Mycoplasma gallisepticum in Avian Species: A Survey of Vaccines, Pathogenicity, Diagnosis, and Control Strategies

Abstract

This survey paper comprehensively examines the challenges and strategies associated with controlling Mycoplasma gallisepticum (MG) infections in avian species, a significant pathogen causing chronic respiratory diseases with substantial economic impacts on the poultry industry. The paper explores MG's pathogenicity, transmission mechanisms, and interactions with the host immune system, emphasizing the complexity of managing infections. Current diagnostic methods, including both traditional serological tests and advanced molecular techniques, are evaluated for their efficacy in accurately detecting MG and informing control strategies. Vaccine development is a focal point, with discussions on the efficacy of live attenuated and inactivated vaccines, highlighting innovative approaches such as multi-epitope vaccines and plant-based production systems, which offer promising avenues for enhancing immune responses in poultry. The integration of biosecurity measures, vaccination, and antimicrobial stewardship is identified as crucial for effective disease management. Future research directions emphasize the need for expanded datasets, refined genotyping methods, and in vivo testing of vaccine candidates to improve understanding of host-pathogen dynamics and enhance vaccine efficacy. The survey underscores the importance of comprehensive management strategies, including improved biosecurity practices and advanced diagnostics, to mitigate the economic burden of MG and enhance the resilience of poultry populations against infections.

1 Introduction

1.1 Significance of Mycoplasma gallisepticum

Mycoplasma gallisepticum (MG) is a significant pathogen in avian species, primarily linked to chronic respiratory diseases (CRD) that adversely affect poultry health and productivity. The economic implications of MG infections are profound, resulting in decreased productivity, increased mortality, and heightened management costs [1]. Clinical manifestations include respiratory rales and coughing, indicative of its role in CRD [1].

The economic burden is further exacerbated by MG's negative impact on growth rates, egg production, and carcass quality, which are essential for poultry profitability. In breeder flocks, MG infections can lead to elevated mortality and diminished performance [2]. The co-infection of MG with other pathogens, such as Mycoplasma synoviae (MS), complicates CRD management, emphasizing the need for effective control measures [3].

In regions like Ethiopia, where MG is prevalent, its significance in avian health necessitates ongoing surveillance and targeted interventions [4]. Understanding MG's pathogenic role and economic impact is crucial for developing strategies to mitigate its effects on the poultry industry [5].

