Emerging infections: From seasonal to avian and pandemic influenza

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Influenza viruses that may cause disease in human can be divided in seasonal, avian, and pandemic influenza viruses. Collectively they are the major cause of serious human respiratory tract infections worldwide. Recent years much attention has been paid to different threats due to influenza virus outbreaks in humans and poultry. The recent Mexican flu pandemic, often fatal avian influenza H5N1 and H7N9 infections and the recent mismatch between the currently circulating influenza H3N2 virus and its counterpart in the seasonal flu vaccine, all illustrate that human influenza is far from being under control. Here we summarize current knowledge on the epidemiology and clinical manifestations of human influenza virus infections. Furthermore the current knowledge on diagnostics, treatment and prevention of influenza is reviewed.

Background

All influenza viruses of the *Orthomyxoviridae* family, cause predominantly respiratory disease manifestations in humans. They are among the most diverse emerging infectious agents. Of the three influenza virus types (A,B and C), influenza A is the best known for its ability to drift and re-assort and yearly cause seasonal human flu outbreaks. Sporadic infections of humans with avian influenza A viruses, may cause serious and sometimes fatal human disease, but these viruses are not efficiently transmitted among humans. However if these avian viruses by mutation and/or re-assortment acquire the capacity to efficiently transmit between humans, they may be at the basis of an emerging pandemic. Four major influenza pandemics have occurred in the past century: in 1918-1920 (Spanish Flu), 1957-1958 (Asian Flu), 1968-1970 (Hong Kong Flu) and recently in 2009-2010 (Mexican Flu). With the recently acquired knowledge that avian influenza viruses can directly be transmitted to humans, and may eventually adapt to the human species by becoming transmissible from human-to-human, avian influenza viruses should be considered a major global health threat (1).

Seasonal influenza

Seasonal influenza is caused by influenza A or B viruses and affects 5-15% of the human population every year (2). Symptoms vary from mild respiratory complaints to fatal respiratory distress possibly with other organs involved. However, outcome of disease and severity of infection are largely depending on immune and health status of the infected individual. Most seasonal influenza virus infections are self-limiting and patients do not need to seek medical care. However, seasonal influenza virus infections do cause a considerable burden of disease especially when aggravated by complications (3). Furthermore, there is a significant economic burden of seasonal influenza due to sick leave, medical care and medication. Influenza A viruses are further subtyped by the antigenicity of their haemagglutinin (HA) and neuraminidase (NA) proteins, resulting in names like H1N1 and H3N2. Point mutations in these

proteins lead to gradual antigenic changes referred to as antigenic drift. Due to this drift in antigen the 'new' virus is no longer neutralized by influenza virus specific antibodies present in the population. This antigenic drift is the major driver of yearly seasonal influenza outbreaks and makes annual re-vaccination with adapted vaccines necessary.

Avian influenza

The first reports of humans infected with highly pathogenic avian influenza (HPAI) virus of the H5N1 subtype date back to 1997 (4,5). Since then H5N1 virus infections have been diagnosed in about 700 individuals of whom more than 400 have died, illustrating the high case fatality rates associated with this virus. Furthermore, in 2013 a low pathogenic avian influenza (LPAI) virus of the H7N9 subtype has emerged in China in humans without any clear outbreaks in poultry prior to the first human cases. About 450 cases were reported in China with more than 100 of which with fatal outcome (6). Avian influenza virus infections may cause severe respiratory distress in humans often accompanied by multi-organ failure, haemorrhage and in many cases also gastro-intestinal manifestations. Recently published data have shown that only a handful of mutations in HPAI H5N1 virus would change its phenotype from barely transmissible to readily transmissible among mammals (4,5,7). This illustrates the pandemic risk associated with these avian influenza viruses

Pandemic influenza

Besides antigenic drift, another evolutionary process of influenza viruses is responsible for the continuous threat posed by newly emerging influenza viruses: antigenic shift. This is defined as the introduction of a new influenza A virus subtype against which little or no pre-existing immunity exists in the human population. Figure 1 illustrates a mechanism by which antigenic shift may take place. When co-infection of a cell with influenza A viruses of different subtypes occurs, a new influenza virus may arise as the result of the emergence of new combinations of gene segments: re-assortment. A virus with a 'new' HA and/or NA that has not circulated in the human population before, may rapidly start spreading among humans as it encounters little or no specific immunity. The most devastating example of antigenic shift was the appearance of the H1N1 virus that caused the 'Spanish flu' in 1918 resulting in approximately 50 million deaths world-wide (8). The three subsequent influenza pandemics occurred in 1957 ('Asian flu'), in 1968 ('Hong Kong flu'), and 2009 ('Mexican flu') caused the deaths of 200.000 to 1 million people each.

