Chapter

Low Pathogenic Avian Influenza: A Permanent Threat to Poultry Farming in Africa

Oumayma Arbani, Mariette Ducatez, Mohammed El Houadfi and Siham Fellahi

Abstract

Initially isolated from turkey flocks in Wisconsin in America in 1966, the avian influenza virus H9N2 has become a serious threat not only to the avian industry but also to human health. Since the 90s, the virus spread in chicken flocks in several countries, starting with China in 1992, then in many parts of Asia, the Middle East, and North Africa. Actually, the LPAI H9N2 subtype is believed to be one of the main causes of chicken respiratory diseases in Africa. Since the first introduction of AIV H9N2 in Morocco in 2016, the virus became enzootic and causes outbreaks in different parts of the country. The intensive uses of inactivated vaccines were insufficient to eradicate the disease, which affects intermittently poultry flocks in different parts of the country at different periods with different degrees of severities, depending on concomitant diseases, management, and other environmental factors. The objective of this chapter will be to explain the H9N2 infection with regard to both animal and human health in Africa and to highlight the assessment of African strategies for control of LPAI in poultry.

Keywords: low pathogenic avian influenza virus, H9N2, poultry, Eurasian lineage, Africa, Morocco

1. Introduction

The low pathogenicity avian influenza (LPAI) H9N2 virus is the most widespread subtype in poultry around the world, posing a concern for animal and public health [1]. Despite their low pathogenicity, H9N2 avian influenza viruses (AIV) are causing heavy economic losses, particularly during coinfection with other respiratory pathogens [2, 3]. Globally, the virus has become endemic in multiple regions of the world counting Asia, the Middle East, and Africa [4]. On the African continent, the first A(H9N2) outbreak was reported in Libya in 2006 [5, 6], then in Egypt in late 2010 [7]. Even though many studies later showed that the virus was present in the country earlier, cocirculating with highly pathogenic avian influenza viruses (HPAIV) of the

H5N1 and H5N8 subtypes have been associated with heavy economic losses in the poultry industry [2, 8–10]. Since then, many African countries started surveillance programs for influenza viruses in poultry and the emergence of G1 lineage H9N2 viruses has been documented. LPAI H9N2 viruses emerged in Tunisia in December 2009 leading to the circulation of the disease in many parts of the country [11]. Rapidly spread in the African continent, the disease has been declared in Morocco in early 2016 [12], then in Algeria in late 2017 showing more than 99% genetic and antigenic similarities with Moroccan strains [13]. Since then, the virus started to spread southward making its way to several Sub-Saharan countries: it was first detected in Burkina Faso in 2016 [14], in Ghana in 2018 [15], and it expanded to Togo, Benin, Uganda, Kenya, Nigeria between 2017 and 2020 and Senegal, with a human case reported in 2020 (**Figure 1**) [16–19].

LPAI H9N2 has not only been detected in poultry but also in some human cases, being a real threat to human health and a global concern for public health. Thus, different studies showed that circulating H9N2 strains acquired an affinity to mammalian like-receptors and gained high virulence and pathogenicity through amino acid substitutions in their viral proteins [11, 12]. Human infections with LPAIV H9N2 have so far been reported in just two African countries; Egypt with four cases, since 2015 [20] and recently Senegal with a case in a 16-month-old child [17]. To date no report of AIV H9N2 in poultry in Senegal is available. Finally, it has been reported that LPAIV H9N2 can easily undergo genetic reassortment and donate internal gene segments to HPAIV H5 and H7 [21, 22].

