Eastern Journal of Medicine 19 (2014) 119-125

Review Article

Molecular epidemiology of influenza in Asia

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Abstract. Influenza means 'flu', caused by RNA viruses of *Orthomyxoviridae* family which is an infectious agent of birds and mammals. It causes mild to severe symptoms including chills, fever, sore throat, muscle pains, headache, coughing, fatigue but about 33% of the cases with influenza are asymptomatic. Occasionally it leads to pneumonia in both healthy and immunosuppressive person. Influenza is transmitted through the air by coughing, sneezing or creating aerosols containing influenza. It can also be transmitted by direct contact with bird droppings or nasal secretions or through contact with contaminated surfaces. Influenza now spreads all over the world and it is also known as seasonal epidemics. Several reports depicted both emergence and pandemic potential of the virus in the perspective of earlier pandemic influenza viruses of 1918 (H1N1), 1957 (H2N2) and 1968 (H3N2) by comparison of the available genetic sequence data. An avian strain named H5N1 raised the concern of a new pandemic after it emerged in Asia in 1990s. After several years 'swine flu', also known as influenza A/ H1N1, emerged in Mexico, USA and several other nations. The principal objective of the present work is to investigate the evolutionary history of the viruses circulating in Asia and to understand the relationship between epidemiologic and evolutionary process within the affected human population.

Key words: Influenza, Pandemic, Avian, H5N1, Epidemiology, Isolates

1. Introduction

Influenza viruses are evolutionary dynamic viruses with high mutation rate (1). The molecular epidemiology of the influenza viruses circulating in Asia is of wide international concern because strong travel and large number of migratory birds makes the viruses easy to spread between Asia and other countries (2). *Influenza A* virus is one of the most progressive pathogens causing regular, yearly epidemics worldwide associated with significant morbidity and mortality in humans (3,4). This was proved by recent emergence and continued prevalent 2009 swine origin pandemic H1N1 *Influenza A* virus, eliciting first true pandemic in the past 40 years (5). Many respiratory pathogens can present with "influenza-like" symptoms. Thus, infections caused by other respiratory pathogens may occasionally be complex to distinguish from actual influenza infection on the basis of clinical manifestation alone (6). Therefore, accurate laboratory diagnosis is important in managing influenza virus infection.

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Received: 15.12.2013
Accepted: 05.08.2014

Types of Influenza

There are three different types of *influenza virus – A, B,* and *C*. The type A viruses are the most virulent human pathogens among the three influenza types and cause the most severe disease. The *influenza A* virus can be subdivided into different serotypes based on the antibody response to these viruses (7). Two different proteins which are present on the surface of these viruses are called hemagglutinin (HA) and neuraminidase (NA). There are 16 different versions of HA and 9 different versions of NA (8). *Influenza B* almost exclusively infects humans (7) and is less common than *influenza A*. The only other animals known to be susceptible to *influenza B* infection are the seal and the ferret (9,10). This type of influenza mutates at a rate 2–3 times slower than type A (11) and consequently is less genetically diverse, with only one *influenza B* serotype (7). *Influenza C* virus infects humans, dogs and pigs, sometimes causing both severe illness and local epidemics (12). However, *influenza C* is less common than the other types and usually only causes mild disease in children (13).

Molecular Epidemiology of Influenza in Asia

Since its emergence, influenza viruses have become panzootic in several Asian and African countries, resulting in frequent outbreaks in poultry and increased cases of human infection,

giving rise to a persistent pandemic risk. These devastating viruses have caused damage in domestic poultry and have killed over 60% of infected humans. The spread of influenza have occurred in three waves, wave one to East Asia and Southeast Asia, wave two through Qinghai Lake, China, to Europe, India and Africa, and wave three to Southeast Asia again (14). The spread of highly pathogenic *avian influenza virus* (H5N1) at a place raises concerns regarding the serious impact of this infection on wild birds, domestic poultry and human health. This pathogenic subtype has become endemic in poultry in Asian countries since 2003 (15).

