

Stockpiling prepandemic influenza vaccines: a new cornerstone of pandemic preparedness plans

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The history of pandemic influenza, along with the evolving epizootic of the highly pathogenic avian influenza A (H5N1) virus and the severity of associated human infections, serve as a warning to the world of the threat of another influenza pandemic. Conservative estimates suggest that up to 350 million people could die and many more would be affected, causing disruption to health-care systems, society, and the world's economy. WHO has encouraged countries to prepare in advance by developing influenza pandemic preparedness plans that involve public-health and pharmaceutical interventions. Vaccination is a cornerstone of these plans; however, a pandemic vaccine cannot be manufactured in advance because the next pandemic virus cannot be predicted. The concepts of vaccine stockpiling and prepandemic vaccination have thus become attractive. Human H5N1 vaccines are currently available and can induce heterotypic immunity. WHO and governments should give urgent consideration to the use of these vaccines for the priming of individuals or communities who would be at greatest risk of infection if an H5N1 influenza pandemic were to emerge.

Introduction

Influenza outbreaks have threatened the health of animal and human populations for centuries.¹ In the last century, there were three human influenza pandemics: Spanish in 1918, Asian in 1957, and Hong Kong in 1968. The 1918 pandemic caused the most severe morbidity and mortality of the three pandemics, and is estimated to have killed 40–100 million people, predominantly young healthy adults, in less than 1 year.^{1–3} Although the 1957 and 1968 pandemics were much milder, and caused an estimated 2 million and 1 million deaths, respectively, mainly in elderly people,⁴ they still stressed the capacity of the health systems of many countries to respond. It is impossible to predict when the next pandemic will occur, although it is important that we learn as much as we can from past pandemics.

The 1957 (H2N2) and 1968 (H3N2) influenza A viruses both evolved after the reassortment of the circulating human influenza A virus with an avian virus. The retention of the neuraminidase (N2) gene during the evolution of the H3N2 virus meant that most people exposed to the previous H2N2 virus had some heterotypic immunity and were partially protected, thus limiting the impact of the pandemic.^{5,6} The 1918 A (H1N1) virus is now known to have evolved directly from an avian antecedent,⁷ effectively entering a highly susceptible population with little or no pre-existing immune protection. Another pandemic involving a virus with the pathogenicity approaching that of the 1918 virus could have a far more devastating outcome economically and socially, particularly as the world's population has more than trebled to about 6·5 billion.^{8–10} Estimates of between 175–350 million people could die worldwide.⁸

The evolving avian influenza epizootic

Since late 2003, an epizootic of the highly pathogenic avian influenza A (H5N1) virus has been occurring among domestic poultry.^{3,11} The H5N1 virus is continuing to evolve, with ten clades now recognised, and differences

between the viruses within individual clades occurring.¹² Human infections and deaths were initially reported in Vietnam and Thailand, and have subsequently occurred in an increasing number of countries.¹³ Clusters of human infection have been small, suggesting that if human-to-human transmission is occurring, it is very inefficient. However, the overall mortality of H5N1-confirmed cases exceeds 60%, which is of concern.¹³

Although the H5N1 virus is a likely candidate for the next human influenza pandemic, other avian influenza viruses (subtypes H7 or H9) have recently caused infections in human beings and are possible candidates for the next human influenza pandemic.¹⁴ Nevertheless, the H5N1 virus has given us a reminder of how lethal influenza can be both in animals and human beings. For this reason, WHO's present level of pandemic influenza alert remains at phase 3 (table).^{4,15}

Current pandemic preparedness planning

As of August 2008, 47 countries had published preparedness plans for pandemic influenza^{16,17} following repeated calls from WHO.^{18–20} The primary objectives of these plans are to mitigate the medical, social, and economic consequences of an influenza pandemic. Control strategies in these plans are categorised as (1) non-pharmaceutical (or public-health) measures, and (2) pharmaceutical measures, which include antivirals and vaccines. Non-pharmaceutical measures range from case isolation, household quarantine, school or workplace closure, restrictions on travel, to hand-washing and basic respiratory hygiene or cough etiquette, which may slow the effects of pandemic influenza, whereas only antivirals and vaccines are clearly efficacious in preventing infection or treating illness.²¹

Antiviral drugs

Antivirals are now being produced in increasing quantities. However, to ensure that they are widely available at the beginning of the next pandemic, WHO

Phases		Overarching public-health goals
Interpandemic period		
Phase 1	No new influenza virus subtypes have been detected in human beings. An influenza virus subtype that has caused human infection may be present in animals. If present in animals, the risk of human infection or disease is thought to be low	Strengthen influenza pandemic preparedness at the global, regional, national, and subnational levels
Phase 2	No new influenza virus subtypes have been detected in human beings. However, a circulating animal influenza virus subtype poses a substantial risk of human disease	Minimise the risk of transmission to human beings; detect and report such transmission rapidly if it occurs
Pandemic alert period		
Phase 3	Human infection(s) with a new subtype, but no human-to-human spread, or at most, a rare instance of spread to a close contact	Ensure rapid characterisation of the new virus subtype and early detection, notification, and response to additional cases
Phase 4	Small cluster(s) with limited human-to-human transmission, but spread is highly localised, suggesting that the virus is not well adapted to human beings	Contain the new virus within limited foci or delay spread to gain time to implement preparedness measures, including vaccine development
Phase 5	Larger cluster(s), but human-to-human spread still localised, suggesting that the virus is becoming increasingly better adapted to human beings, but may not yet be fully transmissible (substantial pandemic risk)	Maximise efforts to contain or delay spread, to possibly avert a pandemic, and to gain time to implement pandemic response measures
Pandemic period		
Phase 6	Pandemic: increased and sustained transmission in general population	Minimise the impact of the pandemic

