

Emerging Zoonoses in Israel: Avian Influenza viruses. The Threat is Around the Corner

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ABSTRACT

Influenza A viruses constitute major threat to both human and poultry. These viruses are characterized by their ability to change and mutate frequently, which impact their adaptation potential and virulence. Several factors may congregate and result in emergence of novel strains of avian influenza in Israel: Egypt is considered endemic to both H9N2 and H5N1 and previously was the leading country in human illness resulting from HPAI H5N1. This have resulted from spillover through routine commerce. Another essential public health aspect of Egypt's endemicity to avian influenza viruses is the genotypic signature of H9N2 isolates which is "mammal"-oriented. Israel is located on the central migratory route of wild birds that serve both as reservoir and spreaders of avian influenza viruses (e.g. H5N8). Being endemic to H9N2, could support a process of reassortment with variety of strains, introduced through various ways. Environmental sentinels should be viewed and surveyed in order to mitigate future emergence of novel strains.

Key words: Zoonoses; Israel; Egypt; Avian Influenza.

INTRODUCTION

Influenza A viruses belong to the family *Orthomyxoviridae*. Influenza A, circulates in a wide variety of animals including humans, swine, wild birds, horses, cats, dogs, and waterfowls, which constitute the reservoir of these viruses. It is a RNA virus, which is composed of a segmented genome (eight segments) that encodes 10 core proteins and a variable number of accessory proteins (1, 2). Influenza A viruses are commonly characterized and designated by their combinations of surface proteins, hemagglutinin (HA) and neuraminidase (NA), giving rise to a multitude of different subtypes, such as, H1N1, H5N6 or H9N2.

Influenza A viruses express an error-prone RNA polymerase which lacks proof-reading activity and post replicative repair properties, facilitating the rapid accumulation of mutations subject to negative and positive selection, which is host-dependent (3). These changes can be of two types: point mutations ("genetic drift") such as in the seasonal 'flu

strain (H3N2) or major changes ("genetic shift", reassortment) following the emergence of two genetically distinct strains in a host cell.

Why is Israel at risk of reemergence? Egypt is facing a complex ecology and epidemiology of a both highly pathogenic avian influenza strain (HPAI) H5N1 and a low pathogenic avian influenza variant (LPAI) H9N2. HPAI H5N1 has emerged in Egypt in 2006 and has been declared to be enzootic in 2008 (4). Since then, Egypt has become a major focus of both epizootics among birds as well as a leading country of human cases. Up to January 2018, 860 human cases due to H5N1 have been reported worldwide, 42% of these cases have been reported in Egypt with a case fatality rate of 27-30% (5, 6). The majority of clinical cases have been women and children, who are the main caretakers of household flocks in rural areas (7, 8). Nonetheless the number of human cases is likely underreported since a serologic survey may demonstrate that the true number would

probably amount to several hundred thousand human cases (4). In addition, HPAI H5N1 outbreaks in poultry in Egypt are suspected to be heavily underreported (9). As for the efforts to control these epizootics, limited human resources and low vaccination coverage, coupled with improper use of vaccines and limited biosecurity precautions practiced by the vaccination squads, have been a major contributory factor for the HPAI H5N1 endemicity (6).

In 2010, Egypt has experienced incursion of the LPAI H9N2 strain and since then, the virus has established endemic status among the Egyptian poultry population, causing serious economic problems to the poultry industry (10, 11). It is noteworthy that the continuous spread and circulation of LPAI H9N2 in the Egyptian poultry population has been linked to LPAI H9N2 cases in humans and pigs (12). In January 2015, three human cases of LPAI H9N2 following exposure to infected poultry was recorded indicating the zoonotic potential of these viruses. Importantly, this ranks Egypt as the third country, after China and Bangladesh, reporting H9N2 infections in humans. The vast majority of Egyptian H9N2 viruses were found to have undergone a shift in the affinity of the HA from the “avian” receptor (alpha 2-3 sialic acid linkage) to the “human” receptor (alpha 2-6 sialic acid linkage) (13).