China

The emergence of highly pathogenic Asian H5N1 influenza virus was first detected in Guangdong in the People's Republic of China (China) in 1996. Later in early 1997 birds were entering Hong Kong SAR from the People's Republic of China. Although it cannot be definitively confirmed it is believed that viruses within the H5N1 group were first evolving in the agricultural ecosystem of southern China earlier in the 1990s. It appears that the viruses have arisen by reassortment among former progenitor viruses including H9N2 and H6N1, both of which have been found primarily in quail in Hong Kong (16). H9 viruses consist of three different lineages, one isolated from quail and the other two from chickens, ducks and aquatic birds. The quail originated virus appears to have contributed the viral replicating mechanism to the H5N1 virus which caused the 1997 outbreak in Hong Kong SAR. During 1999 to 2002, H5N1 viruses were circulating in aquatic poultry in the People's Republic of China (17), where they could be isolated from healthy ducks (18). The viruses detected were highly pathogenic for chickens, and showed increasing pathogenicity for mammals.

Siberia

Western Siberia is of major significance in ecology and epidemiology of influenza. This district is nesting area for vast amount of bird species. This area is an intersection point of bird migration in different regions of the world: Europe, Africa, Middle East, Central Asia, India, and South East Asia (19). It is believed that reassortant influenza viruses that can cause outbreak among population may emerge in Western Siberia with high probability. In western part of Siberia large variety of influenza A viruses among different wild bird species was found (20). It was found that during 10 years *influenza A*/H3N8 and *A*/H4N6 virus subtypes prevail among birds (20). Throughout the 2008–2009 epidemic seasons in Western Siberia *influenza A*/H1N1, *A*/H3N2 and *influenza B* viruses circulated. Percentage of isolates was almost equal between *A*/H1 and *A*/H3 strains. All of the strains were similar to pandemic strain A/California/04/2009. During the epidemic season of 2010–2011 matched criteria of post-pandemic season, first of all due to circulation of several etiologic agents and initiate antigenic drift of A/H1N1pdm09 virus. However, pandemic influenza strains dominated in epidemic process. In the 2011–2012 season A/H1N1pdm09 virus did not already dominate. Moreover, in the South of Western Siberia in 2011–2012 we did not isolate any of strains of this subtype (19).

Vietnam

The outbreak of A(H1N1)pdm09 infection in Vietnam was confirmed in May 2009 via the United States and rapidly spread throughout the country (21). According to the findings 11,047 cases of novel A (H1N1) pdm09 infection were identified up to 21 December 2009, with 50 deaths (22). The outbreak started at the end of June 2009, and the clinically reported cases increased in the following months, reaching the peak in October and November. The total number of clinically identified cases from the beginning of the outbreak to 30 December 2009 was 2,051, and no deaths were reported from the Provincial Health Service (23). It was reported that 93.7% of the total *influenza A* isolates belong to the new A (H1N1)pdm09 virus and the remaining 6.3% belong to the previously circulating seasonal H1N1 subtype (24,25). By sequencing the HA and NA genes of some example isolates from Thua Thien Hue suggests that they are genetically very close and most probably originated from the same clade of A(H1N1)pdm09. Recent reports have shown that a small proportion of *influenza A* (H1N1) pdm09 viruses have an NA mutant substitution at H275Y (N1 numbering, H275Y) that has been reported to give a high degree of resistance to oseltamivir (26-29). This mutant isolate of influenza A(H1N1)pdm09 virus was also detected in Vietnam (27,29,30).

Thailand

The first wave in Thailand, occurred in a patchwork of geographical areas concentrated in the north, with a smaller focus in the far south – neither of which are areas where commercial poultry production is significant, and neither is an area with strong emphasis on duck-raising (31). Early in the epidemic the viruses isolated in Thailand and Vietnam are nearly identical

suggests that they came from the same primary source (31).

Nepal

The government of Nepal has been classified the Kathmandu as a high-risk area for highly pathogenic avian influenza (HPAI) (32). While ducks have a vital role in the transmission of *avian influenza viruses* (AIV), including HPAI, seroprevalence of antibodies to AIV in domestic ducks of Kathmandu has never been reviewed. From April through July of 2011, a cross-sectional study was conducted and a total of 310 ducks in the main duck-raising areas of Kathmandu were sampled (32). The estimated prevalence of AIV antibodies was 27.2%. Of 62 enrolled farms, 42% had at least one seropositive duck. Half of the enrolled farms also kept pigs of which 52% had at least one seropositive duck (32). Bivariate study showed the association between ducks' seroconversion to AIV and their age, sex and farm size. However, the final multivariable model, after controlling for clustering of ducks within farms, identified age as the only significant risk factor. Based on this model, ducks older than 1 year of age were more likely to be seropositive compared to ducks <6 months of age. These outcomes supply baseline information about the AIV seroprevalence in domestic ducks in the major duck-raising areas of Kathmandu and recognize a high-risk group that can be targeted in surveillance activities.

