Mycoplasmosis: A Zoonotic Threat - Epidemiology, Pathogenesis and Economic Impact

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ABSTRACT

The world faces a growing threat from mycoplasmas, the smallest and most adaptable microorganisms that can infect a range of warm-blooded animals, birds, reptiles, insects, and plants. This chapter explores the epidemiology, pathogenesis, and economic impact of mycoplasmosis, emphasizing its zoonotic potential. Mycoplasmas, with their minimal genomes and lack of cell walls, navigate various host tissues, causing infections in the alimentary canal, respiratory and urogenital tracts, ocular region, mammary organs, and joints. Human infections involve species like M. pneumoniae and M. genitalium, responsible for respiratory diseases, joint infections, and reproductive issues. The chapter highlights the alarming rise of macrolide-resistant M. pneumoniae, impacting global health. Animal infections, such as contagious bovine pleuropneumonia (CBPP) and contagious caprine pleuropneumonia (CCPP), result in painful symptoms and economic losses, with M. bovis being a significant pathogen in cattle.The zoonotic potential is evident as species primarily infecting animals, like M. ovis and M. suis, are found in humans. The economic impact spans various regions, with financial losses attributed to decreased productivity, embryonic mortality, and prevention efforts. Avian mycoplasmosis, affecting birds like chickens and turkeys, adds to economic burdens through decreased egg yield and hatchability. The chapter delves into the pathogenesis of mycoplasmas, highlighting their intracellular lifestyle and unique features such as variable surface proteins. The epidemiological landscape reveals their presence in chronic obstructive pulmonary disease (COPD) and sexually transmitted diseases. Vaccination efforts are explored, addressing diseases in various species, with emphasis on the challenges of developing cost-effective vaccines. Successful eradication programs for diseases like CBPP in China and M. hyo infections in Norway are discussed. In conclusion, mycoplasmosis poses a complex challenge globally, impacting both human and animal health. The chapter emphasizes the need for innovative strategies to address the limitations of existing control measures. Successful eradication programs offer hope, and a deeper understanding of mycoplasma biology is crucial for developing effective preventive and therapeutic interventions.

Keywords: Economic impact, Avian mycoplasmosis, Public health, Vaccination, Eradication

CITATION

Soomro MA, Soomro H, Hassan MF, Rajput ZI, Khanzada M and Meghwar M, 2023. Mycoplasmosis: A Zoonotic Threat - Epidemiology, Pathogenesis and Economic Impact. In: Altaf S, Khan A and Abbas RZ (eds), Zoonosis, Unique Scientific Publishers, Faisalabad, Pakistan, Vol 4: 17-28. https://doi.org/10.47278/book.zoon/2023.135

CHAPTER HISTORY Received: 25-Mar-2023 Revised: 20-Apr-2023 Accepted: 28-Jun-2023

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1. INTRODUCTION

The smallest and easiest-to-replicate microorganisms are mycoplasmas. In warm-blooded animals, birds, reptiles, insects, and plants, various species occur as adept microbes. Owing to their trivial genome and walllessness, they are cautious, and some of them are difficult to develop due to their limited metabolism. Thus, they might work as extracellular and intracellular organisms whose endurance depends on their hosts' liberality. In vivo, mycoplasmas are pantropic. The predilection sites of mycoplasmas are the alimentary canal, the mucous surface of respiratory and urogenital tracts, the ocular region, mammary organs, and joints (Dawood et al. 2022).

Through their interaction with cell membranes of specific target cells, certain Mycoplasma species, such as Mycoplasma pneumoniae, M. hominis, and M. gallisepticum (MG), can confer to and enter these cells (Shibata et al. 2000; Vogl et al. 2008). Horizontal gene transfer (HGT) can occur when two Mycoplasma species coexist in a single habitat, leading to the emergence of pathogenic mycoplasmas and significantly affecting their disease-causing abilities (Bürki et al. 2015). The advent of drug resistance due to the exchange of resisting alleles among various microorganisms is becoming an alarming issue (Faucher et al. 2019).

In the context of human infections, research has demonstrated that six Mycoplasma species, namely M. pneumoniae, M. gentenitalum, Ureaplasma urealyticum, U. parvum (Lobão et al. 2017), M. hominis and M. penetrans, are responsible for various human illnesses, including acute respiratory diseases, joint infections, genital and urinary tract infections, and neurological disorders (Dawood, Ali et al. 2022). Conversely, species like M. ovis, M. suis, and M. haemofelis, which primarily infect animals, are noticed in humans and are considered communicable agents (Maggi et al. 2013). Additionally, severe circumstances, for instance, chronic obstructive pulmonary disease (COPD) and infertility, may arise owing to such infections (Feng et al. 2021; Kusanovic et al. 2020).

