An updated comprehensive review on ornithobacteriosis: A worldwide emerging avian respiratory disease

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Abstract
Ornithobacteriosis is an important emerging respiratory disease of domestic and wild birds caused by *Ornithobacterium rhinotracheale* (ORT) bacterium. The disease has been detected in some countries since 1980, which rapidly spread worldwide later on. Ornithobacteriosis can transmit either horizontally or even vertically. Infection with ORT is mainly characterized by respiratory distress, poor performance, acute death, and a drop in egg production. However, the most characteristic necropsy lesions of dead turkeys and chickens are yoghurt-like airsacculitis and pneumonia, usually unilateral. Unfortunately, infection with ORT was misdiagnosed in most of the poultry flocks due to similarity with other respiratory pathogens and the lack of the ideal protocols for diagnosis. Recently, some molecular and serological techniques have been used to detect the infection. Treatment of ORT with antibiotics is very difficult and variable as a result of acquired resistance. Many vaccines have been developed to counteract such infection in broiler, layers, and breeder chicken and turkey flocks. Inactivated, live, and sub-unit vaccines have been used with satisfactory results. Thus, this review paper aimed to address ornithobacteriosis, emphasizing the distribution, transmission, clinical picture, diagnosis, and disease control.

Keywords: Diagnosis, Incidence, ORT, Treatment, Vaccination.

Introduction
Respiratory infections of poultry are regarded as very important problems that cause high economic losses in the production system. One of these infections is ornithobacteriosis. It is a relatively novel emerging respiratory contagious disease among turkeys and chickens caused by *Ornithobacterium rhinotracheale* (ORT) bacterium. The bacterium is a highly polymorphic Gram-negative rod, non-motile or spore former, and belongs to genus nov., species nov. in the rRNA superfamily V and family Flavobacteriaceae (Vandamme et al., 1994). Ornithobacteriosis induces severe adverse negative impact on the poultry industry worldwide. Poor growth rate, acute mortalities, increasing the medication costs, high condemnation rates at processing, and decreasing the quantity and quality of eggs and hatchability are the economic losses of infection (Chin et al., 2013). The disease showed rapid evolution and spread all over the world with increase in the incidence rate. Ornithobacteriosis is mainly characterized by respiratory manifestations with the presence of yoghurt-like fibrinous exudates in the airsacs and uni/or bilateral lung consolidation (Hafez, 1996; Banani et al., 2001). However, the severity of the clinical picture is affected by the presence of other complicating infectious agents and non-infectious environmental conditions along with some virulence factors (van Empel and Hafez, 1999; Barbosa et al., 2019). Accordingly, ornithobacteriosis may be regarded as a part of a complex of other respiratory viral and bacterial pathogens that synergize to induce the infection (Welchman et al., 2013; Kursa et al., 2021). Definitive diagnosis of ornithobacteriosis is based on isolation and identification of ORT bacterium using either conventional phenotypic methods (De la Rosa-Ramos et al., 2018; Hassan et al., 2020) and/or molecular techniques (Ellakany et al., 2019; Veiga et al., 2019; Hassan et al., 2020; Karimi-Dehkordi et al., 2021). Despite the fact that ORT infection can be successfully treated with antibiotics, the bacterium can rapidly develop antibiotic resistance (Devriese et al., 2001). Therefore, some trials have been undertaken to produce inactivated, live, and sub-unit vaccines to counteract ORT infection (Lopes et al., 2002; Schuijf et al., 2006; Ghasemipour et al., 2020).

This review paper aimed to address ornithobacteriosis, emphasizing the distribution, transmission, clinical picture, diagnosis, and control of the disease.

