BMC Veterinary Research

REVIEW

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Discontools supplement *Mycoplasma hyopneumoniae* infections in pigs: update and knowledge gaps

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Abstract

Background This manuscript reviews current knowledge on *Mycoplasma hyopneumoniae*, the primary agent of enzootic pneumonia in pigs, integrating advances in epidemiology, pathogenesis, immunity, diagnostics, and control. The pathogen is globally endemic, with transmission driven mainly by direct contact within a herd, and by purchase of animals and airborne transmission between herds. Infection dynamics are shaped by production systems, sow-piglet transmission, and co-infections, while strain diversity and subclinical infections complicate disease expression and control.

Pathogenesis is understood as a complex, multifactorial phenomenon rather than being determined by single virulence factors. Adhesion, biofilm formation, extensive posttranslational processing, metabolic adaptation, and immune evasion collectively enable persistent colonization. A major conceptual advance is the discovery of migrasome-mediated dissemination, which may explain chronic infection and reduced antimicrobial efficacy.

Conclusions Despite significant advances, important knowledge gaps remain in multiple areas of Mycoplasma hyopneumoniae research. Uncertainties persist in transmission and epidemiology, including the role of environmental spread, wild boar reservoirs, and the extent of subclinical infections. The impact of strain diversity on virulence, transmission, persistence, and vaccine performance is not yet fully understood, and predictive markers are lacking. Key aspects of host–pathogen interactions, such as immune evasion, occasional intracellular survival, macrophage polarization, and the in vivo relevance of migrasome-mediated dissemination, require further clarification. Protective immunity remains poorly defined, with unresolved questions on correlates of protection and the roles of mucosal and systemic responses. Diagnostic challenges include distinguishing active from residual infection and improving specificity and Differentiating Infected from Vaccinated Animals (DIVA) compatibility. Evidence on antimicrobial effects on transmission and resistance monitoring is limited. In addition, variability in vaccine efficacy and the influence of maternal immunity remain unclear. Finally, scalable elimination strategies, particularly for very large production systems and reduced antimicrobial use, are still needed.

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Keywords *Mycoplasma hyopneumoniae*, Pigs, Review, Knowledge gaps

Background

Mycoplasma hyopneumoniae is found worldwide in nearly all countries and pig farms. The pathogen induces long-term colonization of the ciliated respiratory epithelium, causing damage to the mucociliary apparatus, and interferes with innate and acquired immunity. This facilitates infections with other respiratory pathogens contributing to disease [1]. It is the primary pathogen of enzootic pneumonia (EP) in pigs, a disease characterized by chronic bronchointerstitial pneumonia complicated with suppurative bronchopneumonia, high morbidity, low mortality, and decreased production performance [1]. The economic impact is significant and is primarily related to decreased performance. EP occurs mainly in grower-finisher pigs, but also younger animals may be affected, especially in continuous-flow systems. *M. hyopneumoniae* is also one of the major pathogens involved in the porcine respiratory disease complex (PRDC), a polymicrobial disease in which bacterial (e.g. *Pasteurella multocida (P. multocida)*, *Actinobacilus pleuropneumoniae (A. pleuropneumoniae)*, *Glaesserella parasuis* and *Streptococcus suis*) and viral pathogens (e.g. porcine reproductive and respiratory syndrome virus (PRRSV), swine influenza A virus (swIAV) virus and porcine circovirus 2 (PCV2)) can be involved.

The present manuscript reviews the current knowledge and recent research findings on *M. hyopneumoniae* and emphasizes areas for further research. It is part of the global DISCONTOOLS (Disease Control Tools) initiative (https://discontools.eu/about.html). Its mission is to identify research gaps in animal health and prioritize areas where new tools to accelerate the development of improved vaccines, pharmaceuticals, and diagnostics are most needed.

Epidemiology

Domestic pigs and wild boar are the only species known to become naturally infected with *M. hyopneumoniae*. Given that the disease is not notifiable and does not hinder trade, prevalence information at national level is not available except for countries enrolled in national elimination programmes such as Switzerland, Norway and Finland. To date, disease elimination efforts are ongoing in other countries, which are limited to farms, herds, companies or even states, but they have not yet reached application at a national level.

In recent years, the list of countries which reported evidence of *M. hyopneumoniae* infection in wild boar population has extended [2]. Although *M. hyopneumoniae* infection in the wild boar population probably has resulted from spillover events [3], the detection of identical sequence types in both species [4] together with the marked increase in the wild boar population in different regions, may potentially pose a risk for pathogen transmission especially in those countries pursuing eradication. The growing interest on *M. hyopneumoniae* elimination highlights the need to intensify research into the infection of wild boar populations to explore potential changes in disease epidemiology and to implement effective infection preventive measures.

Nose-to-nose contact is the most efficient transmission route, although indirect transmission through airborne spread has also been documented. In this scenario, pathogen DNA has been detected in barn airspace, pen surfaces, sow body locations and even in drinker wipes samples in farms with acutely affected animals [5]. These findings might be relevant considering that *M. hyopneumoniae* isolates may survive outside the host in dry surfaces for up to 8 days at low temperatures [6]. Of note, in subclinically infected herds, *M. hyopneumoniae* was not detected in air samples but rather in stall surfaces [5]. This environmental detection warrants further investigations to clarify its diagnostic implication and to characterize the intra-farm transmission. *M. hyopneumoniae* airborne transmission through long distances (from m to several kms) has also been experimentally documented [7] and suspected [8]. However, under natural conditions, its frequency and practical importance for pathogen spread at different scales (barn, herd or regional level) is largely unknown. Another aspect not elucidated yet and which could prove useful in gaining a better understanding of the epidemiology of this pathogen is the effect of co-infections on *M. hyopneumoniae* transmission. Additionally, although vectors do not appear to have a significant role in the transmission, this topic has received limited attention.

Other factors influencing *M. hyopneumoniae* infection may include housing and climatic conditions. In this sense, in a large-field study, the prevalence of *M. hyopneumoniae* infection was higher during winter when compared to the other seasons [9].

Empirical data and experimental studies suggest the sow population is the main reservoir of *M. hyopneumoniae* infection within a herd. Although the pathogen can be transmitted by sows of all parities, gilts are more frequently infected and test positive at earlier stages of gestation [10]. Piglets are born free from *M. hyopneumoniae* and are first exposed to the pathogen through contact with their dams during the lactation period. Indeed, presence of infected sows in the farrowing unit and a long lactation period are associated with higher *M. hyopneumoniae* prevalence at weaning [11]. The