The unhindered routine utility of macrolides has been the global source of macrolide-resistant M. pneumoniae (MRMP). MRMP is believed to prevail from 15% to 30% in Taiwan (2010 to 2017) and less than 30% in Europe and America between 2008 and 2013. Conversely, MRMP prevalence has reached anywhere from 60% to 90% in China, Japan, and Korea (Waites et al. 2017; Yang et al. 2019). Clinical manifestations of infections vary from mild and self-restricting to potentially dreadfully lethal, as illustrated in Figure 1. For instance, it is a leading cause of community-acquired pneumonia (CAP), chiefly in infants and grown-ups (Li et al. 2019).

2. ANIMAL INFECTIONS

Numerous domestic and wild animals are susceptible to mycoplasmosis, with contagious bovine pleuropneumonia (CBPP) and contagious caprine pleuropneumonia (CCPP) being notable diseases, particularly in low- and middle-income regions. These conditions are characterized by painful symptoms, reduced productivity, and fatalities, as depicted in Fig. 1 (Bolajoko et al. 2020).

2.1. BOVINE

Mycoplasma mycoides mainly prevails in cattle and water buffalo sprouting CBPP. WOAH alerts about this ailment as an alarming condition (OIE 2021). Amongst Other mycoplasmas, *M. bovis* is the most significant pathogen affecting cattle worldwide. Likely, it proliferates swiftly from the stage of infancy to old age. Calves under three months of age, mainly those weaned, exhibit the utmost incidence of *M. bovis* pneumonia, as indicated in a recent United Kingdom survey from 2006 to 2017 (Anne Ridley et al. 2018; Hazelton et al. 2020).

