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REVIEW ARTICLE

A review on Infectious Coryza in Chickens: Emergence, Diagnostic Tools, Prophylaxis and Therapy

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Abstract

Haemophilus paragallinarum (*H. paragallinarum*) or *Avibacterium paragallinarum* (*A. paragallinarum*) is a Gram-negative bacterium causing infectious coryza (IC) in chickens. Infectious coryza is an acute upper respiratory infection that causes significant economic and productivity losses worldwide. Despite the use of prophylactic measures and treatment, the infection persists due to antibiotic resistance and a superior advantage in its outer protective antigen, resulting in a complicated disease pattern. Definitive diagnosis of the disease is hindered due to major challenges that are related to the complicated bacteriological isolation of the bacterium, which could be isolated only during the acute stage of infection, in addition to the fastidious and slow growth pattern of the organism. Egypt, as a key supporter of the chicken sector, is constantly threatened by this insidious infection, necessitating the development of new technology to combat it. The significance of *A. paragallinarum* infection, the prevalence of serotypes, clinical signs, characterization, diagnostic tools, prophylactic approaches, and therapies are discussed in this review. This article aims to provide more knowledge about the disease organism, newer diagnostic and therapeutic techniques for efficient containment of the organism therefore reducing the disease's negative economic impact.

Keywords: *Haemophilus paragallinarum*, Infectious coryza, Hemagglutination inhibition, Antimicrobial resistance, Vaccination.

Introduction

Haemophilus paragallinarum (*H. paragallinarum*) or *Avibacterium paragallinarum* (*A. paragallinarum*) is a Gram-negative, non-motile, coccobacillus in the family *Pasteurellaceae.* The bacterium is a fastidious microorganism that can be inactivated rapidly outside the host [1]. Bacterial strains are classified into three serogroups (A, B, and C), which have nine hemagglutinin (HA) serovars (A-1 to A-4, B-1, and C-1 to C-4**)** [2]. *A. paragallinarum* is an important avian pathogen worldwide causing infectious coryza (IC); a highly contagious acute respiratory disease in chickens. It is associated with decrease in egg production up to 40% in layer flocks [3,4] . The disease is normally acute and spreads rapidly with high morbidity up to 60-80% in chicken flocks. The mortality may range from 1 to 15% and tends to increase when complicated by other pathogens [5]. In young chicks, *A. paragallinerum* causes diarrhea, decreased feed and water consumption and retarded growth, whereas the laying hens showed reduced egg production with respiratory distress [6]. This bacterium may share in the formation

of respiratory disease complex that leads to severe clinical signs with a negative economic impact on the poultry industry [7]. Mixed infection with other bacteria is common and lead to complicated IC cases as *Mycoplasma gallisepticum, Staphylococcus aureus* [2], *Ornithobacterium rhinotracheale* [8], *Salmonellae enterica* (e.g. *S.* Enteritidis and *S.* typhimurium) [9], *Pasteurella multocida* [10], *Escherichia coli*, and *Proteus* species [11].

The traditional definitive method for diagnosis of IC requires the isolation of suspected bacterium on an enriched media as blood or chocolate agar followed by extensive biochemical characterization to confirm the isolates [4]. Polymerase chain reaction (PCR) is now routinely performed for the identification of *A. paragallinarum* in nasal swabs and confirmation of the bacterium in the laboratories [12]. Also, serotyping of the isolates could be performed according to Kume serotyping scheme using specific antisera in hemagglutination inhibition test [13, 14].

The reasons of vaccination programs' failure against IC may be related to multiple *A. paragallinarum* serovars and the lack of cross-protection between them [15, 16]. Inactivated multivalent vaccines are used worldwide for the control of IC, most of them comprising serovars of serogroup A, B and C [5]. This review spots the light on to clinical disease of *A. paragallinarum*, virulence attributes and pathogenesis, susceptibilities to antimicrobial agents and validated vaccines for countering infection.

