6. Priority diseases and reasons for inclusion

6.2 Pandemic influenza

See Background Paper 6.2 (BP6_2Pandemic.pdf)

Background and developments since 2004

The WHO estimates that annual influenza epidemics account for about 3 to 5 million cases of severe illness and 250,000 to 500,000 deaths worldwide. However, the disease burden of influenza is difficult to quantify as patients may have a wide range of symptoms that can lead to under-diagnosis. In addition, patients are not laboratory-confirmed as having influenza, diagnostics tests are not 100% sensitive or virus-specific, and influenza can be masked by other comorbidities. Despite a substantial increase in laboratory testing during the most recent pandemic in 2009, recorded hospitalizations and deaths are a crude underestimation of the true pandemic burden.

There are three types of influenza virus that affect humans (A, B and C) but only one of these, type A, has been known to cause pandemics. Influenza A viruses circulate naturally in a global avian reservoir. However, some viral strains have crossed the species barrier, infecting pigs, horses, and, most notably, humans. Many RNA viruses such as influenza have high mutation rates which can lead to new, distinct antigenic variants. Genetic diversity among influenza viruses accounts for the recurring seasonal influenza epidemics of varying patterns and severity, as well as the continuing risk of the emergence of a novel pandemic strain.

The 1997 A (H5N1) influenza outbreak in Hong Kong was the first known incidence of a purely avian virus causing severe human disease and death. By 2006, the A (H5N1) virus had spread across 54 countries spanning three continents. Inefficient human-to-human transmission was the only factor preventing H5N1 from becoming a pandemic virus. However, there is a substantial possibility that, in the event of the correct combination of genetic modifications, this rapidly replicating and highly mutable virus could re-emerge as a pandemic virus.

The 2009 influenza A (H1N1) pandemic

In early April 2009, a new influenza A (H1N1) virus emerged in Mexico and the USA and rapidly advanced beyond the possibility of successful containment. The virus spread worldwide through human-to-human transmission, and on 11 June 2009 the WHO elevated the influenza pandemic alert level to Phase 6, officially declaring a global pandemic – the first in the 21st century. Box 6.2.1 outlines a generally accepted understanding of the 2009 influenza pandemic. The inability to predict which specific subtype will trigger the next pandemic demonstrates the need to address the gaps in knowledge in order to more effectively manage the next pandemic.

The economic impact of an influenza pandemic includes direct health care costs as well as the indirect costs of work absenteeism and loss of productivity. Studies evaluating
economic impact on interpandemic seasonal influenza epidemics demonstrate that the most significant expenses are the indirect costs, accounting for more than 80% of the total societal cost of interpandemic seasonal influenza epidemics. However, total economic burden can be difficult to quantify as recent studies conclude that the global economic impact from the 2009 H1N1 pandemic still remains unknown. One study conducted in the United Kingdom used a computational general equilibrium modelling experiment to estimate the economic impact and found that depending on the severity of the disease (low to high fatality scenarios), a pandemic could result in losses of between 0.5% and 4.3% in the United Kingdom Gross Domestic Product (GDP). While this range of economic loss may not seem dramatic, a strained economy and indirect costs may compound the impact of disease.

Box 6.2.1 General summary of the 2009 H1N1 influenza pandemic

- The pandemic virus was less virulent than was anticipated in many pandemic preparedness plans.
- Highest disease incidence was in 0 to 4 year old age group although cumulative incidence of infection was in school-aged children.
- Deaths associated with virologically confirmed influenza were lower than the number of excess deaths typically associated with seasonal influenza.
- The majority of deaths occurred at a younger age than typically seen with seasonal influenza.
- Although older adults had lower morbidity rates, this population had the highest case fatality ratio.
- Pregnant and postpartum women and indigenous populations, recognized risk groups during interpandemic seasonal influenza seasons, were also at increased risk for a severe outcome.
- Intensive care units were burdened by the increase in the number of young adults with severe disease due to the pandemic virus, though this was not experienced in all countries.
- Although the 2009 pandemic influenza A (H1N1) seems to have replaced all seasonal influenza A (H1N1) subtypes, it has not replaced influenza A (H3N2) subtypes, which have continued to co-circulate as a small proportion of all types influenza A viruses. This is contrast to previous pandemics where the pandemic virus replaced all influenza A viruses.
- When the H1N1 vaccines were produced they were highly antigenic and only a single dose was required for most individuals.
- Unlike the pattern for interpandemic seasonal influenza A (H1N1) viruses, no significant neuraminidase resistance of the 2009 pandemic influenza A (H1N1) has been reported to date, although variants with reduced oseltamivir sensitivity may be emerging in the Asia-Pacific region.
**Influenza vaccines**

