General Consensus Statement of the International Association for Paratuberculosis

Approved by 95% of voting Association Members and Unanimous approval of the Governing Board*

Guidelines for certification with respect to the movement of livestock for

Mycobacterium avium subsp *paratuberculosis* (MAP) infection

Compiled by DJ Kennedy, G Benedictus, SS Nielsen, K Lybeck, E Schwan, J Frossling, E Sergeant, D Kelton and H Nauholz

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*95% of the membership voted to approve and 5% voted to have additional discussions. There were no disapproval votes.

Purpose

To provide guidance for scientifically sound risk assessment of MAP infection that can be used by risk managers to reduce the risk of spread of MAP between populations of **livestock**, consistent with WTO standards for international trade.

NOTE: These guidelines do **not** consider the risks of

- MAP infecting people (EFSA 2017, Chiodini et al 2012, Waddell et al 2015, Waddell et al 2016), nor
- Transmission via bovine semen (EFSA 2004).

1. Introduction

Despite increasing understanding of MAP and paratuberculosis (Johne's disease), little progress has been made in limiting the spread of MAP between regions and countries. MAP has been detected in most countries where it has been investigated. Regrettably however, interest in MAP often only increases in countries and regions as they realise, too late, that they have endemic Johne's disease (JD) or when another country wants to include MAP in health certification for animals or products. Knowledge gaps constraining successful control have been reviewed recently (Barkema et al, 2017).

Article 3 of the World Trade Organization *Agreement on the Application of Sanitary and Phytosanitary Measures* (the SPS Agreement, World Trade Organisation, 2016) states that

> "To harmonize sanitary and phytosanitary measures on as wide a basis as possible, Members shall base their sanitary or phytosanitary measures on international standards, guidelines or recommendations, where they exist."

There has also been little progress in developing and applying scientifically sound movement requirements for MAP. Since 2001, efforts through official channels such as OIE have not borne fruit and, for the past decade, the OIE Terrestrial Animal Health Code Chapter on Paratuberculosis has provided little guidance in this area (OIEa 2015). Concern about the low accuracy of diagnostic tests in individual animals has been a major reason that the Code chapter has not been developed further. However, the OIE Diagnostic Manual (OIEb 2015) has been updated to also refer to diagnostic testing at herd level. Herd level testing and other certification based on large scale surveillance has been implemented for other diseases for which negative individual animal tests provide limited assurance, such as bovine brucellosis, bovine tuberculosis and the prion diseases.

The International Association for Paratuberculosis (IAP) agreed in 2015 to develop its own guidelines for importers and exporters who want to implement rational movement requirements, based on current understanding of managing MAP risks and consistent with the principles of the SPS Agreement. These recognise and recommend risk management that is justified and appropriate for different situations.

2. Rationale

One of the *Basic Obligations* outlined in Article 2 of the SPS Agreement is that.

> "Members shall ensure that any sanitary or phytosanitary measure is applied only to the extent necessary to protect human, animal or plant life or health, is based on scientific principles and is not maintained without sufficient scientific evidence, except as provided for in paragraph 7 of Article 5."

which states that,

> "In cases where relevant scientific evidence is insufficient, a Member may provisionally adopt sanitary or phytosanitary measures on the basis of available pertinent information, including that from the relevant international organizations as well as from sanitary or phytosanitary measures applied by other Members. In such circumstances, Members shall seek to obtain the additional information necessary for a more objective assessment of risk and review the sanitary or phytosanitary measure accordingly within a reasonable period of time."

The IAP is a "relevant international organisation" under the SPS Agreement for paratuberculosis. Founded in 1989, the IAP is a non-profit organization devoted to the advancement of knowledge and scientific achievement toward the eradication of paratuberculosis in domestic livestock and other species affected by MAP. It has approximately 150 members from 30 countries, who are broadly representative of scientific and disease control expertise globally.

Flawed Requirements

Many official movement protocols have hindered, rather than enhanced, control of MAP infection as they are scientifically flawed and ineffective.

Certification based on the recent herd or flock history of clinical disease and on testing of the individual animals to be moved is still common for a broad range of types of animals. However, the *negative predictive value* of such certification from endemically infected regions (ie the probability that a test negative animal is truly free from MAP) approaches zero.