An overview of *A. paragallinarum* clinical disease

Infectious coryza can infect both broilers and layers [2]. The main economic impact of the disease is the increased number of culling rates in meat chickens, a decrease in egg production (10 to 40%) in laying and breeding hens, especially in multiage farms in addition to some mortality (2-10%) [3]. In case of uncomplicated outbreaks in which antibiotic treatment was used, a drop in egg production, averaging 15%, lasted for 6 weeks. Infectious coryza is now regarded as a disease limited to the upper respiratory tract. The main clinical signs are nasal discharge, conjunctivitis, swelling of the sinuses, wattles, and face. Some diseased birds showed diarrhea, decreased feed and water consumption, decreased growth in young birds and reduced egg production in laying flocks [6]. A single infection is mainly characterized by an acute disease with a short course (nearly two weeks). Whereas the duration of the disease is prolonged (up to seven weeks) in mixed infection with other bacteria [2, 8-11] or viral agents as *Infectious Bronchitis Virus* (IBV), *Infectious Laryngotracheitis* (ILT), *New Castle Disease Virus* (NDV) or *Pneumo Virus*. The latter leads to complicated IC disease resulting in increased culling rate of the recovered birds or chronically diseased chickens; those are considered carriers of the bacterium and act as the main source of infection.

Virulence attributes of *A. paragallinarum*

The virulence refers to the degree of pathogenicity of the bacteria and associated with its ability to invade, colonize and multiply in the host by using various tools as capsule and toxic substances. For *A. paragallinarum*, the hemagglutinin (HA) protein possesses a very crucial vital key role in the immunogenicity and pathogenicity of *A. paragallinarum.* The hemagglutination (HA) of *A. paragallinarum* has been attributed to a 210-kDa protein (HMTp210), although the biological role of HMTp210 protein is not well defined. The HMTp210-deficient mutants showed no HA activity and failed to induce hemagglutination-inhibition (HI) antibodies in immunized chickens Furthermore, HMTp210-deficient mutants have a decreased ability to adhere to HeLa cells and to produce biofilms on abiotic surfaces. According to virulence assays, the HMTp210-deficient mutants were confirmed to be less virulent than their isogenic wild-type strains. HMTp210 protein carries significant similarity to the

proteins of trimeric autotransporter adhesin (TAA) family, and recombinant HMTp210 expressed in *Escherichia coli* formed a trimeric structure. So, HMTp210 is a TAA that confers HA, cell adherence, and biofilm formation activities [17].

Bacterial capsules are mainly associated with virulence. Previous studies have confirmed that encapsulated bacteria are more virulent than non-encapsulated ones [18]. The capsule of *A. paragallinarum* has proved to be associated with colonization [19], but its role in lesion production is still controversial. *A. paragallinarum* mainly attached and multiplied on the surface of the chicken's nasal mucosa [20], which is mediated by the capsule. Thus, the lesions in chickens are mainly produced by the highly encapsulated organisms, whereas the non-encapsulated organisms are considered avirulent [21]. Moreover, this capsule may share in the resistance of *A. paragallinarum* against chicken serum bactericidal activity. When the encapsulated *A. paragallinarum* was treated with hyaluronidase, the capsule was destroyed and completely lost. Despite being recognized to be responsible for protective immunity, somatic antigens were unable to induce the process of adherence in non-encapsulated strains [22, 23]. Also it was confirmed that *A. paragallinarum* has outer-membrane proteins [24], which was proved to share similarities to those associated with iron regulation mechanisms in other pathogens such as *Pasteurella multocida* [25].

The ability to resist the lytic action of host complement is considered a well-known virulence-associated parameter [26]. Although avian complement activation pathways have not been well developed, bactericidal action of chicken sera is identified to involve complement, as has been noticed through the loss of bactericidal activity against bacteria including *A. paragallinarum* by heating at 56ºC for 30 min and subsequently restoring by addition of fresh sera [21]. These data indicate the importance of serum resistance in the pathogenesis of IC in chickens.

Pathogenesis of *A. paragallinarum* in chickens

The pathogenesis of *A. paragallinarum* after intranasal inoculation could be summarized in the following points: (i) adherence to ciliated mucosa of upper respiratory tract, (ii) the capsule and hemagglutinin antigens play an important role in colonization, (iii) toxic substances that released from the organism during proliferation. All are important in development of clinical signs. With immunosuppression or concurrent infection, the organism reached different organs producing lesions. The lesions include rhinitis, congested blood vessels, hyperplasia of mucous glands, acanthosis of nasal epithelium, progressive pneumonic lesions, focal hepatitis and fatty change in heart with lipid granuloma [27].