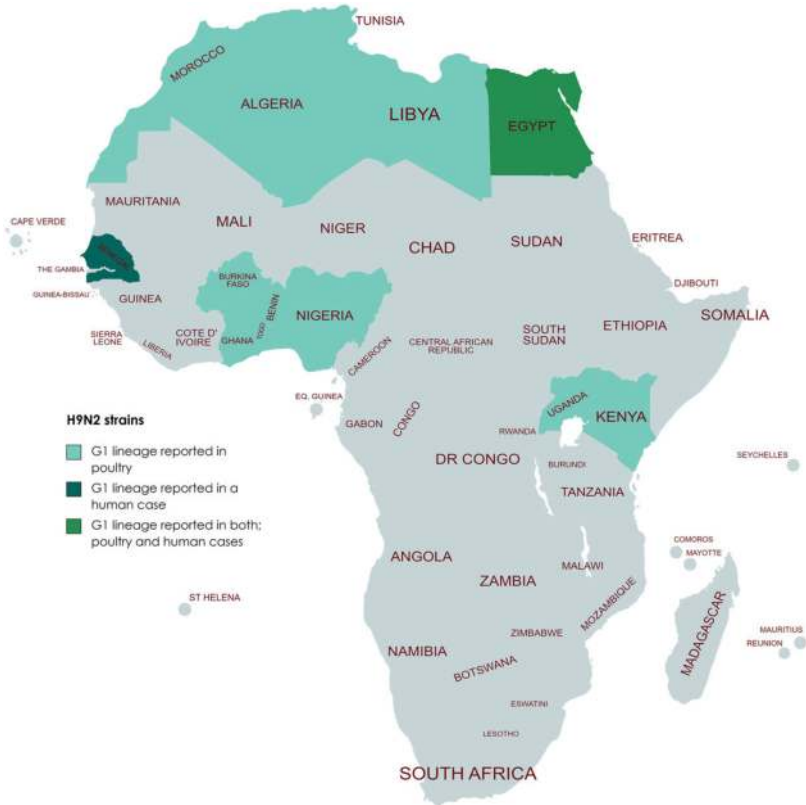

Figure 1.
Phylogenetic spectrum of H9N2 lineage in African countries. The emergence of G1-West lineage is shown in green reported in poultry and some humane cases (figure created with www.mapchart.net).

2. Low pathogenic avian influenza H9N2 subtype: a threat to both animal and human health worldwide

AIV belongs to the *Orthomyxoviridae* family, genus Alphainfluenzavirus (genus A) [23, 24]. These viruses are enveloped and contain negative-stranded RNA. AIV genome contains eight unique segments encoding no less than 10 core proteins including RNA polymerase subunits PA, PB1, and PB2, hemagglutinin (HA), nucleoprotein (NP), neuraminidase (NA), matrix proteins 1 and 2 (M1 and M2), and nonstructural proteins 1 and 2 (NS1 and NS2) [24, 25]. Based on the genetic and antigenic variants of HA and NA surface glycoproteins, they are classified into 18 HA and 11 NA subtypes, of which 16 HA (from H1 to H16) and 9 NA (from N1 to N9) subtypes circulate in avian species. H17N10 and H18N11 influenza A subtypes were detected in bats in South America [26, 27]. Furthermore, based on molecular markers in the hemagglutinin (HA), AIVs can be broadly classified into two groups that affect their pathogenicity in chickens: HPAIV is highly pathogenic in chickens (high mortality rates in experimental chickens intravenously infected using the intravenous pathogenicity index; IVPI) and contain polybasic cleavage sites in HA; and LPAIV, characterized by low pathogenicity in chickens and mono- to tri-basic cleavage sites in HA. To date, only the H5 and H7 subtypes have shown HPAIV phenotypes in the field [28].

AIV H9N2 viruses are LPAIV and were first detected in turkeys in Wisconsin in America in 1966 [A/turkey/Wisconsin/1/1966(H9N2)] [29]. Since then, these viruses have been circulating worldwide and became the most prevalent AIV isolated from the poultry industry in the world. The subtype has even become endemic in a number of different countries in the Middle East, Asia, Africa, and Europe [30, 31]. Wild birds of the orders Anseriformes (like ducks, geese, and swans) and Charadriiformes (like gulls, waders, and terns) are the main natural reservoir of influenza A virus subtypes [24, 32]. However, there is no clear evidence for the international spread of H9N2 via migratory birds [33]. Instead, the trade and transportation of live poultry may contribute to the viral spread [34].