- Clinical disease is not a sensitive indicator of MAP infection and requiring a negative clinical history discourages farmers who want to trade from investigating or reporting suspect cases.
- It encourages traders to move, or falsify the identity of, animals so as not to exclude farms with a positive history from trading opportunities.
- Movement testing is often of consignments of young animals and sometimes with outdated tests.

Such protocols also have perverse effects by discouraging participation in herd classification programs and by penalising regions and herd owners actively trying to control MAP through surveillance, testing and vaccination.

Unjustified Requirements

The World Trade Organization Agreement on the Application of Sanitary and Phytosanitary Measures (the SPS Agreement, World Trade Organisation, 2016) opens,

> "*Reaffirming* that no Member should be prevented from adopting or enforcing measures necessary to protect human, animal or plant life or health, subject to the requirement that these measures are not applied in a manner which would constitute a means of arbitrary or unjustifiable discrimination between Members where the same conditions prevail or a disguised restriction on international trade"

Furthermore, Article 2 paragraph 3 states that,

> "Members shall ensure that their sanitary and phytosanitary measures do not arbitrarily or unjustifiably discriminate between Members where identical or similar conditions prevail, including between their own territory and that of other Members."

And Article 5 paragraph 4 includes,

> "Members should, when determining the appropriate level of sanitary or phytosanitary protection, take into account the objective of minimizing negative trade effects."

Yet some countries, in which MAP is endemic, require certification when they themselves have no significant surveillance or control programs in place. And some markets require negative farm level assurance for young animals destined for slaughter in the short term.

In contrast, the few regions that have vigorously controlled and stamped out MAP, may struggle for recognition and acceptance that they should set an allowable level of protection and require appropriate entry requirements based on risk analysis.

3. MAP Risk Assessment

Risk assessment and management programs (RAMPs) have become the keystone of modern on-farm JD control programs. Many of the same principles can be applied at a regional level.

Article 5 of the SPS Agreement defines risk assessment as

1. "Members shall ensure that their sanitary or phytosanitary measures are based on an assessment, as appropriate to the circumstances, of the risks to human, animal or plant life or health, taking into account risk assessment techniques developed by the relevant international organizations.

2. "In the assessment of risks, Members shall take into account available scientific evidence; relevant processes and production methods; relevant inspection, sampling and testing methods; prevalence of specific diseases or pests; existence of pest- or disease-free areas; relevant ecological and environmental conditions; and quarantine or other treatment."

The epidemiology and pathogenesis of MAP infection is complex and varies between species. However, on balance, the scientific evidence indicates that the following key characteristics of MAP infection should be considered in assessing the risks of livestock being infected with MAP

Herd or population level
1. MAP is endemic in developed livestock industries worldwide and has been spreading around the world with the movement of livestock for over a century.
2. Any country that has imported large numbers of livestock in recent decades from developed livestock industries is likely to have endemic MAP infection unless it has taken sound and vigorous action to reduce the risk of entry and/or to stamp it out.
3. The likelihood that a country, region or herd/flock is not infected can only be demonstrated by ongoing negative herd or population testing and active surveillance on a large scale over long periods.
4. A negative clinical history of MAP infection has a low negative predictive value of herd or flock status.

Individual animal level
1. Animals may become infected at any age but are most susceptible to becoming infected in the first few months of life.
2. Infected animals may excrete some MAP organisms at any stage but excretion may be intermittent and the likelihood and rate and amount of excretion increases as the infection progresses with age.
3. Diagnostic tests usually have low sensitivity until the later stages of infection and so a negative test of an individual animal has a low predictive value.
4. Clinical signs of Johne's disease occur late in infection and are not pathognomonic; the absence of clinical signs usually has a low predictive value in determining whether an animal is infected.
5. The most important source of MAP is faeces, both in the clinical and pre-clinical stages.
6. Infectious MAP organisms survive in the environment in large numbers for months with longer survival in areas protected from extreme heat, ultraviolet light and dessication (Jørgensen, 1977; Whittington et al 2004; Eppleston et al 2014).
7. MAP strains that have adapted to one species can infect others, but little is known if the dynamics of interspecies transmission and the frequency of transmission may be greater if there is close contact between different species at the farm level (Verdugo et al 2014).

