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REVIEW

Distribution, Infection, Diagnosis, and Control of *Avibacterium paragallinarum* in Poultry

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ABSTRACT

Avibacterium paragallinarum is widely distributed all over the world in poultry farms. The purpose of this review was to describe IC disease in chickens caused by *A. paragallinarum* in terms of incidence, pathogenicity, diagnosis, and management. The disease is characterized by upper respiratory affection that is represented by conjunctivitis, sinusitis, facial and wattle edema, growth retardation, a marked drop in egg production, and a high morbidity rate. Complications with other bacterial and viral infections and environmental stressors increase the severity of the clinical signs, lesions, and mortality rate. For serological evaluation of the bacterium, there were two schemes. Page scheme classified the bacterium into serovars A, B, and C, whereas Kume scheme divided it into serogroups I, II, and III. Page serovars were further classified and associated with the Kume serogroup. There are 9 *A. paragallinarum* serovars of Kume scheme represented as A-1, A-2, A-3, A-4, B-1, C-1, C-2, C-3, and C-4. Laboratory diagnosis of *A. paragallinarum* is based on conventional methods of isolation and identification as well as serotyping and molecular detection. Strict biosecurity measures are important for the prevention of such infections. However, inactivated polyvalent bacterins are widely used to prevent the possibility of infection. The lack of cross-protection among serovars is the major challenge in the vaccination program.

Keywords: Clinical signs, Incidence, Infectious coryza, Treatment, Vaccination

INTRODUCTION

Respiratory affections result in severe negative economic impacts on poultry production [1]. Snot or infectious coryza (IC) is a widely distributed cosmopolitan bacterial [2] and highly contagious acute upper respiratory disease of chickens caused by a bacterium of the Pasteurellaceae family, *Avibacterium paragallinarum* commonly known as *Haemophilus paragallinarum* [3]. As a result of phenotypic and genotypic characterization, taxonomic differences showed the designation of the bacterium as *A. paragallinarum* [4].

Chicken is the most susceptible host for *A. paragallinarum* and can acquire the infection mainly via aerosol droplets or direct contact with carrier birds [5]. The clinical syndrome of IC has been recognized since the 1930s [6]. Growth retardation and increased culling rate of broilers, drop in egg production of layers and breeders (10-40%), mortality (2-10%), and increased medication costs are the most common economic losses caused by IC [7]. Infection with *A. paragallinarum* is characterized by conjunctivitis, nasal discharge, facial edema, drop in egg production in layers, and high morbidity with a low mortality rate [8]. The epidemiology of the disease is complicated. However, outbreaks of IC are most common in multiple age farms. Severe cases of the disease were also recorded in intensive poultry production systems, especially in developing countries, where poor management conditions and the existence of multiple infections are common [9,10].

Page and Kume schemes subtyped *A. paragallinarum* into 3 serogroups (A, B, and C) and 9 serovars (A-1, A-2, A-3, A-4, B-1, C-1, C-2, C-3, and C-4) based on hemagglutination inhibition (HI) test [11]. Diagnosis of IC infection relies on conventional isolation and identification of the causative agent and serotyping [12]. However, recent molecular techniques are used for the rapid and accurate identification of *A. paragallinarum* [13]. Prevention and control of IC can be achieved through the application of strict biosecurity measures, vaccination, antimicrobial agents, and probiotic supplementation [14,15]. Inactivated autogenous water or oil-based bacterins, including *A. paragallinarum* of serovars A, B, and C, are commercially available for breeders and laying hens [16]. The applied vaccines should be crossly ponded with the

predominant local serovars. Moreover, an antibiotic sensitivity test is a must to overcome such an infection. Despite the presence of several antimicrobial agents that are effective in eliminating *A. paragallinarum* infection, the development of resistance is a common issue [17,18].

Therefore, this review article was designed to discuss IC disease caused by *A. paragallinarum* in poultry with emphasis on the disease incidence, pathogenicity, clinical and pathological signs, diagnosis, and control.

History

In Holland, De Blieck [19] described a disease in chickens termed as "contagious or infectious catarrh, roup, or cold" caused by *Bacillus haemoglobinophilus coryza gallinarum*. However, Elliot and Lewis [20] and Delaplane et al.[21] proposed the name *H. gallinarum* as a causative agent of IC based on bacteriological characterization and binomial nomenclature system. Both X (hemin) and V (nicotinamide adenine dinucleotide, NAD) factors were discovered as essentials for the cultivation of the bacterium in media [22-25]. As a result of discovering X-factor-independent isolates of the bacterium [26,27], *H. paragallinarum* became the name of the causative microorganisms of IC [28]. Therefore, *H. paragallinarum* was V-factor-dependent, but X-factor-independent although V-factor-independent strains have been recently identified.

Incidence

Table 1 presents different reports on the incidence of IC in birds such as poultry, quail, and emu in different countries.

Etiology

Avibacterium paragallinarum (formerly *H. paragallinarum)* is a fastidious, Gram-negative, polar staining, non-motile, and non-spore former coccobacillus of the family Pasteurellaceae [55]. There are 2 schemes for the serological classification of *A. paragallinarum*. Page scheme classifies the bacterium into 3 major serovars of A, B, and C using the plate agglutination test [27], while Kume scheme divides it into 3 major serogroups as I, II, and III using HI test [56]. Page serovars are further classified by the HI test associated with the Kume serogroup. Accordingly, Page serovars A, B, and C represent the modified Kume serogroups I, II, and III, respectively. The 9 *A. paragallinarum* serovars of Kume scheme are then classified into A-1, A-2, A-3, A-4, B-1, C-1, C-2, C-3, and C-4 [56,57]. Serotyping of *A. paragallinarum* strains is performed using specific antisera in HI test as described by Kume serotyping scheme [11]. Countries, such as the United States, Germany, Mexico, China, South Africa, Thailand, and Taiwan, reported the presence of serovars A, B, and C of *A. paragallinarum*. However, Japan and Australia reported only serovars A and C [39,58].

