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WHO Guidelines on the Use of Vaccines and Antivirals during Influenza Pandemics



World Health
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Department of Communicable Disease
Surveillance and Response

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1. Introduction

Influenza pandemics are sudden and unpredictable yet inevitable events. They have caused several global health emergencies during the last century. The first and most severe of these is estimated to have resulted in more than 40-50 million deaths worldwide¹. Experts anticipate that the next pandemic, whenever it happens, will be associated with a high death toll and a high degree of illness requiring hospitalization, thus producing a considerable strain on health care resources. Pandemics are global by their very nature, and few countries are likely to be spared. In developing countries, where health care resources are already strained and the general population is frequently weakened by poor health and nutritional status, the impact is likely to be greatest (Annex 1).

Conditions surrounding the 1997 Hong Kong outbreak of “chicken influenza” highlight the need for advance planning to ensure an adequate response to a health emergency that is certain to be unpredictable, complex, rapidly evolving and accompanied by considerable public alarm. Once a pandemic begins it will be too late to accomplish the many key activities required to minimize the impact. Therefore, planning and implementation of preparatory activities must start well in advance. Planning for pandemics will also enhance the capacity to respond to other large-scale health emergencies, including bioterrorist threats, that require mass access to prophylactic and therapeutic interventions and strong national plans which include a risk communication component to help calm public fears. The impact of pandemic influenza is likely to be far greater, by orders of magnitude, than most bioterrorism scenarios. Unlike most other health emergencies, pandemics occur in several waves and last one to two years. Response efforts will, therefore, need to be sustained for a prolonged period. In addition, preparation for an influenza pandemic will enhance the response to influenza epidemics, which occur each year and are thought to kill every year from 500 000 to 1 million people worldwide. Investment in pandemic preparedness thus has direct and immediate utility as a measure for reducing the impact of a certain and recurring event.

Influenza vaccines and antiviral drugs for influenza are essential components of a comprehensive pandemic response, which also includes planning for antibiotic supplies and other health care resources. However, the current reality is that most countries have no or very limited supplies. Such a situation would force national authorities to make difficult decisions concerning which citizens should receive first call on limited vaccines and drugs.

This document provides guidance to health policy-makers and national authorities on planning principles and options for the prioritization of vaccine and antiviral use during an influenza pandemic. It includes recommendations on actions that can improve future supply for the many countries that currently have no national vaccine or antiviral production.

The document was drafted during a WHO Consultation on Guidelines for the Use of Vaccines and Antivirals during Influenza Pandemics, held from 2-4 October 2002 in Geneva, Switzerland. Participants are listed in Annex 2. The document represents a contribution of the WHO Global Influenza Programme to the implementation of the Global Agenda on Influenza, reproduced in Annex 3.

¹ Potter, C., Chronicle of Influenza Pandemics. Textbook of Influenza. Edited: Nicholson, K. G., Webster, R.G., Hay, A.J., Blackwell Science Ltd. 1998

2. Background

Influenza vaccines have been available for over 60 years. Extensive experience during this long period has demonstrated their safety and efficacy. In populations at risk of severe complications, vaccination is known to reduce hospital admissions and deaths. Vaccination is thus the cornerstone of influenza prevention. As influenza viruses are constantly evolving, vaccine is produced each year with a composition based on the most relevant strains of virus identified through a global surveillance system. Stockpiling of vaccine in preparation for a pandemic is not an option, as vaccine composition depends on the responsible virus and must await its appearance and identification at the start of the pandemic. Vaccine will thus be in limited supply during the first part of the pandemic, and may not be available at all in some parts of the world.

The influenza antivirals currently in use will likely be effective in the prophylaxis and therapy of illness caused by a new pandemic virus. However, supplies would quickly be exhausted in the first part of the pandemic, when vaccine is not yet available and demand for an alternative control tool would be greatest. Advance stockpiling of the drugs for special purposes or special populations is one solution. As the drugs are relatively stable, stockpiling is feasible; however, for most countries, cost will be an issue. Also, differences do exist between the M2 inhibitors, such as amantadine, and the neuraminidases, such as oseltamivir, requiring identification of their specific roles in a pandemic. Because of these factors, countries will need to consider the potential for complementary use of vaccines and antivirals in planning for various phases of a pandemic. Vaccine will remain the primary means of influenza prevention once available, though antivirals will have a role for use in special situations.

Countries will be able to address pandemic requirements only if they plan for supplies of vaccines and antivirals now. Although vaccines and antivirals are a key part of a pandemic response strategy, the current market-based system has limited or no surge capacity to respond to sudden increases in demand. Manufacturers require regular estimates of demand on which to base production plans. However, there are currently no estimates on the global use and demand for influenza vaccine and antivirals. In addition, vaccine distribution systems are often fragmented and may not be readily adapted to respond to a single overall national plan. Issues of liability also require resolution in advance of the next pandemic.

3. Guidelines for the use of vaccines and antivirals

The response to the next influenza pandemic will need to address an inevitable shortage of vaccines and antivirals. Thus, each country should decide in advance which groups will have first call on scarce supplies. When establishing goals and setting priorities, policy-makers need to keep in mind the several years needed to construct new production facilities and significantly increase production capacity. Budgetary constraints may extend the time required to stockpile an adequate supply of antivirals to several years. Setting goals related to influenza pandemic preparedness will provide some of the data and incentives needed to increase production or to plan stockpiles. The need for setting goals and establishing priorities extends beyond the borders of any individual country. Estimates of global demand for vaccines and antivirals depend on national estimates fixed in line with the priorities set by individual countries. Priority setting at the national level is thus the first step towards global preparedness for a global event.

Setting goals and priorities for a pandemic is a process that will provide significant health benefits every year. A pandemic influenza planning process will identify problems with the current supply, distribution and use of vaccines and antivirals. Implementing plans to reduce the magnitude of these problems will enhance the availability of vaccines and antivirals for inter-pandemic periods. Investment in pandemic preparedness thus brings an annual return. Setting goals in a formal, rational, measured process also demonstrates the competence and forward-thinking of leaders and policy-makers as custodians of public health.