Malaysia

The seroprevalence of pandemic *influenza A* (H1N1) 2009, seasonal H1N1 and H3N2 was isolated in Kuala Lumpur, Malaysia (27). The seroprevalence of A(H1N1)pdm09 increased from 3.7% pre-pandemic to 21.9% post-pandemic, giving an overall cumulative incidence of 18.1% (95% CI, 13.8-22.5%), mainly due to increases in those <5, 5-17, and 18-29 years old (33). On the contrary with findings from USA, Europe, and Australia, pre-existing seroprevalence to A(H1N1)pdm09 was low at 5.6% in the elderly age group of >55 years (33). A (H1N1)pdm09 affected almost a third of those <30 years in Kuala Lumpur. Pre-pandemic seroprevalence was 14.7% for seasonal H1N1 and 21.0% for H3N2, and these rates did not change significantly after the pandemic (33). Seasonal and pandemic influenza cause a significant burden in tropical Malaysia, particularly in children and young adults.

Singapore

In Singapore, a study showed 18% positivity for the presence of *influenza A* virus and 3% for *influenza B* virus from the 266 study samples taken from the students and stuffs of National University of Singapore (NUS) during May 2007 to October 2007 (1). Eighteen percent of the samples were positive for *influenza A* virus by RT-PCR and 8% by viral isolation method. The predominant subtype was *influenza A*/H3N2 (55%) and the rest were A/H1N1 (45%) (1). Majority of the Singapore strains were closely related to each other by sequence analysis, this suggests that the majority of influenza was localized. This has implications for the response to future pandemics.

Bangladesh

The first introduction of clade 2.3.2 into South Asia occurred in Nepal in February 2010, and successive outbreaks occurred in Eastern India and Bangladesh in 2011 (34). The majority of H5N1 viruses isolated in Bangladesh from 2007 to 2011 belonged to clade 2.2, another 9 viruses belonged to clade 2.3.2 and only 3 viruses were in clade 2.3.4. According to the World Organization of Animal Health (OIE), a total of 519 outbreaks of HPAI occurred in Bangladesh prior to 22 October 2011, of which 164 occurred in 2011 (35). Forty-nine of the 64 districts in Bangladesh have been affected by a variety of clades of H5N1 between 2007 and 2011. Three human cases caused by clade 2.2 virus have been reported up to 2011, all of which were non-fatal.

India

In India the H1N1pdm virus is circulating through its emergence continuously and viral cases are being reported from different parts of the country in post pandemic phase (36,37). The number of cases of H1N1pdm started rising from September 2010 with maximum number of cases. All the four probes viz. *Influenza A,* Swine *Influenza A*, Swine H1, RNase P (Inf A, swA, swH1, RNP) were found positive for H1N1pdm virus. Almost all the representative circulating H1N1pdm viruses from India were studied in the phylogenetic analysis from 2009–2012. Comparison of each individual gene segment at protein level with respect to A/California/04/2009 (H1N1pdm prototype strain) and A/India/Pune/NIV6447/2009 (previously sequenced Indian strain) revealed a total of 73 substitutions scattered throughout the eight gene segments in four Indian viruses. The H1N1/2009 viruses have remained antigenically and genetically stable and are relatively low virulence in humans since its detection in April 2009. Most genetic changes in H1N1pdm to date have not been clearly linked to changes in antigenicity, disease severity, antiviral drug resistance, or