Table 1 Integrated overview of *M. hyopneumoniae* pathogenicity determinants

Functional category	Factor / process	Detailed mechanisms	Biological consequences	Level	References
Initial colonization	Adhesion to ciliated epithelium	Binding to cilia of trachea, bronchi, bronchioles	Initiates infection, ciliostasis, ciliary loss	Host interface	[29]
	Growth dynamics	Strain-dependent growth differences	Colonization efficiency, epithelial damage	Population	[30]
Adhesins	P97, P102	Adhesion + proteolytic processing	Coordinated virulence, not independent factors	Population	[31, 32]
	Mhp390 (P68)	Plasminogen binding	Extracellular matrix (ECM) degradation, inflammation, apoptosis	Surface	[33, 34]
Host receptor interaction	Actin binding	Alternative receptor	Expanded adhesion repertoire	Host interface	[31, 35]
Surface plasticity	Endoproteolytic processing	Extensive cleavage of proteins	Molecular diversity, immune evasion	Population	[32, 36, 37]
	Degradomics / N-terminomics	Cleavage of adhesins, lipoproteins	Plastic surface topography	Population	[31, 32]
	Atypical translation initiation	Lack of formylated N-terminal methionine	Protein diversity, plasticity	Molecular	[38]
Host interaction	Fibronectin binding	Surface fragments	Adhesion, signaling	Surface	[31, 39]
	Glycosaminoglycan binding	Surface exposure after cleavage	Strengthened host interaction	Surface	[31, 32]
	Plasminogen binding	Includes Mhp390	ECM degradation, inflammation	Surface	[31, 34]
Moonlighting proteins	EF-Tu	Fibronectin binding + Factor H binding	Adhesion + complement evasion	Dual	[23, 32, 40]
	Aldolase	Adhesion	Host cell interaction	Dual	[39]
	Enolase	Adhesion + immune recognition	Species-specific loops, evolution	Dual	[41, 42]
Immune activation	P97-derived peptides	TLR5 agonists	Innate immune activation	Host interface	[43]
Antigenicity	P46	Structural antigenicity	Antibody recognition	Molecular	[44]
Immune modulation	Surface proteases	Cleavage of bradykinin, neuropeptides	Modulate inflammation	Local	[45]
	Nucleases (global)	Conserved activity	Immune modulation, persistence	Population	[32, 46]
	Mhp597	Cytotoxicity, IFN pathway interference	Immunosuppression	Molecular	[47, 48]
Secretome	Secreted proteins	Strain-dependent secretion	Host interaction modulation	Population	[49]
Surface proteins	Reannotated proteins	Surface exposed candidates	Potential adhesion/virulence	Molecular	[50]
Antigenic variability	P146 (LppS)	Repeat variation, cleavage	Immune evasion, genotyping marker	Population	[51]
Strain dynamics	Circulation and diversity	Continuous diversification	Persistence in populations	Population	[21, 22, 52]
Biofilm	Biofilm formation	Structured community	Persistence, antimicrobial tolerance	Population	[19, 53]
Cell damage	LAMPs	Induce apoptosis	Tissue damage, immune dysregulation	Host	[54, 55]
	MAPK / ROS / caspases	Apoptotic signaling	Cell death	Molecular	[54, 56]
	Signal peptidase proteins	Pro-apoptotic	Epithelial damage	Molecular	[56]
Metabolic adaptation	Lack of TCA cycle	Reductive evolution	Host dependence	Global	[57, 58]
	Cholesterol uptake	Host exploitation	Adhesion, macrophage survival, apoptosis	Host	[54]
	Arginine/nucleotide scavenging	Resource competition	Stress, mitochondrial dysfunction	Host	[54, 57]
Toxic metabolites	Hydrogen peroxide	Glycerol metabolism	Limited, strain-dependent toxicity	Variable	[59, 60]
	Glycerol / myo-inositol	Metabolic flux	Lower toxicity than other species	Metabolic	[57]
	Local toxicity	No accumulation in vitro	Local epithelial effect	Local	[60]
Stress response	Oxidative/heat stress	Transcriptomic regulation	Indirect virulence modulation	Regulatory	[61]
	Flavin oxidoreductases	Redox metabolism	Inflammation linkage	Molecular	[62]

Table 1 (continued)

Functional category	Factor / process	Detailed mechanisms	Biological consequences	Level	References
	Lipoate ligase	Supports virulence	Independent of metabolism	Molecular	[63]
	Strain-specific proteomics	Environmental adaptation	Virulence variability	Population	[64]

ECM extracellular matrix

following infection dynamics will be shaped largely by the production system [9, 12]. Those systems housing different age groups (single-site production) favour earlier infections, while segregated systems (two- and three-site) may exhibit late infection patterns [9, 12]. According to Boeters et al., the infection progression and lung lesion development might also depend on the prevalence of infected pigs entering the finishing units [13]. Simulation of infection dynamics and lung lesion development of pigs originating from a single multiplier herd endemically infected with *M. hyopneumoniae* and transferred to a compartment (using an all-in/all-out management system) of a commercial fattening farm through stochastic modelling indicated that high prevalence in the finishing units resulted in a fast infection spread, peaking four weeks post entry. When the prevalence at entry was lowered, the between-pen transmission was reduced, and the peak of lung lesions was delayed up to slaughter [13].

It is well recognized that once *M. hyopneumoniae* infection is established in a herd, animals can develop subclinical, acute or chronic forms of disease [13]. The subclinical infected animals do not develop clinical signs but act as reservoirs. The proportion of subclinical infected pigs, as well as the reasons why a subset of exposed (infected) animals do not develop clinical signs, remains poorly understood.

During the acute phase of infection, shedding may occur before clinical signs are shown, which normally emerge one to three weeks post-infection and lasts for several weeks after onset [13]. Under experimental conditions, lung lesion development reaches its peak approximately four weeks post-infection and may persist for up to an additional eight weeks [14]. The impact of strain diversity, virulence, and co-infections on disease outcome remains incompletely understood and deserves further investigation. While in some studies the increase in strain diversity at individual or batch level has been postulated to be a key factor for lung lesion severity [15, 16] in other investigations it has shown to lack relevance [17, 18]. Nevertheless, the existence of multi-strain infections at individual level reaffirms the need to study the cross-protection between strains and re-infection events. Strain-dependent virulence has been demonstrated through experimental inoculations. Highly virulent strains show higher colonization efficiency causing more severe clinical signs, strong tissue inflammation and extended lung lesions [19, 20]. Under field conditions, the circulation of different strains is demonstrated using molecular characterization methods based on the comparison of specific loci or gene sequences [21]. In recent years, this genetic characterization has been used to gather information on the variability at herd or production system [16], on geographical distribution [22], persistence [4, 23], disease implication [16], disease severity [15, 16], and antimicrobial resistance [24] of specific strains. It is important to note that, these molecular approaches do not provide information about strain virulence or antigenic properties.

During the chronic phase of the infection, pigs usually do not show clinical signs but may remain infectious for several months [13]. Indeed, *M. hyopneumoniae* infection has been detected up to one year in naturally or artificially exposed breeding populations, especially when co-infected with other respiratory pathogens of either viral or bacterial origin [25, 26]. Further investigations to expand the knowledge on breeding herd epidemiology should focus on the length of transmission and the shedding pattern in the gilt/sow population, as well as the impact of co-infection on persistent infections.

The slow and persistent infection progression of *M. hyopneumoniae* can be explained by low adjusted reproduction ratios and transmission rates. Values for both parameters may vary in the literature due to differences in the contact period and the virulence of the strain [27]. Regardless, the direct consequence of such inefficient transmission is that a proportion of animals may remain susceptible to the infection despite being in contact with infected pigs. Takeuti et al. [28] reported that almost 20% of a gilt group remained negative to *M. hyopneumoniae* for up to one full year after their introduction into a positive herd.

Pathogenesis

Colonization factors, surface dynamics and population-dependent pathogenicity

Pathogenicity in *M. hyopneumoniae* is now regarded as an emergent population-level property resulting from coordinated processes including adhesion, surface remodeling, biofilm formation, metabolic adaptation, and immune modulation, rather than the action of individual virulence factors. No single adhesin, lipoprotein or enzyme is sufficient to explain virulence. Instead,

pathogenicity arises from the integrated activity of multiple surface-associated systems acting collectively during colonization and disease progression. Key determinants and mechanisms contributing to the pathogenicity of *M. hyopneumoniae* are summarized in Table 1.

Adhesion to the ciliated respiratory epithelium represents the initial and critical step of infection and is followed by ciliostasis and progressive ciliary loss [29]. This process occurs at the level of the trachea, bronchi and bronchioles and progressively impairs mucociliary clearance, facilitating bacterial persistence within the respiratory tract. Differences in growth dynamics between highly virulent and low virulent strains influence colonization efficiency and epithelial damage [30]. Major adhesins such as P97, P102 and Mhp390 contribute to colonization but act within a coordinated network dependent on proteolytic processing and population-wide expression. Biofilm formation further supports persistence, antimicrobial tolerance and infection maintenance [19, 65]. Consequently, successful colonization depends not only on bacterial attachment but also on the ability of the population to persist and adapt within the respiratory environment.

