OIE Standards for Diagnostic Tests and Vaccines for Brucellosis and Tuberculosis

Dr. Glen Gifford
Chargé de mission
Science and New Technologies Department
World Organisation for Animal Health

FAO-APHCA/OIE Regional Technical Workshop on the Prevention and Control of Animal Brucellosis and Tuberculosis in Asia
Bangkok, Thailand 11-13 September 2017
World Organisation for Animal Health (OIE)

- Intergovernmental animal health standard setting organisation, based in Paris. Currently 181 Member countries.

- **Technical standards** for animal health and welfare, and safe international trade in animals and animal products - recognised by World Trade Organization (WTO).

- Originally created as **Office International des Epizooties (OIE)** in 1924.
Who we are today…

Improving animal health and welfare worldwide

STANDARDS
for international trade of animals and animal products

under the mandate given by the WTO

TRANSPARENCY
of the world animal disease situation

including zoonoses

EXPERTISE
Collection and dissemination of veterinary scientific information

animal disease prevention and control methods

SOLIDARITY
between countries to strengthen capacities worldwide

Capacity building tools and programmes
The One Health Collaboration - Tuberculosis

Global leader for food and agriculture

Global leader for animal health and welfare standards

Global leader for human health

Tripartite FAO/OIE/WHO will define a common strategy to increase awareness and knowledge of the burden of zoonotic tuberculosis to advocate for the control of the disease at the animal source.
OIE: Who we are today...

Protecting animals, Preserving our future

181 Member Countries

One World One Health

313 Reference Centres

71 Partner Organisations

Headquarters (Paris) 95 staff

Regional Offices (12 Locations) 100 staff

Dr Monique Eloit Director General
Regional & Sub-Regional Representations

- **Bamako**: Gaborone, Nairobi, Tunis
- **Tokyo**: Bangkok, Panama
- **Buenos Aires**: Beirut
- **Moscow**: Brussels, Astana
OIE Mandate, Priorities, Activities

- Animal health and welfare standards (Terrestrial & Aquatic)
  - Aquatic Animal Health Code (Aquatic Code)
  - Manual of Diagnostic Tests for Aquatic Animals (Aquatic Manual)

- Disease surveillance, reporting, diagnosis, prevention, control and eradication (e.g. WAHIS)

- Networking, scientific expertise, training, capacity building
  - Specialist Commissions (e.g. Biological Standards Commission)
    - Working Groups
    - *Ad hoc* Groups
OIE Standards - Based on Science

• The source of the scientific information provided to the OIE for this process is a network of internationally recognised experts, mainly coming from the OIE Collaborating Centres and Reference Laboratories.

• OIE’s standards are regularly updated to take account of new information:
  1. Experts assess, provide advice, and draft text for inclusion in the relevant standard.
  2. OIE elected Specialist Commissions review and amend draft text in Codes and Manuals as appropriate.
     • Scientific Commission on Animal Diseases (SCAD)
       • Terrestrial Code
     • Biological Standards Commission (BSC)
       • Terrestrial Manual
  3. Member Countries are consulted through OIE Delegates, and invited to comment.
  4. Once the new text is agreed, it is adopted by the World Assembly of Delegates in May each year.
OIE Standards – Procedures for Development & Adoption

OIE Standards are developed and adopted by 181 Member Countries in a transparent, democratic process.

Once adopted, the standards are applicable in all OIE Member Countries, and become the internationally agreed basis for trade, under WTO SPS agreement.

OIE International Standard
(Published in OIE Code or Manual)
OIE Brucellosis and Tuberculosis Standards


    - *Brucella* spp. Chapter 8.4
    - *Mycobacterium Tuberculosis* Complex Chapter 8.11.

    - *Brucellosis* spp. Chapter 2.1.4
OIE Brucellosis and Tuberculosis Standards, continued

- **WAHIS** data collection to improve knowledge on the distribution of brucellosis and tuberculosis in animals worldwide.


- **Secretariat for Registration of Diagnostic Kits.** Applications for registration are evaluated by a panel of experts, mainly from OIE Collaborating Centres and Reference Laboratories. Secretariat serves as liaison with kit manufacturers, expert panel, and OIE Specialist Commissions.

1. **Expert panel** – Conducts technical evaluation and prepares summary report and recommendations.

