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Review article

## Zoonotic aspects of *Mycobacterium bovis* and *Mycobacterium avium-intracellulare* complex (MAC)

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**Abstract** – Pathogens that are transmitted between the environment, wildlife, livestock and humans represent major challenges for the protection of human and domestic animal health, the economic sustainability of agriculture, and the conservation of wildlife. Among such pathogens, the genus *Mycobacterium* is well represented by *M. bovis*, the etiological agent of bovine tuberculosis, *M. avium* ssp. *paratuberculosis* (Map) the etiological agent of Johne disease, *M. avium* ssp. *avium* (Maa) and in a few common cases by other emergent environmental mycobacteria. Epidemiologic surveys performed in Europe, North America and New Zealand have demonstrated the existence and importance of environmental and wildlife reservoirs of mycobacterial infections that limit the attempts of disease control programmes. The aim of this review is to examine the zoonotic aspects of mycobacteria transmitted from the environment and wildlife. This work is focused on the species of two main groups of mycobacteria classified as important pathogens for humans and animals: first, *M. bovis*, the causative agent of bovine tuberculosis, which belongs to the *M. tuberculosis* complex and has a broad host range including wildlife, captive wildlife, domestic livestock, non-human primates and humans; the second group examined, is the *M. avium-intracellulare* complex (MAC) which includes *M. avium* ssp. *avium* causing major health problems in AIDS patients and *M. avium* ssp. *paratuberculosis* the etiological agent of Johne disease in cattle and identified in patients with Crohn disease. MAC agents, in addition to a broad host range, are environmental mycobacteria found in numerous biotopes including the soil, water, aerosols, protozoa, deep litter and fresh tropical vegetation. This review examines the possible reservoirs of these pathogens in the environment and in wildlife, their role as sources of infection in humans and animals and their health impact on humans. The possibilities of control and management programmes for these mycobacterial infections are examined with regards to the importance of their natural reservoirs.

### *Mycobacterium* / zoonosis / wildlife / environment

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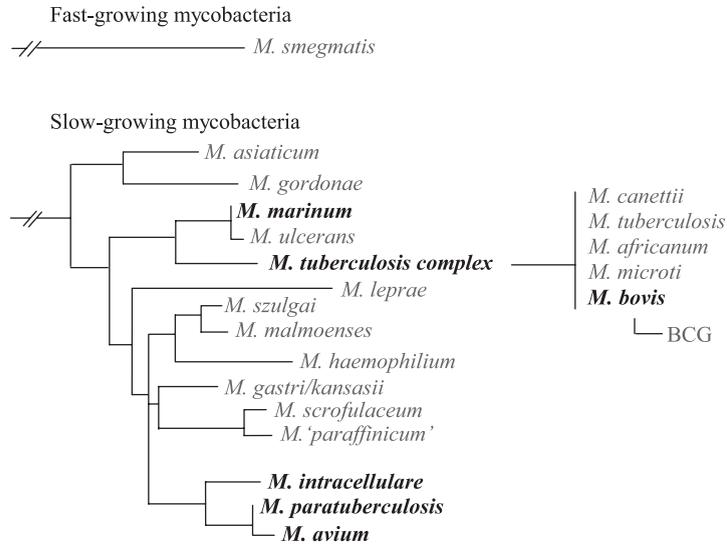
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## 1. INTRODUCTION

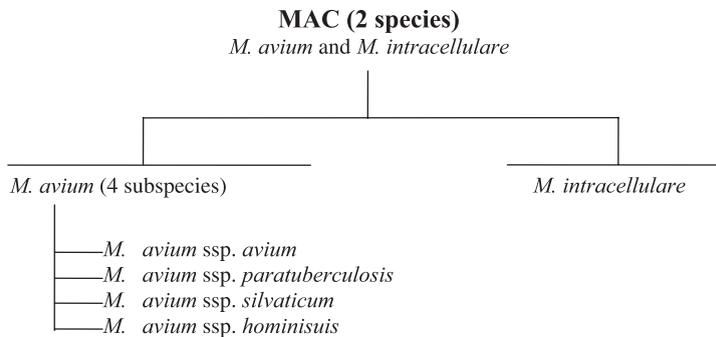
The bacteria of the genus *Mycobacterium* are Gram-positive, acid-fast organisms that include a number of major human and animal pathogens [49, 142, 158]. Although human tuberculosis is caused mainly by *M. tuberculosis*, *M. bovis* the etiological agent of bovine tuberculosis can also be responsible for human disease, which makes this bacterium an important zoonotic species (see Fig. 1) [34, 120]. *M. bovis* is a serious constraint in the international trade of animals and their products, and causes major economic losses to livestock. Environmental nontuberculous mycobacteria species that are not members of the *M. tuberculosis* complex, are ordinary inhabitants of a wide variety of environmental reservoirs and their role in human and animal diseases has been fully recognised [49, 138]. There have been a number of excellent reviews by Falkingham [49], and others on epidemiology, health impacts, clinical presentations

and treatment of these environmental nontuberculous mycobacteria [130, 135, 170]. Among the nontuberculosis mycobacteria species classified by Runyon [149] into four major groups (photochromogens, scotochromogens, nonphotochromogens and rapid growers) the best studied are those of the *M. avium-intracellulare* complex (MAC) (Figs. 1 and 2) and *M. kansasii* [48, 74, 82]. *M. avium* is subdivided into four subspecies (ssp.): ssp. *avium*, ssp. *paratuberculosis*, ssp. *silvaticum* and recently ssp. *hominissuis* [109] (Figs. 1 and 2).

This review focuses on the role of mycobacteria present in the natural environment and in wildlife as a source of infection in humans, directly or via livestock. The first part is focused on the *M. bovis* species, a member of the *M. tuberculosis* complex, which has been classified as a list B disease by the Office International des Epizooties (OIE) and has important socio-economic or public health effects within the affected countries, with a potential significant impact



**Figure 1.** Phylogenetic tree of mycobacteria, based on 16S rRNA sequence from [17] and [159]. The species treated in this review are represented in bold and show that the tuberculosis complex including *M. tuberculosis* and *M. bovis* differ genotypically from the *M. avium-intracellulare* complex.



**Figure 2.** The *M. avium-intracellulare* complex (MAC). MAC includes two species *M. avium* and *M. intracellulare*, and the species *M. avium* is divided into four subspecies: *M. avium* ssp. *avium*, *M. avium* ssp. *paratuberculosis*, *M. avium* ssp. *silvaticum* and *M. avium* ssp. *hominisuis*.

on the international trade of animals and animal products. The second part concerns the environmental mycobacteria, limited in this review to the fully studied MAC member and, in particular *M. avium* ssp. *avium* (Maa), an opportunist pathogen of AIDS

patients, and *M. avium* ssp. *paratuberculosis* (Map), the etiological agent of paratuberculosis or Johne disease in ruminants, which has also been isolated from tissue of Crohn disease patients leading to concerns that it may be pathogenic for humans.