In 1989, new isolates of *A. paragallinarum* were identified in South Africa where they did not require nicotinamide adenine dinucleotide (NAD) for growth [49]. These isolated strains of the bacterium were regarded as NAD-independent. Most of them are Page serovar A [59] and some strains are serovar C [34]. The NAD-independent *A. paragallinarum* strains become more common than classic strains and they are incriminated in the production of airsacculitis and vaccination failure than NAD-dependent strains [34].

Pathogenicity

The pathogenicity and virulence of *A. paragallinarum* depend on the presence of hemagglutinin protein (HMTp210) which is important for the hemagglutination (HA) process [60]. The HMTp210 deficient mutants cause no HA and accordingly do not induce HI antibodies in vaccinated chickens. Besides, they indicate a decrease in their adherence to tissue cultures and biofilm production. Therefore, these mutants have less virulence than their wild-type strains.

The other essential virulence factor of *A. paragallinarum* is the capsule which plays an important role in the adhesion, colonization, and multiplication of the organism to the nasal mucosa of infected chickens [61]. The encapsulated bacterium is virulent and produces pathological signs, while the non-encapsulated one is regarded as non-virulent [62]. Thus, the somatic antigen of non-encapsulated strains of *A. paragallinarum* is unable to adhere to the host cells [63]. The presence of the capsule may help an increase in the resistance of the bacterium against the bactericidal activity of the host.

In the same context, the similarity of the outer-membrane proteins of *A. paragallinarum* to iron regulation mechanisms of other bacterial pathogens as *Pasteurellae* is demonstrated [64].

Susceptibility of Avian Species

All types of chickens in multiage flocks could be infected with *A. paragallinarum* [65]. Although chicken is the most common host of IC, some reports have confirmed the susceptibility of other avian species, such as ornamental birds [30], Japanese quail [11,66], emu [32], and pheasant in any age [42]. The disease has not been reported in turkeys [6]. Indigenous domestic local fowls are also liable to IC [51,67,68]. Intensive layer chicken farms after 20 weeks, especially on large-scale egg production complexes, and breeding farms are more vulnerable to IC infection than younger ages [5]. Moreover, the spread of IC to successive age groups usually happens within 1-6 weeks after moving chickens from brooder houses to growing batteries close to older groups of infected birds.

Table 1. *Incidence of Avibacterium paragallinarum infection in different countries all over the world from 1991 to 2022*

Country	Reference	Animal Species	Detection and Prevalence	Antibiotic Sensitivity
	Rajurkar et al.[29]	Layer	Six isolates of *A. paragallinarum* were characterized from 109 samples of adult chickens	All the isolates were sensitive to enrofloxacin, ampicillin, and kanamycin, and 100% resistant to tetracycline and streptomycin. Two isolates were sensitive to cotrimoxazole (33%)
	Priya et al.[30]	Ornamental birds	The *A. paragallinarum* isolates were morphologically and biochemically identified from ornamental birds	The bacterium was sensitive to gentamicin, ceftriaxone, tobramycin, chloramphenicol, and nitrofurantoin, but it was resistant to neomycin, sulfadiazine, tetracycline, enrofloxacin, metronidazole, and ciprofloxacin.
	Thenmozhi and Malmarugan [31]	Japanese quail	The cultural and molecular identifications of *A. paragallinarum* isolates from 53 samples of Japanese quail revealed the presence of 8 strains with an amplicon size of 500 bp.	All strains showed 100% resistance to ampicillin, neomycin, pefloxacin, cotrimoxazole, furazolidone, streptomycin, cephalexin, and amikacin. 90% resistance to gentamycin and 70% to oxytetracycline
	Nabeel Mohammad and Sreedevi [32]	Emu	The presence of *A. paragallinarum* was confirmed by PCR. The prevalcne was 30-72% among collected samples.	
China	Guo et al.[33]	White leghorn chicken	Forty strains of *A. paragallinarum* were isolated and identified from diseased chickens during 2019 to 2020. The HI test results revealed presence of 11 isolates with serovar A, 10 with serovar B, and 19 with serovar C	High sensitivity to sulfamethoxine and oxytetracycline was detected. Out of 40 A. *paragallinarum* isolates, sulfamethoxine with concentrations of 30%, 10%, and 15% had minimum inhibitory concentration values of 64 µg/mL, 128 µg/mL, and 256 µg/mL, respectively. However, 85% of strains showed minimum inhibitory concentration values of 64 µg/mL or more for oxytetracycline. The minimum inhibitory concentration values for β-lactamase (amoxicillin, ampicillin, and ceftiofur) were low, with 77.5%, 70%, and 92.5% of strains showed minimum inhibitory concentration values of ≤1 µg/mL, respectively.
	Chen et al.[34]	Layer, broiler, and breeder	The PCR detected 14/14 of the infected chickens in a challenge trial as compared with 13/14 for culture. In addition, PCR yielded 15/39 birds and 6/8 commercial farms positive as compared with 8/39 birds and 4/8 farms positive by culture. All positive farms by PCR had chickens showing the typical signs of IC, indicating that culture failed to confirm coryza on 2 farms that had the typical signs of the disease	
	Mei et al.[10]	Layer	The existence of *A. paragallinarum* Page serovar A was confirmed from chicken cases using isolation and a species-specific PCR test. Moreover, fowl adenovirus-4 was molecularly identified from these chickens as a concurrent infection	

Table 1. *Incidence of Avibacterium paragallinarum infection in different countries all over the world from 1991 to 2022 (continued)*