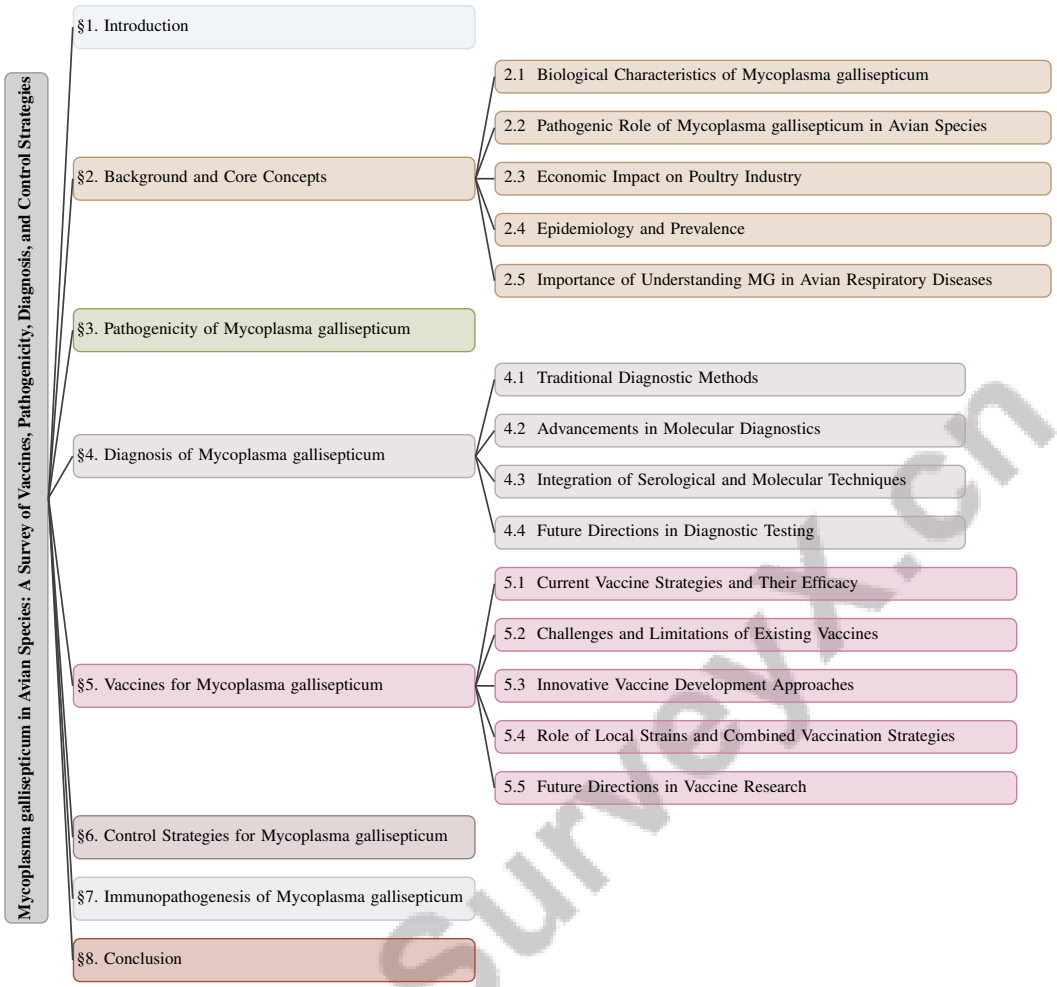


Figure 1: chapter structure

1.2 Scope of the Survey

This survey provides an in-depth exploration of Mycoplasma gallisepticum (MG), focusing on its pathogenicity, diagnostics, vaccine development, and control strategies. It examines MG's biological characteristics and its role in avian respiratory diseases, emphasizing the economic impact on the poultry industry. The survey investigates transmission routes and pathogenic mechanisms, including MG's interactions with the host immune system and the effects of co-infections and microbiota on MG pathogenicity [3].

In diagnostics, the survey reviews traditional and advanced molecular techniques, emphasizing the integration of serological and molecular methods to enhance the accuracy of MG and Mycoplasma synoviae (MS) detection [3]. Current vaccine strategies, including live attenuated and inactivated vaccines, are evaluated for their efficacy and limitations, alongside innovative approaches such as multi-epitope vaccine candidates targeting cytotoxic T-cells, helper T-cells, and B-cells [6].

Furthermore, the survey addresses control strategies, including biosecurity measures and antimicrobial stewardship, aimed at preventing and mitigating MG outbreaks. By integrating diagnostic methods, control practices, and the pathobiology of MG and MS infections, this survey offers a comprehensive framework for understanding and managing MG infections in avian species [3].

1.3 Structure of the Survey

This survey is structured to thoroughly examine Mycoplasma gallisepticum (MG) and its impact on avian species. The organization includes several key sections, each focusing on different as-

pects of MG research. The initial section discusses MG's biological characteristics, elucidating its pathogenicity and mechanisms of disease in avian hosts [7].

The following section explores the epidemiological features of MG, highlighting its prevalence and distribution across various avian populations globally, which is vital for effective control strategies. The economic impact of MG on the poultry industry is then addressed, detailing the financial burdens associated with MG infections, including reduced productivity and increased management costs.

A substantial portion of the survey is dedicated to MG diagnostics, reviewing both traditional and advanced molecular techniques. This includes the integration of serological and molecular methods to improve diagnostic accuracy, essential for effective disease management. The discussion then shifts to vaccine development, evaluating current strategies such as live attenuated and inactivated vaccines, as well as innovative approaches like the multi-epitope peptide vaccine (MEPV) derived from immunogenic segments of MG cytoadherence proteins [1].

Finally, the survey outlines control strategies encompassing biosecurity measures, vaccination, and management practices, with an emphasis on antimicrobial stewardship to prevent and mitigate MG outbreaks. By categorizing MG research into biological characteristics, pathogenic mechanisms, epidemiological features, and control strategies, the survey provides a comprehensive framework for understanding and managing MG infections in avian species [7].The following sections are organized as shown in Figure 1.

2 Background and Core Concepts

2.1 Biological Characteristics of Mycoplasma gallisepticum

Mycoplasma gallisepticum (MG) is a pivotal avian pathogen causing chronic respiratory diseases, leading to significant economic losses in the poultry industry due to its impact on health and productivity [8]. Its pleomorphic nature and resistance to antibiotics, stemming from the absence of a cell wall, complicate treatment [7]. MG's pathogenicity is attributed to its adherence to avian respiratory epithelial cells via specialized surface proteins, enabling immune evasion and chronic infections [9]. The variability in immune responses among MG strains results in diverse disease severities [9]. Additionally, MG's interaction with the respiratory microbiota can exacerbate disease conditions [10]. Diagnostic approaches include serological tests like ELISA and molecular techniques such as PCR, which enhance detection accuracy and epidemiological insights [11, 12].

2.2 Pathogenic Role of Mycoplasma gallisepticum in Avian Species

MG is a primary agent of chronic respiratory diseases (CRD) in avian species, significantly impacting poultry health and productivity [13]. Its pathogenicity involves adherence to respiratory epithelial cells, facilitated by surface proteins that aid in immune evasion and chronic infection [14]. Co-infections with pathogens like Avian Metapneumovirus (AMPV) can worsen disease severity, complicating diagnosis and treatment [15]. These interactions lead to economic losses due to decreased productivity and increased mortality [11]. The host-pathogen interaction is complex, with cytokine production varying between infections by different MG isolates, indicating the role of pathogen evolution in immune response and disease outcome [16].

2.3 Economic Impact on Poultry Industry

MG infections impose substantial economic burdens on the poultry industry through reduced productivity, increased mortality, and disease management costs. In Pakistan, MG's prevalence as a cause of CRD has intensified economic challenges, highlighting the need for effective interventions [17]. Reliance on costly imported vaccines, often unavailable, exacerbates financial strains [18]. Ineffective vaccination strategies against MG and Mycoplasma synoviae (MS) further contribute to economic losses [19]. Misdiagnosis due to variable diagnostic test results hinders effective control measures [12]. In Thailand, MG critically affects poultry health and economic viability [20]. Antibiotic-resistant MG strains complicate treatment and increase financial burdens, as existing vaccines may have limited efficacy [6]. Comprehensive biosecurity measures, effective pathogen detection, and farmer education are essential to mitigate these economic impacts [21]. Developing effective vaccines,

improving diagnostic accuracy, and implementing integrated management practices are crucial for sustaining the poultry industry's economic viability amid MG infections [3].