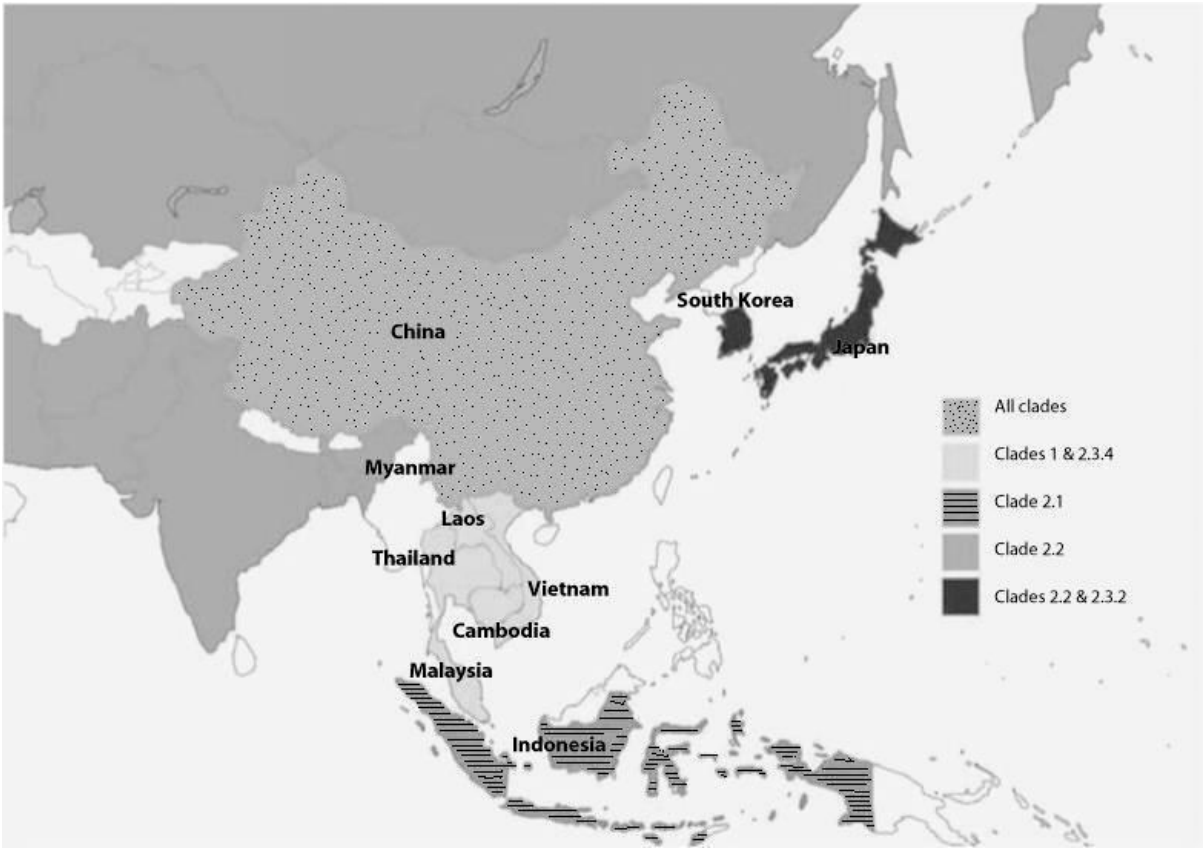

Fig. 1. Distribution of A/Goose/Guangdong/1/96-like H5N1 virus haemagglutinin clades reported from poultry and wild birds since 1996 (53).

transmission efficiency. However, rapid evolution rate characteristic of influenza viruses suggest that changes in antigenicity are inevitable in future (38).

Pakistan

In Pakistan the first laboratory recognized infection with A(H1N1)pdm09 influenza was detected on 18 June 2009. In a span of few weeks, A(H1N1)pdm09 viruses had diversified adequately to form 7 distinct clades, although the epidemiological behaviour of these viruses was largely the same with certain risk groups (such as pregnant women, diabetics, obesity) more prominently vulnerable than others (39). It was confirmed in a study that even the earliest imported isolates clearly belonged to clade 7. All the sequenced viruses belonged to clade 7 with signature change S203T, and no clade 5 or 6 that initially appeared in Asia in May–September, 2009 (40,41). The antigenic profile of all tested 2009–2010 Pakistan isolates showed that these viruses were antigenically close to the A/California/7/2009 vaccine virus. The sequence data of the Pakistan viruses showed a high homology for all eight genes to the A(H1N1)pdm09 viruses from bordering countries and to A/California/07/2009. The isolates group indistinguishably with other viruses on phylogenetic analysis. There is no evidence of gene re-assortment between pandemic strain and co-circulating seasonal influenza H1N1 or H3N2 viruses during this time period (42).