Prevalence of *A. paragallinarum* serotypes in Egypt

In 2000, Aly [28] monitored the characteristics and pathogenicity of 26 *A. paragallinarum* isolates recovered from 36 outbreaks of IC in Upper Egypt during a period from 1995 to 1999. All isolates were pathogenic for chicken embryos with a mean death time from 14 to 34 h. Twenty-three isolates varied in their virulence for chickens' embryos, whereas, three were non-pathogenic. Serological characterization adopting page serotyping scheme was applied using HI test in comparison with plate agglutination test. There was complete correlation for both tests for 18 *A. paragallinarum* isolates; 8 were serovar A, 4 serovar B, and 6 serovar C. For the remaining 8 isolates, three were not typable and five isolates were serotyped only by HI test that confirmed as 2 serovar A, 1 serovar B, and 2 serovar C.

In Upper Egypt during 2004, clinical, bacteriological and postmortem examinations of diseased broilers (n = 205) and layers (n = 162) of various ages and breeds suffering

from respiratory symptoms revealed 33% prevalence of *A. paragallinarium* with distribution of all serovars among isolates [29].

Another study was performed in Dakahlia Governorate to determine the prevalence of *A. paragallinarum*, where 180 samples were collected from diseased commercial layers, broilers, breeders, and native breed farms scattered all over the Governorate. Twelve isolates were identified and confirmed as *A. paragallinarum*, 8 of them were serovar A and the remaining 4 were serotype C. [30]

On the other hand, Fedawy and coauthors [31] performed phenotypic and genotypic characterization of *A. paragallinarum* isolated from 120 field samples (infra orbital sinus swabs) collected from layer chicken flocks in Egypt during the period from 2013-2015. The chickens suffered from respiratory symptoms suspected to be IC with marked drop in egg production. Molecular characterization of the isolates revealed nine *A. paragallinarum* isolates, four of them were serovar A, three were serovar C and two were serovar B.

Conventional identification of *A. paragallinarum*

Isolation and growth conditions

The process of isolation of *A. paragallinarum* is difficult due to: (i) the organism can be isolated only during the acute stage of infection; (ii) mixed infection with concurrent colonization from other bacteria is common; (iii) fastidious and slow growth pattern of the organism [32]. The organism requires enriched media as Brain Heart Infusion (BHI) broth supplemented with Nicotinamide Adenine Dinucleotide (NAD, 0.25 %) as supporting growth factor and 1% chicken serum for enhancement of bacterial growth [33]. Also, most strains of *A. paragallinarum* can grow under microaerobic or anaerobic conditions with 5-10% CO_2 at 37 ºC [34]. An alternative method to provide optimum atmosphere is the candle jar method [35].

A. paragallinarum can grow in 5 to 10 % sheep blood agar containing X and V factors as well as the feeder organism, *Staphylococcus aureus*, which was cross streaked perpendicularly on an *A. paragallinarum* isolate for the detection of satellitism phenomenon [36]. Moreover, the chocolate agar plate (CAP) supplemented with V factor is necessary for *A. paragallinarum* growth. Chocolate agar (CA) medium can produce more *A. paragallinarum* colonies, which are tiny dewdrop like [1]. However, fresh isolates from acute cases of IC showed big mucoid colonies [37]. In an earlier study in Egypt, phenotypic characterization for *A. paragallinarum* isolates showed dewdrop like colonies on BHI agar and CA after 24 h of incubation with the need of Nicotinamide adenine dinucleotide hydrogen (NADH) and microaerobic or anaerobic condition (5-10% CO_2) for growth [31].

Microscopical examination

A. paragallinarum is a Gram-negative, polar staining, non-motile and non-sporulated bacterium. In 24 h cultures, it appears as short rods, or coccobacilli 1-3 mm in length and 0.4-0.8 mm in width, with a trend for pleomorphic formation and the organism undergoes degeneration within 48-60 h, showing fragments and indefinite shapes [1, 7].

