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H5N6 influenza virus infection, the newest influenza

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ABSTRACT

The most recent new emerging infection is the H5N6 influenza virus infection. This infection has just been reported from China in early May 2014. The disease is believed to be a cross species infection. All indexed cases are from China. Of interest, the H5N6 influenza virus is the primary virus for avian. The avian H5N6 influenza virus in avian population is a low virulent strain. However, the clinical manifestation in human seems severe. In this mini-review, the authors summarize and discuss on this new emerging influenza.

1. Introduction

Influenza is an important virus. This virus can cause the infection in both human beings and animals. It is considered as an important virus. Medically, this infection can be seen in any countries around the world. The classical influenza infection can cause respiratory illness and becomes an important consideration in medicine. However, for a long time, the emerging of new influenza can be problematic. In medical history, the best example is the Spanish flu [1], which is a previous emerging influenza that killed millions of population. Hence, the emerging influenza becomes the important situation to be discussed in medicine [2]. Within the past few years, there are several new emerging influenzas. Those emerging influenza infections include H5N1 bird flu [3], H1N1 swine flu [4], H7N9 influenza [5] and H5N2 influenza [6]. Webster *et al.* recently said that “continuing challenges in influenza include the emergence of pandemic H1N1 influenza in 2009, human infections with avian H7N9 influenza in 2013, and sporadic human cases of highly pathogenic avian H5N1 influenza [7].” However, there are not only those mentioned new emerging influenza infections, but also other continuous new emerging influenza infections.

The most recent new emerging infection is the H5N6 influenza virus infection [8]. This infection has just been reported

from China in early May 2014. The disease is believed to be a cross-species infection. The first indexed case is an old male patient presenting with acute respiratory illness, pneumonia, and ended up with death. Of interest, the H5N6 influenza virus is the primary virus for avian. There is also an available avian vaccine for this virus [9]. An interesting opinion is that the avian H5N6 influenza virus is a low virulent strain. It does not cause severe disease in the avian population. However, the clinical manifestation in human seems severe. In this mini-review, the authors summarize and discuss on this new emerging influenza.

2. Emerging of human H5N6 influenza in 2014: a new problem

As already noted, the H5N6 influenza is considered a new emerging infection. This viral disease is caused by influenza virus. It is considered as a new atypical viral infection and a member of new emerging bird flu with medical importance. Any new bird flu might cause serious disease that is hard for control and management. Since the first emerging of bird flu H5N1 in human beings, there are many following bird flu that lead to worldwide concern. The great concern is on its possible pandemic, which can be a serious event (as the case of Spanish flu in medical history). For sure there is also a great concern for the newest emerging H5N6 influenza infection.

The H5N6 influenza virus infection is mainly confined among avian population. However, the cross-species infection to human beings becomes a new episode of the new emerging

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infection. As a possible new worldwide pandemic zoonosis, it has attracted a lot of attention of medical society. WHO documents that the emerging influenza infection is becoming an actual threaten to global public health system and recommends that the international collaboration to manage this problem is required [10]. For the new emerging avian influenza infection, Anderson *et al.* concluded that the main aims towards management include “(1) identify virological characteristics of avian influenza viruses (AIVs) important for zoonotic and pandemic disease, (2) evaluate the factors affecting evolution and emergence of a pandemic influenza strain and identify existing monitoring systems, and (3) identify modes of transmission and exposure sources for human zoonotic influenza infection (including discussion of specific exposure risks by affected countries) [11].”

To reach the success in management of the new influenza, there are several requirements. Duaphin *et al.* mentioned the important things in coping with new emerging influenza which include “commercial diagnostic kit evaluation, applied epidemiology, biosafety, vaccination, proficiency testing, development of standardized reference materials for sera and RNA, and issues at the human–animal interface [12]”. For the new emerging H5N6 influenza infection, it is no doubt that those mentioned requirements have to be fulfilled and should be the priorities for the present focus. Morikane noted that “there is still much uncertainty” regarding the emerging influenza and noted that the “flexibility of the policy in response to its nature might have saved us from an initial catastrophe in affected regions, and should be well-reflected for the preparation of the next, unforeseeable pandemic of emerging infectious disease [13].”