Table: Phases and overarching public-health goals of WHO's global influenza preparedness plan*

has encouraged health authorities to consider stockpiling antiviral drugs, and many countries now have active stockpiles of the neuraminidase inhibitors oseltamivir and zanamivir.²² At least 40 countries have stockpiles of neuraminidase inhibitors to cover more than 5% of their total population (24 can cover more than 25%, 12 more than 30%, and two 50% or more; Smith J; F Hoffmann-La Roche Ltd, CH-4070, Basel; personal communication, May, 2008). WHO has also established an antiviral stockpile of oseltamivir for rapid response to an emerging influenza epidemic.²³ The stockpiling of the adamantanes (M2 protein inhibitors) has been discouraged because of potential adamantane resistance among recent H5N1 viruses.²⁴ The development of high levels of adamantane resistance among seasonal human influenza A viruses since 2004 has compounded this concern.²⁵ Furthermore, recent reports of high levels of resistance to oseltamivir among influenza A (H1N1) viruses in some world regions reinforces the need for multiple pharmaceutical strategies to be included in preparedness planning.²⁶

Vaccination

The primary strategy for prevention and control of influenza, particularly pandemic influenza, is vaccination.²⁷ However, in identifying the lessons learned from the three pandemics of the last century, WHO has pointed out that, although vaccines were available in 1957 and 1968, limited production capacity resulted in the late arrival of inadequate quantities, and thus their impact on a pandemic remains to be shown.²⁸

WHO has also clearly identified the need to develop the control strategies already in place for seasonal influenza as an important part of pandemic preparedness: "In the best-case scenario, an influenza pandemic will cause excess mortality at the extremes of the lifespan and in persons with underlying chronic disease. As these risk

groups are the same as during seasonal influenza epidemics, countries with good programmes for seasonal influenza vaccination will have experience in the logistics of vaccine administration to at least some groups requiring priority protection during an influenza pandemic. While such a strategy can reduce excess mortality, sudden and large increases in morbidity, and a correspondingly high demand for medical care, should nonetheless be anticipated".²⁹

Global and timely access to vaccines will be of paramount importance. However, the current influenza A (H5N1) threat, and attempts to develop a vaccine against this evolving virus, have led to an awareness of several new challenges that now include vaccine antigen content in addition to vaccine manufacturing capacity.

Current influenza vaccine strategies

Seasonal vaccines

The most widely used seasonal vaccines are the trivalent inactivated influenza virus vaccines containing three viruses: two influenza A viruses (H1N1 and H3N2), and an influenza B virus (15 µg haemagglutinin protein of each virus).³⁰ Adults require a single dose of vaccine to establish protective levels of antibody, whereas children aged 6 months to 8 years require two doses because they are more likely to be immunologically naive.³¹ Seasonal influenza outbreaks and epidemics occur as new influenza virus variants emerge through mutations in the haemagglutinin and neuraminidase genes, resulting in antigenic drift. These changes are sufficient to require modification of the seasonal influenza vaccine each year. WHO holds two vaccine formulation meetings annually to make recommendations on the most up-to-date vaccine composition for the northern hemisphere (in February) and southern hemisphere (in September). Seasonal trivalent vaccines are standardised on their haemagglutinin content, the most abundant viral surface protein, with

little attention being placed on the neuraminidase content, because, unlike antibodies to haemagglutinin, the anti-neuraminidase antibodies induced are not neutralising and do not prevent infection, although they do attenuate virus replication and disease severity.³²

Prepandemic vaccines

Prepandemic influenza virus vaccines are developed in response to a pandemic threat before WHO pandemic phase 6 (table). They may be developed against human isolates of animal influenza viruses that are challenging the species barrier and have caused or are causing sporadic human infections, but have not established efficient and sustained human-to-human transmission, and are regarded by WHO as a potential pandemic threat. Because emergence in human populations necessarily indicates genetic changes within the novel (ie, not currently circulating) influenza virus, and because drift may have taken place, it is difficult to tell whether the prepandemic vaccines will be a good match for the pandemic strain that ultimately emerges, and thus protection may vary.

Most populations are expected to be susceptible to infection with a novel pandemic virus, and two doses of

vaccine (a priming dose followed by a booster dose) are likely to be required to provide adequate protection.³³ Pandemic influenza, in the recent past, has been associated with viruses that are substantially different antigenically (ie, have undergone an antigenic shift) from the virus strains that have previously circulated.

Pandemic vaccines

The production of a vaccine that matches the newly emerged influenza strain cannot begin until after a pandemic virus has emerged. Thus, a well-matched vaccine is unlikely to be available before the virus begins to spread. To develop a fully effective pandemic influenza vaccine that is close in antigenic characteristics to the circulating virus and for distribution to commence is currently estimated to take at least 4–6 months from the time a pandemic is declared by WHO and vaccine seed stock made available, with current vaccine technology.⁴

Spread of the next pandemic virus is thought likely to be enhanced by international air travel, giving the world little time to prepare vaccine for the first wave of disease. Even during the 19th century (1889 and 1899) pandemics, when only steamship travel was available, the virus had spread across the Atlantic to the USA within 2 months of activity in Europe.³⁴ A pandemic influenza vaccine is thus very unlikely to be available in time.

In September, 2006, WHO released an action plan to increase the pandemic influenza vaccine production capacity (panel).³⁵ The plan is the product of a consultation that identifies and prioritises practical solutions for reducing the potential shortfall in pandemic influenza vaccine supply.