The worldwide incidence and distribution
Ornithobacteriosis has been detected in domestic and wild birds with respiratory conditions in several countries worldwide. Early in 1987 in Hungary, *Pasteurella* species-like organisms were isolated from ducks with respiratory signs. In addition, *Riemerella anatipestifer* like bacteria was found in turkeys showing respiratory affection in 1991 and 1992 in Germany. However, in 1991 in South Africa, highly pleomorphic Gram-negative rods were isolated from a
28-day-old broiler chicken flock suffering respiratory manifestations, mortalities, bad performance, foamy yolk and airsacculitis and pneumonia (van Beek et al., 1994). Moreover, in the Netherlands and Germany in 1993, respiratory problems, poor growth rate, and acute mortalities have been observed in turkey and chicken broiler flocks (Hafez et al., 1993; Hijz et al., 1994; van Beek et al., 1994). Later on, the disease was seen rapidly spreading across many countries like the USA (Charlton et al., 1993), France (LeÂorat, 1998; El-Gohary and Sultan, 1999; El-Gohary et al., 2010; Asadpour et al., 2005) and Peru (Arns et al., 1994), polymorphic Gram-negative rod bacterium (Charlton et al., 1993), and TAXON 28 (van Empel and Hafez, 1999). However, ORT was genotypically and taxonomically classified in the early 1990’s as a new genus and species (Hafez et al., 1993; Vandamme et al., 1994). The species rhinotracheale belongs to genus Ornithobacterium. The bacterium was classified as a Gram-negative and highly pleomorphic rod of the rRNA superfamly V, in the taxonomic neighborhood of the genera Cytophaga, Riemerella, and Flavobacterium (Vandamme et al., 1994; Canal et al., 2005). The genus Ornithobacterium belongs to the family Flavobacteriaceae (Hafez et al., 1994), which also includes the genus Riemerella with R. anatipestifer and the genus Coenonia with C. anatina. Besides a new species named Candidatus Ornithobacterium hominis sp. nov., ORT is the only species described within the genus Ornithobacterium. Before the first taxonomic identification of ORT bacteria, misdiagnosis of infection was common, and the causative agent was attributed to some other bacteria such as Pasteurella, Riemerella, Bordetella, or Haemophilus (Hafez et al., 1993; Bragg et al., 1997) as well as other viruses as Pneumovirus (Marien et al., 2005).

The Pathogenicity and persistence of ORT organisms in the host are influenced by environmental conditions, biofilm formation, and coinfection with other organisms (Marien et al., 2005; De la Rosa-Ramos et al., 2015, 2018). Serotypes A, B, C, D, and E of ORT showed different virulence factors with variable adherence profiles (Chansiripornchai et al., 2007; De Haro-Cruz et al., 2013). The tissue’s adherence and colonization with ORT are associated with the presence of some virulence factors such as hemagglutinin, neuraminidase, and other glycoprotein (Kastelic et al., 2013; De la Rosa-Ramos et al., 2018). Hemolytic isolates of ORT have been described and differentiated from R. anatipestifer isolates (Walters, 2014). Figure 1 shows the factors that influence the severity of ornithobacteriosis infections.

Host susceptibility and transmission of infection

Ornithobacteriosis is incriminated in infection of all commercial avian species and wild birds in many countries of the world. There is a wide range of birds that could be infected with ORT or carry the bacterium in their respiratory tracts. The bacterium is present in the apparent healthy captive and free-ranging non-galliform species. Turkey, chicken, duck, goose, guinea fowl, gull, ostrich, partridge, pheasant, pigeon, quail, and rook showed ornithobacteriosis (Charlton et al., 1993; Anonymous, 1995; Devriese et al., 1995; Buys, 1996; Hafez, 2002). Infection with ORT was first
Table 1. The incidence of ornithobacteriosis in Egyptian poultry flocks.