2.4 Epidemiology and Prevalence

Understanding MG's epidemiology is crucial for managing its prevalence across regions and poultry species. In Italy, a dataset of 40 MG isolates from 2010 to 2019 revealed genetic diversity, informing control strategies and vaccine development [22]. A large-scale survey in Pakistan involving 1,200 samples highlighted MG's widespread presence and implications for poultry management [17]. Research in Poland and Thailand provided insights into MG distribution and vaccine efficacy [23, 8]. Sero-prevalence studies showed higher infection rates in breeder flocks [24]. In Ethiopia, the lack of comprehensive data necessitates ongoing research to improve disease management [4]. Epidemiological studies indicate significant variations in MG prevalence and sero-prevalence rates, with seasonal peaks from October to December [17, 22, 11, 8, 24]. These insights are vital for developing effective control strategies to mitigate MG's impact on the global poultry industry.

2.5 Importance of Understanding MG in Avian Respiratory Diseases

Comprehending MG is essential for avian respiratory health due to its complex management challenges. MG is a major cause of chronic respiratory diseases, complicating vaccination and control measures [25]. Its immune evasion capabilities exacerbate disease severity [2]. Mixed infections with other pathogens complicate clinical presentations and management [23]. The poultry respiratory microbiota's ecology influences infection severity, necessitating a comprehensive understanding of MG's interactions for effective control [10]. Understanding MG's transmission dynamics is crucial for developing vaccines and alternative treatments [7]. The emergence of MG in house finches highlights its adaptive nature, emphasizing the need for continuous research [16]. In Ethiopia, gaps in understanding respiratory diseases and MG strains necessitate targeted interventions [4]. Transcriptional profile changes during infections provide insights into immune responses, crucial for improving vaccine efficacy [5]. Understanding MG's pathogenic mechanisms, transmission dynamics, and host interactions is vital for enhancing avian respiratory health, improving control measures, and addressing co-infections with other pathogens like AMPV [15, 13].

3 Pathogenicity of Mycoplasma gallisepticum

3.1 Transmission Routes and Pathogenic Mechanisms

Mycoplasma gallisepticum (MG) is highly contagious among avian species, primarily spread through direct contact, aerosols, and contaminated equipment, with infected birds shedding the bacterium in their respiratory tracts, thereby contaminating the environment [22]. Although less common, vertical transmission occurs when infected hens pass MG to offspring via eggs, impacting breeding operations. Upon host entry, MG employs pathogenic mechanisms, notably adhering to the avian respiratory tract's epithelial cells using specialized surface proteins, facilitating colonization and immune evasion. Its lack of a cell wall complicates immune defense and confers resistance to antibiotics targeting cell wall synthesis, such as beta-lactams [10]. MG's interaction with the host's respiratory microbiota is critical, as disruptions in microbial balance due to MG colonization can exacerbate respiratory diseases, highlighting the need to understand these interactions for effective disease management [10].

3.2 Interaction with Host Immune System

MG's complex interaction with the host immune system is pivotal for its pathogenicity and ability to establish chronic infections. It manipulates both innate and adaptive immune responses, significantly contributing to its persistence in avian hosts [25, 2]. Diverse gene expression profiles and metabolic changes characterize the immune response to MG, varying with the strain involved. For instance, the evolved isolate NC2006 elicits stronger pro-inflammatory cytokine responses in house finches than the original isolate VA1994, underscoring the influence of host immune responses on MG pathogenicity [16]. Vaccination modulates immune responses, with transcriptional profiles of the tracheal mucosa during subsequent infections influenced by responses elicited by specific MG strains,

such as ts-304, indicating vaccines' potential to shape immune landscapes and optimize disease outcomes [5]. MG employs sophisticated evasion strategies, such as altering antigen expression and modulating inflammatory pathways, with variability in host immune responses arising from genetic predispositions and environmental conditions. Vaccination plays a critical role in enhancing immune modulation, as evidenced by differences in antibody titers and histopathological changes between vaccinated and unvaccinated chickens [25, 2, 5, 26, 9]. Understanding these interactions is vital for developing effective strategies to control MG infections and improve avian health.

3.3 Impact of Co-Infections and Microbiota

Co-infections with MG and other pathogens, such as Avian Metapneumovirus (AMPV), significantly influence MG pathogenicity in avian species. These co-infections can exacerbate respiratory diseases, impacting pathogen replication and host immune responses. The sequence of pathogen introduction can further affect lesion severity and immune reactions, complicating respiratory disease management in poultry flocks [15]. The interaction between MG and the host's microbiota is another crucial factor affecting disease progression. The avian respiratory microbiota, consisting of diverse microbial communities, can influence susceptibility to infections. Disruptions in microbial balance due to MG colonization may lead to altered immune responses and increased disease severity, emphasizing the need to understand the microbiota's role in modulating host immunity and pathogen virulence [2]. The impact of co-infections and the respiratory microbiota on MG pathogenicity underscores the necessity for integrated management strategies that consider the interplay of multiple pathogens and the host's microbial environment. A comprehensive understanding of immune response mechanisms and pathogenic interactions associated with MG infections is essential for developing targeted interventions aimed at mitigating MG's detrimental effects on poultry health and productivity. This encompasses the roles of innate and adaptive immunity, identification of virulence factors, and effective management strategies critical for addressing chronic respiratory disease caused by MG [13, 2, 20, 8, 10].