Country	Reference	Animal Species	Detection and Prevalence	Antibiotic Sensitivity
Indonesia	Poernomo et al.[35]	Layer	*A. paragallinarum* were found in 24 out of 30 samples (80%) from vaccinated layers. The isolates showed tiny, circular, transparent, dewdrop-like Gram-negative coccobacilli colonies based on Gram staining. The isolates were non-motile, negative in urease, catalase, indole, and oxidase tests and were able to ferment sorbitol, lactose, mannitol, and maltose	24 *A. paragallinarum* isolates were sensitive to ampicillin and amoxicillin (100%), 91.6% of isolates were sensitive to chloramphenicol, 79.2% sensitive to enrofloxacin, 75% to Fosfomycin, and 54.2% to ciprofloxacin
	Wahyuni et al.[11]	Quail	Five out of 9 strains (55.5%) from quails were identified as NAD-independent *A. paragallinarum* using traditional isolation methods. Three out of the isolated strains were serovar B	All strains were susceptible to amoxicillin and ampicillin, but resistant to amikacin, erythromycin, gentamycin, and tetracycline. In addition, 80% of strains were resistant to kanamycin and trimethoprim, 60% to chloramphenicol, and 20% to enrofloxacin
	Tangkonda et al.[36]	Layer	Four strains of *A. paragallinarum* were isolated from 12-layer chicken using conventional identification techniques. Serotyping of strains using plate HA method revealed that 2 were serotype B and the others were serotype C	
	Fauziah et al.[37]	Layer	Out of the total 30 samples from layer chickens, 24 (80%) were biochemically identified as *A. paragallinarum*	The isolated strains were sensitive to ampicillin and amoxicillin (100%), and chloramphenicol (91.6%), but resistant to erythromycin (100%), tetracycline (87.5%), streptomycin (83.3%), doxycycline and kanamycin (70.8%), and trimethoprim (62.5%)
Thailand	Akter et al.[38]	Layer	From 21 sinus and tracheal swabs of layer chickens, 3 only were positive for *A. paragallinarum* after cultural, staining, morphological, motility, and biochemical characterizations of the bacterium	Strains were sensitive to ciprofloxacin, chloramphenicol, and gentamicin, but resistant to ampicillin, amoxicillin, oxytetracycline, erythromycin, and sulphamethoxazole
	Chukiatsiri et al.[39]	Layer	Eighteen isolates of *A. paragallinarum* were confirmed by PCR. However, 10, 5, and 3 isolates were serovar A, B, and C, respectively	All isolates were sensitive to amoxicillin-clavulanic acid, but there was a high level of resistance to lincomycin, erythromycin, cloxacillin, and neomycin. The challenge test in 4-week-old layers showed that all isolates induced typical signs of IC and could be re-isolated at 7 days post-challenge

Table 1. *Incidence of Avibacterium paragallinarum infection in different countries all over the world from 1991 to 2022 (continued)*

Country	Reference	Animal Species	Detection and Prevalence	Antibiotic Sensitivity
Korea	Han et al.[40]	Layer	In the period from 2009 to 2012, *A. paragallinarum* was detected in 7 chicken farms using PCR and they were serotyped as serovar A by multiplex PCR. The serological surveys using the HI test showed high positivity for serovar A in rates of 86.4% in 2009, 78.9% in 2010, 70.0% in 2011, and 69.6% in 2012	Isolated strains showed susceptibility to erythromycin, gentamicin, lincomycin, neomycin, oxytetracycline, spectinomycin, and tylosin.
	Jeong et al.[41]	Layer and broiler	Twenty strains of *A. paragallinarum* were identified in chickens using HPG-2 PCR assay and biochemical tests. Sixteen out of 20 strains required NAD and an enriched CO_2 for growth, while one isolate needed increased levels of NAD and serum for good growth. Three isolates showed NAD-independent growth on blood agar under aerobic conditions. Three biochemical biovars were demonstrated. The 16 typical NAD-dependent strains were serovar A, however both NAD-independent strains and that with increased NAD dependency (variants) were untypeable	All strains were sensitive to amoxicillin-clavulanic acid, ceftiofur, gentamicin, and spectinomycin, but resistant to lincomycin, cloxacillin, and erythromycin. Variants were more resistant to antibiotics than the typical NAD-dependent strains
United States of America	Crispo et al.[42]	Broiler	Both *A. paragallinarum* and infectious bronchitis virus were detected in the respiratory tract and brain of 29-day-old broiler chickens	
	Crispo et al.[43]	Broiler, layer, and backyard chickens	Fifty-four samples represented as broilers (n = 40), layers (n = 11), and backyard chickens (n = 3) were examined. *A. paragallinarum* was identified by PCR from the respiratory tract and from extra-respiratory organs. Concomitant infections with infectious bronchitis virus and infectious bursal disease virus as well as *Mycoplasma* species, *Escherichia coli*, *Ornithobacterium rhinotracheale*, and *Gallibacterium anatis* biovar *haemolytica* were reported. Thirteen A. *paragallinarum* strains were serovar C2. Isolates of *A. paragallinarum* shared a unique enterobacterial repetitive intergenic consensus PCR	Isolates showed high minimum inhibitory concentration values for tetracycline
USA (Pennsylvania)	Kuchipudi et al.[13]	Broiler, layer and pullet	Real-time PCR was applied on 419 samples from broilers, layer pullets, and laying hens. Positive *A. paragallinarum* was detected in 94 samples based on culture isolation. Moreover, the recN PCR assay with HPG-2 based real-time PCR assay showed a PCR efficiency of 79%	
Bulgaria	Giurov [44]	Layer poults	Based on culturing and biochemical reactions, *A. paragallinarum* strains were detected. Strains were pathogenic for 8-week-old birds and poults and also induced death of 4-7-day-old chick embryos within 48 h of inoculation	The disk-diffusion method showed sensitivity of isolates for streptomycin, tetracycline, chloramphenicol, gentamycin, erythromycin, spectinomycin, furazolidon, imekil, cosumix, trimetoprim, and sulfadoxin