The fact that two avian influenza viruses (AIV) subtypes, HPAI H5N1 and LPAI H9N2, co-circulate among poultry and wild birds creates suitable conditions for reassortant viruses. Another virus subtype namely HPAI H5N8 was first detected in Egypt during November-December 2016, when it was isolated from wild migratory birds (14). Recently, simultaneous detection of the three subtypes (H5N1, H5N8, and H9N2) has been described in a poultry farm in Egypt (15).

In 2014, a reassortant LPAIV H9N2 was reported in pigeons containing five internal gene segments (PB2, PB1, PA, NP, and NS) from Eurasian avian influenza viruses subtypes (16). Furthermore, following an outbreak of respiratory disease in commercial broiler farms, a novel reassortant subtype of avian influenza virus was documented and designated as HPAIV H5N2 (17). The HA segment was found to be derived from H5N8 virus, with the closest homology of viruses circulating in ducks in Egypt in 2017, whereas the other segments originated from two other H9N2 viruses from pigeons and chickens (17, 18).

H9N2 viruses are known as “gene donors”. The 1997

HPAI H5N1 outbreak in Hong Kong was retrospectively been shown to have received its internal genes cassette (all genes except HA and NA) from H9N2 viruses (19).

From 2013 onwards, reassortment between H9N2 viruses and other circulating subtypes resulted in the generation of multiple zoonotic avian influenza viruses with a high propensity to cause disease in humans and poultry, such as H7N9 (20), H10N8 (21) and H5N6. All of which contain the six genes of H9N2 (genotype G57) internal gene cassette. It has been shown, particularly for H7N9 viruses that the H9N2 (G57) internal gene cassette greatly contributes to the pathogenicity of these viruses in mammals, again highlighting that the endemicity of H9N2 viruses may drive the emergence of future zoonotic influenza virus strains (22, 23).

In Israel, the H9N2 virus was initially isolated in May 2000 and after a 1.5 year break, starting in December 2001, this virus became predominant among avian influenza viruses in the country (24). Most of the Israeli isolates (related to G1 lineage) have been shown to harbor the human-like motif L216 in the HA receptor binding site and exhibit the preference for binding of (alpha2-6 sialic acid) receptors (25). This potential endemicity is based on apparent recurring epidemics of the virus, although the vaccine regimen, which began in 2003 has had some success in limiting the endemicity of the virus (24).

Israel also experienced six events in which HPAI H5N1 was involved (2006, 2008, 2010, 2011, 2012 and 2015) (26). The virus first emerged in Israel in March 2006, shortly after it was detected in Egypt (February 2006). Then, outbreaks were detected simultaneously in the Palestinian Authority's Gaza strip and in Israel. Molecular characterization of the isolates from Israel and Gaza performed in the Veterinary Services Central Laboratory showed that they were different from influenza (H5N1) viruses recently isolated in Indonesia (27), however, they belonged to a single strain and were closely related to other HPAI H5N1 strains isolated during this period in European, Asian, and African countries. Noteworthy, during the 2012 outbreak cats, feeding on carcasses of turkeys, became infected and showed clinical signs characteristic of avian influenza. This event demonstrate the virus capacity to overcome the species barrier, as demonstrated in several outbreaks in the past (28, 29).

On November 11, 2016, HPAI H5N8 hit a large poultry farm near Heftsiba, in the northern district of Israel. This was the country's first emergence of this strain. Following

this outbreak, HPAI H5N8 was responsible for several other events in 2017 and 2019 that culminated in 2020. During this year, 12 temporally clustered and spatially spread outbreaks in commercial poultry farms and 5 discrete isolations in wild birds, have been documented in Israel (30). Emergence and spread of HPAI H5N8 tightly correlates with wild waterfowl migration routes.

CONCLUSION

Emergence of existing or novel AIV strains poses a major risk to public health. The main risk for such emergence in Israel is based on 3 different strains namely H5N1, H9N2 and H5N8. The epidemiological, ecological and geographical conditions that exist in our region, and specifically the situation in Egypt, supports this possibility.