Diagnostics

Influenza virus can be difficult to diagnose based on the combination of clinical symptoms and signs since much overlap exists in clinical presentation with other respiratory pathogens. However during an influenza epidemic a well-trained physician can diagnose influenza with a specificity and sensitivity of approximately 70%, on the basis of well-defined clinical parameters (9). Early diagnosis of influenza can reduce the unnecessary use of antibiotics and provides a short window in which antiviral treatment can be useful (10). Diagnostic tests useful in clinical settings all are based on the detection of the virus, its

antigen or nucleic acid. Commercial rapid tests are available and could provide a test result within 15-30 minutes (10). Most rapid test show reasonable results regarding sensitivity and specificity but are only useful in combination with clinical and epidemiological information to suggest the likelihood of an influenza virus infection.

Treatment

Currently two drug classes are available to treat influenza: the neuraminidase inhibitors (oseltamivir, zanamivir and peramivir) and the M2 membrane protein inhibitors (amantadine and rimantadine) (see also Figure 1) (11). The high level of mutation in influenza viruses hampers effective antiviral treatment due to the rapid development of resistance. Currently almost all circulating H3N2 seasonal influenza viruses show resistance against amantadine and rimantadine and are not effective against influenza B viruses (12). Currently this class of drug is only sporadically used in combination with a neuraminidase inhibitor to treat severe H1N1 cases, early in infection. Currently, more viruses circulate resistant to oseltamivir compared to zanamivir. Future treatment strategies may make use of new generation broadly reactive monoclonal antibodies. In addition a viral RNA polymerase inhibitor, favipiravir, is registered for the treatment of pandemic influenza in Japan (13).

Prevention

There are basically two strategies to prevent influenza or reduce its burden. First, the yearly prevention of seasonal influenza virus infections by vaccination. National guidelines defining risk groups to be vaccinated differ considerably, but in general all the elderly, and individuals with known co-morbidities are yearly vaccinated against seasonal influenza. The vast majority of current seasonal influenza vaccines are produced from virus grown in fertile hens' eggs and inactivated (14) and consist whole virus, split products or purified HA and NA surface antigens of three or four virus strains recommend by the World Health Organization. Another important aspect in the field of influenza virus prevention are the preventive measures taken against avian or pandemic influenza. Because all known influenza A virus subtypes are discovered in aquatic wild birds in nature, large part of prevention focuses on avoiding direct and indirect contact between domestic poultry and wild birds (15). For prevention in high risk groups (poultry workers) or in case of outbreaks vaccination seems the best strategy. Recently, the safety and immunogenicity of a vector based vaccine expressing the H5 protein of H5N1 showed promising results (16).

Conclusion:

Influenza viruses are a constant threat to humanity. Syndrome and virological surveillance in humans to monitor the impact of newly introduced seasonal influenza virus strains, as well as the occasional or sporadic introduction of animal and pandemic influenza viruses is of utmost importance for our epidemic and pandemic preparedness. In addition, syndrome and virological surveillance of potential animal reservoirs is essential for the timely identification threats of new cross-species introductions and re-assortments. The challenge of influenza virus containment will probably become more difficult due to the increasing population worldwide, subsequent increase in poultry industry and the more rapid spread

of new viral variants due to increasing air travel. The ongoing development of new, more effective and more universal influenza vaccines will be of great value in decreasing the burden of influenza virus disease. In addition the effective use of current and new generation antiviral compounds may be an important addition to the medical armamentarium.

