BoHV 1.2b is less virulent and causes only subclinical or very mild clinical signs (Muylkens *et al*., 2007).

The incubation period is two to four days, with uncomplicated disease lasting about five to 10 days. Mortality is very low, but secondary bacterial infections can lead to severe complications (Lawrence, 2012; Wang *et al*., 2006).

The virus is mainly shed in nasal discharges in the respiratory form of the disease and genital discharges in the genital form of the disease (Biswas *et al*., 2013; Muylkens *et al*., 2007; Nandi *et al*., 2009). Viral shedding peaks at three to six days post-infection and clears by 12 to 14 days post-infection (Babiuk *et al*., 2008). After initial replication, the spread of virus occurs by three routes: local dissemination, systemic spread (by viraemia) and neuroinvasion. Viraemia spread the virus to a boarder range of tissues and organs (Muylkens *et al*., 2007), but the viraemic levels can be low in IBR (Nettleton and Russell, 2017).

Transient viraemia can occur following primary infection, which can be followed by acute generalised disease, especially in newborn calves (Pastoret *et al*., 1982). Kaashoek and others (1996) demonstrated the presence of the virus in serum samples of calves following experimental intranasal inoculation with highly virulent strains of BoHV-1. Kniazeff and others (1975) confirmed that BoHV-1 is one of the significant viral contaminants of commercially supplied fetal bovine serum.

Once exposed to the virus, cattle can become latent carriers for life. The latent state is reactivated by stress and treatment with corticosteroids. In lifelong latent infections, the virus is sequestered in trigeminal (in the respiratory form) and sacral ganglia (in the genital form) (Broaddus *et al*., 2007; DAWR, 2016; Nettleton and Russell, 2017). There is also evidence of latency in non-neuronal sites such as tonsillar lymphoid cells, peripheral blood and lymph nodes (Biswas *et al*., 2013). Reactivation of the latency can results in viral shedding at levels similar to the primary infection (Muylkens *et al*., 2007) but for a shorter duration.

Transmission

Transmission of BoHV-1 predominantly occurs through airborne (close contact between animals) and genital routes. The primary source for virus transmission is the infected body secretions like nasal exudates, cough droplets, genital secretions, semen, fetal fluids and other infected tissues (Nandi *et al*., 2009). Indirect transmission through food, water and fomites can also occur. Transmission can also occur from artificial insemination with

semen from subclinically infected bulls (Babiuk *et al*., 2008) and virus-contaminated semen (Van Engelenburg *et al*., 1995).

Diagnosis

Clinical diagnosis of BoHV-1 infection can be made based on clinical, pathological and epidemiological findings. Definitive diagnosis can be achieved only by laboratory examinations such as serological detection of antibodies in serum or direct detection of the virus (OIE Terrestrial Manual, 2018k).

Serological tests with the highest specificity and sensitivity for BoHV-1 detection include virus neutralisation (VN) tests and various enzyme-linked immunosorbent assays (ELISAs) (OIE Terrestrial Manual, 2018k). ELISA is the OIE-recommended testing method for identifying population freedom from infection, identifying individual animal freedom from infection prior to movement, determining eradication policies, surveillance monitoring for the prevalence of infection and determining immune status post-vaccination. Serological tests can help to detect infections (acute and latent stages) (DAWR, 2016; OIE Terrestrial Manual, 2018k) and evaluation of antibody response after vaccination (OIE Terrestrial Manual, 2018k).

Virus isolation (VI) and real-time polymerase chain reaction (PCR) methods can be used for virus identification (OIE Terrestrial Manual, 2018k). Samples used for virus identification are nasal swabs and genital swabs from affected cattle in the early phase of infection (OIE Terrestrial Manual, 2018k). Real-time PCR is the OIE recommended test for confirmation of clinical cases. PCR is more sensitive and rapid than virus isolation, as it can be done in one to two days. Real-time PCR also enables differentiation of field strains of BoHV-1 from vaccine strains (OIE Terrestrial Manual, 2018k).

Treatment, control and prevention

There is no specific treatment for the virus. Supportive care for secondary bacterial infections can be done using antibiotics.

Prevention and control of the disease depend on on-farm management practices, vaccination, and culling of infected animals within the herd.

Prevention based on vaccination is the recommended action. Vaccination can significantly reduce the transmission in the herd, prevent the development of clinical signs and reduce shedding of the virus after infection (OIE Terrestrial Manual, 2018k). Different forms of vaccines; modified live vaccines, inactivated vaccines and marker vaccines are available (Maresca *et al*., 2018). Vaccination with the modified live vaccine can produce latent infections in cattle, and animals inoculated intranasally with modified live vaccines can shed virus for 7 to 14 days (Biswas *et al*., 2013).

11.2. RISK ASSESSMENT

11.2.1. Entry assessment

BoHV-1 is one of the major contaminants in unprocessed and processed FBS (Kniazeff *et al*., 1975). Kaashoek and others (1996) demonstrated the presence of the virus in serum samples of calves following experimental intranasal inoculation with highly virulent

strains of BoHV-1. Cattle vaccinated with a modified live virus vaccine can produce latent infection and shed virus (Biswas *et al*., 2013). Lifelong latency can be established in infected animals, and these animals show no clinical signs. It is likely that bovine serum obtained from blood collected from subclinically or latently infected animals may be contaminated with the virus. It is also likely that bovine serum collected from cattle vaccinated with a modified live vaccine can be contaminated with the virus.

While all strains of BoHV-1 are present in the United States, only subtype 1.2b has been isolated from Australia. Since the subtype 1.2b is already present in New Zealand and is not under a control programme, bovine serum from Australia is not a risk commodity for BoHV-1.

The likelihood of entry of abortifacient and virulent strains of BoHV-1 in bovine serum from Australia is therefore assessed as negligible, while the likelihood of entry through bovine serum imported from the United States is assessed as moderate.

11.2.2. Exposure assessment

BoHV-1 primarily affects cattle and other animals susceptible to the infection include goats, sheep, water buffaloes and camelids.

Vaccines produced from contaminated bovine serum could contain the viable virus and could infect cattle. Parenteral administration of contaminated vaccines is the primary pathway for transmission through vaccines. Experimental studies to confirm the pathogenic properties of BoHV-1 suggests that following intravenous inoculation of BoHV-1, cattle can develop infection (Muylkens *et al*., 2007). There is limited information available on the infectious dose of BoHV-1, which leads to a higher level of uncertainty about virus transmission via contaminated vaccines. Although the infectious dose is uncertain, the contaminated vaccine could cause infection. Vaccination is generally implemented as a herd management tool, and a large number of animals could be exposed through the contaminated vaccine.

BoHV-1 virus transmission predominantly occurs through close contact between animals. If the abortifacient and virulent strains of BoHV-1 is introduced, the virus could become established in New Zealand through further transmission by close contact with infected animals.

Fetal bovine serum is a common component of cultures used in in-vitro fertilisation of embryos. It is likely that BoHV-1-infected bovine serum could contaminate the culture medium used for in-vitro fertilisation, resulting in the transmission of the disease (Gonçalves et al., 2015).

Based on the factors discussed above, the overall likelihood of exposure, establishment and/or spread of abortifacient and virulent strains of BoHV-1 via bovine serum is assessed as moderate.

11.2.3. Consequence assessment

IBR, caused by BoHV-1 is an OIE listed disease affecting multiple species of animals, and the subtypes BoHV 1.1 and 1.2a are absent from New Zealand. Since BoHV-1.2b is

already present in New Zealand, trade impacts would be negligible in the event of introduction of the subtypes BoHV 1.1 and 1.2a.

Even though mortality rates are low, BoHV-1 could cause economic loss to livestock industries, especially the cattle industry (Biswas *et al*., 2013). The introduction of subtype 1.1 or 1.2a, both of which potentially cause abortion (Muylkens *et al*., 2007), has the potential to impact the cattle industry of New Zealand (Horner, 1990; Lawrence, 2012). Infection with BoHV-1 may result in abortion storms, especially with short, concentrated calving seasons in New Zealand. It may also lead to a reduction in milk yield. Additionally, there could be indirect losses in terms of surveillance, control and compensation costs.

Wild and feral ruminants could be infected, but there is no direct evidence of BoHV-1 causing significant disease in wild animals. Wild cervids can carry the virus and may act as reservoirs for the virus.

The virus does not infect humans; therefore, the consequences for human health are negligible.

Considering that contaminated bovine serum products are likely to be used on subpopulations of livestock and the disease is limited to cattle, the overall consequences of abortifacient and virulent strains of BoHV-1 as a result of the entry, exposure, establishment and/or spread are assessed as moderate.

11.2.4. Risk estimation

The likelihood of entry of abortifacient and virulent strains of BoHV-1 in bovine serum from Australia is negligible, and therefore, the risk estimate is negligible, and risk management measures are not required.

The likelihoods of entry, exposure, establishment and/or spread of abortifacient and virulent strains of BoHV-1 in bovine serum from the United States are assessed as moderate, and the consequences of BoHV-1 are assessed as moderate. Therefore, the overall risk is estimated as moderate.

Since the likelihood of entry and exposure and the consequences are non-negligible for bovine serum imported from the United States, abortifacient and virulent strains of BoHV-1 are a risk in the commodity. Therefore, risk management measures are justified for bovine serum imported from the United States.

11.3. RISK MANAGEMENT

The following points were considered when describing options for managing the risks:

- IBR and IPV are OIE-listed diseases.
- BoHV-1 is recognised as one of the major contaminants in FBS.
- BoHV-1 is a hazard to animal health and is likely to cause significant economic loss to the cattle industry through production loss.
- BoHV-1.2b is present in New Zealand, but other strains of the virus are absent.
- Only BoHV-1.2b is present in Australia; however, all BoHV-1 strains are present in the United States.

- BoHV- 1 is a disease primarily affecting domestic and wild cattle.
- IBR, IPV and IPB are not zoonotic diseases, and the virus does not constitute a hazard to human health.
- BoHV-1 produces viraemia and latent infection.
- Cattle vaccinated with modified live vaccine can develop transient viraemia.
- BoHV-1 can develop latent and subclinical infections where the virus remains undetected, and the virus could be shed following reactivation of latency.

11.3.1. Options

One or a combination of the following options could be considered for the management of the risk associated with BoHV-1. These options have been adapted based on some of the OIE recommendations for infection with IBR/IPV (OIE Terrestrial Code, 2019g).

1. Bovine serum could be imported from countries free from IBR/IPV as per the relevant OIE Code chapter.
2. The animals used for blood collection showed no clinical sign of IBR/IPV on the day of collection, and no other evidence of the infection were reported in the animal or herd.
    a. For abattoir-sourced bovine serum, the serum was derived from animals originated in a country or zone or herd free from IBR/IPV in accordance with the requirements of the OIE Code. The animals passed antemortem examination and were processed in premises under the oversight of the competent authority.
    b. For donor-animal-derived bovine serum, the animals were under veterinary supervision in a country or zone or herd free from IBR/IPV in accordance with the requirements of the OIE Code, or the donor was tested with an MPI-approved/recommended test, with negative results, at the time of blood collection.
3. Bovine serum could be either:
    a. tested with an MPI-approved/recommended test, with negative results; or
    b. subjected to gamma irradiation at a minimum dose of 35 kGy.

12. Bovine herpesvirus 5

12.1. TECHNICAL REVIEW

12.1.1. Aetiology

Family: *Herpesviridae*
Genus: *Varicellovirus*
Species: *Bovine herpesvirus 5* (BoHV-5)

Four subtypes of BoHV-5 are BoHV-5a, BoHV-5b, BoHV-5 non-a, and non-b (Maidana *et al*., 2011). Maidana and others (2017) examined the natural intra and inter-species recombination of bovine herpesviruses. Their study indicated that BoHV-5b should be considered as a natural recombinant of BoHV-5a and BoHV-1.2b.

BoHV-5 was previously classified as a subtype of BoHV-1 (subtype 1.3) and was also known as bovine encephalitis herpes virus (Silva *et al*., 1999).

12.1.2. OIE List

Infection with BoHV-5 is not an OIE-listed disease.

12.1.3. New Zealand status

BoHV-5 is not present in New Zealand (MPI, 2009b). BoHV-5 is not listed as a notifiable organism under the Biosecurity (Notifiable Organisms) Order 2016 (MPI, 2016a).

12.1.4. Zoonotic potential

BoHV-5 infection is not a zoonotic disease.

12.1.5. Epidemiology

Host range

BoHV-5 primarily affects young cattle (Favier *et al*., 2012). Calves up to four months of age are most susceptible (Delhon *et al*., 2003). Experimental inoculation by Silva and others (1999) showed that sheep are susceptible hosts and could have either an acute or latent form of infection (Thiry *et al*., 2006).

Geographical distribution

Outbreaks of BoHV-5 infection have been reported in Australia, North America, South America and Europe (Delhon *et al*., 2003). In the United States, BoHV-5 is present, and sporadic cases have been reported in various parts of the country (Cascio *et al*., 1999; d'Offay *et al*., 1995; Favier *et al*., 2012). BoHV-5 is present in Australia (Favier *et al*., 2012).

Pathogenesis

BoHV-5 causes meningoencephalitis in calves (Delhon *et al*., 2003), which can be fatal (Patel and Didlick, 2008; Perez *et al*., 2002).

BoHV-5 is genetically, antigenically and biologically related to BoHV-1 (Favier *et al*., 2012; Silva *et al*., 1999). The difference is in the tissue tropism, where BoHV-5 replicates significantly in the central nervous system, inducing neurological disease (Delhon *et al*., 2003). BoHV-1 replicates in trigeminal and sacral ganglia but does not cause neurological disease (DAWR, 2016; Nettleton and Russell, 2017).

BoHV-5 induces a transient viraemia (Thiry *et al*., 2006). Systemic spread by viraemia results in the spread of the virus to the liver, kidneys and leucocytes (Zajac *et al*., 2010).

Clinical signs include depression, anorexia and general weakness, with neurological signs developing later (Zajac *et al*., 2010). Like BoHV-1 infection, a latent state develops in surviving animals after a primary infection with BoHV-5 (Thiry *et al*., 2006). Latent infections are established in trigeminal ganglia and also throughout the central nervous system (Favier *et al*., 2014; Thiry *et al*., 2006). Latency is reactivated by natural stimuli and treatment with glucocorticoids (Zajac *et al*., 2010).

Transmission

Transmission of BoHV-5 mainly occurs through close contact between animals from nasal, ocular and genital secretions (Favier *et al*., 2012). Transmission is also possible through contaminated semen (Kirkland *et al*., 2009) and infected oocytes and embryos (Favier *et al*., 2012).

Diagnosis

Virus isolation is considered to be the most effective diagnostic tool for BoHV-5 (Zajac *et al*., 2010) and multiplex polymerase chain reaction (PCR) assays could be used to differentiate BoHV-5 from BoHV-1(Thiry *et al*., 2006).

Serological assays such as virus neutralisation (VN) and ELISA could also be used, however, because of the antigenic similarity of BoHV-5 to BoHV-1 interpretation of the results is more difficult when compared with virological assays (Thiry *et al*., 2006).

Treatment, control and prevention

There is no commercially available vaccine for BoHV-5 (Thiry *et al*., 2006), due to sporadic nature of the disease and the restricted geographical distribution (Zajac *et al*., 2010). BoHV-1 vaccines could provide cross-protection against BoHV-5 infection (Thiry *et al*., 2006), and the use of BoHV-1 vaccines is considered the best option to protect against BoHV-5.

Prevention and control of the disease depend on general management practices for alphavirus infections. Good management practices on farm, culling seropositive and infected animals and preventing contact between infected and susceptible animals could assist in prevention and control of the disease (Thiry *et al*., 2006).

12.2. RISK ASSESSMENT

12.2.1. Entry assessment

The likelihood of entry of BoHV-5 into New Zealand is similar to BoHV-1. BoHV-5 is present in Australia and the United States. BoHV-5 induces transient viraemia. Infected animals could develop a latent stage, which is usually undetected. It is assumed that blood collected from latent or subclinically infected animals could be contaminated with the virus.

Bovine serum collected from infected animals (with subclinical or latent infection) may contain the virus. It is likely that if the contaminated bovine serum is used in vaccine production, embryo transfer, and in cell culture media preparation, BoHV-5 could be introduced into New Zealand.

The likelihood of entry of BoHV-5 through bovine serum imported from Australia and the United States is assessed as low.

12.2.2. Exposure assessment

BoHV-5 primarily affects calves and adult sheep. Bovine serum imported from Australia and the United States could potentially be contaminated with BoHV-5. The use of

contaminated bovine serum in the manufacture of vaccines could increase the likelihood of exposure of animals, especially cattle. Parenteral administration of these contaminated vaccines is the most likely pathway for transmission for animals in New Zealand. The use of bovine serum in vaccines and other products is likely to cause infection. Usually, cattle vaccines are used as a herd management tool, and therefore a large number of cattle could be inoculated at the same time. Therefore, it is reasonable to assume that animals could get the infection with BoHV-5 following vaccination using a contaminated vaccine.

Natural transmission predominantly occurs through close contact between animals. If BoHV-5 is introduced, the virus could become established in New Zealand, and cases of encephalitis could occur.

Transmission through infected oocytes and embryos (Favier *et al*., 2012) is also possible. Therefore, contaminated bovine serum used in embryo culture media could possibly transmit the disease to the recipient.

Based on the factors discussed above, the overall likelihood of exposure, establishment and/or spread of BoHV-5 via bovine serum is assessed as low to moderate.

12.2.3. Consequence assessment

Infection due to BoHV-5 is not an OIE-listed disease, and it affects mainly cattle. Nevertheless, if BoHV-5 was to establish in New Zealand, limited trade impacts may occur.

Introduction of BoHV-5 can result in outbreaks of encephalitis in cattle in New Zealand. Sheep have been experimentally proven to be susceptible to the disease. Introduction of BoHV-5 could have an impact on the cattle and sheep industry and for individual farmers due to loss of production and animals. Since bovine serum is used in the production of vaccines for multiple species of animals, exposure to a contaminated vaccine could have significant consequences in animals.

There could also be indirect losses in terms of surveillance, control containment or eradication programmes and compensation costs. These indirect consequences may have an impact on the New Zealand economy.

Only experimental infection is observed in sheep, and there is no evidence to suggest that BoHV-5 would cause significant disease in other wildlife species. Therefore, the consequences for the environment are negligible.

The virus does not infect humans; therefore, the consequences for the human population are negligible.

The overall consequences of BoHV-5 entry, exposure, establishment and/or spread are assessed as very low.

12.2.4. RISK ESTIMATION

The likelihood of entry of BoHV-5 in bovine serum from Australia and the United States is assessed as low, the likelihood of exposure, establishment and/or spread of BoHV-5 is assessed as low to moderate, and the consequences of BoHV-5 are assessed as very low. Therefore, the overall risk is estimated as low.

Since the entry, exposure, and consequence assessments are non-negligible for bovine serum imported from Australia and the United States, BoHV-5 is a risk in the commodity. Therefore, risk management measures are justified for bovine serum imported from Australia and the United States.

12.3. RISK MANAGEMENT

The following points were considered when describing options for managing the risks:

- BoHV-5 infection is not an OIE-listed disease.
- BoHV-5 is present in Australia and the United States but not in New Zealand.
- Infection with BoHV-5 will have a negative impact on the cattle industry.
- BoHV-5 infection is not zoonotic.
- BoHV-5 could cause latent or subclinical infections where the virus remains unidentified.
- BoHV-5 induces transient viraemia.
- BoHV-5 is genetically, antigenically and biologically related to BoHV-1.

12.3.1. Options

One or a combination of the following options could be used to manage the risk associated with BoHV-5. Since BoHV-5 is genetically, antigenically and biologically related to BoHV-1, these options have been adopted based on some of the OIE recommendations for infection with IBR/IPV.

1. Bovine serum could be imported from countries free from BoHV-5 or BoHV-1 infections as per the relevant OIE Code chapter.
2. The animals used for blood collection showed no clinical signs of the infection on the day of blood collection, and no other evidence of the infection was reported in the animal or herd; and:
    a. For abattoir-sourced bovine serum, the serum was derived from animals kept in a country or zone or herd free from the disease in accordance with the requirements of the OIE Code for infection with IBR/IPV. The animals passed antemortem examination and were processed in premises under the oversight of the competent authority.
    b. For donor-animal-derived bovine serum, the serum was derived from herds that were under veterinary supervision in a country or zone or herd in accordance with the requirements of the OIE Code for infection with IBR/IPV, or the donor was tested with an MPI-approved/recommended test, with negative results, at the time of blood collection.
3. Bovine serum could be either:
    a. tested with an MPI-approved/recommended test, with negative results; or
    b. subjected to gamma irradiation at a minimum dose of 35 kGy.

13. Bovine influenza D virus

13.1. TECHNICAL REVIEW

13.1.1. Aetiology

Family: *Orthomyxoviridae*
Genus: *Deltainfluenzavirus*
Species: *Influenza D virus* (IDV) (ICTV, 2018)

13.1.2. OIE List

Influenza D virus (IDV) infection is not an OIE-listed disease.

13.1.3. New Zealand status

IDV infection is not reported in New Zealand to date, and there is no evidence indicating its presence in the country (Tana, 2020c).

13.1.4. Zoonotic potential

IDV infection is a zoonotic disease; however, its zoonotic potential is not adequately studied. Despite its zoonotic potential, Su and others (2017) suggested that the significance of IDV for public health is low. IDV is considered an emerging occupational hazard for people working with cattle (Asha and Kumar, 2019; White *et al*., 2016). White and others (2016) detected high seroprevalence (94–97%) of IDV in cattle workers in a cross-sectional study conducted in Florida during 2011–2012. Genetic analysis conducted by Hause and others (2014) indicated that IDV has a moderate similarity (53%) to the human influenza C virus (ICV).

13.1.5. Epidemiology

Host range

IDV has been isolated from cattle, pigs, camelids, horses, sheep and goats (Ferguson *et al*., 2016; Nedland *et al*., 2018; Quast *et al*., 2015; Zhang *et al*., 2019). Cattle are considered the primary host and natural reservoir of IDV (Salem *et al*., 2019; Su *et al*., 2017). There is a high prevalence of the virus in cattle, especially in calves in the United States (Su *et al*., 2017). Ferguson and others (2018) investigated the seroprevalence and transmissibility of IDV in feral pigs and found that IDV was present in several states in the United States. They also found that IDV could be transmitted among feral pigs (Ferguson *et al*., 2018).

Geographical distribution

IDV was first identified and isolated from pigs in 2011 in the United States. Later the virus was isolated from a variety of hosts including cattle, camelids, horses, sheep and goats from the United States, Mexico, China, Japan, France, Italy, Ireland and Canada (Asha and Kumar, 2019; Ferguson *et al*., 2016; Flynn *et al*., 2018; Foni *et al*., 2017; Zhai *et al*., 2017). Silveira *et al*. (2019) reported 77.5% seropositivity of IDV in cattle in the United States from their serosurveillance study.

IDV infection is not reported in Australia to date, and there is no other evidence indicating its presence in the country.

Pathogenesis

IDV is one of the significant pathogens commonly associated with the bovine respiratory disease (BRD) complex (Zhang *et al*., 2019). Bovine respiratory disease is one of the most significant diseases of cattle. It has a high economic impact on the cattle industry and contributes 70–80% of the morbidity among cattle in the United States (Asha and Kumar, 2019).

Salem and others (2019) reported that the incubation period in IDV inoculated groups is one to three days. In experimentally infected cattle, IDV is predominantly detected from the upper and lower respiratory tract (Su *et al*., 2017). Virus replication occurs in the upper respiratory tract (Asha and Kumar, 2019). The soft palate is considered a significant site of infection for IDV (Zhang *et al*., 2019). Cattle can shed IDV for up to nine days post-infection (Asha and Kumar, 2019; Ferguson *et al*., 2016).

Zhang and others (2019) studied the viraemia associated with IDV infection. Their study suggests that IDV infection can lead to viraemia in cattle, and IDV enters the blood through the soft palate. Other studies also suggested the presence of influenza viraemia in cases with acute infection of IDV or before the death of the host (Asha and Kumar, 2019; Zhai *et al*., 2017). Zhai and others (2017) confirmed the presence of IDV RNA in cattle serum samples in their study and inferred that the virus entered the circulatory system through capillaries lining the respiratory system.

IDV causes mild respiratory signs and tracheal inflammation in cattle (Asha and Kumar, 2019; Zhang *et al*., 2019). Experimentally infected calves show clinical signs of respiratory tract infection, like dry coughing and nasal discharges (Ferguson *et al*., 2016).

Influenza viraemia was detected in almost 20% of severe cases of IDV (Zhai *et al*., 2017). There is no published literature on the minimum infectious dose of IDV to date.

Transmission

IDV is mainly transmitted through direct contact with infected animals (Ferguson *et al*., 2016) and contaminated aerosols (Salem *et al*., 2019). Compared to other influenza viruses, very high thermal and acid stability of IDV facilitates its survival outdoors and increases its capacity for airborne transmission (Salem *et al*., 2019).

Diagnosis

There is no OIE-recommended diagnostic method to isolate and confirm IDV. IDV has been detected and isolated from clinical tissue samples of infected cattle, including the nasal turbinate, trachea, bronchus, and lungs (Ferguson *et al*., 2016). IDV has also been detected from serum samples of infected cattle (Zhai *et al*., 2017). Salem and others (2019) detected the virus between days 3 and 13 post-infection in air samples collected from the infected zone.

Reverse transcription polymerase chain reaction (RT-PCR) is the most commonly used diagnostic method to detect IDV. RT-PCR has a high sensitivity and specificity, and thus

is useful for detecting and confirming IDV infection (Asha and Kumar, 2019; Faccini *et al.*, 2017).

The most common methods of serological diagnosis and confirmation of IDV are the haemagglutination inhibition (HI) and virus neutralisation (VN) assays. Moreno and others (2019) developed and validated a monoclonal antibody (MAb) based competitive ELISA test to detect IDV antibodies.

Treatment, control and prevention

There is no effective treatment for IDV infection. Antiviral strategies and vaccination against the virus are some measures to control diseases outbreaks (Asha and Kumar, 2019). An inactivated vaccine was developed recently for IDV, which can provide partial protection (Hause *et al.*, 2017; Su *et al.*, 2017).

13.2. RISK ASSESSMENT

13.2.1. Entry assessment

IDV is one of the pathogens that is commonly associated with the BRD complex. IDV has been identified in a wide range of hosts, including cattle, pigs, camelids, sheep and goats. IDV has been detected in cattle of all ages with a higher prevalence rate than other host species.

The incubation period is short for the disease; experimental data suggests one to three days. Infected cattle can shed IDV up to nine days post-infection. Viraemia is reported in cattle infected with IDV, especially in acute cases. IDV has been detected from bovine serum samples (Zhai *et al.*, 2017). Since IDV infection causes viraemia, and the virus is isolated from the serum of infected cattle, it is evident that unprocessed bovine serum could harbour IDV.

In the United States, IDV has been isolated from cattle, pigs, sheep and goats. Silveira *et al.* (2019) conducted a serosurvey for IDV exposure in cattle in the United States and reported a high (77.5%) seropositivity for IDV. There are no reports or other evidence that IDV is present in Australia and New Zealand.

Therefore, the likelihood of entry of IDV in bovine serum from Australia is assessed as negligible, and from the United States is assessed as low.

13.2.2. Exposure assessment

IDV is mainly transmitted through direct contact with infected animals and possibly through aerosol. If IDV enters New Zealand through unprocessed bovine serum from the United States, it is unlikely that live animals will be exposed directly to bovine serum. The likelihood of contaminated bovine serum infecting animals through direct contact with unprocessed bovine serum is negligible.

Vaccines produced from contaminated bovine serum could contain viable virus and could infect cattle. Parenteral administration of these contaminated vaccines is the most likely pathway for transmission to animals in New Zealand, because vaccination is generally implemented as a herd management tool, and several animals could get exposed.

There is potential for IDV to cause human infection, especially among people occupationally exposed to cattle. Laboratory technicians are also at risk of acquiring the infection after exposure to infected bovine serum. Zoonotic transmission of IDV has been proven in humans following direct contact with infected cattle.

Since the virus is predominantly transmitted through close contact between animals, any introduction to New Zealand could result in establishment among resident cattle, pig, sheep and goat populations.

There are no reports of IDV being transmitted between animals through vectors or germplasm. Therefore, establishment and/or spread may only be through direct contact or contaminated vaccines.

Based on the factors discussed above, the overall likelihood of exposure, establishment and/or spread of IDV via bovine serum is assessed as low.

13.2.3. Consequence assessment

IDV is considered a significant pathogen of the BRD complex. IDV is known to infect a wide range of host species, which include cattle, pigs, camelids, sheep and goats. If IDV contaminated end products are used, it is likely that significant BRD-related production losses would ensue, especially in the cattle industry.

IDV is not an OIE-listed disease, and trading partner countries are unlikely to impose trade restrictions related to the disease.

IDV is considered a zoonotic disease, with people working with cattle being predominantly at risk. Zoonotic transmission of IDV from animals to human has been demonstrated only in people who have direct contact with infected cattle.

Since IDV has never been reported in New Zealand, indirect consequences of the virus's introduction may involve surveillance, control, containment or eradication programmes, which may impact the New Zealand economy.

IDV infects multiple species of animals, including cattle, pigs, sheep and goats. Ferguson and others (2018) investigated the seroprevalence and transmission of IDV in feral swine populations and suggested that feral swine can get infected with IDV and might be vital in the ecology of IDV.

Therefore, the overall consequences of IDV to New Zealand are assessed as low to moderate.

13.2.4. Risk estimation

The likelihood of entry of IDV in bovine serum from Australia is negligible, and therefore, the risk is estimated as negligible. Bovine serum can be imported from Australia without any measures to control bovine IDV.

The likelihood of entry of IDV in bovine serum from the United States is assessed as low. The likelihoods of exposure, establishment and/or spread are assessed as low, and the consequences of IDV as a result of establishment are assessed as low to moderate. Therefore, the overall risk is estimated as low.

Since the entry, exposure, and consequence assessments are non-negligible for bovine serum imported from the United States, IDV is a risk in the commodity. Therefore, risk management measures for IDV are justified for bovine serum imported from the United States.

13.3. RISK MANAGEMENT

The following points were considered when describing options for managing the risks:

- Infection with IDV is not an OIE-listed disease.
- IDV is absent from New Zealand and Australia but present in the United States.
- Infection with IDV is considered an emerging zoonotic disease, especially among people occupationally exposed to cattle.
- IDV affects multiple species of animals and all ages.
- In infected animals, a short period of viraemia has been reported.
- IDV has been isolated from the serum of infected cattle.
- There is no effective treatment for IDV infection.
- Inactivated vaccines can only provide partial protection against IDV.

13.3.1. Options

The following options, individually or in combination, will manage the risk associated with IDV:

1. Bovine serum can be imported from IDV-free countries.
2. The animals used for blood collection showed no clinical signs of the infection on the day of blood collection, and no other evidence of the infection has been reported in the animal or herd during the preceding 30 days.
    a. For abattoir-sourced bovine serum, the serum has been derived from animals originating in a country free from IDV or from premises with no case history of IDV for the last 30 days. The animals passed antemortem examination and were processed in premises under the oversight of the competent authority.
    b. For donor-animal-derived bovine serum, the serum has been derived from a herd that was under veterinary supervision in a country free from IDV or from premises with no case history of IDV for the last 30 days, or the donor was tested with an MPI-approved/recommended test, with negative results, at the time of blood collection.
3. Bovine serum could be either:
    a. tested with an MPI-approved/recommended test, with negative results; or
    b. subjected to gamma irradiation at a minimum dose of 35 kGy.

14. Bovine viral diarrhoea virus (BVDV)

14.1. TECHNICAL REVIEW

14.1.1. Aetiology

Family: *Flaviviridae*
Genus: *Pestivirus*
Species: *Bovine viral diarrhoea virus 1* (BVDV1); *Bovine viral diarrhoea virus 2* (BVDV2), (Booth *et al*., 1995); *Bovine viral diarrhoea virus 3* (Hobi-like virus or BVDV3) (Bauermann *et al*., 2013)

Cytopathic and non-cytopathic biotypes occur in all three species.

