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How effective would antiviral vaccination and antiviral drug prevention and treatment strategies be for reducing the impact of the next influenza pandemic?

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EVIDENCE FOR DECISION-MAKERS

ABSTRACT

This is a Health Evidence Network (HEN) synthesis report on the potential effectiveness of antiviral vaccination and antiviral drug prevention and treatment for reducing the impact of an influenza pandemic. An influenza pandemic seems inevitable, but it is not known weather this will be caused by H5N1 or another virus or how severe it will be.

Major finding:
Until the actual emergence of the influenza virus strain responsible for an influenza pandemic, there is no direct evidence of the effectiveness of vaccine and antiviral drug prevention and treatment strategies for lowering mortality and morbidity, or for containing or delaying the spread, of an influenza pandemic.

This HEN synthesis report is a summary of existing information (including but not limited to WHO policy documents) and evidence related to influenza pandemics that might be useful to policy makers. The list of references includes links to several policy documents for further details.

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Summary

The issue

An influenza pandemic seems inevitable. The H5N1 influenza virus, known as the avian influenza, is currently circulating in Asia and has appeared in other regions. Avian influenza (flu), which has been transmitted from birds to humans on a limited basis, can be rapidly fatal, with a reported death rate of at least 50% in the documented human cases to date. If a human-to-human transmissible form emerges and spreads rapidly, it will pose a great threat to global public health, although the mortality rate may not be as high as that observed thus far. While various factors suggest that this strain could be the cause of the next pandemic, it is unknown when it will occur, whether it will be caused by H5N1 or another new virus or how severe it will be.

This report assembles and presents evidence on the potential effectiveness of antiviral vaccination and antiviral drug prevention and treatment for reducing the impact of an influenza pandemic caused by the avian flu virus or another viral strain.

Findings

Until the actual emergence of the influenza virus strain responsible for an influenza pandemic, there is no direct evidence of the effectiveness of vaccine and antiviral drug prevention and treatment strategies for lowering mortality and morbidity, or for containing or delaying the spread, of an influenza pandemic.

Direct evidence of the effectiveness of vaccine and antiviral drug prevention and treatment strategies for reducing the health impacts, lowering mortality and morbidity and stopping or limiting influenza pandemics is extremely limited. Even so, vaccination is well established as the most effective means of preventing influenza. However, vaccine development against a particular influenza strain can start only once a pandemic begins and the strain is identified. Then it can take another six months or more for mass production of the vaccine using current technology. Therefore, virus-specific vaccines are unlikely to be available during the initial wave of a pandemic.

Due to the lack of vaccine for a possible influenza pandemic and insufficient supplies of antiviral drugs for preventing or treating influenza, mass vaccination and use of antiviral drugs would probably be impracticable for a pandemic arising in the near future. Targeted use of vaccine – once it becomes available – and certain antiviral drugs in priority groups and infected patients is supported by available evidence. At least 50 mostly developed countries are moving to stockpile limited supplies of antiviral drugs, and some are also seeking to stockpile limited supplies of experimental vaccine for the H5N1 strain. However, the effectiveness of this strategy is uncertain. This vaccine is likely to be only minimally effective against evolving strains. The options for using antiviral drugs are limited by the resistance of prevailing flu strains to some of them, the possibility that pandemic strains may require higher doses and longer treatment regimens (as recommended for H5N1 infections) and the high costs of some antivirals. Other preventive strategies for which supporting evidence is limited include targeted vaccination with non-pandemic flu vaccine and targeted vaccination of poultry to reduce the spread of infection among poultry and transmission of a novel virus to humans.

Policy considerations

The impact of any strategies for vaccination and antiviral drug use depends on how soon the pandemic starts. If it starts when there is no vaccine available and only limited supplies of antiviral drugs, it is more likely that targeted strategies for vaccine and antiviral drug use will be the only potential options, and the vaccine will be less effective if the pandemic virus is a new strain. High priority strategies for closing existing gaps in pandemic response capacity include:

- developing a detailed, cross-sectoral operational plan at global, regional and national levels for diminishing the impact of the initial one-to-three years of a pandemic;
- increasing research on production of an effective vaccine;
- further developing reverse genetics and cell culture based technology for more efficient vaccine production to replace current insufficient egg-based production;
- increasing research on dose-stretching strategies such as adjuvants and intradermal injections to increase the number of doses that can be made from any given level of vaccine production capacity;
- ensuring the manufacturing capacity to produce sufficient vaccine during the early stage of a pandemic, supported by increasing the use of interpandemic (seasonal) influenza vaccination in developed and developing countries;
- accelerating formation of public-private partnerships for vaccine development;
- increasing manufacturing capacity and stockpiling of likely effective antiviral drugs;
- increasing research on new antiviral drugs; and
- developing effective means for delivering preventive and therapeutic interventions.

Type of evidence

This synthesis is based on evidence from systematic reviews, narrative reviews, epidemiological and other observational studies, modelling and related analyses (based in part on clinical or epidemiological evidence), practice guidelines, other guidance and policy documents from national and international health agencies and recent news reports.

Contributors

Authors

Clifford Goodman, PhD
Vice President
The Lewin Group
3130 Fairview Park Drive, Suite 800
Falls Church, Virginia 22042
tel +1 703-269-5626
fax +1 703-269-5501
clifford.goodman@lewin.com

Debjani Mukherjee, MHP
Associate
The Lewin Group
3130 Fairview Park Drive, Suite 800
Falls Church, Virginia 22042
tel +1 7030269-5561
fax +1 703-269-5501
debjani.mukherjee@lewin.com

Eric Faulkner, MPH
Senior Associate
The Lewin Group
3130 Fairview Park Drive, Suite 800
Falls Church, Virginia 22042
tel +1 703-269-5721
fax +1 703-269-5501
eric.faulkner@lewin.com

Reviewers

Professor Michael Osterholm, Center for Infectious Disease Research and Policy, School of Public Health, University of Minnesota, Minneapolis, Minnesota.

Dr Richard Laing, Policy, Access and Rational Use Medicine Policy and Standards, World Health Organization, Geneva, Switzerland.

Ms Marja Esveld, Coordinator of International Affairs, Centre for Infectious Disease Control, The Netherlands.

Dr Kees de Joncheree, Health Technologies and Pharmaceuticals Programme, WHO Regional Office for Europe.