Existing vaccine production capacity

The current global seasonal influenza vaccine-manufacturing capacity is estimated at 565 million doses per year of trivalent vaccine.³⁶ This production capacity could theoretically provide 1.7 billion doses of same-strength (15 µg haemagglutinin) monovalent pandemic vaccine for less than 18% of the global population. Assuming that two doses of vaccine will be required to provide adequate protection,³³ 850 million people could be vaccinated with a 15 µg monovalent vaccine, leaving 80–90% of the global population unprotected.³⁷

Initiatives by the Influenza Vaccine Supply International Task Force are underway to establish new and expand existing vaccine production capacity. Currently, over 95% of the global manufacturing capability is based in nine countries (Australia, Canada, France, Germany, Italy, Japan, Netherlands, UK, and USA).^{8,30} Other countries, including China, have either started or are planning to manufacture influenza vaccines. WHO now projects that by 2010, global production capacity for trivalent vaccine will be 1 billion doses.³⁶ Despite these efforts, if a pandemic influenza virus emerges in the near future, vaccine

Panel: WHO's action plan to increase the global production and supply of pandemic influenza vaccine³⁵

- 1 Develop an immunisation policy to increase demand for seasonal vaccines
 - Develop regional and national plans for seasonal influenza vaccination programmes
 - Mobilise resources for the implementation of seasonal influenza vaccination programmes
- 2 Increase influenza vaccine production capacity
 - Increase capacity for inactivated influenza vaccines:
 - Improve production yield of H5N1 viruses and immunogenicity of prototype H5N1 inactivated vaccine
 - Build new production facilities in developing and developed countries
 - Assess formulations of influenza vaccine other than those commonly used for seasonal vaccine:
 - Do clinical trials of adjuvant vaccines
 - Explore the possibility to scale-up production of live, attenuated influenza vaccines
 - Further assess whole-cell vaccines
 - Assess alternative vaccine delivery routes (ie, intradermal administration)
- 3 Promote research and development for new influenza vaccines
 - Enhance protective efficacy and immunogenicity of existing vaccine types
 - Develop novel vaccines that induce broad-spectrum and long-lasting immune responses
 - Improve evaluation of vaccine performance

For the Influenza Vaccine Supply International Task Force see <http://www.ifpma.org/influenza>

supplies would fall short of the anticipated global demand. Furthermore, the task of vaccinating a global population of 6.5 billion people within a limited timeframe, which will place enormous operational and logistic demands on public-health authorities, has barely been considered.³⁸

WHO has consistently encouraged countries to expand the use of seasonal vaccines as a strategy for increasing capacity. However, many countries are not currently using influenza vaccine and do not have influenza vaccination guidelines in place.³⁹ The European Scientific Working Group on Influenza and Asia-Pacific Advisory Committee on Influenza have focused on influenza awareness education, and support the development of guidelines in countries for the vaccination of those at greatest risk from influenza: elderly people and individuals with certain ongoing medical conditions, including children from 6 months of age.³¹ Initiatives that are now being introduced in some countries involve decreasing the age eligibility for government-subsidised vaccine from 65 years to 50 years and the vaccination of healthy children up to 2 years or 18 years of age, whereas universal vaccination has been introduced in Ontario, Canada. The movement towards universal vaccination would help sustain manufacturing capacity building. If countries in southeast Asia and Asia-Pacific regions, including India and China, which contain approximately 52% of the world's population, start using influenza vaccine routinely, then global manufacturing capacity will increase, and surge capacity for pandemic vaccine production would be substantially improved. However, the H5N1 global threat is upon us and alternative strategies need to be considered to ensure an equitable vaccine supply.

Mechanisms that ensure vaccine availability

To ensure that the pharmaceutical industry is ready to manufacture a pandemic vaccine when it is needed, government and industry funding initiatives are supporting the development of pandemic prototype vaccines. These vaccines (so-called "mock-up" influenza vaccines) mimic a potential future pandemic influenza vaccine in terms of its composition and manufacturing method. In the event of an influenza pandemic, the marketing-authorisation holder of the mock-up vaccine can submit additional data to allow the introduction of the actual pandemic strain into the vaccine. The European regulatory authorities approved the first mock-up influenza vaccines in 2007.⁴⁰ The US Food and Drug Administration, the Australian Therapeutics and Goods Administration, and the Japanese Pharmaceuticals and Medicinal Devices Agency will also need to harmonise strategies for the fast-tracking of vaccine registration.

Government funding in the form of advanced purchasing agreements with the pharmaceutical industry has given additional financial security to the industry.⁴¹ These contracts, in principle, will ensure that these countries will have access to a vaccine after the next

pandemic is declared. However, the possibility of governments nationalising vaccine production during a pandemic will remain.⁸

Other vaccine strategies

Strategies of vaccine supply and demand have generally focused on inactivated vaccines, although other vaccine strategies are also being explored.⁴² These strategies have attempted to improve and broaden influenza vaccine immunogenicity by allowing the use of lower (antigen sparing) doses.^{30,43} Progress was initially slow because of the poor immunogenicity of the strain A (H5N1) haemagglutinin antigen.

Subunit vaccines

Initial reports of a safe and immunogenic inactivated subunit A (H5N1) vaccine showed a requirement for 90 µg haemagglutinin doses a month apart (total 180 µg) to produce protection in 50% of the trial participants.⁴⁴ With the current seasonal influenza vaccine manufacturing capacity (requiring 15 µg haemagglutinin of each of three viruses), production of a pandemic vaccine in large quantities would not be feasible.⁴⁵ Furthermore, the surge capacity required in egg production would not be possible. Early studies on inactivated subunit vaccines against low pathogenic avian viruses suggest that these vaccines were poorly immunogenic by comparison with seasonal influenza H1 and H3 subtype vaccines, and that two doses and administration with an adjuvant were needed to produce an adequate response.⁴⁶

Adjuvanted vaccines

Whole-virus H2N2 and H9N2 vaccines containing 1.9–7.5 µg haemagglutinin, combined with aluminium adjuvant, were found to be adequately immunogenic after two doses in naive adults.⁴⁷ However, in trials with the A/Vietnam/2004 (H5N1; clade 1) virus, immunogenicity was not improved at haemagglutinin concentrations below 30 µg by the aluminium hydroxide adjuvant.⁴⁸ Proprietary oil-in-water adjuvants (ie, MF59) have the advantage that they are licensed and well tolerated.^{49,50} Other novel oil-in-water emulsion or squalene adjuvants (ie, AS03 and AP03)⁵¹ are undergoing clinical trials. In a trial of an H5N1 clade 1 split-virus vaccine, with and without AS03 adjuvant, and containing 3.8 µg, 7.5 µg, 15 µg, and 30 µg haemagglutinin, the adjuvanted vaccine at all dose levels met the European Committee for Medicinal Products for Human Use (CHMP) and US FDA criteria for seroconversion and seroprotection after two doses. The unadjuvanted vaccine met the CHMP criteria only at the 30 µg dose.⁵²