BVDV3 is a new putative pestivirus species, tentatively called "Hobi-like", "BVDV-3", or "atypical pestivirus". BVDV3 viruses are related to BVDV at the genetic and antigenic levels (Bauermann *et al*., 2013).

14.1.2. OIE List

Bovine viral diarrhoea (BVD) is an OIE-listed disease (OIE, 2020).

14.1.3. New Zealand status

According to the OIE, BVD is present in New Zealand among the domestic animal population (WAHIS, 2019a). Of the three strains of BVDV, only BVDV1 is endemic in New Zealand (Horner, 2000; Packianathan et al., 2017). BVDV2 and BVDV3 have not been reported in New Zealand, and BVDV2 is listed as a disease absent from New Zealand (MPI, 2020).

14.1.4. Zoonotic potential

BVDV does not infect humans and is of no consequence to human health (OIE Terrestrial Manual, 2018g).

14.1.5. Epidemiology

Host range

BVDV strains are predominantly pathogens of cattle. Interspecies transmission can occur following close contact with sheep, goats or pigs. BVDV infections have been reported in both New World and Old World camelids (OIE Terrestrial Manual, 2018g). Evans and others (2018) reported that cattle persistently infected with BVDV1 were a source of infection for Australian alpacas when comingling occurred.

Geographical distribution

BVDV1 has worldwide distribution, including New Zealand and Australia (Horner, 2000; Vilcek *et al*., 1998). In New Zealand, the prevalence of antibodies to BVDV1 is around 60% (Littlejohns and Horner, 1990). Gates and others (2019) estimated, based on the data from commercial laboratories in New Zealand, that 40.6% of dairy herds and 45.6% of beef herds tested positive for BVDV antibodies.

BVDV2 occurs in North America (Potgieter, 2004), South America (Monteiro *et al*., 2019), Asia (Giangaspero *et al*., 2019) and several European countries. The prevalence of BVDV2 in North America ranges from 24–47% (Bolin and Ridpath, 1998). A review of the status and perspective of BVD control by Moennig and others (2005) indicated that 50% of all BVDV isolates in North America are BVDV2. The only isolation of a BVDV2 strain in New Zealand was from a batch of FBS imported from the United States (Horner, 2000). The virus was contained and later destroyed in the laboratory. BVDV2 has not been described in Australia.

BVDV3, which was first described by researchers in Europe in 2004, was isolated from a batch of FBS imported from Brazil (Stalder *et al*., 2005). Since then, it has also been detected in FBS that was processed and/or packaged in Europe but supposedly originated in Australia, Canada, Mexico, and the United States (Xia *et al*., 2011). The claim that BVDV3 was detected in FBS originating from Australia (Xia *et al*., 2011) remains controversial due to the lack of reports indicating the circulation of these viruses in that country. Natural infection in cattle with BVDV3 has been reported in Southeast Asia (Ridpath and Fulton, 2009), Italy (Decaro *et al*., 2012), Argentina (Pecora *et al.*, 2019) and Brazil (Stalder *et al*., 2005).

Pathogenesis

The incubation period is usually about three to seven days (Brownlie, 2005), and animals may remain viraemic for 4 to 15 days after initial infection (Potgieter, 2004). During acute infections, the viraemia lasts only for 7 to 10 days (OIE Terrestrial Manual, 2018g). Viraemia seldom exceeds 10 to 14 days (Brownlie, 2005). Antibodies develop two to four weeks after infection.

BVDV1 infection of non-pregnant cattle usually results in a mild infection typified by pyrexia and leukopenia from about three to seven days. Viraemia and nasal excretion of the virus occurs during this period (Brownlie, 2005). The clinical signs are often so mild that they are not observed, but occasionally diarrhoea is seen (Potgieter, 2004).

Since BVDV is widely distributed in most cattle herds in infected countries, cattle are commonly infected before they become pregnant, resulting in populations that are substantially immune and do not carry the virus. Infection of naive pregnant animals, particularly during the first trimester, may result in the death of the conceptus or full-term or near full-term delivery of immunotolerant persistently infected (PI) calves (Brownlie, 2005; Littlejohns and Horner, 1990; Potgieter, 2004; Stokstad *et al*., 2003). Persistently infected animals are a key reservoir for the virus and may either appear clinically healthy or weak and unthrifty (OIE Terrestrial Manual, 2018g). The pregnancy rate of cattle was significantly lowered when animals were infected with BVDV around the time of insemination (McGowan *et al*., 1993).

BVDV2 strains that cause a more severe form of the disease following an initial infection were described in the United States (Pellerin *et al*., 1994). In these cases, the mortality rate was up to 10% (Potgieter, 2004), and the disease was characterised by severe leukopenia and haemorrhagic disease (Brownlie, 2005).

Immunotolerant persistently infected animals may be clinically normal or may be unthrifty and die within a year. They are always infected with non-cytopathic strains of the virus

(Brownlie, 2005). Superinfection of persistently infected animals with a cytopathic BVDV strain results in the development of mucosal disease (Brownlie, 2005; Potgieter, 2004). The cytopathic strain that reinfects the persistent carrier animals may result from a mutation of the persistent non-cytopathic strain or from infection with a new extrinsic cytopathic virus (Brownlie 2005; Potgieter 2004). Mucosal disease is invariably fatal. In acute cases, death occurs in 2 to 21 days, while in chronic cases, the animal may survive for up to 18 months (Potgieter, 2004). In 2012, an outbreak of BVDV2 in western Germany resulted in a case fatality rate of 60% and mortality on outbreak farms of between 2.3% and 29.5% (Gethmann *et al*., 2015).

In addition to infecting several fetal cell types, BVDV is found in fetal bovine serum (Kniazeff *et al*., 1975; Makoschey *et al*., 2003; Nims and Plavsic, 2012). This creates a problem for diagnostic laboratories because fetal bovine serum is frequently used to supplement media used for cell culture, and a variety of cell cultures from several species are susceptible to infection with BVDV (Potts *et al*., 1989). Contaminated FBS has also been known to be a source of contamination of live viral vaccines (Falcone *et al*., 2000; Studer *et al*., 2002; Toohey-Kurth *et al*., 2017).

Because non-cytopathic BVDV does not induce a cytopathic effect, infection of cell cultures may not be detected unless the cultures are tested by immunocytochemical procedures (Bolin *et al*., 1991). There is a high frequency of contamination of batches of fetal bovine serum used as a culture medium supplement (OIE Terrestrial Manual, 2018g).

The disease caused by the new BVDV3 (Hobi-like virus) resembles clinical presentations historically associated with BVDV infection, including growth retardation, reduced milk production, respiratory disease, reduced reproductive performance, and increased mortality among young stock (Bauermann *et al*., 2013). The study conducted by Xia and others (2011) to detect and identify atypical bovine pestiviruses in commercial FBS batches reported that all three species of BVDV were found to be contaminants in FBS. Giammarioli and others (2015) tested batches of commercial FBS for pestiviruses and to examine the genetic diversity of the Hobi-like viruses present as contaminants. They also confirmed the presence of all three species of BVDV in the FBS batches tested.

Transmission

BVDV is normally transmitted by direct contact between infected animals and/or by aerosol transmission over short distances (Potgieter, 2004). The virus can also be transmitted by fomites and vehicles.

Transmission between species has been demonstrated from cattle to alpacas (Evans *et al*., 2018) and goats (Broaddus *et al*., 2007). However, the alpacas and goats did not show any clinical signs of infection.

Outbreaks of BVD following vaccination with contaminated vaccines have been reported (Falcone *et al.*, 2000). Fox and others (2019) confirmed fatal BVD in captive rocky mountain bighorn sheep at a wildlife facility in Colorado following the use of a vaccine that was contaminated with BVDV. Barkema and others (2001) reported BVD in Dutch dairy farms following vaccination for *Bovine herpesvirus 1*. The batch of vaccine was later confirmed to be contaminated with BVDV type 2. BVDV has also been confirmed to be

transmitted to piglets born to sows vaccinated against swine fever with contaminated vaccine (Wensvoort and Terpstra, 1988).

BVDV is also transmitted in semen, particularly from persistently infected bulls, which continue to shed virus in their semen for years (Potgieter, 2004). Epidemiological investigations found that the semen of donor bulls was the only plausible source of infection with BVDV in 10 Finnish dairy herds (Rikula *et al*., 2008). Meyling and Jensen (1988) also demonstrated that cows could become infected with BVDV and produce persistently infected calves after insemination with semen from persistently infected bulls (Meyling and Jensen, 1988).

Diagnosis

The diagnosis of BVDV infection can sometimes be complex because of the delay between infection and clinical expression. While detection of persistently infected animals should be readily accomplished using current diagnostic methods, the recognition of acute infections can be more difficult. Diagnostic methods include virus detection tests such as virus isolation, real-time reverse transcription polymerase chain reaction (real-time RT-PCR) for nucleic acid detection, antigen detection by enzyme-linked immunosorbent assay (ELISA) and immunohistochemistry (IHC). Serological tests that can be used for diagnosis include ELISA and virus neutralisation (OIE Terrestrial Manual, 2018g).

To prevent the shipment of bovine serum that could be infected with BVDV, it is necessary to test for the presence of the virus (virus isolation), viral antigens (antigen detection ELISA) or RNA (real-time RT-PCR). Buffy coat cells, whole blood, washed leucocytes and serum can be used for virus isolation (OIE Terrestrial Manual, 2018g).

Virus isolation is the OIE-recommended test for identifying individual animal infection status and confirmation of clinical cases. Antigen detection by ELISA is the OIE-recommended test for identifying individual animal infection status, determining eradication policies, determining prevalence of infection, surveillance and confirmation of clinical cases. Real-time RT-PCR is the OIE-recommended test for identifying population freedom from infection, identifying individual animal infection status, determining eradication policies, determining prevalence of infection, surveillance and confirming clinical cases.

Serological tests such as ELISA and virus neutralisation are the OIE-recommended tests for identifying the immune status in individual animals or a population post-vaccination.

Treatment, control and prevention

Treatment of BVDV remains limited primarily to supportive therapy. Control is based on sound management practices that include the use of biosecurity measures, elimination of persistently infected cattle, and vaccination.

Vaccination to control BVDV infections can be challenging due to the antigenic variability of the virus and the occurrence of persistent infections that arise as a result of fetal infection. Ongoing maintenance of the virus in nature is predominantly sustained by persistently infected animals that are the product of in-utero infection. The goal for a vaccine should be to prevent systemic viraemia and the virus crossing the placenta. If this

is successfully achieved, it is likely that the vaccine can prevent the wide range of other clinical manifestations, including reproductive, respiratory and enteric diseases and immunosuppression with its secondary sequelae (OIE Terrestrial Manual, 2018g).

BVDV is a particularly significant hazard to the manufacture of vaccines and biological products for other diseases due to the high frequency of contamination of batches of fetal bovine serum used as a culture medium supplement (OIE Terrestrial Manual, 2018g).

Cross-protection against BVDV3 conferred by current BVDV vaccines is likely to be limited (Bauermann *et al*., 2013).

14.2. RISK ASSESSMENT

14.2.1. Entry assessment

BVDV has been described as one of the major contaminants in FBS (Makoschey *et al*., 2003; Nims and Plavsic, 2012; Xia *et al*.,2011). Metagenomic assessments of adventitious viruses in commercial bovine sera conducted by Toohey-Kurth and others (2017) confirmed that BVDV is the most common contaminant of bovine serum. The incidence of BVDV in serum depends on the disease prevalence of the donor population and number of donors in the pool of blood donors. For example, sera drawn from a donor pool of 1,000 cattle will be positive for BVDV in a population where the disease prevalence is 1%. Sera obtained from a pool of 100 animals from the same population has a 60% probability of being positive for the virus, while pooled sera from 20 animals from this population likely to be positive 20% of the time (Doelger *et al*., 2020).

Historically, a BVDV2 strain has been isolated in New Zealand from a batch of contaminated bovine serum imported from the United States.

Prevalence of BVDV2 in North America ranges from 24% to 47%. BVDV2 has not been described in Australia. There are reports of BVDV3 isolates from FBS that is claimed to be of Australian and United States origin; however, there are no official reports of BVDV3 in cattle in these countries.

Infected animals may remain viraemic for 4 to 15 days after initial infection (Potgieter, 2004). Mild infection typified by pyrexia and leukopenia may go undiagnosed during clinical examination of donors or postmortem inspections at slaughter plants. Therefore, infected blood may be collected from infected donor animals. There are numerous reports of BVDV present as a contaminant in serum.

The likelihood of entry of BVDV in bovine serum is assessed as moderate.

14.2.2. Exposure assessment

Contaminated FBS is known to be a source of contamination for live viral vaccines (Falcone *et al.*, 2000; Studer *et al.*, 2002; Toohey-Kurth *et al.*, 2017). Animal vaccines produced from contaminated bovine serum could contain viable BVDV, and animals inoculated with the contaminated vaccine could develop the disease. Parenteral administration of these contaminated vaccines is the most likely pathway for transmission. However, due to the lack of published literature, there is uncertainty around the infectious dose. Outbreaks of BVD following vaccination with contaminated vaccines have been

reported in cattle and sheep and also in piglets born to sows vaccinated against swine fever with contaminated vaccine. A large number of animals could get exposed through contaminated vaccine.

If the media and solutions used for collection, processing and storage of embryos are contaminated with BVDV, recipient cows could be infected. The infectious dose in the embryo-processing medium would be lower compared to the dose in infected semen.

BVDV is predominantly transmitted through close contact with infected animals. If BVDV were to be introduced into New Zealand, the virus could become established and/or spread through further transmission by close contact with infected animals.

The overall likelihood of exposure, establishment and/or spread of BVDV via bovine serum based on the factors discussed above is assessed as high.

14.2.3. Consequence assessment

BVDV1 is endemic in New Zealand. It costs New Zealand's 25,000 beef farmers and 12,000 dairy farmers more than $150 million per year in direct production losses or about $4,000 per farm (BVD free New Zealand, 2018). New Zealand bovine serum is a sought-after export commodity due to the country's relatively disease-free status. Since BVDV1 is endemic in New Zealand, the trade impacts would be negligible in the event of introduction of the other strains.

BVDV2 and BVDV3 have not been reported in New Zealand and are considered exotic. If introduced, they are likely to spread amongst susceptible cattle. Even those immune to BVDV1 would not be fully protected. Although some BVDV2 strains are of low virulence, mortalities of up to 10% could result from initial infection with virulent BVDV2 strains (Potgieter, 2004).

The virus does not infect people, and there would be no impacts on human health. Therefore, the consequences to human health in New Zealand are negligible.

BVDV1 is known to infect deer, goats (Horner, 2000) and alpacas (Evans *et al*., 2018). Antibodies to the virus are known to develop in these species, but the disease has not been described. It is therefore likely that BVDV2 and BVDV3 could also infect other species, but it is not known whether these strains would cause significant disease in these species. Therefore, the consequences for the New Zealand environment are very low to negligible.

The overall consequences from entry, exposure, establishment and/or spread of BVDV are assessed as moderate.

14.2.4. Risk estimation

The likelihood of entry of BVDV in bovine serum from Australia and the United States is assessed as moderate, the likelihoods of exposure, establishment and/or spread are assessed as high, and the consequences of BVDV as a result of establishment are assessed as moderate. Therefore, the overall risk is estimated as moderate.

Since the entry, exposure, and consequence assessments are non-negligible, BVDV is identified as a hazard posing a risk in the commodity. Therefore, risk management measures are justified.

14.3. RISK MANAGEMENT

The following points were considered when presenting options for managing the risks:

- BVD is an OIE-listed disease.
- BVDV1 is endemic in New Zealand, but BVDV2 and BVDV3 have never been reported in New Zealand.
- BVDV strains are predominantly pathogens of cattle, interspecies transmission can occur following close contact with sheep, goats or pigs.
- The incubation period is usually about three to seven days.
- Animals may remain viraemic for 4 to 15 days after initial infection.
- BVDV3 (Hobi-like viruses) has been isolated from FBS from Canada, Mexico, the United States and Australia.
- The diagnosis of BVDV infection can sometimes be complex because of the delay between infection and clinical expression.
- BVDV is recognised as a hazard in the manufacture of vaccines and biological products for other diseases due to the high frequency of contamination of batches of fetal bovine serum used as a culture medium supplement.

14.3.1. Options

There is no OIE code chapter for BVD, and no international standards exist for BVD risk management for bovine serum. One or a combination of the following options could be considered to manage the risk associated with BVDV.

1. Bovine serum could be imported from BVDV2- and BVDV3-free countries.
2. Since it is not always possible to differentiate BVDV1 from BVDV2 and BVDV3, bovine serum that tests positive for any BVDV strain and originates in a country where BVDV-2 and BVDV-3 occurs should not be imported.
3. The animals used for blood collection showed no clinical signs of the infection on the day of blood collection, and no other evidence of the infection were reported in the animal or herd during the last three months; and:
    a. For abattoir-sourced bovine serum, the serum was derived from animals kept since birth in countries free from the disease. The animals passed antemortem examination, were declared fit for human consumption and were processed in premises under the oversight of the competent authority.
    b. For donor-animal-derived bovine serum, the serum was derived from animals kept since birth in countries free from the disease. The animals were under veterinary supervision, or the donor tested negative for BVDV with an MPI-approved/recommended test, at the time of blood collection.
4. Bovine serum could be either:
    a. tested with an MPI-approved/recommended test, with negative results; OR

b. subjected to gamma irradiation at a minimum dose of 35 kGy. However, this option must be used with caution, as gamma irradiation may not inactivate all BVDV present in sera, depending on the initial viral load.

15. Cache Valley virus

15.1. TECHNICAL REVIEW

15.1.1. Aetiology

Family: *Bunyaviridae*
Genus: *Orthobunyavirus*
Species: *Bunyamwera virus*

Cache Valley virus (CVV) is a member of the Bunyamwera (BUN) serogroup (ICTV, 2011; OIE, 2018d).

CVV was the first North American *Orthobunyavirus* to be linked to fetal arthrogryposis and hydrancephaly; however, other related viruses have been shown experimentally to have the potential to cause similar signs (OIE, 2018d). Viruses in the BUN serogroup that have been identified in the United States include Lokern virus (LOKV), Main Drain virus (MDV), Northway virus (NORV), Potosi virus (POTV) and Tensaw virus (TENV) (Johnson *et al*., 2014). All these viruses are considered to be epidemiologically similar to CVV. None of these viruses have been widely investigated for their ability to cause disease (Johnson *et al*., 2014).

In this assessment, CVV is considered a representative for all these viruses in the BUN serogroup.

15.1.2. OIE List

CVV infection is not an OIE-listed disease.

15.1.3. New Zealand status

CVV infection has never been reported in New Zealand, and there is no other evidence indicating its presence in the country (Tana, 2020b).

15.1.4. Zoonotic potential

CVV infection is a zoonotic disease (Armstrong *et al*., 2015; Noronha and Wilson, 2017) and is considered a significant emerging vector-borne zoonotic disease in Canada (Kulkarni *et al*., 2015). Armstrong and others (2015) reported that the antibody prevalence in humans exposed to the virus in endemic regions ranges from 3% to 19%. According to Waddell and others (2019), only six clinical cases of CVV have been reported to date in the United States. In people, symptoms of CVV include fever, headache, vomiting, body aches and confusion (Campbell *et al*., 2006; Nguyen *et al*., 2013; Wilson *et al*., 2017). All

patients were initially diagnosed with meningitis and meningoencephalitis, which were later confirmed to be CVV-associated (Waddell *et al*., 2019).

15.1.5. Epidemiology

Host range

CVV infection is a teratogenic, mosquito-borne disease affecting mainly sheep (OIE, 2018d). However, all domestic and wild ruminants are shown to be susceptible to natural infection (Edwards, 1994; Noronha and Wilson, 2017). Among wild ruminants, deer are the most affected by CVV and are amplifying hosts (Noronha and Wilson, 2017; Uehlinger *et al*., 2018). Serological surveys have confirmed the prevalence of antibodies in horses, dogs and pigs as well (OIE, 2018d).

Geographical distribution

CVV is endemic in the United States, Canada and Mexico (Edwards, 1994; OIE, 2018d). CVV or its subtypes have been identified in Central America, South America and the Caribbean (Blitvich *et al*., 2012).

In the United States, CVV was first isolated from a mosquito pool in Utah in 1956 (OIE, 2018d). Since the first isolation of CVV, the virus or neutralising antibody have been isolated from sheep, cattle, deer, dogs, horses, pigs and humans (Armstrong *et al*., 2015; Grimstad, 2001; Sahu *et al*., 2002) in the United States. Sahu and others (2002) examined bovine sera in the United States to identify specific neutralising antibodies to CVV. The results indicated that 4% to 28% of cattle had specific neutralising antibodies to CVV (Sahu *et al*., 2002).

CVV infection is not reported in Australia to date, and there is no other evidence indicating its presence in the country. Wilson and others (2017) reported a single human clinical case of CVV in Australia in a patient with travel history to the United States.

Pathogenesis

CVV infection affects animals of all ages, including fetuses. CVV infections are subclinical in most adult animals. Viraemia is brief during acute infections and is detectable (Edwards, 1994). Even though viraemia lasts for a short time, it induces a lifelong immune response in infected animals (Noronha and Wilson, 2017).

Experimental infections confirmed that CVV could cause embryonic death and multiple congenital malformations in sheep and cattle (Calisher and Sever, 1995; Edwards, 1994).

In utero infection with CVV impacts developing fetuses, and the outcome in the fetus is age-dependent (Edwards *et al*., 1989; OIE, 2018d). Transplacental transmission results in fetal malformations, including mummification and death during the first four weeks of the gestation. Later, between four to seven weeks of gestation, infected fetuses develop arthrogryposis with hydrancephaly (AGH), hydrocephalus, microencephaly, porencephaly, torticollis, scoliosis and oligohydramnion (Noronha and Wilson, 2017). No gross defects have been detected in the fetus when infection occurs after seven weeks of gestation. For infection occurring after 11 weeks of gestation (76 days), the fetus becomes

immunocompetent and produces antibodies, and no pathognomonic signs can be detected (OIE, 2018d).

Clinical signs of CVV infection are similar to those of Akabane disease. In ruminants, initial signs of CVV infection include malaise with low-grade fever, inappetence and reluctance to move (Edwards, 1994). Infected adult cattle and sheep have decreased calving and lambing rates, abortions, stillbirths and severely deformed calves and lambs (Edwards, 1994; Noronha and Wilson, 2017). In sheep fetuses, the pathological signs include malformations of the central nervous system and the musculoskeletal system (Edwards *et al*., 1989; Johnson *et al*., 2014).

Sahu and others (2002) reported that 4% to 28% of the cattle in the United States have specific antibodies against CVV. There is no published literature or reports on the infectious dose, mortality and morbidity rates of CVV in cattle.

CVV has been reported to be a contaminant in FBS (Hanson *et al*., 2019), and CVV has made its way to biological products such as veterinary vaccines and cell culture growth medium (Hsieh *et al*., 2008). Hsieh and others (2008) reported that the contamination of culture growth media with CVV is due to the use of non-gamma irradiated FBS. Using metagenomics to assess adventitious viruses in bovine sera, Toohey-Kurth and others (2017) could not detect any evidence of CVV in the 26 serum samples they tested from 12 commercial manufacturers.

Transmission

CVV infection is an arthropod-borne disease transmitted to adult animals mainly by mosquitoes (Noronha and Wilson, 2017; Sahu *et al*., 2002) and *Culicoides* midges (OIE, 2018d). Edwards (1994) reported that CVV had developed overwintering mechanisms such as persistent insect vector infection and transovarial infection. These mechanisms help the virus persist in adverse conditions (Edwards, 1994). Sylvatic transmission contributes to the maintenance and amplification of CVV, involving permissive hosts such as white-tailed deer and arthropod hosts (Edwards, 1994; Noronha and Wilson, 2017).

Mosquito genera that play a role in the transmission of CVV include *Aedes*, *Anopheles*, *Coquillettidia* and *Culiseta* (Waddell *et al*., 2019). Waddell and others (2019) made a list of all 44 mosquitoes from which CVV was detected during observational and experimental studies. Of the 44 mosquito species, only one (*Culex quinquefasciatus)* is present in New Zealand (Heath, 2019). *Culex quinquefasciatus* is experimentally proven to be able to transmit the disease (Waddell *et al*., 2019).

New Zealand has a vector surveillance programme for *Culicoides* spp., and no *Culicoides* midges have been detected to date (Peacock *et al*., 2019a).

Transplacental transmission from the dam to the fetus has also been reported as a method of CVV transmission in vertebrate hosts (Noronha and Wilson, 2017).

Diagnosis

CVV has been isolated from mosquito pools, brain tissue, cerebrospinal fluid and blood of febrile and viraemic adult animals (Edwards, 1994; OIE, 2018d). For CVV isolation, baby hamster kidney (BHK), African green monkey kidney (Vero) and rhesus monkey kidney

(LLC-MK2) cell lines have been used (OIE, 2018d). CVV cannot be isolated from the neonates at birth, because the fetal immune response clears the virus (Edwards, 1994). Group-specific and virus-specific polymerase chain reaction (PCR) methods are available for orthobunyaviruses. Reverse transcription polymerase chain reaction (RT-PCR) can be used to distinguish BUN serogroup from other viruses of the genus *Orthobunyavirus* (OIE, 2018d).

Serological tests used for detecting antibodies to CVV include virus neutralisation (VN) and enzyme-linked immunosorbent assay (ELISA) (OIE, 2018d). Serum from heart blood collected during the necropsy of lambs can also be used for serological tests (Edwards, 1994). Although a haemagglutination inhibition (HI) test for CVV has been described, it is only about 50% as sensitive as the virus neutralisation test. The complement fixation test (CFT) cross-reacts within the Bunyamwera group and is therefore of little use (OIE, 2018d).

For suspected cases in endemic areas, absence of CVV antibodies in dams giving birth to malformed calves or lambs can eliminate the possibility of CVV as the cause. However, the presence of CVV antibodies in dams cannot be used as a confirmation for diagnosis of CVV, because many mature animals may have an antibody titre to CVV from earlier exposures (Edwards, 1994).

Treatment, control and prevention

There is no effective treatment or vaccine against CVV infection. Vector control and herd management strategies such as reproductive timing are the best preventive measures (Noronha and Wilson, 2017) for CVV infection (Edwards, 1994; OIE, 2018d). Infected animals show a lifelong durable immune response to CVV.

15.2. RISK ASSESSMENT

15.2.1. Entry assessment

CVV infection is an arthropod-borne disease transmitted by mosquitoes and *Culicoides* midges. It affects a wide range of ruminants, both domestic and wild, primarily infecting sheep. There are no reports or other evidence that CVV is present in Australia. However, CVV infection is endemic in the United States (Edwards, 1994; OIE, 2018d), but the prevalence information in animals is sparse.

Although CVV infects animals of all ages, its effects are seen only in fetuses. CVV infection in the fetus causes fetal malformations. CVV has been isolated from the blood of febrile and viraemic adult animals (Edwards, 1994; OIE, 2018d). Viraemia in infected animals is short but induces a lifelong immune response. Since CVV can be isolated from the blood of viraemic animals including cattle, it is hypothesised that bovine serum can harbour CVV. There have been reports of CVV contaminating FBS (Hanson *et al*., 2019), and CVV has made its way to biological products such as veterinary vaccines and cell culture growth media (Hsieh *et al*., 2008). Hsieh and others (2008) reported that the contamination of culture growth media with CVV was due to the use of non-gamma irradiated FBS.

In the United States, CVV infection has been reported in multiple species of animals, including cattle. The virus has been isolated from mosquito vectors in the United States. Even though the specific mortality and morbidity rates in cattle in the United States are not available, serological surveys have indicated that 4–28% of cattle had specific neutralising antibodies to CVV (Sahu *et al*., 2002).

The likelihood of entry of CVV in bovine serum from Australia is, therefore, assessed as negligible, while the likelihood of entry through bovine serum imported from the United States is assessed as moderate.

15.2.2. Exposure assessment

CVV has been reported to be a contaminant of non-gamma irradiated FBS, and thus, it is plausible for CVV to contaminate bovine serum imported from the United States. The resulting biological products manufactured from contaminated bovine serum are likely to contain CVV. Contaminated vaccines, when used parenterally, could potentially infect animals in New Zealand. Once infected, CVV would produce viraemia in animals. Vaccination is generally implemented as a herd management tool, and many animals could get exposed through contaminated vaccines.

Out of two primary vectors transmitting CVV, mosquitoes and *Culicoides*, only a single mosquito species is likely to have the capacity to spread CVV is present in New Zealand. *Culex quinquefasciatus* is one of 44 mosquito species listed as a potential vector of CVV in the review by Waddell and others (2019), and it is present in New Zealand (Heath, 2019). This vector could transmit CVV to susceptible host species in New Zealand, but its vector competence has only been shown experimentally. Other mosquito genera that play a role in the transmission of CVV include *Aedes*, *Anopheles*, *Coquillettidia* and *Culiseta.* Even though none of the mosquito species in these genera capable of transmitting the disease are present in New Zealand, other species in these genera are present. However, they have not been shown to be competent vectors for CVV infection.

There are no references of CVV being transmitted between animals by direct contact or through germplasm. Therefore, exposure could be only through contaminated vaccines, and further establishment and/spread to other animals is unlikely in the absence of any competent vectors.

The overall likelihood of exposure, establishment and/or spread of CVV via bovine serum, considering all the factors mentioned above, is assessed as low.

15.2.3. Consequence assessment

CVV is known to infect all ruminants, especially sheep. CVV has never been reported in New Zealand. The most likely CVV-contaminated end product would be vaccines for livestock, which are used in comparatively large groups of animals. Contaminated livestock vaccines could lead to considerable losses to the livestock industry in terms of animal deaths and production losses.

CVV is not an OIE-listed disease, and it is unlikely that any trade restrictions related to CVV infection would be imposed, so trade impacts due to CVV infection would be negligible to very low.

CVV is a zoonotic disease, and *Culex quinquefasciatus* mosquitoes present in New Zealand could contribute to the spread of CVV to the human population. According to Waddell and others (2019), only six clinical cases of CVV have been reported to date in the United States. New Zealand has a naive population susceptible to CVV; therefore, the consequences for human health in New Zealand would be significant.

CVV has never been reported in New Zealand. If a control or containment programme including culling of infected animals were to be implemented following the establishment of CVV, the impacts would be significant.

CVV infects multiple species of ruminants, including domestic and wild ruminants. Horses are also considered potential hosts. Among wild ruminants, deer are most affected by CVV and are considered amplifying hosts. In the event of establishment of the disease in New Zealand, the disease can be transmitted to wild animals through *Culex quinquefasciatus* mosquitoes.

Therefore, the overall consequences from the entry, exposure, establishment and/or spread of CVV are assessed as low.

15.2.4. Risk estimation

The likelihood of entry of CVV in bovine serum from Australia is negligible, and therefore, the risk estimate is negligible. Risk management measures are not required for CVV in bovine serum imported from Australia.

The likelihood of entry of CVV in bovine serum from the United States is assessed as moderate, the likelihoods of exposure, establishment and/or spread are assessed as low, and the consequences of CVV are assessed as low. Therefore, the overall risk is estimated as low.

Since the entry, exposure, and consequence assessments are non-negligible for bovine serum imported from the United States, CVV is a risk in the commodity. Therefore, risk management measures are justified for bovine serum imported from the United States.

15.3. RISK MANAGEMENT

The following points were considered when describing options for managing the risks:

- CVV infection is not an OIE-listed disease.
- CVV is absent from New Zealand and Australia but present in the United States.
- CVV infection is a zoonotic disease.
- CVV is reported as a possible contaminant in FBS.
- Mosquitoes and *Culicoides* midges transmit CVV.
- *Culicoides* midges are absent from New Zealand.
- *Culex quinquefasciatus*, an experimentally proven vector for CVV, is present in New Zealand.
- CVV infects multiple species of animals and all ages, including fetuses, with varying effects.
- In infected cattle, a short period of viraemia has been demonstrated.
- There is no effective treatment or vaccination for CVV infection.

