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EDITORIAL
INFLUENZA

Influenza: from zoonosis to pandemic

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Global surveillance and advances in vaccine technology are essential to answer the threat of influenza pandemics http://ow.ly/Yt3e4

Probable epidemic influenza outbreaks have been described as early as the 5th century BC, as part of the Cough of Perinthus associated with the winter solstice, in Hippocrates' *Corpus Hippocraticum* "Of the Epidemics" [1]. The word "influenza" was first introduced in the 16th century, defining the illness of the cold season that in the early 1930s was shown to be caused by "filterable agents", since then called influenza viruses. Three types or genera of influenza viruses have been recognised (influenza A, B and C viruses), while a fourth genus has been recently proposed [2]. Today, we distinguish three manifestations of influenza in humans, which may impose from mild to severe morbidity and mortality burdens: zoonotic, pandemic and seasonal influenza, all caused by an infection with an influenza virus. Although our arsenal of intervention strategies for influenza has advanced in the past decades and a growing public conception has arisen of influenza as a usually seasonal inconvenience, threats posed by influenza A viruses, with their different manifestations and associated complications, are continuously knocking on our door.

Morbidity and mortality burdens of influenza have affected humanity since ancient times. The most spectacular influenza burden is caused by pandemic influenza A viruses, upon their introduction in a human population with little or no pre-existing specific immunity. Four influenza pandemics, or global epidemics, have affected humanity in the past century. The most devastating of these occurred in 1918, causing influenza in about half the world population, with 30–50 million deaths worldwide, affecting principally the young and otherwise healthy [3]. The subsequent influenza pandemics of 1957 ("Asian flu"), 1968 ("Hong Kong flu") and 2009 ("Mexican flu") were milder, each claiming the lives of 0.3–2 million individuals. Pandemic influenza A viruses circle around the world in several waves, eventually replacing an existing seasonal influenza A virus. Seasonal influenza viruses cause annual winter epidemics that infect 5–15% of the world population, resulting in 3–5 million severe cases and 250 000–500 000 deaths every year [4]. Seroprevalence studies reported that influenza viruses infect most children by the age of 6 years [5]. In fact, school-age children are considered primarily responsible for influenza virus transmission in the community [6]. Inter-pandemic periods have ranged between one and four decades, bringing collective seasonal influenza burdens to levels comparable to those reached by influenza pandemics.

The burden of zoonotic influenza A virus infections has made the headlines ever since the identification of avian and swine influenza viruses that, without apparent prior adaptation, infected and caused severe disease in humans and other mammals. The diversity of zoonotic influenza A viruses that circulate in avian or swine reservoirs expands every year. Influenza A viruses are classified into subtypes defined by their surface haemagglutinin and neuraminidase glycoproteins. Zoonotic influenza virus subtypes of particular concern include highly pathogenic avian influenza virus (HPAIV) H5N1, low pathogenic avian influenza viruses H7N9, H9N2 and most recently H10N8, as well as swine influenza viruses H1N1 and H3N2. Although, altogether, these viruses have caused disease or death in not more than 2000 individuals, their typically high case fatality rate (reaching, for example, up to 60% for hospitalised patients

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with an HPAIV H5N1 infection) is worrisome. Moreover, mortality caused by some of these viruses, including HPAIV H5N1, has been highest in children and young adults [7]. Zoonotic influenza viruses generally are little or not transmissible among humans *via* the air. Should they acquire such ability, they could spark a novel influenza pandemic.

Humankind is today better prepared to face a new influenza pandemic and to curb the burden of zoonotic, pandemic and seasonal influenza than ever before. However, continued effort is needed to fully build on our advanced knowledge of influenza threats and burdens in order to efficiently combat these infections. The recurring burden of seasonal influenza weighs heavier on the population of older adults and other at-risk groups, such as the very young, pregnant women and individuals with underlying conditions like immunocompromised individuals [4]. They may develop life-threatening complications requiring hospitalisation. These include the development of bacterial pneumonia and worsening of underlying conditions, but also primarily viral complications, such as viral pneumonia and influenza virus infection of the central nervous system [8]. In particular, paediatric patients aged <5 years are at high risk of developing severe disease, with a global incidence of influenza-associated severe acute lower respiratory tract infection estimated at 1 million cases, causing 28 000–111 500 deaths every year [9].

Timely administration of antivirals (currently in the form of neuraminidase inhibitors) is recommended and was recently shown to be beneficial in reducing severity and duration of influenza virus infection and preventing lower respiratory tract complications, thereby limiting hospitalisation and death [10], including in critically ill paediatric patients [11]. Moreover, the use of antiviral treatment in primary care is currently being studied [12, 13]. The emergence of antiviral-resistant viruses nonetheless continues to threaten the efficacy of such treatments, especially in individuals with immunocompromised conditions [14]. This was for example illustrated in 2009 with the report of a 5-year-old boy with an underlying disease who was hospitalised with pandemic influenza (pH1N1) infection and succumbed despite treatment with oseltamivir, zanamivir and peramavir due to development of antiviral resistance [15].