| Findings                                                                 | References                              |
|-------------------------------------------------------------------------|-----------------------------------------|
| The incidence rate of ORT was demonstrated as 8.6% in layer chicken flocks showing depressed egg production. | Youssef and Ahmed, 1996                 |
| The vertical transmission of ORT is possible as the bacterium has been associated with hatching problems in chicken and turkey eggs. | El-Gohary, 1998                        |
| Concomitant ORT and *E. coli* infections has been recorded in chicken broilers with an incidence rate of 8.5% for ORT. | El-Gohary and Awaad, 1998              |
| Both ORT and *Pasteurella haemolytica* have been isolated from commercial larger chickens in percentage of 4.3%. | El-Gohary *et al*., 1998               |
| ORT has been isolated from meat-type breeder chickens in incidence of 3.2%. | El-Gohary and Sultan, 1999             |
| The incidence of ORT infection in 75 broiler chicken farms representing different Egyptian governorates was carried out. The bacterium has been biochemically and molecularly characterized from air sacs (3.5%), lungs (2.2%), trachea (0.44%), pericardium (0.22%) and liver (0.22%). All isolates were belonging to serotype A, and were sensitive to amoxicillin and chloramphenicol. The results of pathogenicity test revealed that the isolated ORT strains were pathogenic for 2 weeks old chickens, while other infection with *E. coli* and infectious laryngotracheitis increased the severity of the clinical picture. | Abd El-Ghany, 2000                     |
| The incidence of ORT infection in chicken flocks in Upper Egypt (Assuit governorates) has been demonstrated in percentage of 5.8%. | Amal, 2002                              |
| In El-Sharkia governorate, ORT has been isolated and characterized rabbits. | Shahata and Ibraheem, 2004             |
| ORT was isolated from chicken embryos and layers and this indicated possibility of vertical transmission of the bacterium. In addition, the in-vitro antibiotic sensitivity test results showed that amoxicillin, enrofloxacin and tetracycline were the most effective antibiotics against ORT. | Shahata *et al*., 2006                  |
| In Kafr El-Shiekh governorates, ORT infection has been detected and investigated in rabbit’s flocks. | Elbestawy, 2010                         |
| Both ORT and *M. gallisepticum* have been discovered in chicken flocks in El-Behera and Kafr El-Sheikh governorates. The rate of ORT isolation was 7.27%. | Hegazy *et al*., 2015                   |
| The positive correlation between the presence of antibodies against ORT and decreased body weight in broilers has been proven. Besides, ORT isolates resistant to gentamycin, norofloxacin, ciprofloxacin, cefotaxim, sulphamethoxazole trimethoprim and colistin sulphate, but were sensitive to amoxicillin, ampicillin and doxycycline. | Masoud *et al*., 2015                   |
| Five broiler’s ORT strains have been detected and showed 94%-98% similarity to some American and Asian ones after sequencing of 16s rRNA. | El-Abasy *et al*., 2016                 |
| Interestingly, ORT has been isolated and characterized from 21 out of 300 (7%) diseased rabbits showed respiratory manifestations, decreased feed intake with poor performance and expectoration of blood stained mucus just prior to death In Kafr El-Shiekh governorate. All ORT isolates were serologically belonging to serotype A. All of ORT strains were sensitivity to sulphamethoxazole/trimethoprim, spiramycin, neomycin, ampicillin, amoxicillin, ciprofloxacin and tetracycline, while non-sensitive to penicillin, streptomycin, clindamycin, lincomycin, gentamycin, vancomycin and colistin sulphate. Induction of experimental ORT infection in 3-months-old rabbits were successfully carried out and the animals showed respiratory disease picture. Moreover, treatment of experimentally infected animals with sulpha-trimethoprim and coconut oil relief the severity of the lesions. | Ellakany *et al*., 2019                 |
| Conventional isolation of ORT revealed presence of the bacterium in an incidence rate of 11.66%. Broilers and layers isolates of ORT were identified molecularly using PCR. These ORT isolates were closely related to Asian, European, and American strains (98%–100%). The role of live infectious bronchitis vaccines on the severity of ORT infection was investigated after experimental infection of broiler chickens. The results revealed that live infectious bronchitis vaccines that are usually used in the Egyptian poultry field may concomitantly increase the pathogenicity of ORT infection. This combination can led to decreasing in body weight, weight gain, and increasing in feed conversion ratio. | Continued |
described in turkeys, the main susceptible host (Hafez, 1996; Karimi-Dehkordi et al., 2021, Kursa et al., 2021), as well as in chickens (Roussan et al., 2011; Hassan et al., 2020). It has been reported that the incidence rate of ORT in turkeys was higher (41%) than that in chickens (6.9%) (Hauck et al., 2015). Besides, the disease has been reported in the Egyptian Muscovy and Balady ducks (El-Abasy, 2008), and the bacterium has been molecularly detected in pigeons and birds of prey (Tsai and Huang, 2006; Thieme et al., 2016). Interestingly, ORT has been demonstrated in rabbit farms with respiratory problems in some Egyptian governorates (Shihata and Ibraheem, 2004; Attia, 2008; El-Abasy et al., 2016).

Ornithobacteriosis spreads horizontally through inhalation and direct contact or indirectly through the drinking water (Chin and Charlton, 2008). Provide strong evidence of vertical transmission (from the hen to the egg through the ovary), the entrance of the bacterium via eggshell is different. It is also probable since ORT was isolated from reproductive organs, infertile and hatching eggs, and from dead embryos (Tanyi et al., 1995/1996; El-Gohary, 1998; Shahata et al., 2006). The bacterium was also found on the eggshells and in the yolk sacs of day-old chicks but at very low incidence (1%) (van Empel, 1997). This type of transmission can occur either trans-ovarian or by cloacal contamination (van Empel, 1997). Experimental studies showed that ornithobacteriosis infected turkey breeder hens showed survival of the bacterium in the ovary and oviduct without signs (Back et al., 1996, 1998a; Nagaraja et al., 1998).