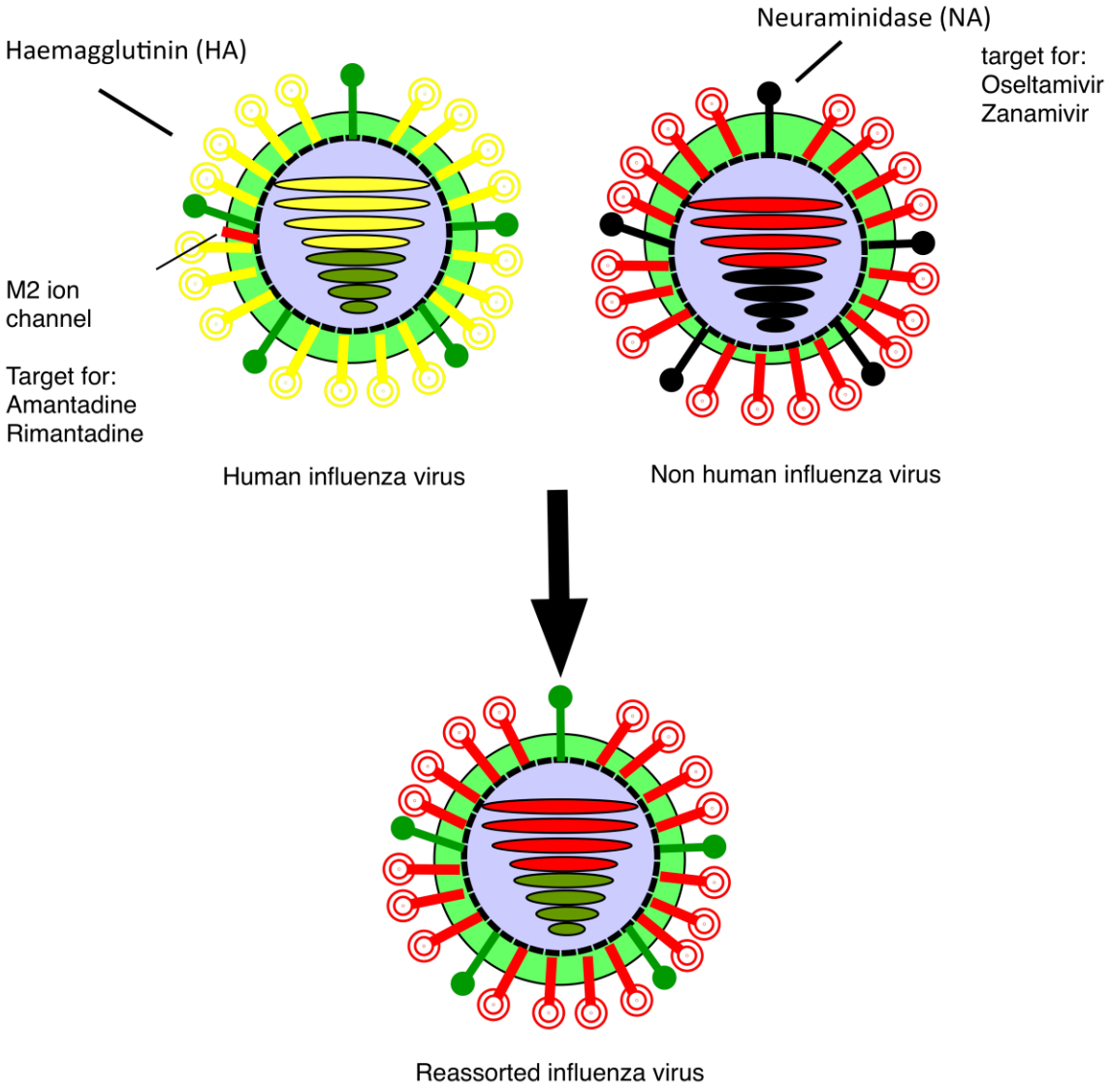

Figure 1. mechanism of reassortment in influenza A viruses.
When co-infection of a cell with different influenza A viruses occurs re-assortment results in the emergence of new influenza viruses. This may lead to introduction of a new type of HA or NA that did not circulate in humans prior to the outbreak and therefore little or no protection is present in the population.

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