Technical Editors

Professor Alicia Granados (Main Editor), Professor Karen Facey and Dr Leena Eklund, Health Evidence Network, WHO Regional Office for Europe.

Because this is a novel area of information and there is not yet robust evidence available on the pandemic flu we welcome any new information on this issue.

Introduction

Influenza (flu) is an acute illness caused by viral infection in humans and animals. It typically involves inflammation of the respiratory tract accompanied by fever, chills, muscular pain, and weakness. Effects of influenza can range from mild to fatal, depending on such factors as the virulence of a particular viral strain and risk factors such as a person's age, pre-existing illness and genetics.

Influenza viruses are highly unstable. They can rapidly mutate (undergo genetic changes), be highly contagious and develop resistance to available treatments, spreading rapidly throughout regional and global populations. In most years, typical flu epidemics infect 5–20% of the population, and result in anywhere from 250 000 to 500 000 deaths, according to WHO, although other estimates accounting for deaths due to complications of the flu are as high as 1–1.5 million. Pandemics (global epidemics) occur when influenza spreads globally, infecting 20–40% of the world population in one year, resulting in a few million to tens of millions of deaths *(1,2,3)*.

The typical (seasonal) flu epidemics that occur almost every year are caused by viruses that have been circulating for decades and change only slightly from year to year. (These are also known as "interpandemic" years.) In contrast, a pandemic is caused by a new influenza strain that emerges from a chance "reassortment" of the genetic material from animal and human flu viruses, resulting in a highly contagious strain to which the majority of the world's population has little or no immunity. This may also include strains that have never circulated among people or have not done so for many years. The behaviour of influenza viruses in pandemics is difficult to predict.

Pandemics have occurred about every 10–50 years for at least several centuries *(4),* including three in the twentieth century. The "Spanish flu" of 1918–1920 was caused by an H1N1 virus; the "Asian flu" of 1957–1958 was caused by an H2N2 virus; and the "Hong Kong flu" of 1968–1969 was caused by an H3N2 virus. By far the most severe pandemic was the flu in 1918–1920, which resulted in a two-year toll of as many as 50–100 million deaths worldwide, or 2.5–5% of the world's population *(5)*. The mortality rate of this pandemic was several times higher than the contemporary average for seasonal influenza epidemics *(4)*. Many people died within the first few days of infection, and other deaths resulted from secondary bacterial lung infections at a time when antibiotics were not available. A major factor contributing to this high mortality rate was likely the immune reaction to the new virus, known as a "cytokine storm", whereby the body over-reacts to a strange virus with a cascade of responses pouring immune cells and immune system substances into the lungs, leading to acute respiratory distress syndrome (ARDS) and suffocation. A flu that induces this severe reaction is less likely to respond to treatment with antiviral drugs *(2)*. In 2005, genetic research revealed that the 1918-1920 pandemic was caused by an H1N1 virus closely related to avian viruses, and probably originated from a bird-to-human transmission *(6,7)*.

Estimates for the death toll from the next influenza pandemic range from fewer than 2 million to as high as 175 to 360 million, the latter range based on projecting death rates of the 1918–1920 pandemic to today's population *(8)*. WHO's best case scenarios, modelled on the mild 1968–1969 pandemic, are for between 2 million and 7.4 million deaths *(9)*. There is no certainly regarding the severity of the next pandemic. If a pandemic virus emerges with a virulence similar to that of the 1918-1920 pandemic and becomes as readily transmissible as usual pandemic influenza viruses, it would have a disastrous impact on the global population *(10)*.

The avian flu virus currently circulating in Asia and recently appearing in other regions is the H5N1 strain. More than 150 million birds have died from the virus or been killed in order to limit its spread. It has infected a small number of humans and has the potential to develop into a pandemic strain. H5N1 first "jumped" from birds to humans in Hong Kong in 1997. It is highly virulent in humans, who generally lack immunity to it. As of December 2005, the reported human fatality rate was 50%, based on at least 69 deaths among at least 134 confirmed cases reported to WHO since December

2003 *(11,12)*. A small number of human-to-human transmissions have been reported. Autopsies of human victims of H5N1 infections and laboratory studies have revealed lung damage characteristic of cytokine storms *(12,13)*. Most of the human cases to date have been reported in Viet Nam, with additional cases in Thailand, Indonesia, Cambodia, and China *(11)*. The appearance of H5N1 in humans prompted WHO to declare a phase 3 pandemic alert period *(9,14)*[1].

It is unknown whether the next pandemic will be caused by H5N1 or another new virus. The extent and nature of the outbreaks of H5N1 infections, along with other genetic and environmental factors (including ample opportunities for the strain to mutate as it jumps among large populations of birds with closely interacting humans) suggest that H5N1 is a likely, though not certain, source of the next pandemic.

Sources of evidence

This synthesis of information is based on a comprehensive search of peer-reviewed, published literature (including PubMed/MEDLINE, the Cochrane Databases, EMBASE and other key literature databases), reports or guidance documents from agencies involved in public health response (WHO, the European Union Commission on Community Influenza Preparedness and Response, the Centers for Disease Control and Prevention [CDC], and the United States Institute of Medicine) and relevant grey literature. As this is a synthesis and not a systematic review, not all relevant articles are cited. Details of the search strategy are provided in Annex 1.

Pandemics are infrequent events and H5N1 avian influenza is only recently emerging as a pandemic threat. Therefore, current evidence of the effectiveness of specific vaccine and antiviral drug prevention and treatment strategies for reducing the health impacts of a potential pandemic is limited. Many of the newer vaccine interventions being suggested for use in an emerging pandemic have only been tested in the last few years in small clinical trials (including some randomized controlled trials [RCTs[2]], the strongest form of scientific evidence for assessing causal effects of interventions on health outcomes) involving healthy patients, not in people actually exposed to influenza or in the context of an actual epidemic or pandemic.