The following section provides guidelines and recommendations for national health authorities and policy-makers on the process of setting goals and prioritizing the use of available vaccines and antivirals.

3.1 Establishing goals and priorities

Setting goals and choosing priorities will require the consideration of logistic, ethical, moral, cultural, legal, and other issues that surround decisions to allocate scarce resources. It is therefore essential that national health authorities work in close collaboration with other public and private sector groups that have roles and interests in protecting public health.

Countries should consider establishing a technical advisory committee with broad representation. The committee should advise policy-makers on goals and priorities, and on ways to improve the supply of vaccines and antivirals².

The technical committee should first list all goals that should ideally be achieved with available resources. Examples include:

- reduction of mortality
- reduction of morbidity
- limiting social disruption
- ensuring maintenance of health care systems
- ensuring integrity of social infrastructure
- limiting economic losses

It is useful to explicitly state the units for measuring success. For example, the goal of reducing morbidity could be stated as ‘reduction in morbidity as measured by years of healthy life lost’ or ‘disability-adjusted life-years lost.’

When setting goals, it may also be useful to identify population subsets, such as medical personnel, emergency responders, and leaders, who require priority protection because of their roles during the pandemic response. Definition of these subsets should be flexible, allowing for changes in critical personnel based on likely exposure scenarios. However, when identifying such subsets, it is important to think through the potential practical (financial, political, ethical and health) consequences. For example, if a group is targeted to receive priority prophylaxis or treatment, will their family members also be given first priority? When setting goals, measures considered equitable and essential for each country need to be discussed.

As supplies of vaccines and antivirals are likely to be scarce, meeting all goals simultaneously will be difficult. Planners and policy-makers should therefore prioritize goals. This will facilitate the distribution of supplies in an optimal manner. The strategy for meeting priority goals will also be heavily influenced as the pandemic unfolds and its epidemiology, in terms of who falls ill and who dies, becomes apparent.

In order to define and prioritize goals, advisors and policy-makers will need estimates of the impact of a pandemic, including the number of persons who may become ill (by age and risk group) and the societal and economic consequences of their illness (medical resources used for treatments, costs of treatments, losses in productivity and social functions). Such estimates of impact are important for

² For further information: Influenza Pandemic Plan. The Role of WHO and Guidelines for National and Regional Planning WHO/CDS/CSR/EDC/99.1 (document in revision)

allocating resources for planning and responding to a pandemic. Thus there is a need to collect data from which estimates can be made, for example, the average cost of a case of influenza (including value of lost productivity) and the cost of distributing and administering vaccines and antivirals. To fully appreciate the limitations of current supply, policy-makers also need to know who currently gets vaccines and how they receive them.

When prioritizing goals, the technical advisory committee should consider the practical aspects, such as the logistics, of actually meeting a given goal and identifying those in the priority groups. It may be useful to use mathematical models to generate possible scenarios of impact and the potential benefit gained from proposed interventions. These scenarios should describe who might become ill, what happens to them and the mitigating impact of proposed interventions. A few scenarios for industrialized countries have been published. However, no scenarios appropriate to developing countries are readily available.

3.2 Guidelines on vaccine use during a pandemic

Vaccination is the primary means of preventing influenza. At the beginning of a pandemic, vaccine supplies will be limited or non-existent. This is because the emergence of a pandemic is unpredictable, vaccine cannot be stockpiled and vaccine production can only start once the pandemic virus has been recognized. With current technology, the first doses of vaccine are unlikely to become available within the early months of the pandemic. A country not currently producing vaccine is unlikely to secure supplies. Forward planning will be necessary to increase the likelihood that vaccine will progressively become available as the pandemic unfolds. Therefore, national or regional priorities need to be defined for the rational use of existing supplies according to predetermined objectives. These may differ from interpandemic priorities.

3.2.1 General considerations

- Ideally, sufficient vaccine should be available for the whole population. However, due to limited vaccine supplies, priorities for vaccination need to be established prior to a pandemic.
- Production and use of vaccines during the interpandemic period will influence their availability during a pandemic, by improving the infrastructure for vaccine production and administration, and by improving public and professional familiarity with influenza vaccine.
- Strategies need to be sufficiently flexible to accommodate different epidemiological scenarios (including subsequent pandemic waves) and degrees of vaccine availability.
- Demographics and size of priority groups should be estimated (by occupational, age, and disease risk categories).
- Two doses of vaccine per person will likely be necessary for adequate protection in a pandemic situation. The implication for planning is that countries may need twice the amount of vaccine.
- Countries should determine how to procure vaccines for a pandemic in advance.
- Mechanisms for efficiently delivering influenza vaccine and monitoring its safety and efficacy should be developed in advance.

The following are general guidelines to assist countries or regions in developing strategies for addressing supply and setting priorities.

3.2.2 Establishing priority groups

With present technology, the current worldwide production capacity for influenza vaccine is able to cover less than 5% of the world's population. It is recognized that there could be tremendous disparities in vaccine supply, especially in countries with no manufacturing capacity, for which there is no easy solution.

Considerations for vaccine prioritization will be different for each country, not only because of differences in vaccine availability and resources for administration of vaccine, but also because of differences in population structure and the organization of essential services. Furthermore, vaccination priorities may differ from those during the interpandemic period. Means for identifying priority groups will need to be clearly defined. General principles for setting primary goals for pandemic response and prioritization of use of vaccines and antivirals are described in section 3.1 Establishing goals and priorities .

The following strategies are examples of goals in vaccine use and are offered as planning guidance only. Some countries have adopted these in descending order of priority. However, the priorities may need to be adjusted in each country or region according to local needs and epidemiological circumstances.

Essential service providers, including health care workers

Goal: *maintain essential services.*

Definition of those considered "essential" will vary from country to country. The purpose of vaccinating these individuals would be to allow them to continue to provide services, including health care, to those in need. As vaccine supplies will most likely be inadequate, prioritization within individual categories of essential service workers may be necessary.