Preventive influenza vaccines are by far the most cost-effective tools to combat seasonal influenza. Despite long-standing debates, they have been shown to be effective in preventing or reducing the severity of influenza and influenza-related disease and death in at-risk individuals [16]. The governments of many countries, such as the USA, Finland, the UK and Australia, have implemented vaccination programmes for healthy children of defined age groups to further limit transmission and spread of the viruses. Yet two major stumbling blocks impede the benefits of seasonal influenza vaccination: overall low vaccination coverage, and the need for continuous update of the influenza vaccine strains to match circulating strains evolving through antigenic drift. The use of alternative routes of administration of influenza virus vaccines, such as the intranasal application of live attenuated vaccines, especially in children, together with the advent of large meta-analyses demonstrating the benefits of influenza vaccination, may favour higher coverage rates in the future.

Seasonal influenza A viruses circulate throughout the year in East and Southeast Asia, which are considered the source regions of the H3N2 strains that cause winter epidemics in the northern and southern hemispheres [17]. A different pattern of global circulation of H1N1 viruses, with longer local persistence and less frequent global movement, has recently been described [18]. Seasonal influenza H3N2 and, to a lesser extent, H1N1 strains constantly evolve to escape pre-existing immunity in the population. New antigenic variants that are not neutralised by this pre-existing immunity regularly emerge to replace previous lineages or antigenic clusters [19]. Detailed antigenic cartography of H3N2 viruses and molecular engineering of recombinant viruses revealed that a limited number of amino-acid positions located around the receptor binding site of the haemagglutinin protein are primarily involved in their antigenic drift [20]. Only one or two substitutions in this region of the protein typically differentiate newly emerging antigenic virus clusters. However, infection by a particular H3N2 variant was recently shown to boost immunity against most H3N2 antigenically distinct strains that circulated previously [21]. Such increasingly detailed understanding of influenza antigenic drift and antibody landscapes has strong potential to improve the strategic selection and engineering of seasonal influenza vaccine strains.

Influenza pandemic preparedness will continue to benefit from advances in influenza vaccine technology, as well as from improving global surveillance of animal and human influenza virus infections. One of the major obstacles currently faced by the global health community upon the emergence of a pandemic influenza virus is the delay between the identification of the new viral threat and the delivery of specific vaccines against it [22]. The prevailing manufacturing technology applied to influenza vaccine production today is based on techniques that are more than half a century old and require the propagation of vaccine viruses in embryonated chicken eggs, before inactivation and/or purification. This approach requires >6 months before the first vaccine doses can be used. Furthermore, the availability of fertilised chicken eggs limits the production capacity and rapid up-scaling at times of urgency.

Novel technologies are currently being developed for the production of next-generation nonreplicating and live attenuated influenza vaccines, based on reverse genetics techniques and *in vitro* cell culture systems [22]. In addition, the use of adjuvants can improve the vaccines' protective efficacy, especially in individuals who are naïve towards a pandemic virus. The holy grail of influenza vaccinology is the development of a "universal influenza vaccine" or, perhaps more realistically, an influenza vaccine eliciting broader and longer-lasting immune responses against a range of influenza virus strains and subtypes. Advances in the identification of new correlates of protection, on the role of more conserved antigens and T-cell-mediated immune responses in protection are opening new avenues towards this goal [23]. Together, these modern approaches will undoubtedly improve the responsiveness of the global health community upon the emergence of a new pandemic.

Zoonotic influenza viruses that acquire the ability to transmit efficiently among humans *via* the air, through mutation, re-assortment or both, are at the origin of emerging influenza viruses with pandemic potential. The global surveillance of the diversity of circulating animal and *a fortiori* zoonotic influenza viruses can greatly improve our ability to anticipate which strains are more likely to evolve pandemic potential. Determining factors governing efficient airborne transmissibility of influenza viruses are the subject of thorough (and heavily debated) studies in the laboratory (for review see [24]). It has become clear that a handful of mutations suffice for an HPAIV H5N1 to acquire transmissibility among mammals. These have shed light on several genetic and phenotypic attributes associated with efficient airborne transmissibility, including haemagglutinin receptor binding specificity, glycosylation profile, thermostability and preferred pH for membrane fusion, as well as enhanced nuclear transport and viral transcription in mammalian cells [25–30]. Efficient replication in the human upper respiratory tract and in the soft palate may be phenotypic clues heralding the evolution of new pandemic viruses [31], yet their evolution remains difficult to forecast [32–34]. Furthermore, the evolution and adaptation of avian influenza viruses in mammalian species other than humans may provide unique opportunities to follow such gain of function in nature, further calling for dedicated surveillance programmes [35].

The race between influenza viruses that continually evolve towards inter- and subsequent intra-mammalian species transmission on the one hand, and humans aiming at gaining the ability to anticipate this evolution on the other, is at its fiercest. The threats will not cease to knock on our door; the stake lies in our ability to answer them.

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