15.3.1. Options

The following options or a combination of these options can be considered to manage the risk associated with CVV.

1. Bovine serum could be imported CVV-free countries.
2. Since CVV antibodies protect from reinfections and last for life, blood for bovine serum production could be collected from animals that test positive for CVV antibodies.
3. The animals used for blood collection showed no clinical signs of the infection on the day of blood collection and were not viraemic.
    a. For abattoir-sourced bovine serum, the serum was derived from animals kept since birth or for the last three months in a country free from the disease. The animals passed antemortem examination, were declared fit for human consumption and were processed in premises under the oversight of the competent authority.
    b. For donor-animal-derived bovine serum, the serum was derived from animals kept since birth or for the last three months in a country free from the disease, and were under veterinary supervision; or the animals were tested with an MPI-approved/recommended test, with negative results, at the time of blood collection.
4. Bovine serum could be either:
    a. tested with an MPI approved/recommended test, with negative results for CVV, OR
    b. subjected to gamma irradiation at a minimum dose of 35 kGy.

16. Epizootic haemorrhagic disease virus including Ibaraki

16.1. TECHNICAL REVIEW

16.1.1. Aetiology

Family: *Reoviridae*
Genus: *Orbivirus*
Species: *Epizootic haemorrhagic disease virus* (EHDV)

Ten EHDV serotypes (EHDV1 through EHDV8, 318, and Ibaraki virus) have been described. Of these, seven (EHDV1, EHDV2, and EHDV4–EHDV8) are globally distributed (Ahasan *et al.*, 2018; Anthony *et al.*, 2009; Kitano, 2004; OIE, 2019b).

Ibaraki disease, which occurs in parts of Asia, is caused by the Ibaraki strain of EHDV2 (formerly Ibaraki virus).

16.1.2. OIE List

Epizootic haemorrhagic disease (EHD) is an OIE-listed disease.

16.1.3. New Zealand status

EHD is absent from New Zealand (MPI, 2019a), and both EHDV and *Culicoides* midges, the vector transmitting the disease, are monitored in New Zealand under the Arbovirus Surveillance Programme (Peacock *et al*., 2019a). EHDV and *Culicoides* have never been detected through this surveillance programme to date in New Zealand. EHDV is listed as a notifiable organism in the Biosecurity (Notifiable Organisms) Order 2016 (MPI, 2016a).

16.1.4. Zoonotic potential

There is no evidence that EHDV infects humans.

16.1.5. Epidemiology

Host range

Epizootic haemorrhagic disease (EHD) is an infectious non-contagious viral disease transmitted by insects of the genus *Culicoides*.

Various cervid species can be infected with EHDV, and clinical cases have been reported in some species. White-tailed deer are highly susceptible (Brodie *et al*., 1998).

Outbreaks and sporadic clinical cases caused by various serotypes, including EHDV1, EHDV2, EHDV6 and EHDV7 have been reported in cattle, although subclinical infections are more common (Coetzer and Tustin, 2004; Spickler, 2006).

Clinical cases have also been seen in other ruminants (yaks, American bison and bighorn sheep) in the United States, but rarely in sheep and alpacas (Brodie *et al*., 1998; Stevens *et al*., 2015). Antibodies have been found in goats, although viruses could not be recovered from experimentally infected animals (Spickler, 2006).

Other animals reported to have serological or virological evidence of infection include water buffaloes, Arabian oryxes, black rhinoceroses, white rhinoceroses and black bears (Spickler, 2006).

Geographical distribution

EHDV has been reported from North America, South America, the Caribbean, Australia, Asia, Africa and the Middle East. Serotypes 1, 2 and 6 are currently endemic in North America. Serotypes 1, 2, 5, 6, 7 and 8 are known to occur in Australia (Spickler, 2006).

In Georgia (USA), a serosurvey by Odiawa and others (1985) revealed that 67% of the 175 cattle farms surveyed had EHDV with precipitating antibodies.

The seroprevalence of antibodies against EHDV in cattle herds in Illinois and Indiana was 15.3% in 2000, 13.4% in 2001 and 5.2% in 2002 (Boyer *et al*., 2008).

Ibaraki disease was initially reported in Japan in 1959, and since then, there have been epidemics of the disease in East Asia (Bak *et al*., 1983) Antibodies to the virus have been found in bovine sera in Australia and Indonesia (Daniels *et al*., 1995).

EHD viruses are generally in temperate and tropical climates that support vector populations (Ruder *et al*., 2015).

Pathogenesis

Naturally occurring disease has not been observed in cattle, deer or other susceptible species in Australia (Spickler, 2006), although the virus has been isolated regularly in the Northern Territory and Queensland under a sentinel cattle detection programme (the National Arbovirus Monitoring Program) (Weir and Agnihotri, 2014).

Australian EHD viruses were isolated from blood clots or whole blood of experimentally infected cattle for a mean duration of one to four weeks, with a maximum of eight weeks, depending on the serotype. The Australian EHDV serotypes 2, 5, 6, 7 and 8 caused no clinical signs in cattle (Uren, 1986; Weir, 2003; Weir and Agnihotri, 2014).

EHDV has been isolated from blood samples of clinically affected cattle in Colorado (Foster *et al*., 1980) and French island of Réunion in the Indian ocean (Bréard *et al*., 2004; Sailleau *et al*., 2012).

Deaths have been reported occasionally in cattle, but most animals seem to recover in 3 to 30 days (Spickler, 2006). The duration of acquired immunity is still unknown, but evidence from natural infections suggests it may last for life. Neutralising antibodies and the virus can coexist in the infected animal, likely because of the strong association between EHDV and red blood cells (OIE Terrestrial Manual, 2018j).

Cattle are likely the primary domestic ruminant host of EHDV in North America, based on the serological surveys, sentinel animal studies (Odiawa *et al*., 1985), outbreak investigations (Foster *et al*., 1980) and the isolation of EHDV from diagnostic samples (Foster *et al*., 1980). Most cattle appear to experience subclinical infections or mild to moderate transient febrile disease. In cattle, there has been an increase in clinical disease associated with EHDV infection in numerous parts of the world, including the United States (Bréard *et al*., 2004), Israel, Turkey, Morocco, Algeria, Tunisia and Jordan (Ruder *et al*., 2015).

The morbidity rate of the outbreak in Reunion Island which occurred in 2003 was 7% of 3,607 cattle, but the mortality rate was not determined (Bréard *et al*., 2004). The morbidity rate of the 2009 Reunion Island outbreak was 0.8%, and the case fatality rate was estimated at 11%. However, this could be attributed to both *Bluetongue virus* and EHDV (Sailleau *et al*., 2012). The 2006 EHDV outbreak in Israel resulted in a 5–80% within-herd morbidity in dairy herds and a mortality rate of less than 1% (Yadin *et al*., 2008).

Ibaraki disease, which occurs among cattle in parts of Asia, can result in mortality rates of up to 10% (Inaba, 1975; Weir, 2003). Common clinical signs of Ibaraki disease include fever, anorexia, conjunctival infection with lachrymation, nasal discharge and foamy salivation. Infected animals may develop oedema, haemorrhages, erosions and ulcerations in the mouth, on the lips and around the coronets. They can also be stiff and lame, and the skin may be thickened and oedematous (Inaba, 1975). Swallowing difficulties, which are the pathognomonic sign of Ibaraki disease, occur in 20–30% of affected animals. Abortions, fetal malformations and stillbirths were reported during the 1997–1998 Ibaraki disease outbreak in Japan, in the Caribbean in 2011, and in the United States in 2012. The

clinical signs in these and earlier outbreaks include fever, oral lesions (erosions, ulcers, necrotic lesions, erythema and swelling) excessive salivation, nasal discharge and crusting of the muzzle, inappetence or difficulty eating, ocular signs (conjunctival oedema, palpebral swelling and ocular discharge), stiffness, lameness associated with coronitis, mammary gland lesions (teat erythema, red to purple udder discolouration) and weight loss. Milk yield dropped significantly during some outbreaks. Haemorrhagic lesions, together with diarrhoea with tarry faeces or frank undigested blood in the faeces, were described on some farms in the United States.

Illnesses attributed to EHDV were described in two sheep flocks in Turkey. The clinical signs in one flock were high fever, oedema of the head, which was especially prominent under the chin, and mouth and nose lesions, including hyperaemia and foamy saliva. In the second flock, signs included anorexia, lethargy, oedema of the head, lameness, abdominal distension, oral hyperaemia and mild cyanosis of the tongue (Spickler, 2006).

Transmission

EHDV is transmitted by biting midges in the genus *Culicoides*, which act as biological vectors (Maclachlan *et al*., 2015b). Mosquitoes or other bloodsucking insects might theoretically be able to transmit this virus mechanically, although mosquitoes are thought to have little or no role in the epidemiology of this disease. There is one report of virus isolation (EHDV4) from two Anopheles mosquitoes in Indonesia (Brown *et al*., 1992).

Diagnosis

Virological evidence of EHDV can be found in the blood of viraemic animals or tissue samples (especially spleen, lymph nodes and lung) collected at necropsy (OIE Terrestrial Manual, 2018j).

The virus can be identified with immunofluorescence, serogroup-specific sandwich ELISAs, or reverse transcription polymerase chain reaction (RT-PCR) assays. Methods to identify the viral serotype include virus neutralisation or plaque inhibition tests with reference antisera, or serotype-specific RT-PCR assays (OIE Terrestrial Manual, 2018j).

Currently available serological tests are enzyme-linked immunosorbent assays (ELISAs), virus neutralisation (VN) and agar gel immunodiffusion (AGID).

The OIE recommends a monoclonal antibody-based competitive ELISA (C-ELISA) for identifying an individual animal's infection status. AGID and some ELISAs cannot distinguish EHDV from bluetongue or other orbiviruses. Antibodies to EHDV can usually be found 10 to14 days after the animal was infected, and neutralising antibodies and viruses may be found concurrently in infected animals. Many deer and cattle have preexisting antibodies to EHDV, and a rising titre should be diagnosed with paired serum samples (OIE Terrestrial Manual, 2018j).

Treatment, control and prevention

According to WAHIS (2019), the United States has general surveillance and disease notification in place for EHD in cattle and *Cervidae*. Australia has general surveillance,

disease notification, precautions at the border and monitoring for cattle, *Cervidae* and wild species (WAHIS, 2019b).

In countries free from EHD, preventing the introduction of infected animal hosts and vectors would be an appropriate preventive measure. Prophylactic or therapeutic strategies may be used in enzootic or incursive areas (Maclachlan *et al*., 2015b). Domestic livestock rarely suffer from clinical disease and do not require treatment. An exception to this is infection with Ibaraki disease in cattle. Clinical signs in these animals may be prevented and treated to limit mortalities (Maclachlan *et al*., 2015b).

Preventive measures could include protection from vectors and vaccination against EHDV. Vaccines are not widely available for the control of EHDV infection, but both live modified and inactivated vaccines have been developed to control Ibaraki disease (EFSA Panel on Animal Health and Welfare (AHAW), 2009).

16.2. RISK ASSESSMENT

16.2.1. Entry assessment

It has been reported that the EHDV can be isolated from experimentally infected cattle for a mean duration of four weeks, with a maximum of eight weeks depending on the serotype. This implies that the viraemia may last for this period. Most infections in cattle, including infections with the viruses causing Ibaraki disease, are thought to be subclinical. There are no reports of carrier status of EHDV, and most cattle are reported to recover in 3 to 30 days. The duration of acquired immunity is still unknown, but evidence from natural infections suggests it may last for life (OIE 2018).

If the infection is clinically inapparent or results in mild signs, it may go undiagnosed during clinical examination of donors or postmortem inspections at slaughter plants. Therefore, infected blood may be collected from infected donor animals.

EHDV has been reported as a contaminant of FBS (Hanson *et al*., 2019; Nims, 2011; Toohey-Kurth et al., 2017). Rabenau and others (1993) investigated the presence of EHDV as a contaminant in genetically engineered Chinese hamster ovary (CHO) cells during production for biological use. They concluded that the source of contamination was the batches of FBS that were used as a supplement during CHO cell culture.

Australia has not reported any naturally occurring clinical cases, but various serotypes are known to be circulating within the cattle population (Spickler, 2006; Weir and Agnihotri, 2014). Prevalence data for EHDV in Australia is not available.

The herd prevalence of EHDV in cattle from herds in Georgia (USA) was reported to be 67%. The seroprevalence of antibodies against EHDV in cattle herds in Illinois and Indiana was 15.3% in 2000, 13.4% in 2001 and 5.2% in 2002. However, in recent years, there has been an increase in clinical cases (i.e. the likelihood of infected cattle showing clinical disease is increasing). The likelihood of collecting infected blood from cattle in the United States is low, based on the assumption that blood will not be collected from clinically affected animals. The likelihood of collecting infected blood from cattle in Australia is moderate due to the presence of several serotypes causing subclinical disease.

The overall likelihood of entry of EHDV is assessed as low to moderate.

16.2.2. Exposure assessment

Animal vaccines produced from contaminated bovine serum may contain viable EHDV. Parenteral administration of these contaminated vaccines is the most likely pathway for transmission through vaccines. Vaccination is generally implemented as a herd management tool, and a large number of animals could get exposed through contaminated vaccine. Sera prepared from viraemic animals could potentially represent some risk if introduced parenterally into naive animals (OIE 2018). The likelihood of the vaccine containing an infectious dose is uncertain; however, this cannot be ruled out, and thus, there is the likelihood of an animal becoming infected after being vaccinated with a contaminated vaccine.

The vector that transmits EHD, a biting *Culicoides* midge, is not found in New Zealand (Peacock *et al*., 2019a). Mosquitoes or other bloodsucking insects might theoretically be able to transmit this virus mechanically, although they are thought to have little or no role in the epidemiology of this disease. Since the EHDV transmission is dependent on geographic and seasonal vector distribution of *Culicoides* within New Zealand, the likelihood of establishment and/or spread is negligible.

There are no references of EHDV being transmitted between animals by direct contact or through germplasm. Therefore, exposure may only be through contaminated vaccines, and further establishment and/or spread to other animals is unlikely in the absence of any competent vectors.

The overall likelihood of exposure, establishment and/or spread of EHDV via bovine serum based on the factors discussed above is assessed as low.

16.2.3. Consequence assessment

Most cattle appear to experience subclinical infections or mild to moderate transient febrile disease. However, there has been an apparent increase in clinical disease in cattle associated with EHDV infections in numerous parts of the world. The widespread epizootic in domestic cattle in Israel resulted in significant economic losses for the dairy industry (Yadin *et al*., 2008). Outbreaks in the United States reported low morbidity and case fatality rates. Australia has not reported naturally occurring disease although the virus was found circulating in the cattle population. Infection with different strains may result in varying clinical manifestation. New Zealand's cattle population likely to be naive to EHDV; therefore, the clinical picture of an introduction of the virus is uncertain.

If EHDV enters New Zealand, it could affect multiple species including deer, sheep and goats. The consequences for the sheep and goat industry would be low because the overt disease is rare in these animals. However, the consequences for the deer industry would likely be high because clinical disease, morbidity and mortality rates could be significant (Ruder *et al*., 2015; Ruder *et al*., 2012), depending on the strain.

There is no evidence that EHDV infects humans, and there would be no consequences for human health. Therefore, the consequences to human health in New Zealand are negligible.

EHD is an OIE-listed disease, and there are likely to be trade impacts, which would be moderate.

EHD has never been reported in New Zealand. If a control or containment programme is implemented following the establishment of EHD, the impacts would be moderate.

Among wild animals in New Zealand, deer are the only animals that are highly susceptible to EHDV. The absence of competent vectors in New Zealand negates the likelihood of further spread of the infection among wild animals. Therefore, the consequences for the New Zealand environment would be negligible.

The overall consequences from the entry, exposure, establishment and/or spread of EHDV are assessed as low to moderate.

16.2.4. Risk estimation

The likelihood of entry of EHDV in bovine serum from Australia and the United States is assessed as low to moderate, the likelihoods of exposure, establishment and/or spread are assessed as low, and the consequences of EHDV are assessed as low to moderate. Therefore, the overall risk is estimated as low.

Since the entry, exposure, and consequence assessments are non-negligible for bovine serum imported from Australia and the United States, EHDV is a risk in the commodity. Therefore, risk management measures are justified for bovine serum imported from Australia and the United States.

16.3. RISK MANAGEMENT

The following points were considered when presenting options for managing the risks:

- EHD is an OIE-listed disease.
- EHDV is listed as a notifiable organism on the Biosecurity (Notifiable Organisms) Order 2016.
- There is no evidence that EHDV infects humans.
- EHD is an infectious non-contagious vector-borne disease, with *Culicoides* as the primary vector.
- EHDV isolation from mosquitoes has been reported in Asia.
- EHDV have been reported in cattle, although subclinical infections are more common.
- EHDV antigen has been isolated from bovine serum.
- Various cervid species can be infected with EHDV, and clinical cases have been reported in some species.
- EHDV has been isolated from cattle in Australia and the United States.
- EHDV has been isolated from experimentally infected cattle for a mean of one to four weeks, with a maximum of eight weeks, depending on the serotype.
- Diagnosis can be made by virus isolation, serology and PCR. The OIE recommends a monoclonal antibody-based competitive ELISA.

16.3.1. Options

The following options individually or in combination could be considered to manage the risk associated with EHDV in bovine serum. These options have been considered based on some of the OIE recommendations for infection with EHDV (OIE Terrestrial Code, 2019e).

1. Bovine serum could be imported from countries free from EHD as per the relevant OIE Code Chapter.
2. The animals used for blood collection showed no clinical sign of EHD on the day of collection, and no other evidence of the infection were reported in the animal or herd.
    a. For abattoir-sourced bovine serum, the serum was derived from animals kept in a country or zone free from EHD or a seasonally free country or zone during the free season in accordance with the requirements of the OIE Code. The animals passed antemortem examination, were declared fit for human consumption and were processed in premises under the oversight of the competent authority.
    b. For donor-animal-derived bovine serum, the animals were under veterinary supervision and came from animals kept in a country or zone free from EHD or a seasonally free country or zone during the free season in accordance with the requirements of the OIE Code, or the donor was tested with an MPI-approved/recommended test, with negative results, at the time of blood collection.
3. Bovine serum could be either:
    a. tested with an MPI-approved/recommended test, with negative results; or
    b. subjected to gamma irradiation at a minimum dose of 35 kGy.

17. Palyam virus group (orbiviruses)

17.1. TECHNICAL REVIEW

17.1.1. Aetiology

Family: *Reoviridae*
Genus: *Orbivirus*
Species: *Palyam virus*

Palyam serogroup orbiviruses are arthropod-borne viruses. There are 13 serotypes recognised by the International Committee on Taxonomy of Viruses as members of this serogroup (Ebersohn *et al*., 2019; Swanepoel, 2004). They are Palyam, Kasba, Vellore, Adadina, D'Aguilar, Nyabira, CSIRO Village, Marrakai, Gweru, Bunyip Creek, Petevo, Morondera and Kindia.

For this risk analysis, the term 'Palyam virus' refers to all serotypes of the virus mentioned above.

17.1.2. OIE List

Infection with Palyam virus is not an OIE-listed disease.

17.1.3. New Zealand status

Palyam virus is not present in New Zealand. Palyam virus is not listed as a notifiable organism under the Biosecurity (Notifiable Organisms) Order 2016 (MPI, 2016a).

Palyam virus was being monitored as part of the Arbovirus Surveillance Programme in New Zealand, but surveillance testing for Palyam virus was discontinued after 2014 (Peacock, 2019b). Palyam virus has never been detected through this surveillance programme or any other disease monitoring programmes in New Zealand. Vector surveillance for *Culicoides* spp., the vector transmitting Palyam virus, is part of this surveillance programme. No *Culicoides* have been detected to date in New Zealand (Peacock *et al*., 2019a).

17.1.4. Zoonotic potential

Infection with Palyam virus is not zoonotic.

17.1.5. Epidemiology

Host range

The primary hosts for Palyam virus are cattle. Other susceptible host species include sheep and goats (Swanepoel, 2004), in which antibodies have been detected experimentally.

Geographical distribution

Palyam viruses have been isolated from Africa, Asia and Australia (Harasawa *et al*., 1988; Whistler and Swanepoel, 1990; Swanepoel, 2004).

There is no published literature indicating the presence of the Palyam virus group in the United States.

Pathogenesis

The Palyam serogroup of orbiviruses comprises 13 antigenically related viruses (Ebersohn *et al*., 2019; Harasawa *et al*., 1988). The viruses usually cause mild or subclinical infections but have been associated with cattle abortions in Zimbabwe (Whistler and Swanepoel, 1988).

Clinical signs in adult cattle include leukopenia, viraemia and mild fever (Swanepoel, 2004). Palyam serogroup viruses cause abortion and teratogenesis in cattle (Whistler and Swanepoel, 1990). Retained placenta can be a complication of infection with Palyam serogroup viruses. In calves, clinical signs include opisthotonus, impaired mobility, inability to suckle, hydranencephaly and cerebral hypoplasia (Miura *et al*., 1991; Swanepoel, 2004).

After infection with Kasba virus, one of the Palyam serogroup members, Goto and others (1988) reported that cattle could be consistently viraemic for two weeks and intermittently viraemic for eight weeks. With Chuzan virus, another Palyam serogroup member,

viraemia lasts for four to eight weeks, and the virus can be recovered in higher titres from erythrocytes and only intermittently from plasma (Miura *et al*., 1991; Swanepoel, 2004). Gard and Melville (1992) confirmed that 64% of detectable viraemia occurs in less than eight days of Palyam virus infection.

Transmission

Palyam virus infection is a vector-borne disease. The primary vectors for transmission of the viruses are *Culicoides* spp., but Palyam viruses have also been isolated from ticks in Africa and mosquitoes in India (Doyle, 1992; Swanepoel, 2004).

The virus has been isolated from *Culex brevitarsis*, *Culex vishnui* and *Culex pseudovishnui* mosquito species. *Amblyomma variegatum* is the tick species from which the virus has been isolated. Despite the isolation from mosquitoes and ticks, natural transmission through these vectors has not been demonstrated (Whistler and Swanepoel, 1988). None of these mosquitoes and tick species are present in New Zealand (Heath, 2019).

Diagnosis

Virus isolation can be conducted using fetal tissues in cell culture or suckling mice. The specimens used for virus isolation include aborted fetuses, brains, spleens, kidneys, lungs, placentas, blood and serum of infected animals. Viruses are identified using immunofluorescence or complement fixation tests. Definitive diagnosis is achieved with serological tests (Swanepoel, 2004).

Palyam serogroup infected animals can produce long-lasting antibodies, which can be detected serologically with a virus neutralisation test (Afsar and Gard, 1992). Another diagnostic test that can also be used is the agar gel immunodiffusion (AGID) test. The AGID test can cross-react with other related orbiviruses such as *Bluetongue virus* (Ryan *et al*., 1991) and is not considered a reliable test for detecting Palyam virus. Monoclonal antibody (MAb) based competitive enzyme-linked immunosorbent assay (C-ELISA) has been used to solve this problem and is used with the AGID test (Eto *et al*., 1991).

Treatment, control and prevention

There is no specific treatment for Palyam virus infection.

Control and prevention are dependent on effective vector control and eradication programmes (Miura *et al*., 1991). There is no specific vaccine for the Palyam virus infection. Kim and others (2011) developed an inactivated trivalent vaccine for Aino, Akabane and Chuzan virus of the Palyam serogroup. The in-vivo evaluation of the vaccine indicated that the vaccine could simultaneously produce antibodies against all three diseases and prevent them from occurring.

17.2. RISK ASSESSMENT

17.2.1. Entry assessment

The primary host species for the Palyam virus is cattle. Sheep and goats have only been experimentally proven to be infected (Swanepoel, 2004). Palyam virus has been recovered in higher titres from erythrocytes and only intermittently from the plasma of infected cattle during the viraemic phase (Miura *et al*., 1991; Swanepoel, 2004), and there is no evidence

of recovery of the virus from serum. All erythrocytes are removed during serum processing; however, it is likely that the serum collected from infected cattle could be contaminated with the virus, considering the intermittent recovery from plasma.

Palyam virus is present in Australia, and the vector for the transmission of the disease is prevalent in Australia. Even though bovine serum undergoes further processing before its use in the end product, there is no evidence to prove that any processing is effective in reducing Palyam virus contamination in bovine serum.

There is no evidence to prove the presence of the Palyam virus in the United States.

Therefore, the likelihood of entry of the Palyam virus is assessed as negligible to very low for bovine serum imported from Australia and negligible for bovine serum imported from the United States.

17.2.2. Exposure assessment

Palyam virus could potentially be present as a contaminant in bovine serum imported from Australia. It is assumed that if the contaminated bovine serum is used in end products such as vaccines, then exposure of animals to the virus is likely. Parenteral administration of contaminated vaccines is the most likely pathway for transmission through vaccines. Since vaccines are used as a herd management tool, a large number of cattle can be exposed and infected. The infectious dose or proof of infection post-vaccination using contaminated vaccines are uncertain.

Palyam virus infection is a vector-borne disease, and the primary vectors for transmission are *Culicoides* spp. The mosquito and tick species from which the virus has been isolated, *Culex brevitarsis*, *Culex vishnui*, *Culex pseudovishnui* and *Amblyomma variegatum* are absent from New Zealand (Heath, 2019). Other species of mosquitoes in these genera are present in New Zealand, and these mosquito species are not shown to be competent vectors for the disease.

Palyam virus has never been detected through the Arbovirus Surveillance Programme or any other disease monitoring programmes in New Zealand. No *Culicoides* have been detected to date in New Zealand (Peacock *et al*., 2019a). Based on the demonstrated freedom from vectors of the Palyam virus in New Zealand, the likelihood of transmission through vectors is negligible.

There are no reports of the infection being transmitted between animals by direct contact or through germplasm. Therefore, exposure may only be through animals receiving contaminated vaccine, and in the absence of the competent vector in New Zealand, establishment and/or spread to other animals is not likely. Considering the negligible to very low likelihood of entry, the exposure and further transmission through vaccination could be very minimal. Further transmission and spread of the virus are negligible because the vector responsible is absent from New Zealand.

Therefore, the overall likelihood of exposure, establishment and/or spread of the Palyam virus via bovine serum considering the above factors is assessed as negligible.

17.2.3. Risk estimation

The likelihood of entry of the Palyam virus in bovine serum from the United States is assessed as negligible, and therefore, the risk estimate is negligible. Risk management measures are not required for the Palyam virus in bovine serum imported from the United States.

The likelihood of entry of Palyam virus in bovine serum from Australia is assessed as negligible to very low, and the likelihoods of exposure, establishment and/or spread are assessed as negligible.

The overall risk is estimated as negligible. Therefore, risk management measures are not justified.

18. *Bacillus anthracis*

18.1. TECHNICAL REVIEW

18.1.1. Aetiology

Family: *Bacillaceae*
Genus: *Bacillus*
Species: *Bacillus anthracis* (Pilo and Frey, 2011)

Bacillus anthracis is the causative agent of anthrax. It is a gram-positive, rod-shaped, aerobic, endospore-forming bacterium. It is 1–1.5 µm wide and 3–10 µm long (De Vos and Turnbull, 2004).

18.1.2. OIE List

Anthrax is an OIE-listed disease (OIE, 2020).

18.1.3. New Zealand status

Anthrax has not been reported in New Zealand since 1954 (Gill, 1993), in either domestic or wild animal populations (WAHIS, 2019a). Anthrax is listed as a disease absent from New Zealand (MPI, 2020), and *Bacillus anthracis* is a notifiable organism under the Biosecurity (Notifiable Organisms) Order 2016 (MPI, 2016a).

18.1.4. Zoonotic potential

Anthrax is a zoonotic disease (De Vos and Turnbull, 2004; OIE, 2018a) that can be transmitted from animals to humans through direct and indirect contact with infected or contaminated animals and animal products (WHO, 2008). The alimentary form of the disease has been reported in people who consumed meat from infected animals or handled infected carcasses. The cutaneous form of the disease has occurred in veterinarians handling infected carcasses for postmortem examinations (Radostits *et al*., 2007).

18.1.5. Epidemiology

Host range

Bacillus anthracis affects most warm-blooded vertebrates, including humans, causing high mortality in affected animals, primarily in domestic and wild herbivores (WHO, 2008). Mortality associated with anthrax has been reported in most mammals and several bird species (OIE Terrestrial Manual, 2018a).

Geographical distribution

Anthrax occurs in most countries and is most common in agricultural regions of Central America, South America, Central Asia, some Mediterranean countries, several Sub-Saharan African countries, western China and certain geographic zones in Australia, Canada and the United States (WHO, 2008).

According to the OIE, anthrax is present in Australia among domestic animals but is limited to certain zones (WAHIS, 2019a). It occurs most commonly in a specific area known as the 'anthrax belt', which extends from southeast Queensland through the centre of New South Wales and into northern Victoria. Isolated outbreaks have also occurred in Western Australia and Queensland. The most recent case of anthrax in Australia was near Dirranbandi in March 2017 (Queensland Government, 2018).

The OIE records that anthrax is present in the United States among domestic animals but limited to certain zones. In the United States, the disease is suspected to be present in wildlife, but this has not been confirmed (WAHIS, 2019a). Despite anthrax being present, it is a rare disease, with sporadic outbreaks occurring among domestic grazing animals in the United States (CDC, 2015). The disease has been reported to be present in a few persistent zones in North Dakota, South Dakota, Minnesota, Nebraska, Nevada and Texas (WHO, 2008).

Pathogenesis

Bacillus anthracis is not an invasive organism, and natural infection in animals mainly acquired by ingesting spores. Infection may also occur through abraded skin or spore inhalation (De Vos and Turnbull, 2004). Infected hosts shed the vegetative bacilli, which sporulate on exposure to air. The spores remain viable in the soil for decades until gaining access to another host where they can germinate and multiply (WHO, 2008). *Bacillus anthracis* only multiplies in animals, and if a carcass is opened, vegetative cells sporulate, and spores in turn contaminate soil and the environment. In unopened carcasses, the organism does not sporulate and is destroyed during the carcass putrefaction process (De Vos and Turnbull, 2004).

After entering the host, the spores germinate to form actively dividing vegetative bacilli. From the primary site of infection, the bacteria get transported to the regional lymph nodes where they multiply, and the vegetative bacilli enter the bloodstream. The anthrax bacillus contains an anti-phagocytic capsule, which helps the bacteria evade immune systems. The bacteria also produce a tripartite protein toxin, which increases capillary permeability and delays blood clotting (De Vos and Turnbull, 2004).

Peracute, acute, subacute and, rarely, chronic forms of the disease have been reported (OIE Terrestrial Manual, 2018a). The incubation period varies from 1 to 14 days. In the peracute form in susceptible species, the course of the disease is only a few hours before death (De Vos and Turnbull, 2004). In the acute form of the disease, death usually occurs within 48 hours. Cattle, sheep, goats and some wild ruminants predominantly manifest the peracute and acute forms of the disease. Subacute and chronic forms of the disease occur in less susceptible animals such as pigs and carnivores (De Vos and Turnbull, 2004).

In the peracute form of the disease, cattle can be found dead before any clinical signs appear. There may be fever, muscle tremors, dyspnoea and congestion before the animal collapses and dies. After death, the discharge of blood from body orifices is common in this form of the disease.

The acute form runs for about 48 hours and can be accompanied by fever, depression, inappetence, weakness, prostration and death. Pregnant cows with the acute form can abort. In milking cows, there can be reduced production and blood in the milk (De Vos and Turnbull, 2004; OIE Terrestrial Manual, 2018a; Radostits *et al*., 2007).

Transmission

Domestic and wild animals become infected when they breathe in or ingest spores in contaminated soil, or other infected material like plants, or water. Biting and non-biting flies and other (hematophagous) insects can also disseminate *Bacillus anthracis* mechanically after they feed on carcasses. In many cases, these flies only spread organisms to nearby vegetation. Biting flies have been suggested to transmit *Bacillus anthracis* to animals during widespread outbreaks. Infection through skin wounds and abrasions may also occur and is a common route of infection for humans (De Vos and Turnbull, 2004; Radostits *et al*., 2007; WHO, 2008).