Wild birds may also be considered as an important source of infection to the commercial poultry flocks. Ornithobacteriosis is regarded as a threatening but not a zoonotic disease (Cobb and Smith, 2015; World Organization for Animal Health, 2018).

**Clinical signs and lesions**

Birds infected with ORT showed reduced food intake, decreased weight gains, sneezing, nasal discharge, wet
eyes with lacrimation, sinusitis, facial edema followed by coughing, dyspnea, prostration, and death (Canal et al., 2005; Rahimi and Banani, 2007; Asadpour et al., 2008). Sudden death with or without respiratory signs has been found in chickens with nervous manifestations (Chin et al., 2008). Certain reported cases showed that ornithobacteriosis might induce sudden death due to meningitis (van Empel and Hafez, 1999). Experimental infection of chickens and turkeys with ORT revealed decrease in body weight and growth retardation (van Empel et al., 1996; Ellakany et al., 2019). The clinical picture of ORT could be vanished within a week or become more complicated in the presence of other pathogens or even non-recognized as an ORT infection anymore (van den Bosch, 2001).

The necropsy findings of ornithobacteriosis are associated with sinusitis, tracheitis, pericarditis, airsacculitis, peritonitis, and exudative pneumonia (Amonsin et al., 1997). However, the most characteristic post-mortem lesions are the presence of foamy white, “yoghurt-like” exudate in the airsacs, predominantly in the abdominal airsacs and fibrino-purulent pneumonia (Hinz et al., 1994; Banani et al., 2001). Moreover, in South Africa, subcutaneous oedema over the cranium and severe osteitis without respiratory affections have been detected in 28-day-old broiler chickens (Goovaerts et al., 1998).

Actually, the lesions become more severe if other complicating infectious pathogens are associated with ORT infection and often lead to death (Abd El-Ghany, 2000; Chin et al., 2013). Accordingly, the severity of the clinical picture of ornithobacteriosis, disease duration, and mortality rates are extremely variable and influenced by the virulence of the bacterial strain, the immune status of the host, the environmental conditions like bad management, poor ventilation, overcrowding, poor litter quality, bad hygiene, and high ammonia levels along with the presence of concurrent or secondary infections (Travers, 1996; Bisgaard et al., 2008). For instance, administration of live Newcastle (ND) La Sota vaccine at 5 days before ORT challenge induced a more serious increase in airsacculitis and pneumonia scores compared to both ORT challenge and ND La Sota vaccine administration alone (van Empel et al., 1996). Furthermore, Abd El-Ghany (2000) revealed that ORT strains were pathogenic for 2-week-old chickens, while co-infections with Escherichia coli (E. coli) and infectious laryngeotracheitis increased the severity of the clinical picture. Pan et al. (2012a) demonstrated that the experimental infection of broiler chickens with ORT could induce a mortality rate of around 50%. In comparison, mixed co-infection of ORT with H9N2 avian influenza virus (AIV) led to a higher mortality rate of 70% and 90%, respectively, if ORT inoculation was simultaneously made with H9N2 or if H9N2 AIV was inoculated after 3 days. In the same context, ORT infection alone could induce a disease condition with mortalities, but co-infection with Streptococcus zooepidemicus was more lethal (Pan et al., 2012b). Recently, Ellakany et al. (2019) confirmed that concomitant experimental ORT infection and Mycoplasma galliseptica increased the severity of clinical respiratory signs and lesions and hurts the performance and growth parameters of broiler chickens.

The histopathological lesions of ORT were represented as granulomatous pneumonia, tracheitis, and fibrinous airsacculitis (van Empel and Hafez, 1999; Abd El-Ghany, 2000; Chin et al., 2008; Ellakany et al., 2019). Kilie et al. (2009) described the microscopic lesions after experimental ORT infection in chickens as focal epithelial hyperplasia along with necrosis and inflammatory lesions of the lamina propria in the upper respiratory tract, air sacs, as well as around bronchioles and some lung areas.