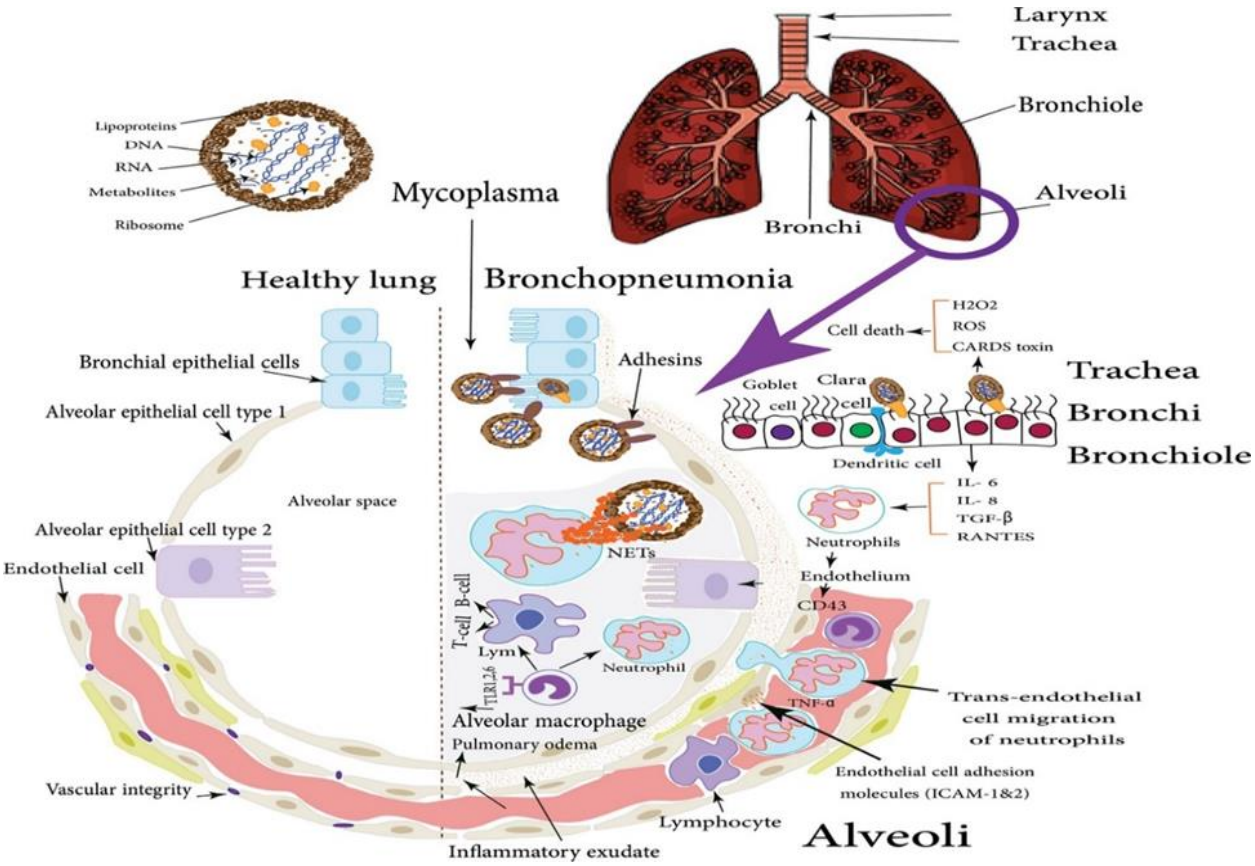

Fig. 1: the pivotal role of *M. pneumonae* In lung infection (Dawood Ali et al. 2022).

Notably, the agent that marauds the upper respiratory tract is *M. bovis,* in calves in the initial days of their infancy via infected dairy products utility and from already inflicted calves (Maunsell et al. 2009). Moreover, it ranks among the four vital bacterial agents allied with bovine respiratory disease (BRD), resulting in substantial fiscal deprivation due to increased morbidity and fatality rates, impaired growth, and elevated expenses related to prevention and panacea (Kudirkiene et al. 2021).

2.2. GOAT

Mycoplasma capricolum is a causative agent that inflicts CCPP, a dreadfully infectious ailment, in goats vitally proliferates in East Africa, specifically in Kenya, Ethiopia, and Tanzania (Falquet et al. 2014; Abd-Elrahman et al. 2020).

M. agalactiae triggers an OIE-notifiable ailment known as infectious agalactia (CA), which induces mastitis in dairy goats, resulting in substantial economic downgrading owing to arthritis, decreased or termination of milk production, cachexia, and corneal opacity leading to visual impairment (Santos et al. 2015).

Hemoplasmas, also known as pleomorphic minute bacteria, derive their name from their tendency to adhere to erythrocyte surfaces, potentially causing hemolytic anemia in several mammals. Two notable hemoplasmas, *M. ovis,* and *Candidatus M. haemovis*, are identified as tainting small ruminants, with increased mortality rates in young, elderly, and pregnant animals. In goats, *M.ovis* represents the obstinate infection. Surveys on the frequency of *M. ovis* contagion vary, as absentees in Australia and Tunisia exist in Hungary (20%) and in Malaysia (94%) (Dawood et al. 2022).

2.3. SHEEP

In the realm of ovine health, the first identification of *M. ovipneumoniae,* often referred to as "sheep atypical pneumonia," has been associated with infections in sheep and goats (Besser et al. 2013). This pathogen has triggered numerous global epidemics, which have been perilous to the lambing industry due to reduced ewe productivity and stunted lamb growth (Jaÿ et al. 2020). It's worth noting that Maggi and his research team predominantly identified species identical to M. ovis- in humans, indicating its potential for zoonotic transmission (Maggi et al. 2013).

2.4. SWINE

In the porcine world, *M. hyosynoviae* and *M. hyorhinis* are opportunistic microbes in the tonsils and upper respiratory tract. They are known to cause arthritis and polyserositis in piglets aged between 6 and 10 weeks, while older pigs above three months typically experience milder arthritis symptoms. Adult pigs with *M. hyosynoviae* arthritis are more susceptible, but the lesions primarily affect the synovial membranes and joints (Neto 2012; Gomes et al. 2015).
M. hyo pivotally intensifies the progression of the porcine respiratory disease complex (PRDC) infection, minimizing feed efficiency, decreasing animal growth performance, and lowering the typical routine improvement. This complex disease scenario often increases mortality, particularly when compounded with other pathogens (Olaniyi et al. 2020).
Additionally, the pig industry faces the threat of infectious anemia caused by *M. suis* hemoplasma species. Among others, *M. suis* is the primary pathogen responsible for pig hemoplasmosis. It adheres to the surface of RBCs, leading to their clearance by the spleen and resulting in reproductive failures, primarily stillbirths, as documented in Southern Brazil (Petri et al. 2020; Bordin et al. 2021).