4. MAP Risk Management

The results of risk assessments are not perfect, largely because of uncertainties in the input parameters and assumptions. Therefore, importing countries and regions that require certification for MAP should take responsibility for preventing MAP spreading in their own areas, both from local animals and from imported animals, should it be inadvertently introduced.

The likelihood of MAP infection spreading from introduced animals and infecting populations into which they are introduced may be **managed** by:

1. Preventing exposure of susceptible animals to infectious sources, especially feed, water and other materials contaminated by faeces.
2. Removing from the population introduced and exposed animals that are suspected of being infected.
3. Removing MAP from contaminated environments and disposing of contaminated materials.

Although not permitted in all countries, increasing the immunity of susceptible animals by vaccination has also been successfully used to reduce the risk of spread of MAP in infected populations.

5. Risk Classifications of Areas

Free and low-prevalence areas are recognised under Article 6 of the SPS Agreement:

2. "Members shall, in particular, recognize the concepts of pest- or disease-free areas and areas of low pest or disease prevalence. Determination of such areas shall be based on factors such as geography, ecosystems, epidemiological surveillance, and the effectiveness of sanitary or phytosanitary controls.
3. Exporting Members claiming that areas within their territories are pest- or disease-free areas or areas of low pest or disease prevalence shall provide the necessary evidence thereof in order to objectively demonstrate to the importing Member that such areas are, and are likely to remain, pest-or disease-free areas or areas of low pest or disease prevalence, respectively. For this purpose, reasonable access shall be given, upon request, to the importing Member for inspection, testing and other relevant procedures."

For the purpose of these guidelines it is recommended that four concepts for area classifications be used:

Free Area
A country, zone or compartment in which MAP infection is notifiable and extensive and large-scale surveillance for MAP infection by the animal health authority has not identified endemic infection for ten years or where infection has been introduced it has been demonstrably stamped out by slaughter and intensive tracing of suspect infection

and intensive surveillance has not identified MAP for 2 years. A Free Area will retain its status as long as appropriate area biosecurity and surveillance are maintained.

Eradication Area

A country, zone or compartment in which MAP infection is at low prevalence, is notifiable and extensive and large-scale <u>compulsory</u> surveillance for MAP infection by the animal health authority continues to demonstrate a low herd prevalence of infection and where the herd prevalence of infection is demonstrably being reduced as infection is stamped out.

Officially sanctioned and recognised voluntary or compulsory herd or flock classification programs, with a certification component based on negative herd and/or flock testing and surveillance, may also operate to objectively classify herds and/or flocks for MAP risk.

Certification Area

A country, zone or compartment in which an officially sanctioned and recognised <u>voluntary</u> herd or flock classification programs, with a certification component based on sound farm biosecurity and negative herd and/or flock testing and surveillance operates to objectively classify herds and/or flocks for MAP risk. A certification area may not necessarily be a low prevalence area.

Other Area

All other countries and regions.

6. Herd or Flock Classification

In Free Areas, herds and flock status is derived from the area status.

A herd or flock classification program in areas other than Free Areas should satisfy the following criteria:

a. Sanctioned and recognised by the official animal health authority of the Area.
b. Herds and flocks are under the supervision of a veterinarian who has been trained and approved for the purpose of the program.
c. An officially recognised register of classified herds and flocks.
d. Within each herd or flock the program will include:
   - permanent individual animal identification.
   - traceability of animals entering and leaving.
   - a farm-level biosecurity and management component to minimise the probability of MAP entering and spreading.
   - screening of adult animals by a sensitive and specific diagnostic test that is recommended by the IAP and approved by the regulator for the purpose.