Vaccination is considered to be the most effective way to prevent the spread of influenza and to mitigate the severity of illness and impact of the disease. The EU has instituted procedures, managed by the European Medicines Agency (EMA), to expedite the authorization and availability of vaccines in the event of an influenza pandemic.

Interpandemic Seasonal influenza immunization presents substantial challenges, including the need for annual vaccination, the co-circulation of multiple virus strains, antigenic variation in the influenza virus, and the broad age spectrum of people affected by the disease. The development of pandemic influenza vaccines brings additional challenges, including the need to: induce a broad spectrum and long-lasting immune response; ensure a much more rapid manufacturing time; and increase production capacity so it is large enough to reach populations at risk worldwide. These challenges have led to the use of a myriad of approaches to influenza vaccine development.

During the 2009 influenza A (H1N1) pandemic, monovalent vaccines without adjuvants were used in the United States and Australia (and to a limited extent in Europe). In contrast, within the EU, adjuvant vaccines were more widely used. Adjuvants are compounds that enhance the ability of a vaccine to elicit strong and robust immune responses. At the time of the pandemic, adjuvant vaccines had been approved by the EMA for use in all populations whereas the United States had not approved the use of any adjuvant influenza vaccines. Available data in 2010 demonstrated that pandemic influenza vaccines were safe and well tolerated. However, Pandemrix, one of the adjuvant vaccines used in the EU was found to have an association with narcolepsy in children. Future studies are needed to further elucidate the role of adjuvants in the possible association with narcolepsy prior to further use of adjuvants in pandemic vaccine development.

Equitable access to influenza vaccines is a key component of global prevention and control strategies for influenza. In 2003, the World Health Assembly (WHA) adopted a resolution on the “Prevention and control of influenza pandemics and annual epidemics,” which called on Member States with influenza vaccination policies to increase vaccine coverage for all high-risk individuals. The results from a 2010 study (involving 157 countries) indicated that the global distribution of influenza vaccines increased by 72% between 2004 and 2009 (from 262 million doses to 449 million doses, respectively). However, despite encouraging growth at national, regional, and global levels, none of these countries distributed sufficient vaccines to immunize half of its total population and one-third of countries did not distribute enough vaccine to protect even 1% of their population. Meanwhile, only 20% of the countries achieved the study “hurdle” rate of 159 doses per 1000 population (see Figure 6.2.1). Low vaccination uptake rates in many countries and disproportionate global production capacities continue to be two important factors contributing to low global vaccine coverage.
Efforts to increase vaccine coverage rates require public education campaigns and additional funding for immunization. In addition, efforts are needed by health care workers to proactively recommend immunization to people at-risk. Continued efforts to increase vaccine coverage are critical. The use of seasonal influenza vaccines not only protects against annual epidemics, but also provides the foundation for pandemic preparedness. It is important to note that the use of annual seasonal vaccines sustains production capacity and facilitates the global capability to respond during a pandemic.
Figure 6.2.1 Global interpandemic influenza vaccine dose distribution per 1000 population (2009)

Doses distributed per 1,000 population

Antiviral therapeutics

Current antiviral therapy remains unchanged since 2004 with four commercially licensed products including: neuraminidase inhibitors (oseltamivir and zanamivir) and adamantanes (amantadine and rimantadine). Only one of these products, oseltamivir, was included on the WHO Model List of Essential Medicines for selected high-risk patients. The increasing use of these antiviral agents has led to the emergence of drug-resistant variants of the virus and reduced drug efficacy.\textsuperscript{16} There is a need for the development of new antiviral agents that are active against all virus strains and subtypes.