Recent advances have highlighted that the mycoplasmal surface is highly dynamic, largely driven by extensive post-translational processing and endoproteolytic cleavage mechanisms generating functional diversity despite a reduced genome [31, 36, 37]. Rather than representing a static collection of adhesins, the mycoplasmal surface continuously generates new protein variants that increase functional diversity and adaptive potential. These processes distinguish *M. hyopneumoniae* from commensal species such as *M. flocculare* [66].

Proteolytic processing and moonlighting functions of metabolic enzymes expand adhesion capacity and play multifunctional roles in host interaction and immune evasion, while processed surface fragments retain binding to fibronectin, actin, glycosaminoglycans and plasminogen [31, 32, 39, 41]. The retention of binding activity after proteolytic cleavage increases the number of potential host targets and reinforces host–pathogen interactions. Actin has been identified as an additional receptor [35]. Secretome analyses further highlight strain-dependent host interaction profiles [64]. These findings indicate that variation in surface composition among strains may influence their interaction with host tissues and contribute to differences in pathogenic potential.

Surface-associated proteins collectively contribute to immune modulation through a multifactorial network, including TLR2- and TLR4-mediated signaling, proteolytic cleavage of inflammatory mediators, nuclease activity, and induction of apoptotic pathways. Additionally, functional studies suggest that P97-derived peptides may act as TLR5 agonists, potentially linking adhesion processes with innate immune activation [43, 45, 47, 54, 55]. Together, these mechanisms connect bacterial attachment to activation and modulation of the host immune response, while simultaneously promoting tissue damage, epithelial dysfunction and bacterial survival. Mhp390 further illustrates the multifunctional nature of surface proteins by contributing to adhesion, inflammation and apoptosis.

Beyond these direct effects on host-pathogen interactions, persistence within the host is also facilitated by antigenic variability and population-level diversification mechanisms. Antigenic variability is supported by proteins such as P146 and continuous strain diversification in production systems [51]. Variation in repeat regions and proteolytic processing patterns contributes to adaptation under host immune pressure and may facilitate long-term persistence of circulating strains.

Overall, these data support a model in which virulence arises from a highly plastic and functionally redundant surface architecture operating at the population level, with no single determinant sufficient to predict pathogenicity [31]. Colonization, persistence, immune modulation and tissue damage therefore result from the combined action of multiple interconnected mechanisms acting throughout the course of infection rather than from individual virulence factors alone.

Toxic metabolites, metabolic adaptation, and stress responsiveness

Metabolic adaptation, toxic metabolites, and stress-response mechanisms further contribute to pathogenicity (Table 1). *M. hyopneumoniae* does not produce canonical exotoxins, and the role of toxic metabolites such as hydrogen peroxide remains limited and strain dependent [59, 67]. Metabolic modelling suggests involvement of glycerol and myo-inositol pathways, although at lower levels than in other mycoplasma species in which glycerol-dependent hydrogen peroxide production constitutes a major cytotoxicity mechanism [57], and toxicity appears to act locally rather than systemically [60].

As a pathogen lacking the tricarboxylic acid (TCA) cycle, *M. hyopneumoniae* relies on host-derived nutrients, particularly cholesterol, arginine and nucleotides, linking metabolic processes directly to host cell dysfunction, epithelial damage, and pathogenicity [54]. Recent studies emphasize the role of stress-responsive regulation and multifunctional metabolic enzymes in modulating virulence, including oxidative stress responses, flavin oxidoreductases linking redox balance to inflammation, and lipoate ligase contributing to pathogenicity independently of core metabolism [61–63]. Comparative proteomic analyses further highlight strain-specific adaptation profiles associated with environmental conditions

and virulence variability [64]. However, these findings also suggest that the contribution of these pathways is likely indirect and context dependent. In this context, the relative contribution of metabolic toxicity and stress-response mechanisms to pathogenesis, compared with adhesion-driven and immune-modulatory processes, remains insufficiently quantified and requires further investigation.

Comparative studies with other Mycoplasmas and strain variability

Comparative studies of antigen-presenting cell responses highlighted intra- and inter-species differences in cytokine production induced by *M. hyopneumoniae*, *M. hyorhinis* and *M. flocculare* [68]. Pathogenicity studies in pigs pre-infected with *M. hyopneumoniae* further demonstrated that interactions with other mycoplasmas influence disease severity [69].

Comparative genomic and proteomic analyses between pathogenic *M. hyopneumoniae* and commensal *M. flocculare* demonstrated that pathogenicity cannot be explained by the presence or absence of single virulence genes [66]. Instead, differences in gene regulation, post-translational processing, and protein expression profiles shape virulence [70].

Experimental infection models confirmed pronounced strain-dependent differences in virulence, immune activation and lung lesion severity [71]. Field studies and slaughterhouse investigations further demonstrated that strain diversity impacts disease expression and lesion scores [15, 72, 73]. Enhanced biofilm formation and extracellular DNA release have been associated with persistence and increased virulence [19, 65].

Comparative transcriptomic analyses revealed strain-specific regulation of adhesion-related genes during in vivo infection [74]. Quantitative proteomic comparisons between virulent and attenuated strains demonstrated that attenuation is associated with reduced expression of adhesins and other virulence-associated factors [75, 76].

Metagenomic and metatranscriptomic surveys revealed substantial heterogeneity in *M. hyopneumoniae* strain composition across farms and regions [77]. This heterogeneity includes the coexistence of genetically diverse strains differing in accessory gene content and potentially in pathogenic potential. Interactions between *M. hyopneumoniae* strains and the resident lung microbiota further influence colonization dynamics and disease expression [72]. Large-scale lung microbial gene and genome catalogues generated from pigs with lung lesions provided an integrated view of *M. hyopneumoniae* strain diversity and highlighted the contribution of accessory genes to pathogenic potential [78].

Mobile genetic elements and integrative conjugative elements contribute to genome plasticity but do not appear to act as direct virulence determinants [79].

Nevertheless, the precise contribution of strain diversity, host genetic background, and polymicrobial interactions to disease severity and transmission dynamics is not yet fully resolved, and robust predictive markers of pathogenic potential remain lacking under field conditions.

Host-pathogen interaction and migrasome-mediated dissemination

Chronic *M. hyopneumoniae* infection is sustained by active immune evasion rather than weak immunogenicity [80]. Post-2017 studies have defined a multifaceted immune-subversion network centered on antigenic variation, signaling interference, and cellular reprogramming. Antigenic variability driven in part by post-translational protein processing, combined with modulation of innate immune responses, further supports long-term persistence [81].

In parallel, *M. hyopneumoniae* interacts with host plasminogen to promote extracellular matrix degradation and inflammation [82]. Ultrastructural studies have demonstrated a low degree of intracellular localization within epithelial cells [53] and macrophages [83]. Paracellular migration across airway epithelial barriers represents an additional dissemination route [84]. Extracellular vesicles produced by *M. hyopneumoniae* strains may participate in intercellular communication and immune modulation [85].

A conceptual breakthrough is the discovery of migrasome-mediated intercellular transmission, in which *M. hyopneumoniae* can be packaged within host migrasomes for protected cell-to-cell spread. While the frequency and in vivo relevance of this mechanism remain unclear, it may provide an explanation for persistent colonization and limited i*n vivo* antimicrobial efficacy despite favorable in vitro susceptibility [86]. Further research could explore to which extent migrasome formation is actively induced by *M. hyopneumoniae*, which pulmonary cell populations are primarily involved in vivo, and how this mechanism interacts with other persistence strategies.

The conserved mycoplasma immunoglobulin-binding and mycoplasma immunoglobulin-protease (MIB-MIP) system cleaves IgG at the bacterial surface, further disabling humoral clearance [87]. Long non-coding RNAs regulate necroptosis and inflammation during infection, adding a host-derived regulatory layer to immunopathology [88]. Protein microarray studies confirm that natural infection and vaccination induce distinct antibody profiles, with minimal correlation between humoral responses and protective immunity [89].