**Laboratory diagnosis**

Signs and lesions associated with ornithobacteriosis are of little value and not sufficiently specific to diagnose the disease since a similar clinical picture could be seen in other infections (Hafez and Sting, 1996). Hence, diagnosis of ornithobacteriosis mainly relies on phenotypic and molecular detection of the bacterium or immunogenic detection of antibodies (Ellakany et al., 2019).

Despite conventional ORT isolation method could be difficult owing to the overgrowth by other opportunistic bacteria (Churria et al., 2011, 2012), it is still necessary for serotyping, determination of in vitro antimicrobial sensitivity test as well as production of autogenous vaccines (Vandamme et al., 1994; Hafez and Sting, 1996; Hegazy et al., 2015). Techniques of isolation and identification may differentiate ORT bacterium from other similar respiratory bacteria as Pasteurella multocida, E. coli, or Avibacterium paragallinarum.

For successful isolation of ORT, samples should be from the airsacs, lungs, and trachea after natural and experimental infections (Joubert et al., 1999; Abd El-Ghany, 2000; Welchman et al., 2013; Hauck et al., 2015; Gavrilović et al., 2016). Moreover, ORT bacterium was isolated from the nasal mucosa and orbital sinuses swabs of infected turkeys (Karimi-Dehkordi et al., 2021). Isolation of the bacterium from the heart, liver, kidney, spleen, ovaries, and brain is suggestive after systemic infection (van Beek et al., 1994; Nagaraja et al., 1998; Umali et al., 2017). Samples should be collected from suspected flocks as early as possible. Tissues and swabs could be maintained at 4°C for 2 days or at −20°C for 5 days without adverse effect on the variability of ORT organism or growth of other bacteria (Numee et al., 2012).

Samples should be inoculated on 5%–10% sheep blood agar media and incubated under microaerophilic (5%–10% CO₂) or anaerobic conditions for 24–48 hours. As ORT is a growing fastidious organism, it needs special media’s supplement and special environmental conditions (Travers, 1996). Most ORT isolates showed resistance to gentamycin or polymyxin. So, adding these antibiotics (5–10 µg/ml) to the media can suppress
other contaminating overgrowing bacteria such as *Pseudomonas, Portis*, and *E. coli* species (Back et al., 1997; Hassan et al., 2020). Positive cultures of ORT appear as non-hemolytic, pinpoint to pinheaded, gray to grayish white, circular, convex, and reddish glow colonies with a distinct butyric acid odor (Shahtahal et al., 2006). Some isolates of ORT showed incomplete β hemolysis, especially after 96 hours of incubation. In addition, the bacterium can grow in brain heart infusion broth and on trypticase soya agar but not on MacConkey agar (Roepke et al., 1998; Post et al., 1999; Asadpour et al., 2008; Mayahi et al., 2016; Hassan et al., 2020).

Microscopic identification of stained smears from suspected ORT colonies showed Gram-negative, highly pleomorphic, non-motile, or spore-forming rods (van Empel and Hafez, 1999; Chin and Charlton, 2008; Espinosa et al., 2011; Chin et al., 2013).

Regarding the biochemical identification, ORT isolates are positive oxidase and negative catalase (van Empel et al., 1996; Chin and Droual, 1997; Hafez, 1998; van Empel, 1998; Ryll et al., 2002). Commercial kits (API-20 NE and API-ZYM) are used for the biochemical characterization of ORT isolates. The bacterium is positive for arginine dihydrolase, β-galactosidase, gelatin liquefaction, and Voges-Praskauer tests, while negative for L-lysine decarboxylase, ornithine decarboxylase, and H2S production tests (Chin and Charlton, 2008; Hassan et al., 2020). Regarding sugar fermentation tests, ORT reveals positive sucrose, arabinose, lactose, fructose, galactose, and maltose, but negative glucose, mannitol, inositol, and sorbitol (Rahimi and Banani, 2007; Mayahi et al., 2016).

There is a great possibility to reduce the detection rate of ORT after culturing due to the presence of tiny colonies, slow growth of the bacterium, and the need for enriched media and microphonic conditions (Zahra et al., 2013). Therefore, molecular detection of ORT DNA using polymerase chain reaction (PCR) and gene sequencing of 16S rRNA and *rpoB* genes are now used for the routine diagnosis (Hafez and Beyer, 1997; Veiga et al., 2019). These recent techniques are regarded as very important and fruitful tools for the definitive detection of infection (Ozbey et al., 2004; Banani et al., 2009; Ellakany et al., 2019). Moreover, they are fast, sensitive, and specific for the characterization of bacterial strains (Huang and Alvarado, 2001; Li and Diao, 2009; Montes de Oca-Jimenez et al., 2018; Veiga et al., 2019).