Phylogenetically, the HA gene of H9N2 viruses can be roughly divided into two main phylogeographic branches, Eurasian and American branches. Many clusters can be identified from these two major lineages. The American H9N2 viruses are mainly found in wild birds, especially sea birds, but they have been reported to infect farmed turkeys without the stable transmission in poultry [35]. However, during routine surveillance programs and at sporadic occurrences of other LPAIV in poultry, there have been no detections of the H9 avian influenza viruses in poultry in North America since 2001. In contrast, frequent isolations of the virus from wild birds have been detected [36].

Regarding the Eurasian H9N2 viruses branch, it is divided into four main lineages based on the hemagglutinin gene; G1 (A/Quail/HK/G1/97-like viruses), Y280 (also known as BJ94 or G9 lineage) (A/Duck/HK/Y280/97-like viruses), Korean-like or Y439 (A/Chicken/Korea/38349-p96323/96-like viruses) and European lineage primarily reported in turkeys. Lineages G1 and Y280 are most prevalent, and highly adapted to poultry [21, 35].

Genetic relatedness of H9N2 isolated in the Middle East and North Africa suggested the existence of two major lineages in the main G1 lineage: lineages A and B. Lineage A represents viruses detected in all countries of the Middle East and North Africa between 1998 and 2016, while lineage B represents viruses isolated in Saudi Arabia, Iran and Israel between 1998 and 2007 earlier [22]. Furthermore, lineage A contains the widespread H9N2 viruses (Panzootic-AIV H9N2) reported more recently in many of the Middle East and African countries.

H9N2 viruses are endemic in poultry populations. They are associated with mild to severe respiratory signs, among which are sneezing, coughing, rales and excessive lacrimation, and rattles [32, 37, 38]. Moreover, other clinical signs are reduction in egg production in breeder or layer flocks, reduced feed conversion with sometimes high rates of morbidity, and up to 20% mortality [31]. In commercial turkeys, H9N2 viruses mainly lead to acute respiratory syndromes and a drop in egg production. Vaccination programs are commonly undertaken in several Asian countries to reduce the economic impact of the H9N2 infection in poultry [28, 39, 40]. The virus also induces transient immunosuppression, which may exacerbate other concomitant or secondary infections. Thus, the severity of clinical signs and mortality rates in infected birds are often increased by co-infection with other avian pathogens, which can increase viral titers in oropharyngeal swabs and tissues [41, 42].

In recent years, A/H9N2 posed a global concern for animal and public health. It has been reported to infect humans by occasionally broadening its host range and crossing the mammalian species barrier. Since its first detection in humans, at least 59 cases have been reported so far and are often associated with mild flu-like symptoms [1]. However, studies in humans exposed to poultry in endemic countries showed that many people harbor H9N2 specific antibodies, demonstrating that subclinical infections are common in many countries, including China, Vietnam, Iran, Pakistan, Romania, and Hong Kong [31].

H9N2 viruses have been circulating among poultry and have acquired human-type receptor specificity, and thus recognize the pattern of sialic acids related to adjacent galactose in conformation α (2, 6) [9]. In addition, they are potentially posing a threat to public health because of their ability to contribute to the genetic diversity of AIVs with serious effects on humans. The internal gene segments of the AIVs responsible for fatal infections in humans (e.g., H5N1, H7N9, and more recently H5N6 and H10N8) are indeed derived from H9N2 viruses [1]. Moreover, A/H9N2 virus infection has been reported in pig farms in Hong Kong and China [21, 34], increasing the risk of zoonotic events. However, no evidence of human-to-human transmission of LPAI H9N2 viruses has yet been observed [9].

3. Assessment of national strategies for control of LPAI in poultry

Although all H9N2 are considered LPAIV based on the lack of mortality in the standardized *in vivo* pathotyping test in specific pathogen-free (SPF) chickens [14], their infections in poultry are quite different in the field compared to controlled experimental conditions. As mentioned earlier, birds show respiratory disease signs, decrease in egg production, and mortality is regularly observed [15]. The difference in the more severe clinical disease observed in the field is thought to be caused by co-infection with other pathogens including mycoplasma, Newcastle disease virus and infectious bronchitis virus (IBV), immunosuppressive infections with viruses like infectious bursal disease virus, and stressful environmental conditions including high temperature or high ammonia levels [43, 44]. Thus, in the last 20 years, the poultry-adapted H9N2 viruses have become a major concern not only for poultry health but also for human health as some of the H9N2 lineage viruses are zoonotic [45–47]. Moreover, one of the most outstanding characteristics of the H9N2 viruses from the G1 lineage is their ability to infect and efficiently spread in domestic bird species [48].