## 2. ENVIRONMENTAL AND ANIMAL RESERVOIR OF *M. BOVIS*

### 2.1. Environmental reservoir

#### 2.1.1. Locations

*M. bovis* is considered to be an obligate intracellular pathogen whose most efficient way of infection is direct animal contact [136]. However, experimental evidence has shown that *M. bovis* can survive for long periods outside an animal host in an environment directly or indirectly contaminated by discharges of infected animals, suggesting other possible ways of transmission. Yet in cattle, the natural host of *M. bovis* and the main source of human spread, transmission via the oral route or even the respiratory route by inhalation of dust particles in fields where no wildlife reservoir are implicated in transmission to livestock, would play a less important role since the excretion of the organisms in faeces even from heavily infected cattle occurs irregularly and at a low frequency [107]. There are no records of human infection by *M. bovis* coming from a direct environmental source, revealing that this way of transmission is not the most important one for this pathogen.

#### 2.1.2. Physiological characteristics for environmental survival

The success of tubercle bacilli as pathogens comes mainly from its ability to persist in the host for long periods and cause disease by overcoming host immune responses [57] (see Sect. 2.2.2). Nevertheless, the possibility of surviving for long periods in the environment is explained by the mycobacterial impermeable cell wall [14] and slow growth [62]. In contrast, other features render these species more sensitive to environmental survival, like a more enhanced pH sensitivity of the tuberculosis complex compared to MAC species [21, 35]. Genomic comparisons between MAC and *M. tuber-*

*culosis* complex members will not only allow to elucidate differences in virulence determinants between these two mycobacterial complexes but also the disparities in environmental survival factors.

### 2.2. Animal reservoir

#### 2.2.1. Wildlife as a source of *M. bovis*

Domestic and non-domestic animals may be considered either as maintenance (or reservoir) hosts or non-maintenance (or spill-over) hosts for bovine tuberculosis (see Tab. I). In reservoir host species, infection can persist through horizontal transfer in the absence of any other source of *M. bovis* and may as well be transmitted to other susceptible hosts. In contrast, spillover hosts become infected with *M. bovis* but the infection only occurs sporadically or persists within these populations if a true maintenance host is present in the ecosystem. If the source of infection is removed, the prevalence for this disease is reduced and it can only be maintained in the long term by re-infection from another source [76].

A main trait of *M. bovis* is its broad host range, actually the largest of any member of the *M. tuberculosis* complex. *M. bovis* causes disease in a wide range of domestic but also free-ranging and farmed wildlife animals as well as in humans. Only a small proportion of these animal species that become infected can act as maintenance hosts of this organism. Table I is a non-exhaustive list summarising two excellent reviews by G.W. de Lisle [42, 43], which describe *M. bovis* in reservoirs and spill-over wildlife species as well as their distribution.

It is worth examining which factors render a species as a maintenance host. Physiopathogenesis, i.e. the capacity of excretion, ethology (for example gregarious or not gregarious behaviour) and ecology (alimentary behaviour, population density and interactions with other species) determine their

**Table I.** A non exhaustive list showing the distribution of *M. bovis* in wildlife hosts.

Species	Epidemiological status	Route of transmission	Countries	References
African buffalo ( <i>Syncerus caffer</i> )	Maintenance host	Respiratory	Uganda	[43]
Baboon ( <i>Papio ursinus</i> )	Spill over	Oral/respiratory	Kenya	[43]
Badger ( <i>Meles meles</i> )	Maintenance host	Respiratory	Ireland, England	[42, 43]
Bison ( <i>Bison bison</i> )	Maintenance host	Respiratory	United States of America, Canada	[43]
Black bear ( <i>Ursus americanus</i> )	Spill over	Oral	United States of America	[43]
Bobcat ( <i>Felis rufus</i> )	Spill over	Oral	United States of America	[43]
Brush-tail possum ( <i>Trichosurus vulpecula</i> )	Maintenance host	Respiratory	New Zealand	[43]
Cheetah ( <i>Acinonyx jubatus</i> )	Spill over	Oral/respiratory	South Africa	[43]
Coyote ( <i>Canis latrans</i> )	Spill over	Oral	United States of America	[43]
Deer ( <i>Cervus elaphus</i> )	Maintenance host/Spill over	Respiratory/oral	New Zealand	[43]
Feral pig ( <i>Suis scrofa</i> )	Maintenance host/Spill over	Oral	Italy, Spain, Australia, Hawaii, New Zealand	[42, 43]
Ferret ( <i>Mustela putorius</i> )	Maintenance host/Spill over	Oral	New Zealand	[43]
Greater kudu ( <i>Tragelaphus strepsiceros</i> )	Spill over	Scarification/oral	South Africa	[43]
Leopard ( <i>Panthera pardus</i> )	Spill over	Oral/respiratory	South Africa	[43]
Lion ( <i>Panthera leo</i> )	Spill over	Oral/respiratory	South Africa	[43]
Raccoon ( <i>Procyon lotor</i> )	Spill over	Oral	United States of America	[43]
Red Fox ( <i>Vulpes vulpes</i> )	Spill over	Oral	England, United States of America	[42, 43]
Warthog ( <i>Panchochoerus aethiopicus</i> )	Spill over	Oral/respiratory	Uganda	[43]
White-tailed deer ( <i>Odocoileus virginianus</i> )	Spill over	Oral/respiratory	United States of America, Canada	[43]

capability to participate in a particular biotope as an *M. bovis* reservoir.

One of the greatest threats to any control programme in domestic animals is infection in feral maintenance hosts that cannot be controlled and can re-introduce infection in livestock which in turn could transmit the

disease to humans. Main examples are the badger (*Meles meles*), which has been suggested to act as a significant source of infection in Great Britain and Ireland [29]. In New Zealand the eradication of bovine tuberculosis is threatened especially by the brush-tail possum (*Trichosurus vulpecula*)

[172]. The presence of *M. bovis* infection in white tailed deer (*Odocoileus virginianus*) in Michigan poses a serious menace to the control and eradication programmes for bovine tuberculosis in the United States [131]. Infection with *M. bovis* has also been described across a range of animals such as buffalo, kudu, lion, baboon and antelope in the Kruger National Park in South Africa, having severe consequences on the biodiversity of this region [172]. In France, a high non-negligible proportion of *M. bovis* infected wild deer (*Cervus elaphus*) were found in regions where cattle outbreaks were reported, opening-up the suspicion of transmission from wildlife (Boschioli et al., unpublished results).