Many types of modified PCR techniques are used for the characterization of ORT. Enterobacterial repetitive intergeneric consensus-PCR, repetitive element palindromic-PCR, random amplified polymorphic DNA-PCR, and multilocus sequence typing have been developed (Szabó et al., 2017). Great variations among ORT isolates have been found using phylogenetic analyses of the 16S rRNA gene (Banani et al., 2009; Montes de Oca-Jimenez et al., 2018). Lately, Veiga et al. (2019) suggested using ORT *rpoB* gene for partial sequencing of isolates from different avian species.

The phylogenetic relationship indicated the existence of a greater genetic variability (Montes De Oca-Jimenez et al., 2018; Veiga et al., 2019), particularly between ORT strains from different hosts (Thieme et al., 2016). Serotyping of ORT isolates has been carried out using agar gel precipitation test and enzyme-linked immunosorbent ssays (ELISA) with specific antisera against 18 (A–R) serotypes (van Empel et al., 1997; van Empel, 1998; Türkyilmaz, 2005; Wu et al., 2010; Hassan et al., 2020). Within ORT species, several serotypes and strains with different virulence are present (Ryll et al., 1996). The different ORT serotypes have no direct relationship with virulence. Rapid slide agglutination test was also used to type ORT isolates (Back et al., 1998b). Reports indicated that all the tested ORT isolates belong to serotype A, which is the most prevalent among strains of chickens (94%) and turkeys (57%) (Siddique et al., 2008). Serotypes A, B, D, and E are most common in turkeys, while serotypes F, K, and M are sometimes isolated from chickens and turkeys (van Empel and Hafez, 1999). A cross-reaction between serotypes B and A and between serotypes I and L were observed after using rapid serum plate agglutination test in layers. Besides, cross-reactions have been detected for serotypes A, E, and I, but not with serotype C (Türkyilmaz, 2005). Serological identification of ORT is hampered by limitations, such as cross-reactivity between strains (Szabó et al., 2017). Due to the difficulties in serotyping methods, the presence of un-determined new serotypes of ORT has been suggested (Numee et al., 2012; De la Rosa-Ramos et al., 2018).

To overcome these disadvantages, a wide range of techniques have been implemented over the last years. The matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) has become more efficient than biochemical tests for routine laboratory diagnosis of microorganisms as it is a rapid, reliable, and direct technique for the identification (Alispahic et al., 2014). In the recent study of Alispahic et al. (2021), the molecular characterization of 47 ORT field strains derived from Austrian turkey farms was carried out using MALDI-TOF MS and whole genome sequencing techniques. The results of MALDI-TOF MS revealed that most ORT strains were grouped within one cluster although they comprised of different serotypes, except serotypes F, K, and M that formed a different cluster. The whole genome sequencing results confirmed that the previous data indicated that serotypes F, K, and M were clearly different from the other ORT strains and may belong to different *Ornithobacter* species.

High seroprevalence of ORT was demonstrated among broiler and breeders chicken and turkey flocks in several regions worldwide using ELISA (van Empel et al., 1996; Canal et al., 2003; Hegazy et al., 2015). For instance, Hafez and Sting (1996) detected antibodies to ORT in 79% of broiler breeder chicken flocks, and
26% and 55% of broiler chickens and meat turkey flocks, respectively. Furthermore, Ryll et al. (1997) demonstrated the presence of antibodies in 96.6% of the sera of broiler turkeys. In Iran, antibodies of ORT were found in 205 (44.2%) out of 463 broiler chickens and in 340 (72%) out of 472 breeder chicken serum samples (Allymehr, 2006). Another study showed the presence of antibodies in the sera of 289/460 (83%) broiler breeder flocks (Asadpour et al., 2008). Moreover, of the 420 serum samples, 134 (31.9%) were positive for ORT antibodies (Ghanbarpour and Salehi, 2009). High (100%) seroprevalence to ORT was detected in broiler breeder chicken flocks in Brazil (Canal et al., 2003) and layer chicken flocks in the United States (Heeder et al., 2001).