Direct transmission between living animals is not a significant transmission mode, but carcasses are important in contaminating the environment. Opening an infected carcass can result in anthrax bacilli sporulating, resulting in contamination of soil and the environment (De Vos and Turnbull, 2004).

Natural transmission to humans has been reported through direct and indirect contact with infected animals (WHO, 2008).

Diagnosis

Anthrax can be diagnosed by examining blood or tissue smears for the presence of the bacteria. Samples must be collected carefully to avoid contamination of the environment and to prevent human exposure to the bacteria. For suspected cases of anthrax, bacteriological confirmation is required. Suitable samples such as blood, mesenteric fluid, other oedematous fluid and small tissue excisions from relatively fresh carcasses can contain large numbers of *Bacillus anthracis*, which can be seen under a microscope, cultured and isolated in a laboratory, or detected by polymerase chain reaction (PCR) (De Vos and Turnbull, 2004; OIE Terrestrial Manual, 2018a).

The OIE's *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals* provides laboratory procedures for detecting anthrax (OIE, 2018a) and recommends real-time PCR for surveillance.

Treatment, control and prevention

Anthrax is responsive to antibiotics such as penicillin and streptomycin. The clinical course of the disease is so rapid that there may not be an opportunity to treat affected animals (OIE Terrestrial Manual, 2018a). Treatment is recommended even in advanced stages of the disease to reduce the bacterial load so that subsequent environmental contamination can be reduced (De Vos and Turnbull, 2004).

Control measures for anthrax include treatment of infected animals, surveillance, vaccination, quarantine of possible sources of infection, proper disposal of infected carcasses and disinfection of infected materials (De Vos and Turnbull, 2004).

Vaccination is a control measure that is widely used, and several vaccines are available (Radostits *et al*., 2007). In endemic areas, modified live vaccines can prevent anthrax in livestock. Animals are vaccinated annually, before the season when outbreaks generally occur. The live spore Sterne vaccine is the vaccine most widely used for prevention. The Sterne vaccine is non-pathogenic to cattle, and a single inoculation can provide effective immunity for a year (De Vos and Turnbull, 2004).

18.2. RISK ASSESSMENT

18.2.1. Entry assessment

The ultimate reservoir of *Bacillus anthracis* is contaminated soil, in which spores remain viable for long periods (De Vos and Turnbull, 2004). Infection occurs as a result of the ingestion of spores and not from vegetative forms of the organisms (De Vos, 1994). Spores do not form in host tissues unless the infected body fluids are exposed to air (Spencer, 2003). Moreover, the OIE code states, "There is no evidence that anthrax is transmitted by animals before the onset of clinical and pathological signs" (OIE Terrestrial code, 2019a). Therefore, there is a negligible likelihood that serum collected or processed from healthy animals that have passed antemortem examination or postmortem inspection or clinically healthy live donor animals to be infected with *Bacillus anthracis*.

The likelihood of *Bacillus anthracis* entering in bovine serum from Australia and the United States is assessed as negligible.

18.2.2. Risk estimation

Since the likelihood of entry is negligible, the risk estimate for *Bacillus anthracis* is negligible, and it is not be a risk in the commodity. Therefore, risk management measures are not justified.

19. *Borrelia burgdorferi*

19.1. TECHNICAL REVIEW

19.1.1. Aetiology

Family: *Spirochaetaceae*
Genus: *Borrelia*
Species: *Borrelia burgdorferi* (sensu lato) complex

Borrelia burgdorferi is the spirochaete causing Lyme disease, also known as Lyme borreliosis (Hodzic and Barthold, 2004). The *B. burgdorferi* sensu lato (s. l.) complex comprises 18 named spirochaete species and one unnamed species (Chomel, 2015).

Borrelia burgdorferi is 10 to 30 μm in length and 0.2 to 0.3 μm in diameter (Hodzic and Barthold, 2004).

19.1.2. OIE List

Lyme disease is not an OIE-listed disease.

19.1.3. New Zealand status

There are no reports of *B. burgdorferi* in New Zealand. *B. burgdorferi* is not listed as a notifiable organism under the Biosecurity (Notifiable Organisms) Order 2016 (MPI, 2016a). Lyme borreliosis is not present in New Zealand.

19.1.4. Zoonotic potential

Lyme disease is a zoonotic disease. In the United States, around 30,000 cases of Lyme disease in humans are reported annually (Chomel, 2015).

19.1.5. Epidemiology

Host range

Borrelia burgdorferi has been isolated from a wide range of animals, including domestic animals and livestock, and most of the host species harbour subclinical infections (Boulouis *et al*., 2006; Hodzic and Barthold, 2004). Animals that can be infected and show clinical signs of the disease include dogs, horses, sheep and cattle (Ben Said *et al*., 2016; Boulouis *et al*., 2006). Ji and Collins (1994) did a seroepidemiological survey of *B. burgdorferi* exposure of dairy cattle between August 1989 and April 1990 in Wisconsin, which has one of the highest annual incidences of the disease in humans. The survey stated that only 7% of the cows were seropositive, but the herd prevalence was 66%. Seroprevalence rates reported from other studies in cattle in Minnesota and Wisconsin range from 38% in spring to 50% in summer (Spickler, 2011). Wild animals and birds act as reservoir hosts. Rodents are major reservoir hosts (Boulouis *et al*., 2006).

Geographical distribution

Borrelia burgdorferi is mostly found in temperate regions of the northern hemisphere (Chalada *et al*., 2016; Hodzic and Barthold, 2004). Lyme disease has been reported in North America, Central America, South America, Europe and Asia (Chomel, 2015; Sala

and De Faveri, 2016). Lyme disease is one of the most critical vector-borne zoonotic diseases in the United States (US EPA, 2016).

Lyme disease has never been reported in Australia or New Zealand (RCPA, 2016) but has been reported occasionally in travellers returning from endemic countries (Collignon *et al*., 2016).

Pathogenesis

In cattle, the disease often occurs as a herd problem and is often seen in heifers (Boulouis *et al*., 2006). *B. burgdorferi* is transmitted after an infected tick attaches to the host. *Borrelia burgdorferi* can remain and multiply in the host attachment site for several days and then disseminate to various organs and tissues in the host (Hodzic and Barthold, 2004).

The incubation period for Lyme disease in cattle is not known but is reported to be prolonged, based on the appearance of clinical signs in infected hosts and seasonal emergence of adult ticks. Larvae of ixodid ticks that feed on reservoirs such as infected rodents acquire the infection. Later, larvae moult and harden into nymphs, which primarily parasitise birds, reptiles and mammals. Adult ticks that parasites livestock transmit the disease to the livestock (Hodzic and Barthold, 2004). The organism can be present in blood, urine, colostrum and synovial fluid of affected cattle, and positive antibody titre can be detected from serum, colostrum and synovial fluid of infected cattle (Parker and White, 1992).

Cattle display variable clinical signs, which include erythema on the udder and between digits, chronic weight loss, laminitis, decreased milk production and abortion (Hodzic and Barthold, 2004; Parker and White, 1992). Experimental infections in cattle have estimated the infectious dose to be between 10^6 and 10^7 organisms (Hodzic and Barthold, 2004).

Lyme disease is a tick-borne disease, and its prevalence is associated with the presence, distribution and density of the tick populations (Sala and De Faveri, 2016).

Transmission

Lyme disease is a vector-borne disease and predominantly transmitted by ixodid ticks. Major *Ixodes* ticks involved in the transmission of the disease include *Ixodes ricinus, Ixodes persulcatus, Ixodes scapularis* and *Ixodes pacificus* (Constable *et al*., 2017). In the United States, *Ixodes scapularis*, a three-host tick, is primarily responsible for the transmission of the disease in the eastern and central regions. *Ixodes pacificus* transmits the disease on the Pacific coast (USDA ARS, 2016). In New Zealand, none of the ixodid tick species that can transmit the disease have been reported.

Wild animals and birds, which act as reservoir hosts, also play an important role in transmission. Reservoir hosts maintain the pathogen in the geographical area and contribute to expanding it, where ticks harbouring the organism are distributed (Hodzic and Barthold, 2004).

Transplacental transmission and ingestion of contaminated milk have been proposed as possible routes of transmission due to the detection of the bacteria in fetuses and milk, but this is not scientifically proven (Boulouis *et al*., 2006).

Diagnosis

Diagnosis of Lyme disease is based on clinical signs, epidemiology, differential diagnosis from other diseases and isolation and identification of the organism (Parker and White, 1992). The most practical diagnostic method in humans and animals is based on serological assays (Chomel, 2015). Cattle should be carefully examined to rule out other diseases with similar clinical signs (Boulouis *et al*., 2006).

Isolation of the organism is done by examining under dark microscopy or culturing of blood, cerebrospinal fluid, synovial fluid, urine or colostrum samples of infected animals (Parker and White, 1992; Radostits *et al*., 2007). Polymerase chain reaction (PCR) can be used as a tool for detection of the organism. Although PCR detects the presence of the spirochaetal DNA, it does not distinguish the live organism from its genetic material (Constable *et al*., 2017; Hodzic and Barthold, 2004). Classical and real-time PCR are available (Boulouis *et al*., 2006).

Confirmation of the disease is through serological testing (Boulouis *et al*., 2006; Parker and White, 1992). Immunofluorescent assays and enzyme-linked immunosorbent assays (ELISA) are the most common and reliable serological tests available (Constable *et al*., 2017; Fritz and Kjemtrup, 2003; Radostits *et al*., 2007). Positive antibody detection using serological tests aid in diagnosis but cannot be conclusive evidence for current infections, as subclinical infection can interfere with the test result (Parker and White, 1992).

Treatment, control and prevention

Treatment with appropriate antibiotics has shown to be effective in animals with clinical signs.

The best preventive measure for controlling Lyme disease is tick control (Hodzic and Barthold, 2004). Vaccination is available for dogs, but there is no evidence of vaccine efficacy in livestock (Fritz and Kjemtrup, 2003; Hodzic and Barthold, 2004).

19.2. RISK ASSESSMENT

19.2.1. Entry assessment

Lyme disease is a vector-borne disease mainly transmitted by ixodid ticks. It is a zoonotic disease and animals that can be infected and show clinical signs of the disease include dogs, horses, sheep and cattle. Wild animals and birds can be infected and can act as reservoir hosts. The transmission of the disease is dependent on the geographic and seasonal vector distribution.

Lyme disease is present in the United States, but not in Australia. Prevalence data for dairy cattle in Wisconsin, which has one of the highest annual incidences of the disease in humans, suggests only 7% of the cows were seropositive in 1989-1990, but the herd prevalence was 66%. Seroprevalence rates reported from other studies in cattle in Minnesota and Wisconsin range from 38% in spring to 50% in summer. Lyme disease is seen as one of the most critical vector-borne zoonotic diseases in the United States (US EPA, 2016).

The incubation period for Lyme disease is prolonged, and animals with subclinical infections have been reported. The organism has been identified in the blood of infected animals, including subclinically infected animals (Parker and White, 1992). Since the organism can be isolated from the blood of infected animals, it is likely that bovine serum can harbour *B. burgdorferi.*

The likelihood of entry of *B. burgdorferi* in bovine serum from the United States is assessed as low to moderate and from Australia is assessed as negligible.

19.2.2. Exposure assessment

Borrelia burgdorferi could be present as a contaminant in bovine serum imported from the United States. The contaminated bovine serum used in biological end products such as vaccines could potentially harbour *B. burgdorferi.* Parenteral administration of contaminated vaccines is the most likely pathway for transmission to animals who could then develop the disease. Vaccination is generally implemented as a herd management tool, and a large number of animals could get exposed through contaminated vaccine.

Lyme disease is a vector-borne disease, and the infection is transmitted predominantly by the ixodid ticks *Ixodes ricinus, Ixodes persulcatus, Ixodes scapularis* and *Ixodes pacificus* (Constable *et al*., 2017). In New Zealand, none of the ixodid tick species that are capable of transmitting the disease have been reported. Other species of ixodid ticks are present in New Zealand but have never been shown to be competent vectors for Lyme disease. As ticks with vector capability are absent from New Zealand, the risk of establishment and/or spread is negligible.

There are no references documenting infection being transmitted between animals by direct contact or through germplasm. Therefore, exposure may only be through the administration of contaminated vaccines, and further establishment and/or spread to other animals in New Zealand is unlikely in the absence of any competent vectors.

The overall likelihood of exposure, establishment and/or spread of *B. burgdorferi* via bovine serum considering the factors discussed above is assessed as very low.

19.2.3. Consequence assessment

Lyme disease is not an OIE-listed disease. Significant international trade restrictions are unlikely to be imposed, and therefore, associated economic losses are expected to be minimal. If Lyme disease is introduced to New Zealand, a number of animal species such as cattle, sheep, dogs and horses could be affected. Decreased milk production and abortion in cattle may lead to production losses to the industry. Considering the very low likelihood of exposure of the bacteria, the economic and social impacts of the disease in both animals and humans, production losses to multiple livestock industries and international market losses will be very low.

Even if the disease is introduced into New Zealand through contaminated bovine serum, the transmission will be limited to the animals inoculated with contaminated end products. Consequences due to further transmission and spread will be negligible because there is no competent vector for the pathogen in New Zealand.

Lyme disease is zoonotic, and the infection can spread to the human population from infected animals. The disease is transmitted through ixodid ticks, and the prevalence of competent vector is a critical factor for the transmission of the disease. Currently in New Zealand, Lyme disease is reported occasionally in travellers returning from endemic countries. Based on the above factors, the consequence for human health is negligible.

Wild animals and birds only act as reservoir hosts, and there is no evidence of any fatal infection among wild animals and birds. Therefore, the consequences for the New Zealand environment are negligible.

The overall consequences from entry, exposure, establishment and/or spread of *B. burgdorferi* are assessed as very low.

19.2.4. Risk estimation

The likelihood of entry of *B. burgdorferi* in bovine serum from Australia is negligible, and therefore, the risk estimate is negligible. Risk management measures are not required for *B. burgdorferi* in bovine serum imported from Australia.

The likelihood of entry of *B. burgdorferi* in bovine serum from the United States is assessed as low to moderate, the likelihood of exposure, establishment and/or spread are assessed as very low, and the consequences of *B. burgdorferi* are assessed as very low. The overall risk is estimated as very low.

Since entry, exposure, and consequences are non-negligible for bovine serum imported from the United States, *B. burgdorferi* is a risk in the commodity. Therefore, risk management measures are justified.

19.3. RISK MANAGEMENT

The following points were considered when describing options for managing the risks:

- Lyme disease is not an OIE-listed disease.
- Lyme disease is absent from New Zealand and Australia but present in the United States.
- Lyme disease is a zoonotic disease.
- Lyme disease affects multiple species of animals.
- *Borrelia burgdorferi* can be isolated from the blood of infected animals.
- *Borrelia burgdorferi* is 10 to 30 μm in length and 0.2 to 0.3 μm in diameter.
- Subclinical infections can occur in infected animals.
- Ixodid ticks transmit the disease, and the prevalence of the vector is an essential factor in transmission.
- The species of *Ixodes* capable of transmitting the disease are absent from New Zealand.

19.3.1. Options

The following options or a combination of these options can be considered to manage the risk associated with *B. burgdorferi*.

1. Bovine serum could be imported from countries free from *B. burgdorferi*.

2. The animals used for blood collection showed no clinical signs of the infection on the day of blood collection, and no other evidence of the infection were reported in the animal or herd during the last three months.

    a. For abattoir-sourced bovine serum, the serum was derived from animals kept since birth or for the last three months in a country or zone or herd free from the disease. The animals passed antemortem examination, were declared fit for human consumption and were processed in premises under the oversight of the competent authority.

    b. For donor-animal-derived bovine serum, the serum was derived from herds that were under veterinary supervision, and the donors were disease-free since birth or for the last three months, or the donor animals were tested with an MPI-approved/recommended test, with negative results, at the time of blood collection.

3. Bovine serum could be either:

    a. tested with an MPI-approved/recommended test, with negative results; OR

    b. subjected to gamma irradiation at a minimum dose of 35 kGy; OR

    c. subjected to sterile filtration with a membrane filter pore size of 0.2 μm or less.

20. *Brucella abortus, B. melitensis* and *B. suis*

20.1. TECHNICAL REVIEW

20.1.1. Aetiology

Family: *Brucellaceae*
Genus: *Brucella*
Species: *Brucella abortus, B. melitensis, B. suis*

Brucella abortus is a gram-negative coccobacillus, 0.6 μm to 1.5 μm in length and 0.5 to 0.7 μm in diameter (Godfroid *et al.*, 2004). *Brucella melitensis* and *B. suis* are morphologically indistinguishable from *B. abortus* (Godfroid *et al.*, 2004).

Brucellosis in cattle is usually caused by *B. abortus*, less frequently by *B. melitensis*, and occasionally by *B. suis* (OIE Terrestrial Manual, 2018h). For this risk analysis, the term 'bovine brucellosis' refers to infection of cattle with *Brucella abortus, B. melitensis* or *B. suis.*

20.1.2. OIE List

Brucellosis, caused by *Brucella abortus, B. melitensis* or *B. suis*, is an OIE-listed disease (OIE, 2020).

20.1.3. New Zealand status

New Zealand has been free from bovine brucellosis since 1989 (Hellstrom, 1991; MacDiarmid, 1994; WAHIS, 2018). According to the OIE, brucellosis due to *B. abortus* was last reported in New Zealand in 1989. *B. melitensis* and *B. suis* have never been reported in New Zealand (WAHIS, 2018). Brucellosis, caused by *B. abortus, B. melitensis*

or *B. suis,* is listed as a disease absent from New Zealand (MPI, 2020) and all three organisms are listed as notifiable organisms under the Biosecurity (Notifiable Organisms) Order 2016 (MPI, 2016a).

20.1.4. Zoonotic potential

Brucellosis is a zoonotic disease. *Brucella abortus, B. melitensis* and *B. suis* are highly pathogenic to humans (OIE Terrestrial Manual, 2018h). Human brucellosis is also known as 'undulant fever'. In humans, brucellosis is often an occupational disease in people who have direct contact with infected animals. Ingestion of unpasteurised milk can be a source of infection for humans who have no direct contact with infected animals (Godfroid, Bosman *et al*., 2004).

20.1.5. Epidemiology

Host range

Brucella abortus predominantly infects cattle and other ruminants and causes severe disease in humans. Other host species infected include buffaloes, yaks, elk, bison, gayal, sheep, goats, horses, pigs, camels, dogs, opossums and humans (DAWR, 2017; OIE Terrestrial Manual, 2018h; Spickler, 2018b).

Brucella melitensis mainly infects sheep and goats. However, *B. melitensis* infection has been encountered in cattle and camels that are in contact with infected sheep and goats (Godfroid, Garin-Bastuji *et al*., 2004; OIE Terrestrial Manual, 2018h). Other host species reported to be infected include yaks, water buffaloes, alpacas, dogs, horses, pigs and humans. Among wildlife, it is reported in chamois, ibexes, wild goats, impalas and antelopes (Godfroid *et al*., 2004; Spickler, 2018a).

Brucella suis infects pigs, both domestic and wild (OIE Terrestrial Manual, 2018h). *B. suis* has been isolated from cattle, sheep, goats, horses, dogs, opossums and humans. Among wildlife, infected hosts include reindeer, caribou, bison, foxes and wolves (Godfroid, Thoen *et al*., 2004; Spickler, 2018c). In cattle, *B. suis* causes a chronic infection of the mammary gland. Brucellosis due to *B. suis* in cattle has not been reported to cause abortion or spread to other animals (Godfroid *et al*., 2004; OIE Terrestrial Manual, 2018h).

Geographical distribution

Bovine brucellosis occurs worldwide except in those countries where the disease has been eradicated. Canada, Japan and New Zealand, as well as several countries in western and northern Europe, are believed to be free from the disease (OIE Technical Disease Card, 2018).

Bovine brucellosis is a notifiable disease in Australia (DAWR, 2015), which has been free from *B. abortus* since 1989 (DAWR, 2017; WAHIS, 2018). *Brucella melitensis* has never been reported in Australia (WAHIS, 2018). Although *B. suis* has been reported to be absent from domestic animals in Australia since December 2010, it is reported to be present in wildlife (WAHIS, 2018).

Brucellosis due to *B. abortus* in domestic animals has been absent from the United States since November 2018 (WAHIS, 2019a). Bovine brucellosis caused by *B. abortus* is present in the United States in the wild and is limited to free-ranging bison (*Bison bison*) and wapiti (*Cervus canadensis*) in the Greater Yellowstone National Park area (WAHIS, 2018).

Brucellosis caused by *B. melitensis* was last reported in the United States in 1999. Brucellosis due to *B. suis* in the United States is present in the wild but is limited to certain geographic zones among the domestic herds (WAHIS, 2018).

Since *B. melitensis* has never been reported in either Australia or the United States, it is not a hazard and is not assessed further in this risk analysis.

Pathogenesis

Brucellosis is a highly contagious disease that can cause severe production losses to the livestock industry. The incubation period for brucellosis is variable from two weeks to a year or even longer (USDA APHIS, 2010) and depends on the animal's age, sex, sexual maturity and stage of pregnancy (Godfroid *et al*., 2004). The most prolonged recorded incubation period in a cow is nine years (Godfroid *et al*., 2004). Infections in calves infected in utero or at birth can remain latent for 18 months or more before the calves show clinical signs. During the latent period, infected heifers can remain seronegative (Godfroid *et al*., 2004). Infected bulls can shed the bacteria in their semen, seminal fluid and urine (Godfroid *et al*., 2004).

Duration of the infection is also variable; some infected animals can be free of the disease within months, and others may develop chronic disease (FAO, 2003; Godfroid *et al*., 2004). Entry and multiplication of *Brucella* in infected animals is followed by bacteraemia, which may occur periodically and transiently (Olsen and Tatum, 2010). Bacteraemia can last for several weeks or months in chronically infected animals (DAFF, 2016). During bacteraemia, organisms are carried inside neutrophils and macrophages or transported free in plasma to various organs (Godfroid *et al*., 2004).

Brucellosis is usually subclinical in young animals and non-pregnant heifers. The clinical signs in pregnant adult cows include abortion, stillbirth, the birth of weak offspring, retained placenta, reduced milk yield and, rarely, arthritis (Godfroid *et al*., 2004; OIE Terrestrial Manual, 2018h). The abortion rate in cattle varies from 30–80% in infected herds (Godfroid *et al*., 2004). In bulls, orchitis, epididymitis and seminal vesiculitis occur (Godfroid *et al*., 2004). Mortality is rare, except in the fetus or newborn (Spickler, 2018b). Hygromas and non-suppurative arthritis are also reported in infected cattle (Godfroid *et al*., 2004; OIE Terrestrial Manual, 2018h). Brucellosis due to *B. suis* has not been reported to cause abortion in cattle (Godfroid *et al*., 2004).

Brucella is a zoonotic organism that is highly pathogenic to humans and causes a severely debilitating disease (OIE Terrestrial Manual, 2018h). Humans can contract the disease by drinking unpasteurised milk or having contact with infected animals.

Since infection with *B. suis* in cattle only causes a chronic infection of the mammary gland and has never been reported to cause abortion or spread to other animals (Godfroid *et al*.,

2004; OIE Terrestrial Manual, 2018h), *B. suis* is not a hazard in the commodity and is not assessed further in this risk analysis.

Transmission

Transmission is by direct contact with fluids and tissues from infected animals (Olsen and Tatum, 2010). However, transmission through ingestion of contaminated feed and water in cattle have also been reported (Aparicio, 2013; Godfroid *et al*., 2004). Vertical transmission also occurs in utero (Godfroid *et al*., 2004) and through the shedding of *B. abortus* in colostrum and milk (Olsen and Tatum, 2010). Infected semen can also act as a source for the transmission of the disease in animals (Aparicio, 2013; Godfroid *et al*., 2004). In humans, transmission occurs through contamination of mucous membranes and abraded skin, inhalation of contaminated aerosol or ingestion of contaminated unpasteurised milk (Godfroid *et al*., 2004).

A contaminated environment and contaminated equipment used for artificial insemination and milking can also transmit the disease to animals (Godfroid *et al*., 2004).

Diagnosis

Diagnosis is by bacteriological and serological methods. Bacteriological diagnosis involves isolating and identifying the causative organism through microscopic examination (staining methods), culture and typing, and polymerase chain reaction (PCR) methods (Nielsen, 2002; OIE Terrestrial Manual, 2018h, Spickler, 2018b).

Commonly used serological tests are complement fixation tests (CFTs), indirect or competitive ELISAs, fluorescence polarisation assay (FPA) and buffered Brucella antigen tests (rose Bengal test and buffered plate agglutination test) (OIE Terrestrial Manual, 2018h). Both *B. abortus* and *B. suis* could elicit the same serological response to brucellosis serological tests, requiring bacteriological isolation to differentiate *B. abortus* and *B. suis* infection (Olsen and Tatum, 2010).

The definitive diagnosis of clinical infection can be achieved by using an appropriate serological test initially and confirming by isolation and identification of the agent (FAO, 2003).

Treatment, control and prevention

Because of the persistence of the bacteria in lymph nodes and other tissues, no effective treatment is available to completely cure bovine brucellosis infected cattle (Godfroid *et al*., 2004) (Spickler, 2018b). None of the currently available chemical therapeutic agents are proven to be cost-effective in treating infected herds.

Vaccination could reduce the prevalence of bovine brucellosis (DAWR, 2017) and help control the clinical signs (Spickler, 2018b). The *B. abortus* strain 19 vaccine and strain RB51 vaccine are commonly used vaccines. The S19 vaccine induces post-vaccinal antibodies that are detected in serological tests and interfere with diagnostic test results (Godfroid *et al*., 2004). Vaccine strains and post-vaccinal antibodies can be identified using specific PCRs or their growth characteristics in culture (OIE Terrestrial Manual, 2018h). RB51 is a rough attenuated strain, and vaccination does not interfere with serological tests (Spickler, 2018b).

20.2. RISK ASSESSMENT

20.2.1. Entry assessment

B. abortus affects a wide range of ruminants, primarily infecting cattle. Bovine brucellosis affects animals of all ages. It is a chronic disease, and the infected animals can be lifelong carriers of the organism. Bacteraemia occurs periodically and transiently (Olsen and Tatum, 2010), or sometimes last for several weeks or months in chronically infected animals (DAFF, 2016). During bacteraemia, *B abortus* can be transported free in plasma to various organs (DAWR, 2017; Godfroid *et al*., 2004). Since the organism is isolated from plasma during bacteraemia, it is likely that bovine serum can harbour *Brucella*.

Australia is free from brucellosis due to *B. abortus* since 1989, both in domestic and wild animals.

In the United States, *B. abortus* is present in certain geographical zones in wildlife (WAHIS, 2018). The natural transmission of brucellosis from wild elk to cattle in the United States has been shown and this transmission has also been proven experimentally (O'Brien *et al*., 2017). There are active surveillance and eradication programmes in the United States (USDA APHIS, 2010).

The likelihood of entry of bovine brucellosis in bovine serum from Australia is assessed as negligible and the likelihood of entry from the United States is assessed as low.

20.2.2. Exposure assessment

Brucella could be a contaminant present in bovine serum imported from the United States. If unprocessed contaminated bovine serum is used in end products such as vaccines, an infection could occur in the recipients. However, due to the lack of published literature, there is uncertainty around the infectious dose or proof of infection post-vaccination. Parenteral administration of contaminated vaccines is the most likely pathway for transmission through vaccines. Vaccination is generally implemented as a herd management tool, and a large number of animals could get exposed through contaminated vaccine.

Brucellosis can be transmitted by direct contact with contaminated fluids, tissues, cultures in the laboratory and other materials from infected animals. Inhalation of contaminated aerosols and ingestion of contaminated materials are also transmission modes.

If *Brucella* entered New Zealand through unprocessed bovine serum, it is unlikely that live animals would be directly exposed to the serum. However, animals infected using contaminated end products such as vaccines can transmit the disease to a wide range of ruminants and humans in New Zealand.

Brucellosis is a zoonotic disease, and people handling contaminated bovine serum could also get infected. The introduction of brucellosis to New Zealand could cause infection in the human population.

There are no reports of the infection being transmitted between animals through vectors or germplasm; therefore, these are not possible exposure pathways.

Considering the factors mentioned above, the overall likelihood of exposure, establishment and/or spread of bovine brucellosis via contaminated bovine serum is assessed as moderate.

20.2.3. Consequence assessment

Brucellosis is an OIE-listed disease, and trade restrictions related to brucellosis can be imposed, which would have moderate impacts for New Zealand.

B. abortus predominantly infects cattle and other ruminants. Brucellosis is a highly contagious disease which can cause severe production losses to the livestock industry due to reproductive failure and abortion. The abortion rate in cattle varies from 30–80% in infected herds (Godfroid *et al*., 2004). Considering the large-scale livestock farming industry and its contribution to the New Zealand economy, the consequences due to economic losses from animal infection, disease and production loss to New Zealand in the event of establishment of brucellosis are high.

New Zealand has been free from brucellosis since 1989, and reintroduction of this disease could have significant direct and indirect consequences. Brucellosis can affect multiple species of animals, including wild animals. This could lead to the implementation of large-scale surveillance control and eradication programmes. Loss of international market access for New Zealand products, severe production losses in multiple livestock industries and human disease would be among the consequences of *Brucella* entering New Zealand.

As brucellosis is zoonotic, the introduction of brucellosis to New Zealand could cause infection in the human population. The consequences of brucellosis for human health are high.

B. abortus infection is described in other species of animals including sheep, goats, horses, pigs, dogs and deer (OIE Terrestrial Manual, 2018h; Spickler, 2018b). Infection in sheep and goats is usually sporadic (OIE Terrestrial Manual, 2018h), and there is no evidence of severe infection in other wild animals. Therefore, the consequences for the New Zealand environment are moderate.

The overall consequences of bovine brucellosis as a result of entry, exposure, establishment and/or spread are assessed as high.

20.2.4. Risk estimation

The likelihood of entry of *Brucella* in bovine serum from Australia is negligible, and from the United States is assessed as low. The likelihoods of exposure, establishment and/or spread for bovine serum imported from the United States are assessed as moderate, and the consequences of *Brucella* are assessed as high. Therefore, the overall risk of *Brucella* in bovine serum from the United States is estimated as moderate.

Since the entry, exposure, and consequence assessments are non-negligible for bovine serum imported from the United States, *Brucella* is a risk in the commodity. Therefore, risk management measures are justified for bovine serum imported from the United States.

20.3. RISK MANAGEMENT

The following points were considered when describing options for managing the risks:

- Bovine brucellosis is an OIE-listed disease.
- Bovine brucellosis is absent from New Zealand.
- Bovine brucellosis could cause significant impacts to the cattle industry.
- Bovine brucellosis is a zoonotic disease.
- Bovine brucellosis affects multiple species of animals, including wild animals.
- In infected animals, bacteraemia has been reported to last for several months.
- *Brucella* spp. are 0.6 μm to 1.5 μm in length and 0.5 to 0.7 μm in diameter.
- Heifers with latent infections can remain seronegative.
- The incubation period for brucellosis can be prolonged, and long-term carriers are known to occur.
- There is no effective treatment to cure bovine brucellosis completely.

20.3.1. Options

The following options individually or in combination can be considered to manage the risk associated with bovine brucellosis. The options noted below are based on the OIE recommendations for infection with *Brucella* spp. (OIE Terrestrial Code, 2019c).

1. Bovine serum could be imported from countries free from bovine brucellosis as per the relevant OIE Code chapter.

2. The animals used for blood collection are from a country or zone or herd free from infection with *Brucella* spp. in accordance with the requirements of the OIE Code, and animals showed no clinical sign of infection with *Brucella* spp. on the day of collection.

    a. For abattoir-sourced bovine serum, the serum was derived from animals that were kept in a country or zone or herd free from infection with *Brucella* spp. in accordance with the requirements of the OIE Code. The animals passed ante-mortem examination, were declared fit for human consumption and were processed in premises under the oversight of the competent authority.

    b. For donor-animal-derived bovine serum, the animals were under veterinary supervision and came from a disease-free country or zone or herd in accordance with the requirements of the OIE Code, or the donor animals were tested with an MPI-approved/recommended test, with negative results, at the time of blood collection.