Some systematic reviews of the general clinical impact and cost-effectiveness of influenza vaccination and antiviral drugs do exist and are cited here. However, some of the relevant studies consider one or more aspects of certain strategies in a limited, not global, context, and rely heavily upon non-systematic reviews or expert consensus. Some of the studies used modelling and related analyses (based in part on clinical or epidemiological evidence) that rely on incomplete evidence or evidence not derived from rigorous studies in practice or research settings. Some of the available relevant evidence is becoming outdated due to new information regarding flu strains and emerging resistance to antiviral drugs, for example. Thus, this synthesis includes both highly rigorous evidence (from large randomized controlled trials and systematic reviews) and less rigorous evidence (from small RCTs,

[1] In 2005, WHO redefined the phases of increasing public health risk associated with the emergence of new influenza virus subtypes that may pose pandemic threats. These phases are: **Interpandemic period:** *Phase 1.* No new influenza virus subtypes have been detected in humans. 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 considered to be low. *Phase 2.* No new influenza virus subtypes have been detected in humans. However, a circulating animal influenza virus subtype poses a substantial risk of human disease. **Pandemic alert period:** *Phase 3.* Human infection(s) with a new subtype, but no human-to-human spread, or at most rare instances of spreading to a close contact. *Phase 4.* Small cluster(s) with limited human-to-human transmission but spreading is highly localized, suggesting that the virus is not well adapted to humans. *Phase 5.* Larger cluster(s) but human-to-human spreading still localized, suggesting that the virus is becoming increasingly better adapted to humans, but may not yet be fully transmissible (substantial pandemic risk). **Pandemic period:** *Phase 6.* Pandemic increased and sustained transmission in general population.

[2] Randomized controlled trials [RCTs] are the strongest form of scientific evidence for assessing causal effects of interventions on health outcomes.

observational studies, reviews, and recent news articles), and does not include a structured assessment of the quality of the body of evidence referenced.

Findings

Direct evidence of the effectiveness of vaccine and antiviral drug prevention and treatment strategies for reducing the health impacts of influenza pandemics is extremely limited. Because vaccination is the most effective means of defence against influenza, most relevant articles focus on increasing timeliness and availability of vaccines for pandemic response, with less emphasis on the role of antiviral drugs. While this synthesis focuses on the effectiveness of vaccines and antivirals in the prevention and treatment of pandemic influenza, any strategy for containing an influenza pandemic must consider their use in combination with other interventions, including infection control, quarantine, social distancing and antibiotics against bacterial infections that often arise in flu victims.

Vaccination

Prevention and treatment
Vaccines are the most effective primary strategy available for preventing and lowering the impact of an influenza outbreak. One systematic review of RCTs of influenza prevention concludes that vaccination with both inactivated (killed) and live-attenuated (weakened) vaccines is moderately effective in healthy adults and children over six months old *(8)*. An emerging pandemic would create a global surge in demand for a vaccine against the pandemic strain. However, mass vaccination during the first wave of a pandemic is probably not feasible due to the current limitations on developing and manufacturing a sufficient supply of vaccine for the pandemic strain and delivering it in a timely manner *(8,15)*.

Compared to ongoing strategies for vaccination against typical seasonal influenza strains, strategies for an influenza pandemic are severely limited *(3)*. There are likely to be three main phases in the vaccine response to an influenza pandemic: no vaccine available, vaccine in limited supply, and vaccine widely available *(16)*. Vaccine development for a specific human-to-human strain can start only once a pandemic begins and the strain is identified; then it may take six months or more using current technology to begin mass production *(2)*.

In the three twentieth-century pandemics, infection occurred in multiple waves separated by months. Some regions were affected only several months after the initial outbreak, some regions were affected by several waves of infection, and later waves tended to have more severe health effects than the initial wave. Such unfolding of a pandemic over time could provide an opportunity for a large, responsive vaccine production and distribution capacity to reduce its impact *(10)*. However, the modern extent of international travel, population density, and other factors may limit even this opportunity.

Table 1 shows the main types of vaccination strategies discussed in the literature. As elaborated below, these strategies are supported by evidence of varying rigour.

Table 1. Potential vaccination strategies for pandemic response	
Prevention	1. **Mass vaccination with strain specific vaccine:** • effective but not feasible for the first wave due to production time requirements and current manufacturing capacity. 2. **Targeted vaccination with strain-specific vaccine (as it becomes available) by priority:** • essential services workers, including health care workers who treat patients and others in close contact with infected or high-risk

	groups; • groups at high risk of death and severe complications requiring hospitalization, including those who are at least 65 years old with high-risk conditions and younger people with high-risk chronic conditions; • people without risk factors for complications (healthy adults and children). 3. **Targeted vaccination with currently available vaccines:** • increased use of interpandemic (trivalent) flu vaccine (potential for cross-protection against pandemic virus); • stockpiling of the current H5N1 strain vaccine; • prior to pandemic, prime populations with current H5N1 strain vaccine; at time of pandemic, follow with booster vaccine made from strain specific pandemic virus; may induce sufficient immunity. 4. **Vaccine development, dosage and administration:** • develop advanced vaccine production technologies, including reverse genetics to develop seed strains and cell culture based production; • use low-dose monovalent vaccines and adjuvants to increase number of doses from available supply; • use intradermal injection (requiring smaller dosages) as alternative to traditional intramuscular injection.
Treatment	1. **Using vaccines to treat those already infected to reduce health effects and transmission:** • considered unfeasible for highly virulent strains that can kill days after symptoms occur (effective immune response typically requires 2–3 weeks to develop and a primary and booster regimen may be required for naïve populations).

Sources: *(3,15,17–27)*

The literature recommends vaccination with strain-specific vaccine according to priority. This usually starts with essential services workers, including health care workers who treat patients and others in close contact with infected or high-risk groups, followed by groups at high risk of death and severe complications requiring hospitalization (including those who are at least 65 years old with high risk conditions and younger people with high-risk chronic conditions), followed by people without risk factors for complications (healthy adults and children). Some guidelines give higher priority to groups who are likely to spread flu rapidly, particularly school-age children and people in residential homes *(3,15,19,24–26)*.

A recent systematic review of the available evidence of effectiveness of influenza vaccines in the elderly found more modest benefits than those generally cited by national and international agencies, particularly where the match between the vaccine strains and the circulating strains was poor or unknown *(28)*. Targeted vaccination of priority groups alone may do little to reduce mortality, morbidity or the spread of influenza in the broader population, and may have to be accompanied by other strategies such as quarantine and border controls. Although annual targeted vaccination of children (and perhaps other high-risk groups) during interpandemic years may have potential to induce partial cross-protection against a pandemic strain and reduce its transmission, there is little direct evidence to support this option *(25)*.