Adjuvanted H5 influenza vaccines have, in addition to increasing seroconversion rates, been shown to elicit a cross-clade antibody response.⁵³ In a recent trial, more than 75% of vaccinees who received 3.8 µg AS03-adjuvanted H5N1 clade 1 inactivated vaccine developed neutralising antibodies against a clade 2

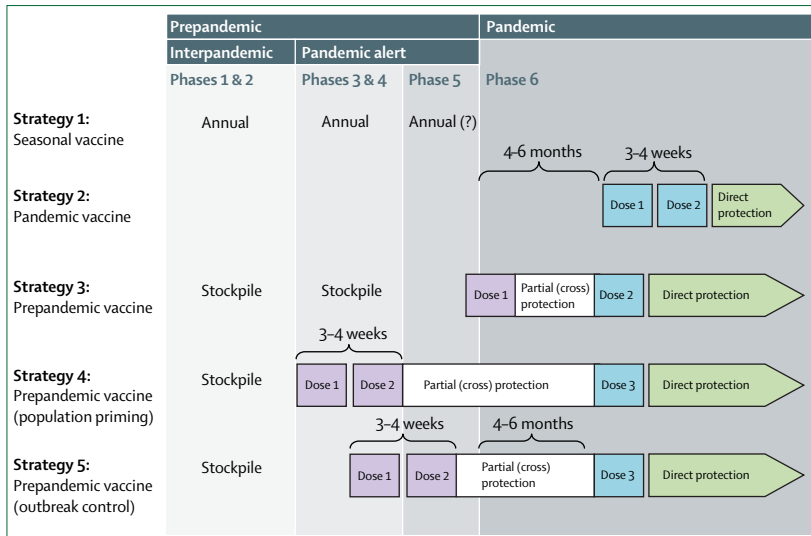


Figure: The use of influenza vaccines during WHO's inter-pandemic, pandemic alert, and pandemic periods
 (1) Seasonal vaccines are likely to be produced and administered during a pandemic alert period; however, uncertainty will remain about their continued production and their usefulness during a pandemic. (2) Pandemic vaccines can only be produced once a novel pandemic virus has been identified and, with current technology, are unlikely to be available during the first wave. (3) Prepandemic vaccines, if produced and stockpiled in advance, could be used at the start of the next pandemic for targeted or population priming, followed by boosting with the pandemic vaccine. (4) Prepandemic vaccines could be used for targeted or population pre-emptive priming during the early pandemic alert phases. (5) Prepandemic vaccines could also be used for targeted outbreak control.

strain.⁵² These AS-adjuvanted H5N1 split candidate vaccines ($\geq 3 \cdot 8 \mu\text{g}$) have also been shown to produce full cross-protection in ferrets.⁵⁴ Although this finding will be difficult to confirm in human clinical trials, it does support the potential pandemic role for ameliorating disease of this and other vaccines that evoke similar high titres of cross-clade antibodies.

Evidence is also becoming available on the persistence of H5N1 antibodies for at least 6 months after primary vaccination. Early studies on the immunogenicity of MF59-adjuvanted H5N3 vaccine showed that two-thirds of vaccinees had protective levels of antibody 16 months after primary vaccination.⁵⁵ After a primary series of two doses of unadjuvanted H5N1 vaccine,⁴⁴ immune memory was retained for at least 6 months, and after a third dose, an amnestic response occurred that was substantially greater than after the second dose.⁵⁶

Another attraction towards adjuvanted vaccines is the possibilities for stockpiling, because the antigen and adjuvant could theoretically be stored separately. This would allow the stockpiling of individual H5N1 clade vaccines or other candidate pandemic vaccines that could be updated as necessary to match newly emerging virus strains.⁵⁷ Storage strategies and the shelf life of both the vaccine (currently <1 year) and adjuvants will need to be explored.

Cell-culture-based vaccines

Cell-culture-based influenza vaccines have been developed and are currently being submitted for licensure. They

have the potential for faster scaling-up of production capacity after a pandemic alert and will have one important advantage over conventional inactivated vaccines that rely on the production of millions of embryonated hens' eggs, because their supply and handling are likely to be limiting factors with pandemic vaccine production. Preliminary unpublished data suggest that protective immunity against H5N1 viruses is developed, that this immunity is cross-protective, and that non-adjuvanted formulations are highly immunogenic.⁵⁸

Live, attenuated virus vaccines

The live, attenuated influenza virus (LAIV) vaccine approach is also a promising option for pandemic vaccination, because seasonal LAIV vaccines are highly immunogenic in unprimed populations and a single dose will provide a protective immune response. LAIV H5N1 vaccine candidates are currently being assessed in clinical trials.⁵⁸ Cross protection between different clades of H5N1 virus has been shown in mice and ferrets.⁵⁹ However, if these LAIV vaccines are used in naive populations, transmission and reassortment with circulating human viruses may lead to the emergence of a virus with increased virulence.²⁷ This concern can be dealt with by restricting the deployment of LAIV vaccines until after the initiation of an influenza pandemic. A major advantage of LAIV vaccines is their superior production capacity and the possibility for the pre-production and stockpiling of a range of candidate pandemic vaccines. The development, assessment, and storage of H2, H4, and H6-16 candidate vaccine seed virus stocks would be required in advance.

New technologies

Clearly, vaccines are now available that are safe, allow antigen dose sparing, show high levels of immunogenicity in association with an adjuvant, and, at least for A (H5N1) viruses, induce cross-clade immunity that is relatively long-lasting. However, the search for a universal vaccine continues.⁶⁰ Of the newer technologies, the baculovirus recombinant haemagglutinin antigen vaccines seem to have the potential for large-scale production, and like cell-culture vaccines, do not require large numbers of hens' eggs.⁶¹ Furthermore, these newer technologies could potentially shorten the time for vaccine availability after a pandemic is declared.