3. Genetic alteration in the new H5N6 influenza infection

An important consideration on any new emerging influenza infection is its origin. “Why the new virus occurs?” is a basic query to be answered. In fact, any virus has the genetic component. A classical virus might have a specific genetic component. This is also a basic concept when a scientist talks about the influenza virus. However, as a virus, its rapid replication means many multiplication cycles comparing to that of other living things. With many cycles, the chance of error in process during cycle can be expected. This can be simply explained by probability in mathematical statistical theory [14]. This is a real fact for the emerging avian influenza infection. Trampuz *et al.* concluded that “the widespread epidemic of avian influenza in domestic birds increases the likelihood for mutational events and genetic reassortment [15]” and “the threat of a future pandemic from avian influenza is real [15].” It is apparently proposed that genetic alteration is the basic problem causing existence of the new influenza virus. Reid and Taubenberger concluded that “novel influenza virus strains emerge periodically to which humans have little immunity, resulting in devastating pandemics [16].”

Generally, the genetic alteration which is called genetic reassortment is the basic findings in any new emerging influenza virus infections [17]. The observation is well described in the case of H5N1 bird flu [18–20] and H1N1 swine flu [21–23]. The pathogenic H5N6 influenza virus is proved to be a new emerging influenza virus. There are some recent reports on the genetic alteration of the new H5N6 influenza virus. Bi *et al.*

recently reported the problem within the genetic component of the new emerging H5N6 influenza virus [8]. Bi *et al.* reported that “genetic and phylogenetic analyses revealed that these H5N6 viruses are novel reassortants between H5N1 clade 2.3.4 and H6N6 viruses, and have evolved into two distinct lineages (Sichuan and Jiangxi) [8]”. Bi *et al.* found that “H5N6 viruses contained a T160A substitution in the HA protein and an 11-amino acid-deletion in the neuraminidase (NA) stalk, which may aid in enhancing viral affinity for human-like receptors, and virulence in mammals [8].” The genetic clarification of the new emerging H5N6 influenza virus is very important for further research and development on this new infection.

Indeed, the genetic reassortment that leads to the new virus has previously been observed [24,25]. As noted by Qi *et al.*, “phylogenetic analysis showed that the isolate was a novel reassortant virus with a neuraminidase gene from H6N6 viruses and the other seven genes from H5N1 viruses, which may pose a potential threat to human and animal health [25].” However, there has never been human case. A good example was reported by Ma *et al.* [24]. The observation was on the H10N6 variant [24]. Ma *et al.* noted that “H10 viruses further reassorted, apparently with H5N6 viruses, and generated an H10N6 variant [24].”

4. Clinical presentation of the new H5N6 influenza infection

Clinical presentation of the new H5N6 influenza infection is very interesting. As an influenza virus infection, the classical signs and symptoms of the classical influenza are expected to be detectable in new H5N6 influenza infection. The classical clinical feature of the classical influenza is an acute febrile illness with respiratory signs and symptoms. However, H5N6 influenza infection is a new atypical bird flu, the typical clinical signs and symptoms can be expected. Generally, a new atypical influenza infection usually manifests non respiratory signs and symptoms such as gastrointestinal and neurological manifestations [26,27].

For the new emerging H5N6 influenza virus infection, there are few information on the clinical presentation since there are only 2 recorded human cases at present (all cases are adults). The first case of H5N6 influenza virus infection presented with severe clinical features. Severe pneumonia was observed in this case and the patient ended up with death. Focusing on the second case, which is also recorded from China, similar clinical features and clinical course could be observed. Both cases have signs and symptoms of severe respiratory tract illness. A rapid progression of illness to pneumonia can be seen and this is considered the reflection of severity of the infection. The atypical non respiratory illness is not significantly noted in these two cases. The common risk factor as exposure to death poultry could be identified in the indexed cases. According to the suggestion by local Chinese Centers for Disease Control (CDC), it is concluded that “both the first and second human H5N6 infections are sporadic cases. Thus far, there is no evidence of sustained human-to-human transmission of the virus. Travelers visiting China are urged to practice good personal hygiene and avoid contact with poultry and birds to ward off infection [28].” The local CDC also suggested for preventive measures including “avoiding visiting live poultry market and live bird market, avoiding direct contact with poultry and birds or their droppings, consuming only thoroughly cooked poultry and eggs, and washing hands frequently [28].”