Groups at high risk of death and severe complications requiring hospitalization

Goal: *prevent or reduce deaths and hospital admissions.*

In the interpandemic period, those who have underlying disease or are older are the ones most likely to experience severe morbidity and mortality³. In a pandemic, previously healthy individuals are more likely to experience a severe outcome than they would in an ordinary outbreak. However, it is still individuals in the "high risk group" who have the greatest risk of hospitalization and death. Such persons should be targeted for vaccination if the goal is to prevent such events. They are individuals who are 65 years of age or older and have a high-risk condition (see above). Younger individuals with underlying disease are also at higher risk of experiencing severe morbidity and mortality. Owing to difficulties in prioritization on the basis of chronic diseases, age is often used as a surrogate for identifying those at greatest risk of complications. However, the epidemiologic characteristics of the pandemic will need to be considered, as the main population groups affected may vary.

³ Individuals (adults and children aged more than 6 months) in the community who have chronic cardiovascular, pulmonary, metabolic or renal disease, or are immunocompromised

Persons without risk factors for complications

Goal: *prevent or reduce morbidity.*

This is the largest group and would include both healthy adults and children. The main goal in vaccinating this group would be twofold: to reduce demand for medical services and to allow individuals to continue normal daily activities. This is particularly important for working adults. Simultaneous absence of large numbers of individuals from their site of employment could produce major disruption even in non-essential personnel. Medical facilities could also be overwhelmed by demand, even for outpatient services. This might compromise care of those with complications. While children's absence from school might not have the direct economic and disruptive impact of illness in adults, it could have that effect indirectly, since care for ill children would be required. There is no evidence that use of inactivated vaccine in children will reduce the spread of a pandemic in the community, and this strategy is not recommended.

The decision to vaccinate healthy adults and healthy children could be justified for the above reasons. However, for both groups, a much larger amount of vaccine would need to be used to prevent hospitalization and death than for older persons and those with underlying conditions, because of demographic considerations and differences in risks. In the final analysis, a decision to vaccinate healthy individuals depends on having an adequate supply of vaccine.

3.3 Guidelines for antiviral use during a pandemic

3.3.1 General considerations

- Antivirals are effective for both treatment and prophylaxis and are an important adjunct to vaccination as a strategy for managing influenza.
- Current supplies of antivirals are very limited and surge capacity is negligible. *Unless a country has a stockpile, it will not have antivirals available to use in a pandemic.*
- During a pandemic, antivirals could have a significant beneficial impact in reducing morbidity and mortality. Given that vaccine is unlikely to be available for the early months of the pandemic, antivirals will be the only virus-specific intervention during the initial response.
- Protection afforded by antivirals is virtually immediate and does not interfere with the response to inactivated influenza vaccine.
- Use of antivirals during a pandemic should take into account the epidemiology of the pandemic, in particular the groups most seriously affected.
- Timing of the use of antivirals during a pandemic should be guided by data derived from local surveillance.
- Mass prophylaxis of children to “control” a pandemic is not recommended.
- **Information about the performance characteristics, side effects, and costs of the available agents should be used to select the specific antiviral drugs to be used for prophylaxis or treatment.**

There are important differences in pharmacokinetics, side effects, antiviral drug resistance and costs between the two current classes of antivirals (see Annex 5). The selection of antivirals should take into account drug characteristics. Where available, neuraminidase inhibitors are preferred for treatment.

3.3.2 Options for antiviral use

The options for using antivirals depend on the size of the available antiviral supply, the size of groups targeted for antiviral use, and the specific goals to be achieved in the pandemic response.

Main options include:

Prophylaxis

- Long term prophylaxis (prevention) of defined populations for the duration of a pandemic wave of activity (minimum of 4 weeks)
- Prophylaxis during outbreaks in closed institutions (usually lasting about 2 weeks)
- Protection of individuals for the period between vaccination and the development of protection (could range from 2–6 weeks depending on whether one or two doses of vaccine is recommended)
- Prophylaxis of individuals following exposure to pandemic influenza (approximately one week per course)

Treatment

- Ill persons for whom treatment can be initiated within the first 48 hours of their illness
- Exposed persons for whom influenza vaccination is contraindicated

In general, prophylaxis is more likely to prevent serious complications from influenza than treatment because prophylaxis prevents cases of influenza from developing in the first place. However, use of antivirals for prophylactic purposes will require a much larger drug supply. **For countries where stock piles of antivirals would be cost prohibitive, antiviral use as *treatment* should be emphasized, while vaccination should be the primary method of prophylaxis.**

3.3.3 Establishing priority groups

As with vaccines, plans for antiviral use may differ among countries because of differences in country-specific goals, antiviral availability and resources for purchasing antivirals. Also, the options for use of antivirals are more complicated than options for vaccines, given such considerations as cost, side effect, and drug interactions. Priorities for antiviral use may differ from those during the interpandemic period.

The following potential strategies are offered as general planning guidance. However, each country will need to choose its own strategy depending on country priorities, specific pandemic response goals and resources.

Essential service providers, including health care workers (prophylaxis or treatment)

Goal: *Maintain essential services and support the ability to respond to a pandemic*

Definition of those considered “essential” will vary from country to country. Health care personnel are in a unique position of being exposed to persons infected with influenza, of being in a position to transmit infection to highly vulnerable persons, and of taking care of ill persons. Other examples include certain community services such as fire and police personnel, and those involved in vaccine manufacture or delivery.

Groups at high risk of death and severe complications requiring hospitalization (prophylaxis or treatment)

Goal: *Reduce mortality and serious morbidity*

Prophylaxis or early treatment of ill persons with high-risk conditions could be conducted in several different situations. Examples include:

- high-risk persons living in the community
- outbreaks in institutional high-risk populations
- treatment of seriously ill hospitalized patients (but the effectiveness of this approach has not been established)
- prophylaxis of high-risk individuals between the time of vaccination and the development of protection
- treatment of patients for whom influenza vaccination is contraindicated

Persons without known risk factors for complications from influenza (treatment)

Goal: Reduce morbidity and utilization of health care resources, including antibiotic use

This strategy would be difficult and costly to implement because it would require very large supplies of antivirals and rapid access to care. However, this approach is also most likely to limit the economic losses and social disruption traditionally associated with a pandemic.