Strategies for vaccine use

Vaccines to a novel influenza virus can potentially be used during two of the three WHO influenza pandemic periods (figure): (1) during the pandemic period as a pandemic vaccine (strategy 2); (2) as a pandemic emerges, based on evidence of human-to-human transmission of a novel virus and a WHO pandemic alert (strategy 3); and (3) early in the pandemic alert period as a prepandemic vaccine when there is heightened risk of a novel virus, as currently exists with the H5N1 virus (strategy 4).

Simulation modelling has provided insights into how best to use a pre-pandemic vaccine, such as the human H5N1 vaccine either before pandemic phase 6 for virus containment or during phase 6 for mitigation of disease.^{62,63} The control of an emerging pandemic at its source is theoretically possible by use of a range of interventions that include quarantine, physical distancing, antivirals, and vaccines.³⁸ A pre-pandemic vaccine, however, would need to be used as early as possible for containment to be achieved (figure).⁶² Relatively few doses of pre-pandemic vaccine would be required. However, there would be many challenges in getting the vaccine to the outbreak, especially in isolated areas, distributing it, and administering it to the targeted population. During phase 6, models suggest that the use of a pre-pandemic vaccine, even if it is a poor match to the pandemic strain and only available as a single dose, would mitigate morbidity and mortality.^{38,63} Early intervention, irrespective of WHO pandemic phase, will require adequate availability of vaccines.

Challenges in the stockpiling of vaccines

The stockpiling of candidate influenza vaccine strains has in recent years been mooted as a pandemic preparedness strategy, but until late 2006, was not seen as a real possibility.⁶⁴ However, with the development and production of a safe inactivated subunit A (H5N1) vaccine,⁴⁴ discussion on how best to use it has become possible. A major issue with this early inactivated H5N1 vaccine, which required 180 µg haemagglutinin, was that large quantities would need to be produced and stockpiled in advance of a pandemic.⁴⁵ Now with improved immunogenicity of egg-based vaccines through the use of adjuvants and the recent development of cell-culture vaccines, antigen sparing is possible and stockpiling of pre-pandemic human H5N1 vaccines has become an option in the short term for WHO and governments. In the longer term (next 5–10 years) other options will undoubtedly become available.

Recent clinical trials with adjuvanted subunit H5N1 vaccines suggest that some cross-clade neutralising antibody responses are produced, opening the possibility of a stockpiled human H5N1 vaccine being used as a pre-pandemic vaccine and administered to prime a population. The vaccine could then be given in advance, with full protection being provided by a pandemic vaccine that matches the pandemic virus (assuming it to be an H5N1 virus) as the pandemic advances (figure). The obvious time to use such a vaccine is after there is evidence of a novel virus emerging and spreading in a population (WHO phase 4 or 5). However, a major issue with waiting until it has emerged is that two doses will be needed and logistical difficulties may mean that it is delivered too late.

The maximum benefit from using a pre-pandemic vaccine may be gained from priming populations before phase 4, when systematic supply, distribution, and

vaccination strategies can be put in place. Furthermore, the persistence of immune memory for at least 6 months and subsequent amnestic response after a third delayed booster dose supports this approach.⁵⁶ Countries that may initially benefit from this are those currently affected by the circulation of H5N1 virus in avian species. Two doses of vaccine are thought to be required; however, evidence on the effectiveness of a single priming dose needs to be obtained. The experience of adverse events from the use of monovalent H1N1 vaccine for mass vaccination in 1976, in the face of an unconfirmed H1N1 threat,^{8,65} ensures that a high degree of caution will continue to remain around such an approach. If a priming strategy before phase 4 were to become an acceptable strategy, the inclusion of an H5N1 antigen into existing seasonal influenza vaccines should be assessed.^{56,66} In future, it may be possible to use such a strategy to prime against multiple clades of H5N1 virus and the H2, H6, H9, and other influenza viruses of concern.

Ethical and other considerations will have been taken into account for the use of vaccines in country-specific pandemic plans. However, information on age-specific attack rates and severity of a novel virus will need to be established as soon as possible after such a virus starts to spread. This information will be pivotal for the best use of stockpiled pre-pandemic vaccines, whether to protect individuals at greatest risk of severe disease or target specific groups such as health-care workers and other essential workers to ensure the overall protection of public health and social stability. Decision making will also be dependent on how much vaccine is available, in which case, prioritisation issues will need to have been established in advance.

The use of the evolving stockpiles of H5N1 vaccine in the current pandemic alert period is unclear. However, as these vaccines near their expiry date, governments will need to decide whether they are used or wasted. Possible uses are in clinical trials to further assess their safety and efficacy in larger numbers of people, or alternatively, in certain populations deemed to be at higher risk.

Access to vaccines by low-income countries

Broader access to vaccines is an issue, particularly for countries that have no vaccine manufacturing capability or cannot afford stockpiling as part of their pandemic preparedness planning. The creation of a global stockpile of H5N1 vaccine was seen to be feasible by the WHO Strategic Advisory Group of Experts (SAGE) in April, 2007.⁶⁷ The consensus was that H5N1 vaccines had now been shown to be safe and immunogenic, and that the production of vaccines providing cross-protection was also realistic. Furthermore, it was also seen as possible to separately develop a mechanism to ensure broader access to pandemic influenza vaccine for use in countries without influenza vaccine production capability or resources to create national stockpiles.^{67,68} Subsequently, a

donation of 50 million doses of H5N1 adjuvanted human vaccine, over the next 3 years, was made to support WHO's stockpiling initiative.