5. Epidemiology of the new H5N6 influenza infection

The epidemiology of the emerging H5N6 influenza infection is presently widely studied. The infection can be seen in avian population worldwide. Nevertheless, the information on human infection in the new emerging episode is a focused point for medical community. In fact, the information on new emerging human H5N6 influenza infection is limited. The two indexed cases of new emerging H5N6 influenza infection occurred in China but in different provinces (Sichuan Province and Guangdong Province). Both cases are adult (49 years old and 58 years old). As already noted, both cases have the history of contact to dead poultry before getting infection. Qi *et al.* noted that “live poultry markets may play an important role in the evolution and transmission of avian influenza viruses [25].” Indeed, at present, the existence of circulating H5N6 influenza virus can be seen in many areas of China [28]. For the possible human-to-human transmission, the investigation on the closely related persons to both patients showed no evidence of infection [28]. Nevertheless, information from only two indexed cases are extremely few for reaching the conclusion on the epidemiology of the new emerging infection. Qi *et al.* concluded that “the epidemiology and biological characterization of the H5N6 virus are still unknown in China [25].”

6. Clinical diagnosis of the new H5N6 influenza infection

The clinical diagnosis of the new H5N6 influenza infection is a big challenge. Indeed, the diagnosis of the new emerging influenza infection is not easy. The disease cannot be diagnosed by clinical presumptive diagnosis. The clinical findings are usually not differentiable from other acute respiratory illness and this makes the difficulty to reach the definitive diagnosis. In both indexed cases, the final diagnoses can be derived after the molecular diagnosis of the genetic components of the isolated viruses [28]. PCR is usually the tool for definitive diagnosis. Focusing on the specific observation from genetic study, Qi *et al.* reported that the new virus has “the full lengths of the polymerase PB2 and PB1, polymerase acidic protein (PA), hemagglutinin (HA), nucleoprotein (NP), neuraminidase (NA), matrix (M), and nonstructural (NS) genes were 2,341, 2,341, 2,233, 1,776, 1,565, 1,464, 1,027, and 890 nucleotides, respectively [25]” and “the amino acid sequence of the cleavage site in the HA protein was PLREKRRKR↓GLF [25]” which confirmed the nature of the highly pathogenic bird flu [29].

However, an important consideration on the diagnosis is the availability of the diagnostic tool and consideration of the practitioner to recognize the possibility of occurrence of the new infection. The local CDC suggested that the investigation should be considered in any cases with unexplained acute febrile illness with severe respiratory manifestation and have history of contact to dead poultry or travel to the risk area [28].

7. How to treat the patient with new H5N6 influenza infection

As a new emerging infectious disease, it is difficult to manage the infected cases. Since there is no knowledge, the treatment is usually a new trial. However, as a member of influenza, the management of the case can be based on the

general treatment of influenza. The antiviral drug for the influenza virus infection is presently available [30]. Also, the management of the influenza should also include the symptomatic and supportive management. This is the basic requirement in clinical management of influenza.

The widely used antiviral at present is oseltamivir [31]. In fact, oseltamivir is the antiviral drug for management of classical influenza infection. It was also used for management of the patients with the new atypical influenza infection [32]. However, the common problem is the unknown effectiveness of the drug. For sure, the information is usually lack and it is usually problematic in the first phase of disease outbreak [32]. Based on the data on the available two indexed cases, it was not proved that the use of oseltamivir can be effective against the new emerging H5N6 influenza infection. Nevertheless, the use of oseltamivir in avian infection is still proved to be effective and there is no problem of drug resistance [33].

8. Prevention for the new H5N6 influenza infection

Vaccine is usually a hope for disease control and prevention. As a new emerging infection, there is no specific vaccine for it. However, it should be noted that the vaccine is available for animal. The “adjuvanted heterologous H5N6 avian influenza virus vaccine” is available and can be used for disease prevention in animal [9]. This vaccine was studied in feline model and also found to be effective for prevention against H5N1 bird flu [9]. Nevertheless, there is still no trial of the mentioned vaccine on human beings. It is urgently needed to find the new vaccine to correspond to the possible pandemic of H5N6 influenza. The use of bioinformatics might be helpful for finding the new vaccine. The ongoing researches on this specific area can be seen in several modern medical research laboratories [32].

Apart from the use of vaccine, the basic prevention measures towards H5N6 influenza infection should not be forgotten. Basic sanitation seems to be important for prevention of any new emerging influenza infections [34]. This should include the promotion of hand washing and use of face mask. However, the success of the prevention depends on good plan and management. To manage the new emerging infection, Coker *et al.* proposed that “the challenges in control of emerging infectious diseases are formidable and range from influencing the factors that drive disease emergence, to making surveillance systems fit for purpose, and ensuring that regional governance mechanisms work effectively to improve control interventions [34].”