Diagnostics

Rapid and accurate laboratory diagnosis of viral infection is critical to reducing the disease burden of influenza and its associated social and economic consequences. Rapid influenza diagnostic tests (RIDTs) are simple-to-use, point-of-care antigen tests that can generate results in 10 to 30 minutes. However, studies on the use of RIDTs to diagnose seasonal influenza have demonstrated high specificities but varying levels of sensitivity.\textsuperscript{17,18,19} Most of the currently used RIDTs are not able to distinguish between the different influenza A virus subtypes.

Rapid influenza diagnostic tests are useful in patient and outbreak management as they enable clinicians to initiate prompt infection-control measures and provide earlier access to antiviral treatment for high-risk populations. However, the 2009 influenza A (H1N1) virus pandemic underlined the importance of precise assays with brief turnaround times and the ability to differentiate influenza strains in order to accurately monitor the spread of an outbreak and ensure effective clinical management of patients.

EU-funded pandemic influenza projects

The European Commission’s current 7th Framework Programme (FP7), which supports health research, is providing significant funding for R&D in emerging epidemics of infectious diseases including influenza. EU-funded influenza projects relate to the preclinical and clinical development of new, innovative, safe, and effective vaccines and diagnostics.\textsuperscript{20} Research is also focused on the development of “universal” influenza vaccines, designed to provide longer-lasting and broader protection against multiple strains of influenza virus, with the ultimate aim of protecting against both seasonal and pandemic influenza. Various complementary scientific aspects such as basic virology, diagnostics, epidemiology, pathogenesis, surveillance, immune responses, animal viruses, novel drugs, clinical management of patients, behavioural aspects and optimized communication strategies are also covered by FP7 research.\textsuperscript{21}
6. Priority diseases and reasons for inclusion

**Remaining challenges**

Following the initial outbreak of avian influenza in 1997, the threat of a potential influenza pandemic was widely recognized by key stakeholders. A substantial amount of financial support and research has since been allocated to increasing pandemic influenza preparedness at the international level. The subsequent emergence of the 2009 A (H1N1) influenza pandemic challenged these efforts in every aspect of pandemic preparedness. Fortunately, the new virus appeared to be less virulent than anticipated.

The EU has recognized the public health impact of influenza through the establishment of a wide range of influenza-related surveillance networks, consortiums, and research projects. The information collected through these will provide the basis for an improved response to the next influenza pandemic. However, the prevention and control of influenza requires immense efforts and collaboration during the interpandemic seasonal and pandemic periods. Cooperation and collaboration between all key stakeholders will provide the foundation for a rapid and effective response in the event of a future pandemic.

**Research needs**

Research should be prioritized in the following areas:
- The virology and pathogenicity of influenza viruses in order to predict and prepare for the next pandemic.
- Improved quantification methods to more accurately assess the economic burden of influenza.
- Understanding barriers to uptake for seasonal immunization, combined with evaluation of interventions to increase uptake.
- Global and country-level vaccine coverage information and monitoring systems.
- Rapid scale-up of vaccine production in case the next pandemic is caused by a subtype that is less antigenic and requires two doses of vaccine.
- Vaccine “platforms” that produce safe, effective, and cross-strain vaccines with long-lasting protection against influenza.
- New antiviral agents with broad reactivity against all virus strains and subtypes.
- The ability of RIDTs to accurately detect and distinguish between different influenza virus subtypes.

**References**


20 Shobugawa, Y. et al. Clinical effectiveness of neuraminidase inhibitors—oseltamivir, zanamivir, laninamivir, and peramivir—for treatment of influenza A(H3N2) and
6. Priority diseases and reasons for inclusion