#### **2.2.2. Physiological characteristics for host adaptation**

Only some of these characteristics will be discussed in this section. For further information, see reference [160]. Although the course of infection, clinical signs and development of disease can vary within different host species, it can be presumed that certain essential physiological characteristics are common for successful infection in any susceptible host. The analysis of the complete genome sequence of *M. bovis* [59] provides a means to dissect these characteristics. To begin with, the cell wall protects the bacteria from harsh environments but also promotes intracellular persistence [14]. The ability to infect and persist in the macrophage by inhibiting phagosome-lysosome fusion, creating a privileged compartment and remaining sequestered away from the terminal endocytic organelles, is central to the success of the pathogen [45]. The presence of acidic, glycine-rich proteins (PE and PPE families) also found in *M. leprae* [30] and *M. marinum* [140] whose genes are involved in virulence are worth mentioning. Another important genetic factor implicated in the attenuation of the *M. bovis* BCG strain is the lack of the RD1 locus [140], which is involved in a novel described secretion system [140].

Latency is another important aspect of tubercle bacilli pathogenesis. The molecular basis for the persistence phenotype and the pertinent host immune mechanisms that contribute to the maintenance of tuberculosis latency are just beginning to be understood. The bacillus releases peripheral cell-wall lipids into their host cells, which induce the granulomatous response. This represents active manipulation of the host's response to ensure the maintenance of the infection. The granuloma appears as a balance structure that walls off the infection and limits its metastasis. However, the very prison that limits spread could well restrict the capacity of the host to activate the macrophages required to kill the bacteria [150].

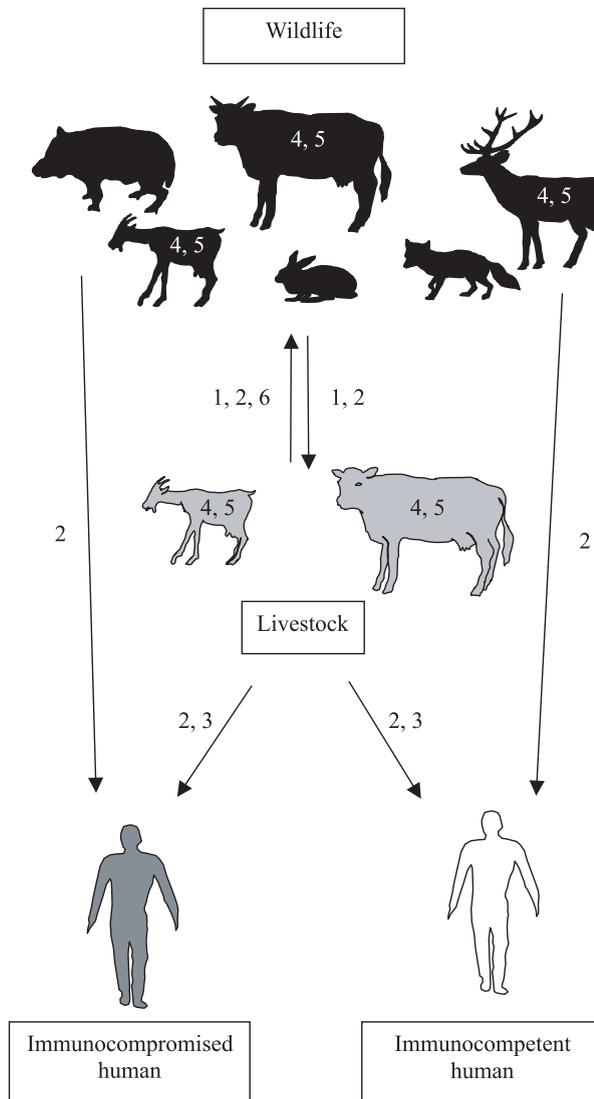
#### **2.2.3. Spread in domestic livestock**

Within domesticated animals, cattle, farmed buffalo and goats are considered reservoir hosts of *M. bovis*, while pigs, cats, dogs, horses and sheep are considered spillover hosts. For further reading, see [36]. The realisation that wildlife is infected with *M. bovis* may result in apparent failure programmes to eradicate the infection from cattle [44]. Knowledge of wildlife tuberculosis through appropriate surveillance programmes in feral animal populations may be important in the research strategies for the total elimination of livestock tuberculosis.

### **3. HEALTH IMPACTS OF *M. BOVIS***

#### **3.1. Transmission and route of infection**

In cattle as well as in other animal hosts, the route of transmission of *M. bovis* can be deduced by the pattern of lesions observed in slaughtered animals. Animals with lesions restricted to the thoracic cavity are presumed to have been infected by the inhalation of aerosols, while those with lesions in mesenteric lymph nodes are thought to have acquired the infection by ingestion [136]



**Figure 3.** Transmission and routes of infection of *M. bovis*. Illustration of possible transmission pathways of *M. bovis* between the environment, wildlife, livestock and humans. 1: Infection by contaminated materials; 2: Infection by aerosol; 3: Infection by ingestion of derivative products; 4: Vertical transmission; 5: Horizontal transmission; 6: Infection by predation.

(Fig. 3). In field cases of cattle, the majority of lesions is found in the upper and lower respiratory tract and associated lymph nodes. Thus, it is considered that the inhalation of *M. bovis* is the most probable route of infection [125]. In fact, the development of tuberculosis lesions which invade the airways is

thought to be required to facilitate active excretion and aerosol spread of *M. bovis* [107]. Respiratory excretion and inhalation of *M. bovis* is considered to be the main route through which cattle-to-cattle transmission occurs in bovines (Fig. 3). Droplets of contaminated water, eructation while

ruminating infected pastures or inhaling contaminated dust particles can also be an alternative way of aerogenous infection. This is, in fact, suspected to be the most likely way cattle could get infected in a contaminated environment by badger excretions [134]. Ingestion of *M. bovis* directly from infected animals or from contaminated pastures, water or fomites is considered secondary to respiratory spread, as deduced from the minor presence of mesenteric lesions in cattle cases [107]. Congenital infections and vertical transmission to calves as well as genital transmission are uncommon in regions where intensive eradication programmes operate. Within wildlife, routes of transmission are listed in Table I and illustrated in Figure 3.

Infection of humans may occur by the inhalation of aerosols or through the consumption of contaminated milk (see Fig. 3). The aerosols are the result of animal excretion but can also be produced by handling lesioned carcasses [124]. This route of infection leads to respiratory tuberculosis. Human to human transmission is possible if an immunodeficient status of the potential host is encountered [64].