A follow-up SAGE meeting in November, 2007, recommended that the WHO stockpile should be increased to 150 million doses, of which two-thirds was to be reserved for resource-poor countries and one-third for outbreak management.⁶⁹ The mechanisms for management and coordination for the recommended stockpile were not agreed on and other issues regarding sustainability have yet to be resolved.⁷⁰

Several countries are planning or have already established stockpiles of H5N1 vaccine.⁷¹ Eight countries, all medium to high-income nations, have human H5N1 vaccine stockpiles of sizes ranging from an estimated 1.7% to 50% of the population covered (Jennings LC, unpublished data). Although no consensus exists on stockpile volumes, these initiatives are providing industry with experience in producing novel influenza vaccine candidates at a commercial scale and providing confidence for industry to develop new technologies. Funding issues still remain for many countries and strategies used by the Pan American Health Organization for the purchase of childhood vaccines could well be extended to include the stockpiling of pre-pandemic influenza vaccines.

The way forward

Although the current H5N1 avian epizootic is unprecedented, whether it will eventually evolve into an H5N1 pandemic is unclear. Because of the high mortality associated with H5N1 human infections in teenagers and young adults, as seen during the 1918 pandemic, and the high economic burden of pandemic influenza, we simply cannot afford to ignore it as a major global threat. The concerns are that a pandemic vaccine will be produced too late to ameliorate the first and possibly the second waves of a pandemic. Antiviral drugs for treatment and post-exposure prophylaxis could reduce attack rates, but only if given after symptom onset to patients and their contacts.

A pre-pandemic vaccine stockpile has the potential to cut the number and severity of cases, but only if two doses are delivered before the onset of a pandemic, which may be logistically difficult to organise. Moreover, a vaccine stockpile that is stored for use at the onset of a pandemic may need to be replaced because of loss of potency, which would increase the financial costs. There might be no warning of a pandemic and phases 4 and 5 may not be recognised.

However, pre-pandemic priming has the potential to evoke a more rapid antibody response that might ameliorate the disease, cutting hospital admissions, deaths, and onward transmission of the virus. A downside is the possibility of an unexpected severe side-effect or other serious rare events, either from the vaccine or the adjuvant, which could damage subsequent seasonal

vaccination programmes. We therefore think that WHO and governments should give urgent consideration to the potential risks and benefits of priming people who would be at greatest risk of infection if a pandemic of H5N1 influenza were to emerge (frontline laboratory and health-care workers), with the view to cautiously introducing a programme of immunisation. Such a programme is likely to vary from country to country and the decision to proceed could depend on the assessment of risk based on the current occurrence of H5N1 influenza in avian species.

Conflicts of interest

LCJ has received honoraria and travel assistance from GlaxoSmithKline, Hoffmann-La Roche, Sanofi Pasteur, Solvay, Baxter, and Quidel Corporation for participation in advisory groups and scientific meetings. ASM has received honoraria from Novartis, Solvay, GlaxoSmithKline, and Hoffmann-La Roche for participation in advisory groups and research support from Sanofi Pasteur. PKSC has received honoraria and travel assistance from GlaxoSmithKline, Hoffmann-La Roche, Merck Sharp & Dohme, and Baxter. TDS has received honoraria from Sanofi Pasteur, Merck Sharp & Dohme, and research support from the European Vaccine Manufacturers Association. KGN has received honoraria from GlaxoSmithKline, Novartis, and Berna-Biotech, and funding for his research group from Novartis, Crucell-Berna, and Hoffmann-La Roche.

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References

- Potter CW. Chronicle of influenza pandemics. In: Nicholson KG, Webster RG, Hay AJ, eds. Textbook of influenza. Oxford: Blackwell Sciences, 1998: 3–18.
- Johnson NP, Mueller J. Updating the accounts: global mortality of the 1918–1920 “Spanish” influenza pandemic. *Bull Hist Med* 2002; **76**: 105–15.
- de Jong MD, Hien TT. Avian influenza A (H5N1). *J Clin Virol* 2006; **35**: 2–13.
- WHO. WHO global influenza preparedness plan: the role of WHO and recommendations for national measures before and during pandemics. November, 2005. http://www.who.int/csr/resources/publications/influenza/GIP_2005_5Eweb.pdf (accessed July 29, 2008).
- Monto AS, Kendal AP. Effect of neuraminidase antibody on Hong Kong influenza. *Lancet* 1973; **1**: 623–25.
- Kawaoka Y, Krauss S, Webster RG. Avian-to-human transmission of the PB1 gene of influenza A viruses in the 1957 and 1968 pandemics. *J Virol* 1989; **63**: 4603–08.
- Reid AH, Taubenberger JK. The origin of the 1918 pandemic influenza virus: a continuing enigma. *J Gen Virol* 2003; **84**: 2285–92.
- Fedson DS. Preparing for pandemic vaccination: an international policy agenda for vaccine development. *J Public Health Policy* 2005; **26**: 4–29.
- Osterholm MT. Preparing for the next pandemic. *N Engl J Med* 2005; **352**: 1839–42.
- Taubenberger JK, Morens DM. 1918 influenza: the mother of all pandemics. *Emerg Infect Dis* 2006; **12**: 15–22.
- Webster RG, Peiris M, Chen H, Guan Y. H5N1 outbreaks and enzootic influenza. *Emerg Infect Dis* 2006; **12**: 3–8.
- WHO. Antigenic and genetic characteristics of H5N1 viruses and candidate H5N1 vaccine viruses developed for potential use as human vaccines. February, 2008. http://www.who.int/csr/disease/avian_influenza/guidelines/H5VaccineVirusUpdate20080214.pdf (accessed July 29, 2008).
- WHO. Epidemic and Pandemic Alert and Response (EPR). Cumulative number of confirmed human cases of avian influenza A(H5N1) reported to WHO. 28 May 2008. http://www.who.int/csr/disease/avian_influenza/country/cases_table_2008_05_28/en/index.html (accessed July 29, 2008).