- a test-strategy that appropriately documents a specific probability of freedom from infection

For the purposes of these guidelines a single herd or flock classification is proposed in areas other than Free Areas, *MAP Certified*, which satisfies the importing Area's appropriate level of protection and is defined as follows:

a. Located within an Eradication Area or a Certification Area which is under the control of the animal health authority which also sanctions and recognises the herd or flock classification program for MAP, and

b. Taking into consideration its location, history and management, the herd or flock has
   i. implemented biosecurity measures to minimise the likelihood of introduction and/or spread of MAP, and
   ii. repeatedly screened a representative sample of adult animals from the herd or flock (or the whole adult herd/flock) using IAP recommended tests and appropriate sample sizes to provide a specified level of confidence of detecting a specified low prevalence of infection (if present). See Martin et al (1992) and MacDiarmid (1988) and More et al (2013) for more information.

Individual programs may use other and/or additional classifications to denote various risk statuses.

7. Recommended tests

Numerous tests have been developed for detection of statuses related to MAP, but few have been evaluated using state-of-the-art diagnostic test evaluations. (See Table 1 Test methods available for diagnosis of paratuberculosis and their purpose in the OIE Terrestrial Manual Chapter 2.1.11 adopted 2014).

Testing for only one target condition is currently relevant to trade of livestock:

- *MAP infected animal*, which is any animal carrying MAP intracellularly

To detect **MAP infection**, the indirect antibody ELISA (for serum or milk), faecal PCR and faecal bacteriological culture are appropriate.

Detection of a *MAP exposed animal* (ie any animal that has been known or suspected to have been exposed to MAP infected animals in their lifetime, directly or indirectly via the environment), could also be relevant, but at present no tests have been satisfactorily evaluated.

If "MAP exposure" is included as a target condition for certification, PCR and faecal culture may be considered 100% specific.

For the combined target condition, ie MAP exposure or MAP infection, the sensitivity of PCR is likely to be the highest, followed by culture and ELISA. However, the specific test that is used should be evaluated for the specific purpose prior to use in a certification programme.

Experience with tests such as faecal smears, complement fixation test (CFT) and agar gel immunodiffusion test (AGID) indicate that they have inherently low sensitivity and/or specificity and are therefore not recommended.

8. Test strategies

In developing test strategies to suit the local livestock production systems a number of factors should be taken into account. Most importantly, testing of individuals does not provide sufficient information to certify the individual or the herd/flock. The certification is affected by animal and herd/flock factors, and may be further affected by other local factors. For example:

- The probability of an animal being free of MAP infection can be calculated if multiple animals from the same herd or flock have been tested (Sergeant et al., 2008; More et al., 2013). However repeated sampling is required to achieve a high level of confidence that the herd or flock is free from MAP.
- Current knowledge (ie prior information) about the prevalence of MAP in the region and in the herd or flock of origin and the probability of introduction of MAP into the herd or flock are important. The higher the probability of existing infection, or of past introduction of infection, the higher the number of samplings and the longer the period of time that will be required to attain a high level of confidence of freedom.
- Diagnostic sensitivity does not only depend on the test used, but also on the strain of MAP and age structure of target population.
- Test antigens could be derived from local strains of MAP where required, but for standardisation of interpretation in an international context this should be minimised.
- Average test sensitivity will be lower in a young population, because many infections will not have progressed to detectable stages. On the other hand, an old population may have many animals that are more likely to have remained in the herd or flock because they were un-infected (This is recognised as "healthy worker survivor bias" and should be avoided). Therefore, the highest sensitivity can likely be achieved by testing the age-groups where infected animals would normally be expected to have started excreting detectable amounts of bacteria or to have sero-converted. It is usually recommended to test animals between 2 and 5 years of age. However, consideration should be given to the species, management systems and the pressure of infection in the herd or flock. For instance, in systems with high stocking densities and high faecal contamination, the pressure of infection is likely to be higher and infection is likely to progress more quickly.

Specifically, we recommend that

- As many animals (above 2 years of age) as possible are tested with standardised and evaluated ELISAs, PCRs or culture methods.

- Test-evaluations should be carried out locally and age-stratified, if possible.
- Test-prevalences (ie apparent prevalences) should be converted to true (calculated) prevalences, including 95% confidence intervals, and probabilities of freedom, and historical data should be included in the process, such as described in Sergeant et al. (2008) and More et al. (2013). Where random sampling has been used, these calculations take into account the test-accuracy and the size and age-structure of the tested population.

