Pandemic influenza vaccines: development, supply and finance issues

What is the potential impact of an influenza pandemic and what can be done to limit its impact?

The potential impact of the next pandemic is unknown but it is estimated that, in past pandemics, 25-35% of the global population was infected during the first year. The number of deaths as a result of the pandemics varied widely. Nonetheless, the next pandemic could result in considerable illness and death, resulting in substantial social and economic disruption and worker absenteeism. If available quickly and in substantial amounts, the most important specific medical intervention for reducing illness and death during a pandemic would be an effective pandemic influenza vaccine.

How much vaccine could be produced in the event of a pandemic?

Supplies of pandemic influenza vaccines are currently expected to be inadequate in all countries at the start of a pandemic and for many months thereafter. This is of particular concern, as vaccines are considered to be not only the most effective but also the most cost effective line of defence in protecting populations against influenza.

Annual global influenza vaccine production is currently limited to the production capacity for seasonal influenza vaccines, i.e. 300 million doses per year. It is estimated that it would take approximately three months following the emergence of a pandemic virus to begin full-scale vaccine production under current conditions if all goes well. In the best case scenario and using existing technologies, vaccine sufficient for approximately 1 billion people could be produced within an additional nine months. Given this, within a year of emergence of a pandemic virus, vaccine production capacity would be sufficient to supply only a small number of countries and possibly only after a pandemic has already spread to many countries.

The World Health Organization and partners have recently developed a global action plan to reduce the gap in influenza pandemic vaccine supply. Strategies include: increasing demand for seasonal influenza vaccine in order that manufacturers will increase their manufacturing capacity and that populations will be protected against seasonal influenza; developing “antigen-sparing” strategies and improvement of production processes; shortening the time lag between the emergence of an influenza pandemic virus and the start of large-scale pandemic vaccine production; and increasing global surge capacity for influenza pandemic vaccine production.

What are the challenges of developing a pandemic influenza vaccine?

- It is unknown which of the 16 influenza A sub-types will cause a pandemic. Predictions about the potential vaccine efficacy of one sub-type cannot be made based on testing of vaccine formulations using a different sub-type.

- Dose-finding studies have not been finalized and are much more difficult than anticipated. Vaccine formulations need to be found which contain the least possible amount of antigen per dose to make best use of limited resources.

- Determining the efficacy of pandemic vaccines against infection, illness or death is not possible currently because there is no pandemic influenza at this time. Therefore current testing of potential pandemic vaccines is reliant on “surrogates” of protection, such as the development and levels of antibodies in the blood resulting from vaccination. Unfortunately, these antibody tests are not necessarily reliable indicators of clinical protection. Additional research is urgently needed to assess the validity of surrogates of protection and will be needed to determine the clinical efficacy of influenza pandemic vaccines when a pandemic begins.
What is the current status of vaccine development?

Three companies (Sanofi, CSL, Omninvest Ltd.) have completed vaccine trials in humans using recently-circulating H5N1 virus. None of the lower dose vaccines tested with the inexpensive and safe alum as the adjuvant (immune enhancer) fulfilled regulatory requirements.

In all, seventeen companies are conducting or are planning to conduct 23 clinical trials using various adjuvants, doses, applications (intradermal as opposed to intramuscular or subcutaneous), production technologies (e.g. cell culture, as opposed to growth on eggs) and virus particles; most of them will use vaccine virus dosages that are equal to or lower than what is typically used in seasonal influenza vaccines. Nine of these 23 H5N1 clinical trials will be finalized in 2006.

What more needs to be done in the short term?

Effective international coordination and advocacy are needed to address the challenges listed above. Such coordination should relate to:

- advocacy for and initiation of clinical trials using: different H5N1 viruses; new adjuvants; new formulations; and new routes of immunization with low antigen doses and also live attenuated influenza vaccines;
- rapid sharing of data from clinical trials to inform design of future clinical trials;
- research on alternative surrogates of protection to keep antigen-sparing an option for influenza pandemic vaccines;
- global reassessment of regulatory pathways for influenza pandemic vaccines, given anticipated data from research and development on surrogates of protection;
- improvement of comparability of results of clinical trials using H5N1 influenza pandemic vaccines through for example establishing an international biological standard or establishing a central laboratory facility for serological testing;
- establishment of post-marketing surveillance procedures, given that efficacy assessment of influenza pandemic vaccines will only be possible during a pandemic; and
- advocacy for investment into new or increased research and development and production capacity in both industrialized and developing countries.

How much money will be needed for international coordination of pandemic influenza vaccine development in the coming years?

It is estimated that several million United States dollars will be needed for international coordination of pandemic vaccine development efforts at global and regional levels during the next two years.

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1 reducing the amount of the substance in a vaccine that stimulates the production of antibodies in order that greater quantities of vaccine can be produced.