Primarily, the complex epidemiological situation in Egypt may lead to the transmission of HPAI H5N1, the most lethal AIV strain to humans, through commerce of live poultry. Another potential means in which HPAI H5N1 may emerge, is through wild birds, since their migration routes pass twice yearly in our region. Such introductions are responsible for inter-continental dispersal of this strain (31). In the past, introductions of H5N1 resulted in severe losses in the poultry sector.

Secondly, although known to be of reduced hazard to public health, LPAI H9N2 isolated in Egypt, is characterized by a genetic signature that imposes increased affinity to the mammalian receptor. Furthermore, this strain was implicated as “gene donor” that contributed to the emergence of several zoonotic AIV strains. This was recently documented in Egypt, when a novel reassortant AIV H5N2 was isolated from a quail (considered as a “mixing vessel” for AIV, similar to the role of swine). LPAI H9N2 was also implicated in reassortant strains that found to have genetic markers that enhanced virulence in poultry and transmission to humans (16).

The third AIV strain that may constitute an important component of future public health threat is HPAI H5N8. Similar to the process underwent by HPAI H5N1, the epidemiology is primarily based on migration of a waterfowl reservoir. A critical reminder is the ability of the virus to cross the species barrier was documented in several events in which seals (32, 33) and foxes was found to be infected with this strain. Furthermore, a cluster of humans infected by

HPAI H5N8 was recorded in a poultry farm in Russia, this year (34). These outbreaks mark “sentinels” among mammals, regarding the process of the virus’ ability to adapt to mammals “milieu” as well to evade immune reaction. The ability of this strain to reassort was mentioned earlier.

REFERENCES

1. Mostafa, A., Abdelwhab, E.M., Mettenleiter, T.C. and Plechka, S.: Zoonotic potential of influenza A viruses: A comprehensive overview. *Viruses*. 10: 497, 2018.
2. Peacock, P.T., James, J., Sealy, E. J. and Iqbal, M.: A global perspective on H9N2 avian influenza virus. *Viruses*. 11: 620, 2019.
3. Goneau, W.L., Mehta, K., Wong J., L’Huillier, G. A. and Gubbay, B, J.: Zoonotic influenza and human health-Part 1: virology and epidemiology of zoonotic influenzas. *Current Infectious Disease Reports*. 20, 2018.
4. Kayali, G., Kandeil, A., El-Shesheny, R., Kayed, S.A., Maatouq, M.A., Cai, Z., McKenzie, P.P. and Webby, J.R.: Avian influenza A (H5N1) virus in Egypt. *Emerg. Infect. Dis.* 22: 379-388, 2016.
5. Centre for Health Protection. Avian influenza affected areas (Table 1) and global statistics of avian influenza A(H5N1) 2017. http://www.chp.gov.hk/files/pdf/global_statistics_avian_influenza_e.pdf.
6. Geerlings, L. C.E. and Heffernan, C.: Predicting risk of avian influenza a(H5N1) in Egypt: the creation of a community level metric. *BMC Public Health*. 18: 3338, 2018.
7. European Centre for Disease Prevention and Control, Human infection with avian influenza A(H5N1) virus, Egypt, 13 March, 2015. <https://www.ecdc.europa.eu/sites/default/files/media/en/publications/Publications/Rapid-Risk-Assessment-Influenza-A-H5N1-Egypt-March-2015.pdf>
8. Abdelwhab, M. E. and Abdel-Monein, S. A.: Epidemiology, ecology and gene pool of influenza A virus in Egypt: will Egypt will be the epicenter of the next influenza pandemic? *Virulence*. 6: 6-18, 2015.
9. Food and Agriculture Organization, Approaches to controlling, preventing and eliminating H5N1 highly pathogenic avian influenza in endemic countries: <http://www.fao.org/docrep/014/i2150e/i2150e.pdf>, 2011.
10. Monne, I., Hussein, A.H., Fusaro, A., Valastro, V., Hamoud, M. M., Khalefa, A.R., Dardir, N.S., Radwan, I.M., Capua, I. and Cattoli, G.: H9N2 influenza A virus circulates in H5N1 endemically infected poultry population in Egypt. *Influenza Other Respiratory Viruses*. 7: 240-243, 2013.
11. Kandeil, A., El-Shesheny, R., Maatouq, M. A., Moatasim, Y., Shehata, M.M., Bagato, O., Rubrum, A., Shanmuganatham, K., Webby, J.R., Ali, A.M. and Kayali, G.: Genetic and antigenic evolution of H9N2 avian influenza viruses circulating in Egypt between 2011 and 2013. *Arch. Virol.* 159: 2861-2876, 2014.
12. World Health Organization, influenza at the animal-human interface, summary and assessment, 2016. https://www.who.int/influenza/human_animal_interface/Influenza_Summary_IRA_HA_interface_11_15_2016.pdf
13. Naguib, M.M., Arafa, A.S., Parvin, R., Beer, M., Vahelnkamp, T. and Harder, C.T.: Insights into genetic diversity and biological