- 14 Wong SS, Yuen KY. Avian influenza virus infections in humans. *Chest* 2006; **129**: 156–68.
- 15 WHO. Current WHO phase of pandemic alert. http://www.who.int/csr/disease/avian_influenza/phase/en/index.html (accessed July 29, 2008).
- 16 WHO. Epidemic and pandemic alert and response (EPR): national influenza pandemic plans. <http://www.who.int/csr/disease/influenza/nationalpandemic/en/index.html> (accessed Aug 29, 2008).
- 17 European Influenza Surveillance Scheme. Pandemic planning: pandemic plans on the internet. http://www.eiss.org/html/pandemic_plans.html (accessed Aug 29, 2008).
- 18 Uscher-Pines L, Omer SB, Barnett DJ, Burke TA, Balicer RD. Priority setting for pandemic influenza: an analysis of National Preparedness Plans. *PLoS Med* 2006; **3**: e436.
- 19 Coker R, Mounier-Jack S. Pandemic influenza preparedness in the Asia-Pacific region. *Lancet* 2006; **368**: 886–89.
- 20 Mounier-Jack S, Coker RJ. How prepared is Europe for pandemic influenza? Analysis of national plans. *Lancet* 2006; **367**: 1405–11.
- 21 Monto AS. Vaccines and antiviral drugs in pandemic preparedness. *Emerg Infect Dis* 2006; **12**: 55–60.
- 22 Coombes R. UK stocks up on antiviral drug to tackle flu outbreak. *BMJ* 2005; **330**: 495.
- 23 WHO. Interim protocol: rapid operations to contain the initial emergence of pandemic influenza. Updated May 2007. http://www.who.int/csr/disease/avian_influenza/RapidContProtMay07.pdf (accessed July 29, 2008).
- 24 WHO. WHO rapid advice guidelines on pharmacological management of humans infected with avian influenza A (H5N1) virus. http://www.who.int/medicines/publications/WHO_PSM_PAR_2006.6.pdf (accessed July 29, 2008).
- 25 Simonsen L, Viboud C, Grenfell BT, et al. The genesis and spread of reassortment human influenza A/H3N2 viruses conferring adamantane resistance. *Mol Biol Evol* 2007; **24**: 1811–20.
- 26 WHO. Epidemic and Pandemic Alert and Response (EPR). WHO/ECDC frequently asked questions for oseltamivir resistance. http://www.who.int/csr/disease/influenza/oseltamivir_faqs/en/index.html (accessed July 29, 2008).
- 27 Nichol KL, Treanor JJ. Vaccines for seasonal and pandemic influenza. *J Infect Dis* 2006; **194** (suppl 2): S111–18.
- 28 WHO. Avian influenza: assessing the pandemic threat. January, 2005. <http://www.who.int/csr/disease/influenza/H5N1-9reduit.pdf> (accessed July 29, 2008).
- 29 WHO. Global pandemic influenza action plan to increase vaccine supply. September, 2006. http://www.who.int/csr/resources/publications/influenza/CDS_EPR_GIP_2006_1.pdf (accessed July 29, 2008).
- 30 Jennings LC. Pandemic influenza vaccines. In: Wong JP, ed. Recent developments on the avian influenza (H5N1) crisis. Tivandrum, India: Transworld Research Network, 2006: 39–49.
- 31 Centers for Disease Control and Prevention. Prevention and control of influenza. Recommendations of the advisory committee on immunization practices (ACIP). *MMWR Morb Mortal Wkly Rep* 2007; **56**: 1–54.
- 32 Kilbourne, ED, Couch RB, Kasal JA, et al. Purified influenza A virus N2 neuraminidase vaccine is immunogenic and non-toxic in humans. *Vaccine* 1995; **13**: 1799–803.
- 33 Schwartz B, Wortley P. Mass vaccination for annual and pandemic influenza. *Curr Top Microbiol Immunol* 2006; **304**: 131–52.
- 34 Glezen WP. Emerging infections: pandemic influenza. *Epidemiol Rev* 1996; **18**: 64–76.
- 35 WHO. WHO strategic action plan for pandemic influenza. http://www.who.int/csr/resources/publications/influenza/StregPlanEPR_GIP_2006_2.pdf (accessed July 29, 2008).
- 36 WHO. Media centre. Projected supply of pandemic influenza vaccine sharply increases. Oct 23, 2007. <http://www.who.int/mediacentre/news/releases/2007/pr60/en/index.html> (accessed July 29, 2008).
- 37 Stohr K, Esveld M. Will vaccines be available for the next pandemic? *Science* 2004; **306**: 2195–96.
- 38 Germann TC, Kadau K, Longini IM, Macken CA. Mitigation strategies for pandemic influenza in the United States. *Proc Natl Acad Sci USA* 2006; **103**: 5935–40.
- 39 Macroepidemiology of Influenza Vaccination (MIV) Study Group. The macroepidemiology of influenza vaccination in 56 countries, 1997–2003. *Vaccine* 2005; **23**: 5133–43.
- 40 European Medicines Agency. EMEA pandemic influenza preparedness. Pandemic influenza “mock-up” vaccines. <http://www.emea.europa.eu/htms/human/pandemicinfluenza/mockup.htm> (accessed July 29, 2008).
- 41 Montomoli E, Manini I. Pre-emptive vaccination against pandemic influenza virus [letter]. *Vaccine* 2007; **25**: 1921–22.
- 42 WHO. Initiative for Vaccine Research (IVR). Tables on the clinical trials of pandemic influenza prototype vaccines. http://www.who.int/vaccine_research/diseases/influenza/flu_trials_tables/en/index1.html (accessed July 29, 2008).
- 43 WHO. Global distribution of influenza vaccines, 2000–2003. *Wkly Epidemiol Rec* 2004; **79**: 366–67.
- 44 Treanor JJ, Campbell JD, Zangwill KM, Rowe T, Wolff M. Safety and immunogenicity of an inactivated subvirion influenza A (H5N1) vaccine. *N Engl J Med* 2006; **354**: 1343–51.
- 45 Pollard GA. Vaccines against avian influenza: a race against time. *N Engl J Med* 2006; **367**: 1411–13.
- 46 Luke CJ, Subbarao K. Vaccines for pandemic influenza. *Emerg Infect Dis* 2006; **12**: 66–72.
- 47 Hehme N, Engelmann H, Knuzel W, Neumeier E, Sanger R. Pandemic preparedness: lessons learnt from H2N2 and H9N2 candidate vaccines. *Med Microbiol Immunol (Berl)* 2002; **191**: 203–08.
- 48 Bresson JL, Perronne C, Launay O, et al. Safety and immunogenicity of an inactivated split-virion influenza A/Vietnam/1194/2004 (H5N1) vaccine: phase I randomised trial. *Lancet* 2006; **367**: 1657–64.
- 49 Podda A. The adjuvanted influenza vaccines with novel adjuvants: experience with the MF59-adjuvanted vaccine. *Vaccine* 2001; **19**: 2673–80.
- 50 Bernstein D, Edwards KM, Dekker CL, et al. Effects of adjuvants on the safety and immunogenicity of an avian influenza H5N1 vaccine in adults. *J Infect Dis* 2008; **197**: 667–75.
- 51 Baras B, Stittelaar K, Simon J, et al. Cross-protection against heterologous H5N1 challenge in ferrets with low dose adjuvanted split H5N1 vaccine. Proceedings of the IX International Symposium on Respiratory Viral Infections, Hong Kong; March 3–6, 2007. Abstract VI-6a.
- 52 Leroux-Roels I, Borkowski A, van Wolleghem T, et al. Antigen-sparing and cross-reactive immunity with an adjuvanted rH5N1 prototype pandemic influenza vaccine: a randomized controlled trial. *Lancet* 2007; **370**: 580–89.
- 53 Stephenson I, Bugarini R, Nicholson KG, et al. Cross-reactivity to highly pathogenic avian influenza H5N1 viruses after vaccination with non adjuvanted and MF59-adjuvanted influenza A/Duck/Singapore/97 (H5N3) vaccine: a potential priming strategy. *J Infect Dis* 2005; **191**: 1210–15.
- 54 Baras B, Stittelaar KJ, Simon JH, et al. Cross-protection against lethal H5N1 challenge in ferrets with an adjuvanted pandemic influenza vaccine. *PLoS ONE* 2008; **3**: e1401.
- 55 Stephenson I, Nicholson KG, Colegate A, et al. Boosting immunity to influenza H5N1 with MF59-adjuvanted H5N3 A/duck/Singapore/97 vaccine in a primed human population. *Vaccine* 2003; **21**: 1687–93.
- 56 Zangwill KM, Treanor JJ, Campbell JD, Noah DL, Ryea J. Evaluation of the safety and immunogenicity of a booster (third) dose of inactivated subvirion H5N1 influenza vaccine in humans. *J Infect Dis* 2008; **197**: 580–83.
- 57 Osterhaus ADME. Pre- or post-pandemic influenza vaccine? *Vaccine* 2007; **25**: 4983–84.
- 58 WHO. 4th WHO meeting on evaluation of pandemic influenza prototype vaccines in clinical trials, 14–15 February 2008, WHO HQ, Geneva. Summary and meeting documents. http://www.who.int/vaccine_research/diseases/influenza/meeting_140208/en/index1.html (accessed May 30, 2008).
- 59 Suguitan AL, McAuliffe J, Mills KL, et al. Live, attenuated influenza A H5N1 candidate vaccines provide broad cross-protection in mice and ferrets. *PLoS Med* 2006; **3**: e36.
- 60 Gerhard W, Mozdzanowska K, Zharikova D. Prospects for universal influenza virus vaccine. *Emerg Infect Dis* 2006; **12**: 569–74.