3. AVIAN HEALTH

While more than 23 mycoplasma species are acknowledged in birds, four of them, namely *M. gallisepticum* (MG*), M. synoviae* (MS)*, M. meleagridis (MM), and M. iowae (MI)*—are responsible for avian mycoplasmosis. MG and MS are recognized as OIE-notified respiratory infectious agents that have inflicted substantial financial deprivations by causing a significant decrease in egg yield, hatchability, weight gain, and feed conversion efficiency. They also lead to increased embryonic mortality, condemnation of carcasses, and higher precaution and remedy expenses in layers, broilers, and breeder flocks (Yadav et al. 2021; Behboudi 2022).
These pathogens induce consistent respiratory issues in chickens, characterized by labored breathing, sinusitis, airsaculitis, and reduced carcass quality in broilers (Jelani, Ghulam. 2023; Michiels et al. 2016). Free-flying avian species like house finches are highly susceptible to wild MG transmission (Luttrell et al. 2001). Additionally, MI occasionally infects turkeys and, less commonly, chickens. In turkeys, MI infections result in delayed embryonic fatality, reduced hatchability, and limb deformities in young chicks. *MM* primarily causes air sac disease, musculoskeletal problems, and reproductive issues in turkeys and has been sporadically isolated from chickens (Pritchard and Béjaoui Khiari et al. 2011). Fig. 2 illustrates mycoplasmas' broad-ranging invasion into target tissues and their effective interactions with immune cells.

3.1. CANINE

Exceeding fifteen discrete mycoplasma species are so far documented, particularly for dogs. They typically coexist harmlessly, with only a few posing potential health concerns. One such concern is *M. cynos*,

primarily accompanied by a dog's lower respiratory tract (LRT) infections. *M. cynos* primarily leads to upper respiratory ailments in canines and enjoins the amplified severity of the canine respiratory disease complex (CRDC). Clinical manifestations involve coughing, mucus production, and the accumulation of exudate (Jambhekar et al. 2019; Chalker 2005). In addition, two hemoplasma species, *M. hemocanis,* and *M. haematoparvum*, have been observed in dogs (Rosanna et al. 2020).

3.2. FELINE

Focusing on domestic cats, four types of hemoplasmas are commonly encountered: *M. haemofelis, Candidatus M. haematoparvum*-like*, Candidatus M. haemominutum (CMhm), and Candidatus M. turicensis (CMt)* (Zhang et al. 2021). Amongst all, *CMhm* seems to be wildly contagious and causes hemolytic anemia. *M. haemofelis*, on the other hand, causes an extraordinarily appalling and potentially perilous anemia in cats, while others exhibit lesser severity and, nonetheless, can lead to grave illness in immunosuppressed felines (Willi et al. 2006). Non-hemotropic Mycoplasma (*M. felis*) can induce conjunctivitis, respiratory symptoms, and polyarthritis in cats (Greene and Chalker 2012).
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4. PATHOGENESIS

Mycoplasmas, in contrast to other extracellular bacteria, undergo a process of development and adaptation to their parasitic intracellular lifestyle after invading host cells. This adaptation leads to slower intracellular growth rates (Rüger et al. 2021). Their ability to conceal themselves and elude the host's imperishable defensive mechanism is partly due to this reduced intracellular growth rate.
M. bovis invades various cell types. Such foray serves mycoplasma by triggering inflammation, limiting immune cell responses, facilitating movement in the entire respiratory tract, and additional dissemination to multiple tissues from the lungs with the assistance of enormous invading enzymes (Van der Merwe et al. 2010).
M. bovis persists in necrotic lung lesions (Khodakaram-Tafti and Lopez 2004). They produce assaulting enzymes, including proteases, nucleases, sialidases, antioxidants, and hyaluronidases. Nucleases are critical in degrading host nucleic acids, influencing development, endurance, perseverance, and pathogenicity (Yiwen et al. 2021). Proteases can degrade IgG antibodies, as seen in the MIB-MIP system