Interaction with other pathogens

M. hyopneumoniae is a central component of the PRDC. Co-infections with *P. multocida*, *A. pleuropneumoniae* and *Streptococcus suis* exacerbate lung lesions and production losses [16, 90]. In addition, co-infection with the enteric pathogen *Lawsonia intracellular*is has been shown to modulate intestinal integrity and function, further contributing to impaired growth performance [91]. Synergistic interactions with PRRSV and PCV2 have been documented [92]. The association between *M. hyopneumoniae* and PRRSV has also been confirmed in field studies, where the concurrent detection of both pathogens was associated with cranioventral pulmonary consolidation and respiratory lesions in slaughter pigs [93]. Whereas interactions with swIAV appear transient and strain dependent [94]. Co-infections, including PCV2, PCV3 and bacterial pathogens, have been associated with pleurisy severity and lung lesions in slaughter pigs [95]. Molecular studies demonstrated that coinfections induce profound transcriptional changes in the porcine respiratory tract [96].

Non-infectious co-factors, such as mycotoxins, may influence disease severity [97], while host genetic background, including polymorphisms in pattern-recognition receptor genes, modulates susceptibility and clinical outcome [98]. Migrasomes may potentially influence host-microbe interactions, although their role in bacterial persistence and polymicrobial dynamics remains to be established [86].

However, the combined effects of polymicrobial interactions, host genetic variability, and environmental co-factors on disease severity and transmission dynamics are still not fully understood.

Clinical signs and lesions

The classical description of enzootic pneumonia caused by *M. hyopneumoniae*, including chronic non-productive coughing, high morbidity, low mortality and cranioventral pulmonary consolidation [99], remains largely unchanged. However, studies published in the last decade have substantially refined the understanding of disease expression and lesion development, shifting the focus from purely descriptive pathology to concepts that integrate strain virulence, host immune responses and infection dynamics within the PRDC landscape.

Clinical signs: predominance of subclinical infection and variability in expression

Field and experimental studies consistently show that pigs may harbor *M. hyopneumoniae* and develop lung lesions in the absence of evident respiratory signs, particularly in vaccinated or pathogen exposed herds. Consequently, reductions in performance and feed efficiency may occur without conspicuous coughing, emphasizing that clinical silence does not equate to biological or economic irrelevance [29, 100]; the economic impact of such subclinical infections is unknown.

Convincing experimental and field evidence has accumulated suggesting strain-dependent variability in clinical expression. Infection studies using genetically characterized *M. hyopneumoniae* isolates under controlled or natural conditions have revealed considerable differences in coughing frequency, seroconversion kinetics, mucosal IgA responses and degree of lung involvement, despite similar infectious doses and routes of inoculation [20, 71].

In parallel, *M. hyopneumoniae* is increasingly regarded as a disease modulator rather than a strong primary clinical pathogen. Some works highlight its capacity to impair mucociliary clearance and alter innate and adaptive immune responses [17, 29], thereby predisposing pigs to more severe disease when co-infected with viral or bacterial respiratory pathogens, such as PRRSV, PCV2, swIAV, *P. multocida* or *A. pleuropneumoniae* [29, 96]. Moreover, such predisposing capabilities have also been observed in cell culture conditions [90]. In this context, *M. hyopneumoniae* amplifies clinical severity within PRDC even when its pathogen-specific clinical expression is mild.

Gross lung lesions: unchanged morphology but refined interpretation

The macroscopic lung lesions classically associated with *M. hyopneumoniae* infection, well-demarcated cranioventral consolidation affecting mainly the apical, cardiac and cranial diaphragmatic lobes, remain the defining gross pathological feature [100]. However, experimental studies demonstrate that the extent of macroscopic lesions correlates only imperfectly with bacterial load and may instead reflect cumulative host-mediated inflammatory damage [17, 101]. Furthermore, longitudinal observations indicate that cranioventral lesions may partially regress over several weeks, leaving fibrotic scars and altered lung architecture that are not adequately captured by single-time-point slaughterhouse assessments [100, 102]. These findings reinforce the notion that macroscopic lung lesion scoring, while still a valuable monitoring tool, represents an incomplete proxy of disease impact, particularly in herds where infection is largely subclinical or when the peak of infection takes place several weeks or even months before slaughter age.

Microscopic lesions and immunopathology: host-driven mechanisms

Classical histological features, including peribronchiolar and perivascular lymphoid infiltration, hyperplasia of bronchus-associated lymphoid tissue (BALT), epithelial hyperplasia and thickening of alveolar septa, remain consistent hallmarks of *M. hyopneumoniae* infection

[100]. However, recent studies applying molecular and spatial techniques have provided deeper insights into the immunopathological basis of microscopic lesions. Specifically, compartment-specific analyses reveal that immune responses differ markedly between bronchi, BALT and lung parenchyma, with distinct cytokine profiles associated with lesion development [103]. Up-regulation of chemokines and regulatory cytokines, particularly CXCL-8 and IL-10, appears to be a consistent feature, suggesting a balance between sustained neutrophil recruitment and anti-inflammatory counter-regulation.

Collectively, these data support a paradigm in which *M. hyopneumoniae*-associated lesions are predominantly host-driven, resulting from dysregulated immune responses rather than direct cytotoxic effects of the pathogen. This framework explains the frequent persistence of lesions after bacterial loads decline and the limited ability of antimicrobial treatment to reverse established pathology [29].

Extrapulmonary lesions: consolidation of a negative concept

In contrast to *M. pneumoniae* infection in humans, *M. hyopneumoniae* infection in pigs is not associated with extrapulmonary lesions. Although *M. hyopneumoniae* remains largely restricted to the respiratory tract, and no consistent evidence supports systemic colonization, several reports indicated that the bacterium can be found in tissues such as spleen, liver, kidneys and lymph nodes [104]. However, no extrapulmonary lesions were linked to infection. Furthermore, a recent study suggested that *M. hyopneumoniae* can cause fibrinous pericarditis, pleuritis, broncho-interstitial pneumonia with lymphoid depletion in the lymphoid organs, being a bacterial agent present in the infiltrating mononuclear cells, cardiomyocytes, and Purkinje fibers of heart, bronchioles, and alveolar lining epithelium of lungs, and lymphocytes of the depleted lymphoid follicles of the lymph nodes [105]. So far, the evidence of such extra-pulmonary lesions is very weak and has not been supported elsewhere.

Implications for disease interpretation

Taken together, clinical and pathological consequences of *M. hyopneumoniae* infection should not be interpreted solely through the presence of coughing or the extent of cranioventral lung consolidation. Instead, disease impact emerges from the interaction between strain virulence, host immune responses, infection timing and co-infection context. These insights highlight the importance of integrating clinical observation, lung lesion scoring, microbiological detection and immunological data when assessing the role of *M. hyopneumoniae* in modern swine production systems.

Immune responses

The immune responses induced by *M. hyopneumoniae* infection are multifaceted and represent a balance between responses to clear the pathogen from the lung tissues and immune-driven pathologies that exacerbate lung lesions and clinical signs during chronic infection. The underlying immune mechanisms remain, however, largely unresolved. *M. hyopneumoniae* enters the host via the respiratory system and initiates infection by adhering to the airway epithelium. This adhesion to airway epithelial cells results in loss of cilia and eventually cell death [29]. Adhesion also triggers an antimicrobial response from the airway epithelial cells, characterized by an increased production of mucus, reactive oxygen species (ROS) and the secretion of pro-inflammatory cytokines (IL1β, IL5, IL6, IL13, TNFα) and chemokines (CXCL-8) that activate and attract innate immune cells such as neutrophils and alveolar and tissue-resident macrophages to clear *M. hyopneumoniae* infection [55]. Furthermore, neutrophils and macrophages recruited to the site of infection and epithelial damage in turn phagocytose the invading micro-organisms and clear these via a respiratory burst response. These cells also secrete pro-inflammatory cytokines upon recognition of *M. hyopneumoniae* to further activate other innate immune cells as well as to drive adaptive immune responses. Surprisingly, *M. hyopneumoniae* drives and maintains M1 polarisation, a pro-inflammatory state of macrophages that is associated with secretion of pro-inflammatory mediators [106, 107]. Currently, it is unclear how advantageous this is for *M. hyopneumoniae*. In addition, both neutrophils and macrophages can produce extracellular traps (NETs/METs) to kill extracellular micro-organisms [108]. This NETosis entails the expulsion of chromatin from the nucleus together with antimicrobial enzyme to the extracellular environment.

