Research Article

Low Pathogenic Avian Influenza Virus Subtype H9N2 in Poultry in North Africa: Current Status

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Abstract | Low pathogenic avian influenza H9N2 subtype virus is considered among important respiratory pathogens in poultry worldwide. It was isolated from many species of domestic and wild birds. Infection in commercial poultry flocks causes important economic losses, related to high mortality, decrease in animal performance and aggravation of infection by other pathogens. Although H9N2 is endemic in many regions of the world, such as Middle East and North Africa, where the first outbreaks were described since the end of 1990s, many features about epidemiology and genetic characteristics are still little known. This review summarized the epidemiological situation of H9N2 subtype in poultry in Algeria, Egypt, Libya, Morocco, Sudan and Tunisia. Human infection was reported in Egypt and serosurveys programs showed high positivity, particularly in poultry workers. Genetic analysis demonstrated that the most of H9N2 viruses circulating in North Africa were among the G1-lineage group. The presence of mammalian and human genetic markers were reported in several H9N2 strains, indicating possible risk for public health. Control of LPAI H9N2 subtype infection is currently based on biosecurity and the implementation of vaccination in some countries. Regional control strategy needs to be performed. Creation of regional surveillance network is highly recommended.

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Introduction

The H9N2 strains of avian influenza viruses (AIV) circulate worldwide and cause respiratory signs such as sneezing, coughing, ocular and nasal discharge, and swollen infraorbital sinuses in poultry. Sinusitis is common in turkeys. Acute lesions of the upper respiratory tract and lungs are described. In layers and breeders, H9N2 virus can induce a decrease in egg production and fertility (Alexander and Capua, 2008).

The H9N2 subtype was occurred in many countries since 1990s, where outbreaks occurred in domestic ducks, chickens and turkeys in Germany during 1995-1998 and 2004 (Werner, 1998; 1999), in chickens in Italy during 1994-1996 (Fioretti et al., 1998) and in Korea during 1996 (Mo et al., 1998). Outbreaks of H9N2 infection were observed in ostriches (1995, 2018) and pheasants (1997) in South Africa (Banks et al., 2000) and China (Wang et al., 2018) and Ireland (Campbell, 1998), respectively.

After 2000s, H9N2 has been detected from different types of poultry production in the Middle East, Asia and Africa (Alexander and Capua, 2008). In North

Africa, H9N2 seems endemic in several countries, causing severe respiratory disease and predisposing to secondary infections, which inducing important economic losses in the poultry sector. Increase in pathogenicity of H9N2 was demonstrated when live vaccines are used against infectious bronchitis virus (IBV) and Newcastle disease virus (NDV) (Ismail et al., 2018; Ellakany et al., 2018).

Zoonotic risk of H9N2 AIV was illustrated in many studies worldwide. Mutations in the hemagglutinin (HA) gene were detected in several H9N2 strains, suggested a possible pandemic H9N2 in humans (Peiris et al., 1999; Butt et al., 2010; Xu et al., 2018; Push and Suarez, 2018). Isolation of H9N2 has been documented, particularly in person who are in close contact with poultry (Push and Suarez, 2018; Ali et al., 2019).

Phylogenetic analysis of the HA gens from frequently isolated H9N2 AIV subtypes showed three dominant genetic groups represented by A/quail/Hong Kong/G1/97 (G1 lineage), A/chicken/Hong Kong/Y280/97 (Y280 lineage), and A/chicken/Beijing/1/94 (Ck/Bei lineage) (Xu et al., 2007).

The aim of the present article is to review recent reports on LPAI H9N2 subtype in poultry production in the North Africa countries.

Algeria

Despite the high incidence of H9N2 subtype AIV in neighboring African countries, little information is available regarding the circulation of this virus in Algerian poultry flocks. However, co-infections including IBV, avian Metapneumovirus (aMPV) subtype B, AIV and *Mycoplasma gallisepticum* (Mg) were confirmed in poultry flocks manifesting respiratory signs with high mortality (Sid el al., 2015).

Using the real-time PCR (polymerase chain reaction), Sid et al. (2015) confirmed for the first time the circulation of AIV in Algerian poultry flocks, but without characterization of field strains, in the absence of vaccination in the period of study. Serological investigations (Enzyme Linked Immunosorbent Assay: ELISA and Hem agglutination inhibition test: HI) showed no specific antibodies against H7, H9 and H6 AIV subtypes (Sid el al., 2015).

More recently, H9N2 AIV subtype was detected and characterized in chicken flocks, in different regions of Algeria. All virus's strains were monophyletic and belong to the G1 HA lineage (Jeevan et al., 2019). Algerian H9N2 viruses were antigenically and genetically similar to strains detected in North Africa and Middle East countries, in particular Burkina Faso, Morocco, and United Arab Emirates from 2015 to 2017 (Table 1).

However, the sublineage of Algerian H9N2 showed differences compared to H9N2 strains responsible for outbreaks in poultry flocks in Egypt. Consequently, it is unlikely that the Algerian viruses spread from that country. Moreover, H9N2 viruses detected in Uganda in 2017 shared a common ancestor with the Algerian viruses (Jeevan et al., 2019). No confirmed hypothesis was advanced according to the directly source between these viruses.