3. Bovine serum could be either:

    a. tested with an MPI-approved/recommended test, with negative results; OR

    b. subjected to gamma irradiation at a minimum dose of 35 kGy; OR

    c. subjected to sterile filtration with a membrane filter pore size of 0.2 μm or less.

21. *Burkholderia pseudomallei*

21.1. TECHNICAL REVIEW

21.1.1. Aetiology

Family: *Burkholderiaceae*
Genus: *Burkholderia*
Species: *Burkholderia pseudomallei*

Burkholderia pseudomallei causes melioidosis, which is also known as pseudoglanders and Whitmore's disease. The organism was formerly known as *Pseudomonas pseudomallei* (Van Der Lugt, 2004).

Burkholderia pseudomallei is a gram-negative, non-spore forming rod, which is 0.8 x 1.5 μm in size (Sprague and Neubauer, 2004).

21.1.2. OIE List

Melioidosis is not an OIE-listed disease.

21.1.3. New Zealand status

Burkholderia pseudomallei is not present in New Zealand. *Burkholderia pseudomallei* is not listed as a notifiable organism under the Biosecurity (Notifiable Organisms) Order 2016 (MPI, 2016a).

21.1.4. Zoonotic potential

Zoonotic transmission of melioidosis from animals to humans can occur through contact with contaminated or potentially infected animals and materials (OIE, 2019c, Rush and Thomas, 2012). Melioidosis has zoonotic potential (Choy, 2019; OIE, 2019c), but human disease has rarely been documented (Sprague and Neubauer, 2004).

21.1.5. Epidemiology

Host range

A wide range of terrestrial and aquatic mammals, birds, reptiles and fish have been shown to be susceptible to melioidosis (Choy *et al*., 2000; Spickler, 2016a). Goats, sheep and pigs are the most commonly infected species (Choy, 2019; Spickler, 2016a). Other animals that can be infected include cattle, buffaloes, deer, horses, mules, camels, alpacas, dogs, cats, monkeys, crocodiles and aquatic animals (Rush and Thomas, 2012). Although cattle are considered resistant to the disease (Choy *et al*., 2000), sporadic and fatal outbreaks have been reported (Rush and Thomas, 2012; Sprague and Neubauer, 2004).

Geographical distribution

Melioidosis occurs predominantly in Southeast Asia and northern Australia (Limmathurotsakul *et al*., 2016; Sprague and Neubauer, 2004). Other endemic regions include Papua New Guinea, India, southern China, Hong Kong and Taiwan (Currie *et al*., 2008). The wet season in tropical Australia brings an increase in the reported cases of the disease (Choy *et al*., 2000). Choy and others (2000) reported that even though melioidosis

is present in cattle in Australia, the prevalence is low compared to the prevalence in other animals such as goats, sheep and pigs.

Melioidosis is not present in the United States, but occasional human cases have been reported in travellers returning from endemic countries (Beig *et al.*, 2017; CDC, 2006; Corkill and Cornere, 1987; Singh and Mahmood, 2017).

Pathogenesis

Clinical melioidosis in animals is mostly seen in sheep, goats and pigs (Choy, 2019). Melioidosis is rare in cattle, and cases are often chronic and progressive (Sprague and Neubauer, 2004; Van Der Lugt, 2004).

Melioidosis in animals can be subclinical, and the early stages of the disease may have no notable clinical signs. The incubation period can vary from days to years (Choy, 2019; Rush and Thomas, 2012). The clinical signs become apparent only when the bacteria disseminate to various organs. Clinical signs vary between species, and subclinical infection is common in all species of animals (Choy *et al*., 2000; Rush and Thomas, 2012). In cattle, central nervous system disease with staggering gait and respiratory signs with panting and pneumonia are common (Choy, 2019; Sprague and Neubauer, 2004). Young animals usually show acute infection with septicaemia and high mortality rates (Choy *et al*., 2000; Sprague and Neubauer, 2004). In adult animals, initial septicaemia or bacteraemia can be followed by subsequent localisation of the organism in various organs (Van Der Lugt, 2004). Infections may involve a latency period where the organism can remain dormant (Choy, 2019).

Transmission

The primary mode of transmission of melioidosis in both humans and animals is from the contaminated environment rather than from animals (Rush and Thomas, 2012). Common routes of infection in animals include percutaneous inoculation, contamination of wounds, ingestion of contaminated soil, water, feed and carcasses and inhalation of contaminated air or dust particles (Choy *et al*., 2000; Currie, 2015; Sprague and Neubauer, 2004).

Experimental transmission by arthropod vectors, (rat flea, *Xenopsylla cheopis* and mosquito, *Aedes aegypti*) has been described (Rush and Thomas, 2012; Sprague and Neubauer, 2004), but there is no evidence for transmission by these vectors under natural conditions.

Zoonotic transmission rarely occurs (Sprague and Neubauer, 2004).

Diagnosis

Definitive diagnosis is achieved by isolation and identification of the pathogen. The organism can be isolated from pus, blood, urine, milk, sputum and abscess material using culture or staining methods (Rush and Thomas, 2012; Sprague and Neubauer, 2004).

Molecular diagnostic methods such as polymerase chain reaction (PCR) can be used to detect and identify *B. pseudomallei* (OIE, 2019c). The organism can be cultured in routine diagnostic media to identify it (Choy, 2019). There are no specific serological tests validated or commercially available for animals (OIE, 2019c; Rush and Thomas, 2012;

Sprague and Neubauer, 2004). Complement fixation tests (CFT) and indirect haemagglutination (IHA) can be used to confirm the disease and can also be used as herd surveillance tools (Rush and Thomas, 2012).

Treatment, control and prevention

Treating animals with melioidosis is expensive and requires long-term antibiotic regimes (Choy *et al*., 2000; Rush and Thomas, 2012). Prevention and control measures, especially in herds, include removing animals from contaminated sources and soil, culling infected animals, preventing surface water accumulation and providing clean, safe, chlorinated drinking water (Choy *et al*., 2000; Rush and Thomas, 2012). As the most important transmission method for melioidosis is through a contaminated environment, the best control measure is to minimise environmental contamination (Choy, 2019). Disinfection of the premises is also an effective control measure (Van Der Lugt, 2004).

Pasteurisation of milk and condemnation of infected and suspected carcasses in abattoirs can prevent the transmission of melioidosis from animals to humans (Choy *et al*., 2000; Sprague and Neubauer, 2004).

No vaccines are currently available for human or animal melioidosis (OIE, 2019c).

21.2. RISK ASSESSMENT

21.2.1. Entry assessment

Although melioidosis is considered as a rare disease in cattle, sporadic and fatal outbreaks have been reported (Choy *et al*., 2000).

This pathogen is prevalent in Australia, especially northern Australia, and there has been an increase in the occurrence of the disease in tropical regions. It has also been reported in sheep, goats, pigs in Australia. The prevalence of melioidosis in cattle is low compared to the prevalence in other animals in Australia (Choy *et al*., 2000). Melioidosis is not present in the United States.

Melioidosis has a variable incubation period that could last for years. Infected animals usually develop septicaemia or bacteraemia but could remain subclinical in the majority of cases. In infected animals, *B. pseudomallei* can be isolated from the blood, and so it is likely that bovine serum from infected animals can be contaminated with the organism.

Melioidosis is not known to occur in the United States, and so the likelihood of entry of *B. pseudomallei* in bovine serum sourced from the USA is negligible.

Given the limited regional and seasonal distribution of the disease in Australia, the likelihood of entry of *B. pseudomallei* in bovine serum from Australia is assessed as low.

21.2.2. Exposure assessment

B. pseudomallei could be present as a contaminant in bovine serum imported from Australia. If contaminated bovine serum is used in end products such as vaccines, it could infect animals. Parenteral administration of these contaminated vaccines is the most likely pathway for transmission. Animals inoculated with the end products could potentially develop the disease. Animals infected from contaminated vaccines could also act as a

source of contamination to the environment. Vaccination is generally implemented as a herd management tool, and a large number of animals could get exposed.

Melioidosis is mainly transmitted through the contaminated environment, water and soil. It is highly unlikely that the environment, especially soil and water, would be directly exposed to imported serum.

Melioidosis is a zoonotic disease, and transmission from animals to humans can occur through contact with contaminated or infected blood and body fluids. The introduction of melioidosis to New Zealand could result in infections in the human population.

Vector-borne transmission has been proven only in experimental conditions (Rush and Thomas, 2012). There are no references of the infection being transmitted between animals through germplasm. These routes are not considered possible exposure pathways.

The overall likelihoods of exposure, establishment and/or spread of *B. pseudomallei* via bovine serum based on the factors discussed above are assessed as low.

21.2.3. Consequence assessment

Melioidosis is not an OIE-listed disease and is widespread in tropical and subtropical regions of the world. Any significant international trade restrictions are unlikely in the event of the introduction of the disease into New Zealand. Therefore, trade consequences will be negligible to very low.

Melioidosis infection affects a wide range of terrestrial and aquatic mammals, birds, reptiles and fish. While animals of all ages are susceptible, young animals are reported to have a higher mortality rate. There could be a direct consequence of the entry and subsequent exposure of melioidosis in the form of parenteral administration of contaminated vaccines to animals in New Zealand. Animals exposed to contaminated bovine serum could potentially be infected, leading to economic losses to the farming sector. Spillover to wild animal species would be another severe implication. Should the pathogen enter New Zealand, the overall consequence could be significant, as several species may be involved and large-scale surveillance, control and eradication programmes will need to be implemented.

The organism persists in soil, and contaminated soil could be a major transmission pathway for animal and human infections. Considering the controlled handling of imported blood products in the laboratory environment, it is unlikely that imported bovine serum contaminated with the pathogen would directly contaminate the New Zealand environment. Animals infected from contaminated vaccines could contaminate the environment, and thus, it is possible that the wildlife in New Zealand could be affected.

Melioidosis is a zoonotic disease, and so the introduction of melioidosis to New Zealand could cause infection in the human population. Transmission of melioidosis from animals to humans can occur through contact with contaminated or potentially infected animals and materials. Transmission of the pathogen to people from animals infected from contaminated end products such as vaccines cannot be completely ruled out. Therefore, the consequences for human health are low.

The overall consequences of *B. pseudomallei* as a result of entry, exposure, establishment and/or spread are assessed as low.

21.2.4. Risk estimation

The likelihood of entry of *B. pseudomallei* in bovine serum from the United States is negligible, and therefore, the risk estimate is negligible. Risk management measures are not required for *B. pseudomallei* in bovine serum imported from the United States.

The likelihood of entry of *B. pseudomallei* in bovine serum from Australia is assessed as low, the likelihoods of exposure, establishment and/or spread are assessed as low, and the consequences of *B. pseudomallei* are assessed as low. Therefore, the overall risk is estimated as low.

Since the entry, exposure, and consequence assessments are non-negligible for bovine serum imported from Australia, *B. pseudomallei* is a risk in the commodity. Therefore, risk management measures are justified for bovine serum imported from Australia.

21.3. RISK MANAGEMENT

The following points were considered when describing options for managing the risks:

- Melioidosis is not an OIE-listed disease.
- Melioidosis is absent from New Zealand and the United States.
- Melioidosis is present in Australia.
- Melioidosis is a zoonotic disease.
- Melioidosis affects multiple species of animals, including wild animals.
- *B. pseudomallei* is 0.8 x 1.5 μm in size.
- In infected animals, bacteraemia has been reported.
- *B. pseudomallei* can remain dormant in infected animals.
- The incubation period for melioidosis can be prolonged.
- Treatment for melioidosis is expensive and requires long-term antibiotic regimes.

21.3.1. Options

The following options or a combination of these options can be considered to manage the risk associated with *B. pseudomallei* in bovine serum.

1. Bovine serum could be imported from countries free from *B. pseudomallei*.
2. The animals used for blood collection showed no clinical signs of the infection on the day of blood collection.
    a. For abattoir-sourced bovine serum, the serum was derived from animals originated from premises with no cases of melioidosis reported in any species for the preceding three months. The animals passed antemortem examination, were declared fit for human consumption and were processed in premises under the oversight of the competent authority.
    b. For donor-animal-derived bovine serum, the serum was derived from herds that were under veterinary supervision, with no cases of melioidosis reported for the preceding three months, and the donors were disease-free since birth or for the

last three months, or the donor was tested with an MPI-approved/recommended test, with negative results, at the time of blood collection.

3. Bovine serum could be either:

    a. tested with an MPI-approved/recommended test, with negative results; OR

    b. subjected to gamma irradiation at a minimum dose of 35 kGy; OR

    c. subjected to sterile filtration with a membrane filter pore size of 0.2 μm or less.

22. *Chlamydia abortus*

22.1. TECHNICAL REVIEW

22.1.1. Aetiology

Family: *Chlamydiaceae*
Genus: *Chlamydia*
Species: *Chlamydia abortus*

Infectious chlamydial elementary bodies are approximately 0.3 μm in diameter (Campbell *et al*., 1998, Longbottom and Coulter, 2003).

22.1.2. OIE List

Enzootic abortion of ewes (ovine chlamydiosis) caused by *Chlamydia abortus* is an OIE-listed disease (OIE, 2020).

22.1.3. New Zealand status

Chlamydia abortus is listed as a notifiable organism on the Biosecurity (Notifiable Organisms) Order 2016 under "Organisms primarily affecting sheep and goats".

Enzootic abortions in sheep and goats caused by *C. abortus* have never been reported in New Zealand (WAHIS, 2019c).

22.1.4. Zoonotic potential

Chlamydiosis is a zoonotic disease. People may become infected from contact with abortion or parturition material. Exposure has also been reported from laboratory cultures of the organism. Symptoms of infection range from subclinical to acute flu-like manifestation (OIE Terrestrial Manual, 2018i).

22.1.5. Epidemiology

Host range

Chlamydia abortus causes enzootic abortions in sheep and goats. These species are the primary hosts for this organism. It has also been reported in both wild and domestic mammal species including cattle, pigs, horses, deer, yaks and llamas, as well as reptiles and amphibians (Longbottom and Coulter, 2003, OIE Terrestrial Manual, 2018i).

Geographical distribution

The disease is reported to occur in most sheep-rearing countries, with the exclusion of New Zealand and Australia. It is a significant cause of lamb losses in Europe, with the disease also occurring in Africa and North America (Longbottom and Coulter, 2003).

In the United States, enzootic abortions in sheep and goats are limited to certain zones (WAHIS, 2019c).

Australia reported an absence of enzootic abortions in sheep and goats via general surveillance. The OIE also reports that enzootic abortions in sheep and goats caused by *C. abortus* are absent from Australia. The last occurrence of the disease there is unknown (WAHIS, 2019c).

Prevalence data and information on *C. abortus* in cattle in the United States are limited. Current literature places an emphasis on the disease in sheep rather than cattle. For this reason, the prevalence of the disease in cattle in these countries may not be significant enough to warrant investigations. Furthermore, various sources report the absence of *C. abortus* in abortion episodes in Australia (McCauley *et al*., 2010; WAHIS, 2019c). There was, however, one report of isolation of *Chlamydia psittaci* as a cause of sheep abortions 30 years ago (Seaman, 1985). Due to the historical taxonomy, it is uncertain whether this organism was in fact *C. abortus* or *C. psittaci.*

Pathogenesis

Oral infection is the most common route of infection. In sheep, after entering the host, organisms localise in the epithelial cells of the gastrointestinal tract and spread via the blood and lymph vessels to the mesenteric lymph nodes and liver. Following this, infection can be established in other organs or tissues. Systemic infection causes a chlamydaemia that may spread to the placenta, resulting in placental damage. The extent of the damage determines whether offspring are born healthy, weak or stillborn or are aborted (Andersen, 2004).

Jee and others (2004) reported early infection of calves with *C. abortus,* likely caused by environmental sources and infected dams through close contact or milk. The study also suggests that *C. abortus* infections in cattle may not only present as sporadic, severe disease but also as a low-level, subclinical or subtle condition, resulting in impacts on herd health, milk production and fertility.

In cattle, *C. abortus* causes abortions, stillbirths and the birth of weak calves. Abortions, which most often occur during the last trimester, are normally sporadic and may affect 20% of the herd. Affected cows show little evidence of disease. Abortions are caused by placentitis. Calves that are born weak remain unthrifty (Andersen, 2004).

Most chlamydial species have been reported to produce persistent infections that last for months or years (Andersen, 2004; Domeika *et al*., 1994) and intermittent shedding.

Persistent infection of male accessory glands and the presence of *C. psittaci* in semen are also described (Andersen, 2004). Bulls may remain carriers of *C. psittaci* for at least 18 months (Domeika *et al*., 1994).

Ewes that have aborted remain long-term intestinal carriers (Aitken, 1983) and may also be chronically infected in their reproductive tracts (Andersen, 2004). It is likely that a similar scenario takes place in cattle.

Transmission

Chlamydiae have been found in all body secretions. Routes of transmission include inhalation, ingestion and via mucous membranes. *Chlamydia abortus* has been found in semen (Teankum *et al*., 2007) and the milk of ruminants (Jee *et al*., 2004). Venereal transmission has also been suggested (Andersen, 2004).

Large numbers of *C. abortus* organisms are excreted with abortion material, during lambing, in discharged fluids, in faeces, in the placenta and on the coats of newborns. This is considered the primary source of contamination for the environment and oral transmission to other animals and humans (Longbottom and Coulter, 2003).

Diagnosis

Agent identification diagnostic tests are useful for the confirmation of clinical cases, prevalence investigations and surveillance. These test methods include stained smears, bacterial isolation, immunohistochemistry, and polymerase chain reaction (PCR). PCR is considered more reliable than other methods and is recommended by the OIE for confirming clinical cases (Andersen, 2004; OIE Terrestrial Manual, 2018i).

For detection of the immune response, serological tests such as enzyme-linked immunosorbent assay (ELISA) and complement fixation test (CFT) are available (Andersen, 2004; Longbottom *et al*., 2002; OIE Terrestrial Manual, 2018i). ELISA is the OIE-recommended test for identifying population freedom from infection, determining eradication policies, performing prevalence of infection, surveillance and assessing immune status in individuals or populations post-vaccination.

Treatment, control and prevention

Chlamydiae are considered ubiquitous in livestock. Antibiotic therapy and vaccination are the only effective means of control (Andersen, 2004).

Currently, inactivated and live vaccines are commercially available. These vaccines are administered to prevent abortions and reduce excretion of the organism (OIE Terrestrial Manual, 2018i).

22.2. RISK ASSESSMENT

22.2.1. Entry assessment

In cattle, systemic infection causes chlamydaemia (Andersen, 2004). Affected cows show little evidence of disease except for abortions, stillbirths or giving birth to weak calves. Persistent infection has been reported in animals (Andersen, 2004; Domeika *et al*., 1994), with intermittent shedding. It is unknown whether chlamydaemia exists during this period. These subclinical animals could pass antemortem examination and postmortem inspection at slaughter plants. Infected blood may be collected if these animals are chlamydaemic.

Australia reported the absence of enzootic abortions in sheep and goats via general surveillance. Also, the OIE reports that enzootic abortions in sheep and goats caused by *C. abortus* is absent from Australia (WAHIS, 2019a).

The prevalence information for *C. abortus* in cattle in the United States is sparse, and the enzootic abortion is typically a disease of sheep and goats in certain zones in the United States.

Chlamydaemia has been reported in cattle (Andersen, 2004), but there are no reports of isolation from bovine serum. Nevertheless, it is a plausible assumption that *C. abortus* may remain in the serum after separation of the blood cells.

The likelihood of entry of *C. abortus* in bovine serum from Australia is assessed as negligible, and the likelihood of entry from the United States is assessed as very low to low.

22.2.2. Exposure assessment

Animal vaccines produced from contaminated bovine serum could contain viable *C. abortus.* Parenteral administration of these contaminated vaccines is the most likely pathway for transmission to animals, and infection could occur in the recipients. Vaccination is generally implemented as a herd management tool, and a large number of animals could get exposed through contaminated vaccine.

There is evidence demonstrating that sheep have become infected and aborted after experimental inoculation with *C. abortus*. Sheep were inoculated with 2×10^6 inclusion body forming units in 2 mL, which can be considered a high dose. This was administered subcutaneously over the pre-femoral lymph node (Livingstone *et al*., 2017). Although the minimum infective dose is unknown, the likelihood of a processed vaccine containing 2×10^6 inclusion body forming units of bacteria is unlikely.

Infected cattle shed the organism in faeces, and the faecal-oral route is a significant transmission mode. If *C. abortus* infection occurs in New Zealand through contaminated sera, the infected animals are likely to transmit the disease to susceptible animal via this mode.

Chlamydia abortus is a multi-host pathogen. The primary hosts are sheep and goats, but the disease has also been reported in cattle, yaks, llamas, pigs, horses and deer. Vaccines administered to these species may cause infection and abortions. These aborted materials could then become a source of contamination to people.

Venereal transmission has been suggested, and therefore, contaminated bovine serum used in embryo storage media may cause infection and/or abortion in animals.

The overall likelihood of exposure, establishment and/or spread of *C. abortus* via bovine serum considering the factors mentioned above is assessed as low.

22.2.3. Consequence assessment

Chlamydia abortus is a multi-host pathogen. If infected vaccines are used on a variety of species, they may cause disease in these animals.

Clinical manifestations of *C. abortus* in infected cattle could be abortions, stillbirths or giving birth to weak calves, milk production losses and infertility. Abortions could reach 20% in cattle herds. Abortions in sheep and goats are likely to be higher. Infected animals could become persistently infected for months or years and intermittently shed the bacteria, thus providing a long-term source of infection for other species. Several industries including the beef, dairy, sheep, goat and deer industries would be affected. Considering the livestock industry and its contribution to the New Zealand economy, the consequence due to economic losses from animal infection, disease and production in New Zealand could be significant.

Chlamydia abortus is a zoonotic disease. Symptoms of the infection in humans range from subclinical to an acute flu-like manifestation. However, pregnant women may develop life-threatening *C. abortus* infections, resulting in septic abortion and stillbirth (Essig and Longbottom, 2015).

Chlamydia abortus (enzootic abortion of ewes) is an OIE-listed disease. New Zealand's sheep industry is substantial, with exportation of 80–90% of lamb meat produced. In the event of the establishment of this disease in New Zealand, trade impacts on both cattle and sheep industries could be significant.

Chlamydia abortus (enzootic abortion of ewes) has never been reported in New Zealand. If an eradication, control or containment programme were to be implemented following the establishment of the disease in New Zealand, there could be a considerable impact to the New Zealand economy.

The overall consequences of *C. abortus* as a result of entry, exposure, establishment and/or spread are assessed as high.

22.2.4. Risk estimation

The likelihood of entry of *C. abortus* in bovine serum from Australia is negligible, and therefore, the risk estimate is negligible. Risk management measures are not required for *C. abortus* in bovine serum imported from Australia.

The likelihood of entry of *C. abortus* in bovine serum from the United States is assessed as very low to low, the likelihoods of exposure, establishment and/or spread are assessed as low, and the consequences of *C. abortus* are assessed as high. Therefore, the overall risk is estimated as moderate.

Since the entry, exposure, and consequence assessments are non-negligible for bovine serum imported from the United States, *C. abortus* is a risk in the commodity. Therefore, risk management measures are justified for bovine serum imported from the United States.

22.3. RISK MANAGEMENT

The following points were considered when presenting options for managing the risks:

- Enzootic abortion of ewes caused by *C. abortus* is an OIE-listed disease.
- Enzootic abortions in sheep and goats caused by *C. abortus* have never been reported in New Zealand.

- Infection caused by *C. abortus* has been reported in both wild and domestic mammal species, including cattle.
- Infection caused by *C. abortus* is a zoonotic disease.
- Infectious chlamydial elementary bodies are approximately 0.3 μm in diameter.
- In the United States, enzootic abortions in sheep and goats are limited to certain zones.
- Australia reported the absence of enzootic abortions in sheep and goats in 2018 via general surveillance. The last occurrence is unknown.
- Chlamydiae have been found in all body secretions, and the routes of transmission include inhalation, ingestion, via mucous membranes and venereal transmission.
- Diagnosis of *C. abortus* includes stained smears, bacterial isolation, immunohistochemistry, PCR, ELISA and CFT.
- There is evidence demonstrating that sheep have become infected and aborted after experimental subcutaneous inoculation with *C. abortus.*

22.3.1. Options

The following options or a combination of these options can be considered to manage the risk associated with infection with *C. abortus*. These options have been formulated based on some of the OIE recommendations for infection with *C. abortus* (OIE Terrestrial Code, 2019d). Even though the OIE Terrestrial Animal Health Code provides import-related recommendations/guidelines for safe trade of commodities of sheep and goats, the general concept is used in formulating the following options for bovine serum.

1. Bovine serum could be imported from countries free from *C. abortus*.
2. The animals used for blood collection showed no clinical sign of infection with *C. abortus* on the day of collection
    a. For abattoir-sourced bovine serum, the serum was derived from animals that were resident since birth in a country or zone free from infection with *C. abortus* in accordance with the requirements of the OIE Code. The animals passed antemortem examination and postmortem inspection in abattoirs and were processed in premises under the oversight of the competent authority.
    b. For donor-animal-derived bovine serum, the animals were under veterinary supervision and came from a disease-free herd in accordance with the requirements of the OIE Code, or the donor was tested with an MPI-approved/recommended test, with negative results, at the time of blood collection.
3. Bovine serum could be either:
    a. tested with an MPI-approved/recommended test, with negative results; OR
    b. subjected to gamma irradiation at a minimum dose of 35 kGy; OR
    c. subjected to sterile filtration with a membrane filter pore size of 0.2 μm or less.

23. *Coxiella burnetii*

23.1. TECHNICAL REVIEW

23.1.1. Aetiology

Family: *Coxiellaceae*
Genus: *Coxiella*
Species: *Coxiella burnetii*

Coxiella burnetii is a gram-negative, intracellular, bipolar rod measuring 0.2 x 1.0 μm (Kelly, 2004).

Q (Query) fever is a zoonotic disease caused by the intracellular bacterium *Coxiella burnetii.*

23.1.2. OIE List

Q fever is an OIE-listed disease (OIE, 2020).

23.1.3. New Zealand status

Q fever has never been reported in New Zealand (WAHIS, 2019a). Q fever is listed as a disease absent from New Zealand (MPI, 2020) and also a notifiable organism on the Biosecurity (Notifiable Organisms) Order 2016, and the human health schedule of Notifiable Infectious Diseases under the Health Act 1956. Fox-Lewis and others (2019) reported a clinical case of Q fever in a New Zealander following travel to Australia.

23.1.4. Zoonotic potential

Q fever is a zoonotic disease. Some people may experience no symptoms, while others may experience sudden headaches, fever, chills, muscle soreness and, in some cases, pneumonia, fatigue, night sweats, weight loss, joint pain and nausea or vomiting (Maurin and Raoult, 1999).

People working with cattle, sheep or their products are at an increased risk of being infected with *C. burnetii*. High-risk occupations include farm workers, slaughterhouse workers (Plummer *et al*., 2018), workers in meat-packing plants, veterinarians and wool workers.

23.1.5. Epidemiology

Host range

Q fever primarily affects sheep, goats and cattle (Guatteo *et al*., 2011). It also has been implicated in reproductive losses in cats (Marrie *et al*., 1988), dogs (Buhariwalla *et al*., 1996), horses, water buffaloes, deer, and captive exotic ungulates including waterbucks, sable antelopes and several species of gazelle. Sheep, goats and cattle are considered the primary reservoir hosts for *C. burnetii* (Maurin and Raoult, 1999), but farmed red deer are also reported to maintain this organism (González-Barrio *et al*., 2015). Some proposed

wild animal reservoirs include rodents, small mammals, rabbits and western grey kangaroos in Australia (Banazis *et al*., 2010).

Direct and/or serological evidence for *C. burnetii* has been reported in rodents, small mammals, marine mammals (including seals, sea lions and sea otters) (Kersh *et al*., 2012), various Australian marsupials (Banazis *et al*., 2010), and wild or captive exotic ungulates. This organism has also been detected in subclinical birds, including pigeons, swallows, parrots, crows, geese (Syrucek and Raska, 1956) vultures, black kites and other species, as well as in snakes, tortoises and monitors (Maurin and Raoult, 1999).

Geographical distribution

Coxiella burnetii has been found in most countries that have conducted surveillance studies. Infection with *C. burnetii* occurs worldwide in domestic ruminants, as indicated by the presence of seropositive animals in a review by Guatteo and others (2011). The literature review took into consideration publications of *C. burnetii* seroprevalence from five regions (Africa, America, Europe, Asia and Oceania). The apparent prevalence for cattle was 20.0% and 37.7% at animal and herd level, respectively. In sheep and goats prevalence were approximately 15.0% and 25%, respectively, at animal and herd level (Guatteo *et al*., 2011).

Animal level prevalence of *C. burnetii* infection in cattle in California (USA) was 82% (Biberstein *et al*., 1974). Herd level prevalence of *C. burnetii* infection in cattle herds in the United States was between 37.7% and 100% (Biberstein *et al*., 1974; Guatteo *et al*., 2011; Martin *et al*., 1982).

Animal level prevalence of *C. burnetii* infection in cattle in Australia was 0.5–0.6% (Banazis *et al*., 2010). Herd level prevalence of *C. burnetii* infection in cattle herds in Australia was between 10% and 12.2% (Durham and Paine, 1997; Guatteo *et al*., 2011; Hore and Kovesdy, 1972).

New Zealand (Hilbink *et al*., 1993; Wood *et al*., 2019), Norway, Iceland and French Polynesia have reported no evidence of this organism in surveys to date (CFSPH, 2017).

Pathogenesis

In many animals, a transient bacteraemia with *C. burnetii* occurs soon after infection (Maurin and Raoult, 1999). Studies in cattle have shown that seronegative cows develop a transient fever two to three days after subcutaneous inoculation with *C. burnetii.* One cow in the study produced a full-term stillborn calf with *C. burnetii* dissemination in the calf tissues (Agerholm, 2013; Behymer *et al*., 1976).

Coxiella burnetii is a non-motile obligate intracellular bacterium, which completes its life cycle within the phagosomes of infected cells (Woldehiwet, 2004). It remains within the phagosomes after internalisation, and all stages of its development are accomplished within the phagosomes (Baca and Paretsky, 1983; Woldehiwet, 2004). The review conducted by Agerholm (2013) on the association of *C. burnetii* with reproductive disorders in domestic animals described that after initial infection of the placenta, the bacterium may subsequently spread to the foetus either haematogenously or through the amniotic-oral route.

Infection with *C. burnetii* is frequently subclinical in livestock, with clinical disease manifesting most commonly in small ruminants as late-term abortion, stillbirth, and birth of weak offspring. Abortions or reproductive failure rarely manifest in cattle (Plummer *et al*., 2018). *C. burnetii* may also be associated with metritis and infertility in cattle (To *et al*., 1998).

Mortality has not been reported in infected adult animals. However, abortions are often the result of Q fever outbreaks in herds or flocks. Studies showed that placentitis has been mainly associated with abortion in cattle due to *C. burnetii.* However, the bacteria were also found in multiple tissues of stillborn calves, indicating that fetal infections can also be associated with abortions (Agerholm, 2013). In Cyprus, in 2008 and 2009, a study was conducted to determine whether abortions in ruminants (cows, sheep and goats) were caused by *C. burnetii*. Of 59 randomly sampled abortion cases, 22 (37%) were found to be caused by *C. burnetii* (Cantas *et al*., 2011). In Italy, a similar study was conducted. Aborted fetuses (514) from cattle, sheep and goats were tested via a nested PCR. Of the 514 fetuses, 57 tested positive for *C. burnetii*, resulting in a prevalence of 18.9% (Parisi *et al*., 2006).

Domestic ruminants are predominantly subclinical carriers and can shed bacteria in various secretions and excreta (Nogareda *et al*., 2012). The lack of knowledge of shedding patterns among ruminants has made the determination of Q fever status difficult. Concomitant shedding into the milk, faeces and vaginal mucus may be rare (Guatteo *et al*., 2007b; Rousset *et al*., 2009). Shedding may persist for several months (Guatteo *et al*., 2007b). Importantly, shedding and serological responses are associated at the herd level but not at the individual level (OIE, 2018e). Shedding of *C. burnetii* can occur in both seronegative and seropositive ruminants (Guatteo *et al*., 2007a).