Table 1. *Incidence of Avibacterium paragallinarum infection in different countries all over the world from 1991 to 2022 (continued)*

Country	Reference	Animal Species	Detection and Prevalence	Antibiotic Sensitivity
Argentina	Sandoval et al.[45]	Broiler and layer	Seventeen complicated outbreaks of IC in layer, broiler-breeder, and broiler chicken's flocks were detected. Layer flocks were suffered from up to 35% drop in egg production, while broilers showed mortality 2-5%. *H. paragallinarum* was isolated in all of the outbreaks either as a pure or mixed infections from the liver, kidney, tarsal joints, and ocular globes. Serovars A, B, C, and untypable serovars were isolated in 8, 6, 1, and 2 outbreaks. The severity of these outbreaks was increased by concomitant salmonellosis, pasteurellosis, and mycoplasmosis. Under certain circumstances, *H. paragallinarum* was able to cause septicemia. Moreover, 10 of the farms were vaccinated against IC before the outbreaks	
Mexico	García et al.[46]	Layer	Two strains of *H. paragallinarum* were detected in layer chickens using PCR and conventional identification methods. They were NAD-independent, serovars B-1 and C-2, and pathogenic for susceptible chickens The strains were associated with drop in egg production up to 20% over a 3 weeks and mortality ranged from 0.1% to 0.2%	
Germany	Heuvelink et al.[18]	Dutch layer	Almost all 44 field strains of *A. paragallinarum* from 25 outbreaks showed sensitivity to antimicrobial agents that are used for the treatment of IC. However, a quarter of strains with high minimal inhibitory concentration of tetracycline showed *tet* resistance genes. Of most agents, low minimum inhibitory concentration results were determined for the 9 serovars reference strains, and negative PCR results for resistance genes	
Netherlands	Feberwee et al.[3]	Layer	Eighteen NAD-independent *A. paragallinarum* isolates were identified from outbreaks of IC in layer flocks based on isolation, biochemical identification, PCR tests, and serotyping. Molecular typing by ERIC-PCR and sequence analysis of the partial HPG2 region of *A. paragallinarum* were applied. All isolates were detected by the species-specific conventional PCR, but 33% of the isolates were missed by the species-specific real-time PCR. Sequence analysis showed a probe mismatch as a result of a single nucleotide polymorphism. Sequence analysis of the partial HPG2 region was in concordance with ERIC-PCR indicating presence of 2 major genotypes. Serotyping revealed existence of serovars A-1, A-2, and B-1. The pathogenicity test of one strain of the most prevalent genotype of serovar A-1 in layer hens induced typical disease of IC.	
United Kingdom	Welchman Dde et al.[47]	Layer	Strains of *A. paragallinarum* were identified from outbreaks in mixed-age layer flock. Coinfection with *Ornithobacterium rhinotrachale* and infectious bronchitis virus was identified by real time PCR	

Table 1. *Incidence of Avibacterium paragallinarum infection in different countries all over the world from 1991 to 2022 (continued)*				
Country	**Reference**	**Animal Species**	**Detection and Prevalence**	**Antibiotic Sensitivity**
Peru	Morales-Erasto et al.[48]	Pathogen-free chickens	Severe coinfection outbreaks of *A. paragallinarum* and *Ornithobacterium rhinotracheale* were detected through isolation, PCR, and sequencing of the 16S rRNA gene	Isolated strains were sensitive to amoxicillin-clavulanic acid and florfenicol. They were resistant to oxacillin and sulfamethoxazole-trimethoprim. Chickens inoculated with both *A. paragallinarum* and *Ornithobacterium rhinotracheale* showed severe clinical manifestations compared with that inoculated with *A. paragallinarum* alone
South Africa	Horner et al.[49]	Layer, broiler, and pullet	NAD-independent *H. paragallinarum* and *H. avium* were isolated from chickens in an overall age range of 14 days to 64 weeks. The whole cell protein profiles of NAD-independent *H. paragallinarum* isolates were identified from 5 different flocks but they were differed from that of a typical isolate	
Iran	Nouri et al.[50]	Backyard chickens	From 18 collected choanal swab samples, four (22%) isolates of *Av. Paragallinarum* were detected by culture methods and confirmed by the biochemical reaction of Catalase and Oxidase tests. PCR (HPG-2) indicated 12of 18 (66%) of sampled birds were infected with *Av. Paragallinarum*. (66%) positive reactions were detected by observing expected 500 bpb and using PCR (HPG-2) on swab samples.	The isolates were resistant to amoxicillin, oxytetracycline, streptomycin, trimethoprim/ sulfamethoxazole (up to 75%) and sensitive to cefalexin, ceftriaxone, enrofloxacin, florfenicol, gentamycin, linco-spectin, neomycin, doxycycline (50%), danofloxacin (75%), flumequine (50%), ofloxacin (75%)
	Beiranvand et al.[51]	Backyard chickens	*A. paragallinarum* were isolated from 7 out of 10 samples with typical IC clinical signs. Most isolates (4/7) showed the typical requirement for nicotinamide adenine dinucleotide (NAD) and an enriched CO2 atmosphere for growth. Three of the seven strains were obtained to be novel NAD-independent under anaerobic conditions.	All isolates were sensitive to gentamicin and spectinomycin. There was greater antibiotic resistance in the three NAD-independent isolates than in normal NAD-dependent bacteria.
Iraq	Rashid and Poeiecha [52]	Layer	An outbreak of IC in a poultry farm. The morbility was 80%.	
Egypt	Ibrahim et al.[53]	Layer	*A. paragallinarium* was isolated from 162 layers and 205 broiler chicken flocks in the Upper Egypt (33% Prevalence). Serovars A, B, and C were detected	
	Badr et al.[54]	Layer, broiler	From 41 different samples, only four (9.7%) were positive. Three positive samples (7.3%) were confirmed by PCR using HPG-2. Multiplex PCR indicated that all strains were of type B. All positive samples belonged to layer chickens.	