Production capacity
In the absence of greater capacity to produce vaccine, the large-scale vaccination strategies in the early waves of a pandemic will not be feasible. Vaccine production is limited by the current fragile and limited egg-based approach that has been used since the 1950s and requires six or more months and more than one fertilized chicken egg per dose of vaccine. Current global production capacity is probably less than 1 billion doses of monovalent (for one viral strain) vaccine. Nearly all of the world's vaccine production capacity resides in nine countries, mainly five western European countries. If this capacity could be directed exclusively to making monovalent pandemic vaccine, it could deliver that many doses. However, no people or very few will have been infected with an influenza virus similar to the pandemic virus, so almost all will be immunologically naïve. Therefore, it is highly likely that people will most likely need two doses to achieve a successful immune response against the new strain. Therefore, assuming conventional dose levels, there would be enough vaccine only for fewer than 500 million of the world's 6.5 billion people *(8,26)*. Notably, the H5N1 virus is lethal to embryonated eggs, so no vaccine against H5N1 has been produced in the conventional manner.

Alternative vaccine production
Increases in vaccine capacity may be achievable through new approaches, particularly reverse genetics and cell culture based production. Cell culture technology is already established for producing vaccines against such diseases as polio, hepatitis A, and chickenpox. It involves growing key vaccine components in animal or human cells in enclosed vats. Not reliant on adapting viruses for growth in eggs or waiting for chickens to produce enough eggs, this vaccine production technology is more versatile and responsive to surges in demand, and could decrease vaccine production time by at least one month *(29)*. Cell culture production could enable large-scale manufacturing a vaccine that includes antigens that are present in all strains of influenza virus and do not change from year-to-year *(8)*. Cell culture technology also provides an option for vaccinating people who are allergic to eggs.

In reverse genetics, genes from a harmful influenza virus are combined with genes from a relatively harmless influenza virus to form a reassorted, weakened virus that can be used as a "seed strain" for rapid and efficient vaccine production. Experimental H5N1 vaccine seed strains have been produced in less than four weeks using reverse genetics techniques by removing the virulent genetic material from H5N1, and have been found viable for growth in eggs *(10,17,30,31)*. Because the reverse genetics process uses mammalian cells and yields genetically modified organisms, it is subject to strict regulatory requirements in Europe *(32),* while different regulatory requirements prevail the United States. Such reverse genetics techniques have not been licensed for use in humans.

In 2005, an investigational H5N1 vaccine made by Sanofi Pasteur using reverse genetics elicited a positive immune response in healthy adults in an RCT conducted in the United States. Preliminary findings from 117 of the 450 healthy adult recipients who had received the vaccine thus far showed a strong enough response to resist the virus. However, the dosage required for this immune response was much higher than conventional influenza doses, which would strain production capacity and limit the potential number of recipients. Furthermore, it is uncertain whether the vaccine would be successful against a mutated pandemic form of the avian flu virus. The vaccine is also being tested in elderly adults *(33,34)*.

Evidence on the safety, effectiveness, and efficiency of these newer approaches for producing influenza vaccine is currently limited. Aside from scientific hurdles, progress is limited by regulatory, legal and other constraints that inhibit innovation and sharing of novel techniques with key stakeholders *(3,17,21,22).* For example, the willingness of vaccine manufacturers to use reverse genetics technologies is constrained by uncertainty regarding ownership of intellectual property rights for these technologies, in addition to prevailing market disincentives for producing and selling pandemic vaccines *(10,17)*. In order to speed regulatory review of candidate pandemic vaccines, the European Agency for the Evaluation of Medicinal Products (EMEA) and the United States Food and Drug Administration (FDA) are preparing pandemic response plans. Furthermore, EMEA has

produced a fast-track licensing program, an industry task force and detailed guidance for potential applicants *(31)*.

Current demand for seasonal influenza vaccine also limits worldwide vaccine capacity. Influenza vaccination is underused in wealthy as well as less wealthy nations, including in the high-risk, priority populations in the former. As long as demand for influenza vaccine is low and unpredictable, manufacturers have limited incentive to increase production capacity or invest in newer, more efficient processes. Increasing use of seasonal influenza vaccination in priority groups, children, and the general population would promote greater production capacity and encourage development of more efficient production. Even so, other national or international public financing may be required to gain the additional production capacity needed to meet the greater demand that would arise during a pandemic *(8,26)*.

Dose-Stretching Approaches
A small but growing body of evidence suggests promising strategies to extend limited vaccine supplies in order to vaccinate more people. This comes from studies including small RCTs and other clinical trials of these interventions in selected groups of healthy people to assess immune response (based on blood tests) to various influenza strains, though not actual protection against exposure to influenza. Low-dose (or antigen-sparing) influenza vaccines can stimulate immune responses considered adequate to protect against influenza viruses. Adjuvants are substances that can be added to a vaccine formulation to enhance the immune system response (immunogenicity) to the vaccine, thus allowing use of lower doses. They can be low-cost substances such as alum or proprietary substances. Intradermal injections (similar to the technique used in skin tests for tuberculosis) of low-dose (for example, one-fifth of a conventional dose) vaccines have stimulated similar or better immune responses than conventional intramuscular injections in healthy people 18–60 years old, but not in older patients *(18,35,36).* The effectiveness of intradermal injections for actually preventing influenza is not known.

Experimental low-dose vaccines against certain pandemic-like viruses, administered in an initial priming dose followed by a second booster a few weeks later, have led to protective levels of antibodies. Some of these vaccines, particularly those used with adjuvants, have used as little as one-eighth of standard doses of influenza antigen *(21,37,38)*. If medically successful and widely implemented, such antigen-sparing formulations could effectively multiply by several-fold the current global vaccine capacity, yielding pandemic vaccine supplies of a magnitude that could begin to approach global needs *(10)*. These are formidable challenges.

Another strategy that might extend limited supplies of a new vaccine would be to administer a priming dose with a vaccine made from a current virus that is anticipated to be related to a future pandemic virus. For example, a vaccine made from a current H5N1 virus and delivered prior to a pandemic plus a subsequent booster made from a future mutated H5N1 virus causing a pandemic might induce sufficient immunity against the pandemic strain *(39).*

In the absence of a strain-specific pandemic vaccine, WHO has recommended developing and stockpiling the current H5N1 vaccine along with increased use of the annual interpandemic vaccines. (No vaccines against H5, including H5N1, are currently commercially available for humans *(40)*). This type of strategy would involve vaccinating people with high exposure to the virus, such as at-risk poultry workers, to reduce the likelihood of mixing the avian flu virus and the typical human flu virus, which could result in more virulent strains *(41)*, and vaccinating individuals in an area surrounding local outbreaks (ring prophylaxis) with the current H5N1 vaccine *(3)*. A country could later include an emerging pandemic strain in the seasonal vaccine, at least for targeted vaccination. However, given the potential for a pandemic virus to differ from the H5N1 strain, the potential effectiveness of strategies involving existing vaccines is uncertain.