A study by Vincent and others (2015) in human patients demonstrated that *C. burnetii* could be isolated from serum samples of acute Q fever patients who were in the early stage of the disease. Of 65 patients sampled, positive cultures were obtained from 36 (55%). This implies that viable *C. burnetii* may be found in the serum of infected humans. Thus, there is a likelihood that the bacteria may also be found in the serum of infected animals (Vincent *et al*., 2015). It should be noted that in this experiment, serum samples were incubated for up to three months allowing bacterial concentrations to increase vastly. *C. burnetii* also remained viable for 224 days at refrigerator temperature and 371 days at -20°C.

Transmission

Animals are thought to become infected during direct contact, via routes such as inhalation and ingestion, or by aerosols (Maurin and Raoult, 1999). *Coxiella burnetii* is shed in large amounts in birth products such as the placenta (Plummer *et al*., 2018). Transmission to fetuses from infected dams can occur transplacentally or haematogenously (Agerholm, 2013). Organisms can be shed during normal pregnancies as well as after a reproductive loss (Plummer *et al*., 2018). *Coxiella burnetii* also occurs in vaginal secretions, milk (Nogareda *et al*., 2012), faeces and urine (Guatteo *et al*., 2007b) and has been detected in the semen of some species (e.g. cattle, dorcas gazelles and humans) (Kruszewska and Tylewska-Wierzbanowska, 1997).

Coxiella burnetii can be transmitted by ticks and possibly by other arthropods. The bacterium has been found in over 40 tick species (Maurin and Raoult, 1999). These include the genus *Haemaphysalis, Amblyomma* and *Ixodes*. It is not known whether the New Zealand species of ticks from these genera possess the ability to transmit the bacterium (Heath, 2002). Ticks do not play a significant role in the natural cycle of infection in livestock. However, their role is considered significant in the transmission among wild vertebrates, rodents, lagomorphs and birds. New Zealand has numerous native birds that are likely to carry ticks. For this reason, ticks could spread the bacterium to native bird species.

Diagnosis

As a general principle, the methods for the diagnosis of Q fever allow only interpretation at the herd level and not at the individual level.

The polymerase chain reaction (PCR) method is thus far the most reliable test for the diagnosis of clinical cases. However, PCR cannot be relied on to determine the infection status because of the variability of shedding by animals (different shedding routes, potentially intermittent shedding) (OIE, 2018e).

Other serological tests available for clinical cases include enzyme-linked immunosorbent assay (ELISA), complement fixation test (CFT) and immunofluorescence antibody test. Although the ELISA methods are not entirely validated and harmonised, they are robust, can be automated and are recommended for routine serological testing of animals for Q fever (OIE, 2018f; Plummer *et al.*, 2018).

Treatment, control and prevention

Treatment of infected animals with tetracycline can reduce the risk of abortions. Control measures for the infection include tick control and good hygiene practices. Effective control measures include isolation of infected animals, proper disposal of contaminated fluids, membranes and bedding, and cleaning and disinfection of infected areas. Pasteurisation of milk and milk products and reducing human exposure to infected animals and contaminated material can help to control the zoonotic spread of the disease (Kelly, 2004).

Ruminants can be vaccinated using inactivated *C. burnetii* vaccines (OIE, 2018e). The aim of this vaccination is to reduce shedding and the risk of abortions (Agerholm, 2013).

23.2. RISK ASSESSMENT

23.2.1. Entry assessment

In animals, a transient bacteraemia occurs soon after infection. This may occur concomitantly with transient fever, which lasts two to three days. Most ruminants, including cattle, experience subclinical infections and are reported to be carriers of *C. burnetii* (Nogareda *et al.*, 2012). If the infection is clinically inapparent or results in mild signs, it may go undiagnosed during clinical examination of donors or postmortem inspections at slaughter plants. Transplacental or haematogenous transmission of *C. burnetii* to foetuses is also possible. This allows the collection of blood from infected animals, including foetuses.

Considering the significant differences in herd-level prevalence data for Q fever in cattle in the United States (37.7–100%) and Australia (10–12%), the likelihood of collecting infected blood from infected cattle is high in the United States and low in Australia.

Infected blood contains viable bacteria and is thus capable of infecting inoculated animals (Agerholm, 2013; Behymer *et al*., 1976). Viable *C. burnetii* can be found in human serum (Vincent *et al*., 2015), and so it is plausible to assume that the organism could be found in bovine serum.

Therefore, the overall likelihood of entry of *C. burnetii* in bovine serum is assessed as moderate.

23.2.2. Exposure assessment

Animal vaccines produced from contaminated bovine serum could contain viable *C. burnetii*. Parenteral administration of these contaminated vaccines is the primary pathway for transmission to animals. There is evidence that animals can become infected experimentally by inoculation of infected blood and that some may experience reproductive failure (Agerholm, 2013; Behymer *et al*., 1976).

Coxiella burnetii can be transmitted by ticks, implying that a minute volume of tick saliva containing a low infectious dose is capable of causing infection in animals. However, *C. burnetii* remains within the phagosomes of cells after internalisation, and all stages of its development are accomplished within the phagosomes (Baca and Paretsky, 1983; Woldehiwet, 2004). Serum is depleted of cells; therefore, the number of infectious organisms present in the serum is likely to be lower than in the whole blood. Vaccination is generally implemented as a herd management tool, and a large number of animals could be exposed through contaminated vaccine.

Coxiella burnetii can be transmitted by several species of ticks and possibly by other arthropods. The bacterium has been found in over 40 tick species (Maurin and Raoult, 1999). These include the genera *Haemaphysalis, Amblyomma* and *Ixodes.* It is not known whether the New Zealand species of ticks from these genera may also possess the ability to transmit the bacterium (Heath, 2002).

Numerous species are susceptible to *C. burnetii* infection. These species may, therefore, be exposed to *C. burnetii* by secretions and excretions from direct contact with infected animals. Contaminated media used in germplasm could potentially transmit the disease, thus making this a possible exposure pathway. Subclinical carrier animals are capable of shedding bacteria for several months (Guatteo *et al*., 2007b) and could therefore be a source of ongoing infection to other animals and humans.

Considering the factors mentioned above, the overall likelihood of exposure, establishment and/or spread of *C. burnetii* is assessed as low.

23.2.3. Consequence assessment

Q fever is a multi-species OIE-listed disease. There are likely to be negative trade impacts if *C. burnetii* enters New Zealand.

Q fever primarily affects sheep, goats and cattle. For the livestock industry involving small ruminants, economic losses arise from late-term abortion, stillbirth, and birth of weak offspring. Even though abortions or reproductive failure are rarely manifested in cattle, economic impacts associated with Q fever for the cattle industry could arise from metritis and infertility. Considering the large-scale livestock farming industry and its contribution to the New Zealand economy, the consequences due to economic losses from animal infection, disease and production loss could be significant.

Q fever has never been reported in New Zealand. If an eradication, control or containment programme were to be implemented following the establishment of Q fever, there could be considerable impacts to the New Zealand economy.

Q fever is a zoonotic disease. People working with cattle, sheep or their products such as slaughterhouse workers, workers in meat-packing plants, veterinarians and wool workers are at risk of being infected with *C. burnetii*. New Zealand's farming sector is large, employing a vast number of personnel in these professions, and therefore, Q fever could have significant consequences for human health.

Even though Q fever primarily affects sheep, goats and cattle, it has been implicated in reproductive losses in cats, horses, water buffaloes, deer, and captive exotic ungulates including waterbucks, sable antelopes and several species of gazelle. In the wild, rodents, small mammals, rabbits, birds and western grey kangaroos are act as reservoirs. Transmission of Q fever to wild animals can occur through direct contact with infected animals, inhalation, aerosols or ingestion of contaminated material or soil from the environment. Therefore, the consequences for the environment could be significant.

The overall consequences of Q fever as a result of the entry, exposure, establishment and/or spread are assessed as high.

23.2.4. Risk estimation

The likelihood of entry of *C. burnetii* in bovine serum from Australia and the United States is assessed as moderate, the likelihoods of exposure, establishment and/or spread are assessed as low, and the consequences of *C. burnetii* are assessed as high. Therefore, the overall risk is estimated as moderate.

Since the entry, exposure, and consequence assessments are non-negligible for bovine serum imported from Australia and the United States, *C. burnetii* is a risk in the commodity. Therefore, risk management measures are justified for bovine serum imported from Australia and the United States.

23.3. RISK MANAGEMENT

The following points were considered when presenting options for managing the risks:

- Q fever is an OIE-listed disease.
- Q fever has never been reported in New Zealand and is listed as a notifiable organism on the human health schedule of Notifiable Infectious Diseases in New Zealand.
- Q fever is a zoonotic disease.

- *C. burnetii* has been reported to infect several mammalian, reptilian and avian species subclinically.
- *Coxiella burnetii* is an intracellular, bipolar rod measuring 0.2 x 1.0 μm.
- *Coxiella burnetii* is present in both Australia and the United States.
- In animals, a transient bacteraemia occurs early after infection. This may occur concomitantly with transient fever, which lasts 2-3 days.
- Infection with *C. burnetii* is frequently subclinical in livestock, with clinical disease manifesting most commonly in small ruminants as late-term abortion, stillbirth, and birth of weak offspring.
- Subclinical carriers occur that can shed bacteria in various secretions and excreta.
- Shedding may persist for several months (Guatteo *et al*., 2007b).
- Shedding of *C. burnetii* can occur in both seronegative and seropositive ruminants (Guatteo *et al*., 2007a).
- Transmission routes include inhalation and ingestion of aerosolised bacterium, multiple tick vectors and all excretions and secretions of infected animals.
- Diagnostic tests include PCR and serological tests (ELISA, CFT, IFA).

23.3.1. Options

Even though Q fever is an OIE-listed disease, there are no import related recommendations relating to Q fever in the OIE Terrestrial Animal Health Code. The following options individually or in a combination of the following options can be considered to manage the risks associated with infection with *C. burnetii*:

1. Bovine serum could be imported from countries free from *C. burnetii*.
2. The animals used for blood collection showed no clinical signs of the infection on the day of blood collection, and no other evidence of the infection were reported in the animal or herd during the last three months.
    a. For abattoir-sourced bovine serum, the serum was derived from animals that were disease-free since birth or for the previous three months. The animals passed antemortem examination and postmortem inspection and were processed in premises under the oversight of the competent authority.
    b. For donor-animal-derived bovine serum, the serum was derived from herds that were under veterinary supervision, and the donor was disease-free since birth or for the last three months, or the donor was tested with an MPI approved/recommended test, with negative results, at the time of blood collection.
3. Bovine serum could be either:
    a. tested with an MPI approved/recommended test, with negative results; OR
    b. subjected to gamma irradiation at a minimum dose of 35 kGy; OR
    c. subjected to sterile filtration with a membrane filter pore size of 0.2 μm or less.

24. *Leptospira* spp.

24.1. TECHNICAL REVIEW

24.1.1. Aetiology

Family: *Leptospiracaeae*
Genus: *Leptospira*

Internationally, there are more than 300 distinct leptospiral serovars recognised within 13 species of pathogenic leptospires (Evangelista and Coburn, 2010; Picardeau, 2013).

Leptospires are helical in shape. Their length ranges from 3 to 20 μm, and they have a diameter of 0.1 μm. They have a helical amplitude of approximately 0.1 to 0.15 μm and a wavelength of 0.5 μm (Hunter, 2004).

24.1.2. OIE List

Leptospirosis is not an OIE-listed disease. The OIE Terrestrial Animal Health Standards Commission in 2007 replied to the comments provided by New Zealand and Australia that international trade does not increase the risks to human or animal health in regard to leptospirosis (OIE Terrestrial Animal Health Standards Commission, 2007).

24.1.3. New Zealand status

Eight serovars within two species of leptospires have been isolated and confirmed as present in New Zealand. These include *australis*, *canicola*, *copenhageni* and *pomona* within the species *L. interrogans* and serovars *tarrasovi*, *hardjobovis*, *balcanica* and *ballum* within the species *L. borgpetersenii* (Marshall and Manktelow, 2002). Other serovars are exotic to New Zealand.

Leptospira spp. are not included as notifiable organisms under the Biosecurity (Notifiable Organisms) Order 2016.

This IRA only assesses pathogenic species of leptospires that are absent from New Zealand.

24.1.4. Zoonotic potential

Leptospirosis is a zoonotic disease. In New Zealand serovars *canicola* and *australis* have only been isolated in humans and is considered endemic in New Zealand (Marshall and Manktelow, 2002).

24.1.5. Epidemiology

Host range

Leptospirosis is considered ubiquitous in animals. The bacteria have been found in a variety of wild and domestic animal species.

Animals could either be maintenance hosts or be clinically affected. In maintenance hosts, the *Leptospira* serovars are adapted to mammalian hosts that may or may not develop clinical signs. Examples of host-adapted serovars in domestic species include *canicola* in

dogs and *bratislava* and *pomona* in pigs. Cattle are considered the primary reservoir hosts for *hardjo*. In New Zealand *hardjo* is also maintained by red deer and wapiti deer (Ellis, 2015). Rodents and insects may also act as reservoirs. Clinically affected species include dogs, cattle, sheep, goats, horses, pigs and farmed cervids (Hunter, 2004).

Geographical distribution

Bovine leptospirosis has a worldwide distribution and has been found in almost all regions except for the polar regions (Ellis, 2015).

Regional presence of leptospirosis in the United States dairy herds varies from 36% of herds in the Midwest to 91% in California, with an average of 59% (Bolin, 2005). A study of beef cattle in six states in the United States reported a 42% prevalence of *hardjobovis* in cattle herds (Wikse *et al*., 2007).

According to Michigan State University, studies in the United States have reported a herd prevalence for serovar *hardjo* of approximately 60% in dairies and 40% in beef herds in the country. Diagnostic laboratories report that less than 10% of the total number of abortions were associated with leptospirosis. Due to the difficulties in confirming a diagnosis for abortions, the leptospira prevalence is possibly underestimated (Maday, 2018).

Leptospirosis is enzootic in Australia. It occurs in all states and territories. Prevalence is considered higher in the wet tropical areas in comparison to the arid parts of the country. The most common serovars in Australian cattle are *hardjobovis* and *pomona*. Other serovars isolated from cattle include *australis*, *grippotyphosa* and *zanoni* (Perry and Heard, 2000).

In a study by Milner and others (1980), 1,355 random samples from Victoria were tested with microagglutination tests (MATs) for the presence of antibodies for 12 serovars of *Leptospira interrogans*. The seropositivity varied from 24.8% in the metropolitan areas to 56.3% in northeast Victoria (Milner *et al*., 1980).

Pathogenesis

One to two days after infection, bacteraemia develops. This lasts for a week. During this period, leptospires can be isolated from the blood, cerebrospinal fluid and multiple organs. The primary bacteraemic phase ends with the appearance of antibodies, which can be detected 10 to 14 days later (Ellis, 2015).

After the period of bacteraemia, leptospires localise in the kidneys, lung, brain, eyes or pregnant uterus. Here they multiply, and localisation in the brain give rise to nervous signs. Localisation in the kidneys lead to nephritis and excretion of leptospires with the urine. The duration and magnitude of urinary shedding of leptospires (leptospiruria) are dependent on species of animal and the leptospire serovar and may vary (Ellis, 2015; Hunter, 2004).

Leptopsires may also localise in the uterus of pregnant animals. The resultant clinical signs of infection in late gestation are abortions, stillbirths and neonatal disease. However, the pathogenesis of these reproductive conditions is poorly understood (Ellis, 2015).

Clinical signs of leptospirosis depend on the site of the pathogen localisation. Acute clinical signs occur simultaneously with the bacteraemic phase. Young animals are mostly affected by clinical disease caused by specific serovars. Clinical signs include pyrexia, haemolytic anaemia, haemoglobinuria, jaundice, occasionally meningitis, and death (Ellis, 2015). Affected calves may develop diarrhoea (Hunter, 2004).

Severe disease in adult cattle is uncommon. Infected cows may have a reduction in milk yield and may abort. In lactating cows, infections may be associated with small amounts of blood-tinged milk and/or agalactia, soft flabby udders, pyrexia, yellow clotted milk with high somatic cell counts (Ellis, 2015; Hunter, 2004).

Animals can be carriers (Ellis, 2015). Leptospires may be excreted in the urine, often intermittently, for up to 18 months after infection. Cattle may remain serologically positive to leptospirosis for up to seven years (Perry and Heard, 2000).

Transmission

Leptospirosis can be transmitted to animals and humans directly from contact with infected animals or indirectly through contaminated environment such as soil or water sources. Leptospirosis can also be transmitted through direct contact with urine or infected tissue of infected animals. Infection normally occurs through abraded skin or through the mucous membranes of the mouth, eyes, nose or genital tract (Ellis, 2015; Togami, 2016). In rural settings, exposure of people and animals to leptospirosis is mainly attributed to rodents (Togami, 2016).

Venereal and transplacental transmission can also occur (Hunter, 2004). *Leptospira borgpetersenii* serovar Hardjo (hardjobovis, HB) and *Leptospira interrogans* serovar Hardjo (hardjoprajitno, HP) are common cattle strains. Both have the ability to colonise and persist in the genital tract of infected cows and bulls, suggesting venereal spread as a form of transmission (Ellis, 2015).

Diagnosis

Diagnostic methods for leptospirosis can be divided into two groups.

The first group is for the demonstration of leptospires in tissues. The diagnostic tests include direct visualisation of the leptospires under dark-field microscopy, culture, polymerase chain reaction (PCR) and staining. Leptospires can be demonstrated in blood and milk. However, testing of these samples may not be as sensitive due to the transient nature of the disease and lack of clinical signs in most cases. PCR is considered more sensitive than other methods (Ellis, 2015).

The second group consists of serological tests. These are the most widely used tests, with the microscopic agglutination test (MAT) being the test of choice. Enzyme-linked immunosorbent assays (ELISAs) for anti-leptospiral antibodies have also been developed (Ellis, 2015).

Treatment, control and prevention

Antibiotics and supportive symptomatic therapy are used for herd/flock and individual animal treatment. For companion animals, intensive supportive therapy in the form of

fluid therapy, blood transfusions and dialysis may be necessary. In chronic leptospirosis cases, pigs, cattle and sheep may be treated with a combination of vaccination and antibiotics (Ellis, 2015).

Prevention and control strategies are aimed at mitigating the direct and indirect transmission pathways. Numerous methods are used and include vaccination, antibiotic therapy, assessment of herd/population status (profiling), identification and removal of infected animals, rodent control, reducing risk factors through management systems and a combination of some or all these methods (Ellis, 2015).

24.2. RISK ASSESSMENT

24.2.1. Entry assessment

Cattle develop bacteraemia that lasts for one week. A secondary bacteraemic phase has been reported (after 15–26 days) on rare occasions (Hathaway *et al*., 1983). Adult cattle are likely to be subclinical during this time unless they are pregnant and experience abortions. Leptospira carrier status has been reported. Leptospires localise in the kidneys from where they are intermittently voided in the urine. It is unknown whether bacteraemia exists during the carrier phase; however, this is possible.

Donor animals that are carriers may pass antemortem examination and postmortem inspection at slaughter plants. Infected blood may, therefore, be collected from subclinically affected but bacteraemic animals.

The prevalence of leptospirosis in the United States is between 40% and 60% and the prevalence in Australia is between 24% and 56%. These prevalence data are considered high. Although clinical signs are likely to be evident on most farms that are affected by leptospirosis, subclinical animals can be sent to a slaughter plant or be accepted as a blood donor. Therefore, the likelihood of leptospirosis-positive cattle being accepted as blood donors is low.

Leptospires have been isolated from blood (Ellis, 2015). There are no reports of isolation from serum; however, it is likely that leptospires may remain in the serum after separation. Leptospires are slender (0. 1 μm by 8 to 20 μm), tightly coiled bacteria. They have been reported to pass through sterilizing filters with 0.45-μm to 0.22-μm sized pores and have thus been found as contaminants of filter-sterilized media (Russell, 1996).

The likelihood of entry of leptospires in bovine serum is assessed as low.

24.2.2. Exposure assessment

Animal vaccines produced from contaminated bovine serum could contain viable leptospires. Parenteral administration of these contaminated vaccines is the primary pathway for transmission to animals who could then become infected. Vaccination is generally implemented as a herd management tool, and a large number of animals could be exposed through contaminated vaccines.

Leptospira spp. are multi-host pathogens. If cattle or other species become infected, they could become a source of contamination of the environment, resulting in transmission to other animals and humans.

In animals, venereal spread of leptospirosis has also been suggested as a source of infection (Ellis, 2015). Therefore, contaminated bovine serum used as embryo transfer media could result in infection of the recipient dam.

Based on the factors mentioned above, the overall likelihood of exposure, establishment and/or spread of *Leptospira* spp. via bovine serum is assessed as low.

24.2.3. Consequence assessment

Leptospira spp. are multi-host pathogens. If contaminated vaccines are used on a variety of species, they may lead to disease in these animals.

Leptospirosis can affect all ages of cattle, sheep, goats, pigs, cervids and is also likely to cause clinical disease in calves, lambs and pigs (Ellis, 2015). Clinical manifestations of leptospirosis in infected cattle and sheep may include abortion storms, stillbirths and neonatal disease. Cattle may also experience a drop in milk production. If these animals become infected, they could become carrier animals, intermittently voiding leptospires in their urine, which would become a source of contamination of the environment and transmission to other animal species as well as humans.

Various livestock industries are likely to be affected. However, most industries routinely practice vaccination against leptospirosis and apply other control strategies including farm biosecurity and herd/flock health management. In the event of the establishment of a new pathogenic species, it is unlikely that the current vaccines in New Zealand can provide protection.

Leptospirosis is a zoonotic disease. Symptoms in humans include high fever, headache, chills, muscle aches, vomiting, jaundice (yellow skin and eyes), abdominal and diarrhoea in the first phase of infection. If a second phase occurs, the disease is more severe and may include kidney or liver failure or meningitis (CDC, 2017).

Leptospirosis is not an OIE-listed disease, and it is unlikely that any wide-ranging trade restrictions related to the disease would be imposed by trading partners. Therefore, trade impacts are likely to be negligible.

The overall consequences of leptospirosis as a result of the entry, exposure, establishment and/or spread are assessed as low to moderate.

24.2.4. Risk estimation

The likelihood of entry of pathogenic *Leptospira* spp. in bovine serum from Australia and the United States is assessed as low, the likelihoods of exposure, establishment and/or spread are assessed as low, and the overall consequences of pathogenic *Leptospira* spp. are assessed as low to moderate. The overall risk is estimated as low.

Since the entry, exposure, and consequence assessments are non-negligible for bovine serum imported from Australia and the United States, pathogenic *Leptospira* spp is a risk in the commodity. Therefore, risk management measures are justified for bovine serum imported from Australia and the United States.

24.3. RISK MANAGEMENT

The following points were considered when presenting options for managing the risks:

- Leptospirosis is not an OIE-listed disease.
- Eight serovars of leptospires have been isolated and confirmed as present in New Zealand.
- Leptospirosis is a zoonotic disease.
- Leptospirosis is ubiquitous in animals and has been isolated in a variety of wild and domestic animal species.
- Leptospires are helical in shape. Their length ranges from 3 to 20 μm, their diameter is 0.1 μm, and they have a wavelength of 0.5 μm.
- Leptospires can pass through sterilizing filters with 0.45-μm to 0.22-μm sized pores.
- Bovine leptospirosis has a worldwide distribution that includes Australia and the United States.
- Bacteraemia develops one to two days after infection and lasts for one week, with second bacteraemic phase reported to occur.
- Clinical disease is uncommon in adult cattle.
- Carrier status does exist in animals.
- Transmission can occur directly and indirectly. Vertical and venereal transmission are suggested modes of transmission.
- Diagnostic methods include direct visualization of the leptospires under dark-field microscopy, culture, PCR, staining and serological tests.
- Leptospires have been isolated from blood.

24.3.1. Options

The following options or a combination of these options can be considered to manage the risks associated with pathogenic *Leptospira* spp.

1. The animals used for blood collection showed no clinical signs of the infection on the day of blood collection, and no other evidence of the infection was reported in the animal or herd during the last three months.

    a. For abattoir-sourced bovine serum, the serum was derived from animals that were disease-free since birth or for the last three months. The animals passed antemortem examination and postmortem inspection and were processed in premises under the oversight of the competent authority.

    b. For donor-animal-derived bovine serum, the donors came from herds that were under veterinary supervision. The donors were disease-free since birth or for the last three months, or the donor animals were tested with an MPI-approved/recommended test, with negative results, at the time of blood collection.

2. Bovine serum could be either:

    a. tested with an MPI-approved/recommended test, with negative results; OR

    b. subjected to gamma irradiation at a minimum dose of 35 kGy; OR

    c. subjected to sterile filtration with a membrane filter pore size of 0.1 μm or less.

25. *Mycobacterium bovis*

25.1. TECHNICAL REVIEW

25.1.1. Aetiology

Family: *Mycobacteriaceae*
Genus: *Mycobacterium*
Species: *Mycobacterium bovis*

Mycobacterium bovis is the causative agent of bovine tuberculosis (TB). *Mycobacterium bovis* is one of the member species in the *Mycobacterium tuberculosis* complex (OIE Terrestrial Manual, 2018f).

Mycobacteria are gram-positive, non-spore-forming, straight or slightly curved rods, 1.5 μm to 4.0 μm long and 0.3 μm to 0.5 μm wide (Cousins *et al*., 2004).

25.1.2. OIE List

Infection with members of *Mycobacterium tuberculosis* complex is an OIE-listed disease (OIE, 2020).

25.1.3. New Zealand status

Bovine TB is present in New Zealand, and a national pest management plan for bovine TB has been in place since 1998 to eradicate the disease (WAHIS, 2019a). TBfree New Zealand Ltd, which is a part of "Operational Solutions for Primary Industries" (OSPRI), implements the bovine TB eradication programme. TBfree New Zealand controls the disease through livestock testing, movement control and targeted wildlife pest control (OSPRI, 2019).

25.1.4. Zoonotic potential

Bovine TB is a zoonotic disease with significant impacts on human health. *Mycobacterium bovis* has been identified in people mainly among those occupationally exposed to infected cattle by direct contact and inhalation of aerosols. Consumption of raw milk from infected cattle has been identified as another main route of transmission (OIE Terrestrial Manual, 2018f).

According to the New Zealand Ministry of Health, approximately 300 cases of human TB due to the *Mycobacterium tuberculosis* complex are reported each year (Ministry of Health, New Zealand, 2018). The Institute of Environmental Science and Research Limited (ESR) in New Zealand reported that, of the total human TB cases annually, less than 5 cases are due to *Mycobacterium bovis* (ESR, 2019).

25.1.5. Epidemiology

Host range

Bovine TB is a chronic bacterial disease primarily of cattle, but also affects many domesticated and wild animals, including free or captive wildlife species (OIE Terrestrial Manual, 2018f). In New Zealand, possums are the primary wildlife maintenance hosts and

vectors of bovine TB (Livingstone *et al*., 2015). Ferrets, feral deer and pigs can also be infected with bovine TB and can act as spillover hosts. In the United States, *Mycobacterium bovis* has been detected from a wide range of spillover wildlife hosts such as elks, mule deer, bison, raccoons, moose, coyotes, opossums, feral cats, gray foxes, black bears, feral pigs, gray wolves, red foxes and bobcats (USDA, 2018).

Geographical distribution

From January 2017 to June 2018, 82 countries reported the presence of bovine TB to the OIE (OIE, 2019a). The highest prevalence of the disease is in Africa and parts of Asia. The disease is also found in some countries in Europe and America (OIE, 2019a).

In New Zealand, bovine TB is present in both domestic and wild animals (WAHIS, 2019a). Among domestic animals in New Zealand, cattle and deer are the most significant hosts for bovine TB. Brushtail possums are the most significant wild animal hosts because they act as maintenance hosts. Other wild animals infected in New Zealand include ferrets, feral deer and pigs, which serve as spillover hosts (Barron *et al*., 2015; Buddle *et al*., 2015; Nugent *et al*., 2015).

Bovine TB is absent from Australia in both domestic and wild animals. The last occurrence of bovine TB in Australia was in 2002 (WAHIS, 2019a).

Bovine TB is present in the United States but is limited to certain zones (WAHIS, 2019a). In the United States, the National Tuberculosis Eradication Program has been implemented in 1917 and is continuing (USDA, 2019). According to the USDA, TB surveillance in the United States is conducted in slaughter establishments. Livestock is tested during herd investigation of suspected cases, pre-movement and for accredited free herd status (USDA, 2019). The eradication programme reduced the prevalence of bovine TB in the United States to less than 0.006% in 2011 (Verteramo Chiu *et al*., 2019), and the National Tuberculosis Eradication Program is continuing its success in reducing the disease.

Pathogenesis

Bovine TB is a chronic disease which often has a subclinical course in cattle. The signs of bovine TB can take months or years to develop, or the infection can remain dormant until reactivated by stress (Cousins *et al*., 2004). The lesions of the infection vary according to the route of infection. Possible routes of infection include respiratory, alimentary, congenital, cutaneous, venereal, and via the teat canal (Cousins *et al*., 2004), with the respiratory and alimentary routes being the most common and the others being rare.

The initial multiplication of the bacteria inside the host occurs in macrophages, resulting in the formation of the primary lesions spreading to the regional lymph nodes. Mild bacteraemia develops as soon as 20 days post-infection. Infected macrophages may also enter the blood, lymph vessels, ducts or body cavities and disseminate the infection. Miliary tuberculosis develops as a result of massive bacteraemia due to haematogenous spread (Cousins *et al*., 2004).

In the early stages of the disease, clinical signs can be inapparent. In later stages, clinical signs will depend on the route of infection and the organ systems involved (Cousins *et al*.,

2004; Verteramo Chiu *et al*., 2019). Enlarged lymph nodes and extreme emaciation are reported in terminal stages of the disease. Aerosol infections produce pulmonary lesions characterised by cough due to bronchopneumonia and dyspnoea (OIE Terrestrial Manual, 2018f). Haematogenous spread can lead to tuberculous meningitis, infection of the udder and congenital tuberculosis infecting foetuses (Cousins *et al*., 2004).

Transmission

Transmission is primarily by inhalation of aerosol and direct contact with infected animals and secretions. Transmission through ingestion of milk of infected animals, especially in humans, can also occur (Cousins *et al*., 2004; OIE Terrestrial Manual, 2018f).

Diagnosis

Bacteriological confirmation can be achieved by microscopic examinations and isolation of the mycobacteria in selective culture and identification by polymerase chain reaction (PCR) (OIE Terrestrial Manual, 2018f).

The standard test for the detection of bovine tuberculosis is the tuberculin test which is the prescribed test for international trade. This test involves an intradermal injection of bovine tuberculin purified protein derivative and measuring the delayed hypersensitivity (swelling) at the site of injection 72 hours later (OIE Terrestrial Manual, 2018f).

Diagnosis using blood-based laboratory tests are usually used as additional tests because of the cost and complex nature of the assays. The gamma interferon assay (IFN-γ), which uses an enzyme-linked immunosorbent assay (ELISA) as the detection method for interferon, has been approved by several countries and can be used to maximise detection in infected animals (enhance specificity) and to confirm and/or negate the results of the intradermal test (enhance sensitivity) (Buddle *et al*., 2015; OIE Terrestrial Manual, 2018f). Other assays like lymphocyte proliferation, which detects cellular immunity, and ELISA, which detects antibody responses, can also be used for the detection of bovine TB.

Treatment, control and prevention

Antimicrobial treatment of infected animals has been proven to be uneconomic and prolonged.

Control of bovine TB can be achieved by implementing eradication programmes such as test and slaughter, livestock movement control from infected and suspected areas and wildlife vector control. One of the foremost difficulties with the eradication of bovine TB is the occurrence of the disease in wildlife (Cousins *et al*., 2004). Pasteurisation of milk is the recommended control measure to prevent transmission to humans and other animals through milk.