Taiwan

In Taiwan *Influenza A* virus is one of the most active pathogens causing regular, yearly epidemics worldwide related with significant morbidity and mortality in humans (43,44). Surveillance of influenza movement in Taiwan is based on laboratory isolation of influenza viruses and sentinel general practitioner reports of influenza-like illness. Of the Taiwan isolates analyzed using post-infection ferret antisera, 22.3% were H1N1, 40.4% H3N2, and 37.3% *influenza B* viruses illustrating the *influenza A* viruses were somewhat more active during the surveillance period (45). Analysis phylogenetic and antigenic data revealed that H1N1 and H3N2 viruses consistently co-circulated in Taiwan, although they were characterized by different sequential dynamics and degrees of genetic diversity. The patterns of gene re-assortment were different in the two subtypes. The internal

genes of H1N1 viruses moved as a unit, individually from the co-evolving HA and NA genes. The high genetic diversity of *influenza A* viruses observed in Taiwan make possible to capture the evolutionary dynamic and epidemiological rules governing antigenic drift and re-assortment and may provide as a ‘‘warning’’ system that recapitulates the global epidemic (45).

Transmission of Influenza in Asia

H5N1 HPAI outbreaks were recorded approximately in eight eastern and southeastern Asian countries from November 2003 to February 2004, constituting the first H5N1 outbreak and transmission wave (46). All of the viruses detected in these countries during wave 1 were genotype Z. The viruses existing in Vietnam, Thailand, Laos, Cambodia and Malaysia (clade 1) were originated from Yunnan province of China, with which Laos and Vietnam share a land border (showed in figure), while the viruses prevailing in Indonesia were derived from the viruses from Hunan detected in early 2003 (46- 48). Therefore, available information suggests that all H5N1 variants from the first transmission and outbreak wave were initiated from China, possibly via movement of poultry or poultry products.

The second most important transmission and outbreak wave of H5N1 virus was initiated following the Qinghai Lake outbreak in migratory birds in April 2005 (49,50). In spite of continued endemicity of HPAIV H5N1 in China over several years, the Qinghai outbreak created the first observed massive death of migratory birds. Later, viruses closely related to those isolated from the Qinghai Lake outbreak (QH-like virus, clade 2.2) were detected in other countries to the west and northwest (showed in figure). These clade 2.2 viruses were transmitted from China to Mongolia, Siberia, Central Asia, the Middle East, eastern and Western Europe, and were eventually introduced into Africa within seven months (51).

Later in 2006, H5N1 influenza viruses sustained to be panzootic in different species of poultry (48). It was revealed by genetic and antigenic analysis that the emergence and prevalence of an earlier uncharacterized H5N1 virus sublineage. This variant was first isolated from ducks in Fujian in March 2005. Since early 2006, the majority of H5N1 influenza isolates from southern China have belonged to this novel sublineage. This virus was also transmitted to Hong Kong, Laos, Malaysia, Thailand and Vietnam (48). On the basis of epidemiological findings in northern Vietnam suggested that this variant (genotype V, clade 2.3.4) also replaced the previously endemic strains, but in southern Vietnam the viruses still belonged to clade 1 (52). It is quite clear that until the virus population can be effectively brought under control the endemicity of H5N1 virus in poultry across such a vast geographical area will continue to drive genetic and antigenic change.

2. Conclusion

Different influenza subtypes can progress at very different rates. As the plan of effective control and prevention strategies for infectious diseases needs to be notified by epidemiological study and modeling research at animal level, additional essential insight into transmission dynamics can be provided by combining epidemiological with phylogenetic data. H1N1 and H3N2 are the two influenza subtypes that frequently escape population immunity by changing their antigenic properties. In the case of RNA viruses with high mutation rates, such as HPAIV H5N1, significant effects may be inferred at large and small spatial and temporal scales, as discussed in this review. In addition, if vaccination is used as part of a control and prevention strategy for such virus diseases, phylogenetic analysis also becomes significant for surveillance, since the vaccine may only be efficacious for a relatively slight range of genetic variants which in turn results in selection pressure for variants against which the vaccine does not cross-protect. Ideally, risk management policy adaptation should be proof based, but current global and regional HPAIV H5N1 policies do not appear to take adequate account of geographic variability in molecular virus characteristics.

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