It is important to note that antibodies of ORT and other pathogens were detected using ELISA. For example, antibodies of ORT and turkey rhinotracheitis virus (Hafez, 1997a, 1997b) and Chlamydia psittaci were demonstrated (Hafez et al., 1998).

**Prevention and control**

The prevention of ornithobacteriosis in the poultry production system should be considered since the disease has become endemic worldwide. Adoption of strict biosecurity measures and husbandry practices is critical. All in-all out policy should be applied. Thorough cleaning and disinfection of poultry houses are essential to avoid the possibility of ORT re-infection or spreading, especially in endemic areas. In vitro study of Hafez and Schulze (2003) declared that a concentration of 0.05% aldehydes and organic acids (formic and glyoxylic) disinfectant preparations effectively inactivated ORT bacteria within 15 minutes. The in vitro antibiotic susceptibility pattern of ORT strains is greatly inconsistent. It depends on the locality, the source of strain, the inherent genetic differences between bird breeds, and the routinely used antibiotics in the area (Odor et al., 1997; Malik et al., 2003; Türkylmaz, 2005; Mayahi et al., 2016). In addition, the mutation of ORT plasmids plays an important role in developing antibiotic resistance (Back et al., 1997). For instance, an increase in the minimal inhibitory concentration of enrofloxacin from 0.03 to 0.25 mg/ml for ORT treatment in turkeys was due to mutations in the gyrA gene (Marien et al., 2006). Different classes of antibiotics, even the recently used ones, became inefficient against ORT strains, maybe due to transfer of the resistance among them (Deviere et al., 2001) or increase in the resistance for different drugs (Cauwerts et al., 2002). As a result of frequently acquired resistance, the treatment of ornithobacteriosis is difficult and cannot be effectively achieved through antibiotics (Deviere et al., 2001). An early study by van Beek et al. (1994) declared that the oral treatment of ORT infected turkeys using enrofloxacin and trimethoprim/sulphonamide was not effective. However, twice injections of tetracyclines and penicillin gave good results. Treatment of ORT-infected birds with 250 ppm amoxicillin and 500 ppm chlortetracycline in the drinking water for 3–7 days was effective in relieving infection (Hafez, 1997b). In Germany, Hafez (1996) observed that 90%–100% of the ORT strains were sensitive to tetracycline, chloramphenicol, and amoxicillin, while they were resistant to enrofloxacin, gentamycin, neomycin, and trimethoprim/sulphonamide. Although 90% of the abovementioned isolates were resistant to enrofloxacin in Germany, they were sensitive to the same antibiotic in Belgium and France (Devriese et al., 1995; Dudouyt et al., 1995; Roger and LeÂorat, 1997). Moreover, Chin and Droual (1997) demonstrated that water treatment with amoxicillin, tetracycline, and chloramphenicol was satisfactory. Isolates of ORT in France showed resistance to gentamicin and colistin but sensitivity to amoxicillin, spectinomycin, and tyllosin (Roger and LeÂorat, 1997). In USA, 100% of ORT revealed susceptibility to ampicillin, penicillin, spectinomycin, erythromycin, and tyllosin. 79.4% were susceptible to neomycin, tetracycline, and sarafloxacin, and the rest of the isolates were susceptible to streptomycin, gentamicin, and trimethoprim (Nagaraja et al., 1998). Strains of ORT strains in the Netherlands showed susceptibility to amoxicillin, tetracycline, enrofloxacin, and trimethoprim/sulphonamide (van Veen et al., 2001). However, later on, the sensitivity of these ORT strains to amoxicillin and tetracycline decreased from 62% to 14%. Even four out of the strains were non-susceptible to enrofloxacin the combination of trimethoprim-sulphonamide. In Mexico, Soriano et al. (2003) declared that ORT strains were sensitive to amoxicillin, enrofloxacin, and oxytetracycline, while resistant to gentamicin and fosfomycin. In addition, Mohd-Zain et al. (2008) demonstrated that 100% of ORT strains were resistant to amoxicillin, enrofloxacin, and sulfanomide/trimethoprim, while they were sensitive to chloramphenicol. In the study by Asadpour et al. (2011), the authors found that all ORT strains were non-sensitive to enrofloxacin, ciprofloxacin, erythromycin, and tetracycline, while all of them were sensitive to ceftriaxone. Moreover, two strains (66.70%) showed moderate susceptibility to amoxicillin and florfenicol. Churria et al. (2016) reported that all isolates of ORT were resistant to gentamicin. Most of them were resistant to enrofloxacin, erythromycin trimethoprim-sulfamethoxazole, doxycycline, and fosfomycin, while all of them were sensitive to amoxicillin and florfenicol. The recent Egyptian study of Hassan et al. (2020) revealed that 100% of circulating ORT strains were non-susceptible to gentamycin, amoxicillin, and cephradine, while 100% were susceptible to colistin and doxycycline, 50% to ampicillin and streptomycin, and 16.67% to neomycin and trimethoprim.