2. **Specialist Commission** – Reviews report and provides opinion to OIE Director General on acceptance.

3. **Final decision** – Vote by OIE country delegates at General Session.
OIE Brucellosis and Tuberculosis Standards, continued

- Liaison with OIE Reference Centres, partner organisations, funders, research networks
  - OIE Reference Centres
  - Collaborating Centres & OIE Reference Laboratories
  - FAO-OIE-WHO Tripartite
  - The Union (zoonotic tuberculosis strategy and roadmap)
  - Brucellosis vaccine competition
  - AgResults consortium
  - STAR-IDAZ IRC
  - Steering committee / Scientific Committee / Secretariat
  - Tuberculosis Working Group
  - Veterinary Vaccinology Network
  - World Bank, HealthforAnimals, VICH, and others
WAHIS - Mycobacterium bovis January 2015 - October 2016
World Distribution of OIE Reference Laboratories

OIE Reference Laboratories
- 1 or 2 OIE Reference Labs
- 3 to 10 OIE Reference Labs
- 11 to 20 OIE Reference Labs
- more than 20 OIE Reference Labs
- no OIE Reference Labs

Copyright © 2014, OIE
### OIE Bovine Tuberculosis Reference Laboratories

<table>
<thead>
<tr>
<th>Scientist</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr. Bernardo Alonso</td>
<td>Argentina</td>
</tr>
<tr>
<td>Dr. María Laura Boschioli-Cara</td>
<td>France</td>
</tr>
<tr>
<td>Prof. Glyn Hewinson</td>
<td>United Kingdom</td>
</tr>
</tbody>
</table>

### OIE Brucellosis Reference Laboratories

<table>
<thead>
<tr>
<th>Scientist</th>
<th>Country</th>
<th>B. abortus</th>
<th>B. melitensis</th>
<th>B. suis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dra. Ana Maria Nicola</td>
<td>Argentina</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Dr. Bruno Garin-Bastuji</td>
<td>France</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Dr. Heinrich Neubauer</td>
<td>Germany</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Dr. Menachem Banai</td>
<td>Israel</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Dr. Fabrizio De Massis</td>
<td>Italy</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Dr. Moon Her</td>
<td>Korea (Rep. Of)</td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dr. Monaya Ekgatat</td>
<td>Thailand</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Dr. Adrian Whatmore</td>
<td>United Kingdom</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
</tbody>
</table>
**Brucellosis**

**What is Brucellosis?**

Brucellosis is a contagious disease of livestock with significant economic impact. The disease is caused by various bacteria of the family Brucella, which tend to infect a specific animal species. However, most species of Brucella are able to infect other animal species as well.

It affects cattle, swine, sheep and goats, camels, equines, and dogs. It may also infect other ruminants, some marine mammals and humans.

The disease in animals is characterized by abortions or reproductive failure. While animals typically recover, and will be able to have live offspring following the initial abortion, they may continue to shed the bacteria.

Brucellosis in cattle (B. abortus) in sheep and goats (B. melitensis) and in swine (B. suis) are diseases listed in the World Organisation for Animal Health (OIE) Terrestrial Animal Health Code and must be reported to the OIE (Terrestrial Animal Health Code).

---

**Bovine tuberculosis**

**What is Bovine Tuberculosis?**

Bovine tuberculosis (TB) is a chronic disease of animals caused by a bacteria called *Mycobacterium bovis*, (M. bovis) which is closely related to the bacteria that cause human and avian tuberculosis. This disease can affect practically all mammals, causing a general state of illness, coughing and eventual death.

The name Tuberculosis comes from the nodules, called ‘tubercles’, which form in the lymph nodes of affected animals.

Until the 1920s when control measures began in developed countries, it was one of the major diseases of domestic animals throughout the world. Today TB remains an important disease of cattle, wild animals, and is a significant zoonosis (a disease of animals which can also infect humans).