3.4 Variability in Immune Responses

Immune responses to MG infections exhibit considerable variability among avian species, significantly influencing pathogenicity and disease outcomes. This variability arises from genetic differences among species, affecting the magnitude and type of immune response elicited upon infection. For instance, house finches infected with different MG isolates display varied pro-inflammatory cytokine responses, indicating that MG strain evolution can substantially alter host immune dynamics [16]. In chickens, the immune response to MG involves both innate and adaptive immune pathways, but effectiveness varies based on the bird's genetic background and the virulence of the MG strain. The immune response includes specific antibody production and T-cell activation, crucial for controlling infection and limiting bacterial spread [25]. However, the degree of immune activation and clinical outcomes can differ markedly among broilers, layers, and breeders, reflecting the influence of genetic and environmental factors on immune function [17]. Furthermore, co-infections and the composition of the host's microbiota influence variability in immune responses. Co-infections with pathogens like AMPV can modulate immune responses, leading to altered disease manifestations and complicating MG infection management [15]. The interaction with the respiratory microbiota further adds complexity, as microbial community changes can impact immune regulation and pathogen virulence [10]. Understanding the variability in immune responses among avian species, particularly concerning MG, is essential for developing effective vaccines and customized intervention strategies. This knowledge can enhance disease resilience and improve health outcomes in poultry by addressing the unique immunological interactions exhibited by each species when confronted with infections. Insights from studies on cytokine expression and immune profiles can inform vaccine design and implementation, ultimately leading to improved management practices in poultry health [2, 16, 5, 26]. This understanding can also guide breeding programs aimed at enhancing genetic resistance to MG and inform the design of vaccines effective across diverse avian populations.

In recent years, the landscape of diagnostic methods for Mycoplasma gallisepticum has undergone significant transformation. The evolution from traditional serological and culture-based methods to sophisticated molecular diagnostics reflects advancements in our understanding and management of poultry health. This transition underscores the importance of integrating various diagnostic approaches to enhance accuracy and efficacy in disease management. Figure 2 illustrates this hierarchical structure of diagnostic methods, highlighting both traditional and advanced molecular

techniques. The figure not only delineates the integration of serological and molecular approaches but also points to future directions in diagnostic testing, thus providing a comprehensive overview of the current state and future potential of Mycoplasma gallisepticum diagnostics.

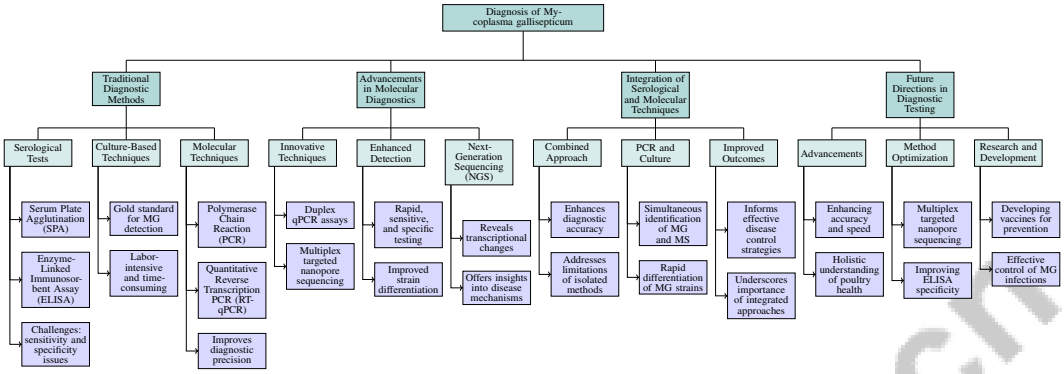


Figure 2: This figure illustrates the hierarchical structure of diagnostic methods for Mycoplasma gallisepticum, highlighting traditional and advanced molecular techniques, the integration of serological and molecular approaches, and future directions in diagnostic testing. The diagram emphasizes the evolution from traditional serological and culture-based methods to sophisticated molecular diagnostics, and the integration of these methodologies for improved accuracy and disease management in poultry health.

4 Diagnosis of Mycoplasma gallisepticum

4.1 Traditional Diagnostic Methods

Traditional diagnostic methods for Mycoplasma gallisepticum (MG) in avian species include serological tests and culture-based techniques, foundational for MG detection and management. Serological tests like Serum Plate Agglutination (SPA) and Enzyme-Linked Immunosorbent Assay (ELISA) are prevalent for screening poultry flocks for MG antibodies. Although SPA is rapid and cost-effective, it is prone to sensitivity and specificity challenges, leading to potential false results, whereas ELISA correlates serological findings with clinical signs, enhancing diagnostic accuracy [11]. Culture-based techniques, considered the gold standard, confirm MG infections by isolating the bacterium from clinical samples. However, they are labor-intensive and time-consuming due to MG's slow growth and the need for specialized media, complicating timely outbreak interventions [27, 4]. To overcome these limitations, molecular techniques such as Polymerase Chain Reaction (PCR) and Quantitative Reverse Transcription PCR (RT-qPCR) have been introduced, improving diagnostic precision by amplifying specific genetic markers and quantifying mRNA expression to provide insights into host-pathogen interactions [16]. Despite these advancements, challenges in reproducibility and strain differentiation remain, necessitating a comprehensive diagnostic approach combining serological and molecular methods [12].