M. hyopneumoniae has evolved several immune evasive tactics to survive and persist within the host: (1) reduce production of host defense proteins like porcine beta-defensin 2 by airway epithelial cells [109], (2) intracellular survival in airway epithelial cells by interfering with autophagy processes [110], (3) impairing phagocytosis by macrophages [111], (4) survival within macrophages by blocking fusion of autophagosomes with lysosomes [112] and (5) use nucleotides in extracellular traps as nutrient source [108]. Infection also triggers early pro-inflammatory responses characterized by the release of IL-1β, IL-6, CXCL-8 and TNF-α, promoting the recruitment and activation of innate immune cells that contribute to lung lesion development and amplify tissue damage through the production of reactive oxygen species (ROS) and other inflammatory mediators [113]. Levels of pro-inflammatory cytokines are increased in BALF and in lung tissue of infected pigs [114].

Natural killer (NK) cells are an innate immune cell type that kills tumor cells or cells infected with intracellular pathogens. Activation of NK cell-mediated cytotoxicity is governed by a balance between activating and inhibitory cell surface receptors. One of the major cues for NK cell-mediated cytotoxicity is a lack of major histocompatibility complex I (MHCI) expression on target cells. Interestingly, *M. hyopneumoniae* reduces surface expression of cluster of differentiation 1a (CD1a) on dendritic cells (DCs) [115]. CD1a is structurally similar to MHCI, however whether *M. hyopneumoniae* downregulates MHCI is unknown. IL10 levels are increased upon infection [115], most likely to create an immune suppressive environment that favors *M. hyopneumoniae* persistence. However, IL10 is a pleiotropic cytokine that also triggers the cytotoxic activity of porcine NK cells [116]. The role of NK cells in *M. hyopneumoniae* clearance remains elusive and warrants further investigation.

Conventional DCs bridge innate and adaptive immune responses and have the unique ability to activate naive T cells. Dendritic cells patrol the tissues for potential invading pathogens, endocytose material, undergo a maturation process, and migrate to the local draining lymph nodes to present antigens to naive T cells via MHC and costimulatory molecules. In addition, T cell polarization into effector phenotypes such as T helper (Th) 1, Th2 and Th17 cells, is driven by cytokine production by these DCs. *M. hyopneumoniae* impairs the DC maturation process and alters their cytokine secretion profile (less IL12, more IL10), at least in in vitro generated bone-marrow derived antigen-presenting cells [68, 115]. Blood-derived DCs are less activated by *M. hyopneumoniae* compared to other mycoplasmas, which might point to an immune evasion mechanism [117]. This might favor persistence of *M. hyopneumoniae* by impairing the induction of adaptive immune responses. Further research should however confirm whether this effect of *M. hyopneumoniae* on DC maturation also occurs in tissue-resident lung DCs.

Clearance of *M. hyopneumoniae* infection requires the presence of balanced effector T cell phenotypes, including Th1 with IFNγ production to activate macrophages, and IL17A producing Th17 cells to fortify the barrier function of the airway epithelium. In that context, persistent IL17A production is known to inflict immune pathologies. CD8 + cytotoxic T cells might also be needed to clear intracellular *M. hyopneumoniae*. Experimental challenge infections showed that *M. hyopneumoniae* infection triggers the presence of cytokine-producing T cells in blood, such as TNFα + IFNγ + cytotoxic T cells, TNFα + IFNγ + CD4 + CD8+ T cells (memory T cells) and IL17A+ CD8 + T cells [118–120]. While robust Th17 cell responses are lacking upon infection, *M. hyopneumoniae* infection most likely induces Th2 responses, as IL5- and IL13-producing mononuclear cells are increased [121]. These cytokines lead to goblet cell hyperplasia and increase mucus production. These Th2 responses typically worsen clinical signs of *M. hyopneumoniae* infection.

In addition to T cells, infection also induces serum IgG and IgA responses and increases *M. hyopneumoniae*-specific IgG and IgA in BALF of infected animals [118–120]. *Mycoplasma hyopneumoniae* directly interacts with IgM + B cells, inducing their proliferation, although B cell subsets differ in their response [117]. The relevance for persistence is yet unknown. While antibody responses are induced, immune evasion strategies, like intracellular hiding of *M. hyopneumoniae* and proteolytic cleavage of its surface proteome, render these antibodies ineffective in protecting the host against chronic infection.

The above clearly illustrates that *M. hyopneumoniae* has evolved multiple strategies that evade innate and adaptive immune responses favoring its persistence and leading to chronic infection. In parallel, robust pro-inflammatory responses are generated that fail to elicit robust protection but contribute to lung lesion development. Which immune evasion mechanisms are at play in the lung tissue during *M. hyopneumoniae* infection remains elusive. It is e.g. unclear whether macrophage polarization represents an actively induced immune evasion niche or a consequence of inflammation. The potential role of autoantibody production against host structures such as actin due to molecular mimicry in pathology remains largely unexplored.

Finally, our understanding of cellular immune responses and protective immunity in the lung tissues is incomplete. Single cell and spatial transcriptomics might help to address these knowledge gaps.

Diagnostics

Over the past decade, developments have progressively expanded diagnostic objectives beyond the identification of infected animals to include monitoring of infection dynamics and demonstration of pathogen freedom in the context of elimination and certification programs [122]. An overview of the main recent advances in diagnostic approaches for *M. hyopneumoniae* is provided in Table 2.

Pulmonary lesions and the use of artificial intelligence

Pulmonary lesions are not pathognomonic, nevertheless, they remain a central indicator of *M. hyopneumoniae* infection severity and its production impact [123]. Visual assessment of lungs at slaughter has long been used for herd-level monitoring, although the degree in which it is employed varies among practitioners in different countries and its applicability is limited by single time point observation and substantial inter-observer variability, reducing reproducibility and comparability across herds and health programs [123, 124].

Table 2 Recent advances in the diagnosis of *Mycoplasma hyopneumoniae* infections in pigs

Recent advances	Key features	Strengths	Limitations	References
Pulmonary lesions and artificial intelligence (AI)	Lung lesion scoring at slaughter; AI-based image analysis	Relevant severity indicator; improved standardization and large-scale analysis with AI	Inter-observer variability; single time point; low etiological specificity in co-infections	[123–130]
Sampling approaches	Lower vs. upper respiratory tract samples; oral fluids; pooling; alternative matrices	Higher sensitivity of deep samples; oral fluids useful for group monitoring	Invasiveness; reduced sensitivity of oral fluids; dilution effects; variable performance of alternative samples	[131–134]
Culture and isolation	In vitro culture for isolate recovery and characterization	Enables strain characterization and downstream analyses	Slow, technically demanding; contamination risk; limited routine use; affected by antimicrobials	[18–22, 26, 30, 51, 58, 135–137]
Tissue detection and PCR	PCR, in situ in situ methods, rapid assays, multiplex detection	High sensitivity/specificity; rapid and quantitative	Cannot distinguish viability; interpretation depends on sampling and stage	[26, 77, 135], 138–144]
Group samples, serology and surveillance	Population-level sampling; ELISA, FMIA, microarrays	Suitable for large-scale surveillance; high-throughput tools	Limited individual sensitivity; no validated DIVA; interpretation difficult in vaccinated herds	[2, 5, 122], 134, 145–150]

Since 2017, artificial intelligence (AI)-based computer vision systems have been developed to address these limitations. Algorithms based on convolutional neural networks and applied to slaughterhouse lung images have demonstrated high reproducibility and robust performance in detecting and quantifying lesions compatible with enzootic pneumonia [124–126]. AI-derived lesion scores show strong agreement with traditional scoring systems and with production parameters such as average daily weight gain and feed conversion ratio, thereby supporting their epidemiological relevance. In addition, they provide further advantages through improved standardization, reproducibility, and large-scale data acquisition, ultimately strengthening the robustness and epidemiological value of lesion-based indicators [123, 127].