9. Future perspective

More researches and studies on this newest emerging influenza infection are necessary. Until present (January 2015), it seems that there are too few data on this specific infection. A possible explanation might be due to the little extension of this disease from its origin. Nevertheless, there is an interesting scientific report from China on the genetics of the H5N6 influenza. Qi *et al.* reported on “whole-genome sequence of a reassortant H5N6 avian influenza virus isolated from a live poultry market in China [25].” Based on this information, it is no doubt that the new H5N6 influenza can be a possible problematic infection and the consideration from the medical society around the world is needed. Finally, due to the confined foci of the infection, the

development of new drugs and vaccines corresponding to this new infection might be little progressed. It should be noted that there is an inactivated, adjuvanted heterologous H5N6 avian influenza virus vaccine which is available for animal [9] but it is not approved for human beings at all. In the next 5 year, it is expected that there will be more cases of the new H5N6 influenza infection and there will also be many new researches and development on diagnostic tool, antiviral drug and vaccine towards this new disease.

10. Conclusion

The emerging of the new H5N6 influenza infection from China leads to several concerns in the medical community. As a new emerging infection, Urgent knowledge collection on the new H5N6 influenza infection is recommended. Several concerns for the present situation of emerging H5N6 influenza in human beings are as followings: (1) It is required to tract the tract of cross-species infection of this new infection. The tools can be genomics, epidemiology and clinical studies. (2) The promotion of health sanitation to prevent spreading of the disease is needed. The basic rule for prevention of respiratory contagious disease can be applied. (3) Surveillance system to identity any new emerging disease is needed. In the mean time, it is required to provide wide scale health education to both medical personnel and general practitioner to cope with this newest infection. (4) Also, finding for a new drug and vaccine to correspond to the new infection must be parallel done. (5) Finally, it calls for international participation and sharing of knowledge towards this new disease.

Conflict of interest statement

We declare that we have no conflict of interest.