Targeted treatment strategies to reduce symptoms and transmission potential by vaccinating infected individuals are considered ineffective compared to giving them antiviral drugs because it takes 2 to 3 weeks to develop post-vaccination immunity. This is usually too late for reducing mortality and morbidity from influenza *(3)*.

Antiviral drugs

Prevention and treatment
Antiviral drugs can be used in prevention and treatment of influenza, resulting in lower mortality and morbidity *(3)*. When taken daily during exposure to influenza, antivirals can prevent the illness or lessen its severity. However, any such protection ends when a person stops taking the drug. In people who have the flu, antivirals can reduce flu severity and duration, but only if taken within 36 to 48 hours of the onset of illness, which requires rapid diagnosis. However, existing and emerging resistance of flu strains to some antivirals threatens their effectiveness. Experience with antivirals during a pandemic and in patients with avian flu is very limited.

Antiviral drugs for influenza currently include two classes, each with two drugs: M2 ion channel inhibitors amantadine and rimantadine, and neuraminidase inhibitors (NAIs) oseltamivir (Tamiflu) and zanamivir (Relenza). Most influenza strains that cause epidemics and pandemics are variations of the influenza A (the more pathogenic for humans) or B viruses. Both drug classes have shown partial effectiveness for prevention and treatment of influenza A viruses. NAIs, but not M2 inhibitors, are also active against influenza B viruses *(3)*. These two classes of antiviral drugs have not been compared in an RCT.

As described below, amantadine and rimantadine have comparable effectiveness in the prevention and treatment of influenza, including some evidence of beneficial treatment during the 1968–1969 pandemic, although they are increasingly subject to viral resistance. Since NAIs are a newer class of antivirals, no data are yet available for their effectiveness for prevention and treatment during pandemic outbreaks.

There is some variation among countries in licensing these drugs and in indications for their use. For example, the M2 inhibitor rimantadine is approved for treatment and prevention of influenza A in the United States *(42)*, but not in the United Kingdom *(43)*. Among the drugs of investigational interest for treatment of H5N1 are zanamivir, the NAI peramivir, long-acting topical NAIs, ribavirin and interferon alfa *(12)*.

Strategies identified in the literature for using antiviral drugs to prevent and treat pandemic influenza are presented in Table 2. As discussed below, these strategies are supported by evidence of varying rigour. The viability of these strategies in any country will depend on the availability as well as the effectiveness of antiviral drugs.

Table 2. Potential antiviral strategies for pandemic response	
Prevention	1. **Mass prevention:** • unfeasible due to insufficient supply and other limitations; • may induce drug resistance. 2. **Targeted prevention:** • stockpiles for targeted use; • amantadine is inexpensive and moderately effective for seasonal flu, can have severe side effects, highly subject to resistance; effectiveness in a pandemic is unknown; • NAIs recommended for stockpiles, but are costlier; • ring prophylaxis/containment for people in areas surrounding limited localized outbreaks in pandemic alert phases 3, 4, and 5 might be effective; not applicable in pandemic phase 6.
Treatment	1. **Mass treatment:** • unfeasible due to insufficient supply and other limitations. 2. **Targeted treatment:** • most effective within 36 to 48 hours of symptom onset; may need earlier treatment for a pandemic H5N1 virus; • amantadine is inexpensive and has been effective for seasonal flu, can have severe side effects, is highly subject to resistance; • NAIs recommended for stockpiles, but are costlier.
Resistance	1. Influenza A viruses are increasingly resistant to M2 inhibitors. 2. H5N1 strain is resistant to M2 inhibitors. 3. H3N2 and H1N1 strains appear to have developed resistance to oseltamivir. 4. H5N1 strain resistance to oseltamivir has been confirmed in at least one patient.

Sources: *(3,15,19,41,44–50)*

Prevention with M2s
RCTs of seasonal prophylaxis with amantadine and rimantadine during the 1968–1969 H3N2 pandemic and the 1977 H1N1 reappearance epidemic showed that both drugs were effective in protecting against the flu in approximately 60% to 70% of healthy adults *(3)*. For M2 inhibitors, the body of evidence for prevention is less definitive than for treatment, and is smaller for rimantadine *(52)*.

Prevention with NAIs
Across population groups, there is less evidence (fewer relevant RCTs) pertaining to prevention than to treatment using these drugs. Two systematic reviews of RCTs assessed the effectiveness of NAIs for prevention during interpandemic flu seasons. Prevention using either NAI reduces the risk of getting laboratory-confirmed flu by about 70% to 90% compared to a placebo. In community practice, the percentage of risk reduction may vary based on the population, strategy employed and choice of NAI *(53,54)*. NAIs may prevent H5N1 infection if taken prior to exposure, although there is no direct evidence of this.

Containment Strategies Using Antiviral Drugs
Ring antiviral prophylaxis is a targeted approach for delivering large amounts of antiviral drugs to people within a defined area surrounding a limited localized influenza outbreak *(45)*. This is intended to preserve limited supplies of antivirals and to contain infection to a limited outbreak, or delay spread of infection to gain time to implement preparedness measures, including vaccine development *(14)*. This approach is unlikely to be effective in an established pandemic with many outbreaks. There is no direct evidence that this approach has worked in outbreaks of influenza. The potential for this approach is based on some experience with smallpox (a disease that behaves differently than

influenza) and on simulations of hypothetical influenza outbreak scenarios, as described below. These simulations suggest that the success of this approach would depend on such factors as how transmissible (contagious) the virus is and the ability to deliver adequate amounts of drugs in a timely manner.

In 2005, researchers reported findings from mathematical simulations of various combinations of antivirals and other measures to contain a potential pandemic in its initial stages. One of the key factors affecting the results of these simulations was the assumed transmissibility rate of the pandemic flu strain. This refers to the average number of additional people in a susceptible population who are infected by transmission from a typical person with the disease; a rate of 1.0 means no transmission. Social distancing, quarantines, and other measures of social management pose their own trade-offs of risks and benefits, and there is little experience regarding their success in practice.

