The Influenza Viruses

Influenza infections are reported globally with an annual attack rate estimated at 5%–10% in adults and 20%–30% in children. This results in about 3–5 million cases of severe illness, and about 250,000 to 500,000 deaths annually. Although the seasonality of influenza differs in the tropical and temperate regions, the overall disease burden and mortality remains comparable [1,2].

Influenza viruses are enveloped, negative stranded segmented RNA viruses belonging to the Family Orthomyxoviridae and Genus Orthomyxovirus that in turn consists of five genera: InfluenzavirusA-C, Isavirus and Thogotovirus [3]. Recent studies have identified a novel genus of influenza virus in cattle and dogs, and have tentatively been named Influenzavirus D [4]. Of these, influenza virus types A and B cause regular epidemics and type A occasionally causes pandemics. Influenza type C can infect humans but causes little or no disease. Influenza types A and B are grouped based on antigenic differences of their nucleocapsid and matrix proteins [5]. Influenza A viruses are further subtyped based on the antigenic differences between two surface glycoproteins, the haemagglutinin (HA) and neuraminidase (NA) [6,7)]. Eighteen HA subtypes and 11 NA subtypes have been identified and they are designated H1-H18 and N1-N11, respectively. Wild aquatic birds are considered to be the natural reservoir of influenza A viruses of subtypes H1-H16 and N1-N9 [8]. Recently novel influenza A H17N10 and H18N11 viruses have been detected in bats [9-10]. However, only limited number of influenza subtypes; 3 HA subtypes (H1-H3) and 2 NA subtypes (N1, N2) are so far known to have established themselves in the human population [6], although a number other subtypes (e.g. H5-H7, H9, H10) have caused occasional zoonotic infection [1].

There are no known animal reservoirs of influenza B and influenza C viruses, and these infections are mainly confined to humans, although infrequently isolated in non human species [7,11,12]. Only single subtypes of HA and NA is recognized in influenza B and C viruses [13]. Influenza B has two designated virus lineages; Victoria and Yamagata that differ in their serological cross-protection [2].

The hallmark of influenza viruses is ability to evolve continuously through the mechanisms of antigenic drift and shift [7]. Antigenic drift is a result of slow antigenic change in the virus HA and NA genes through the accumulation of mutations in the error prone viral genome due to lack of "proof-reading" mechanism of the viral polymerase, under influence of positive selection pressure of the host immune system, which selects mutants that escape preexisting neutralizing antibodies. The emergence of antigenically drifted viral strains forces to change the constitution of influenza virus vaccine strains annually [14, 15].

In addition, influenza A viruses occasionally undergo dramatic changes of the antigenic properties of the HA and NA molecules through reassortment of the RNA genome segments of two different influenza virus subtypes [15]. These unpredictable events lead to dramatic antigenic changes in the major immunogenic surface proteins of the influenza A virus through genetic reassortment between a human and non-human influenza virus, and is known as antigenic shift. If the novel virus that derived from antigenic shift has acquired efficient human-to-human transmission, it could spread rapidly in the immunologically naïve human population leading to a pandemic [15]. Four such pandemics have occurred in the past 100 years; 1918 (H1N1), 1957 (H2N2), 1968 (H3N2) and 2009 (H1N1). Thus, if history is our guide, future pandemics will be inevitable.

Seasonal influenza

The severity of annual seasonal epidemics is determined by viral factors and immune states in the general population [1]. The peak activities of influenza vary depending on the prevailing climate in a given region. For example, in Sri Lanka, influenza virus activity peaks correspond to a peak in rainfall while in Hong Kong SAR, high influenza activity occurs in February–March and July–August. In general influenza viruses in tropical and subtropical regions could be detected at low levels outside the peak periods of viral activity, indicating possible circulation throughout the year with peaks during rainy seasons [17,18]. In contrast, in temperate climates influenza shows a seasonal pattern with high incidents in winter months [16].

Influenza is an acute respiratory disease with incubation period ranging from 1-4 days that spreads by large droplet, small-particle aerosols or through contact with fomites. Peak virus shedding occurs from 1 day before onset of symptoms to 2-3 days after disease onset [5, 15]. Children younger than 2 years and the elderly population >65 years of age, and those with co-morbidities (respiratory or cardiac disease, diabetes and renal failure) have the highest hospitalisation rates [2]. Acute influenza symptoms start abruptly with fever, headache, muscle ache, malaise and fatigue, symptoms, which are caused by a number of inflammatory cytokines released during the early stages of the illness [15]. This is followed by respiratory symptoms such as cough, sore throat and coryza [5]. The clinical spectrum of infection could range from asymptomatic infection to primary viral pneumonia. In general, acute illness lasts for a week or so, although malaise and dry cough may continue for 2-3 weeks or much longer. Known preexisting medical conditions mentioned above, pregnancy and smoking could worsen the clinical outcome. Secondary bacterial pneumonia and exacerbation of underlying chronic health conditions are known complications of influenza. However, myositis, myocarditis, toxic-shock syndrome and Reye's syndrome have also been infrequently reported [5,15].