### 3.2. Human pathology

Tuberculosis in humans caused by *M. tuberculosis* or *M. bovis* is indistinguishable clinically, radiologically and pathologically [171]. In countries where bovine tuberculosis is uncontrolled, or in developed countries before strict control campaigns and milk pasteurisation, most human cases occur in young persons and result from drinking contaminated milk. This alimentary route of infection leads to extra-pulmonary forms of tuberculosis, where infection can become established in the cervix and less frequently in the axillary lymph nodes leading to chronic skin tuberculosis [113]. Adult humans at professional risk, especially farmers or abattoir workers as well as veterinarians, are generally infected with *M. bovis* by the respiratory route through

aerosols from infected cattle and develop typical pulmonary tuberculosis.

The implementation of bovine eradication schemes together with the pasteurisation of milk has had a major impact on the disease with the result that human tuberculosis due to *M. bovis* is now rare in developed countries. However, a small number of cases still occur in elderly people as a result of reactivation of dormant infections [171].

### 3.3. Risk factors

In animals, age, behaviour, environment and prevailing farm practices can have a significant influence [107]. Nutritional deficiencies are associated to reduced resistance to bovine tuberculosis [71]. Immunological dysfunction in cattle may enhance bovine tuberculosis infection, although this has never been assessed.

In humans, risk factors for mycobacterial infections, being especially well described for *M. tuberculosis* [32] include the intensity of exposure, age, immune system, HIV coinfection, genetic factor, vaccination status and also socio-economic factors. Professional exposure and life style, as discussed in Section 3.2, can also be considered as risk factors when *M. bovis* is the etiological agent in human tuberculosis. Reactivation occurs under stress or in old age, since mycobacteria in a latent state may become subject to less stringent control by host systems [113]. The endemic nature of the disease in domestic stock or wildlife and the likely contact with humans, particularly those infected with HIV, poses a serious health problem, since humans could begin to actively transmit the infection within populations. Another risk could come from the increasing contact of humans with infected wildlife animal species, and therefore bovine tuberculosis could become a "leisure" zoonoses (unpublished data). This is a possibility for hunters that handle heavily contaminated animal carcasses capable of producing infective droplets.

**Table II.** Environmental sources of MAC complex mycobacteria.

Species	Isolation origin	References
MAC	Water and soil of brown water swamp	[87, 88]
MAC	Residential water source	[169]
MAC	Hospital recirculating hot water system	[168]
MAC	Public swimming pools and whirlpools	[75, 96]
MAC	Potable water sources	[37]
<i>M. avium</i> ssp. <i>avium</i>	Diptera	[53]
<i>M. avium</i> ssp. <i>avium</i>	<i>Blatta orientalis</i>	[54]
<i>M. avium</i> ssp. <i>avium</i>	Earthworms	[55]
<i>M. avium</i> ssp. <i>paratuberculosis</i>	Slurry	[10, 94]
<i>M. avium</i> ssp. <i>paratuberculosis</i>	River water	[85]
<i>M. avium</i> ssp. <i>paratuberculosis</i>	Trichostrongylid larvae	[98]
<i>M. avium</i> ssp. <i>paratuberculosis</i>	Diptera	[53]
<i>M. avium</i> ssp. <i>paratuberculosis</i>	Nematode larvae	[173]
<i>M. avium</i> ssp. <i>paratuberculosis</i>	Earthworms	[55]
<i>M. avium</i> ssp. <i>paratuberculosis</i>	<i>Blatta orientalis</i>	[54]
<i>M. avium</i> ssp. <i>paratuberculosis</i>	Milk	[65, 66]

#### 4. ENVIRONMENTAL AND ANIMAL RESERVOIR OF MAC AGENTS

##### 4.1. Environmental reservoir

###### 4.1.1. Locations

Environmental mycobacteria such as the members of MAC constitute a very interesting group in terms of ecology. They possess properties that enable them to grow in natural biotopes without losing their pathogenicity for certain living beings. Some strains induce infections via natural biotopes, which can be regarded as reservoirs in the chain of transmission. In spite of their pathogenicity, they possess a number of properties resembling in many respects those of the saprophytes: growth over a wide temperature range, sometimes better at 20 °C than 37 °C, rapid adaptation to new substrates and the capacity to increase their growth rate on synthetic media. MAC agents grow well between pH 4.0 and 7.5 [21] with an optimal pH between 5.4 and 6.5 [137]. In contrast, *M. tuberculosis* has

a comparatively narrow range for optimal growth between pH 6.0 and 6.5. Outside of living beings, mycobacteria species of MAC have been found in many biotopes including the soil, wastewater, water tank, municipal water, aerosols, protozoa, deep litter, fresh tropical vegetation, animals and humans (Tab. II). Among the several opportunistic pathogens affecting patients infected with human immunodeficiency virus (HIV), members of MAC, mainly Maa, are the cause of significant problems for the clinical management of this immunosuppressive disease. Potable water is considered as the primary source of MAC infection in humans [146] and has been shown to be a source of Maa infection in virus-inoculated Simian immunodeficiency macaques [101]. Food has also been shown to be a possible source and route of transmission of Maa, isolated in patients and food [178].

###### 4.1.2. Physiological characteristics for environmental survival

Mycobacteria of MAC have the capacity to survive and multiply under a wide range

of environmental conditions [49, 138], including low pH [21], extreme temperature [152], starvation, chlorine or ozone treatment [128] and low oxygen level [16]. Thus, their ability to utilise many substances as nutrients enables them to grow successfully in many biotopes. Their adaptation for life in the environment is linked to physiological characteristics of the mycobacteria such as the impermeable cell wall [14, 141] and slow growth [62] (see also Sect. 4.2.2).

#### **4.1.3. Interactions with protozoa and insects**

In contrast to *M. bovis*, protozoa and insects play an important role in the dissemination of some of the other species of mycobacteria and interactions with animals or humans [55, 138]. As described in Table II, Maa and Map have been isolated from many different insects and protozoa. The interactions between mycobacteria and insects are very important to the evolution of mycobacterial pathogenesis. Many protozoa harbor bacteria and their ability to survive phagocytosis is a considerable advantage to waterborne bacilli. Maa inhibits lysosomal fusion and possibly kills infected amoebae. Maa can also invade and replicate in *Dictyostelium discoideum* [156]. Compared to bacilli grown in medium, amoeba-grown Maa are more invasive towards amoebae, HT-29 human epithelial cells and macrophages [27] and more virulent in beige mice [27]. Other advantages for these mycobacteria to use protozoa as hosts reside in the fact that they are protected from antimicrobial effects [111] and that they can survive during encystment. Mycobacteria can indeed use the protozoan cysts as carriers to survive starvation and toxic stress and can be released upon excystment [138, 160].