The integration of AI tools into industrial slaughter lines would enable largescale, near real-time monitoring of respiratory health. Combined approaches incorporating lesion analysis, clinical data, cough detection systems and laboratory results have been proposed to improve attribution of lesions within the PRDC [128, 129].

Despite these technological advances, the etiological specificity of lesion-based tools, including AI systems, remains a major limitation in the presence of co-infections, highlighting the need for complementary diagnostic approaches and integrated interpretation frameworks [130].

Sampling approaches for the detection of Mycoplasma hyopneumoniae

Diagnostic performance is strongly influenced by sampling strategy. Sampling from the lower respiratory tract, including tracheal or laryngo-tracheal mucus, has consistently shown higher diagnostic sensitivity than upper respiratory tract samples, particularly during early stages of infection and in low-prevalence settings [131]. These sample types are more closely associated with active colonization and, under specific conditions, bacterial viability.

Comparative studies using Bayesian and experimental designs have confirmed the superior sensitivity of deep respiratory samples over nasal swabs or oral fluids at the individual-animal level, especially when diagnostic confirmation is required [132]. However, their collection remains invasive and requires trained personnel, which may limit applicability under certain field conditions.

Oral fluids have been explored as an alternative matrix for group-level surveillance, mainly due to their ease of collection and suitability for repeated sampling. However, their diagnostic sensitivity remains lower than that of individual samples and is strongly influenced by within-group prevalence, sampling design, and animal behavior. As a result, while oral fluids may offer practical advantages for longitudinal monitoring at the population level, their limitations in sensitivity should be carefully considered when interpreting pathogen detection results [151]. Similarly, pooling of individual tracheal swabs reduces diagnostic sensitivity due to dilution effects. However, it preserves a high probability of herd-level detection, particularly when appropriate sample sizes and pooling ratios are applied [133].

In addition, alternative biological matrices, particularly those derived from processing fluids during castration (e.g., testicular fluids), have been explored for the detection of *M. hyopneumoniae*. Although these matrices can provide useful insights at specific stages of production, their diagnostic performance is variable, especially in terms of sensitivity and consistency across conditions. Therefore, their current application is best regarded as complementary to rather than a replacement for established respiratory sampling approaches.

Culture and isolation

Bacterial culture remains an essential approach for confirming *M. hyopneumoniae* infection and obtaining isolates; however, due to its technical constraints, it is rarely used in routine diagnostics and is mainly reserved for research purposes or specific applications, such as strain characterization, antimicrobial susceptibility testing, or the development of autogenous vaccines. Successful isolation requires specialized mycoplasma culture media and culture conditions, as well as prolonged incubation periods, restricting routine cultivation largely to specialized laboratories. Its routine use is further limited by the slow growth of the organism, demanding technical requirements, and a high risk of bacterial contamination, which can overgrow and compromise culture results. Studies have aimed to optimize the growth of *M. hyopneumoniae* [152] and limit bacterial overgrowth with *M. hyorhinis* [57].

Apart from the growth medium used for cultivation, in vitro growth dynamics also differ markedly between strains, with pathogenic and non-pathogenic isolates exhibiting distinct kinetics, complicating the standardization of culture-based approaches [30].

The interpretation of culture results is further challenged in the context of antimicrobial intervention. Antimicrobial treatment can substantially reduce or prevent recovery of *M. hyopneumoniae* by culture, reflecting impaired bacterial viability and infectious potential, even when bacterial material remains detectable in the respiratory tract [26, 135].

Recent methodological advances have aimed to overcome some of the limitations associated with in vitro cultivation. The development of serum-free culture media has enabled more controlled and scalable production, while metabolic modeling approaches indicate that pyruvate supplementation can enhance growth rates and support improved in vitro proliferation [58, 153].

Once isolates are obtained, molecular identification increasingly relies on PCR confirmation, high-resolution melting analysis, multi-locus sequence typing (MLST), multiple-locus variable number of tandem repeat analysis (MLVA) and next-generation sequencing, enabling refined genotyping and investigation of virulence-associated profiles [19, 20, 22, 51, 136]. Several studies have further highlighted the impact of genetic diversity on diagnostic sensitivity and isolate recovery, emphasizing the need for representative sampling when interpreting diagnostic and epidemiological data [18, 21, 137].

Tissue detection and PCR

Detection of *M. hyopneumoniae* can be achieved by immunohistochemistry, in situ hybridization or PCR. In situ techniques allow precise localization of the pathogen within lesions but are limited to small tissue areas and are mainly used in pathological investigations.

Real-time PCR remains the most widely used routine diagnostic method due to its high analytical sensitivity and specificity, and its ability to provide quantitative measurements [138]. Rapid molecular techniques such as recombinase polymerase amplification, loop-mediated isothermal amplification (LAMP) and CRISPR-based assays have been developed to shorten time to result and enable decentralized testing [139, 140]. Multiplex PCR platforms and broad respiratory panels further allow simultaneous detection of multiple pathogens, although the diagnostic value for *M. hyopneumoniae* remains dependent on the sampling strategy and disease stage [141, 142].

Under defined conditions, PCR detection has been associated with bacterial viability, particularly when DNA is detected in tracheal mucus during active colonization [143]. However, following antimicrobial exposure, PCR positivity may persist despite reduced viability or infectious potential due to residual nucleic acids [26, 135]. This limitation highlights the difficulty in distinguishing active infection from residual detection using conventional PCR approaches, particularly in post-treatment contexts.

Viability PCR approaches targeting messenger RNA or using intercalating agents such as PMA or EMA have been proposed to address this limitation, particularly for post-treatment assessment and pathogen clearance verification [140, 143]. Metagenomic and metatranscriptomic methods provide complementary insights into complex respiratory ecosystems [77, 144]. However, these approaches still require further validation before widespread implementation in routine diagnostic [140, 143].

Group samples, serology and surveillance

Group samples such as oral fluids, air samples and surface swabs are increasingly used for population-level surveillance, providing logistical and economic advantages despite lower individual sensitivity [5, 134].

Antibody detection has historically relied on ELISA tests, but their use in diagnostic laboratories has declined due to limited individual diagnostic value and the absence of robust Differentiating Infected from Vaccinated Animals (DIVA) assays. Fluorescent Microsphere Immunoassay (FMIA) platforms, an antibody-detection approach conceptually like ELISA but allowing multiplex and high-throughput analysis [145], together with protein microarrays [146], provide high-throughput alternatives. Secretory IgA-based ELISAs and antigen-focused assays have been proposed to improve discrimination between infected and vaccinated pigs; however, these approaches remain largely experimental and are not yet

widely implemented in routine diagnostic settings [147, 148]. Specialized ELISAs have also been developed for vaccine production and experimental applications [149, 150]. The continued absence of validated DIVA-compatible assays remains a major limitation for interpretation of serological results in vaccinated populations.