4.2 Advancements in Molecular Diagnostics

Recent advancements in molecular diagnostics, including duplex qPCR assays and multiplex targeted nanopore sequencing, have significantly enhanced the detection and differentiation of Mycoplasma gallisepticum (MG) in avian species. These innovations address traditional method limitations by offering rapid, sensitive, and specific testing capabilities. Enhanced sample collection techniques, such as choanal cleft swabs, further optimize pathogen detection, benefiting poultry industry management [3, 22, 28]. PCR has been crucial in improving MG detection sensitivity and specificity, enabling the identification of MG and Mycoplasma synoviae (MS) in poultry flocks. Duplex qPCR and multiplex targeted nanopore sequencing facilitate simultaneous detection of multiple Mycoplasma species, enhancing diagnostic throughput and accuracy [28, 23]. Gene-targeted sequencing focuses on specific MG genes, improving strain differentiation and understanding of MG epidemiology [8]. Multiplex PCR assays differentiate vaccine strains from wild-type strains, providing insights into vaccine efficacy and pathogen dynamics [29]. Next-generation sequencing (NGS) complements these

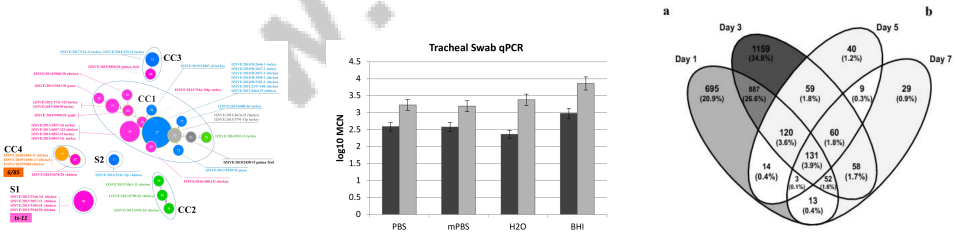
advancements by revealing transcriptional changes in infected tissues, offering insights into disease mechanisms and potential therapeutic targets [9]. Integrating these advanced molecular techniques with traditional methods, such as ELISA and culture-based approaches, provides a robust framework for accurate MG detection and management, achieving significant diagnostic advancements [3].

4.3 Integration of Serological and Molecular Techniques

Method Name	Diagnostic Techniques	Method Synergy	Technological Advancements
ELISA[11]	-	-	-
DPM[14]	Pcr-based Methods	Combining Pcr Amplification	Duplex Pcr Method
MPA[29]	Multiplex Pcr Assay	Combining Diagnostic Methods	Multiplex Pcr Sequencing
MTNS[28]	Multiplex Pcr Amplification	Combines Multiplex Pcr	Multiplex Targeted Nanopore

Table 1: Overview of diagnostic methods integrating serological and molecular techniques for Mycoplasma gallisepticum detection. The table highlights various methods, their diagnostic techniques, synergistic approaches, and technological advancements, emphasizing the enhancement of diagnostic accuracy and efficiency.

Integrating serological and molecular techniques enhances the diagnostic accuracy of Mycoplasma gallisepticum (MG) infections in avian species. This approach leverages the strengths of both methodologies, addressing limitations when used in isolation. Serological methods like ELISA effectively detect MG antibodies, quantifying immune responses [11]. However, specificity issues necessitate precise molecular techniques [3]. Molecular techniques, particularly PCR, have improved MG detection specificity and sensitivity. Duplex PCR allows simultaneous identification of MG and Mycoplasma synoviae (MS), providing a faster, cost-effective alternative to traditional methods [14]. Multiplex PCR assays enable rapid differentiation of MG strains, enhancing diagnostic throughput and accuracy [29]. Innovations in multiplex PCR amplification and nanopore sequencing facilitate rapid identification of multiple pathogens [28]. Integrating these techniques is crucial for improving diagnostic accuracy and disease control in poultry farming. This synergy enhances diagnostic outcomes and informs effective disease control strategies [12]. Isolating Mycoplasma through culture and confirming its identity via PCR underscores the importance of integrated diagnostic approaches for accurate identification and management of MG infections [27]. Table 1 presents a comprehensive comparison of diagnostic methods integrating serological and molecular techniques for Mycoplasma gallisepticum, showcasing their respective diagnostic techniques, synergies, and technological advancements.



(a) The image depicts a network diagram representing a phylogenetic tree of avian influenza viruses (AIVs) based on their nucleotide sequences.[22]

(b) Tracheal Swab qPCR[28]

(c) Venn Diagram of Gene Expression Changes Over Time in a Cell Culture Model[9]

Figure 3: Examples of Integration of Serological and Molecular Techniques

As illustrated in Figure 3, integrating serological and molecular techniques in diagnosing Mycoplasma gallisepticum exemplifies a comprehensive approach that combines various analytical methods to enhance diagnostic accuracy. The first image depicts a network diagram showcasing the phylogenetic tree of avian influenza viruses based on nucleotide sequences, highlighting genetic relationships and evolutionary patterns among strains. This analysis is crucial for understanding genetic diversity and potential transmission pathways. The second image, a bar graph titled "Tracheal Swab qPCR," demonstrates quantitative analysis of viral load using different swabbing media, essential for optimizing sample collection and improving molecular detection sensitivity. Lastly, the Venn diagram of

gene expression changes over time in a cell culture model provides insights into dynamic biological responses during infection, revealing critical time-dependent gene expression patterns. Collectively, these images underscore the importance of integrating serological and molecular techniques for a holistic understanding of Mycoplasma gallisepticum infections, facilitating accurate diagnostics and informed disease management decisions [22, 28, 9].