Zoonotic and pandemic influenza

Antigenic properties of influenza HA are the key determinant of virus tropism and host range as well as pathogenesisof influenza virus [1]. The HA molecules of influenza viruses that have been isolated in avian species and horses showed preference for binding to sialic acids with α2, 3 configurations. In contrast, HAs of influenza viruses from humans and other mammalian species show enhanced binding to α2, 6-linked sialic acids configuration [19]. Additional human studies have shown that α2, 6 receptors are predominant on respiratory epithelial cells in the nasal mucosa, paranasal sinuses, pharynx, trachea and bronchi, and α2, 3 receptors are abundantly found on non-ciliated cuboidal bronchial cells at the junction between the respiratory bronchi and alveolus and on type II cells in the alveolar walls [20]. For influenza viruses to be efficiently transmitted among humans, they need to infect the upper human airways, which predominantly have α2, 6 receptors. Avian viruses that bind to α2, 3 receptors are unlikely to replicate in the upper human airways and fail to be transmitted efficiently between humans. Thus if a highly pathogenic avian influenza (HPAI) H5N1 viruses were to gain access to the human respiratory tract, it could potentially infect and replicate in the lower respiratory tract possibly leading to severe life threatening pneumonia, but shows limited human-to-human transmission [1].

In contrast, pig respiratory tract contains dual receptors (α2, 3 andα2, 6) and has been recognized as a host where co-infection of avian and human influenza viruses may occur. This facilitates genetic reassortment and subsequent adaptation of novel influenza virus leading to pandemics [15].

Despite the common belief that influenza viruses exhibit tight species barrier, zoonotic infection of HPAI have been reported; H5N1 in Asia, H7N7 in the Netherlands, H7N9 in China [21]. A number of low pathogenic avian influenza viruses such as H9N2, H6N1, H10N8 and H5N2 have also been isolated from humans sporadically in Asia [15, 22]. Adaptation of HPAI H5N1, emergence of H1N1pdm09 and a novel swine-origin human A H3N2 variant viruses [A(H3N2)v] in the USA have raised pandemic concern [5, 23].

Treatment and prevention

The adamantanes (amantadine and rimantadine) have antiviral activity against influenza A and act by blocking virus uncoating, but many contemporary influenza virus strains are resistant to these antivirals. Neuraminidase inhibitors (oseltamivir and zanamivir) block the activity of the virus neuraminidase in releasing the virus after replication in infected cells and provide clinical benefit when used within the first 48 hours after onset of disease. Current seasonal and zoonotic influenza viruses are usually sensitive to neuraminidase inhibitors. Occasional resistance to oseltamivir has been reported in individual patients but such resistance is not currently widespread. Early treatment with antivirals could reduce the duration

of illness, antibiotic prescriptions and lower the risk of complications and hospitalisation [1, 24].

Vaccines remain the cornerstone for prevention of seasonal influenza. Such vaccines contain two influenza A subtypes H1N1 and H3N2 and one influenza B virus lineage, viz the one assessed to be the lineage that is likely to become globally dominant [15]. Since the assessment of the influenza B virus lineage that may become globally dominant in the year ahead is difficult, more recently quadrivalent vaccines have been produced. There is an interval of around 10 months between the time of vaccine strain selection and the roll out of the vaccine. Thus the emergence of the unexpected influenza B lineage or the antigenically drifted can occur at repeated intervals. Currently available vaccines against influenza do not induce long-lasting immunity and provide protection only against strains closely related to the vaccine strains. Thus new vaccines are required to be reformulated for every flu season, based on global human influenza surveillance data [2]. The subtype of future outbreaks or pandemic influenza strains is also unpredictable. Hence, development of a successful "universal" (i.e. one vaccine protecting against multiple virus subtypes) vaccination strategy is urgently needed and a number of research teams are currently being involved in production of such a vaccine [25].

History has proven that influenza is and will remain as a grave medical threat to humans and many livestock. Therefore, a systematic approach of interdisciplinary research, increasing use of vaccines and rational usage of antiviral drugs to combat annual influenza outbreaks are essential to reduce the global toll of epidemic and pandemic influenza.

Declaration of Interest

There are no conflicts of interest.