The only vaccine available currently is the bacilli-Calmette-Guerin (BCG) vaccine, which is a live attenuated strain of *Mycobacterium bovis*. Since this vaccine compromises the tuberculin test and other immunological tests, it is not used in countries with bovine TB control programmes and trade measures based on testing (OIE Terrestrial Manual, 2018f).

25.2. RISK ASSESSMENT

25.2.1. Entry assessment

Mycobacterium bovis affects a wide range of wild and domestic animals. Cattle are the primary host of *Mycobacterium bovis*. The disease is present in cattle in New Zealand, but it is under an eradication programme.

Bovine TB is a chronic disease, and the incubation period is reported to be prolonged. Bovine TB is usually subclinical, and the pathogen can remain dormant for a long time inside the host until reactivated by stress. Bacteraemia is reported in infected cattle as early as 20 days post-infection. Infected macrophages that contain the bacteria can enter the blood and disseminate to other organs within the host species (Cousins *et al.*, 2004). Since infected cattle develop bacteraemia and the bacteria can be present in the blood of infected cattle, it is hypothesised that unprocessed bovine serum can harbour *Mycobacterium bovis*.

According to the OIE, bovine TB is absent from Australia, both in domestic and wild animals, but present in the United States, although limited to one or more zones. Since the prevalence of bovine TB in the United States is very low, and there is a surveillance programme in in place for domestic and wild animals, the likelihood of collecting blood for bovine serum production from bovine TB-infected animals in the United States is very low.

Therefore, the likelihood of entry of bovine tuberculosis in bovine serum from Australia is assessed as negligible, and the likelihood of entry from the United States is assessed as very low.

25.2.2. Exposure assessment

Even though the likelihood of entry of *Mycobacterium bovis* through contaminated bovine serum from the United States is very low, it is plausible that *Mycobacterium bovis* could be present as a contaminant in the commodity.

Animal vaccines produced from contaminated bovine serum and subsequent parenteral administration of these vaccines is the most likely pathway for transmission to animals and infection could occur in the recipients. Vaccination is generally implemented as a herd management tool, and a large number of animals could get exposed through contaminated vaccine.

Bovine TB can be transmitted by direct contact with contaminated fluids, tissues, cultures and materials from infected animals. Transmission can also occur through inhalation of contaminated aerosol and ingestion of contaminated materials. If *Mycobacterium bovis* enters New Zealand through unprocessed bovine serum, the likelihood of live animals exposed directly to unprocessed bovine serum is unlikely. Animals infected using contaminated end products such as vaccines can transmit the disease to a wide range of animals and humans in New Zealand.

There are no references of the infection being transmitted between animals through germplasm, and therefore, it is not considered a possible exposure pathway.

Therefore, the overall likelihood of exposure, establishment and/or spread of bovine TB via contaminated bovine serum based on the factors considered above is assessed as moderate.

25.2.3. Consequence assessment

Mycobacterium bovis is one of the species in the *Mycobacterium tuberculosis* complex, and infection with *Mycobacterium tuberculosis* complex is an OIE-listed disease. Since the disease is already present in New Zealand, trade impacts would be limited to decreased trade volumes due to loss of production or culling of animals.

Although bovine TB is present in New Zealand, the disease is under an eradication programme. Therefore, entry and exposure of *Mycobacterium bovis* through contaminated bovine serum can increase the costs of current eradication, control and surveillance programme, as well as increasing the time required to attain eradication. The consequences of movement controls and culling of affected herds would be serious for affected farmers.

Bovine TB is a zoonotic disease, and entry and exposure of *Mycobacterium bovis* through contaminated bovine serum can result in an increase in the spread of the infection to the human population, which is very low at present (ESR, 2019).

Bovine TB can affect wild animals, and entry and exposure of *Mycobacterium bovis* through contaminated bovine serum can result in an increased prevalence of the disease among wildlife. This increased prevalence would have a significant impact on the current wildlife vector control programme for TB eradication in New Zealand.

The overall consequences of bovine TB as a result of the entry, exposure, establishment and/or spread are assessed as low to moderate.

25.2.4. Risk estimation

The likelihood of entry of *Mycobacterium bovis* in bovine serum from Australia is negligible, and therefore, the risk estimate is negligible. Risk management measures are not required for *Mycobacterium bovis* in bovine serum imported from Australia.

The likelihood of entry of *Mycobacterium bovis* in bovine serum from the United States is assessed as very low, the likelihoods of exposure, establishment and/or spread are assessed as moderate, the consequences of *Mycobacterium bovis* are assessed as low to moderate, and the overall risk is estimated as low.

Since the entry, exposure, and consequence assessments are non-negligible for bovine serum imported from the United States, *Mycobacterium bovis* is a risk in the commodity. Therefore, risk management measures are justified for bovine serum imported from the United States.

25.3. RISK MANAGEMENT

The following points were considered when describing options for managing the risks:

- Bovine TB is an OIE-listed disease.

- Bovine TB is present in New Zealand but is controlled under the bovine TB eradication programme.
- Bovine TB is absent from Australia but present in the United States where it is limited to specific zones.
- Bovine TB would have a negative impact on the economy of the livestock industry.
- Bovine TB is a zoonotic disease.
- Mycobacteria are straight or slightly curved rods, 1.5 μm to 4.0 μm long and 0.3 μm to 0.5 μm wide.
- Bovine TB affects multiple species of animals, including wild animals.
- In infected animals, bacteraemia has been reported, and infected macrophages that contain the bacteria can enter the blood.
- The incubation period for bovine TB can be prolonged.
- Bovine TB is usually subclinical, and the pathogen can remain dormant for a long time.
- Treatment to completely cure bovine TB can be uneconomic and prolonged.

25.3.1. Options

The following options or a combination of these options could be considered to manage the risk associated with bovine TB in the commodity. These options have been adapted from the OIE recommendations for bovine TB (OIE Terrestrial Code, 2019f).

1. Bovine serum can be imported from countries free from bovine TB.
2. The animals used for blood collection were kept in a country or zone or herd free from bovine TB in accordance with the requirements of the OIE Code.
3. The animals used for blood collection showed no clinical sign of bovine TB on the day of collection, and no other evidence of the infection was reported in the animals or herd.
    a. For abattoir-sourced bovine serum, the serum was derived from animals that were kept in a country or zone or herd free from bovine TB in accordance with the requirements of the OIE Code. The animals passed antemortem examination and postmortem inspection in abattoirs and were processed in premises under the oversight of the competent authority.
    b. For donor-animal-derived bovine serum, the animals were under veterinary supervision and came from a disease-free country, zone or herd in accordance with the requirements of the OIE Code, or the donor was tested with an MPI-approved/recommended test, with negative results, at the time of blood collection.
4. Bovine serum could be either:
    a. tested with an MPI-approved/recommended test, with negative results; OR
    b. subjected to gamma irradiation at a minimum dose of 35 kGy; OR
    c. subjected to sterile filtration with a membrane filter pore size of 0.2 μm or less.

26. *Salmonella* spp.

26.1. TECHNICAL REVIEW

26.1.1. Aetiology

Family: *Enterobacteriaceae*
Genus: *Salmonella*

The genus *Salmonella* consists of two species: *S. enterica* and *S. bongori*. *Salmonella enterica* is further divided into six subspecies (Brenner *et al*., 2000). The taxonomic groups contain approximately 2,500 serotypes (serovars).

Salmonellae are facultative anaerobic gram-negative rod-shaped bacteria 2–5 μm long and 0.5–1.5 μm wide. Bacterial cells contain peritrichous flagella, which facilitate cell motility (Andino and Hanning, 2015).

26.1.2. OIE List

Salmonella abortusovis is the only OIE-listed species for sheep and goats. However, in the OIE's *Manual of Diagnostic Tests and Vaccines*, salmonellosis is included under the section "Other Diseases".

26.1.3. New Zealand status

Salmonella typhimurium is endemic in New Zealand, but phage type 104 has only occurred rarely in humans and once in dogs and is considered exotic, together with phage 44 (ESR, 2019a; ESR, 2019b).

All exotic serovars and phage types of *Salmonella* are considered "Notifiable" under the Biosecurity (Notifiable Organisms) Order 2016.

26.1.4. Zoonotic potential

Salmonellosis is a zoonotic disease. *Salmonella* spp. isolated in New Zealand from people and animals are identified by the Environmental Science and Research (ESR) laboratory to determine the serovar and phage type and are recorded in a database (ESR, 2019a; ESR, 2019b).

26.1.5. Epidemiology

Host range

Salmonella spp. have been found in all species of mammals, birds (Rubini *et al*., 2016), reptiles and amphibians (Whiley *et al*., 2017). *Salmonella* spp. have also been detected in fish and invertebrates (Bibi *et al*., 2015). Subclinical infections are common in poultry, pigs (Rubini *et al*., 2016), reptiles and amphibians (Whiley *et al*., 2017). Most *Salmonella* species and serovars have a wide host range (Rubini *et al*., 2016), while a few are host-specific. For example, *S. abortusovis* usually infects sheep, *S. choleraesuis* usually infects pigs, and *S. dublin* and *S. typhimurium* are considered cattle pathogens (Guerin *et al*., 2005).

Geographical distribution

Salmonellae species have a worldwide distribution (including Australia and the United States) both in human and animals (Galanis *et al*., 2006; Larson and Spickler, 2013).

Fegan and others (2004) studied the prevalence and numbers of *Salmonella* in beef cattle presented for slaughter at abattoirs across Australia between September 2002 and January 2003. Of the 310 faecal samples tested, *Salmonella* spp. were isolated from 21 (6.8%) samples, indicating a low prevalence (Fegan *et al*., 2004). The serotypes identified were *S. typhimuirum, S. orion, S. give, S. muenchen. S, aberdeen, S. anatum* and *S. senftenberg.*

In 2002, the United States Department of Agriculture's National Animal Health Monitoring System conducted the "Dairy 2002" study. Faecal samples were collected via rectal retrieval on approximately five dairy operations from 21 states. Approximately 40 cows were sampled per operation. In total, 3,709 samples were collected from 97 dairy operations and tested for *Salmonella*. Of the samples collected and tested, 7.3% (269) were positive for *Salmonella*. Twenty-eight different serotypes were identified. The five most common serotypes were *S. meleagridis, S. montevideo, S. typhimurium, S. Kentucky* and *S. agona* (APHIS, 2005).

Pathogenesis

Several salmonella serotypes are known to infect cattle, and the most common cause of bovine salmonellosis is infection with *S. dublin* or *S. typhimuirium* (Richardson, 1975).

The incubation period is variable, but the organisms may be found in the bloodstream of newborn calves within 15 minutes of ingestion. Bacteria are isolated from intestinal lymph nodes after 18 hours in older calves (Radostits *et al*., 2007). After oral infection, *Salmonella* colonises the distal ileum and can be recovered in high numbers from this site within 72 hours. The intestine is initially infected, and inflammation of the gut is the primary lesion. Initial infection may be followed by invasion of the gut and mesenteric lymph node barrier followed by bacteraemia and dissemination to several organs. If the systemic invasion only causes bacteraemia, acute enteritis may develop, and abortion is the common final sequel in cattle (Radostits *et al*., 2007).

S. typhimurium is often associated with enteritis commonly affecting young calves, resulting in marked acute diarrhoea (Rankin and Taylor, 1966). Other clinical signs include fever, anorexia, and dehydration, which are secondary to acute necrotising enteritis (Costa *et al*., 2012).

S. dublin is highly adapted to cattle and affects both adults and young calves (Costa *et al*., 2012). The disease is often associated with systemic infections that may result in shedding or abortion in pregnant cows in subclinical animals (Costa *et al*., 2012; Hall *et al*., 1979; Rankin and Taylor, 1966).

Morbidity rates for salmonella infections are quite variable. Mortality is generally low. In an outbreak in England, mortality associated with all serotypes was 0.9% of 414 diseased cows (Richardson, 1975). Mortality rates from *S. dublin* are usually higher (Field, 1948).

Salmonellosis can affect all age groups and is likely to cause clinical disease in calves, while adult cattle are often subclinical (Richardson, 1975).

When an animal is infected with *Salmonella*, it may become a clinical case or an active, latent, or passive carrier. An active carrier shed organisms constantly or intermittently in faeces. A latent carrier has an infection that persists in lymph nodes or tonsils but no salmonella in the faeces. A passive carrier can constantly acquire the infection from the contaminated environment, and once the passive carrier animal is removed from the contaminated environment, the infection disappears (Radostits *et al*., 2007).

Richardson (1975) reported excretion of *Salmonella* in faeces of cattle for up to four months, while Field (1948) reported a 21-month carrier status in one cow. This suggests that the bacteria are capable of multiplying in the alimentary tract of cattle. Adult cattle that have recovered from the clinical disease can remain lifelong carriers (Field, 1948).

Field (1948) illustrated that there is a long lag period between initial infection and the onset of gastrointestinal signs.

Experimental exposure in cattle has been able to elicit clinical signs, including abortion. However, high infective doses were used for these experiments; 10^8 to 10^9 organisms by intravenous injection (Hall and Jones, 1976) and 10^{10} to 10^{11} organisms by oral infection (Hall *et al*., 1979).

Transmission

Transmission of *Salmonella* occurs via the faecal-oral route and via contaminated water, feed, and pastures (Richardson, 1975). Infected animals are the source of infection contaminating the environment, food and water sources (Radostits *et al*., 2007). Infected birds, rodents, insects, other domestic animals and people may also represent direct or indirect sources of infection.

Diagnosis

Tests that are used to confirm cases of salmonellosis include bacteriological culture followed by serotyping of isolates (Field, 1948). *Salmonella* isolation is the preferred method for population and individual animal freedom and surveillance purposes. It is recommended that alternative methods such as polymerase chain reaction (PCR) should be applied to the same clinical sample for agent identification (OIE, 2018f).

An immune response to *Salmonella* may be identified by serum agglutination tests and enzyme-linked immunosorbent assay (ELISA) (OIE, 2018f).

Salmonella has been isolated from faeces, blood (Tjaniadi *et al*., 1988), milk, and other body fluids and tissues (Radostits *et al*., 2007).

Treatment, control and prevention

Supportive care given to animals in the early stages of the disease is likely to be effective in limiting the progression and severity of salmonellosis. The diarrhoeic phase is often preceded by increased rectal temperature. Oral and intravenous fluids with electrolyte supplementation, non-steroidal anti-inflammatories and antibiotics may be administered once a rise in temperature is detected (Merck and Co., 2019).

The principles of control of salmonellosis include preventing the introduction and limiting spread within the herd (Merck and Co., 2019).

Live and inactivated vaccines against salmonella are available (Merck and Co., 2019).

26.2. RISK ASSESSMENT

26.2.1. Entry assessment

Salmonella carrier status has been demonstrated in cattle. Adult cattle that have recovered from the clinical disease may remain lifelong carriers. Field (1948) illustrated that there is a long lag period between initial infection and the onset of gastrointestinal signs. Serum donor animals that are either active or passive carriers may pass antemortem examination and postmortem inspection at slaughter plants. Infected blood may, therefore, be collected from bacteraemic donors.

The prevalence data for salmonella in cattle in Australia and the United States were 6.8% and 7.3%, respectively. The likelihood of collecting infected blood from *Salmonella* carrier cattle is low in both Australia and the United States.

There is evidence that *Salmonella* can be isolated from whole blood (Tjaniadi *et al*., 1988). However, there are no reports of isolation in serum. Regardless, it is likely that a small number of salmonellae may remain in the serum after separation of cellular components. Salmonellae are facultative intracellular organisms that survive in macrophages (Radostits *et al*., 2007); therefore, most of the bacteria are likely to be removed with the cellular component.

Therefore, the likelihood of entry of *Salmonella* spp. in bovine serum is assessed as very low.

26.2.2. Exposure assessment

Animal vaccines produced from contaminated bovine serum could contain viable *Salmonella* spp. Parenteral administration of contaminated vaccines is the principal pathway of transmission to animals. There is experimental evidence of animals being infected by intravenous inoculation of *S. dublin*.

Salmonella is a facultative intracellular organism that survives in macrophages (Radostits *et al*., 2007). Serum is depleted of cells; therefore, the number of infectious *Salmonella* organisms in the serum is likely to be lower than in whole blood.

Salmonella spp. are multi-host pathogens. If cattle become infected, they could become a source of contamination of the environment and transmit to other animal species as well as humans.

There are no reports of the transmission of salmonella via infected germplasm or their storage media. Chapter 6.13 of the OIE code "Prevention and control of *Salmonella* in commercial bovine production systems" contains management measures for the introduction of bovines into establishments. One of the recommended measures allows the use of new genetic material in the form of semen and embryos. This indicates that the OIE does not consider germplasm a risk for *Salmonella* transmission.

The likelihood of exposure, establishment and/or spread of salmonella via bovine serum based on the factors mentioned above is assessed as negligible to very low.

26.2.3. Consequence assessment

Salmonella spp. are multi-host pathogens. If contaminated vaccines are used on a variety of species, they may result in clinical disease in these animals.

Salmonellosis can affect all age groups in cattle and is likely to cause clinical disease in calves, while adult cattle are often subclinical (Richardson, 1975). If cattle become infected, they could become a source of contamination of the environment and may transmit to other animal species as well as people.

Morbidity in cattle is variable, while mortality is usually low. Morbidity and mortality rates are dependent on multiple factors such as the salmonella species, serotype, age groups affected and management and husbandry practices (Fenwick and Collett, 2004).

Salmonellosis is a zoonotic disease. The Environmental Science and Research Institute reports on all human and non-human *Salmonella* species isolated. In 2018, there were 1,134 human isolates, 346 of which were *S. typhimurium*, with 788 other serotypes and five new human isolates. In 2017, there were seven new human isolates, and in 2016, there were two new isolates. For animals, there were 848 salmonella isolates in 2018, 282 of which were *S. typhimurium*, with 566 being other serotypes.

These statistics demonstrate that New Zealand has a large number of *Salmonella* spp. serovars in circulation. The impacts on animal or human health are presumably being managed by the health and veterinary sectors. Therefore, the consequences on animal and human health as a result of the introduction of a new *Salmonella* sp. are likely to be minimal.

Salmonella abortusovis is the only OIE-listed species and is host-specific for sheep. There are no reports of cattle infected with this *Salmonella* sp., and therefore, it is unlikely to contaminate bovine serum. Trade impacts relating to the entry of other *Salmonella* spp. would be minimal. There would be no costs incurred for eradication and or containment of the disease.

However, there would be costs for on-farm treatment, management, prevention and control. There would also be medical costs for salmonella outbreaks in humans.

The overall consequences of salmonellosis as a result of the entry, exposure, establishment and/or spread are assessed as low.

26.2.4. Risk estimation

The likelihood of entry of *Salmonella* spp. in bovine serum from Australia and the United States is assessed as very low, exposure, establishment and/or spread are assessed as negligible to very low, and the consequences of *Salmonella* spp. are assessed as low. Therefore, the overall risk is estimated as very low.

Since the entry, exposure, and consequence assessments are non-negligible for bovine serum imported from Australia and the United States, *Salmonella* spp. are a risk in the commodity. Therefore, risk management measures are justified for bovine serum imported from Australia and the United States.

26.3. RISK MANAGEMENT

The following points were considered when presenting options for managing the risks:

- The incubation period is variable for salmonellosis.
- Initial infection may be followed by invasion of the gut and mesenteric lymph node barrier followed by bacteraemia.
- The disease is often associated with systemic infections that may result in shedding in subclinical animals.
- Salmonellae are rod-shaped bacteria, 2–5 μm long and 0.5–1.5 μm wide.
- Salmonellosis can affect all age groups and is likely to cause clinical disease in calves, while adult cattle are often subclinical.
- When an animal is infected with salmonella, it may become a clinical case or an active, latent or a passive carrier.
- Transmission of salmonella occurs via direct contact from contaminated faeces, feed, and pastures.
- Diagnosis includes bacterial culture and typing, PCR and serology.
- Experimental production of salmonellosis in cattle, including abortion, has been possible only when large infective doses were used; 10^8 to 10^9 organisms by intravenous injection.
- Salmonella has been isolated from blood.

26.3.1. Options

The following options or a combination of these options can be considered to manage the risk associated with salmonellosis.

1. The animals used for blood collection must have originated from herds with no history of salmonella outbreaks within the last three months preceding the date of blood collection and showed no clinical signs of the infection on the day of blood collection.

    a. For abattoir-sourced bovine serum, the serum was derived from animals that were disease-free since birth or for the last three months. The animals passed antemortem examination and postmortem inspection and were processed in premises under the oversight of the competent authority.

    b. For donor-animal-derived bovine serum, the serum was derived from herds that were under veterinary supervision. The donors were disease-free since birth or for the last three months, or the donor was tested with an MPI-approved/recommended test, with negative results, at the time of blood collection.

2. Bovine serum could be either:

    a. tested with an MPI-approved/recommended test, with negative results; OR

    b. subjected to gamma irradiation at a minimum dose of 35 kGy; OR

    c. subjected to sterile filtration with a membrane filter pore size of 0.2 μm or less.

27. Mollicutes that affect bovids (including *Mycoplasma bovis)*

27.1. TECHNICAL REVIEW

27.1.1. Aetiology

Family: *Mycoplasmataceae*
Genus: *Mycoplasma, Ureaplasma, Acholeplasma*
Species: *Mycoplasma bovis*, *Mycoplasma mycoides* subsp. *mycoides* and others

27.1.2. OIE List

Mycoplasma mycoides subsp. *mycoides* small colony (SC) (contagious bovine pleuropneumonia) and *Mycoplasma agalactiae* (Contagious agalactia) are OIE-listed diseases (OIE, 2020).

Mycoplasma bovis (*M. bovis*) and other mollicutes that affect bovids are not OIE-listed pathogens.

27.1.3. New Zealand status

Mycoplasma mycoides subsp. *mycoides* SC and *Mycoplasma agalactiae*

Mycoplasma mycoides subsp. *mycoides* SC was last detected in New Zealand in 1864 and is on the Biosecurity (Notifiable Organisms) Order 2016.

Mycoplasma agalactiae has never been reported in New Zealand and is on the Biosecurity (Notifiable Organisms) Order 2016.

Mycoplasma bovis

M. bovis was detected in New Zealand in July 2017 in the South Island. Evidence of the organism was later found on both the North Island and the South Island. The current disease management strategy is to eradicate *Mycoplasma bovis* (Biosecurity New Zealand, 2018).

Other mollicutes that affect bovids

The following mollicutes have been identified in New Zealand and are not considered further in this IRA:

Mycoplasma mycoides subsp. *mycoides* LC (Jackson and King, 2002)
Mycoplasma alkalescens (Brookbanks *et al*., 1969)
Mycoplasma arginini (Belton, 1990; Belton, 1996)
Mycoplasma dispar (Hodges *et al*., 1983)
Acholeplasma laidlawi (Belton, 1990; Belton, 1996)
Ureaplasma spp. (Hodges and Holland, 1980; Thornton and Wake, 1997)

The following mollicutes have not been identified or described in New Zealand:

Mycoplasma bovigenitalium
Mycoplasma verecundum

Mycoplasma californicum
Mycoplasma canadense
Mycoplasma Group 7
Acholeplasma axanthum
Acholeplasma modicum
Ureaplasma diversum

It is likely that there are other unidentified species that occur both in New Zealand and overseas.

27.1.4. Zoonotic potential

Certain mollicutes such as *Mycoplasma pneumoniae* are zoonotic and have been reported as the cause of various conditions in humans (Embree and Embil, 1980). Mollicutes have also been demonstrated as the cause of neonatal infections and premature births (Waites *et al*., 2005). There are two reported cases of *M. bovis* infection in immunocompromised people (Madoff *et al*., 1979; Pitcher and Nicholas, 2005).

27.1.5. Epidemiology

Host range

The range of animal hosts which are known to harbour mollicutes varies; non-human primates, domestic (or captive) birds, dogs, cats, laboratory animals, wild mammals, wild birds, fish and reptiles (Nicolet, 1996).

Geographical distribution

Mycoplasma mycoides subsp. *mycoides* SC was last reported in Australia in 1967 and in the United States in 1892 (WAHIS, 2019c) and has been eradicated from these countries. It will, therefore, not be considered further. Should the country disease status change with regards to the above organisms, a risk review would be required.

In a global study by Parker and others (2018) *M. bovis* was isolated in 12 countries, including Australia.

M. bovis was first isolated in the United States in 1961 (Parker *et al*., 2018) and has subsequently spread to numerous countries, achieving worldwide distribution (Nicholas and Ayling, 2003). In 2003, a survey of 871 dairies in the United States was carried out by the USDA (National Animal Health Monitoring System). Bulk tank milk samples were cultured, and results revealed that 6.8% of farms were positive for *M. bovis* (USDA, 2003). Individual cow prevalence varies widely between herds and studies (Maunsell *et al*., 2011).

Recent longitudinal studies in the United States indicate that most calves in *M. bovis* herds become infected. Prevalence in non-stressed beef calves is usually low (0–7%) (Maunsell *et al*., 2011). Calves that are comingled, transported or at feedlots are thought to have high *M. bovis* prevalence without expressing the clinical disease (Boothby *et al*., 1983). Conversely, in a study by Gagea and others (2006), *M. bovis* was identified as a significant

cause of morbidity and mortality in feedlot calves in the United States. Other *Mycoplasma* and *Ureaplamsa* spp. were also found but were less common (Gagea *et al*., 2006).

Significant variations in the prevalence of mycoplasma mastitis are observed globally. Some countries such as Belgium, France, and Greece, have an estimated between herd prevalence ranging from 1–5.4% for *M. bovis*, based on bulk tank surveys (Fox, 2012). In contrast to this, surveys in Mexico and Iran investigating mycoplasma mastitis have indicated herd prevalence rates as high as 55–100% (Fox, 2012).

Disease caused by mycoplasma species have been identified in all major dairy producing regions within Australia (Dairy Australia, 2017). Recent reports assert that relatively few Australian dairy herds are infected. One study showed that one herd was positive (0.4%) with a herd-level prevalence of 0.9% (95% probability interval 0.1–3.7%) when 238 dairy herds were randomly selected and tested via PCR (Dairy Australia, 2017; Morton *et al*., 2014).

Pathogenesis

Although mycoplasmas are generally considered to play a secondary role in infections most often thought to exacerbate preexisting disease, it has been shown that *M. bovis* can play a primary role in cattle (Brishard, 2003).

Mycoplasma species have a global distribution causing severe disease in cattle, including mastitis, arthritis, pneumonia, otitis media and reproductive disorders (Parker *et al*., 2018).

In Australia, the most common disease presentation of mycoplasma infections is mastitis. However, other clinical conditions include arthritis/tenosynovitis, pneumonia, keratoconjunctivitis, otitis, meningitis, endometritis, salpingitis, oophoritis, seminovesiculitis, infertility and abortion (Nicholas and Ayling, 2003; Pfützner and Sachse, 1996).

Sudden mastitis outbreaks associated with high morbidity can be followed by spontaneous elimination of the pathogen. Nicholas and others (2016) noted that the disease is often self-limiting, disappearing within months of outbreaks, sometimes without any intervention (Nicholas *et al*., 2016).

In New Zealand, there have been two reports of explosive outbreaks of mastitis caused by *Mycoplasma alkalescens* in the late 1960s and *Mycoplasma dispar* in the early 1980s respectively (Brookbanks *et al*., 1969; Hodges *et al*., 1983). Recently, *M. dispar* has been diagnosed as part of the current *M. bovis* outbreak investigation. This demonstrates that the agent can be present, presumably at an extremely low level, and is not commonly associated with disease (MPI, 2019b).

Genetic characterisation of *M. bovis* in Australia suggests that host and environmental factors play a significant role in determining the host–pathogen outcomes (Dairy Australia, 2017).

A carrier state has been reported (González and Wilson, 2003). These subclinical carriers may shed the organism through nasal discharges or in milk for months to years without clinical signs (Wilson *et al*., 2007).

Studies of *M. bovis* and other mycoplasmas suggest that they may spread systemically via invasion of peripheral blood mononuclear cells and erythrocytes while evading immune responses (Groebel *et al*., 2009; Vogl *et al*., 2008). This implies that mycoplasmas are found in blood and may remain in serum after separation. *M. arginini* and *A. laidlawii* are two other mycoplasmas contaminating cell cultures and originate in fetal or newborn bovine serum (NBS) (Barile and Rottem, 1993; Nikfarjam and Farzaneh, 2012).

The bulk of the literature on contagious agalactia has reported the disease to be prevalent in sheep and goats. However, there are a few publications where *M. agalactiae* has been described in symptomatic and asymptomatic cattle (Catania *et al*., 2016; Spickler, 2018d). These could be incidental findings.

Literature on contamination of bovine serum with mollicutes is sparse, although contamination is known to have occurred. Nims and others (2011) cited case studies by Dehghani and others. In their review, they described proven occurrence of bovine serum contamination with *Mycoplasma* bovine Group 7. A review article by Hanson and others (2019) also concluded the same, suggesting that all commercial lots of bovine serum are likely to have some level of mollicute contamination.

Transmission

Mycoplasmas are potentially highly contagious pathogens (González and Wilson, 2003) that colonise the mucosal surfaces of mammary glands, nose, respiratory tract, eyes, ears, vagina and prepuce. The organisms are transmitted via secretions from these surfaces (Fox *et al*., 2005).

The main route of transmission is aerosol droplets from infected animals (Stipkovits *et al*., 2000). The spread of the disease occurs primarily through the introduction of infected cattle, ingestion of infected milk and the contamination of equipment such as milking machines. The udder may become infected through the teat canal from contaminated milking pens, milking machines, wiping cloths, milkers and fomites (Dairy Australia, 2017).

Transmission via contaminated semen has also been reported (Haapala *et al*., 2018).

Diagnosis

Direct culture on mycoplasma agar media can be used to identify this group of pathogens. However, limitations to culture methods include the long duration of culture (10 days), need for special conditions, high expense and the lack of primary specificity to distinguish between true pathogens and commensal organisms. Therefore, cultures of bulk milk tank samples are used only as a screening tool to determine the mycoplasma herd status. This type of monitoring lacks sensitivity relating to the detection of *Mycoplasma* spp. in bulk milk tank samples of cows that shed low levels of the organism in their milk (Fox *et al*., 2005).

Currently, *M. bovis* is the only mycoplasma species that has a commercially available polymerase chain reaction (PCR) test, which is considered the fastest and most reliable detection method. However, sensitivity and speed may vary depending on the method. The

disadvantage is that PCR does not distinguish between live and dead cells (Akers *et al.*, 2009).

Enzyme-linked immunosorbent assay (ELISA) test kits are available to detect *M. bovis* antibodies in milk and serum. However, this test merely measures exposure. It is poorly associated with detection of seroconversion for infection status or disease of an individual animal (Fox *et al.*, 2005). It could be used as a herd prevalence test.

Identifying a carrier animal is problematic. There is currently no test that can reliably detect an *M. bovis* carrier animal that has no clinical signs and is not shedding the organism in milk (Dairy Australia, 2017).

Treatment, control and prevention

Even though *Mycoplasma* spp. have shown susceptibility in vitro to various antibiotics, no antibiotic treatment is proven to be effective in treating mycoplasma mastitis in the field (Fox, 2012).

Prevention of *Mycoplasma* spp. in a herd centres on avoiding sources of infections, which include:

- introduced livestock (cows, calves and bulls),
- infected milk (calves),
- equipment (those that contact the mucosal surfaces of animals, e.g. AI guns),
- people (service providers, AI technicians, veterinarians), and
- germplasm (semen, embryos).

The most common source of infection is livestock introductions. Maintaining a closed herd and strict biosecurity would prevent the entry of *Mycoplasma* spp. into a naive herd (Dairy Australia, 2017).

In 2002, Texas Vet Lab completed the USDA licencing requirements for a fully licensed commercial *Mycoplasma bovis* Bacterin. This became the first licensed *M. bovis* vaccine for cattle in the United States, but its use is limited (Texas Vet Lab, 2019).

Currently, there is no registered vaccine against *Mycoplasma* spp. for cattle in Australia (Dairy Australia, 2017).