Biochemical characteristics

For *A. paragallinarum*, biochemical characters include the inability to reduce nitrates and absence of catalase activity. Furthermore, it can ferment glucose, sucrose, fructose, maltose, sorbitol, and mannitol but not galactose nor trehalose. In addition, it gives negative results for hydrogen sulfide, indole production and gelatin liquefaction, whereas litmus and

methylene blue milk are not changed [36, 38] (Table 1).

Table 1: The distinguish biochemical characteristics of avian *Haemophili*, *O. rhinotracheale* and *Pasteurella* species (modified from a previously published review [5])

Criteria	*O. rhinotracheale*	*A. paragallinarum*	*P. avium*	*P. volantium*	*Pasteurella* species taxon A
Catalase	-	-	+	+	+
Urease	+	+	-	-	-
Indole	-	-	+	-	V
ODC[b]	-	-	-	V	-
ß-Galactosidase	+	+	-	+	V
Sugar fermentation: (Acid production)					
Arabinose	-	-	-	-	+
Galactose	+	-	+	+	+
Maltose	+	+	-	+	V
Mannitol	-	+	-	+	V
Sorbitol	-	V	-	V	-
Sucrose	-	V	+	+	+
Trehalose	-	-	+	+	+

All species are Gram-negative rods. *A. paragallinarum*, *P. volantium*, *P. avium*, and *Pasteurella* sp. strain A are variable in their requirement for V factor for growth *in vitro*. *O. rhinotracheale*does not require V factor. +, positive (90%); -, negative (90%); V, variable reaction; ODC, ornithine decarboxylase.

Serological identification

Host's based diagnostics depend mainly on detection of antigen/serovar specific antibody in circulation; therefore, HI is an important test that is widely used. Also, several infrequent doubts were misted up over its sound conclusion to its effective correlation between infection/titer to protection level [39]. By the use of HI test, Chukiatsiri and coauthors [40] identified the presence of serovar B infection.

Some new studies stated that HI is not a confidential tool for diagnosis of *A. paragallinarum* as the rapid progress of antibodies is not likely to be induced in chickens infected with *A. paragallinarum* [31].

The HA/HI tests are currently the only tests used for the classification of *A. paragallinarum*. Page [41] classified *A. paragallinarum* isolates with the plate agglutination tests using whole cells and chicken antisera into serovars A, B and C. Blackall and co-workers [42] recommended the HI test to serotype the isolates by Page scheme. Also, Kume team [43] reported a scheme for serotyping depended on the hemagglutinating antigens obtained through potassium thiocyanate extraction and sonication in a HA test performed with glutaraldehyde-fixed chicken erythrocytes (GA-fixed RBC). The isolates were characterized according to their HI reaction with antisera prepared from rabbits against these different isolates. This scheme indicated that two of the three groups could be subdivided into three serotypes each,

forming a total of seven serotypes designated as HA-1 through HA-7. According to Blackall and Soriano [36], two separate serotyping schemes were used for the detection of *A. paragallinarum* on the serological level, Page [41] and Kume schemes [43]. In Egypt, Ibrahim *et al.* [29] tested 22 morphologically selected isolates and found that 15 of them had HA activity against fixed chicken erythrocytes then applied serological characterization using HI test that revealed the presence of different serotypes (A, B and C).

Molecular characterization of A. paragallinarum using polymerase chain reaction (PCR)

Diagnosis of IC in chickens was performed using a PCR assay [44]. PCR was very specific and sensitive for the detection of IC infection. PCR test is now performed for the identification of the HMTp210 target gene of *A. paragallinarum* from tracheal, infraorbital sinus and nasal swabs. Also, to assert the isolation of *A. paragallinarum* that grows in the laboratories [45]. A study of 18 *A. paragallinarum* isolates obtained from a number of IC outbreaks in broilers, layers and kampung chickens in several parts of Indonesia between 1991 and 1999 was performed [46]. Six field isolates were found to be positive for *A. paragallinarum* using PCR for detecting HMTp210 target gene. Whereas in another study [47], PCR detection of *A. paragallinarum* from 27 samples was studied in which 24 were confirmed positive by PCR. This assay was carried out with the negatively cultured samples, which confirmed that PCR could give better results than that used previously by the traditional culture methods. Eaves *et al.* [13] confirmed that PCR detecting HMTp210 target gene was highly sensitive in screening field samples serving as an easy and rapid diagnostic tool for IC.