Actually, vaccination against H9N2 subtype is implemented in poultry production using different vaccines types, such as killed homologous vaccines and vectored vaccines. No human cases of poultry H9N2 infection was published in Algeria.

Egypt

First report of H9N2 AIV circulation was made since 2006 from live poultry markets by RT-PCR, without virus isolation (Nagy et al., 2017). Isolation and characterization of H9N2 AIV subtype was made from bobwhite quail flock in 2011, with close relationship to the viruses isolated in the Middle East (El-Zoghby et al., 2012). Phylogenetic analysis confirmed the belonging of Qa/Egypt/11 virus to the A/Qa/HK/G1/1997-like lineages isolated from neighboring countries, with new mutations detected the several genes which indicated the similarities between Egyptian H9N2 and viruses circulating in the region since 2006 (Arafa et al., 2012).

Serological investigations revealed the presence of specific antibodies against H9 AIV subtype in chickens flocks in Egypt between 2009 and 2012 (Afifi et al., 2013). Since then, H9N2 subtype circulated in a wide range of birds, including commercial chickens and turkeys, ducks, pigeons and backyard poultry (Hagag et al., 2013; Kandeil et al., 2014). Blast analysis of H9N2 viruses isolated from chicken flocks in Alexandria showed that the, A/chicken/Egypt/BSU-CU/2011, strains was very similar to the other Middle East H9N2 (Abdel-Moneim et al., 2012).

Table 1: *History of low pathogenic avian influenza H9N2 subtype in North Africa.*

Country	Year of first virus isolation	Lineages	Species	Epidemiological status	Recorded human cases	Reference
Algeria	2017	G1-W	Chicken	Potentially endemic	No	Jeevan et al. (2019)
Egypt	2006	G1-W	Chicken, turkey, quail	Endemic	Virus isolation Serology	(El-Zoghby et al., 2012); Monne et al. (2013)
Libya	2005	G1-W	Chicken	Potentially endemic	No	Al-Garib et al. (2007)
Morocco	2016	G1-W	Chicken	Potentially endemic	No	El Houadfi et al. (2016)
Tunisia	2009	G1-W	Chicken, turkey	Potentially endemic	No	Tombari et al. (2011)

Table 2: *Laboratory confirmed human cases of H9N2 infection in Egypt.*

Year	Location	Patient	Clinical signs	Viral lineage	Direct contact with poultry ?	Reference
2015	Aswan	3-year-old, boy	Unknown	Not reported	Yes	WHO (2015)
	Cairo	7-year-old, girl	Influenza-like symptoms	Not reported	Yes	
		9-month-old, girl	Influenza-like symptoms	Not reported	Yes	
2016	Cairo	18-month-old, boy	Influenza-like symptoms	Not reported	Yes	WHO (2016)

However, recent H9N2 viruses isolated from domestic pigeons inherited five internal genes from Eurasian AIV circulating in wild birds (Kandeil et al., 2017).

Outbreaks were observed particularly during cold season, but several cases were diagnosed year-round especially in the Nile Delta region (Arafa et al., 2012; Abdelwhab and Abdel-Moneim, 2015). The H9N2 viruses were frequently detected in co-infected poultry flocks with IBV, NDV, H5 AIV subtype, Mg and *Mycoplasma synoviae* (Ms) (Hassan et al., 2016; Naguib et al., 2017). Moreover, under experimental conditions, Lasota NDV vaccine can significantly affect H9N2 infection in broiler chickens regarding clinical signs, mortality rate, lesions, performance and viral shedding (Ellakany et al., 2018). No reassortment between H9N2 and H5N1 circulating viruses has been reported, but emergence of antigenic drift variants of Egyptian H9N2 was described (Adel et al., 2017; Kandeil et al., 2017; Nagy et al., 2017).

Egyptian H9N2 viruses demonstrated several genetic markers of increased transmission to mammalian hosts (Gomaa et al., 2015), with possibility of a shift in affinity of the HA from the avian-type receptor to the human-type receptor (Kandeil et al., 2014; Kandeil et al., 2017). According to the zoonotic risk of the avian AIV H9N2 subtype, three children were positive in 2015 (Abdelwhab and Abdel-Moneim, 2015) (Table 2). Seroprevalence among 750 poultry-exposed humans was between 5.6% and 7.5% (Gomaa et al., 2015). Vaccination of poultry, older age, and exposure to ducks were the main risk factors for H9N2 infection.

Vaccination against AIV H9N2 is currently used in Egypt using local and non-local strains, with variable efficiency. Recently, a trivalent inactivated vaccine based on circulating AIV was tested against H5N1, H5N8 and H9N2 subtypes (Gomaa et al., 2019).