TB is a disease listed in the World Organisation for Animal Health (OIE) Terrestrial Animal Health Code, and must be reported to the OIE as detailed in the OIE Terrestrial Animal Health Code.
OIE Standards (Codes and Manuals)

**CODES**
- Terrestrial
- Aquatic

**MANUALS**
- Terrestrial
- Aquatic

*Codes and Manuals* available on the OIE website
Where the ‘Terrestrial Code’ requires that tests are carried out for international movement or recommends vaccination; the ‘Terrestrial Manual’ provides recommended laboratory methods and, where applicable, sets vaccine standards.
**Terrestrial Animal Health Code**

- **Format / Contents -**

- General provisions
- Safe commodities
- Recommendations to qualify a country, zone, compartment or herd free in various species (e.g. bovids or cervids).
- Recommendations for importation of live animals
  - for breeding or rearing
  - for slaughter
- Recommendations for importation of semen, embryos/ova; fresh meat and meat products; and milk and milk products
Manual of Diagnostic Tests and Vaccines for Terrestrial Animals
- Format / Contents -

• Description of the disease
• Identification of the agent
• Serological and cellular immunity tests
  • Diagnostic techniques internationally recognised and prescribed for official disease control or eradication programmes and for international trade
• Requirements for vaccines and diagnostic biologicals
OIE Manual of Diagnostic Tests and Vaccines for Terrestrial Animals

Divided into two volumes, parts 1-4.

Vol. I  Part 1  General Standards

Vol. II  Part 2  OIE Listed Diseases and Other Diseases of Importance
        Part 3  Specific Recommendations
        Part 4  OIE Reference Experts and Disease Index
Structure of the Chapters on specific diseases:

- Summary
- A. Introduction
- B. Diagnostic techniques
- C. Requirements for vaccines and diagnostic biologicals
- References
## Recommendations applicable to OIE Listed diseases and other diseases of importance to international trade

<table>
<thead>
<tr>
<th>Section 8</th>
<th>Multiple species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chapter 8.4</td>
<td>Infection with <em>Brucella abortus</em>, <em>B. melitensis</em> and <em>B. suis</em></td>
</tr>
<tr>
<td>Chapter 8.11</td>
<td>Infection with <em>Mycobacterium tuberculosis</em> complex (<em>M. bovis</em>, <em>M. caprae</em> and <em>M. tuberculosis</em>)</td>
</tr>
</tbody>
</table>

Available online at: [http://www.oie.int/international-standard-setting/terrestrial-manual/access-online/](http://www.oie.int/international-standard-setting/terrestrial-manual/access-online/)
<table>
<thead>
<tr>
<th>Part 2</th>
<th>OIE Listed Diseases and Other Diseases of Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Section 2.1</td>
<td>Multiple species</td>
</tr>
<tr>
<td>Chapter 2.1.4</td>
<td>Brucellosis (<em>Brucella abortus, B. melitensis and B. suis</em>) (infection with <em>B. abortus, B. melitensis and B. suis</em>) (Version adopted in May 2016)</td>
</tr>
<tr>
<td>Section 2.4</td>
<td>Bovinae</td>
</tr>
<tr>
<td>Chapter 2.4.6</td>
<td>Bovine tuberculosis (Version adopted in May 2009)</td>
</tr>
</tbody>
</table>

Available online at: [http://www.oie.int/international-standard-setting/terrestrial-manual/access-online/](http://www.oie.int/international-standard-setting/terrestrial-manual/access-online/)
## Part 3 Specific Recommendations

<table>
<thead>
<tr>
<th>Section 3.6</th>
<th>Recommendations for validation of diagnostic tests (May 2014)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Section 3.7</td>
<td><strong>Recommendations for the manufacture of vaccines</strong></td>
</tr>
<tr>
<td>Chapter 3.7.1</td>
<td>Minimum requirements for the <em>organisation and management</em> of a vaccine manufacturing facility (New: May 2016)</td>
</tr>
<tr>
<td>Chapter 3.7.2</td>
<td>Minimum requirements for the <em>production and quality control</em> of vaccines (New: May 2016)</td>
</tr>
<tr>
<td>Chapter 3.7.3</td>
<td>Minimum requirements for <em>aseptic production</em> in vaccine manufacture (New: May 2016)</td>
</tr>
</tbody>
</table>

## Part 4 OIE Reference Experts and Disease Index

- **List of OIE Reference Laboratories**
- Alphabetical list of diseases
Brucellosis

Terrestrial Code

TERRESTRIAL CODE

CHAPTER 8.4.
INFECTION WITH BRUCELLA ABORTUS, B. MELITENSI S AND B. SUIS

2017 © OIE - Terrestrial Animal Health Code - 26/07/2017

OIE - Adapted by the World Assembly of Delegates at the OIE in May 2016.
Tuberculosis

Terrestrial Code

Chapter 8.11. Infection with Mycobacterium Tuberculosis Complex

Infection with Mycobacterium Tuberculosis Complex

General provisions

The recommendations in this chapter are intended to manage the human and animal health risks associated with infection of animals with a member of the Mycobacterium Tuberculosis (M. Tuberculosis) complex.