In an earlier study [48], it was stated that the PCR detection of *A. paragallinarum* is efficient than the use of traditional culture even after 60 days post preservation at -20 ºC confirming a higher sensitivity of PCR for isolation and identification of *A. paragallinarum*. However, Fedawy and coauthors [31] performed a multiplex PCR as an alternative serotyping method using primer sets around the hypervariable region to amplify 0.8, 1.1 and 1.6 kbp fragments for serovars A, B and C, respectively. Multiplex PCR test was introduced previously [49] for serotyping of *A. paragallinarum*, targeted the hypervariable region of HMTp210 sequence, which encodes the HA antigen of the bacterium. Recently, a highly sensitive and specific probe-based real-time PCR targeting a highly conserved sequence in the *recN*, the DNA repair protein gene of *A. paragallinarum*, was used for the detection of *A. paragallinarum* from clinical samples of diseased poultry [32].

Antimicrobial susceptibilities of *A. paragallinarum*

The antimicrobial susceptibility testing of *A. paragallinarum* revealed that all isolates were sensitive to chloramphenicol, erythromycin, furoxone, gentamicin, nalidixic acid, neomycin, novobiocin, spectinomycin and tetracycline [50]. However, drug sensitivity test of five *A. paragallinarum* isolated from poultry in Taiwan between 1975 and 1980 revealed high sensitivity to erythromycin, oxytetracycline, ormetoprim and sulfamonomethoxine or sulfadimethoxine, moderate sensitivity to tylosin and streptomycin, and low sensitivity to sulfadiazine [51].

Investigation of IC in 16 poultry farms in various parts of Bulgaria yielded 10 strains of *A. paragallinarum* sensitive to streptomycin, tetracycline, chloramphenicol, gentamicin, erythromycin and spectinomycin [52]. Moreover, a broth microdilution method was used to examine the susceptibility of 75 *A. paragallinarum* isolates to ampicillin, erythromycin, neomycin, penicillin, streptomycin, and tetracycline [53]. Fifty-five (73%) out of 75 isolates were sensitive to all six drugs. The remaining 20 isolates were resistant to

streptomycin, with one of these isolates also being resistant to tetracycline and another was resistant to neomycin. No isolate showed drug resistance belonged to agglutinin serovar C, despite this being the most frequently identified serovar (27 of 75; 33.33%) in the study. On the other hand, the *in-vitro* and *in-vivo* efficacy of enrofloxacin against 15 field and reference strains of *A. paragallinarum* recovered from 13-16 weeks old chickens, kept separately in cages was estimated. The results showed that enrofloxacin was highly effective against experimental *A. paragallinarum* infections [54]. Furthermore, the susceptibility of 22 strains of *A. paragallinarum* isolated from different areas of India was estimated against ofloxacin, a quinolone derivative, and to 15 antimicrobial agents that used commonly. *A. paragallinarum* demonstrated the highest susceptibility to ofloxacin. The second highest susceptibility was found with the following five agents, thiamphenicol, oxolinic acid, ampicillin, chloramphenicol, and trimethoprim. Also, it was responded relatively well to the following five agents; doxycycline, oxytetracycline, sulfamethoxazole-trimethoprim, tiamulin and tylosin. A medium degree of susceptibility was found with kanamycin and spectinomycin. The strains of *A. paragallinarum* responded with low susceptibility to sulfamethoxazole, sulfadimethoxine and streptomycin, while seven isolates were resistant to streptomycin [55].

Whereas in Indonesia [46], the antimicrobial drug sensitivity test of *A. paragallinarum* isolated from chickens suffering from IC was investigated. An agar disc diffusion method was used to examine the sensitivity of 27 *A. paragallinarum* isolates of 23 local and 4 standard isolates (serotype A) to eight antimicrobial drugs (ampicillin, erythromycin, oxytetracycline, doxycycline, neomycin, streptomycin, colistin, and sulfamethoxazole-trimethoprim). Out of the 23 local isolates, 21 were sensitive to doxycycline, 19 isolates to ampicillin, 18 isolates to oxytetracycline, 17 isolates to sulfamethoxazole-trimethoprim, 16 isolates to erythromycin, and 13 isolates to neomycin, while 13 isolates were resistant to colistin and 11 were resistant to streptomycin.