Libya

LPAI disease was suspected in Libya during 2005-2006 (Alexander, 2007). H9N2 subtype, isolated firstly in mid-2005, was believed to be one of the main causes of chicken respiratory diseases as indicated by field reports (Al-Garib et al., 2007; Fares et al., 2010). Positive correlation has been reported between high mortality rate and respiratory signs and the presence of specific antibodies against H9N2 in studied flocks (Al-Garib et al., 2007). Moreover, seroprevalence in commercial poultry flocks (broiler and layer) in the northwest of Libya revealed the presence of only antibodies against LPAI H9 subtype (Fares et al., 2010).

More recently, Libyan H9N2 has been isolated from layers, broilers and peacock, during 2013. Co-infection with NDV was confirmed in commercial poultry flocks, which explained high mortality and severe respiratory signs, described during outbreaks (Kammon et al., 2015).

Concerning vaccination against AIV H9N2 subtype, there are no reports of vaccines application in the field.

Morocco

Since 2016, H9N2 was isolated from different type of production in Morocco. The first outbreak of LPAI was observed in January 2016 in broiler flocks (El Houadfi et al., 2016). Later, the virus was isolated from layers and breeders in several regions of the country. Important economic losses were registered in infected chicken and turkey flocks, where the mortality ranged from 2% to 15%.

The phylogenetic analysis suggested that the Moroccan isolate could have derived from the Middle East isolate A/chicken/Dubai/D2506.A/2015 (Boumart et al., 2018). Low pathogenic character was confirmed under experimental conditions. However, field H9N2 viruses demonstrate higher pathogenicity under field conditions. This virus could aggravate disease when it was associated to other pathogens (Boumart et al., 2018; Belkasmi et al., 2019).

Control program of the fast spread of H9N2 infection has been performed few months after the first isolation of the virus. Emergency vaccination, using inactivated vaccines, was implemented in all types of production, including broiler flocks.

Sudan

The author failed to find any reports on the prevalence of H9N2 in Sudan.

Tunisia

First LPAI outbreaks was reported during in the end of 2009 (Tombari et al., 2011). The virus was detected in different type of poultry production, where it caused very heavy economic losses, related to mortality, egg drop, and decrease in growth rate and increase in condemnation. H9N2 virus was isolated also from wild birds (Tombari et al., 2016).

Second wave of the described during the second half of 2010. Phylogenetic analysis showed that the Tunisian H9N2, isolated from domestic birds (A/Ck/TUN/12/10) and migratory birds (A/Migratory Bird/TUN/51/10) were closely related to the Middle Eastern isolates belonging to the G1- like lineage of the present subtype (Tombari et al., 2011). In 2012, the AIV H9N2 was isolated from broilers flocks (Aouini et al., 2016).

The lower pathogenic character of Tunisian isolates was confirmed by the absence of multiple basic amino acids in HA cleavage site motif. However, the motif of these viruses is similar to the sequence required for the highly pathogenic H5 and H7 subtypes. These properties suggested the possible potential of Tunisians H9N2 to gain pathogenicity.

Seroprevalence was 28.7% (ELISA, anti-NP antibodies) in 800 chicken and turkey tested flocks, with significantly higher seroprevalence in the coastal areas compared to inland and during the autumn and winter. Broiler flocks showed significantly lower seroprevalence than layers and broiler breeders (Tombari et al., 2013). Many risk factors were incriminated in poultry flocks infection, such as low biosecurity measures and possible contact with wild birds (Tombari et al., 2013).

Ability of Tunisian H9N2 to mutation was illustrated. Strains isolated from broiler flocks during outbreaks in 2012 in the south of Tunisia (A/CK/TUN/145/12) demonstrated different motif at the cleavage site of its HA, compared to older viruses. The presence of Leu at position 234 in the amino acid sequence of HA indicated the virus binding preference to the human cellular receptor α-2,6 sialic acid (Aouini et al., 2016).

Since 2015, vaccination against H9N2 was performed in Tunisia, using inactivated homologous vaccine, for chicken and turkey breeders and layers. A DIVA test, based on sentinel animals (males in breeders) was recommended in the beginning of the vaccination program. No vaccination was used in broiler flocks, until now.

Conclusions and Recommedations

LPAI is currently enzootic in North Africa. AIV H9N2 subtype is considered for few decades among the important respiratory viruses in poultry sector. Moreover, H9N2 strains are able to impair the infection by others pathogens (IBV, NDV, aMPV, other AIV, bacteria). Genetic analysis showed the dynamics of H9N2 strains circulating in North Africa. Some descendants remained located inside the country, while others spread in other countries with a panzootic group. Reassortants viruses were also detected probably because of uncontrolled movements of infected domestic poultry species or of the contact with wild birds. Finally, AIV H9N2 subtype in the North African countries continues causing economic losses even in the vaccinated flocks.

Some viruses had genetic markers of adaptation of mammals, including humans. Thus, circulating H9N2 strains in the countries of North Africa need deepened inquiry, including regional activities of surveillance and control, the revision of used vaccines and the surveillance of human populations and other animal species. The creation of a regional surveillance network of the disease and the infection in North Africa can be very useful. Surveillance of the pathobiology and the genetic characteristics of circulating H9N2 in is very important to assess the risk for public health.

Conflict of interest

Author declares he has no conflict of interest.

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