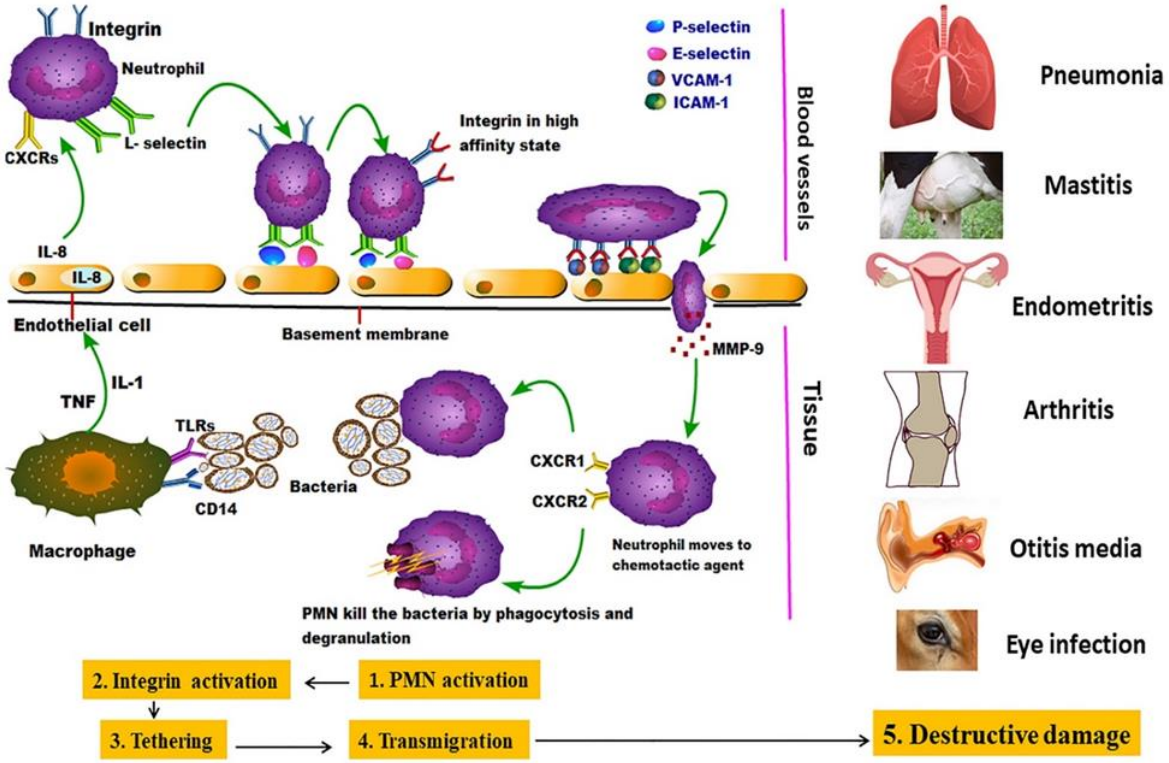

Fig. 2 illustrates the broad-ranging invasion of mycoplasmas into target tissues and their effective interactions with immune cells. This process begins with activating the first line of immune cells, neutrophils. In response to the presence of mycoplasma, neutrophils release various danger signals, setting off a cascade of events that lead to the activation of PMNCs (polymorphonuclear cells). This activation process involves Integrin activation, Tethering, and Transmigration and ultimately results in the deterioration of multiple body parts, giving rise to various inflammatory lesions (Dawood Ali et al. 2022).

(Nottelet et al. 2021). Sialidase and neuraminidase are infective biocatalysts involved in the hydrolysis of sialate, extracellular matrix (ECM) degradation, tissue invasion, and apoptosis (Robinson et al. 2017). MG exhibits a tropism for ciliated respiratory epithelium, allowing it to evade mucociliary clearance and invade host cells (Matyushkina et al. 2016).

Variable surface proteins (VSPs) appear to be strongly immunogenic lipoproteins that can be selectively expressed or silenced in response to environmental changes, resulting in alterations in surface antigenic phenotypes. For instance, in the genome of the *M. bovis* type strain PG45 (American strain), the vsp gene family contains 13 alleles, but only two are expressed, while the others become dormant. Additionally, the size of these proteins is tightly regulated (Clampitt 2021; Lysnyansky et al. 1999; Qi et al. 2012).

Tracking Mycoplasmas throughout their entire parasitic intracellular lifecycle is challenging owing to their small size and the absence of a cell wall, which sets them apart from other microorganisms. Consequently, their discreet intracellular existence significantly impacts cell metabolism, physiology, and immunity (Benedetti et al. 2020).