In India, the antibiogram of *A. paragallinarum* isolated from the cases of IC in chickens was evaluated. Twenty-eight *A. paragallinarum* isolates from cases of IC as well as six NAD-independent *A. paragallinarum* were tested for their sensitivity to cloxacillin, cotrimoxazole, enrofloxacin, gentamicin, pefloxacin, ampicillin, cefalexin, and oxytetracycline. *A. paragallinarum* was sensitive to gentamicin (50%) and enrofloxacin (40.91%). NAD-independent *A. paragallinarum* was highly sensitive to gentamicin (66.67%) [56]. In another Indian study [57], the occurrence of IC in a commercial layer farm having a capacity of 22500 layers and 7500 growers was studied. *A. paragallinarum* isolates were sensitive to ciprofloxacin and gentamicin, moderately sensitive to pefloxacin, and resistant to norfloxacin and cephalexin. *A. paragallinarum* isolates were presented as multidrug-resistant (MDR) and were found resistant to sulphamethoxazole, amoxycillin, ampicillin, erythromycin, and tetracycline but sensitive to chloramphenicol, ciprofloxacin, and gentamicin. In Egypt, there is rare data about the sensitivity pattern of *A. paragallinarum* but there was a previous study performed in 2009 by Awadalla and coauthors [30] in Dakahlia Governorate where they applied antibiotic sensitivity test for 12 *A. paragallinarum* isolates and found the highest sensitivity toward enrofloxacin (91.6%), ampicillin (75%), ciprofloxacin (75%) and amoxycillin (75%), while the least sensitivity was toward neomycin (25%), streptomycin (25%) and penicillin G (16.6%).

Rajurkar *et al.* [58] revealed that all *A. paragallinarum* isolates were 100% sensitive to chloramphenicol, kanamycin,

enrofloxacin, and ampicillin, whereas 100% exhibited resistance to tetracycline and streptomycin, and 66% were resistant to cotrimoxazole. While in a recent research , Fauziah and coauthors [59] studied the antimicrobial susceptibility of *A. paragallinarum* isolates in Indonesia and revealed that all isolates were sensitive to ampicillin and amoxicillin, whereas 91.6% were sensitive to chloramphenicol. The isolates showed intermediate sensitivity to enrofloxacin (79.2%) and ciprofloxacin (54.2%). The resistance pattern of the isolates was 100% to erythromycin, 87.5% to tetracycline, 83% to streptomycin, 70.8% to each of doxycycline and kanamycin.

Acquired immunity produced by natural infection of *A. paragallinarum*

As stated previously [60], the chickens that were infected with IC during their growing period were generally protected against later drop in egg production. Experimentally infected chickens developed across serovar (Page scheme) immunity [61], while bacterins provided only serovar specific immunity [62]. Thus, the HA antigens were considered as protective antigens [63]. Furthermore, the capsule of the bacterin contains protective antigen; the immunogenic nature of the capsular antigen of *A. paragallinarum* has an ability to induce a protective antibody in the host [64].

Types of the available commercial *A. paragallinarum* vaccines

Commercial vaccines of IC are widely available around the world, typically based on inactivated *A. paragallinarum* strains [65]. Until now, most of these vaccines contained only Page serovars A and C. The concept of the bivalent vaccines was mainly based on the previous belief that Page serovar B was not a true serovar and serovars A and C based vaccines provided cross-protection. However, because it has now been conclusively shown that Page serovar B is distinct; some of the vaccines manufacturing companies tend to include serovars A-1, B-1, C-1, or C-2 in IC vaccines [8].

Beside the killed adjuvant vaccine, there are live vaccines available now. As mentioned previously, there is no satisfying, specific protective antigens against multiple serovars of *A. paragallinarum* have been identified so far, a problem of failure of cross protection is still present with this disease [65]. These live vaccines contain non-pathogenic mutated strains derived from serovars A or C parent by chemical mutagenesis creation. A good level of protection against challenge was obtained from either a virulent serovar A or C strain following eye drop vaccination with a non-pathogenic candidate vaccinal strain [66].