Together, group-level sampling approaches and serological tools contribute to a more comprehensive surveillance framework, integrating population-level pathogen detection with immune response monitoring. In this context, studies conducted in wild boar populations and backyard pigs further expand the epidemiological perspective, providing valuable insights into the circulation and maintenance of *M. hyopneumoniae* beyond conventional production systems [2]. Finally, the demonstration of pathogen freedom is becoming increasingly important within elimination and certification frameworks, requiring integrated, multi-level, and well-validated diagnostic strategies that combine direct detection, serology, and population-based surveillance approaches [122].

Treatment

Antimicrobial medication is the most common therapeutic strategy against *M. hyopneumoniae* infections. Potentially active antimicrobials against *M. hyopneumoniae* include tetracyclines, 15- and 16-membered ring macrolides, lincosamides, pleuromutilins, amphenicols, aminoglycosides, aminocyclitols and fluoroquinolones [154]. Without a cell wall, *M. hyopneumoniae* is intrinsically resistant to those antimicrobials that target cell-wall synthesis, such as β-lactams and glycopeptides. Natural resistance to trimethoprim/sulfonamide and to polymyxins has been also described, due to the lack of folic acid synthesis and lipopolysaccharides in this bacterium [155].

Numerous studies have investigated the efficacy of antimicrobials for the treatment of *M. hyopneumoniae* infections under both experimental and field conditions [154]. Several of those antimicrobials can achieve high concentrations at lung tissue level, suggesting bacteriostatic, and sometimes bactericidal effects [156]. There is limited evidence of the impact of antimicrobials on the transmission dynamics of *M. hyopneumoniae in vivo*. More details about the characteristics of antimicrobials used for treatment, treatment strategies and antimicrobial resistance have been reviewed by Maes et al. [154]

In parallel, there is limited consensus on how to define and measure treatment response in a way that demonstrates clinical efficacy without promoting antimicrobial resistance. First, establishing and standardizing what clinical and laboratory indicators should be considered to determine "when-to-treat" thresholds is key. Secondly, the distinction between EP and PRDC is often unclear. Thirdly, little is known about the influence of antimicrobials on the respiratory microbiome and subsequent impact on *M. hyopneumoniae* infections. Toledo et al. described the negative effect of subtherapeutic exposure of tylvalosin, failing to eliminate *M. hyopneumoniae* and to prevent respiratory microbiota dysbiosis [157].

Acquired antimicrobial resistance against *M. hyopneumoniae* does not seem to be a problem [158–160]. However, those studies reported strains with a reduced susceptibility to tetracyclines, macrolides, lincosamides or fluoroquinolones. Genetic and phenotypic variability in susceptibility patterns was described among isolates circulating in different regions, countries and even on the same farm [158]. This highlights the need to eliminate inconsistency between labs, countries and surveillance programs [161, 162].

Antimicrobial susceptibility testing for *M. hyopneumoniae* is performed by broth dilution minimum inhibitory concentration (MIC) testing. However, this technique is underused in practice due to the slow and fastidious growth of this bacterium in vitro [155]. Guidelines for MIC values for species of veterinary importance are still lacking [162]. In addition, the absence of clinical breakpoints makes it hard to translate MIC values into confident treatment decisions. The lack of standardized mutant prevention concentration (MPC), mutant selection window (MSW) and epidemiological cutoffs (ECOFFs) limits the identification of new resistant patterns and delays the consensus for harmonized monitoring of antimicrobial resistances [162].

Rapid molecular antimicrobial resistance testing may be an alternative to MIC testing for detection of resistance-associated mutations, including PCR, sequencing, Mismatch Amplification Mutation Assays (MAMA) and High-Resolution Melt (HRM) [163]. PCR-based methods may help to understand current resistance patterns, whereas whole genome sequencing is better suited for prediction. However, molecular techniques are insufficiently validated against clinical disease caused by *M. hyopneumoniae* and are useless when mutations or mechanisms of resistance are unknown. Jafari et al. underlined the need to apply a multidisciplinary approach combining phenotypic, genomic and bioinformatics data [161]. Today, the main drawback of this tactic is the limited amount of phenotypic and genomic records to feed bioinformatic models. Various consortiums are currently paving the way for the development of standardized methodological guidelines (MyMIC) [162], working on collecting phenotypic data (MycoPath) [159] or improving genomic capabilities (MyMIC). However, more collaborative research is needed.

Finally, there is a growing interest in non-antibiotic therapeutics. Antimicrobial stewardship policies encourage the prudent use of antimicrobials, but also suppress volumes and weaken return of investment, reducing

incentives to invest in the pharmaceutical industry. Advances in our understanding of cytokine-mediated control of inflammation certainly will help with the development of substances with anti-inflammatory effects. New phytopharmaceutical substances have been also developed, including protoberberine alkaloids and herbal extracts showing in vitro anti-inflammatory activity [137, 164].

Control measures

Management and housing conditions should be optimized to reduce the spread of *M. hyopneumoniae* or decrease lung damage by other pathogens. These include all-in/all-out production, proper gilt acclimation, stabilization of herd immunity, appropriate stocking densities, prevention of other respiratory diseases, and optimal housing and climatic conditions [67]. Early weaning strategies combined with moving the piglets to an isolated site reduce and may eliminate vertical transmission from sows [165].

Vaccination is applied worldwide to control *M. hyopneumoniae* infections. Commercial vaccines mostly consist of inactivated, adjuvanted whole-cell preparations that are administered either intramuscularly or intradermally [166]. Commercial vaccines are licensed for either single or double vaccination, and combinations with other pathogens (e.g. PCV2; *Lawsonia intracellularis*) are commonly available. Attenuated vaccines have been licensed in Mexico and in China. Vaccination improves performance, decrease clinical signs and lung lesions, and treatment costs [166]. Although protection against clinical pneumonia is often incomplete and vaccination does not prevent colonization, currently used vaccines reduce the number of organisms in the respiratory tract [118] and bacterial colonization in piglets [167] or pen mates [135]. Different arms of the immune system are triggered by vaccination [168]. The humoral response consists of local mucosal antibodies and serum antibodies. Whether mucosal IgA in the respiratory tract is protective remains unclear. Serum antibodies upon vaccination mainly consist of IgG [168]. These responses depend upon the vaccination scheme (single vs. double vaccination) and vaccine type but are not correlated with protection.

Commercial vaccines, including the adjuvant alone, also alter the response of circulating innate immune cells to a secondary stimulus, hinting at the induction of trained innate immunity [120]. Further research is needed to assess the importance of trained innate immune responses in protection. Vaccination induces systemic cell-mediated immunity (CMI), mainly antigen-specific Th1, Th17, $CD8^+$ cytotoxic T cells, and antigen-experienced double-positive T-cells, which are considered important for protection despite considerable variation among individual pigs [120]. A long-term follow-up study [169], showed that although seroconversion after *M. hyopneumoniae* vaccination of piglets was lacking, *M. hyopneumoniae*-specific cell-mediated immune responses were detected. Polyfunctional cytokine-producing CD4 + CD8+ T cells were present till three months of age and proliferating T cells were observed till the end of the fattening period.

Vaccination of sows against *M. hyopneumoniae* during late gestation induces *M. hyopneumoniae*-specific antibodies and polyfunctional T cells in sows, which are transferred via colostrum to neonatal piglets [170]. *M. hyopneumoniae*-specific cytokine-producing T cells are found in blood of piglets from *M. hyopneumoniae* vaccinated sows. Further studies are warranted to investigate the role of these transferred maternally derived polyfunctional T cells for the immune system in young piglets and for protection of piglets against *M. hyopneumoniae* infection.