One set of simulations evaluated the potential effectiveness of targeted preventive use of antiviral drugs and measures to limit social contact to contain a supposed emerging pandemic in Thailand. The simulations indicate that a pandemic could be stopped using a combination of targeted geographical use of a stockpile of 3 million courses of oseltamivir plus social distancing (closing schools and workplaces), assuming a transmission rate of less than 1.8. This finding also depends on assumptions about such factors as the effectiveness of surveillance, delivery of the antiviral drugs to the target groups and emergence of resistance to antiviral drugs *(55)*.

Another set of simulations evaluated the potential effectiveness of various combinations of interventions to contain a supposed emerging epidemic in rural south-east Asia. The simulations indicate that targeted use of a stockpile of approximately 100 000 to 1 million courses of antivirals would have a high probability of containing the disease, assuming a transmission rate of less than 1.6. If pre-vaccination were also used, then the targeted antiviral use could be effective in containing strains with transmission rates as high as 2.1. Combinations of targeted antiviral prophylaxis, pre-vaccination, and quarantine could contain strains with transmission rates as high as 2.4 *(40)*.

WHO and others have raised the possibility – depending on the pandemic viral strain – of using lower doses of antiviral drugs for prevention and treatment. This approach could extend use of limited supplies of antiviral drugs in the event of a pandemic. Clinical evidence documenting the benefits and risks (for example, longer treatment duration, drug resistance) of this approach is limited *(3)*. Based on resistance of H5N1 to M2 inhibitors and initial experience indicating the need for higher doses and longer regimens of NAIs to manage H5N1 *(12),* a low-dose strategy is unlikely to be effective against that virus.

Treatment with M2 Inhibitors
Several RCTs conducted during the 1968–1969 H3N2 pandemic and the 1977 H1N1 reappearance epidemic showed that both M2 inhibitors were effective in treating uncomplicated influenza in previously healthy adults, with reductions in fever, symptom severity, and time until resuming usual activities. However, most RCTs of M2 inhibitors have enrolled few patients, and none have documented reductions in complications or antibiotic use *(3,45,56)*. The body of evidence for treatment with rimantadine is smaller than for amantadine *(52).*

Treatment with NAIs
Two systematic reviews of RCTs assessed the effectiveness of NAIs for treatment during interpandemic flu seasons. The NAIs provide reductions of roughly 0.5 to 2.0 days in the duration of symptoms. Zanamivir is reported to reduce median duration of symptoms by about 0.8 to 1.26 days for the otherwise healthy adult population, 0.9 to 2.0 days for the high-risk population and 1.0 to 1.3 days for children. Oseltamivir reduces median duration of symptoms by 0.9 to 1.4 days for the otherwise healthy adult population, 0.4 to 0.5 days for the high-risk population and 0.9 to 1.5 days for children. Treating otherwise healthy adults and children with NAIs provided 29–43% relative reduction in the

chances of having complications requiring antibiotics when given within 48 hours of onset of symptoms *(53)*. There are fewer RCTs pertaining to treatment in high-risk populations and little evidence pertaining to reduction of hospitalization and mortality in all groups *(53,54)*. Inhaled zanamivir has not been studied in cases of H5N1 influenza in humans *(12)*.

The treatment effects of antivirals observed in the RCTs used in the systematic reviews may overestimate the effect that would actually occur in community practice. As the proportion of patients with laboratory-confirmed influenza in the more selective context of RCTs is likely to be higher than the proportion of patients identified in community practice who truly have influenza, the average treatment effect of antivirals in community practice is likely to be lower.

NAIs may be useful in treating H5N1 influenza. A recent review summarizing published reports of the experience of a total of 55 patients hospitalized with confirmed H5N1 flu in south-east Asia observed that most of these patients received antiviral drugs (alone or with corticosteroids, along with broad-spectrum antibiotics). Use of these interventions late in the course of the disease did not appear to reduce mortality, although early initiation of antivirals was reported to be beneficial in a small number of patients. However, the small number of patients involved in these separate reports and the lack of other aspects of rigorous study design do not enable rigorous assessment of the effectiveness of antivirals in patients with H5N1 flu *(12)*.

Based on currently limited evidence, early treatment of H5N1 influenza in humans with oseltamivir appears to be beneficial *(12)*. Also, studies of oseltamivir and zanamivir in animals with recent strains of H5N1 indicate that higher doses and longer regimens of these drugs are needed to be effective *(12)*. There is little evidence that any current antiviral drugs would be effective in patients with the sort of cytokine storms observed in recent H5N1 infections and during the 1918–1920 pandemic *(2)*. Aside from the antivirals, current supplies of antibiotics for the bacterial infections that often arise in flu victims would be in short supply during a pandemic *(2)*.

Both M2 inhibitors can induce significant adverse gastrointestinal effects. Amantadine induces more minor central nervous system side effects than rimantadine, including delirium and seizures primarily in elderly people on higher doses *(3,52)*. NAIs generally have fewer side effects than M2 inhibitors, although oseltamivir causes a somewhat higher rate of nausea and vomiting, with very rare reports of elevated liver enzymes and hepatitis, and skin rashes, while zanamivir may exacerbate asthma or other chronic lung diseases *(1,3,53,54,57)*.

Resistance to Antiviral Drugs
Influenza A viruses (H3N2, H1N2, and H1N1) have become increasingly resistant to M2 inhibitors since about 2002. Resistance to antivirals is up to about 12% of influenza A strains worldwide, with much higher resistance in viral samples collected in some regions, including China, with 74% resistance *(44)*. Since 2003, strains of H5N1 isolated from individuals in Vietnam and Thailand have been fully resistant to M2 inhibitors *(45,58)*. It is possible that combination therapy using amantadine and NAIs may reduce the potential for developing drug resistance *(45)*, although available evidence does not report outcomes significantly better than for NAIs alone.

Influenza resistance appears to develop more slowly in NAIs than in M2 inhibitors, reducing the risk of transmitting a new virus for which there is no effective treatment *(3)*. However, resistance to oseltamivir has been detected in H3N2 and H1N1 *(12,51)* and resistance of H5N1 to oseltamivir has been confirmed in at least one patient *(50)*.