- propensities of potentially zoonotic avian influenza H9N2 viruses circulating in Egypt. *Virology*. 511: 165-174, 2017.
14. Selim, A. A., Erfan, A.M., Hagag, N., Zanaty, A., Samir, A.H., Samy, M., Abdelhalim, A., Arafa, A.A.S., Soliman, A. M., Shaheen, M., Ibraheem, M.E., Mahrous, I., Hassan, K.M. and Naguib, M.M.: Highly pathogenic avian influenza virus (H5N8) clade 2.3.4.4 infection in migratory birds, Egypt. *Emerg. Inf. Dis.* 23: 1048-1051, 2017.
 15. Shehata, A.A., Sedeik, M.E., Elbestawy, A.R., El-Abideen, Z.A.M., Ibrahim H.H., Kilany, W.H. and Ahmed, A.: Co-infections, genetic, and antigenic relatedness of avian influenza H5N8 and H5N1 viruses in domestic and wild birds in Egypt. *Poult. Sci.* 98:2371-2379, 2019.
 16. Kandeil, A., El-Shesheny, R., Maatouq, M. A., Cai, Z., Webby, J.R., McKenzie, P.P., Kayali, G. and Ali, A.M.: Novel reassortant H9N2 viruses in pigeons and evidence for antigenic diversity of H9N2 viruses isolated from quails in Egypt. *J. Gen. Virol.* 98:548-562, 2017.
 17. Hassan, K.E., King, J., El-Kady, M., Afifi, M., Abozeid, H.H., Pohlmann, A., Beer, M. and Harder, T.: Novel reassortant highly pathogenic avian influenza A(H5N2) virus in broiler chickens, Egypt. *Emerg. Inf. Dis.* 26:129-133, 2020.
 18. Hagag, N., Erfan, A.M., El-Husseiny, M., Shalaby, G.A., Saif, A.M., Tawakol, M.M., Nour, A.A., Selim, A. A., Arafa, F.A., Hassan, M.K., Hassan, M.M.W., Fahmy, H.A., Ibraheem, E., Attia, M., Abdelhakim, M.M.A., Shahein, A.M. and Naguib, M.M.: Isolation of a novel reassortant highly pathogenic avian influenza (H5N2) virus in Egypt. *Viruses*. 11:565, 2019.
 19. Guan, Y., Shortridge, F. K., Krauss, S. and Webster, G.R.: Molecular characterization of H9N2 influenza viruses: were they the donors of the "internal" genes of H5N1 viruses in Hong Kong? *Proc. Natl. Acad. Sci. U.S.A.* 96: 9363-9367, 1999.
 20. Lam, T-Y, T., Wang, J. and Guan, Y.: The genesis and source of the H7N9 influenza viruses causing human infection in China. *Nature*. 502: 241-244, 2013.
 21. Chen, H, Yuan, H., Gao, R., Zhang, J., Wang, D., Xiong, Y., Fan, G., Yang, F., Xiaodan L., Zhou, J., Shumei Z., Yang, L., Chen, T., Dong, D., Bo, H., Zhao, X., Zhang, Y., Lan, Y., Bai, T., Dong, J., Li, Q., Wang, S., Zhang, Y., Li, H., Gong, T., Shi, Y., Xiansheng, Ni, Jianxiong Li, Zhou, J., Fan, J., Wu, J., Zhou, X., Hu, M., Wan, J., Yang, W., DeXin Li., Wu, G., Feng, Z., Gao, G.F., Wang Y., Jin, Q., Liu, M. and Shu, Y.: Clinical and epidemiological characteristics of a fatal case of avian influenza A H10N8 virus infection: a descriptive study. *Lancet*. 383:714-721, 2014.