For the purposes of the Terrestrial Code, M. tuberculosiss complex comprises M. bovis and M. caprae and M. Tuberculosis, but excludes vaccine strains.

Many different domestic and wild animal species belonging to diverse mammalian taxa are known to be susceptible to infection with M. Tuberculosis complex. Epidemiological significance depends on the degree of susceptibility, the host-virus system, the density, spatial distribution and ecology of populations as well as the pathogens and transmission pathways. In some geographical regions, certain wild animal species can act as reservoirs.

For the purposes of this chapter, ‘animals’ means domestic and captive wild animal populations of the following categories:

1. bovins: this term means bovine (Bos taurus, B. indicus, B. uniformis and B. grizzali), water buffaloes (Bubalus bubalis), and bison (Bison bison and B. bonasus).
2. cervins: this term means red deer (Cervus elaphus elaphus), wapiti (C. elaphus canadensis), sika (C. nippon), sambar (C. unicolor unicolor), roe (Capreolus capreolus), fallow deer (Dama dama), white-tailed, black-tailed and mule deer (Odocoileus hemionus) and reindeer (Rangifer tarandus).
3. goats (Capra hircus).
4. New World camels: this term means alpacas (Lama guanicoe) and llamas (Lama guanicoe).

The chapter deals not only with the occurrence of clinical signs caused by infection with M. Tuberculosis complex, but also with the presence of infection with M. Tuberculosis complex in the absence of clinical signs.

For the purposes of the Terrestrial Code, the following defines the occurrence of infection with M. Tuberculosis complex:

- a member of M. Tuberculosis complex has been identified in an animal or a product derived from that animal.
- OR - positive results to a diagnostic test have been obtained and there is an epidemiological link to a case of infection with M. Tuberculosis complex or there is another reason to suspect infection with M. Tuberculosis complex.

When authorising import or transit of commodities listed in this chapter, with the exception of those listed in Article 8.11.2, Veterinary Authorities should require the conditions prescribed in this chapter relevant to the M. Tuberculosis complex infection status of the animal population of the country, zone or herd of origin.

Standards for diagnostic tests are described in the Terrestrial Manual.

Chapter 2.4.6. Bovine Tuberculosis

Summary

Bovine tuberculosis is a chronic bacterial disease of animals and humans caused by Mycobacterium bovis. In a large number of countries bovine tuberculosis is a major infectious disease among cattle, other domesticated animals, and certain wildlife populations. Transmission to humans constitutes a public health problem.

Aerosol exposure to M. bovis is considered to be the most frequent route of infection of cattle, but infection by ingestion of contaminated material also occurs. After infection, non-coccidioid granulomas known as tubercles may develop. Characteristic tuberculoses occur most frequently in the lungs and the mycothorax, bronchial and mediastinal lymph nodes. Lesions can also be found in the mesenteric lymph nodes, liver, spleen, on serous membranes, and in other organs.

Bovine tuberculosis infection in cattle is usually diagnosed in the live animal on the basis of delayed hypersensitivity reactions. The test is performed subcutaneously, but other clinical signs are not specifically distinct and can include anorexia, emaciation, dyspnea, enlargement of lymph nodes, cough, particularly with advanced tuberculosis. After death, infection is diagnosed by necropsy and postmortem and bacteriological techniques. Rapid nucleic acid methodologies, such as the polymerase chain reaction (PCR), may also be used although these are demanding techniques and should only be used when appropriately validated. Traditional mycobacterial culture remains the gold standard method for routine confirmation of infection.