4. Recommendations

Once a pandemic begins it will be too late to accomplish the many key activities required to minimize its impact. Therefore, planning and implementation of preparations must start now. The *Guidelines for the use of vaccines and antivirals* (section 3) are based on the current reality of vaccine and antiviral supply and existing national and regional pandemic response capacities. The recommendations below, which follow the priority activities identified by the Global Agenda on Influenza (Annex 3), highlight activities which are particularly important to improve availability and use of vaccines and antivirals during the next influenza pandemic and will thus increase management options for policy-makers.

4.1 Recommendations for establishing goals

- In developing a pandemic influenza response plan, each country must set, as soon as possible, goals and priorities for distributing and using scarce resources such as vaccines and antivirals. Preferably, an initial set of goals and identification of a top priority should be done within two years.
- Health authorities and planners should take the lead in promoting awareness of the threat posed by pandemic influenza, factors presently constraining the supply of vaccines and antivirals and the implications of such constraints. They should also take the lead in planning the response.
- Planning should be a collaborative effort, involving representatives from many government agencies and other sectors of society.

- In setting goals and establishing priorities, both at a national and global level, due consideration should be given to the equitable distribution of inevitably scarce resources.
- Countries that currently do not have epidemiological and economic data for influenza are encouraged to establish the burden of influenza in their countries. Without such data, setting goals and priorities will be difficult.
- To assist the process of setting goals and priorities, scenarios describing the potential impact of an influenza pandemic should be developed, incorporating estimates of the impact of proposed interventions.
- Measurement of proposed interventions (effectiveness, impact) should be established and used as a guideline for modifying national pandemic plans for future outbreaks.

4.2 Vaccines

4.2.1 Recommendations for national authorities and vaccine manufacturers

- Expand interpandemic use of vaccines in order to enhance vaccine production capacity.
- Consider establishing vaccine manufacturing capacity in countries where none currently exists.
- Establish or enhance vaccine delivery and monitoring systems.
- Secure national or international agreements between health authorities and vaccine manufacturers for pandemic vaccine supply.
- Address liability issues that will arise with mass immunization using a new pandemic vaccine with an unknown profile of side effects.
- Address issues of intellectual property associated with introduction of new technology, such as reverse genetics, into vaccine production.
- Develop fast track procedures for rapid licensing and testing of current and new types of vaccine and new vaccination strategies, including use of new formats such as multidose vials.

4.2.2 Recommendations for international collaboration

- Support international or regional cooperation to improve vaccine supplies for all countries, whether they currently produce vaccines or not. This may involve technology transfer for local production, collaborative purchase, a revolving fund for procurement or other essential mechanisms.

4.2.3 Recommendations for research

- Public authorities should support evaluation of different types of vaccine (whole virus/split, adjuvant/non-adjuvant, cell culture) and different strategies of vaccination (one/two dose, different doses) using vaccine prepared from different haemagglutinin subtypes.
- Evaluate reverse genetics techniques for development of safe productive vaccine viruses from different haemagglutinin subtypes.
- Prepare libraries of reagents (vaccine virus and vaccine potency reagents) from different haemagglutinin subtypes.

- Evaluate new methods of vaccination, such as "needle free", which may be more suitable for mass immunization and which may improve immune responses.

4.3 Antivirals

4.3.1 Recommendations for national authorities

- Based on their pandemic response goals and resources, countries should consider developing plans for ensuring the availability of antivirals.
- Countries that are considering the use of antivirals as part of their pandemic response will need to stockpile in advance, given that current supplies are very limited.
- If antivirals are to be used, mechanisms and procedures should be developed to efficiently deliver and monitor the safety and effectiveness of antivirals. In addition, the antiviral susceptibility of the circulating influenza strains should be monitored.

4.3.2 Recommendations for research

Research should be conducted in several areas, including:

- the minimally effective dose and duration of therapy or prophylaxis
- whether use of antivirals reduces serious complications from influenza, such as pneumonia, and reduces hospital admissions
- the comparative effectiveness of the M2 and neuraminidase inhibitor antiviral agents
- the appropriate dosages and side effects in selected high-risk populations, such as infants, pregnant women, immunocompromised persons, and elderly persons with underlying disease
- whether antiviral administration blunts the response to live-attenuated influenza vaccines
- mechanisms for antiviral resistance to both classes of agents and assessment of the biological consequences (infectiousness, virulence) of resistance
- the shelf-life of the antiviral agents and raw products.

4.4 Surveillance

Member States should strongly support and encourage the strengthening of national and international influenza surveillance as recommended in the Global Agenda on Influenza Surveillance and Control (Annex 3). Enhancement of the WHO global influenza network is essential to provide comprehensive global coverage for early warning of the emergence of novel viruses of pandemic potential. Expansion of animal influenza surveillance and integration with human influenza surveillance are essential for understanding and preparing for threats to human health posed by animal influenza viruses. Rapid detection and characterization of pandemic viruses will facilitate vaccine production and provide the necessary information to guide vaccine and antiviral intervention strategies.

Annex 1 - Pandemic Influenza⁴

Influenza viruses cause seasonal epidemics and, very occasionally, global pandemics. The word pandemic (from the Greek *pan* meaning all and *demos* meaning people) describes an epidemic that affects the whole population. Typically, several waves of infection, occurring over a few years, are needed before most of the world's population are affected by pandemic influenza.

Influenza viruses are enveloped RNA viruses that belong to the family Orthomyxoviridae and contain a segmented genome. There are three types of influenza viruses: A, B, and C. Types A and B cause widespread outbreaks of influenzal illness nearly every year. Influenza A and B possess two surface glycoproteins: the haemagglutinin (HA) and neuraminidase (NA). Influenza A viruses are subdivided into subtypes dependent on differences in their surface glycoproteins and the genes encoding them. Fifteen HA (H1-H15) and 9 NA (N1-N9) subtypes have been identified for influenza A. Only one HA and one NA have been identified for influenza B viruses. Influenza B viruses are not divided into subtypes and do not cause pandemics. Influenza C is associated with sporadic, often asymptomatic infection with little or no mortality and therefore is not of public health concern.