Table 1. MAP statuses of importing and exporting areas and the recommended standards for various animal movements

Livestock

The following levels of protection and certification requirements are recommended for areas of various MAP status (Column 1) importing various types of livestock (Column 3) from Areas of different MAP status (Column 2).

MAP status of Importing Area	MAP status of Exporting Area	Type of animal	Acceptable Level of Protection/ MAP Certification
Free Area	Free Area	All	Throughout their lifetimes the animals have only resided in a Free Area or have satisfied the requirements to be be introduced to the Free Area.
	Eradication Area	Animals for breeding Other restocking (including feeding for slaughter, but not in quarantine).	Throughout their lifetimes the animals have only resided in a MAP Certified herd or flock.
		Animals for confined feeding for slaughter, in quarantine. Animals for immediate slaughter	No requirements. (The importing regulator will enact quarantine procedures that are sufficient to manage the risk)
	Certification Area	Animals for breeding Other restocking (including feeding for slaughter but not in quarantine).	Throughout their lifetimes the animals have only resided in a MAP Certified herd or flock
		Animals for confined feeding for slaughter,	No requirements. (The importing regulator will enact quarantine procedures that are

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		in quarantine. Animals for immediate slaughter	sufficient to manage the risk)
	Other Areas	Animals for breeding Other restocking (including unconfined feeding for slaughter).	Not permitted
		Animals for confined feeding for slaughter, in quarantine. Animals for immediate slaughter	No requirements (The importing regulator will enact quarantine procedures that are sufficient to manage the risk)

Eradication Area	Free Area	All	Throughout their lifetimes the animals have only resided in a Free Area or have satisfied the requirements to be been introduced to the Free Area.
	Eradication Area	Animals for breeding Other restocking (including unconfined feeding for slaughter).	Throughout their lifetimes the animals have only resided in a MAP Certified herd or flock.
		Animals for confined feeding for slaughter Animals for immediate slaughter	No requirements (The importing regulator will enact quarantine procedures that are sufficient to manage the risk)
	Certification Area	Animals for breeding Other restocking (including unconfined feeding for slaughter).	No requirements. (The importing owner will manage the risk.)
		Animals for confined feeding for slaughter Animals for immediate slaughter	.
	Other Areas	Animals for breeding Other restocking (including unconfined feeding for slaughter).	Not permitted
		Animals for confined feeding for slaughter Animals for immediate slaughter	No requirements
Certification Area	All Areas	All	No requirements. (The importing owner will manage the risk.)
Other Area	All Areas	All	No requirements

Embryos.

Embryos that have been sourced from donors that were clinically healthy at the time of collection and have been treated, handled and stored according to the procedures of the International Embryo Transfer Society may be imported into any Area. The IETS classifies MAP as an organism for which, in cattle, "preliminary evidence indicates that the risk of transmission is negligible provided that the embryos are properly handled between collection and transfer according to the IETS Manual" (IETS).

Manure.

Faeces is the most important carrier of MAP. The identification and traceability of manure is problematic and therefore all manure should be assessed as high risk unless it is derived from a Free Area. Managing the risk presented by manure is also difficult as large numbers of MAP organisms may survive in soil and water and be dispersed in the environment (see Grant, 2010).

References

Anon. The Risk of Transmission of Mycobacterium avium subsp. paratuberculosis via Bovine Semen. *The EFSA Journal* (2004) 110:1-59.

Barkema HW, Orsel K, Nielsen SS, Koets AP, Rutten VPMG, Bannantine JP, Keefe GP, Kelton DF, Wells SJ, Whittington RJ, Mackintosh CG, Manning EJ, Weber MF, Heuer C, Forde TL, Ritter C, Roche S, Corbett CS, Wolf R, Griebel PJ, Kastelic JP, De Buck J. Knowledge gaps that hamper prevention and control of Mycobacterium avium subspecies paratuberculosis infection. Transbound Emerg Dis. 2017:1–24.

Chiodini RJ, Chamberlin WM, Sarosiek J, McCallum RW, 2012. Crohn's disease and the mycobacterioses: a quarter century later. Causation or simple association? CritRev Microbiol. 38:52-93. doi: 10.3109/1040841X.2011.638273.