4.4 Future Directions in Diagnostic Testing

Future advancements in diagnostic testing for Mycoplasma gallisepticum (MG) aim to enhance the accuracy, speed, and comprehensiveness of pathogen detection in poultry populations. Integrating molecular techniques with serological methods promises a holistic understanding of poultry health by leveraging both diagnostic approaches [24]. Continued development of multiplex targeted nanopore sequencing methods is expected to improve sensitivity and speed, enabling rapid and precise identification of MG and other pathogens in diverse environments [28]. Refining assays like multiplex PCR holds potential for broader applications across various conditions and populations, enhancing MG diagnostics' versatility and efficacy [29]. Concurrently, optimizing traditional methods, particularly improving ELISA specificity, is crucial for reliable serological outcomes [11]. Future research should also focus on developing vaccines to prevent Mycoplasma infections, addressing detection and prevention in disease management [27]. Advancing these diagnostic and preventive strategies will enable more effective control of MG infections, enhancing poultry health and productivity.

5 Vaccines for Mycoplasma gallisepticum

The management of Mycoplasma gallisepticum (MG) infections is pivotal in poultry health due to their significant impact on animal welfare and economic productivity. This section delves into various vaccine strategies against MG, focusing on efficacy, challenges, and innovations in vaccine development. Understanding these strategies is vital for enhancing disease resistance and improving flock health. The following subsection will address current vaccine strategies and their efficacy, providing an overview of existing approaches and their implications for poultry management.

5.1 Current Vaccine Strategies and Their Efficacy

Benchmark	Size	Domain	Task Format	Metric
BBCM[21]	16	Poultry Health Management	Risk Assessment	BBCM Score, Pathogen Detection Rate
MG-Benchmark[22]	40	Veterinary Microbiology	Genotyping	Simpson's Discriminatory Index
SPM[24]	1,667	Veterinary Science	Sero-prevalence Analysis	Prevalence Rate
MGM[17]	1,200	Veterinary Microbiology	Prevalence Assessment	Seroprevalence, PCR Positivity
MG-MS[23]	300	Veterinary Microbiology	Pathogen Detection	Prevalence Rate, PCR Detection Rate
MG-MS-Dx[12]	630	Veterinary Microbiology	Disease Diagnosis	Sensitivity, Specificity

Table 2: This table presents a comprehensive overview of various benchmarks utilized in the domain of veterinary science, specifically focusing on Mycoplasma gallisepticum (MG) research. Each benchmark is characterized by its size, domain of application, task format, and the specific metrics used for evaluation. The data underscores the diversity in methodological approaches and evaluative criteria across different studies.

Current vaccine strategies for Mycoplasma gallisepticum (MG) involve live attenuated and inactivated vaccines, each with distinct advantages and challenges. Live attenuated vaccines, such as the ts-304 strain, effectively mitigate transcriptional changes linked to inflammatory responses [5]. However, they often require multiple doses for adequate protection, indicating a need for improved strategies [1]. Inactivated vaccines aim to induce immunity without live pathogens' risks but may require adjuvants like chitosan to enhance efficacy [6]. Multi-epitope vaccines integrating CTL, HTL, and B-cell epitopes show promise for comprehensive immune responses [6]. Despite advancements, existing vaccines' limited efficacy and dosing requirements highlight the need for ongoing research. Subunit vaccines targeting specific virulence factors are critical for addressing MG's antigenic variation and host susceptibility [20, 30, 13]. Table 2 provides a detailed overview of representative benchmarks

used in veterinary science research, highlighting their relevance to current vaccine strategies for Mycoplasma gallisepticum.

5.2 Challenges and Limitations of Existing Vaccines

Developing effective vaccines against Mycoplasma gallisepticum (MG) faces challenges, including inconsistent protection and variable immune responses across poultry populations [5]. The rise of antibiotic-resistant MG strains heightens the reliance on vaccines, yet detection accuracy limitations complicate control efforts [7]. Existing vaccines may reduce respiratory infections but not MG transmission, risking pathogen spread to unvaccinated flocks [20]. Locally produced vaccines, like those in Ethiopia, offer cost-effective solutions but require improved formulations for comprehensive protection [18, 31]. Addressing these challenges involves advanced vaccine formulations, enhanced diagnostics, and strategies to combat antibiotic resistance, aiming to improve MG infection management and control [6, 28].

5.3 Innovative Vaccine Development Approaches

Innovative vaccine development for Mycoplasma gallisepticum (MG) seeks to overcome current limitations and enhance immune responses. Recombinant vaccines incorporating virulence genes from MG and Mycoplasma synoviae target multiple pathogens for broader protection [19]. Combining live and inactivated vaccines may harness both types' benefits for robust immunity [26]. Adjuvants like chitosan enhance immune responses and reduce adverse reactions, offering potential for next-generation vaccines [20]. Incorporating multiple gene sequences for phylogenetic analysis improves vaccine development by enhancing strain diversity understanding [8]. Plant-based expression systems for multi-epitope peptide vaccines (MEPV) present a cost-effective alternative to traditional methods [1]. These strategies aim to enhance MG vaccine development, overcoming efficacy and dosing limitations while improving protection against MG infections in poultry [6, 28, 13, 1, 20].