The natural host and reservoir of all 15 HA and 9 NA subtypes of influenza A are free-living aquatic birds. Since 1900, viruses with only three HAs (H1, H2, and H3) and two NAs have established stable lineages in humans; viruses with two HAs (H1, H3) and two NAs (N1, N2) have become established in pigs; and viruses with two HAs (H3, H7) and two NAs (N7, N8) have formed lineages in horses. Sporadic infections have been documented in mink, whales and seals.

Pandemics and epidemics of influenza in humans arise as a result in changes in the surface glycoproteins known as 'antigenic shift' and 'antigenic drift'. The occurrence of repeated outbreaks of influenza A and B during interpandemic periods is due to an accumulation of gene mutations that affect the antigenic nature of the HA and NA, termed 'antigenic drift', which allows the virus to evade immune recognition. With 'antigenic drift', new strains of influenza evolve that are antigenically related to those circulating during preceding epidemics. Antigenic drift occurs at rates depending on the genetic stability of the virus and the immune pressure. Because of antigenic drift, the World Health Organisation (WHO) reviews the composition of interpandemic vaccines twice annually.

Pandemic influenza is the outcome of 'antigenic shift' and occurs only with influenza A virus.

Antigenic shift involves an abrupt change in the HA and possibly NA antigens, which are totally different from those circulating in humans for many years before. 'Antigenic shift' results in an entirely new or 'novel' virus that is serologically distinct from earlier viruses and could not have arisen from them by mutation. A pandemic is likely when large sections of the population around the world lack immunity to the new virus (i.e., have no or little antibody to the HA of the novel virus), and it is readily transmissible from person to person, causing serious disease. A pandemic is considered imminent when the new virus spreads rapidly beyond the community in which it was first identified.

There are three ways in which viruses with pandemic potential might emerge: genetic reassortment; direct transfer of virus from animals to humans; and virus re-cycling:

- **Genetic reassortment** The segmented nature of the influenza A genome, which contains eight genes, facilitates gene reassortment with up to 256 combinations of genes during co-infection. A reassortment of gene segments during mixed infections with human and avian influenza A viruses of different subtypes has periodically brought into being new pandemic strains. In 1957, the influenza A/Asian H2N2 pandemic virus acquired three gene segments (PB1, HA, and NA) from the avian influenza gene pool in wild ducks and retained five other genes from the

⁴ This paper was prepared by Professor Karl Nicholson (see list of participants) with inclusion of comments from the participants in the WHO Guidelines on the Use of Vaccines and Antivirals during Influenza Pandemics, Geneva 2-4 October 2002.

previously circulating human H1N1 strain. In 1968, the Influenza A/Hong Kong H3N2 pandemic virus acquired two genes (PB1 and an HA coding for H3) from the avian pool and retained 6 genes from the H2N2 virus circulating in humans. It is speculated that the domestic pig serves as the intermediate ‘mixing vessel’ for some human and avian viruses because the respiratory epithelium of pigs possesses sialic acid virus receptors for both avian and human viruses. Typically, newly shifted strains have emerged in south-east Asia where farming practices bringing poultry, ducks, domesticated pigs and humans close together, make this process possible.

- **Direct transfer of virus from animals to humans** Avian and porcine viruses have occasionally been recovered from humans. In 1976, a localised outbreak of swine influenza with one fatality occurred in military personnel in Fort Dix, USA. Sporadic cases of swine influenza infecting humans, with occasional deaths, have also been reported. Until recently, avian influenza was considered unable to be transmitted to humans as avian strains preferentially bind to sialic acid receptors with α 2,3 galactose linkages that are lacking in human respiratory epithelial cells. However, H7 avian virus was recovered from two patients with purulent conjunctivitis in 1980 and 1996, and was associated with purulent conjunctivitis in four others in 1980. While none of these 6 cases suffered with respiratory symptoms, an outbreak of highly pathogenic avian H7N7 influenza in poultry farms in the Netherlands, which began at the end of February 2003, was associated with fatal respiratory illness in one of 82 human cases by April 21. In 1997, an outbreak of avian A/Hong Kong/97 (H5N1) influenza in humans caused 6 deaths among 18 hospital admissions. The infection of humans with a novel avian flu virus was preceded by circulation of highly pathogenic H5N1 viruses in poultry in Hong Kong. The H5N1 outbreak in humans, which immediately preceded infections with H1N1 and H3N2 viruses, evoked concerns of genetic reassortment occurring in humans. In 1998, heightened surveillance in the adjoining Guangdong Province, China, led to recovery of 9 isolates of a novel avian H9N2 virus from patients with influenza-like illness. In 1999, avian H9N2 viruses were also isolated from the nasopharyngeal aspirates of two children in Hong Kong. Infection with H5N1 avian influenza virus was confirmed in two members of a family of Hong Kong residents in 2003. Currently, avian H5N1 virus has been implicated in human fatalities in Viet Nam. To date, the evidence suggests that avian viruses are not readily transmitted from person to person.
- **Virus recycling** By examining blood samples from people of varying ages, it can be shown whether a particular subtype of influenza circulated previously and, if so, approximately when it ceased to circulate. This analysis, termed seroarchaeology, supports the theory of virus recycling, which proposes that only certain HA subtypes are capable of sustained infection and transmission in humans. Seroarchaeology has established beyond reasonable doubt that H2 and H3 subtypes recycled in human beings during the 19th and 20th centuries. In addition, the H1 subtype, which circulated in mankind during the period 1918 to 1957, re-emerged or ‘recycled’ in 1978. Analysis of the RNAs of viruses isolated during the 1977-78 epidemic showed that the virus was more closely related to viruses isolated in 1950 than to strains isolated after that time. If the recycling theory is accepted, then an explanation has to be provided for the dormant or persistent state of influenza virus over many years. Because of antigenic drift, it was speculated that the H1N1 virus must have re-emerged from the frozen state in nature or elsewhere. However, there is evidence that influenza viruses can remain invariant for prolonged periods in swine, which may serve as a reservoir for human infection.