Eppleston J, Begg DJ, Dhand NK, Watt B, Whittington RJ, 2014. Environmental survival of Mycobacterium avium subsp. paratuberculosis in different climatic zones of eastern Australia. Appl Environ Microbiol. 80:2337-42.

European Food Safety Authority**,** 2017**.** Assessment of listing and categorisation of animal diseases within the framework of the Animal Health Law (Regulation (EU) No 2016/429): paratuberculosis**.** http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2017.4960/full.

Grant I, 2010. In *Paratuberculosis – organism, disease, control.* M Behr and D Collins Eds. CAB International, Oxford, UK. p34.

IETS. *IETS Manual* 4th Edition. (http://www.iets.org/pdf/IETS_recommendations_regarding_the_risk_of_disease_transmission_via_in_vivo_derived_embryos.pdf. Accessed 20 March 2017)

Jørgensen JB., 1977. Survival of Mycobacterium paratuberculosis in slurry. Nord. Vet.-Med., 29: 267-270.

MacDiarmid, S.C., 1988. Future options for brucellosis surveillance in New Zealand beef herds. New-Zealand-Veterinary-Journal 36:39-42.

Martin, S.W., Shoukri, M., Thorburn, M.A., 1992. Evaluating the health status of herds based on tests applied to individuals. Prev. Vet. Med. 14:33-43.

More SJ, Sergeant ES, Strain S, Cashman W, Kenny K, Graham D, 2013. The effect of alternative testing strategies and bio-exclusion practices on Johne's disease risk in test-negative herds. J Dairy Sci. 96:1581-90.

OIE a. *Terrestrial Animal Health Code 2015.* Chapter 8.12 Paratuberculosis. http://www.oie.int/index.php?id=169&L=0&htmfile=chapitre_paratuberculosis.htm. (Accessed 17 Feb 2016).

OIE b. Manual of Diagnostic Tests and Vaccines for Terrestrial Animals 2015. Chapter 2.1.11. Paratuberculosis (Johne's disease).

http://www.oie.int/fileadmin/Home/eng/Health_standards/tahm/2.01.11_PARATB.pdf. (Accessed 17 Feb 2016).

Sergeant ES, Nielsen SS, Toft N, 2008. Evaluation of test-strategies for estimating probability of low prevalence of paratuberculosis in Danish dairy herds. Prev Vet Med. 85:92-106.

Verdugo C, Pleydell E, Price-Carter M, Prattley D, Collins D, de Lisle GW, Vogue H, Wilson P, Heuer C, 2014. Molecular epidemiology of Mycobacterium avium subsp paratuberculosis isolated from sheep, cattle and deer on New Zealand pastoral farms. Prev Vet Med. 117:436-46.

Verna AE, Garcia-Pariente C, Muñoz M, Moreno O, García-Marin JF, Romano MI, Paolicchi F, Pérez V, 2007. Variation in the immuno-pathological responses of lambs after experimental infection with different strains of Mycobacterium avium subsp. paratuberculosis. Zoonoses Public Health. 54:243-52

Waddell LA, Rajić A, Stärk KD, McEWEN SA, 2015. The zoonotic potential of Mycobacterium avium ssp. paratuberculosis: a systematic review and meta-analyses of the evidence. Epidemiol Infect. 143:3135-57. doi:10.1017/S095026881500076X.

Waddell LA, Rajić A, Stärk KD, McEwen SA, 2016. The potential Public Health Impact of Mycobacterium avium ssp. paratuberculosis: Global Opinion Survey of Topic Specialists. Zoonoses Public Health. 63:212-22. doi: 10.1111/zph.12221.

Whittington RJ, Marshall DJ, Nicholls PJ, Marsh IB, Reddacliff LA, 2004. Survival and dormancy of Mycobacterium avium subsp. paratuberculosis in the environment. Appl Environ Microbiol. 70:2989-3004.

World Trade Organisation. Agreement on the Application of Sanitary and Phytosanitary Measures
https://www.wto.org/english/docs_e/legal_e/15-sps.pdf (Accessed 20 March 2017)

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