5. EPIDEMIOLOGY

COPD stands as a prominent cause of mortality in the USA, and the death toll rises to 130,000 individuals annually. Globally, over 3 million people succumb to COPD-related complications each

year. Low and middle-income countries bear a heavier burden of this disease. Notably, M. pneumonia has been found in higher concentrations within the lung microbiota of COPD patients (Marciniuk and Schraufnagel 2017).

In females, *M. genitalium* transfers via intercourse and is accompanied by various health issues such as cervicitis, pelvic inflammatory disease (PID), spontaneous abortion, premature birth, and infertility. It has been detected in 4% to 22% of women with PID and 10% to 30% of women experiencing clinical cervicitis (Gaydos et al. 2009). Conversely, *M. genitalium* is responsible for nearly 15%–20% of cases of Nongonococcal Urethritis (NGU) and persistent or recurrent Urethritis in men, both symptomatic and asymptomatic (Bachmann et al. 2020).

Mycoplasma capricolum, shortened as Mccp, accounts for CCPP. They are previously acknowledged as Mycoplasma biotype F38. These microorganisms belong to the Mollicutes class, with a unique characterization of lack of cell wall but possessing galactan and small genomes (0.58-1.35 Mb). They cause various diseases in animals and have limited biosynthetic capabilities. Numerous studies have explored the taxonomic associations within the F38 group of caprine mycoplasmas (Yatoo et al. 2019).

OIE proclaims that CCPP prevails wildly in around 40 countries, particularly Africa and the Middle East, with an enormous goat population. The ailment originated in Algeria in 1873 and has been documented in various countries, including Turkey, Iran, Oman, and Yemen. In Egypt, where the caprines are substantial, *Mccp* was recently separated and identified in sheep and goats in Giza in 2015 and Matrouh during 2017-2018 (Selim et al. 2021).

Mycoplasma gallisepticum, a member of the Mollicutes class, possesses a small genome size (996,422 bp for the Rlow strain) (Papazisi et al. 2003). Mycoplasmas primarily inhabit mucosal layers in the respiratory and urogenital tracts, eyes, mammary glands, and joints. One species of mycoplasma, MG, is capable of causing both acute and chronic diseases at various locations. However, it is commonly recognized as an airborne agent in diseased bird species. When it proliferates unchecked in susceptible birds, the organism spreads to the lungs and air sacs, causing severe inflammation of the sinus mucosa and trachea (Levisohn and Browning et al. 2010).

In poultry, proliferation from hens to chicks via egg becomes a vital way of dissemination. Therefore, outsourcing chicks or poults from MG free breeding is hindered somehow. Older birds, particularly those purchased from markets or mixed sources, can introduce MG into a flock, as seemingly healthy but infected birds can begin shedding the organism under stress, including social stress among other birds. Spread from bird to bird can occur through respiratory or contaminated fomites. However, within a flock, the spread is typically gradual and takes 6 to 21 days. The infection is believed to survive outside its host for 18 months or longer under farm conditions. MG holds between 30 and 70 variation vlhA genes, mostly translationally equipped, leading to genetic variation despite its small genome. Only a single gene seems to be transliterated at any given time, and these genes were acquired through lateral gene transfer between Mycoplasma species, resulting in the expression of a single variant of this lipoprotein on the cell surface. Several isolates have been obtained using various molecular epidemiological typing methods (Behboudi 2022).

6. ECONOMIC IMPACT

OIE has now announced that South Africa, Australia, Europe, and the United States are free of CBPP. In Asia, China and India appear free, yet the status of ailment remains blurred in the rest of Asia (OIE 2019). During the 45-week laying cycle, it has been documented that chickens lose approximately 16 eggs. Fiscal mishaps incited are because of diminished efficiency (around 10-20%), early embryonic mortality (roughly 5%-10%), and expenses of prevention and control of infection (Behboudi 2022).

Table 1: Illustration of Financial Loss of Different Mycoplasma Species in Different Regions.