Past experiences indicate that there is no regularity to pandemics and no reliable basis for predicting when and where they might arise. During the twentieth century, pandemics occurred at relatively long and unpredictable intervals of 9 to 39 years during 1918 (H1N1), 1957 (H2N2), 1968 (H3N2), and to a lesser extent in 1977 (H1N1). In 1957, the H2N2 virus completely replaced the previous H1N1 virus, and in 1968 the H3N2 virus replaced it in turn. The re-emergence of H1N1 virus in 1977 did not cause a ‘true’ pandemic, as many people born before 1957 were partially immune. Moreover, the H1N1 virus did not replace H3N2 virus. Since 1968, both H1N1 and H3N2 subtypes have co-circulated with influenza B causing interpandemic outbreaks in humans.

The H1N1 pandemic of 1918-1919 was the most devastating in history with a total mortality of 40–50 million. In the United States, it killed 550 000 people, representing approximately 0.5% of the population. In Scotland, 1 in 200 to 1 in 300 of the population died. In England and Wales there were 200 000 deaths, and by December 1918, an estimated 4.9 million excess deaths (about 2% of the whole population) occurred in British India, the vast majority occurring within the space of two months. The mortality during the ‘Asian’ H2N2 influenza pandemic in 1957 was moderate in comparison. In England and Wales, mortality was estimated at 33 000 deaths. In the US, 80 000 deaths were attributed to influenza during the 1957-1958 and 1960 epidemics, with nearly half occurring in the first three months of the 1957-58 epidemic. During the ‘Hong Kong’ H3N2 pandemic of 1968, the mortality in the USA was estimated at around 30 000 deaths. In Britain, mortality was estimated at around 30 000 deaths as well. The pandemics in 1957 and 1968 affected all ages, with the greatest excess mortality occurring in the elderly and in people of all ages with underlying medical conditions. The re-emergence of H1N1 virus in 1977 affected young people mostly and the outbreak was benign in comparison with the episodes in 1957 and 1968. The mortality from pandemic influenza in many countries is unknown, but as the outbreak of influenza A/Panama/2007/97-like (H3N2) virus in Madagascar in August 2002 shows, it may be higher in societies with overcrowding, malnutrition, and poor access to health care.

The rate of spread of pandemics can be alarming. During the Asian and Hong Kong pandemics of 1957 and 1968, seeding of virus in Europe and North America occurred within three to four months of the first virus isolations in south-east Asia. The intercontinental spread of SARS in 2003 was more rapid. The opening up of tourism globally, and the recent vast increase in air passenger transport and land-based communications in most parts of the world, may hasten the spread of pandemic influenza. A common characteristic of pandemics is the increasing severity of successive waves of infection. If vaccines are not available for the first wave of a full-blown pandemic, their availability for subsequent waves should still be greatly beneficial.

Besides pandemics, there have been a number of ‘false pandemics’ and ‘pandemic scares’. Occasionally, the genetic mutations associated with antigenic drift can be so profound, as in 1947, that an established subtype causes a severe worldwide ‘false pandemic’. The inactivated vaccines that had recently been introduced were no longer protective. During the winter of 1950-1951, epidemics of H1N1 virus reached major proportions throughout Europe, causing 50 000 deaths in the United Kingdom alone.

A ‘pandemic scare’ or ‘false alarm’ occurs when a novel virus is isolated from human beings, but it fails to spread and does not cause widespread illness. The public health response to a false alarm can have major societal costs. For example in 1976, the outbreak of H1N1 swine influenza in military trainees at Fort Dix, New Jersey, USA, led to the production of 150 million doses of vaccine and the vaccination of 45 million people. In December 1997, all chickens in Hong Kong (approximately 1.5 million) were slaughtered, first to prevent the transmission of avian H5N1 influenza to humans, and second to prevent genetic reassortment in human beings into a more transmissible strain. The territory’s entire poultry population was once again slaughtered when highly pathogenic A/Hong Kong/97 (H5N1) virus re-emerged in flocks in May 2001. Subsequently, a further 900 000 birds were killed in February 2002, and another 30 000 were killed in April 2002.

The events in history show that the recovery of a novel influenza subtype from man has the potential to become a public health emergency, even if the ensuing pandemics resemble the 1957 and 1968 episodes than the calamity of 1918. Past pandemics have occurred unpredictably and with little warning, emphasising the need for ongoing, intensive, worldwide surveillance, and flexible contingency plans that are capable of responding efficiently to a pandemic threat.

Influenza vaccines provide the most cost-efficient method of preventing and reducing the severity of influenza, but the preparation of current vaccines may take more time than is available before the pandemic first strikes. The antiviral drugs, amantadine, zanamivir and oseltamivir, provide another means of controlling influenza, but due to their cost and availability, they are likely to play an important, but limited role. Pandemic plans have been developed by WHO and by a number of

developed countries, but a number of issues that have been addressed do not take into consideration the circumstances of undeveloped regions of the world. This document will be updated regularly on the basis of scientific and socio-economic developments relevant to the control of pandemic influenza.

Annex 2 - List of participants

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Annex 3 - Global Agenda on Influenza Surveillance and Control

Background

Since 1948, the WHO Influenza Surveillance Network has provided an effective basis for annual updating of influenza vaccine formulations and has contributed greatly to the understanding of influenza epidemiology.

However, in response to growing recognition that more needs to be done in preventing, monitoring and controlling influenza worldwide, WHO has sought to raise the profile of influenza as an important public health threat having significant economic as well as health consequences throughout the world. The new drive also responds to the need for stronger links between influenza surveillance and control, better knowledge of the clinical and economic burden of the disease, and greatly improved use of vaccines and other tools for prevention and control.

To this end, the WHO Global Influenza Programme called for proposals to develop a Global Agenda on Influenza Surveillance and Control.