References

1. Medina RA, Garcia-Sastre A. Influenza a viruses: new research developments. Nat Rev Microbiol 2011;8: 590-603.

2. World Health Organization. Influenza seasonal. http://www.who.int/medi acentre/factsheets/fs211/en/; accessed on 18 February 2015

3. McCauley JW, Hongo S, Kaverin NV, et al. Orthomyxoviridae. In: King AMQ, Adams MJ, Carstens EB, Lefkowitz EJ, eds. Virus Taxonomy. Classification and Nomenclature of Viruses. Ninth Report of the International Committee on Taxonomy of Viruses. New York: Elsevier; 2012:749–61.

4. Hause BM, Collin EA, Liu R, et al. Characterization of a novel influenza virus in cattle and Swine: proposal for a new genus in the Orthomyxoviridae family. MBio2014; 5: e3-14.

5. Brown IH, Alexander DJ, Phin A, et al. Influenza. In: Palmer SR, Soulusbay L, Torgerson PR, Brownn DWG, eds. Oxford Textbook of Zoonosis. 2nd ed. NewYork: Oxford University Press, 2011: 332-52.

6. Webby RJ, Webster RG. Emergence of Influenza A Viruses. Philos Trans R Soc Lond B Biol Sci 2001; 356:1817-28.

7. Webster RG, Bean WJ, Gorman OT, et al. Evolution and ecology of influenza A viruses. Microbiol Rev 1992; 56: 152-79.

8. Bao YP, Bolotov D, Dernovoy B, et al. The influenza virus resource at the national center for biotechnology information. J of Virology 2002;2: 596-601.

9. Tong S, Li Y, Rivailler P, et al. A Distinct lineage of influenza a virus from bats. Proc Natl Acad Sci USA 2012; 109: 4269-74.

10. Wu Y, Wu Y, Tefsen B, et al. Bat-derived influenza-like viruses H17N10 and H18N11. Trends Microbiol 2014; 22: 183-91.

11. Suzuki Y, Nei M. Origin and evolution of influenza virus hemagglutinin genes. Mol Biol Evol 2002; 19: 501-9.

12. Hause BM, Ducatez M, Collin EA, et al. Isolation of a novel swine influenza virus from Oklahoma in 2011 which is distantly related to human influenza C viruses. PLoS Pathogens 2013; 2: e1003176.

13. Ohwada KF, Kitame K, Sugawara H, et al. Distribution of the Antibody to Influenza C Virus in Dogs and Pigs in Yamagata Prefecture, Japan. Microbiol Immunol 1987; 31: 1173-80.

14. Bush RM, Bender CA, Subbarao K, et al. Predicting the evolution of human influenza A. Science 1999; 286: 1921–5.

15. Wright PF, Neumann G, Kawaoka Y. Orthomyxovirus. In: Fields of Virology. eds. Knipe DM, Peter M. 6th ed. Philadelphia : Lippincott Williams & Wilkins. 2013: 1186-243

16. Cox NJ, Subbarao K. Global Epidemiology of Influenza: Past and Present. Annual Rev Med 2000; 51: 407–21.

17. Perera KVHKK, Chan KH, Ma E, Peiris JSM. Influenza virus infections among a sample of hospital attendees in Ragama, Sri Lanka. Ceylon Med J. 2010; 55: 40–4.

18. Chiu SS, Lau YL, Chan KH, et al. Influenza-related hospitalizations among children in Hong Kong. N End J Med 2002; 347: 2097–103.

19. Connor RJ, Kawaoka Y, Webster RG, Paulson J. Receptor Specificity in Human, Avian, and Equine H2 and H3 Influenza Virus Isolates. Virology 1994; 205: 17–23.

20. Nicholls JM, Chan MCM, Chan WY, et al. Tropism of avian influenza A (H5N1) in the upper and lower respiratory tract. Nature 2007; 13: 147–9.

21. Watanabe T, Kiso M, Fukuyama S, et al. Characterization of H7N9 influenza A viruses isolated from humans. Nature 2013; 501: 551–5.

22. Wu HS, Yang JR, Liu MT, et al .Influenza A(H5N2) Virus Antibodies in Humans after Contact with Infected Poultry, Taiwan, 2012. Emerg Infect Dis 2014; 20: 857-60.

23. Pearce BM, Jayaraman A, Pappas C, et al. Pathogenesis and transmission of swine origin A(H3N2)v influenza viruses in ferrets. Proc Natl Acad Sci USA 2012; 109: 3944–9.

24. Kelly H, Cowling BJ. Influenza: the rational use of oseltamivir. Lancet 2015 (Epub ahead of print).

25. Valkenburg SA, Olive OTW, Polly WY, Mak PWY, et al. IL-15 adjuvanted multivalent vaccinia-based universal influenza vaccine requires CD4+T cells for heterosubtypic protection. Proc Nat l Acad Sci USA. 2014; 111: 5676–81.

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