Different vaccination strategies are adopted depending on the type of herd, production system and management practices, infection pattern, and the preferences of the pig producer. Since colonization with *M. hyopneumoniae* may already occur during the first weeks of life, vaccination of piglets (< 4 weeks of age) is used most often. Vaccination of breeding gilts in the gilt acclimation or quarantine unit is the most common gilt acclimation practice used in Europe and North America [171]. It aims to stimulate and homogenize the immunity of the replacement gilt population and to avoid destabilization of the breeding stock immunity. Vaccination of sows at the end of gestation is less commonly practiced, although it can reduce the number of positive piglets at weaning [167, 172]. The beneficial effects of vaccination are variable between farms. This may be due, among other factors, to improper vaccine storage conditions and administration, vaccination compliance, infection level, maternally derived antibodies, diversity of *M. hyopneumoniae* strains, and co-infections [166].

Research on the development of novel vaccines that may offer better protection against *M. hyopneumoniae* infections is ongoing. An overview of experimental vaccines tested in mice and in pigs has been published by [166]. They include vector vaccines, subunit vaccines, DNA vaccines and bacterin vaccines. The effect of novel adjuvants including nanoparticles to stimulate proper immune responses has also been investigated [118, 173]. Beuckelaere et al. investigated the efficacy of two *M. hyopneumoniae* strains that were genetically modified by transposon-mediated gene disruption of mmsA and mnuA, encoding methylmalonate semialdehyde dehydrogenase and membrane nuclease A, respectively [119]. A single endotracheal administration of the ΔmnuA strain resulted in coughing post-vaccination, but reduced clinical signs post-challenge and challenge strain DNA load

in BAL. Therefore, a strain mutated in the mnuA gene might be interesting as a potential live vaccine candidate strain. Peer-reviewed studies about nucleic acid-based vaccines against *M. hyopneumoniae* in pigs were not found. Overall, the research with the different experimental vaccines in pigs suggests that the formulation, the type of antigens, the adjuvant and/or carrier, and the route and frequency of immunization could induce variable immune responses and efficacy. The studies point to a large variation in individual animal responses, even if the same vaccine is used under the same conditions.

Elimination

The claim of "freedom of *M. hyopneumoniae* disease" has been made in Switzerland [174], Norway [175] and Finland [176]. In each country, slightly different approaches for elimination have been taken, yet all have led to achieving the same goal. In other regions of the world, elimination has been reported and continues to be documented at the farm, herd, and system levels [177], and in some cases, efforts to eliminate the pathogen from entire geographical states are underway.

The motivation to eliminate *M. hyopneumoniae* is usually based on multiple reasons, which mainly include the goal to achieve high pig health and improved animal welfare [122], the anticipated financial benefits of disease elimination, the decreased use of antimicrobials [122], or the possibility to increase sustainability and decrease the environmental impact of swine production [178].

The methods for elimination of *M. hyopneumoniae* have evolved as more information on the epidemiology of the bacterium has been available. Besides the use of highly effective yet radical strategies, such as depopulation and repopulation for disease elimination [122], managing different pigs ages and stages to break pathogen transmission has worked well for *M. hyopneumoniae* elimination [177]. For instance, partial depopulation has been employed in European countries with herds consisting of small sized farms housing pigs at a single location for the entire production cycle. The use of this strategy stands from the early and continued exposure of the entire herd to infected and shedding older pigs. Fairly uniform exposure and likely development of immunity, together with a lack of susceptible hosts for an extended period has allowed for the elimination of *M. hyopneumoniae* using partial depopulation. On the other hand, large and segregated systems in which pigs are moved to different facilities based on their age and production purpose, like in North America, have applied elimination methods that limit the entry of naïve pigs into herds until pathogen persistence has subsided [26], especially after the entire resident population has been uniformly exposed to *M. hyopneumoniae*. An array of approaches for *M. hyopneumoniae* elimination has been described [177] and made available to the public. Nevertheless, methods for elimination in massive pig production complexes, like those in large Asian countries, have not been developed.

Regardless of the employed method, elimination of *M. hyopneumoniae* is not infallible and success rates, which can reach above 80%, seem to be associated with the use of specific approaches [122]. In most cases, vaccination and antimicrobial treatments are included in elimination programs, although the exact form in which they contribute to elimination may not be completely known. Therefore, the development of new elimination methods that rely less on the use of antimicrobials are of special interest and should be the focus of future research. A major challenge is also maintaining a pathogen-free status after successful elimination and preventing reintroduction of the pathogen. When a herd is surrounded by infected farms, elimination may be a risky strategy and, in some cases, may not be economically justified.

A broader application of elimination programs could be achieved by generating solid information that can support targeting multiple pathogens with a single program, minimal disruption to swine production, decreased use of antimicrobials, less social pressure for farmers and veterinary professionals, and transparent communication with non-agricultural segments of the population.

Knowledge gaps and avenues for further research

Despite progress, major knowledge gaps remain in different areas:

- Transmission & epidemiology: The importance of environmental transmission, the role of wild boar reservoirs, vectors, and co-infections, and the true prevalence of subclinical infection are insufficiently quantified.
- Strain diversity: The impact of genetic variability on virulence, transmission, vaccine performance, and persistence is unresolved, and predictive markers for virulence are lacking.
- Host-pathogen interaction: Mechanisms underlying immune evasion, intracellular survival, macrophage polarization, and the newly proposed migrasome pathway (including its in vivo relevance and interaction with other persistence strategies) remain unclear.
- Immunology: Protective immunity is poorly understood; correlates of protection are lacking, the role of mucosal vs. systemic immunity is unresolved, and the roles of DCs, NK cells, and T-cell subsets need further clarification.
- Diagnostics: Distinguishing active infection from residual detection, improving specificity in

polymicrobial conditions, and developing DIVA-compatible serological tools remain key challenges.
- Treatment: Evidence of antimicrobial effects on transmission, microbiome interactions, and standardized resistance monitoring is limited.
- Vaccination & control: Mechanisms of vaccine-induced protection, variability in field efficacy, and the influence of maternal immunity are unclear.
- Elimination strategies: Scalable approaches for large production systems and reduced reliance on antimicrobials are lacking.

Abbreviations

AI Artificial intelligence
CD1 Cluster of differentiation 1
CMI Cell-mediated immunity
DIVA Differentiating infected from vaccinated animals
ECM Extacellular matrix
ECOFFs Epidemiological cutoffs
EKE Expert knowledge elicitation
EP Enzootic pneumonia
FMIA Fluorescent microsphere immunoassay
HRM High-resolution melt
LAMPs Lipid-associated membrane proteins
LAMP Loop-mediated isothermal amplification
MAMA Mismatch amplification mutation assays
MAPK Mitogen-activated protein kinase
METs Macrophage extracellular traps
MHCI Major histocompatibility complex I
MIB–MIP Mycoplasma immunoglobulin binding and protease
MIC Minimum inhibitory concentration
MLST Multi-locus sequence typing
MLVA Multiple-locus variable number tandem repeat analysis
mmsA methylmalonate semialdehyde dehydrogenase
mnuA membrane nuclease A
MPC Mutant prevention concentration
MSW Mutant selection window
NETs Neutrophil extracellular traps
PCV2 Porcine circovirus type 2
PCV3 Porcine circovirus type 3
PRDC Porcine respiratory disease complex
PRRSV Porcine reproductive and respiratory syndrome virus
swIAV swine influenza A virus
TCA Tricarboxylic acid
Th-cell T-helper cell

Acknowledgements
Not applicable.

Authors' contributions
The different chapters were initially written by different authors; all of them had participated in the Discontools project. Abstract, introduction, conclusions: DM; Epidemiology: MS, MP, CF; Pathogenesis: CMC, GS; Clinical signs and lesions: JS, MS, RDPS; Immune responses: BD, DM; Diagnostics: CMC, JS, MP; Treatment: RDPS, DM; Control measures: LG, DM, BD; Elimination: MP; Once the separate chapters were written, DM compiled and unified them and finally, every author read and thoroughly revised the entire paper.

Funding
Not applicable.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Received: 4 June 2026 / Accepted: 27 July 2026
Published online: 31 July 2026

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