- 61 Treanor JJ, Schiff GM, Hayden FG, et al. Safety and immunogenicity of a baculovirus-expressed hemagglutinin influenza vaccine: a randomized controlled trial. *JAMA* 2007; **297**: 1577–82.
- 62 Longini IM, Nizam A, Xu S, et al. Containing pandemic influenza at the source. *Science* 2005; **309**: 1083–87.
- 63 Ferguson NM, Cummings DAT, Fraser C, Cajka JC, Cooley PC, Burke DS. Strategies for mitigating an influenza pandemic. *Nature* 2006; **442**: 448–52.
- 64 Schwartz B, Gellin B. Vaccination strategies for an influenza pandemic. *J Infect Dis* 2005; **191**: 1207–09.
- 65 Langmuir AD, Bregman DJ, Kurland LT, Nathanson N, Victor M. An epidemiological and clinical evaluation of Guillain-Barre syndrome reported in association with the administration of swine influenza vaccines. *J Epidemiol* 1984; **19**: 841–79.
- 66 Sandbulte MR, Jimenez GS, Boon ACM, Smith LR, Treanor JJ, Webby RJ. Cross-reactive neuraminidase antibodies afford partial protection against H5N1 in mice and are present in unexposed humans. *PLoS Med* 2007; **4**: e59.
- 67 WHO. Media centre. Global stockpile of H5N1 vaccine “feasible”. Meeting at WHO agrees stockpile a realistic expectation. April 26, 2007. <http://www.who.int/mediacentre/news/releases/2007/pr21/en/index.html> (accessed July 29, 2008).
- 68 WHO. Media centre. WHO and manufacturers move ahead with plans for H5N1 influenza global vaccine stockpile. June 13, 2007. <http://www.who.int/mediacentre/news/statements/2007/s14/en/index.html> (accessed July 29, 2008).
- 69 WHO. SAGE conclusions and recommendations. Experts recommend WHO stockpile up to 150 million doses of avian flu vaccine. http://www.who.int/immunization/sage/SAGE_note_19_11_07.pdf (accessed Aug 29, 2008).
- 70 WHO. Options for the use of human H5N1 influenza vaccines and the WHO H5N1 vaccine stockpile. WHO scientific consultation. October, 2007. http://www.who.int/csr/resources/publications/WHO_HSE_EPR_GIP_2008_1d.pdf (accessed July 29, 2008).
- 71 Straetemans M, Buchholz U, Reiter S, Haas W, Krause G. Prioritization strategies for pandemic influenza vaccine in 27 countries of the European Union and the Global Health Security Action Group: a review. *BMC Public Health* 2007; **7**: 236.