Epidemiology

Infection of *A. paragallinarum* usually occurs via the inhalation of infectious droplets and ingestion of contaminated feed and drinking water with infective nasal exudates [27]. Horizontal transmission of the disease commonly occurs through aerosol and direct contact. Recovered chronic carriers or sub-clinically infected chickens are important sources of IC transmission [8]. *Fig. 1* shows the infection and transmission of IC in poultry farms.

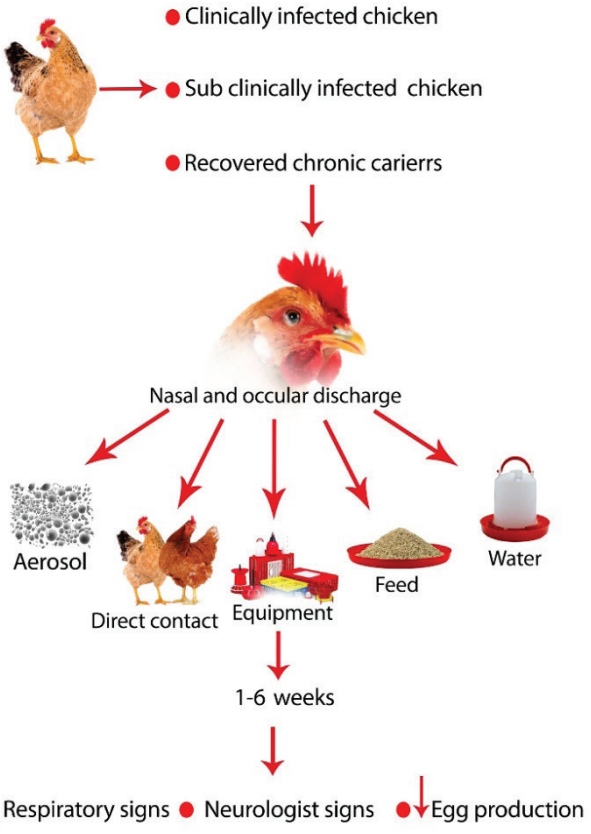

Fig 1. Transmission and infection of *Avibacterium paragallinarum* in poultry farms (The figure is designed by the corresponding author)

Clinical Signs and Pathology

The severity of clinical signs of IC depends on some factors, such as age, breed, feeding, management, parasitism, and mixed infections [69]. Besides, the clinical signs of the disease are independent of the infective serotype [39]. Infectious coryza is associated with acute respiratory distress and a decrease in egg production up to 40% in layer chickens [4]. The clinical findings are limited to the upper respiratory tract and appear as sneezing, nasal and ocular discharge, conjunctivitis, swelling of the infraorbital sinuses and wattles, and facial edema. Young chickens show decreased feed intake, reduced body weight, and diarrhea. A drop in egg production of layers and breeders may reach 10-15% and last for 6 weeks. Severe neurologic signs were also reported in chickens in California where *A. paragallinarum* infection was concomitant with the infectious bronchitis virus [42]. Subclinical form of IC infection is usually without signs but infected chickens are carriers and show intermittent shedding of the bacterium through the respiratory tract. The disease is associated with high morbidity of up to 60-80% and mortality ranges of 1-15% according to the complications with either concomitant infection or environmental stressors [70]. Infectious coriza is characterized as a rapid spread disease with a short incubation that does not last for more than 3 weeks although the duration of the infection can be prolonged and may reach 7 weeks in case of complications. The severity, duration, and mortality rate of IC may increase as a result of infections with bacteria, including *Pasteurella multocida* [45], *Ornithobacterium rhinotracheale* [48], *Gallibacterium anatis* [71], *Staphylococcus aureus* with avian influenza virus [72], *Escherichia coli* with *Proteus* [73], *Salmonellae enterica* [74], viruses, such as infectious bronchitis virus [42], infectious laryngotracheitis virus, and fowlpox virus [16,47], as well as bad environmental conditions [40].

Experimental infection of *A. paragallinarum* is usually associated with the appearance of typical upper respiratory disease signs but without mortality [71]. The bacterium adheres and colonizes the upper respiratory mucosa by both HA antigen and capsule, and then it proliferates and produces some toxic substances to induce the clinical signs. However, some studies have indicated the absence of clinical signs in the inoculated chickens which may be due to an increased level of lipid peroxidation by the epithelial surface and leucocytes in the systemic circulation [75]. The early response strategy against *A. paragallinarum* has been demonstrated in chickens through the anti-oxidant mechanism [76].

The post-mortem lesions of IC are restricted to the upper respiratory tract and reflect themselves as catarrhal to serous rhinitis, conjunctivitis, and sinusitis. However, complicated conditions result in chronic respiratory diseases, swollen head-like syndrome, airsacculitis, and septicemia, especially in broilers [16].

The microscopic observations include sloughing, disintegration, hyperplasia of mucosal and glandular epithelium, and hyperemia with infiltration of heterophil in lamina propria of the mucous membranes. Severe and complicated cases are indicative of severe subacute to chronic pyogranulomatous pneumonia, airsacculitis, pericarditis, perihepatitis, synovitis, and myositis [77]. Complicated immunosuppressant infections such as infectious bursal disease result in severe lymphoid

depletion of the bursa of Fabricius and prepare conditions for co-infections [78].