For vaccination of chickens against *A. paragallinarum*, usually a double dose vaccination with three weeks apart of aluminium hydroxide inactivated IC vaccine produced a long-term immune protection, which lasts for around 30-40 weeks after vaccination. Also, vaccination with live vaccines including avirulent strains of *A. paragallinarum* insinuate extremely close to natural infection, which was confirmed to induce a higher cross serovar protection as compared with inactivated vaccines, apart from easy, natural route of administration. Blackall *et al.* [67] confirmed a similar study, induction of a better cross serovar protection against various virulent serovars after administration of live vaccines containing live attenuated strains of *A. paragallinarum.*

Similarly, chemically mutated strains of the bacteria were also developed and produced a good level of protection that was noticed in experimental studies. Despite of this advancement inactivated or killed vaccines are still predominantly used widely around the world, probably due to fear about genetic transmutation of live strains of bacterium into more pathogenic serovars.

Protective efficacy conferred by infectious coryza vaccines

An alarming issue is the comparison between "local" and "international" vaccines. The major international manufacturing vaccine companies tend to base their vaccines on standard internationally recognized strains. These international vaccines are produced around the world on the basis that local variation is not sufficient to justify adding or removing strains. A number of research groups in South Africa [68] and in Argentina [69] have suggested that such international vaccines are not providing protection against the local variants of *A. paragallinarum*. There is a need for definitive cross-protection trials and researches to determine if "international" vaccines are indeed failing to provide protection against local variants.

Previously, the majority of the available IC vaccine(s) were single serovar based. These types of vaccines either provided a complete protection against homologous serovar(s) or partial protection against heterologous serovar(s). The decreased protective efficacy of the available vaccines over a time period could be attributed to the evolutionary changes in the bacterium and has greatly mystified and perplexed the poultry scientist and poultry business to its new epidemiologic spectrum and genotypic adaptations. Interestingly, the most effective protective antigen was the hemagglutinin of the polysaccharide capsule of this bacterium and was putatively considered as immuno-stimulating [70]. The inactivating agent also has a role in the protective efficacy of the inactivated vaccine. It is evidenced after multiple trials and apparently shown that thimerosal is the best inactivating agent over formalin. When it came to adjuvants, aluminium hydroxide is over mineral oil-based adjuvants in terms of a higher protective efficacy and less adverse reaction to the site of injections.

Vaccination failure against recent infections

Recently, the organism developed and acquired superlative advantage on its evolutionary growth and acquired distinct protein and lipid profiles on its outer membrane surface leading to mask the vaccine onslaught. So, the recent available vaccines against the circulating serovars are no longer more protective against new emerging serovars. The later puts several poultry farms on high risk to this re-emerging trend of infection outbreak(s) in the poultry operation(s). During 2010 in Thailand [40], the researches on isolates from Ecuador, Argentina, Zimbabwe along with its subsequent inclusion to commercial vaccines [71], besides, latest switch over of its host's range specificity [7], exclusively suggests organism's paradigm shift in its virulently and pathogenicity pattern, based on current global geological variations. In Egypt there is minimal data about the protective efficacy of the vaccine on combating the disease. So, that requires application of more researches on IC vaccines as proper prophylactic tools and its protective efficacy for monitoring its positive effect on disease control as the vaccines increase resistance to infection, decrease probability of infection and decrease shedding of the bacteria especially with the alarming problem of antimicrobial resistance.