Protozoa may play a central role in the evolution of mycobacteria pathogenesis. The selection of mycobacteria that can infect and replicate within protozoa has likely resulted in mycobacteria also becoming intracellular pathogens in animals as exemplified by the

adaptation of *Legionella pneumophila* to the infection of human macrophages [153].

Insects that have been in contact with material contaminated with these environmental pathogens may spread mycobacteria. Members of MAC were isolated from Diptera (see Tab. II) collected from both cattle herds infected by Map and *M. intracellulare* and cattle without mycobacterial infections [53]. Earthworms constitute a significant component of soil organisms. Most ingested microorganisms pass through the digestive tract and are excreted in the faeces. However, some species can propagate in the digestive tract and survive in egg cocoons of the earthworm [39, 151]. Whittington et al. have shown that the nematode parasite of sheep might be able to help in the transmission of Map [98, 173]. The role of earthworms as vectors of mycobacterial infection in cattle and goat farms has been identified for Maa and Map [55]. Other omnivorous insects such as cockroaches, which frequently infect hospitals, laboratories and other contaminated habitats, may also be an environmental reservoir of pathogen mycobacteria. Allen et al. have demonstrated the survival of mycobacteria in *Blatta orientalis* that had ingested infected human sputum [1]. Recently Fisher et al. have proposed the cockroach (*Blatta orientalis*) as a passive vector of causal agents of avian tuberculosis and paratuberculosis [54].

## **4.2. Animal reservoir**

### **4.2.1. Wildlife as a source of the MAC agents**

Mycobacterium members of MAC cause infections and diseases in a wide range of different animal species. Concerning ssp. Maa and Map, the known host range includes ruminant and non-ruminant wildlife (Tab. III) [8, 40, 166, 167]. This section is divided into three parts. The first part describes the disease in wild ruminants, the second describes the disease in wild non-ruminants and the last part describes the disease in birds.

**Table III.** Wildlife reservoir.

Strains	Wildlife host	Clinical features	References
<i>M. avium</i> ssp. <i>paratuberculosis</i>	Wild rabbit	JD	[3, 69, 70]
<i>M. avium</i> ssp. <i>paratuberculosis</i>	White-tailed deer	JD	[24, 154]
<i>M. avium</i> ssp. <i>paratuberculosis</i>	Rocky montain goats	JD	[175, 176]
<i>M. avium</i> ssp. <i>paratuberculosis</i>	Bighorn sheep	JD	[174]
<i>M. avium</i> ssp. <i>paratuberculosis</i>	Bison	JD	[19]
<i>M. avium</i> ssp. <i>paratuberculosis</i>	Elk	JD	[176]
<i>M. avium</i> ssp. <i>paratuberculosis</i>	Wild red deer	JD	[122]
<i>M. avium</i> ssp. <i>paratuberculosis</i>	Foxe and Stoat	JD	[7, 8]
<i>M. avium</i> ssp. <i>paratuberculosis</i>	Brown Hare	JD	[8]
<i>M. avium</i> ssp. <i>paratuberculosis</i>	Mandrill	JD	[180]
<i>M. avium</i> ssp. <i>paratuberculosis</i>	Wild boar	TLL	[99]
<i>M. avium</i> ssp. <i>paratuberculosis</i>	Deer	JD	[139]
<i>M. avium</i> ssp. <i>paratuberculosis</i>	Non ruminant wildlife		[8]
<i>M. avium</i> ssp. <i>avium</i>	Bird, wild and domestic mammal		[167]
<i>M. avium</i> ssp. <i>avium</i>	Swine	TLL	[117, 118, 164]
<i>M. avium</i> ssp. <i>avium</i>	Wild boar	TLL	[99]
<i>M. avium</i> ssp. <i>avium</i>	Deer	TLL	[41]
<i>M. avium</i> ssp. <i>avium</i>	Rhesus monkeys	TLL	[56, 63]
<i>M. avium</i> ssp. <i>avium</i>	Horse	TLL	[72]
<i>M. avium</i> ssp. <i>avium</i>	Birds	TLL	[119]
<i>M. avium</i> ssp. <i>avium</i>	Macaque	TLL	[102]
<i>M. avium</i> ssp. <i>avium</i>	Hedgehog	CL	[103]
<i>M. avium</i> ssp. <i>avium</i>	Kangaroo	CL	[100]
<i>M. avium</i> ssp. <i>hominisuis</i>	Wild boar	TLL	[109]
<i>M. intracellulare</i>	Rhesus monkeys	CL	[56]
<i>M. intracellulare</i>	Opossum	CL	[116]

CL: caseous lesions; JD: Johne disease; TLL: tuberculosis lesion like.

(i) In wild ruminants, the Maa and Map infections have been documented worldwide, including in the USA [2, 121, 162], Europe [90, 155, 167, 177], Australia [50], New Zealand [31], Japan [117, 118] or Africa [126]. The data are essentially described as lesions and clinical signs in Map infected wild ruminants, which are similar to those in infected domestic ruminants, and where the disease may be fatal [19, 174]. In deer, the disease is characterized by loss of condition, diarrhoea, faecal staining of the perineum, low serum albumin and total protein

concentration. In other cases, the infection is clinically unapparent [28, 41]. In bison, histologic results are similar to paratuberculosis described in cattle [19].

(ii) In the wild boar (*Sus scrofa*), the prevalence and the pathogenesis caused by MAC agents Maa and Map have been recently reviewed [99]. The lesions, rarely observed, are localised in the head lymph nodes. The number of wild boars with tuberculous lesions increases with age. However mycobacteria are more frequently isolated from

the wild boar without clinical signs of tuberculosis [33]. Ray et al. [143] have also described a more frequent isolation of mycobacteria, including *M. bovis*, Maa and Map, from the tissue of wild boar without tuberculous lesions. In non-ruminant wildlife, the occurrence of Map infections have been recently documented in Scotland [8, 40]. Following the isolation of Map in rabbits, the studies were extended to other wildlife species in farms with a history of paratuberculosis in livestock. Map was isolated from foxes, stoats, weasels, badgers, wood mice, rats, brown hares, jackdaws, rooks and crows [8]. The clinical signs of paratuberculosis in non-ruminant wildlife are largely unknown. Lesions seem to be similar to early, subclinical infections described for ruminants and clinical signs are not systematically observed on positive animals [8, 133].