The use of vaccination of poultry likely provides the most practical control tool to reduce human exposure. Traditional vaccines for AIVs are made from influenza

isolates grown in embryonated chicken eggs (ECE), monovalent whole AIV H9N2 inactivated vaccine, or bivalent whole AIV H9N2 and Newcastle disease virus inactivated vaccine and delivered with mineral oil adjuvant [31]. Killed vaccines provide good protection in layer and breeder flocks, especially with multiple-dose vaccine regimens, where the birds usually receive up to three doses during the rearing period [49]. In broilers, vaccines are less effective and tend to generate modest hemagglutination inhibition (HI) titers compared to what is seen in layers and broiler breeders. This may be due to their shorter life span and the presence of maternal immunity when vaccinated early in life [39, 49–51]. However, production numbers are better in vaccinated broiler flocks compared to non-vaccinated flocks if infected [52]. Furthermore, the extensive use of vaccination in broilers and the continuous infection of vaccinated flocks in endemic countries may lead to the formation of escaped mutant viruses that are antigenically distinct from the vaccine [53]. In addition, we previously showed that LPAI H9N2 vaccination was more efficient on day 7 than on day 1 in reducing disease in a challenging experiment with both AIV H9N2 and IBV [54]. In Morocco, [55] showed a very high level of maternally derived antibodies against LPAIV H9N2 in day-old chicks. This was linked with vaccination or field infection of the parents. Indeed, maternally derived antibodies can interfere with vaccination, partially neutralizing vaccine antigens and they often last for 3–4 weeks in chickens [55].

In 2013, a new AIV H9N2 wild virus was isolated from vaccinated and infected broiler flocks in the Middle East. However, the high similarity of it's HA gene to the classical virus used for manufacturing the classical vaccines produced before 2004 was reported. A similar evolution of a new AIV H9N2 strain in vaccinated flocks in South Korea has been reported and the new strain provided better protection as a vaccine [53]. Hence, a new autogenous vaccine that can induce a higher antibody response in broiler chickens and reduce considerably viral shedding, was manufactured from this new field virus from the Middle East. That is why it is expected that the use of an autogenous vaccine will provide better protection for broiler chickens [52]. The use of high-quality, antigenically matched and properly applied vaccines can greatly reduce clinical disease in poultry and of equal importance can greatly reduce or eliminate virus shedding in birds that do get exposed to the virus.

H9N2 viruses hence continue to cause disease in vaccinated poultry. Sub-optimal vaccination may lead to antigenic drift and possibly clade replacement, with increased risk for zoonotic events [1, 11, 53]. Next-generation vaccines should then be developed with the aims of cost reduction, improved production capacities, increased efficacy, and broader protection against multiple H9N2 lineages.

In Ghana, once the virus was introduced for the first time in 2018, stamping out, which involves culling of potentially infected birds and birds presenting influenza-related morbidity has occasionally been used as the first line of defense against H9N2 [15]. But once the virus is endemic in a country, eradication becomes impractical and uneconomical, so vaccination is usually used after that. Eradication is more commonly used for HPAIV outbreaks as it is a reportable disease regardless of a country's outbreak/epidemic history [1].

4. Conclusion

Despite, the use of vaccination and all other tools as a control method for H9N2, many countries still see outbreaks resulting from H9N2 AIVs. For efficient control

of infection and transmission, the efficacy of vaccine and vaccination needs to be improved with a comprehensive control strategy, including enhanced biosecurity, education, surveillance, rapid diagnosis, culling of infected poultry, and proper management of concomitant viral and bacterial diseases. One health aspect would be particularly important to limit the spread of such AIV by elaborating preventive strategy, educating farmers on effective vaccination, and enhancing biosecurity measures to limit the co-circulation of zoonotic H5N1 and H9N2 viruses that has complicated the epidemiological situation in Africa.

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