Stockpiling Antiviral Drugs
Since an effective pandemic vaccine is unlikely to be available at the time a pandemic begins, initial interventions might focus on use of antiviral drugs *(9,24)*. However, antivirals (particularly the NAIs) are expensive and infrequently used. Therefore, production capacity for antivirals is limited and

current stockpiles are low *(26)*. This eliminates the possibility of mass prevention and treatment with antiviral drugs. Due to their low supply and costs, the literature indicates targeting antiviral drugs to health care workers in contact with patients, essential services workers, and other high-risk individuals *(56)*. The only way to ensure that antiviral drugs, even in limited quantities, are available for pandemic response is to stockpile them *(3,9,19,24)*. The feasibility of this option differs between wealthy and developing nations. WHO recently stated that pandemic threat management requires collaboration of governments, industry and others for successful public funding, research support and international coordination *(24)*. However, there is little discussion, let alone consensus, regarding a practical international mechanism for stockpiling and distributing antiviral drugs for pandemic response.

Plans to increase production and stockpiling of NAIs are subject to evolving views on their benefits and risks. Experts are concerned about their limited effectiveness and adverse effects as well as the current production capacity for these drugs. Given recent initial reports of resistance of H3N2 and other strains to oseltamivir, it is possible that zanamivir is less likely to prompt resistance in influenza viruses. On the other hand, whereas oseltamivir comes in tablet form, zanamivir in its currently available form is a powder that must be inhaled, which may make it more difficult to use *(59,60)*. These distinctions are relevant, as some 50 mostly developed nations are seeking to stockpile oseltamivir, which has been made by Roche at a single plant in Switzerland. Zanamivir currently accounts for only 1% of worldwide sales of antiviral flu drugs. This adds to concerns about the worldwide capacity to manufacture the number of doses of NAIs required in the event of a pandemic avian flu *(2,26,59–61)*.

In late 2005, zanamivir maker GlaxoSmithKline reported that it would be expanding its zanamivir manufacturing capacity and offering free licenses to partners able to manufacture zanamivir. The company also indicated that it was looking at alternative, more convenient mechanisms for delivering the drug *(62,63)*. In late 2005, Roche announced that, through its own expansion and agreements with other manufacturers, it was arranging to scale-up production of oseltamivir to yield a ten-fold increase of the drug, to 300 million treatments annually, by 2007 *(64)*.

Other considerations

Cost and cost-effectiveness
In Europe, North America, and other developed areas, vaccination to prevent influenza is generally regarded as cost-effective or cost-saving relative to non-intervention strategies or the use of antiviral drugs to prevent influenza *(3,15,65)*. In these studies, cost-effectiveness of interventions is generally assessed in differences in costs per some unit of health outcome, such as averted deaths, quality-adjusted life years (QALYs), or disability-adjusted life years (DALYs). The relative cost-effectiveness of these interventions can vary widely, depending on the particular vaccination, antiviral or other strategy used, the costs, the target population, the cost of health care services used or averted due to the interventions and other contextual factors. Prevention strategies that are considered cost-effective or even cost-saving in developed countries may be unaffordable in developing countries.

For prevention of influenza, a set of cost-effectiveness analyses based on findings from a systematic review of RCTs compared vaccination to antiviral therapy in various groups (healthy adults, high-risk adults, elderly residential population and children) in developed countries. In these United Kingdom-based analyses, GB £30 000 per QALY was the threshold for cost-effectiveness. Vaccination was always cost-saving or cost-effective compared to no intervention (ranging from an average of £769 to £10 184 per QALY depending upon the population group). The average cost-effectiveness of antivirals compared to no intervention was less favourable, ranging from £37 710 to £382 920 per QALY for most groups, although it was cost-effective for elderly residential care, ranging from £4 511 to £15 178 per QALY. Compared to vaccination alone, the addition of antivirals was almost never cost-effective, ranging from an average of £64 841 to £2 188 039 per QALY, except for the addition of amantadine in elderly residential care, at £28 290 per QALY *(54)*.

For treatment of influenza, the same systematic review of RCTs could not draw definitive conclusions regarding cost-effectiveness of antiviral drugs compared to no treatment or antibiotics (under non-pandemic conditions), due to limited data on hospitalization and mortality. When hospitalization and mortality data were modelled based on the limited data, NAIs were reported to be moderately or borderline cost-effective for all groups, ranging from £16 819 to £31 529 per QALY. Amantadine was cost-effective for all groups, ranging from £4 535 to £6 190. As found in these analyses, cost-effectiveness may vary significantly according to the prevention or treatment strategy, the target population and the proportion of influenza-like illnesses in a treated target population that are actually influenza *(54)*. The existing analyses are not based on evidence collected during an influenza pandemic, and do not have broader national or global perspectives. Among antivirals, influenza A resistance to the M2 inhibitors and emerging or potential resistance of some influenza strains to NAIs may preclude the need for cost-effectiveness comparisons.

Influenza Surveillance
The type and extent of surveillance for flu outbreaks have implications for the effectiveness of vaccine and antiviral prevention and treatment strategies, particularly given the limited availability of these agents, and that antiviral drug treatment is generally effective only when given within 36 to 48 hours of symptom onset *(3,15)*. Diagnostic laboratories will be needed to confirm diagnoses and identify the characteristics of the virus early in the pandemic. (During a pandemic, most patients will be treated based on their clinical diagnosis alone.) Also, once a pandemic has begun, laboratory surveillance must track genetic changes in the virus, its susceptibility to antiviral drugs, and the causes of bacteria-based complications and their susceptibility to antibiotics *(16)*.

Ongoing initiatives to increase surveillance in regions currently affected by avian flu include a partnership between WHO and the Vietnamese Health Ministry to provide surveillance and laboratory diagnostic training and assistance in investigating potential H5N1 influenza cases and an influenza surveillance initiative in Asia funded by the United States Centers for Disease Control and Prevention *(65)*.

While rapid detection and diagnosis of influenza can contribute to effective targeting of prevention and treatment strategies, there do not appear to be reliable means for this – such as rapid response or portable diagnostic tests – outside of traditional public health disease surveillance practices *(47,66)*.

Compliance
The effectiveness of any influenza vaccination program depends on how many people are immunized. Even where supplies are adequate, many people who would benefit do not get immunized. Factors that contribute to non-compliance include perception of risk, lack of advice or reminders from a doctor or nurse, and negative views of vaccine efficacy and safety *(67)*. There is evidence that compliance for immunizations (including but not limited to immunization for influenza) in developed countries can be improved by using patient reminders and recalls, including postcards, letters, telephone (the most effective and costly) and autodialer calls *(68)*. This evidence has little relevance in developing countries. Factors affecting compliance in pandemic conditions, where an effective vaccine is unlikely to become available until after the disease affects many people, are likely to differ from those in interpandemic years.