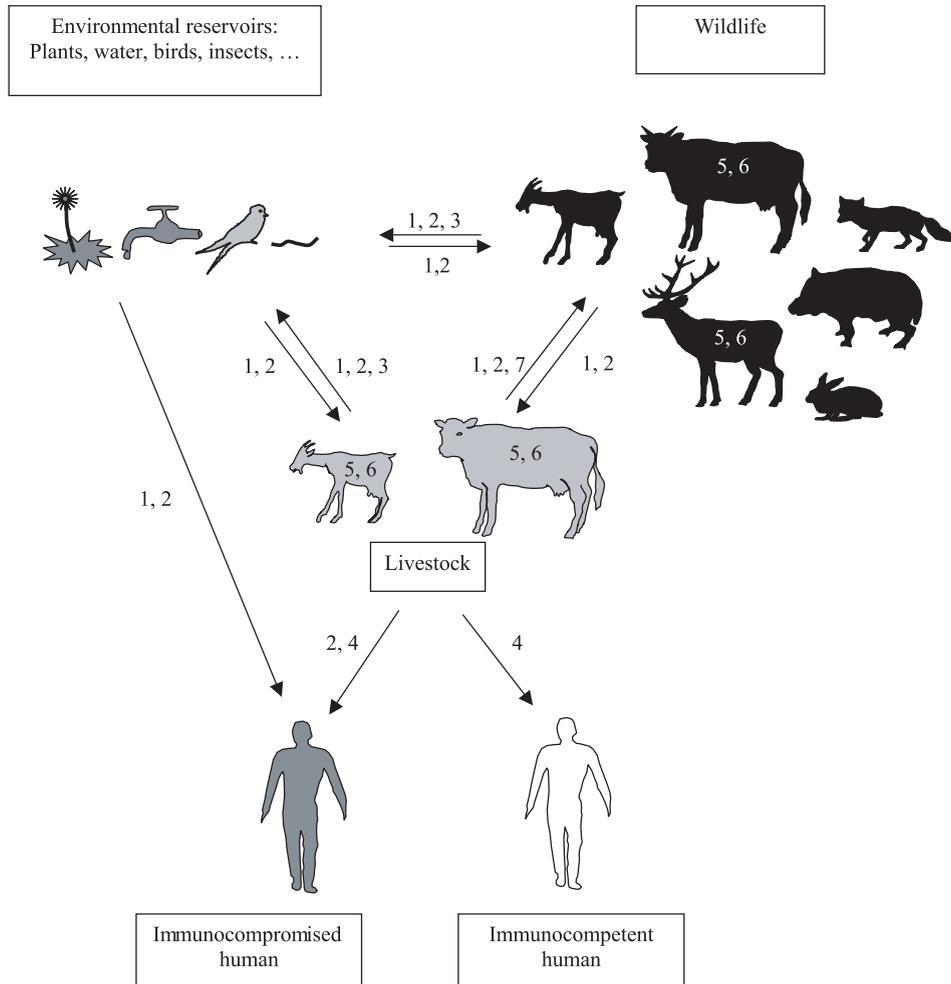
Naturally acquired infections with Maa and *M. intracellulare* have been reported in non-domestic mammal species and non-human primates, as well as in exotic hoofed animals (Tab. II) [166, 167]. MAC agents have also been isolated from kangaroos, macaques and mandrills [79, 105, 115, 163, 180].

(iii) In many countries, the disease caused principally by Maa serotype 1,2,3, occurs in domestic and wild birds as well as in a variety of fowl, game birds and water-fowl (see Thorel et al. for a review [167]). The disease caused by Maa is characterized by its chronic nature, its persistence in a flock or aviary once established, and its tendency to induce wasting and finally death. However, a few clinical signs of the disease are commonly observed in chickens and birds, only during the advanced stages of the disease. Macroscopic lesions are disseminated through the organism most often observed in the liver, spleen, intestine and bone marrow.

These data clearly show the existence and the importance of a wildlife reservoir of mycobacteria of MAC that is still mainly undetermined. The interspecies transmission may occur between livestock and wild-

life and vice-versa. Interspecies transmission has been demonstrated experimentally between non-ruminant wildlife and livestock [114]. These possible transmissions have important implications with respect to the attempted control or eradication of this disease in both wild and domestic animals. The routes and mode of transmission are illustrated in Figure 4. Studies of the transmission of Map in livestock could be transposed to Map transmission in wildlife. The faecal-oral route, i.e. through ingestion of faecal contaminants, milk or colostrum, is the principal pathway of infection in the host. Ingestion of mycobacteria has been proposed as the primary route of infection in paratuberculosis and experimental oral inoculation of organisms has produced enteric disease experimentally in sheep and cattle. Other experimental Map infections have been reported by using different routes of inoculation such as intravenous [89], intramammary [93], intrauterine [108]. Other possible alternative transmission pathways could help to understand the epidemiology of Johne disease. One such pathway could be the aerosol transmission via the respiratory tract which is generally agreed as being the principal route of infection of *M. bovis* in cattle [123]. In cattle, vertical transmission during pregnancy has also been proposed since Map has been isolated from the uterus [91, 132], fetal tissues [95] and semen [92, 173].

Predation is also a possible form of transmission of MAC to carnivores (Fig. 4). For Map, the prevalence in predators, including fox stoats and weasels, is 62% and is higher than in the prey species, including rabbits, rats and wood mice, whose prevalence is 10% [69, 70]. The high prevalence of Map in some non-ruminant wildlife species and their interaction with susceptible ruminant livestock raises the possibility that they play a role in the epidemiology of the disease in the latter. The risk of transmission from wildlife to livestock has frequently been suggested, but it is hard to be proven in the field mainly due to the long incubation period of the disease and the difficulty



**Figure 4.** Transmission and routes of infection of MAC. Illustration of possible transmission pathway of MAC between the environment, wildlife, livestock and humans. 1: Oral infection; 2: Infection by aerosol; 3: Passive infection; 4: Infection by derivative products; 5: Vertical transmission; 6: Horizontal transmission; 7: Infection by predation.

in excluding other potential sources of infection [7, 8, 24, 52, 69, 174]. For Map, livestock may also be a source of contamination for wildlife, by contact and/or by their excreta, including rodents, non ruminants or ruminants.