Species	Disease	Regions	Financial Loss	References
Bovine	CBPP	Global	Sub-Saharan Africa 2 billion US$	(Anonymous 2018)
Avian	*Avain Mycoplasmosis*	Global USA	US $780 million every year $150 million annually	(Behboudi 2022)
Caprine	CCPP	Endemic Areas	US$507 million in endemic areas	(Yatoo Mohd Iqbal et al. 2019)
Ovine	CCPP	Tanzania	2,273,281TZS loss per household annually	(George 2017)

7. VACCINATION

Betlach et al. (2021) delved into the possible effect of various immunizations in reducing *M. hyo* spread. Their findings revealed that a three-dose regimen of commercial bacterin vaccination vitally abolished lung lesions at 28 days post-infection in tested gilts, along with an overall decrease in bacterial load in vaccinated gilts. In another study focusing on the practicality and monetary advantages of immunizing piglets against the bacteria at different ages, it was established that immunization at three days of age conferred a substantial advantage over-vaccination at 7 or 14 days of age (Vangroenweghe, 2021).

Recent investigations into *M. hyo* vaccinations have explored the effectiveness of novel bivalent and trivalent vaccines. These studies have concluded that such immunizations offer high fortification against the infection (Yang et al. 2021).

M. genitalium exhibits zoonotic characteristics, facilitating the transmission of sexually transmitted diseases between humans and animals (Nogueira et al. 2021).

Regarding *M. bovis*, which poses a significant threat to dairy cattle in many countries, vaccination is a central focus for disease control due to the growing antimicrobial resistance. However, commercially economical vaccines for the market are lacking. Based on our previous research, the efficacy of the attenuated P150 *M. bovis* strain was 87.7%, making it a potent adjuvant for a live vaccine (Dawood et al. 2022).

The existing CCPP vaccine is a bacterin with a saponin adjuvant, recommended for administration to kids at 4 months of age and then every 6 months. Its production is relatively expensive, following the meticulous cultivation of the causative agent and the substantial protein requirement for each vaccine dose (Dawood et al. 2022).

For the prevention of MG and MS, there are commercially available live attenuated and recombinant live poxvirus vaccines. Additionally, virulent MG live strains (F, ts-11, and 6/85 strains) can be safely employed (Yadav et al. 2021). Recent studies have shown that a regimen of three consecutive MG vaccinations, consisting of one live vaccine followed by two inactivated vaccine doses, provides an excellent shield in poultry (Kiers 2020). Temperature-sensitive strains such as MS-H and ts-11 exhibit remarkable efficacy when administered as eye drops in chickens and turkeys. These strains are readily available commercially and have significantly reduced the macrolides' utility in poultry and lowered disease prevalence in chickens, as demonstrated in Australia (Purswell et al., 2012)

8. ERADICATION OF MYCOPLASMA

Contagious bovine pleuropneumonia (CBPP) has been successfully eradicated from many regions worldwide. Catering China, where the disease erupted into exponential fiscal deprivation in the cattle industry from 1950-70. An adequate immunization was inoculated from rabbits, such as a virulent strain of Mmm (Ben-1). This vaccine exhibited high immunogenicity and practical efficacy (95-100%) in cattle for

28 months. Ultimately, the last reported CBPP case was observed in 1989, and in 2008, China was declared CBPP-free by the OIE. Initially, in the 20th century in Europe, vaccine administration was abandoned. Slaughtering was the only practical approach to confine the contamination. This approach remained hugely successful, and CBPP was obliterated by the mid-1960s (Dawood et al. 2022).

In Australia, attenuated vaccine strains (KH3J and T1/44) significantly abridged the cases. However, 1973 marks the year of thorough obliteration, primarily through minimized animal movement and a comprehensive elimination policy. In New Zealand, *M. bovis* appeared for the first time in 2017. The Ministry for Primary Industries (MPI) took bold steps to eliminate *M. bovis* from New Zealand despite the challenges posed by identifying and confining the movement of infected livestock. On 19 August 2021, the Chair of the Technical Advisory Group to MPI for the *M. bovis* program announced that *M. bovis* currently has only three active properties. Eradication may be within reach shortly (Dawood et al. 2022).

More recently, Gulliksen and colleagues have reported successfully eradicating *M. hyo* infections from the Norwegian pig population (Gulliksen et al. 2021).

9. CONCLUSION

In recent years, widespread Mycoplasma pathogens have raised significant concerns. This chapter summarizes the epidemiology, pathogenesis, economic impact, vaccination, and eradication programs of mycoplasma species globally in humans and different animals. Moreover, the immune response of Mycoplasma microorganisms as exceptional antigens with restricted metabolic limits poses a conspicuous impact. Accordingly, embracing innovative strategies to check the component of mycoplasmas contamination is fundamental. Lastly, several scenarios for eliminating mycoplasmas in many regions of the world have been successful and can be followed by others.

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