References

- [1] Webster RG. 1918 Spanish influenza: the secrets remain elusive. *Proc Natl Acad Sci U S A* 1999; **96**(4): 1164–6.
- [2] Webster RG, Wright SM, Castrucci MR, Bean WJ, Kawaoka Y. Influenza—a model of an emerging virus disease. *Intervirology* 1993; **35**(1–4): 16–25.
- [3] Subbarao K, Katz J. Avian influenza viruses infecting humans. *Cell Mol Life Sci* 2000; **57**(12): 1770–84.
- [4] Wiwanitkit V. Swine flu: the present pandemic infectious disease. *Kulak Burun Bogaz Ihtis Derg* 2009; **19**(2): 57–61.
- [5] Wiwanitkit V. H7N9 influenza—the laboratory presentations: a letter to editor. *Asian Pac J Trop Biomed* 2013; **3**(7): 584–5.
- [6] Joob B, Wiwanitkit V. Human H5N2 bird flu infection: fact or fallacy? *Asian Pac J Trop Biomed* 2014; **4**(Suppl 1): S49.
- [7] Webster RG, Govorkova EA. Continuing challenges in influenza. *Ann N Y Acad Sci* 2014; **1323**: 115–39.
- [8] Bi Y, Mei K, Shi W, Liu D, Yu X, Gao Z, et al. Two novel reassortants of avian influenza A(H5N6) virus in China. *J Gen Virol* 2015; <http://dx.doi.org/10.1099/vir.0.000056>.
- [9] Vahlenkamp TW, Harder TC, Giese M, Lin F, Teifke JP, Klopffleisch R, et al. Protection of cats against lethal influenza H5N1 challenge infection. *J Gen Virol* 2008; **89**: 968–74.
- [10] WHO. Influenza research at the human and animal interface: report of a WHO working group. Geneva: WHO; 2006. [Online] Available from: http://www.who.int/csr/resources/publications/influenza/WHO_CDS_EPR_GIP_2006_3/en/index.html [Accessed on 13th January, 2014].
- [11] Anderson T, Capua I, Dauphin G, Donis R, Fouchier R, Mumford E, et al. FAO-OIE-WHO joint technical consultation on avian influenza at the human-animal interface. *Influenza Other Respir Viruses* 2010; **4**(Suppl 1): 1–29.
- [12] Dauphin G, Hamilton K, Kim LM, Choudhury B, Capua I, Edwards S. Main achievements of the World Organisation for Animal Health/United Nations Food and Agriculture Organization network on animal influenza. *Avian Dis* 2010; **54**(Suppl 1): 380–3.
- [13] Morikane K. [Changing management of pandemic influenza]. *Rinsho Byori* 2010; **58**(3): 254–62. Japanese.
- [14] Rouzine IM, Rodrigo A, Coffin JM. Transition between stochastic evolution and deterministic evolution in the presence of selection: general theory and application to virology. *Microbiol Mol Biol Rev* 2001; **65**(1): 151–85.
- [15] Trampuz A, Prabhu RM, Smith TF, Baddour LM. Avian influenza: a new pandemic threat? *Mayo Clin Proc* 2004; **79**(4): 523–30.
- [16] Reid AH, Taubenberger JK. The origin of the 1918 pandemic influenza virus: a continuing enigma. *J Gen Virol* 2003; **84**: 2285–92.
- [17] Urbaniak K, Markowska-Daniel I. *In vivo* reassortment of influenza viruses. *Acta Biochim Pol* 2014; **61**(3): 427–31.
- [18] Zeitlin GA, Maslow MJ. Avian influenza. *Curr Allergy Asthma Rep* 2006; **6**(2): 163–70.
- [19] Kida H. [Avian influenza virus]. *Uirusu* 2004; **54**(1): 93–6. Japanese.
- [20] World Health Organization Global Influenza Program Surveillance Network. Evolution of H5N1 avian influenza viruses in Asia. *Emerg Infect Dis* 2005; **11**(10): 1515–21.
- [21] Lam TT, Zhu H, Wang J, Smith DK, Holmes EC, Webster RG, et al. Reassortment events among swine influenza A viruses in China: implications for the origin of the 2009 influenza pandemic. *J Virol* 2011; **85**(19): 10279–85.
- [22] Krueger WS, Gray GC. Swine influenza virus infections in man. *Curr Top Microbiol Immunol* 2013; **370**: 201–25.
- [23] Choi YK, Pascua PN, Song MS. Swine influenza viruses: an Asian perspective. *Curr Top Microbiol Immunol* 2013; **370**: 147–72.
- [24] Ma C, Lam TT, Chai Y, Wang J, Fan X, Hong W, et al. Emergence and evolution of H10 subtype influenza viruses in poultry in China. *J Virol* 2015; **89**(7): 3534–41.
- [25] Qi X, Cui L, Yu H, Ge Y, Tang F. Whole-genome sequence of a reassortant H5N6 avian influenza virus isolated from a live poultry market in China, 2013. *Genome Announc* 2014 Sep 11; **2**(5); <http://dx.doi.org/10.1128/genomeA.00706-14>. pii: e00706–14.
- [26] Wiwanitkit V. Neurological manifestation in new emerging H7N9 influenza: an issue in neurology. *Acta Neurol Taiwan* 2013; **22**(3): 138–9.
- [27] Hui DS. Review of clinical symptoms and spectrum in humans with influenza A/H5N1 infection. *Respirology* 2008; **13**(Suppl 1): S10–3.
- [28] Center of Disease Control. R.O.C. (Taiwan). As human H5N6 infection confirms in Guandong Province, Taiwan CDC advises travelers to take preventive measures. Taiwan: Center of Disease Control. R.O.C.; 2014. [Online] Available from: <http://www.cdc.gov.tw/english/info.aspx?treeid=bc2d4e89b154059b&nowtreeid=ee0a2987cfba3222&tid=39E7EDA567E70E8B> [Accessed on 1st January, 2015].
- [29] Guan Y, Poon LL, Cheung CY, Ellis TM, Lim W, Lipatov AS, et al. H5N1 influenza: a protean pandemic threat. *Proc Natl Acad Sci U S A* 2004; **101**(21): 8156–61.
- [30] Król E, Rychłowska M, Szewczyk B. Antivirals—current trends in fighting influenza. *Acta Biochim Pol* 2014; **61**(3): 495–504.
- [31] Schirmer P, Holodniy M. Oseltamivir for treatment and prophylaxis of influenza infection. *Expert Opin Drug Saf* 2009; **8**(3): 357–71.
- [32] Wiwanitkit V. Current research on drugs and vaccines for fighting bird flu. *Trans R Soc Trop Med Hyg* 2007; **101**(12): 1171–2.
- [33] FAO. Avian influenza A(H5N6): the latest addition to emerging zoonotic avian influenza threats in East and Southeast Asia. Rome: FAO; 2014. [Online] Available from: www.fao.org/3/a-i4199e.pdf [Accessed on 3rd January, 2015].
- [34] Coker RJ, Hunter BM, Rudge JW, Liverani M, Hanvoravongchai P. Emerging infectious diseases in southeast Asia: regional challenges to control. *Lancet* 2011; **377**(9765): 599–609.