#### 4.2.2. Physiological characteristics for host adaptation

Mycobacteria of MAC seem to be well adapted to infect many different wildlife species. These organisms share some of the

same physiological characteristics and molecular determinants of virulence described for other slowly growing mycobacteria as *M. tuberculosis* or *M. leprae*, see [49, 82, 158] for a review. These organisms are surrounded by a cell wall and an envelope characteristic of mycobacteria which confers their distinctive feature of acid fastness [82]. However, MAC-specific C-mycoside glycopeptidolipids (GPL) [13, 15] seem to be related to the resistance of MAC to antimicrobial agents. Members of MAC share a high percentage of DNA and rRNA homology. Map shares over 98% DNA homology with Maa and they have homologous major antigens [6, 74]. However, phenotypic differences between these two subspecies, differentiated by the dependence of Map on mycobactin [165] and genetically by the presence of multiple copies of the Map specific insertion element IS900 [67], are important. These organisms induce, in a wide-ranging animal species, different pathologies associated to distinct clinical signs [28, 82] and host adaptation [49, 74, 82]. With the availability of published microbial genomes, the genomic approach will help in identifying novel genes involved in the physiological adaptation of MAC members to these different wild animal species. This approach will also help to identify specific genes that cause distinct pathologies, avian tuberculosis and Johne disease, with different clinical signs and in different target hosts, despite sharing more than 98% DNA identity.

#### 4.2.3. Spread in domestic livestock

Livestock also represent an important reservoir, not developed in this review and well described in others [74, 166, 167]. As illustrated in Figure 4, livestock could either be infected by mycobacteria present in wildlife and in the environment or be a source of contamination for wildlife and humans and a particularly susceptible population [12, 90, 129]. Livestock could also be a vector of infection in humans directly or by their derivative products (see Fig. 4).

MAC agents are described to be responsible for the infection in a very large range of agricultural and domestic animal species. The range of domestic animals infected by MAC members includes domestic birds, chickens, cattle, swine, farmed deer, sheep and goats, and horses but also cats and dogs which has been reviewed by Harris and Barletta and Thorel et al. [74, 167]. The majority of MAC infections in livestock are detected at slaughter and the diagnosis is confirmed by bacteriological procedures. It is most probable that a common environmental reservoir of infection exists within wildlife.

## 5. HEALTH IMPACTS OF THE MAC

### 5.1. Transmission and route of infection

For humans, exposure to MAC organisms, present in wildlife and in natural biotopes including protozoa and insects, can occur by a variety of routes. Birds are major agents of Maa spread as they excrete bacilli in large amounts in their faeces, where bacteria can persist in the soil or in water for long periods afterwards. Knowledge of the route of infection, pathogenesis, and levels of excretion will assist in determining the potential of each species to act as a reservoir of infection (Fig. 4). As for other environmental mycobacteria, municipal and natural water are important ways of MAC infection. While environmental mycobacteria are opportunistic pathogens in a variety of immunocompromised patients, a wide prevalence results in all humans being commonly and continuously exposed at a low level (50 to 500 bacilli per day). Only a very small percentage of human-mycobacteria interaction progress to outright mycobacterial infection but such progression is much more common in immunocompromised patients, especially those with AIDS [4]. Genomic restriction fragment patterns of Maa from hospital water isolates are similar to those from AIDS patient isolates [5]. Numerous studies have attempted to determine the routes, oral or aerosol, leading to

Maa infection in AIDS patients but no evidence was related to one and a combination of both routes is likely [22, 83, 144].

For Map, studies need to be done to determine the possible ways of direct transmission between wildlife and humans.

It is necessary to develop a better understanding of the epidemiology of MAC and their diseases, especially the transmission pathways, in animals, domestic ruminants and humans with important implications with respect to the attempt to control these diseases.

## 5.2. Human pathology

While humans are highly susceptible to *M. tuberculosis* and *M. leprae* infection, most people who are exposed to these bacteria never develop clinical disease, indicating that the normal immune system can control these organisms [86]. This observation is even more applicable for MAC organisms because, despite evidence of exposure rates, the incidence of clinical disease is remarkably low (10 cases per 100 000 population). For a review see [49, 82, 138].

In immunocompetent patients, the infections caused by MAC agents are principally pulmonary [4]. In children a recent study has shown that the most predominant species in cervical lymphadenitis caused by nontuberculous mycobacteria was *M. scrofulaceum* (60%) followed by the MAC agents (40%) [84].

The number of MAC infection cases in immunocompetent patients has been overwhelmed by the high frequency (e.g. 25 to 50%) of MAC infections in AIDS patients [80, 127]. Among the members of MAC, Maa predominate (87 to 98%) in AIDS patients and induce disseminated mycobacteremia rather than bacteria restricted to the lungs as for immunocompetent patients. Maa appears to have a particular predilection for infecting and disseminating in HIV-infected patients. It has been suggested that Maa isolates that cause disease in AIDS

patients are not simply gratuitous opportunists but possess specific genetic determinants that confer an ability to penetrate and multiply within macrophages and host cells and contribute to the existing immunodeficiency [73]. One of the most interesting aspects of MAC infection in AIDS patients is the discovery of polyclonal infection, one possible explanation for the inability to correlate the outcome of antibiotic treatment with susceptibility patterns [179]. Recently, human infection with Map in a patient with HIV was reported [145]. This report raises the question of systematic Map detection, which is not yet possible by routine techniques. It raises other questions as to why Map has not been detected before and whether this lack of detection was because of its slow and difficult growth, or because it has been misidentified with Maa, or because its occurrence in infections is low.

The isolation of Map from tissues of Crohn patients [23, 26, 106] has led to concerns that Map may be pathogenic for humans [112]. Physical and causal association of Map in Crohn disease is still controversial. Since cell-wall deficient Map usually cannot be identified by Zeihl-Neelsen staining, identification of Map in humans either requires fastidious culture or detection of Map DNA or RNA, which is not always reproducible [74]. However, the Koch postulates may be met for Map [68]. Map has been isolated, with technical difficulties of Map culture, from patients with Crohn disease [26, 61]. Milk and water are potential sources for acquiring Map [78, 110]. However, only a few samples of milk, positive by PCR for the presence of Map, have been shown to be positive for culture, suggesting that either Map remains undetectable because of a too low number of viable Map in a sample or due to the absence of live Map in the sample [11]. Serological response to Map does not conclusively prove that the subject has had an active infection [11]. The development of Crohn disease depends upon an interaction between the host and environmental factors but also genetic factors. In humans, it has been suggested that the

*NOD2/CARD15* gene product confers susceptibility to Crohn disease [81]. The gene *NOD2/CARD15* identified on chromosome 16 is involved in the recognition of luminal bacterial products and is important in mucosal defence [60]. For instance, *NOD2/CARD15* mutations have only been documented in around one-third of Crohn disease patients and at least seven other susceptibility loci in inflammatory bowel disease have been identified [38]. A deficient induction of defensins also seems to be involved in the development of Crohn disease [51]. Interestingly in one 21-year-old Canadian-born man the coexistence of Map disease and a permissive *NOD2/CARD15* mutant has been documented [9]. The proportion of Crohn disease cases potentially attributable to Map and host susceptibility should be studied for a better understanding of the aetiology of Crohn disease. European governments are addressing the possibility of a causal connection between Map and Crohn disease [47]. To resolve these possible links between Crohn disease and paratuberculosis, further research, including large-scale epidemiological studies of Crohn disease, the in situ detection of Map and pathology of Map in the human gut, and the route of infection and drug trials, are required. Even if such an association is proved, there is still the considerable task of determining whether Map has a primary etiological significance or is a secondary invader. Further research is required to unravel the cause of Crohn Disease.