Objectives of the Global Agenda

- Provide impartial and prioritized guidance to all parties on research and development and national/global action for influenza control
- Support coordination of action for influenza control and surveillance
- Support implementation of identified priorities
- Support advocacy and fund raising

How the Global Agenda was developed

The Global Agenda was developed in a spirit of collaboration beginning with a call for proposals in July 2001. Over one hundred proposals were received and formed the basis of a draft posted on the internet in November 2001. Public discussion then followed through an electronic discussion group active until January 2002. In May 2002, WHO convened a consultation of influenza experts, virologists, epidemiologists, public health officials, and representatives of the pharmaceutical industry to debate and finalize the world's first global agenda on influenza surveillance and control. The Global Agenda was adopted by consensus.

Global Agenda

Strengthen Virological and Epidemiological Surveillance Nationally and Internationally

There is a special need for support for developing countries.

I. Enhance and integrate virological and disease surveillance

- Evaluate the activities/physical facilities of the National Influenza Centres (NICs)
- Develop standardized methods and training for laboratory and disease surveillance (develop reagents/manuals, provide training and proficiency testing)
- Encourage integrated surveillance based on clinical and virological data
- Facilitate shipment of influenza isolates/specimens
- Encourage NICs to collect additional data (e.g., influenza-related hospitalization, use of emergency services, and mortality) in different age groups
- Incorporate antiviral resistance monitoring

The WHO Influenza Surveillance Network must be utilized more effectively in order to improve global influenza surveillance.

II. Expand virological and disease surveillance

- Identify gaps in geographical coverage of the WHO Influenza Surveillance Network and explore the use of polio and other networks to expand surveillance coverage
- Investigate and integrate into the WHO surveillance system other sources of samples and information, including rapid tests, commercial testing and clinical trial samples
- Arrange regional/global meetings to improve laboratory and disease surveillance and support interactions between “sister” laboratories

Expansion of the WHO global influenza network is essential to provide comprehensive global coverage for early warning of the emergence of variants and novel strains.

III. Expand animal influenza surveillance and integrate with human influenza surveillance

- Expand and formalize the WHO Animal Influenza Network (AIN)
- Establish close interactions between OIE (Office International des Epizooties) and WHO influenza networks
- Encourage studies at the human/animal and at the domestic/wild bird interfaces and provide training to carry out studies

- Develop and distribute reagents for identifying influenza viruses of all subtypes and establish the total gene pool among influenza viruses

Extension of animal influenza surveillance and integration with human influenza surveillance is essential for understanding and preparing for threats to human health posed by animal influenza viruses.

IV. Improve data management, utilization and exchange

- Encourage communication between surveillance systems and harmonization of data
- Improve collation/analysis/dissemination of existing data, including an electronic bulletin board for special announcements
- Facilitate and support central databases (e.g., FluNet and the LANL sequence database) for recording epidemiological, virological and genetic information, and for modeling purposes

Existing surveillance must be better harmonized and data sets and information must be made more rapidly and widely available in order to maximize their usefulness.

Increase Knowledge on Health and Economic Burden of Influenza

I. Capacity strengthening in epidemiological and statistical techniques for studies on influenza disease burden

- Develop common protocols including case definitions

To enable studies on burden of influenza disease.

II. Evaluation of the clinical and economic burden of disease in countries where there is no recognition of influenza or no control policies are in place

- Establish comprehensive studies in countries representative of a geographical area and socio-economic status
- Conduct additional smaller epidemiological studies for national influenza policy development

To establish the magnitude of influenza as a public health problem.

To determine the proportion of acute respiratory infections and febrile illnesses that is due to influenza, and to prioritize influenza in relation to other major infectious diseases.

III. Re-evaluate the clinical and economic burden of influenza in countries where influenza control policies are in place

- Encourage the evaluation of the burden of disease in different age and risk groups in relation to control policies
- Provide tools and protocols for evaluating effectiveness of current and alternative strategies for influenza control
- There is a need for better information to sustain and improve influenza control.

Increase Influenza Vaccine Usage

The recommendations represent a logical but not necessarily sequential progression and support one another in enhancing vaccine coverage.

I. Encourage assessment of disease burden and cost-effectiveness analyses

- Depends on antecedent activities, but considered absolutely essential to improve coverage

Required to justify vaccine programmes and establish as a national priority given competing priorities.

II. Encourage countries to establish national policies and set immunization targets

- WHO regularly to collate and publish policies, immunization rates and reimbursement mechanisms

Each element is an important determinant of vaccination coverage.

III. Promote awareness amongst policy makers, health care providers, and the public

- Develop, compile and disseminate relevant information, initiate demonstration projects, provide training

An important determinant of vaccination coverage.

IV. Encourage countries to identify and develop effective strategies for vaccine delivery

- Develop, compile and disseminate information, initiate demonstration projects, provide training

Important determinants of vaccination coverage.

V. Develop and implement methods for measurement and feedback of the progress of national and local programmes

- Develop and standardize approaches to assessing national vaccination rates, rates within target groups and vaccine effectiveness to close the audit loop

Measurement and feedback are important determinants of vaccination coverage.

Accelerate National and International Action on Pandemic Preparedness

I. Increase awareness of the need for pandemic planning

- Transform scientific message on pandemic preparedness into political action
- WHO to table pandemic preparedness at the World Health Assembly

Authorities must understand the potential impact and threat of pandemic influenza, so that they will see the importance of pandemic planning and provide enough resources to carry it out. With adequate preparation, the morbidity, mortality and social disruption associated with a pandemic should be reduced

II. Accelerate the development and implementation of national pandemic plans

- WHO to develop a model national plan and assist with regional planning
- Develop a tool for country self assessment of pandemic planning progress
- Exchange expertise / provide consultations in pandemic planning
- Publish the progress/status of pandemic planning periodically

WHO published the Pandemic Preparedness Plan in 1999; however, only a few countries have begun pandemic planning. There are many obstacles to planning, especially in developing countries. Providing motivation and assistance will accelerate the planning process and decrease the risk of a world unprepared for the next pandemic.