27.2. RISK ASSESSMENT

27.2.1. Entry assessment

M. bovis subclinical carrier animals have been identified. These animals may shed the organism through nasal discharges or in milk for months to years without clinical signs. During this period, mycoplasmas may be present in the blood. As a result, subclinically infected animals could pass antemortem examination and postmortem inspection at slaughter plants or be considered as clinically healthy donor animals. Therefore, collecting infected blood from these subclinically infected carrier animals is plausible.

Several studies have identified mycoplasmas as contaminants of bovine serum.

The herd-level prevalence of *M. bovis* alone in the United States was reported to be 6.8% in dairy herds and 0–7% in non-stressed beef calves. The prevalence was higher in stressed beef calves. Individual cow prevalence varies widely between herds and studies (Maunsell *et al*., 2011). However, these reported prevalence figures are generally considered low.

Recent studies in southeastern Australia reported low herd-level prevalence of 0.9% (95% probability interval 0.1–3.7%).

Based on prevalence data, the likelihood that blood collected from a mollicute-infected animal in Australia and the United States is likely to be low.

Therefore, the likelihood of entry of mollicutes in bovine serum is assessed as low.

27.2.2. Exposure assessment

Vaccines produced from contaminated bovine serum could contain viable mollicutes. Parenteral administration of the contaminated vaccines is the principal pathway of transmission to animals. Even though there is no evidence for animals getting infected through vaccination, animals inoculated with the contaminated vaccine could develop the disease and subsequently act as a source for other susceptible animals. Because vaccination is generally implemented as a herd management tool, a large number of animals could get exposed through contaminated vaccines.

The infective dose of mollicutes in processed vaccine is unknown. Thus, the likelihood of the infected vaccine resulting in infection and disease in vaccinated animals or humans is unknown.

Following experimental infection of *M. bovis* by uterine inoculation, the agent has been associated with genital lesions including endometritis, salpingitis, salpingoperitonitis (Hartman *et al*., 1964) as well as placentitis, fetal deaths and abortions (Stalheim and Proctor, 1976). More recently, a study by Guo and others (2014) found that intrauterine infusion with *M. bovis* triggered an endometrial inflammatory response and increased inflammatory cytokines. If the media and solutions used for the collection, processing and storage of embryos are contaminated with mycoplasmas, this could result in infection of recipient cows.

Should animals become infected with mollicutes, they could in turn become a source of ongoing contamination of the environment, equipment and other animals.

The overall likelihood of exposure, establishment and/or spread of mollicutes via bovine serum based on the factors considered above is assessed as low.

27.2.3. Consequence assessment

Mollicutes have the ability to infect and cause disease to a wide range of animal hosts (Catania *et al*., 2016; Spickler, 2018d).

M. bovis is considered to be very host specific to cattle, but there are infrequent reports of *M. bovis* in hosts such as sheep, goats and deer (Ayling *et al*., 2004; Dyer *et al*., 2004; Egwu *et al*., 2001; Kumar *et al*., 2012).

The consequences of *M. bovis* infection is limited to the cattle industry. *M. bovis* impacts the health and production of cattle herds, thereby causing economic losses. Production losses, including reduced milk production and increased culling as a result of therapy-resistant mastitis, reduced daily weight gain due to calf pneumonia and arthritis, are observed in affected herds. Currently, there is an emphasis on keeping *M. bovis* out of New Zealand as a result of the detection in the country in 2017 and the subsequent eradication programme.

Some mollicutes are zoonotic, and introduction of zoonotic mollicutes to New Zealand could cause infection in the human population. Vaccines contaminated with mycoplasmas injected into infants, elderly or immunocompromised people could result in infection.

The only OIE-listed mollicute of significance is the causative agent of contagious agalactia, *Mycoplasma agalactiae*. It is suspected to be present in the United States. As disease in cattle caused by this organism has only been reported on rare occasions, the likelihood of this organism entering via bovine serum is low. Therefore, trade impacts would be low.

The consequences of the entry and establishment of mollicutes for the economy (trade and market access) and animals (non-bovine species) remains low. However, the consequences of entry and establishment of mollicutes for the cattle industries would be high, both in terms of production losses and resultant economic losses and in terms of social impacts associated with disease control activities.

The overall consequences of mollicutes as a result of the entry, exposure, establishment and/or spread are assessed as moderate.

27.2.4. Risk estimation

The likelihood of entry of mollicutes in bovine serum from Australia and the United States is assessed as low, the likelihoods of exposure, establishment and/or spread are assessed as low, and the consequences of mollicutes are assessed as moderate. Therefore, the overall risk is estimated as low.

Since the entry, exposure, and consequence assessments are non-negligible for bovine serum imported from Australia and the United States, mollicutes are a risk in the commodity. Therefore, risk management measures are justified for bovine serum imported from Australia and the United States.

27.3. RISK MANAGEMENT

The following points were considered when describing options for managing the risks:

- *M. bovis* was detected in New Zealand in July 2017. Evidence of the organism was later found on both the North Island and South Island. The current disease management strategy is to eradicate *M. bovis* (Biosecurity New Zealand, 2018).
- Some mollicutes are zoonotic.
- Mollicutes may be multi-host pathogens.
- *Mycoplasma mycoides* subsp. *mycoides* SC was last reported in Australia in 1967 and the United States in 1892 and was eradicated from these countries.
- Mycoplasma carrier state has been reported (González and Wilson, 2003).

- Transmission is via aerosol droplets produced by mucosal surfaces of mammary glands, nose, respiratory tract, eyes, ears, vagina and prepuce.
- Diagnostic tests include direct culture, PCR and ELISAs.
- There is currently no test to reliably detect an *M. bovis* carrier animal that is exhibiting no clinical signs and is not shedding the organism in milk.
- Mollicutes have been found in blood and serum.

27.3.1. Options

The following options or a combination of these options can be considered to manage the risk associated with mollicutes in bovine serum:

1. The animals used for blood collection showed no clinical signs of the infection on the day of blood collection.
    a. For abattoir-sourced bovine serum, the serum was derived from animals originated from mollicute-free herds. The animals passed antemortem examination and postmortem inspection and were processed in premises under the oversight of the competent authority.
    b. For donor-animal-derived bovine serum, the serum was derived from herds tested free of mollicutes that were under veterinary supervision, or individual animals tested with an MPI-approved/recommended test, with negative results, at the time of blood collection.
2. Bovine serum could be either:
    a. tested with an MPI-approved/recommended test, with negative results; OR
    b. subjected to gamma irradiation at a minimum dose of 35 kGy; OR
    c. subjected to sterile filtration with a membrane filter pore size of 0.1 μm or less.

28. *Babesia bovis* and *B. bigemina*

28.1. TECHNICAL REVIEW

28.1.1. Aetiology

Family: *Babesiidae*
Genus: *Babesia*
Species: *Babesia bovis* and *Babesia bigemina* (Petersen and Ahmed, 2016)

28.1.2. OIE List

Bovine babesiosis is an OIE-listed disease (OIE, 2020).

28.1.3. New Zealand status

Bovine babesiosis is subject to general surveillance in New Zealand and has never been reported (WAHIS, 2019a). Bovine babesiosis is listed as a disease absent from New Zealand (MPI, 2020). Both the pathogen and the tick vector are absent from

New Zealand and are listed as notifiable under the Biosecurity (Notifiable Organisms) Order 2016.

28.1.4. Zoonotic potential

Although some species of *Babesia* (e.g. *B. microti*) can affect people, most bovine *Babesia* species do not seem to affect humans. There are no reports of zoonotic diseases caused by the species under consideration in this assessment. There are, however, reports of another species, *B. divergens,* causing rapidly progressing, life-threatening haemolytic anaemia in people who have had splenectomies (Morch *et al*., 2015; Zintl *et al*., 2003).

28.1.5. Epidemiology

Host range

Cattle are the primary hosts and reservoirs for *B. bovis* and *B. bigemina*. Both these organisms have been detected by PCR in other animals including water buffalo (da Silva *et al*., 2013; Romero-Salas *et al*., 2016), white-tailed deer (Cantu *et al*., 2007; Cantu-C *et al*., 2009; Holman *et al*., 2011), nilgai antelope (Cardenas-Canales *et al*., 2011) and pampas deer.

Geographical distribution

Babesia bovis and *B. bigemina* have a worldwide distribution in tropical and subtropical regions where the *Rhipicephalus* tick vector occurs (Bram *et al*., 2002). Although there are some differences in their distribution, these two organisms have been reported from Asia, Africa, the Middle East, Australia, Central America, South America, parts of southern Europe, and some islands in the Caribbean and South Pacific.

In Australia, the disease in domestic animals is restricted to certain zones/regions of the country (WAHIS, 2019a). The disease is typically seen in warm, humid, northern and northeastern, coastal and subcoastal regions where the cattle tick *Rhipicephalus microplus* occurs (Bock, de Vos, and Molloy, 2006).

Bovine babesiosis is absent from the United States (WAHIS, 2019a). The United States carried out an intensive national eradication campaign, which was completed in 1943. The eradication program successfully eliminated the tick vector *Rhipicephalus*, which currently persists only in a quarantine buffer zone between the United States and Mexico (Bram *et al*., 2002). In the United States, the last reported occurrence of the disease in domestic animals was in 1943. Babesia is subject to general surveillance (WAHIS, 2019a).

Pathogenesis

Infection of red blood cells with *B. bigemina* leads to rapid and sometimes massive intravascular haemolysis. The pathogenic effects of this erythrocyte destruction include haemoglobinuria, anaemia, and jaundice.

In the case of *B. bovis,* pathogenesis is primarily related to the host's immune response and the overproduction of cytokines and other pharmacologically active agents. The sequelae to this being vasodilation, hypotension, increased capillary permeability, oedema, vascular collapse, coagulation disorders, endothelial damage and circulatory stasis.

Lesions include swollen liver; enlarged gall bladder containing thick, granular bile; enlarged soft and friable spleen; kidneys with possible petechial haemorrhages; and ecchymotic haemorrhages of the epicardium and endocardium. The grey matter of the brain may also appear pink (Bock *et al*., 2004).

Clinical signs most commonly associated with infection with *Babesia* include fever, haemolytic anaemia, haemoglobinuria, and, in severe cases, death (Bram *et al*., 2002). Although the clinical signs that develop during infections with *B. bovis* or *B. bigemina* are similar, the respective courses of disease can differ markedly.

Infection with *B. bovis* is characterised by high fever, anorexia, ataxia, and general circulatory shock. Neurological signs such as circling, head pressing, mania and convulsions can occur as a result of sequestration of infected erythrocytes in cerebral capillaries. Anaemia and haemoglobinuria may appear later in the course of the disease. In acute cases, the maximum parasitaemia (infected erythrocytes) in circulating blood is less than 1%, and signs are often seen before parasites can be detected in blood smears (Bock *et al.*, 2006; OIE Terrestrial Manual, 2018d).

In contrast, clinical signs associated with *B. bigemina* typically develop late in infection when patent parasitaemia is advanced. During parasitaemia, the percentage of infected erythrocytes in circulating blood is often 10% and may be as high as 30%. In cattle infected with *B. bigemina*, haemoglobinuria occurs more consistently, anaemia and jaundice occur more rapidly, and death can occur with little warning (Bock *et al*., 2006; OIE Terrestrial Manual, 2018d).

Morbidity and mortality rates can vary according to virulence and other attributes of the agent, as well as age and breed of the host. Babesiosis is more severe in older cattle and is unusual in cattle less than nine months old due to the higher innate resistance observed in younger cattle between three and nine months of age. *Bos indicus* breeds have milder signs than *Bos taurus* breeds. *B. bovis* is generally more pathogenic than *B. bigemina* (Bock *et al*., 2006; Suarez *et al*., 2019). The overall mortality rate for bovine babesiosis is reported to be 5–10%, even with treatment. *B. bovis* mortality can reach 50–100% in untreated animals infected with this organism (Bock *et al*., 2004).

Transmission

Babesia bovis and *B. bigemina*, the causal agents of bovine babesiosis, are arthropod-borne pathogens transmitted by the tick vectors *Rhipicephalus microplus* (formerly *Boophilus microplus*) and *R. annulatus* (formerly *Boophilus annulatus*). Additional members of the genus, including *R. decoloratus*, *R. geigyi,* and *R. evertsi*, have also been suggested as vectors in some regions (Bock *et al*., 2004).

Rhipicephalus microplus and *R. annulatus* are one-host ticks that complete their life cycle on a single host and preferentially feed on cattle. They require high humidity and ambient temperatures of at least 15–20°C for egg-laying and hatching (Bock *et al*., 2006). *Babesia bigemina* is transmitted by the adult and nymphal stages of *R. microplus* and *R. annulatus*, while *B. bovis* is transmitted only by the larval stages of these vectors.

In the vertebrate host (cattle), *Babesia* sporozoites invade red blood cells and transform into trophozoites. Mature sporozoites are approximately 2.2 by 0.8 μm in size (Homer *et*

al., 2000). Two merozoites are generated from each trophozoite by binary fission. The merozoites are released from the red blood cells, with some infecting new red blood cells, while others can be picked up by adult ticks to continue their cycle in the invertebrate host (Jonsson *et al*., 2008; Mosqueda *et al*., 2012).

In the invertebrate host (tick), the merozoites are freed from the ingested red blood cells in the tick midgut and develop to gametocytes. The gametocytes transform into male and female gametes that form a zygote after fusion. The zygote develops into an infecting stage and penetrates the tick intestinal cells. Motile kinetes develop and escape into the haemolymph and distribute into the different cell types and tissues (Bock *et al*., 2004).

Of note is their ability to invade the ovaries where embryo cells are infected, giving rise to transovarial transmission: when the female tick lays her eggs, the embryos are already infected. Hatched infected larvae attach to a vertebrate host (cattle). The larvae feed on bovine blood, and the sporozoites are released with saliva into the animal's circulatory system.

Cattle that recover from *B. bigemina* clinical disease remain infective for ticks for four to seven weeks and carriers for only a few months. In the case of *B. bovis*, recovered cases remain symptomless carriers for several years with the duration of infection being breed dependent (Bock *et al*., 2004).

Non-vector borne routes of transmission may occur where the parasite is transmitted directly between animals in blood. Such pathways include blood transfusions and iatrogenic spread through the reuse of needles or field surgical instruments. Transplacental transmission has been demonstrated for *B. bovis* and *B. bigemina* in cattle, but seems to be infrequent (Bock *et al*., 2004).

Diagnosis

A diagnosis of bovine babesiosis may be achieved through identification of the causal organism using direct microscopy or antigen detection, or demonstration of an immune response (OIE Terrestrial Manual, 2018d).

Using direct microscopic examination, the organisms can be seen in thin smears of blood, brain, kidney, liver and spleen from recently dead cattle, and in thick and thin smears of blood from superficial skin capillaries such as the tip of the ear or tip of the tails of live cattle (Bock *et al*., 2006). Direct microscopy is usually adequate for detection of acute infections, but not for detection of carriers where the levels of parasitaemia is very low. The most appropriate use of this diagnostic method is for confirmation of clinical cases (OIE Terrestrial Manual, 2018d).

An alternative method of agent identification is the nucleic acid-based diagnostic assays. Polymerase chain reaction (PCR) assays are 1,000 times more sensitive than microscopy, particularly for detecting *B. bovis* and *B. bigemina* in carrier cattle. The PCR assay is useful as a confirmatory test and for regulatory testing, since it is the OIE-recommended test for identifying individual animal infection status.

There are several serological tests that can be used for detecting antibodies to *B. bovis* and *B. bigemina*. These include the indirect fluorescent antibody test (IFAT), the enzyme-

linked immunosorbent assay (ELISA), the competitive ELISA (C-ELISA), and the complement fixation test (CFT).

ELISA is currently the preferred method for large-scale population testing and epidemiological studies. ELISA is the OIE-recommended method for identifying population freedom from infection, determining eradication policies, performing prevalence of infection surveillance and assessing immune status in individuals or populations post-vaccination. It is not an appropriate test for establishing the infection status of an individual animal.

Treatment, control and prevention

Treatment of infected animals involves the administration of anti-babesia drugs such as imidocarb dipropionate (imidocarb) or diminazene aceturate, with appropriate supportive therapy such as blood transfusions.

Prevention and control strategies for bovine babesiosis mostly centre on immunisation, anti-babesia drugs, tick management or a combination of these approaches (Mosqueda *et al*., 2012).

Live attenuated vaccines are available for *B. bovis* and *B. bigemina*. Vaccines are typically administered to calves less than one year of age. Vaccines may be administered to older animals, but such animals should be monitored for adverse reactions and treated with a babesiacide if required. Protective immunity develops in three to four weeks and is usually lifelong (OIE Terrestrial Manual, 2018d).

Tick control may be carried out using acaricides, cattle tick vaccination or modification of tick habitats. Eliminating *B. bovis* and or *B. bigemina* is difficult once the organisms have been introduced into a region where there are competent tick vectors. However, eradication of the parasite through the elimination of tick vectors and/or intensive chemotherapeutic regimes may be successful in some cases, as evidenced by the eradication of *B. bovis* and *B. bigemina* from the United States.

Natural endemic stability, a condition that implies a high incidence of organisms in cattle but rarely the presence of clinical disease, is unreliable as the sole control strategy for bovine babesiosis as it can be disrupted by climate, host and management factors (Jonsson *et al*., 2008).

28.2. RISK ASSESSMENT

28.2.1. Entry assessment

Cattle that recover from *B. bovis* infection or *B. bigemina* infection can remain carriers of the pathogen for several years or months, respectively. Given that chronic or carrier cases are unlikely to show clinical signs of disease, it is plausible for an animal with parasitaemia to be selected as a donor. Therefore, it is possible that blood collected from an animal experiencing a parasitaemia would contain the hazard. It is difficult, however, to state with any great certainty how likely this would be. The level of parasitaemia can vary according to several factors including prevalence, *Babesia* species, stage of infection, and breed of animal.

Although mostly associated with the red blood cells, the sporozoite and merozoite stages also occur outside the red blood cell, free in the plasma (Jonsson *et al.*, 2008; Mosqueda *et al.*, 2012).Bovine serum produced from blood containing sporozoites and/or merozoites may contain these developmental stages of *Babesia* species.

Therefore, the likelihood of entry of *B. bovis* and/or *B. bigemina* is assessed as very low.

28.2.2. Exposure assessment

Bovine serum sourced from an infected animal could contain the hazard as outlined above. Therefore, it could be assumed that susceptible cattle in New Zealand could potentially be exposed to the hazard in animal vaccines or germplasm products produced using the contaminated serum.

Given the epidemiology of the agent, the most viable pathway of infection would be the parenteral administration of vaccines produced using babesia-contaminated bovine serum. As there are no reports of transmission of *Babesia* spp. via germplasm, this pathway is not assessed further.

The likelihood that exposed animals would become infected following the use of contaminated vaccines is uncertain. Given that sporozoites and merozoites are predominantly associated with red blood cells, it would seem highly unlikely that the low volume serum component of vaccines would contain sufficient organisms to constitute an infective dose.

The biological vectors of *B. bovis* and *B. bigemina*, *R. microplus* and *R. annulatus* are not found in New Zealand. In the event that animals exposed to a contaminated vaccine become infected, the likelihood of subsequent transmission and establishment is negligible.

Although *Haemaphysalis longicornis*, the cattle tick found in New Zealand is a competent vector of *Babesia ovata,* it has not been demonstrated to be a competent biological vector of *B. bovis* or *B. bigemina*.

If New Zealand cattle are exposed to *Babesia* spp. via contaminated vaccines, the likelihood of infection is very low. In the unlikely event that infection does occur, the likelihood of establishment and/or spread of the hazard in New Zealand in the absence of a competent vector is negligible.

28.2.3. Risk estimation

Since the exposure assessment is negligible, the risk estimation is also negligible. Therefore, risk management measures are not required.

29. *Anaplasma marginale, A. centrale, A. caudatum, A. phagocytophilum*

29.1. TECHNICAL REVIEW

29.1.1. Aetiology

Family: *Anaplasmataceae*
Genus: *Anaplasma*
Species: *Anaplasma marginale, A. centrale, A. caudatum, A. phagocytophilum*

Anaplasma phagocytophilum is a new name. This species includes species previously known as *Ehrlichia phagocytophila, E. equi* and human granulocytic ehrlichiosis (HGE) agent (Dumler *et al*., 2001).

For this IRA, 'bovine anaplasmosis' refers to the infection in cattle with either *Anaplasma marginale, A. centrale* or *A. caudatum*. Tick-borne fever (TBF) refers to the infection in cattle with *A. phagocytophilum.*

29.1.2. OIE List

Bovine anaplasmosis is an OIE-listed disease (OIE, 2020)

29.1.3. New Zealand status

Bovine anaplasmosis has never been reported in New Zealand (WAHIS, 2018) and is listed as a disease absent from New Zealand (MPI, 2020). All *Anaplasma* spp. are listed as notifiable under the Biosecurity (Notifiable Organisms) Order 2016 (MPI, 2016a).

29.1.4. Zoonotic potential

Most of the *Anaplasma* spp. do not seem to affect humans. *Anaplasma phagocytophilum* is zoonotic and causes human granulocytic anaplasmosis (Woldehiwet, 2010). All the other species of *Anaplasma* considered in this IRA are not zoonotic (OIE Terrestrial Manual, 2018c).

29.1.5. Epidemiology

Host range

Bovine anaplasmosis is a tick-borne disease of cattle. Cattle are the primary hosts and water buffalo, bison, African antelopes and some species of deer can also be infected (Aubry and Geale, 2011; Kocan *et al*., 2010; Woldehiwet, 2010). *Bos indicus* cattle breeds are more resistant to bovine anaplasmosis than *Bos taurus* breeds (Potgieter and Stoltsz, 2004). Cattle of all ages become infected with the disease, but calves are less susceptible (Aubry and Geale, 2011).

TBF is a tick-borne disease caused by *A. phagocytophilum.* Cattle and sheep are the primary hosts, but infection has been detected in goats, horses, donkeys, dogs, cats and wild ruminants (Atif, 2015; Woldehiwet, 2010). Pusterla and others (2001) confirmed that cattle are not susceptible to infection with related species of *A. phagocytophilum,* like *E. equi* and human granulocytic ehrlichiosis (HGE) agent (Pusterla *et al*., 2001).

Geographical distribution

Bovine anaplasmosis has a worldwide distribution (Potgieter and Stoltsz, 2004) in tropical and subtropical regions, including South and Central America, the United States, Europe, Africa, Asia and Australia (Aubry and Geale, 2011).

In Australia, the disease is restricted to parts of the country (WAHIS, 2018) where the vector, *Rhipicephalus* (formerly *Boophilus*) *microplus*, is present (Bock *et al*., 2006). This includes the warm and high humid areas of northern and northeastern coastal and subcoastal regions (Animal Health Australia, 2018). In other regions of Australia, which are considered tick-free areas, anaplasmosis is a notifiable disease (Animal Health Australia, 2018; Bock *et al*., 2006).

In the United States, bovine anaplasmosis in domestic animals is present in all regions (Kocan *et al*., 2010; WAHIS, 2018) and is considered enzootic in every state except Hawaii (Aubry and Geale, 2011; McCallon, 1976).

Although *A. phagocytophilum* is found worldwide, the species infecting ruminants and causing TBF has only been reported in Europe, India and South Africa (Woldehiwet, 2019; Woldehiwet, 2010).

Since *A. phagocytophilum* causing TBF in ruminants is absent from Australia and the United States, *A. phagocytophilum* is not assessed further in this assessment.

Pathogenesis

Bovine anaplasmosis is caused by an intra-erythrocytic organism of the genus Anaplasma (Aubry and Geale, 2011; OIE Terrestrial Manual, 2018c). The incubation period for the infection varies from 7 to 60 days, depending on the dose of infective agent, with an average of 28 days (Kocan *et al*., 2010). Once infected, cattle become persistently infected carriers (latently infected) for life (Aubry and Geale, 2011). Carrier cattle have lifelong immunity and do not develop any clinical disease under stress or challenge exposure (Kocan *et al*., 2003). This could help to develop immune populations of cattle in endemic areas.

After the initial infection and incubation period, the organism invades erythrocytes and replicates (Kocan *et al*., 2004). Erythrocytes are the only site of infection for the bacteria, and phagocytosis of the infected erythrocytes result in anaemia and icterus without haemoglobinemia or haemoglobinuria (Kocan *et al*., 2010). During acute infection, 70% or more erythrocytes will be affected, and the membrane-bound inclusions within the cells will harbour four to eight organisms (Kocan *et al*., 2003). There is no evidence to prove the presence of the organism outside erythrocytes.

Bovine anaplasmosis is generally characterised by fever, progressive anaemia and icterus (Potgieter and Stoltsz, 2004). Pyrexia may occur in the very early stage of the infection and fever over 40°C persists throughout rickettsaemia (Kocan *et al*., 2010). Cattle of all ages can be affected, but the severity of the disease is age dependent. Calves are less susceptible to the disease, but cattle over two years can have an acute and fatal infection (Aubry and Geale, 2011).

The acute phase of the disease often results in death and is characterised by weight loss, fever, abortion and drop in milk production (Kocan *et al*., 2004). Mortality rates in acute infection vary from 29–49% (Aubry and Geale, 2011). Peracute infections with high mortality rates have been reported (Kocan *et al*., 2010; Potgieter and Stoltsz, 2004). Necropsy findings include anaemia, icterus, splenomegaly and hepatomegaly (Kocan *et al*., 2010).

Transmission

Bovine anaplasmosis is an arthropod-borne haemolytic disease transmitted by 19 different species of ticks worldwide (Aubry and Geale, 2011; Kocan *et al*., 2004). The principal methods of transmission of the disease are biological, mechanical and transplacental (Aubry and Geale, 2011).

Rhipicephalus microplus is the primary arthropod vector involved with the biological transmission of the disease in Australia (Bock *et al*., 2006). In the United States, *Dermacentor* spp. are the primary tick vectors involved (Aubry and Geale, 2011; McCallon, 1976).

Mechanical transmission occurs through fomites, including contaminated needles, dehorning equipment, ear-tagging devices and nose tongs (Aubry and Geale, 2011; Kocan *et al*., 2010). Biting flies, including stable flies (genus *Stomoxys*) and horse flies (genus *Tabanus*), also have the potential to mechanically transmit the disease (Aubry and Geale, 2011; Kocan *et al*., 2004; McCallon, 1976).

Diagnosis

Clinical diagnosis of bovine anaplasmosis can be made based on clinical signs and necropsy findings. Confirmation of clinical diagnosis may be achieved through direct microscopic evaluation of stained blood smears, and/or antigen detection and demonstration of immune response using serological or molecular procedures.

Light microscopy of blood and organ smears from liver, kidney, heart and lungs stained with Giemsa, Wright-Giemsa or Diff-Quick can be used to confirm the organism in the erythrocytes (Kocan *et al*., 2010; OIE Terrestrial Manual, 2018c). Identification is possible 2-6 weeks following transmission. This is the most appropriate method to confirm clinical cases but is not recommended in latent infections where the level of rickettsaemia is low (OIE Terrestrial Manual, 2018c).

Polymerase chain reaction (PCR) is the nucleic acid based test that can detect a lower level of infection (Aubry and Geale, 2011). The OIE recommends PCR for identifying individual animal infection status and for confirmation of clinical cases. A nested PCR and RT-PCR techniques have been recommended to identify carrier cattle (OIE Terrestrial Manual, 2018c).

Serological tests used to detect antibodies to *Anaplasma* spp. include the indirect fluorescent antibody test (IFAT), enzyme-linked immunosorbent assay (ELISA), competitive ELISA (C-ELISA) and complement fixation test (CFT).

The ELISA is the OIE-recommended test for identifying population freedom from infection, determining eradication policies, surveillance monitoring for the prevalence of

infection and for determining immune status post-vaccination (OIE Terrestrial Manual, 2018c).

Treatment, control and prevention

Treatment for bovine anaplasmosis involves the administration of tetracycline antibiotics, imidocarb, and a variety of chemotherapeutic agents.

Control measures for anaplasmosis include arthropod control, prevention of mechanical transmission, administration of antibiotics as a prophylactic measure and vaccination. Tick control measures include the use of acaricides and modification of habitats.

Vaccination has been the most economical and effective control method for bovine anaplasmosis. Live and killed (inactivated) vaccines are available and less virulent strains of *A. marginale or A. centrale* are used in the production of live vaccines (Aubry and Geale, 2011; OIE Terrestrial Manual, 2018c).

29.2. RISK ASSESSMENT

29.2.1. Entry assessment

Bovine anaplasmosis is an arthropod-borne disease caused by intra-erythrocytic organisms of the genus *Anaplasma*. The disease has a worldwide distribution, particularly in tropical and subtropical regions.

The organism is present in the blood, but it is always within erythrocytes. Post-blood collection processing for serum manufacturing, where all blood cells are removed, would be likely to remove all erythrocytes. There is no evidence documenting the presence of the organism outside erythrocytes.

Therefore, the likelihood of entry of *Anaplasma marginale, A. centrale, A. caudatum* and *A. phagocytophilum* in bovine serum is assessed as negligible.

29.2.2. Risk estimation

Since the likelihood of entry from this assessment is negligible, *Anaplasma marginale, A. centrale, A. caudatum* and *A. phagocytophilum* are not a risk in the commodity. Therefore, risk management measures are not required.

Appendix 1: Summary of Assessments

Risk organisms	OIE-listed	Zoonotic	Entry assessment rating*		Exposure assessment rating*	Consequence assessment rating*	Overall rating
			Australia	United States			
Virus							
Aino virus (Simbu virus group)	No	No	Low	Negligible	Very low	Very low	Very Low
Akabane virus (Simbu virus group)	No	No	Low	Negligible	Very low	Very low	Very Low
Bluetongue virus	Yes	No	Moderate	Moderate	Low	Moderate	Moderate
Bovine ephemeral fever virus	No	No	Very low to low	Negligible	Very Low	Very Low	Very Low
Bovine herpes virus 1	Yes	No	Negligible	Moderate	Moderate	Moderate	Moderate
Bovine herpes virus 5	No	No	Low	Low	Low to moderate	Very Low	Low
Bovine influenza D virus	No	Yes	Negligible	Low	Low	Low to Moderate	Low
Bovine viral diarrhoea virus (BVDV)	Yes	No	Moderate	Moderate	High	Moderate	Moderate
Cache Valley virus	No	Yes	Negligible	Moderate	Low	Low	Low
Epizootic haemorrhagic disease virus including Ibaraki	Yes	No	Low to moderate	Low to moderate	Low	Low to Moderate	Low
Palyam virus group (orbiviruses)	No	No	Negligible to very low	Negligible	Negligible	-	-
Bacteria							
Bacillus anthracis	Yes	Yes	Negligible	Negligible	-	-	-
Borrelia burgdorferi	No	Yes	Negligible	Low to moderate	Very Low	Very Low	Very Low

Risk organisms	OIE-listed	Zoonotic	Entry assessment rating*		Exposure assessment rating*	Consequence assessment rating*	Overall rating
Brucella abortus, *B. melitensis* and *B. suis*	Yes	Yes	Negligible	Low	Moderate	High	Moderate
Burkholderia pseudomallei	No	Yes	Low	Negligible	Low	Low	Low
Chlamydia abortus	Yes	Yes	Negligible	Very low to low	Low	High	Moderate
Coxiella burnetii	Yes	Yes	Moderate	Moderate	Low	High	Moderate
Leptospira spp.	No	Yes	Low	Low	Low	Low to moderate	Low
Mycobacterium bovis	Yes	Yes	Negligible	Very low	Moderate	Low to moderate	Low
Salmonella spp.	No	Yes	Very low	Very low	Negligible to very low	Low	Very low
Mollicutes							
Mycoplasma bovis and other molllicutes	No	Yes	Low	Low	Low	Moderate	Low
Protozoa							
Babesia bovis and *B. bigemina*	Yes	No	Very low	Very low	Negligible	-	-
Rickettsia							
Anaplasma marginale, *A. centrale*, *A. caudatum*, *A. phagocytophilum*	Yes	No	Negligible	Negligible	-	-	-
* Entry, exposure and consequence assessments are overall ratings of all the factors considered.							

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