5.4 Role of Local Strains and Combined Vaccination Strategies

Utilizing local Mycoplasma gallisepticum (MG) strains in vaccine development enhances efficacy by targeting regional pathogen profiles [18]. Combining live and inactivated vaccines leverages both types' strengths for comprehensive defense, with adjuvants like Montanide ISA70 enhancing stability and safety [18]. Incorporating recombinant proteins and specific adjuvants augments immune responses, targeting key MG antigens for specificity and effectiveness [30]. Focusing on local strains and combined strategies optimizes vaccine efficacy and controls MG infections, enhancing avian health and productivity [20, 31, 2, 10].

5.5 Future Directions in Vaccine Research

Future research in Mycoplasma gallisepticum (MG) vaccine development will explore multi-epitope vaccines targeting multiple antigenic sites for comprehensive protection [13]. Plant-based vaccine production offers a cost-effective alternative for large-scale manufacturing [1]. Optimizing vaccine dosages and administration methods is critical for efficacy and longevity, while understanding age-related immune responses tailors protocols to enhance efficacy [5]. Adjuvant formulations, particularly chitosan, require optimization for field conditions [20]. Advancing MG vaccine development involves translating research into practical applications to enhance poultry health and productivity, focusing on immune response mechanisms, diagnostic advancements, and effective management strategies [2, 3, 13].

6 Control Strategies for Mycoplasma gallisepticum

Addressing the challenges posed by Mycoplasma gallisepticum (MG) necessitates diverse control strategies to mitigate its impact on poultry health and productivity. The following subsection discusses biosecurity measures, a fundamental preventive strategy in poultry operations. Implementing stringent biosecurity protocols can significantly reduce MG transmission risk, thereby safeguarding flock health and enhancing production efficiency. This discussion outlines essential components of effective biosecurity practices and their implications for managing MG outbreaks.

6.1 Biosecurity Measures

Biosecurity is critical in controlling Mycoplasma gallisepticum (MG) spread in poultry operations. Effective protocols involve strict hygiene, controlled facility access, and regular health monitoring to prevent MG introduction and dissemination [21]. Neglecting biosecurity, as observed in Nepal, correlates with disease outbreaks and public health issues, highlighting its importance [21]. Differentiating field and vaccine MG strains is pivotal for epidemiological studies and outbreak management, with enhanced techniques aiding in designing targeted measures [22]. High sero-prevalence in breeder birds underscores the need for robust biosecurity in breeder operations [24]. In high-prevalence areas like parts of Pakistan, improved biosecurity and surveillance are essential [17]. Effective practices have controlled MG in Polish turkey flocks, demonstrating biosecurity's efficacy [23]. Challenges like limited diagnostics, low biosecurity, and restricted veterinary access hinder poultry health management, emphasizing comprehensive frameworks [4]. Vaccination is also crucial, complementing biosecurity to enhance flock health. A comprehensive approach integrating biosecurity, licensed strain vaccination, and continuous surveillance is vital for mitigating outbreak risks and safeguarding poultry health and productivity [21, 22].

6.2 Integrated Management Practices

Controlling Mycoplasma gallisepticum (MG) requires integrated management practices combining biosecurity, vaccination, and antimicrobial strategies to enhance poultry health and productivity. Exploring gut-respiratory microbiota interactions is crucial, as these communities significantly influence immune responses and pathogen resistance [10]. Probiotics in poultry diets offer a promising therapeutic strategy, enhancing gut health, immune function, and reducing pathogenic bacteria colonization [10]. Future research should focus on evaluating probiotics and microbiota-targeted interventions for effective integration into management systems. Vaccines designed for local MG strains, informed by genetic diversity studies, should complement biosecurity measures for comprehensive defense [31, 8, 13]. Integrating these strategies can enhance flock health, reduce disease outbreaks, and improve economic viability. This comprehensive framework addresses MG and other pathogens, mitigating antimicrobial resistance risks and promoting sustainable poultry production [21, 10].

6.3 Antimicrobial Stewardship

Antimicrobial stewardship is vital in controlling Mycoplasma gallisepticum (MG) by promoting responsible antibiotic use and minimizing antimicrobial resistance (AMR) development. Effective stewardship optimizes antibiotic selection, dosage, and duration to ensure efficacy while reducing resistance potential [21]. Tiamulin and spiramycin are effective for MG and Mycoplasma synoviae (MS) infections when used judiciously [14]. Balancing antibiotic use with enhanced biosecurity and vaccination programs is crucial for sustainable disease management. Plant-based vaccine production offers a promising alternative, reducing antibiotic dependence and maximizing safety and efficacy [1]. Antimicrobial stewardship, robust biosecurity, and innovative vaccination strategies are essential for mitigating AMR spread, protecting poultry health, and enhancing production efficiency [14, 21, 30, 28].

6.4 Future Directions in Control Strategies

Future control strategies for Mycoplasma gallisepticum (MG) should focus on novel vaccines, enhanced detection techniques, and understanding MG's ecological interactions with wild birds and other pathogens [7]. Robust PCR techniques are essential for tackling antibiotic resistance in Mycoplasma species [14]. Expanding Gene Targeted Sequencing (GTS) with additional genes and integrating it with other molecular methods will enhance MG epidemiology understanding, aiding effective control measure development [8]. Optimizing vaccine formulations, conducting large-scale trials, and incorporating additional adjuvants are critical for improving immune responses and stability. Field trials are necessary to evaluate optimized vaccines' efficacy across diverse poultry populations [19]. Exploring host-pathogen interaction mechanisms and testing therapeutic interventions in vivo can provide insights into novel treatment strategies [15]. Developing nuanced infection models incorporating host immune variability is crucial for understanding MG dynamics and tailoring interventions [9]. Future research should also develop cost-effective diagnostics and

enhance biosecurity and infection control measures [3]. Addressing these areas will improve MG infection control and poultry resilience against this pathogen.