Discussion

The roles of vaccines and antiviral drugs for prevention and treatment of influenza during interpandemic periods are well established yet shifting, given new information pertaining to emerging resistance to antiviral drugs and other developments. For pandemic response, evidence of the effectiveness of vaccine and antiviral drug strategies is very limited.

Although mass vaccination is recognized as the most effective approach for preventing influenza, it will not be feasible under current or near-term conditions for the first wave of an influenza pandemic. With current production technology, it will take at least six months from the time that the causal viral strain is identified to manufacture a vaccine in large batches, which with current capacity would be enough for only a small percentage of the global population. To the extent that they are adequately available, targeted use of vaccines and antiviral drugs are the most effective available means for reducing influenza mortality and morbidity. These include using antiviral drugs in priority groups and initial cases of infected individuals, ring vaccination of at-risk humans and poultry (with either early strain H5N1 avian flu vaccine or regular trivalent interpandemic influenza vaccine), strain-specific vaccination (once it becomes available) and continued use of antiviral drugs for prevention and treatment as available. There is an urgent need for research on vaccine dose-stretching strategies that could multiply the number of doses that could be made from any given level of vaccine production capacity, on more efficient vaccine production technologies and on new antiviral agents, particularly those that could target emerging viruses.

Execution of targeted strategies may not be feasible without stockpiles of NAIs and potentially the H5N1 avian flu vaccine or interpandemic flu vaccine (though this is not well supported by the evidence). Limited stockpiling of these expensive products, currently underway in some 50 mostly developed nations, may not be attainable for developing nations in the absence of cooperative international purchasing and distribution alliances. Despite the very limited experience or evidence pertaining to the effectiveness of such a strategy in pandemics, stockpiling of antivirals that remain active against known prevailing influenza viruses is warranted, recognizing that emerging viral resistance could render these products ineffective. Both surveillance and rapid diagnosis can influence the timing and effectiveness of vaccine and antiviral drug strategies, particularly when the availability of these agents is limited.

Policy considerations

The impact of any strategies for vaccination and antiviral drug use against the next influenza pandemic depends on when the pandemic starts *(2,18)*:

- If the pandemic were to start now, a strain-specific vaccine would not be available for at least six months under the best of circumstances. Given current vaccine production capacity, the likelihood that two doses would be required for adequate protection, and current dosage practices, there may be enough vaccine for fewer than 500 million of the 6.5 billion global population.
- Vaccine production capacity is limited by low and uncertain demand in interpandemic years, which diminishes incentives for manufacturers to increase capacity and develop more efficient production processes.
- If the pandemic were to start one year from now, there might be more time to develop dose-stretching strategies for extending the vaccine supply.
- If the pandemic were to start in a decade, it might be possible to respond effectively if we begin now to develop new vaccine-manufacturing technology and significantly greater production capacity.
- The sooner that a pandemic starts, the more likely that targeted strategies for vaccine and antiviral drug use will be the only potential options, though both will be in short supply.
- Although stockpiling limited supplies of antiviral drugs is recommended, capacity is low. This will require advance funding and international cooperation, including negotiation with the pharmaceutical industry on prices, production and distribution.
- While stockpiling H5N1 strain flu vaccine may prove to be an effective precautionary strategy, there is little evidence to support this approach.

Conclusions

An influenza pandemic seems inevitable. When this will happen and whether it will be caused by H5N1 or another viral strain is unknown. The potential seriousness of the next pandemic derives from the high death rate in humans infected thus far with H5N1, the limited supplies of the small number of antiviral drugs likely to be effective, existing and emerging viral resistance to some antiviral drugs, uncertain effectiveness of current H5N1 vaccines, the time lag for producing a pandemic strain-specific vaccine, the 50-year old technology still used to produce vaccine and the limited capacity for its mass production.

Although vaccination is the most effective means of preventing influenza, a strain-specific vaccine is unlikely to be available during the initial wave of a pandemic. In the absence of such a vaccine, targeted use of antiviral drugs for prevention in priority groups and treatment of infected patients is indicated. As pandemic vaccine becomes available, the limited supplies should be directed first to priority groups.

High priority strategies for closing gaps in pandemic response capacity include:

- developing a detailed and cross-sectoral operational plan at global, regional and national levels for diminishing the impact of the initial one to three years of a pandemic;
- increasing research on production of an effective vaccine;
- further developing reverse genetics and cell culture based technology for more efficient vaccine production to replace current insufficient egg-based production;
- increasing research on dose-stretching strategies such as adjuvants and intradermal injections to increase the number of doses that can be made from any given level of vaccine production capacity;
- ensuring the manufacturing capacity for sufficient vaccine during the early stage of a pandemic, supported immediately by increasing the use of interpandemic (seasonal) influenza vaccination in developed and developing countries;
- accelerating formation of public-private partnerships for vaccine development;
- increasing manufacturing capacity and stockpiling of likely effective antiviral drugs;
- increasing research on new antiviral drugs; and
- developing effective means for delivering preventive and therapeutic interventions during a pandemic.

Annex 1: Literature review inclusion and exclusion criteria

Category	Inclusion criteria	Exclusion criteria
Language	English text (or abstracts)	Non-English abstracts
Study population	Human	Animal
Topics of interest	Avian influenza, influenza, pandemic planning, antiviral therapy, vaccination	Vaccination and antiviral therapy for non-influenza illnesses
Study type	• Systematic reviews • Meta-analyses • Prospective/retrospective observational studies • Practice guidelines • Narrative (non-systematic) reviews • Grey literature, recent news reports	• Editorials • Letters

The present synthesis has relied upon a comprehensive review of peer-reviewed literature (including PubMed/MEDLINE, the Cochrane Databases, EMBASE and other key databases), reports or guidance documents from agencies involved in public health response (such as the World Health Organization, the European Union Commission on Community Influenza Preparedness and Response, the United States Centers for Disease Control and Prevention and the United States Institute of Medicine), recent news reports and relevant grey literature.

The following medical subject heading (MeSH) and text words were used alone or in combination: vaccines, influenza vaccine, antiviral agents, influenza, avian influenza, pharmaceutical, medical device, effectiveness, safety, efficacy, costs and cost analysis, cost-effectiveness, pandemic, epidemic, disease outbreaks, prevention, treatment, manufacturing, public health and virus diseases.

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