Laboratory Diagnosis

Conventional Phenotypic Characterization

Laboratory diagnosis of IC is based on conventional methods of isolation and identification of the causative agent. Swabs from nostrils, infraorbital sinuses, or trachea should be taken for the isolation process of *A. paragallinarum*. However, for the first time, Abd El-Ghany [79], and Odor et al [80] demonstrated the isolation of the bacterium from the non-respiratory organs, such as liver, kidney, and tarsus of septicemic cases. *Avibacterium paragallinarum* should be isolated during the acute stage (1-7 days) of infection to prevent complications that counteract the isolation process [81]. The bacterium grows well in brain heart infusion broth or on blood or chocolate agar containing supportive growth factors, such as 0.25% NAD or feeder organism of *Staphylococcus aureus* (V factor), hemin (X factor), and 1% chicken serum [41]. The organism grows at 37°C under microaerophilic or anaerobic conditions for 24-48 hours. Some isolates of *A. paragallinarum* are NAD-dependent, but others are NAD-independent. On blood agar plates, NAD-dependent *A. paragallinarum* isolates produce tiny dewdrop, circular, convex, smooth, non-pigmented, and non-hemolytic colonies that only grow near the feeder strain. Besides, NAD-dependent strains produce satellite growth after 24 or 48 h of inoculation, while NAD-independent strains produce no satellite growth [82]. Cultures from acute pathogenic strains of *A. paragallinarum* appear as big mucoid colonies, while those of non-pathogenic strains are much smaller colonies [83].

Avibacterium paragallinarum is a Gram-negative, non-motile, and non-spore former pleomorphic coccobacilli that appear as 1-3 µm in length and 0.4-0.8 µm in width with filament formulation. After 48-60 hours of incubation, the bacterium shows degeneration with the formation of fragments and indefinite shapes [11,41,84,85].

The biochemical identification of *A. paragallinarum* isolates has revealed negative reactions to catalase, oxidase, urease, indole, methyl-red, hydrogen sulfide, Voges-Proskauer, and gelatin liquefaction tests. The bacterium shows positive fermentation of lactose, maltose, sucrose, mannitol, glucose, fructose, and sorbitol with the production of acid, but does not ferment galactose or trehalose [36].

Traditional characterization of *A. paragallinarum* has some limitations. These limitations include isolation of the bacterium in the acute stage of infection, fastidious and slow growth nature of the bacterium, and the presence of a usual mixed overgrowth of other bacteria and faster-growing commensals [13]. The presence of NAD-independent *A. paragallinarum*, *Ornithobacterium rhinotracheale*, and NAD-independent strains of *Pasteurella* species increases the complexity of phenotypic detection of the bacterium [82].

Serological Tests

Hemagglutination Assay Test: The plate HA test using chicken antisera was used to classify *A. paragallinarum* into serovars A, B, and C according to the Page classification scheme [27]. Two of the three *A. paragallinarum* groups were subdivided into 3 serotypes each forming a total of 7 serotypes designated as HA-1 to HA-7. Thus, both Page and Kume schemes are mainly used for serotyping of *A. paragallinarum* strains [85].

Hemagglutination Inhibition Test: The HI test has been also recommended for serotyping of *A. paragallinarum* strains by Page scheme [57]. Kume scheme depended on the characterization of the isolated *A. paragallinarum* strains with specific rabbit's antisera using HI tests [56]. Yamaguchi et al.[86] demonstrated the importance of the HI test for the detection of the relation between the titer of infection and the protection level against IC. There are 3 types of HI tests. The simple HI test using whole bacterial cells of *A. paragallinarum* Page serovar A and chicken erythrocytes can detect antibodies only to serovar A [6]. The eracted HI test is based on using sonicated cells of *A. paragallinarum* and glutaraldehyde-fixed chicken erythrocytes and can detect only Page serovar C [36]. Most of the infected chickens with serovar C show a seronegative reaction [86]. Finally, the treated HI test that is based on using hyaluronidase-treated whole bacterial cells of *A. paragallinarum* and formaldehyde-fixed chicken erythrocytes is employed to detect Page serovars A, B, and C in vaccinated chickens [87]. Accordingly, the simple HI test is suitable for detecting infections or vaccinations associated with serovar A, the extracted HI test is used for vaccination associated with serovar C, while the treated HI test is good for infections and vaccination associated with all serovars. In an Egyptian study, Ibrahim et al.[53] reported 15 out of 22 *A. paragallinarum* isolates of layer chicken flocks, which showed HA against chicken erythrocytes with the presence of serotypes A, B, and C using the HI test. In Thailand, *A. paragallinarum* serovar B was detected in a layer farm using HI [85]. It could be concluded that the presence of antibodies against IC is not likely to be induced by *A. paragallinarum* infection, thus, HI may not be a reliable tool for the diagnosis of infection [88]. Page or Kume serogroups delineate three different immunovars [70]. No cross-protection among serovars has been found and the cross-protection within Page serovar B is not common [89]. There is generally good cross-protection among serotypes A1-A4. However, some of the serotypes (C1-C4) showed partial cross-protection [90]. Serovar B-1 is common in the Americas, Ecuador, Mexico, and Panama [91].

Enzyme-Linked Immuno-Sorbent Assay: Despite Enzyme-Linked Immuno-Sorbent Assay (ELISA) being specific and sensitive, it can detect antibodies only against *A. paragallinarum* Page serovars A and C. Accordingly, the monoclonal antibody-based ELISA has shown the potential for the diagnosis of IC, particularly based on Page serovar B [70].

Multiplex molecular-based serotyping is used for molecular serotyping of *A. paragallinarum* [92]. According to a recent study by Tan et al.[12], serovar A-2 contains a chimeric haemagglutinating HMTp210 gene caused by the recombination of serovar A-1 and serovar C-1 and this gene is enough to distinguish serogroups A, B, and C.