7 Immunopathogenesis of Mycoplasma gallisepticum

7.1 Immune Evasion Mechanisms

Mycoplasma gallisepticum (MG) exhibits sophisticated immune evasion strategies, complicating infection management in avian hosts. A key mechanism is antigenic variation, allowing MG to alter surface proteins and evade host immune detection, thereby facilitating chronic infections and complicating vaccine development [2, 25]. MG also manipulates host immune responses by modulating cytokine production, which is crucial for immune signaling, thus evading clearance [16]. These strategies, including suppression of inflammatory responses and interference with immune cell functions, underscore the challenges in developing effective vaccines and therapies [5, 25, 6, 13]. Understanding these evasion tactics is essential for improving MG infection management in poultry.

7.2 Host Immune Response and Pathogenicity

The interaction between host immune responses and MG pathogenicity is crucial in determining disease outcomes in avian species. The host's immune system engages both innate and adaptive responses against MG, though efficacy varies with host genetics, MG strain virulence, and co-infections [23]. Innate immunity involves macrophage and dendritic cell activation and pro-inflammatory cytokine production, serving as the first defense. However, MG's modulation of these responses often results in suboptimal clearance and chronic infection, especially when compounded by other respiratory pathogens [23]. Adaptive immune responses, characterized by specific antibody production and T-cell activation, are crucial for long-term protection. MG's antigenic variation allows evasion and persistence, contributing to chronic infections and immunosuppression, posing challenges for vaccine development [25, 13, 2, 5, 20]. A comprehensive understanding of these interactions is essential for developing effective vaccines and therapeutic strategies.

7.3 Vaccine-Induced Immune Profiles

Understanding vaccine-induced immune profiles against MG is key to promoting protective immunity in avian species, especially given MG's immune evasion tactics [2, 25, 26, 13]. Effective vaccines aim to induce robust immune responses to protect against MG infections and reduce chronic respiratory disease incidence. Innovative candidates like the plant-derived multi-epitope peptide vaccine (MEPV) show promising immunogenicity, suggesting potential for inducing both humoral and cellular immune responses essential for combating MG [1]. Vaccine-induced immune profiles typically involve specific antibody responses and T-cell-mediated immunity, which are vital for neutralizing MG and preventing colonization. Given MG's capacity to evade immune detection, the ability of vaccines to elicit memory responses is crucial for ensuring long-term protection and rapid immune activation upon re-exposure [2, 25, 5, 9]. A thorough understanding of immune profiles elicited by various vaccine formulations is essential for refining vaccination strategies.

7.4 Future Research Directions

Future research on MG immunopathogenesis should focus on elucidating the complex interactions between MG and host immune responses, critical for advancing vaccine development and improving disease management strategies [25]. Investigating molecular mechanisms behind MG's immune evasion tactics, such as antigenic variation and cytokine modulation, will provide insights into pathogen persistence and adaptation to immune pressures. Exploring roles of co-infections and respiratory microbiota in shaping immune responses to MG is essential, given the influence of virulence mechanisms, host immune responses, and co-infection dynamics [2, 15, 13]. Developing advanced immunological models that account for host genetic variability and environmental influences will enhance understanding of host-pathogen dynamics and guide effective vaccine creation. Research should prioritize optimizing vaccine formulations and delivery methods to maximize immune activation and long-term protection. Exploring multi-epitope vaccines and plant-based production systems presents promising avenues for cost-effective and broadly protective vaccines. By addressing key

research areas, the poultry industry can significantly improve control measures against MG infections, reducing morbidity and mortality associated with chronic respiratory disease and enhancing poultry resilience [2, 13].

8 Conclusion

The survey elucidates the profound impact of Mycoplasma gallisepticum (MG) on avian health and the poultry industry, emphasizing the necessity for integrated management strategies. It underscores the importance of combining biosecurity measures, vaccination, and advanced diagnostics to mitigate the economic challenges posed by MG. Oil-based inactivated vaccines have shown promise in inducing immunity, providing a viable option for disease management. The synergy of serological and molecular diagnostics enhances detection precision, facilitating timely interventions.

Future research directions should prioritize the expansion of datasets and refinement of genotyping techniques to enhance their relevance across diverse poultry settings. A deeper exploration of cytokine responses in varied tissues and the inclusion of more MG isolates are crucial for understanding host-pathogen evolutionary dynamics. The role of respiratory microbiota in poultry health warrants further investigation to elucidate microbial interactions and their impact on disease control. Expanding sampling efforts to include diverse poultry environments, such as backyard flocks, will improve insights into pathogen transmission and inform control strategies.

Continued research should focus on in vivo testing of vaccine candidates and optimizing epitope selection to enhance vaccine efficacy. Addressing these areas will not only improve vaccine performance but also contribute to developing more effective treatments, bolstering poultry resilience against MG. Strengthening biosecurity practices is critical to reducing disease risks and addressing antimicrobial resistance, especially in regions with high MG prevalence.

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