From the above-mentioned studies, it could be concluded that most ORT strains became resistant to the majority of the used antibiotics in the field (Watteyn et al., 2016; Umali et al., 2017). Therefore, vaccination
may be a promising and effective strategy to counteract ornithobacteriosis. Inactivated, live, and recombinant sub-unit vaccines of ORT have been developed with variable results (Gornatti Churria et al., 2013). An early trial has been done to vaccinate day-old-broiler chickens and turkeys with autogenous inactivated oil adjuvant bacterin (Bock et al., 1997). Moreover, this type of bacterin significantly reduced ORT lesion scores after vaccination of broilers at 26-days-old (van Empel and van den Bosch, 1998). However, it has been found that vaccination of birds at 8-week-old was more effective than vaccination at 4-week-old to avoid interfering with maternal immunity (Gopala Krishna Murthy et al., 2007). Vaccination of breeders using inactivated bacterin was found to be effective and protective against the development of pathologic changes of ORT infections in the progeny (Bisskop, 2005). No cross-protection between serotypes was induced after vaccination with bacterins in oil adjuvant (Bock et al., 1995, 1997). Many types of inactivating substances and adjuvants were added to 18 ORT vaccines to choose the best one (Gopala Krishna Murthy et al., 2007). It has shown that a vaccine containing mineral oil adjuvant induced the highest immune response and the lowest respiratory lesions in vaccinated birds. Cauwerts et al. (2002) also observed decreasing mortalities and increasing production of the offspring from the vaccinated breeders. Vaccination of breeder broiler chicken flocks with inactivated ORT bacterin containing serotype A induced 39% increase in the production rate and 22.3% decrease in progeny loss (De Herdt et al., 2012). Autogenous inactivated oil adjuvant ORT bacterins showed a successful reduction of ornithobacteriosis outbreaks in Turkey (Erganis et al., 2010), Israel (Chin et al., 2013), and Iran (Ghasemipour et al., 2020). Mention if there is cross protection between different serotypes of ORT. It has been shown that inactivated or subunits vaccines of ORT mostly give low or only partial cross-protection and not always for all serotypes. However, live type vaccines can provide this cross protection (Schuijffel et al., 2005, 2006).

van Empel and van den Bosch (1998) found that the vaccination of breeders against ornithobacteriosis using live vaccine provided satisfactory protection against pneumonia and airsacculitis in their progeny until 28 days of age. The protective efficacy of a live, temperature-sensitive mutant ORT vaccine against a bacterial challenge has been evaluated in day-old turkey poult’s (Lopes et al., 2002). The vaccine strain colonized the upper respiratory tract and recovered 13 days post vaccination with protective humoral immune response.

Nevertheless, the presence of different ORT serotypes within the bacterium species represent a major challenge in vaccine production. So, the production of recombinant or sub-unit vaccines becomes urgent to induce homologous and heterologous protection along with the rapid immune response (van Empel and Hafez, 1999; Schuijffel et al., 2006). Schuijffel et al. (2005) showed that recombinant subunit vaccine containing eight encoded cross-reactive antigens induced homologous and heterologous protection against ORT challenge as well as production of protective antibodies.

**Conclusion**

Despite the continuous progress in ORT characterization in almost all countries around the world, there is a gap of knowledge and a lack of information in some aspects. Thus, more research is needed. For example, the mechanism and pathogenesis of ORT infection in the host, the development of more recent diagnostic tools, and the design of treatment and vaccination protocols are still in need. Besides, it is necessary to include some national monitoring programs for emerging respiratory affections like ornithobacteriosis to avoid the adverse economic losses caused by such infection.

**Conflict of interest**

The author declares that there is no conflict of interest.

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**Authors’ contribution**

Wafaa A. Abd El-Ghany collected the data, prepared and revised the manuscript, and approved the final version.

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