### 5.3. Risk factors

Although MAC agents cause a variety of pathologies including tuberculosis-like diseases in animals and human immunocompetent or immunocompromised patients, they are first ubiquitous in the soil and water. Susceptibility to mycobacterial infection depends on various risk factors.

In animals, the susceptibility to Map infection is the highest in animals under 30 days old, but clinical disease does not usually develop in cattle until 2–5 years of age. The

establishment of infection has been shown to be experimentally favoured with the intensity of exposure and the use of young animals [28]. Other risk factors including intensive farming systems, acid soils, low dietary intake, stress, lactation and parturition and immunosuppression by pathogens such as bovine virus diarrhoea virus (BVDV) [25, 97] have been described. Investigations are needed to clarify the relative contributions of genetic and environmental influences in the susceptibility of breeds such as the Scottish Blackface, Shetland sheep or Limousin cattle.

In humans, the same risk factors described as for *M. tuberculosis* [32] and for *M. bovis* already discussed in Section 3.3, were identified for exposure to MAC agents. For pulmonary MAC infection in immunocompetent individuals, an additional risk factor is cigarette smoking with the associated chronic obstructive pulmonary disease [49]. Local traumas, surgical procedures, injury, injection are risk factors for localised soft-tissue MAC infections [77]. Profound immunodeficiency such as that seen in the late stage of AIDS patients is the most important risk factor for disseminated MAC infections and for Maa in particular. Other observations suggest that there are host immune defects, possibly unrelated to the underlying HIV infection, which predispose patients to disseminated infections [4]. The variant of *CARD15/NOD2* gene product that confers susceptibility to Crohn disease may predispose humans to Map infection.

## 6. CONTROL

Control and eradication programmes of bovine tuberculosis, paratuberculosis or other mycobacterial pathogens could be extremely complicated by the existence and the strong involvement of wildlife and environmental reservoirs.

Management of natural reservoirs should take into account many different factors including (i) the potential sources of infection and routes of transmission (see Figs. 3

and 4) i.e. MAC agents are viable for long periods in water, feces and cattle slurry [10, 94], (ii) the pathogens ability to infect many different animal species (see Tabs. I, II and III).

The management of wild-animal herds for either profit or preservation of endangered species can exacerbate mycobacterial infections in livestock such as bovine tuberculosis [46] and paratuberculosis by modification of their natural environment to domesticated conditions of husbandry. A study has shown that the presence of farmed deer on land currently inhabited by dairy cattle increased the risk of paratuberculosis in the dairy cattle population [20]. Another study showed that the same strain of Map isolated from bighorn sheep was able to infect other species of wild animals as well as domestic ruminants [174, 175]. Conversely, some wildlife animals such as rodents, may be infected through scavenging livestock feed on floors contaminated with livestock feces [40].

Epidemiological knowledge of these pathogens in their natural reservoirs is an important factor to be taken into account for the success of control programmes. For assessing epidemiological studies of mycobacteria in wildlife and the environment, improved diagnostic tools are needed. As described for tuberculosis in free-ranging wildlife [43], detection and diagnosis of mycobacteria infections in wildlife are extremely difficult, due to: (i) common occurrence of sub-clinical infections and deficiencies of the currently available diagnostic tests, (ii) individual variability of the infection with long asymptomatic phases, (iii) serological tests with low sensitivity and low specificity, (iv) difficulty to develop routine tests measuring cell-mediated immune responses in most species, and (v) paucity of direct diagnosis. Bacterial culture remains the gold standard for diagnosis, however isolation of mycobacteria strains from the environment or wildlife is often particularly difficult and long. Recently promising methods have been developed, using the

complete genome sequence of some Mycobacteria, for differentiation or subtyping of bacterial strains. This provides important information for molecular epidemiologic analysis and assists in providing an understanding of the genetics and pathogenesis of Mycobacteria. A strain typing technique using repetitive DNA sequence interspersed in the genome, and being highly discriminatory, highly reproducible and convenient has been exploited for the *M. tuberculosis* complex [58, 104, 148, 157, 161] and recently adapted to *M. bovis* and Map [2, 147].

Few management options are available, especially for protected wildlife. Considering safety and animal welfare concerns, an effective vaccine is the best option for the control of wildlife reservoirs of mycobacterial infection, but such vaccines are not yet available. The main goal would be to reduce or prevent the excretion of bacilli from wildlife thereby breaking the chain of infection from feral to domestic animals. Nevertheless, further development is required before this strategy could be used to control mycobacterial infections. Reviews of vaccine approaches to control the disease in wildlife reservoirs are available [18, 74, 171]. Efforts have to be maintained to ameliorate existing diagnosis assays and to improve new diagnosis tests that could more specifically detect the early phase of infection. Diagnostic assays that distinguish between vaccinated and infected animals should be available in the near future.

## 7. CONCLUSION

Zoonotic aspects of mycobacteria transmitted by the environment and wildlife highlights a major health problem worldwide. Furthermore, increasing the incidence of interactions between human and mycobacteria are predicted in coming years. This is based on the increase in clinical cases attributed to environmental mycobacteria. Mycobacteria and MAC agents in particular, seem to be more resistant than other pathogens to water treatment such as chlorination. This rising incidence also takes into

account the increasing percentage of mycobacterial infections in the population with predisposing conditions, AIDS, age, immunosuppressive regimens after transplantation for example, and socioeconomic factors. It is also a reflection of better research on these novel opportunistic mycobacterial species that are and will be better identified by more rapid and sophisticated methods.

As countries engage in programmes to control bovine tuberculosis and paratuberculosis in domestic animals, the determination of the role of wildlife and the environment as sylvatic reservoirs of mycobacteria pathogens such as *Maa*, *Map* or *M. bovis* will become increasingly necessary. This will require the use of the appropriate diagnostic procedures to perform robust epidemiological investigations on different wildlife species. Research in order to understand the physiological ecology of mycobacteria in wildlife and the environment is needed to fully discover the effects that mycobacteria have on human health and to allow new approaches for management and control of their environmental and wildlife reservoirs.

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