Identification of the agent: Bacteriological examinations may consist of the demonstration of acid-fast bacilli by microscopic examination, which provides presumptive confirmation. The isolation of mycobacteria on selective media is confirmed by cultural and biochemical tests or DNA techniques, such as PCR, confirm infection. Animal inoculation, which has been used in the past for confirming infection with M. bovis, is now rarely used because of animal welfare considerations.

Delayed hypersensitivity test: This is the test used for detection of bovine tuberculosis. It involves measuring skin thickness, injecting bovine tuberculin intradermally into the measured area and measuring any subsequent swelling at the site of injection 72 hours later.

The comparative intradermal tuberculin test with bovine and avian tuberculin is used to differentiate between animals infected with M. bovis and those sensitised to tuberculin due to exposure to other mycobacteria or related genera.

The decision to use the single or comparative test generally depends on the prevalence of tuberculosis infection and on the level of environmental exposure to the other mycobacterial organisms.

Due to their higher specificity and easier standardisation, purified protein derivative (PPD) products have replaced heat-concentrated synthetic medium tuberculin. The recommended dose of bovine PPD in cattle is at least 2000 International Units (IU) and in the comparative tuberculin test, the dose should be no lower than 2000 IU. The reaction is interpreted on the basis of the test method used.

Blood-based laboratory tests: Diagnostic blood tests are now available, such as the gamma-interferon assay, which uses an enzyme-linked immunosorbent assay (ELISA) as the detection method for the lymphocyte proliferation assay, which detects cell-mediated immune responses, and the indirect ELISA, which detects antibody responses. The logistics and laboratory
Terrestrial Animal Health Code: Chapter 8.11

Infection with *Mycobacterium tuberculosis* Complex (new merged chapter, adopted 2017)

Ch 11.5 + Ch 11.6 → Ch. 8.11

- In 2017, Chapter 11.5 and 11.6 were updated and merged to form new Chapter 8.11. Infection with *Mycobacterium tuberculosis* complex (*M. bovis*, *M. caprae* and *M. tuberculosis*)
  - Pathogen-based approach
  - Infection with *Mycobacterium tuberculosis* complex
  - Implication of wildlife reservoirs in the management of tuberculosis.

- Chapter 11.5. Bovine tuberculosis
- Chapter 11.6. Bovine tuberculosis of farmed cervidae

Recommendations to manage/control human and animal health risks associated with *Mycobacterium bovis* (*M. bovis*) infection in:
  - domestic (permanently captive and owned free-range) bovines;
  - domestic farmed cervidae.
Manual of Diagnostic Tests and Vaccines for Terrestrial Animals: Chapter 2.1.4 Brucellosis (Brucella abortus, B. melitensis and B. suis) (Revised version, adopted May 2016)

Requirements for vaccines and diagnostic biologicals (excerpt):

Brucella abortus strain 19 and B. melitensis strain Rev.1 remain the reference vaccines for the control of Brucella infections in cattle and in sheep and goats, respectively, with which any other vaccines should be compared. Both should be prepared from adequately derived seed cultures.

The rough B. abortus strain RB51 vaccine has also become the official vaccine for prevention of B. abortus infection in cattle in some countries. No suitable vaccines exist for the control of Brucella infection in swine.

Brucellin preparations must be free of smooth lipopolysaccharide, and antigens for serological tests must be prepared from smooth B. abortus strain 1119-3 or 99 and, in the case of indirect ELISA, from smooth B. melitensis strain 16M as well.

Vaccines and brucellin preparations must comply with relevant standards.
Requirements for vaccines and diagnostic biologicals (excerpt):

Vaccines are being developed and evaluated for use in bovine and wildlife species, but at this time are not routinely administered as they may compromise the use of the tuberculin skin test and other immunological tests to detect infected animals.

There are standard methods for the production of bovine PPD tuberculins. PPD, used for performing the tests specified, should be prepared in accordance with the World Health Organization requirements and should conform to these requirements with respect to source materials, production methods and precautions, added substances, freedom from contamination, identity, safety, potency, specificity and freedom from sensitising effect. The bioassays for biological activity are of particular importance, and the potency should be expressed in IUs.
Thank you for your attention

Glen Gifford
Science and New Technologies Department
World Organisation for Animal Health,
Paris, France
g.gifford@oie.int

12, rue de Prony, 75017 Paris, France
www.oie.int
media@oie.int - oie@oie.int