 22. Liu, D., Shi, W. and Gao, F.G.: Poultry carrying H9N2 act as incubators for novel human avian influenza viruses. *Lancet*. 383: 869, 2014.
 23. Bi, Y., Xie, Q., Zhang, S., Li, Y., Xiao, H., Jin, T., Zheng, W., Li, J., Jia, X., Sun, L., Liu, J., Qin, C., Gao, F.G. and Liu, W.: Assessment of the internal genes of influenza A (H7N9) virus contributing to high pathogenicity in mice. *J. Virol.* 89: 2-13, 2015.
 24. Davidson, I., Shkoda, I., Golender, N., Perk, S., Lapin, K., Khinich, Y. and Panshin, A.: Genetic characterization of HA gene of low pathogenic H9N2 influenza viruses isolated in Israel during 2006-2012 periods. *Virus Genes*. 46: 255-263, 2013.
 25. Matrosovich, N.M., Krauss, S. and Webster, G.R.: H9N2 influenza A viruses from poultry in Asia have human virus-like receptor specificity. *Virology*. 281: 156-162, 2001.
 26. <https://www.gov.il/he/departments/general/outbreaks-h5n1-avian-influenza>.
 27. Banet-Noach, C., Panshin, A., Golender, N., Simanov, L., Rozenblut, E., Pokamunski, S., Pirak, M., Tendler, Y., Garcia, M., Gelman, B., Pasternak, R. and Perk, S.: Genetic analysis of nonstructural genes (NS1 and NS2) of H9N2 and H5N1 viruses recently isolated in Israel. *Virus Genes*. 34: 157-168, 2007.
 28. Tiensin, T., Chaitaweesub, P., Songserm, T., Chaisingh, A., Hoon-suwan, W., Buranathai, C., Parakamawongsa, T., premashthira, S., Amonsin, A., Gilbert, M., Nielsen, M. and Stegeman, A.: Highly pathogenic avian influenza H5N1, Thailand, 2004. *Emerg. Infect. Dis.* 11:1664-1672, 2005.
 29. Leschnik, M., Weikel, J., Mostl, K., Revilla-Fernandez, S., Wodak, E., Bago, Z., Vanek, E., Benetka, V., Hess, M. and Thalhammer, G.J.: Subclinical infection with avian influenza A H5N1 virus in cats. *Emerg. Inf. Dis.* 13:243-247, 2007.
 30. <https://www.cidrap.umn.edu/news-perspective/2016/11/h5n8-detected-poultry-israel-hungary-india>.
 31. Xu, Y., Gong, P., Wielstra, B. and Si, Y.: Southward autumn migration of waterfowl facilitates cross-continental transmission of highly pathogenic avian influenza H5N1 virus. *Nature*. 6:30262, 2016.
 32. Shin, D-L., Siebert, U., Lakemeyer, J., Grilo, M., Pawliczka, I., Wu, N-H., Valentin-Weigand, P., Haas, L. and Herler, G.: Highly pathogenic avian influenza (H5N8) virus in gray seals, Baltic sea. *Emerg. Inf. Dis.* 25:2295-2298, 2019.
 33. <https://www.poultrymed.com/Poultrymed/Templates/showpage.asp?DBID=1&LNGID=1&TMID=178&FID=4970&PID=0&IID=80221>.
 34. <https://www.euro.who.int/en/countries/poland/news/news/2021/3/avian-influenza-ah5n8-infects-humans-in-russian-federation>.