Latest updates on therapeutic and prophylactic measures against *A. paragallinarum*

Despite the means of vaccination practices with application of strict hygienic measurement and all-in all-out system have a great tremendously success to overcome the disease, some of the recent IC vaccines are not totally capable to provide protection against the disease. So, the disease assumed fulminating potential in these circumstances and resulting in gradual and enormous outbreaks. In these circumstances, antibiogram susceptibility becomes the best second approach to overcome such consequent losses to vaccination failures. The perusal of literature(s) confirmed

different antimicrobial sensitivity results as well as a fluctuating pattern from regionally based pathotypes of this organism. The author Blackall [38] characterized many isolates of an Australian origin into five antimicrobial drug resistance patterns and similar work on Mexican isolates was endorsed later [72]. In a broader perspective, Asian countries particularly emanated the majority of the recent findings/observations on antimicrobial sensitivity studies [73]. These organisms were found to be susceptible to penicillin as well as few new penicillin generations such as amoxicillin, ampicilin, etc. Also, some isolates found to be partially affected by macrolide antibiotics such as erythromycin and third generation fluroquninolone like enrofloxacin. The majority of isolates have shown resistance mainly against sulphonamides and partially to aminoglycosides and tetracycline groups with rare sensitivity to gentamycin and oxytetracycline. As noted previously, the advent of vaccine against Asian isolates of *A. paragallinarum* especially at South East Asian countries didn't guarantee its good faith ever [58, 74].

Recently, western and developed countries afforded development of a vaccine much earlier including local strains. However, the occurrence of several cases of vaccination failures is due to the emergence of new biovariants. The best part of their disease control program was keen reorganization of ill effects of antibiotics to their public health domain and immediately abstained from antibiotic usage. Despite their failure in counteracting the disease outbreak(s), they continued to strive for research on new vaccines as well as newer strategy to vaccination procedure(s) and vaccine development. To this direction, many efforts were undertaken and one such important development was molecular designing and synthesis of recombinant hemagglutinating antigen but gave poor immune-protection [75].

Conclusion

A. paragallinarum is an important chicken pathogen causing severe upper respiratory tract infection that negatively affects the poultry industry. *A. paragallinarum* causes severe economic losses due to reduction of egg production and mortalities. Limitation of traditional identification methods, due to difficult isolation, has contributed to development of molecular methods for identification and characterization. For treatment, updated antibiotic sensitivity profile is required to select the best effective antibiotic in controlling infection due to the alarming problem of resistance. Vaccines are still the best prophylactic tool to this disease, however sometimes vaccination failure occurred due to mutational changes in protective antigen of *A. paragallinarum.*

Conflict of Interest

No conflict of interests is declared.

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الملخص العربي

مراجعة عن الزكام المعدى فى الدجاج : الظهور, أدوات التشخيص؛ وسائل العلاج والوقاية

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أخصائي بحث وتطوير-شركة ميدل ايست للقاحات -الصالحية الجديدة-الشرقية – مصر

تسبب بكتريا الهيموفيلاس باراجالينيرم أو أفيباكتيريم بارا جالينيرم وهي سالبة لصبغة الجرام مرض الزكام المعدي في الدواجن. يعتبر مرض الزكام المعدي مرض تنفسي حاد يؤثر علي الجهاز التنفسي العلوي مسببا خسائر انتاجية واقتصادية هائلة حول العالم. بالرغم من تطبيق الإجراءات الوقائية والعلاجية لكن العدوي مستمرة وذلك بسبب مقاومة المضادات الحيوية بالأضافة لاكتساب الطفرات في المستضد الوقائي الخارجي مما يؤدي إلي نوع معقد من المرض. تعوق بعض التحديات عملية التشخيص النهائي للمرض وذلك بسبب صعوبة وتعقيد في عزل البكتريا لأنها تعزل في وقت الإصابة الحادة من المرض ؛ كما أن العدوي المشتركة مع البكتريا الأخري شائعة بالأضافة الي صعوبة وبطء نمو البكتريا. تعتبر مصر بما أنها حاضنة بشكل كبير لصناعة الدواجن معرضة لتهديدات كبيرة من هذه العدوي كل عام مما يستدعي استراتيجيات جديدة لمجابهة المرض. تناقش هذه المراجعة التطور المرتبط بعدوي الهيموفيلاس باراجاينيرم, العترات السائدة, الأعراض المرضية, تصنيف البكتريا بالإضافة الي توضيح للوسائل الوقائية والتشخيصية. يكرس هذا لفهم أفضل للبكتريا والمرض عن طريق عرض وسائل تشخيصية وعلاجية حديثة وذلك لإحتواء المرض وتقليل أثاره الإقتصادية.