Molecular Techniques

Polymerase Chain Reaction: Polymerase Chain Reaction (PCR) techniques are a more rapid diagnostic means of *A. paragallinarum* infection, compared to conventional methods [3,46,51]. In comparison with the traditional methods, PCR is regarded as an accurate, sensitive, easy, highly sensitive, efficient, and reliable diagnostic tool for the detection of *A. paragallinarum* field isolates from any clinical samples [93]. Species-specific (HPG-2 PCR), DNA restriction endonuclease analysis, ribotyping, ERIC-PCR, real-time PCR, and 16S ribosomal RNA (rRNA) sequencing have been implemented in the rapid diagnosis of IC [90,94-96]. For example, a rapid HPG-2 PCR test is used after isolation to replace the biochemical tests and reduce the complexity and costs of other diagnostic techniques [97]. The HMTp210 gene, which encodes *A. paragallinarum* HA antigen, could be also detected using PCR [98].

A multiplex PCR is used to amplify 0.8, 1.1, and 1.6 kbp fragments for A, B, and C serovars, respectively [88]. Moreover, multiplex PCR can be used for serotyping of *A. paragallinarum* targeted HMTp210 gene [92]. This technique is employed for molecular identification of the bacterium using 16S ribosomal RNA (rRNA) sequencing [99]. Corney et al.[95] detected *A. paragallinarum* in the presence of other bacteria using a 5' Taq nuclease assay. Real time PCR is considered as the most sensitive and specific technique for the detection of the DNA repair protein gene of *A. paragallinarum* [13].

Therefore, molecular diagnostic methods can replace traditional cultural characterization methods for the epidemiological studies of IC. Furthermore, they would be much valuable for the quick and correct prevention and control measures against IC infection [99].

Prevention and Control

Biosecurity Measures

One-day-old chicks should be chosen from vaccinated breeder flocks and they should be kept away from the old flock during rearing. Depopulation of the infected or recovered flock which are reservoirs of infection is important. It has been documented that *A. paragallinarum* can survive in exudates at low temperatures for many days [84]. Accordingly, the crucial preventive measures include strict husbandry and management procedures, good cleaning and disinfection of the houses and equipment, and keeping houses vacant for 2-3 weeks before restocking [6]. Isolation of age groups of chickens on an all-in-all-out basis should be taken into consideration. According to Crispo et al.[43], high biosecurity standards and proper immunization of susceptible, multi-age flocks should always be implemented and adjusted as needed.

Vaccination

Infected chickens with Avibacterium *paragallinarum* during the growing period were protected against a drop in egg production in the laying period [100]. It has been found that IC bacterin produced in broth culture was more protective than that produced in the chicken embryo [101]. Inactivated IC bacterin is effective based on the relief of the clinical signs and the decrease in the bacterial re-isolation rate [40]. The ability of the IC vaccine to elucidate protective immunity relies on the stimulation of innate immune organs via recognition of immunostimulatory components, such as adjuvants and other intrinsic pathogen-associated molecular patterns (bacterial cell wall). The HA antigen of the bacterium [63] and the polysaccharide capsule are regarded as antigens of *A. paragallinarum* and they can induce protective immunity [102,103]. Most IC bacterins contain only a single serovar which provided complete protection against the homologous serovar or partial protection against heterologous serovar. Therefore, bacterins provided only serovar-specific immunity [104].

A bivalent bacterin containing *A. paragallinarum* Page serovars A and C [105], a trivalent bacterin containing serovars A, B, and C [105], and a tetravalent bacterin containing serovars A, B, C, and B variant [106] have been used to prevent IC infection in chicken flocks. There has been a cross-protection between *A. paragallinarum* serovars A and C. The bivalent bacterin depends on the concept that Page serovar B was not a true serovar, while serovars A and C-based bacterins provide cross-protection. Nevertheless, Page serovar B become distinct and commercial trivalent and tetravalent bacterins are available [107]. Serovars A-1, B-1, C-1, or C-2 are also used in IC bacterins [48]. Page serovars could be distinguished from each other as the antibodies for each serovar cannot protect chickens from the other serovars, but can protect against serovars of the same group. For instance, a bivalent vaccine that contains serovar A and C cannot provide protection against serovar B-1 infected chickens, while it protects chickens against serovars A-1, A-2, A-3, A-4, C-1, C-2, C-3, and C-4 infection [58].

The challenge study is still the best method to evaluate the protective efficacy of IC vaccines [108]. Aluminum hydroxide adjuvanted IC bacterin could be used in double doses with 3 weeks interval for increasing the immunity that ends 30-40 weeks post-vaccination of chickens. In another study, aluminum hydroxide gel and montanide ISA71 adjuvanted bacterins containing *Salmonella* Typhimurium and *Salmonella enteritidis* combined with *A. paragallinarum* serovars A, B, and C were prepared in Egypt [53]. Both vaccines were tested in 6-week-old layer chickens by inoculation of double doses of each vaccine 3 weeks apart. The results indicated that both bacterins were efficient in terms of induction of better immune response and higher protection rates in vaccinated chickens, as compared with non-vaccinated ones. A similar study was conducted by Akeila et al.[109] who reported that a combined bacterin against *A. paragallinarum* and *Salmonella enteritidis* could protect chickens against both bacteria and elucidated maximum antibody titers levels at week 6 post-vaccination. Furthermore, inactivated multivalent bacterins that compromise *A. paragallinarum*, infectious bronchitis virus, egg-drop syndrome' 76 viruses, and Newcastle disease virus have been developed to reduce the time and costs of vaccination [110,111].

A virulent or live attenuated strain of *A. paragallinarum* was used for the production of live IC vaccines. Although living IC vaccines showed better cross-serovar protection when compared with inactivated vaccines, genetic transmutation of live *A. paragallinarum* strains into more pathogenic serovars is possible [112]. Thus, inactivated vaccines are still widely used around the world.

The protective efficacy of the IC vaccines decreases over time due to the continuous changes in the antigenic structure of *A. paragallinarum* and the development of new biovariants. The absence of local pathogenic serotypes of the bacterium in vaccines and the presence of multiple serovars with lacking cross-protection among them results in ineffective vaccination protocols [96,106]. Ideal vaccines against IC should induce protective immunity and decrease the possibility of infection and bacterial shedding. According to Conde et al.[113], 56 chicks were subcutaneously vaccinated at the hatchery with 0.1 mL of the Hepa Inmuno NC vaccine including bacterial antigens of *A. paragallinarum* (serogroups A, B, variant B, and C). On day 31 of the mentioned study, the broilers were challenged with three serogroups A, B, or C of *A. paragallinarum*. On days 2 and 5 post-challenge, the clinical signs were recorded and the infraorbital sinuses were sampled for the presence *of A. paragallinarum*, respectively. The vaccine could reduce the number of broiler chickens with clinical signs after a challenge with serogroup B, and significantly fewer vaccinated broilers were positive for the presence of *A. paragallinarum* after challenge with serogroup C. On the other hand, no significant protection was observed when broiler chickens were challenged with *A. paragallinarum* from serogroup A necessitating the need for further cross-protection studies on vaccines to include all *A. paragallinarum* strains in a vaccine, especially a serogroup A.

Treatment

Despite the application of strict hygienic measures and using of prophylactic vaccines, outbreaks of IC are still worldwide. Vaccines provide incomplete protection against the disease. Accordingly, using antimicrobials either in feed or drinking water is a must to overcome such infection. Many antibiotics can alleviate the severity and course of IC, however, no antibiotics have a bactericidal effect on *A. paragallinarum*. The development of bacterium resistance since the presence of multidrug-resistant plasmid has been reported [84,114]. For instance, more than 75% of *A. paragallinarum* isolates were found resistant to some antibiotics in Taiwan [115]. In addition, discontinued treatment results in relapses and the development of persistent carrier birds [116]. Thus, the choice of appropriate antimicrobial against *A. paragallinarum* infection should be taken into consideration as the treatment can only reduce the severity of the clinical signs but not completely cure and eradicated the disease [14]. According to Wodegebriel et al.[117], the medicinal plant families including Solanaceae, Rutacceae, and Maliaceae have been more frequently used by farmers to prevent and treat infectious diseases of poultry, such as IC.

Effective Antibiotics

An early study by Rimler [118] demonstrated that isolates of *H. paragallinarum* were susceptible to erythromycin, chloramphenicol, gentamicin, nalidixic acid, furoxone, novobiocin, neomycin, spectinomycin, and tetracycline. However, in Taiwan, Lu et al.[119] found that *A. paragallinarum* isolates were sensitive to oxytetracycline, erythromycin, sulfamonomethoxine, sulfadimethoxine, ormetoprim, tylosin, and streptomycin. Sensitivity to tetracycline, chloramphenicol, streptomycin, gentamicin, erythromycin, and spectinomycin was also reported for 10 *A. paragallinarum* Bulgarian isolates [120], while susceptibility to erythromycin, neomycin, ampicillin, penicillin, streptomycin, and tetracycline was detected in 73% of 75 isolates [114]. Regarding the effectiveness of quinolone derivative against *A. paragallinarum* infection, isolates were sensitive to enrofloxacin [121], ofloxacin [122], and ciprofloxacin and pefloxacin [123]. There were also reports on the sensitivity of *A. paragallinarum* to a combination of sulfachloropyridazine/trimethoprim [124], and sulfamethoxazol/trimethoprim [122,125]. It should be mentioned that sulfa drug compounds may cause a decrease in egg production in layers and their overdoses may be

toxic. Streptomycin, erythromycin, sulfodimethoxine, tylosin tartrate, and spectinomycin were also used successfully [5]. Isolated Indian strains of *A. paragallinarum* showed that 28 NAD-dependent isolates were sensitive to gentamicin (50%) and enrofloxacin (40.91%), while 6 NAD-independent isolates revealed high susceptibility to gentamicin (66.67%) [126]. Rajurkar et al.[29] demonstrated that all Indian *A. paragallinarum* strains were 100% sensitive to chloramphenicol, enrofloxacin, kanamycin, and ampicillin. The antimicrobial susceptibility test of 24 *A. paragallinarum* Indonesian isolates revealed that all isolates were sensitive to ampicillin and amoxicillin (100%), and 91.6% of isolates were sensitive to chloramphenicol. The isolates were 79.2% sensitive to enrofloxacin, 75% to Fosfomycin, and 54.2% to ciprofloxacin [35]. Recently, 100% of *A. paragallinarum* isolates were susceptible to ampicillin and amoxicillin, while 91.6%, 79.2%, and 54.2% were sensitive to chloramphenicol, enrofloxacin, and ciprofloxacin, respectively [37].

On the contrary, some strains of *A. paragallinarum* showed resistance to cloxacillin, erythromycin, ampicillin, and lincomycin [127] as well as neomycin, cotrimoxazol, amikacin, and cephalexin [128].

As a result of poor vaccine protective efficacy and antibiotic resistance, stimulating the production of antimicrobial peptides is an innovative antimicrobial strategy for the prevention of IC [129]. Some pro-inflammatory cytokines such as Il1β are produced at a high level and induced β-defensins to remove *A. paragallinarum*.

Conclusion

It could be concluded that IC is an important disease of economic importance in the poultry production system. Accordingly, there is a need to conduct more studies addressing the disease epidemiology, diagnosis, prevention, and control.

Competing Interests

The authors declared that there are no competing interests.

Authors' Contributions

WAA suggested the subject of study and wrote the draft of the manuscript. DB contributed to gathering the data, designed the original image of the study, and revised the draft of the manuscript. All authors revised and approved the final version of the manuscript.

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