III. Enhance the utilization of influenza vaccine and antivirals in the inter-pandemic period

- Set up a specific working group to develop guidelines for the use of antivirals
- Enhance the surveillance of antiviral resistance
- Provide assistance to countries where there is no existing or limited influenza vaccine manufacturing capacity and there is a wish to produce influenza vaccine

Wide scale use of antivirals and vaccines during a pandemic will depend on familiarity with their effective application during the inter-pandemic period. The increasing use of these modalities will expand capacity and mitigate the morbidity and mortality of annual influenza epidemics. Studies conducted during the inter-pandemic period can refine the strategies for use during a pandemic.

IV. Develop strategies for the utilization of vaccines and antivirals and securing adequate supplies for a pandemic

- Develop and rehearse strategies for emergency production, licensing and testing of vaccines and antivirals
- Develop models and guidelines for the use of vaccines and antivirals when they are in short supply and adjust these at the start of the pandemic
- Incorporate antiviral stockpiling into pandemic plans
- Equity of supply between countries should be addressed by a multidisciplinary working group under the auspices of the WHO

Vaccines will not be available at the start of a pandemic. The only specific intervention possible in the absence of vaccines would be the use of antivirals but their adequate availability requires stockpiling. It is essential that action is taken to accelerate availability of vaccines and antivirals and to develop guidelines for their use when they are in short supply.

V. Advocate research on pandemic viruses, vaccines, antivirals and other control measures

- Investigate mechanisms underlying the emergence of pandemic viruses
- Develop novel vaccines and production strategies/technologies
- Evaluate the immunogenicity and safety of conventional and novel vaccines
- Update libraries of seed viruses and vaccine potency reagents
- Evaluate the effectiveness of antivirals for complications; relative effectiveness and side-effects of M2 and NA inhibitors
- Investigate the feasibility of alternative models of antivirals access
- Evaluate the effectiveness of community control strategies other than vaccines and antivirals

With more knowledge on pandemic viruses, vaccines, antivirals and other control measures, it will be possible to design more appropriate intervention strategies, and governments will be encouraged to commit resources.

Annex 4 - Considerations for the Use of Vaccines during an Influenza pandemic⁵

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⁵ This paper was prepared by Dr Arnold Monto (see list of participants) with inclusion of comments from the participants in the WHO Guidelines on the Use of Vaccines and Antivirals during Influenza Pandemics, Geneva 2-4 October 2002.

1. Safety and efficacy of influenza vaccines

1.1 Background

Vaccination is the primary means of preventing influenza. Immunity is typically produced after a period of two to three weeks following a single vaccine dose when the viruses contained are ones to which the vaccinees have had past experience. A second inoculation may be required in other circumstances. Currently only inactivated vaccines produced in embryonated eggs are available in all countries of the world. Other influenza vaccines are either approved in small numbers of countries or are in development. These will be discussed in section 3 of this paper.

Inactivated influenza vaccines similar to those currently in use were first introduced during the 1940's (1). Since that time, they have been improved in terms of their standardization and purity. Throughout, they have been produced by inoculating the current influenza virus strains into embryonated hens' eggs for vaccine production. Often, in recent years, the viruses used have either been genetically reassorted with a standard high growth virus or have been selected from among those available to obtain good growth characteristics. Initially, vaccines contained whole virus particles; later partially disrupted virus particles (split vaccines) or purified envelope antigens (sub-unit vaccines) were introduced to further improve safety, and replaced the whole virus vaccines in many countries (2, 3). The types of vaccines which are now available for use in a pandemic thus have a long record of safety and efficacy.

1.2 Use of influenza vaccines in interpandemic years

Inactivated vaccines presently available contain an appropriate strain from each of the circulating influenza types/subtypes, type A (H3N2), type A (H1N1), and type B. The composition of the vaccine is reviewed semi-annually based on surveillance data is updated as necessary.

Current WHO and most national influenza vaccination recommendations are directed to protecting those at greatest risk of severe outcomes (4). Vaccine may also be recommended for those who can transmit to individuals at risk of complications, such as persons providing essential health care and emergency response services. Other, healthy individuals who wish to prevent influenza morbidity may receive vaccine when supplies are adequate.

1.3 Health benefits of vaccination

From 1943 through 1969, the inactivated influenza vaccine was evaluated on an annual basis in the United States. The vaccine was 70-90% efficacious in preventing laboratory confirmed influenza in otherwise healthy adults, when the vaccine virus was similar to the circulating strains (5).

Older individuals are a principal target for vaccination in interpandemic years in most countries. Some randomised trials have been conducted to demonstrate protection in these populations; one such study demonstrated a protective efficacy of 60% in individuals 60 years of age or older (6-10). More commonly, studies have been observational. These studies consistently confirmed the effectiveness of the vaccine in the independently living elderly, particularly in preventing complications resulting in hospitalization and in some cases, death. Calculated effectiveness has ranged from 30-70% in preventing hospitalization (11,12,13,14,15,16). The wide range is in part a result of the intensity of the outbreak and methods used in these effectiveness studies, where endpoints were not confirmed virologically. Similar studies have been conducted in the frail elderly living in nursing homes. Protection was 30-40% against influenza-like illness, especially in those above 85 years of age (17, 18). However, even though such persons may still develop influenza-like illness, vaccine demonstrated a greater level of effectiveness in reducing the frequency of pneumonia, hospitalization and especially death during influenza outbreaks (19).

Over the years, observations of influenza illnesses rates among vaccinees have led to the conclusion that haemagglutination inhibiting antibody titer of 1:40 correlates with protection (20, 21). The studies on which this observation was based were carried out with both whole virus and disrupted virus. This allowed antibody produced by vaccination to be used as a surrogate in many situations for protection with the entire class of inactivated vaccines.

Studies in the United States conducted during the 1976 "swine influenza" or A/New Jersey/8/76 (H1N1) episode, and following the initial spread of the A/USSR/90/77 (H1N1) viruses in 1977-78, demonstrated clear differences in the ability of whole virus and the split vaccines to produce antibodies at protective levels and to cause side effects in children (22, 23, 24, 25, 26). Adults who had prior experience with both of these A (H1N1) viruses had good antibody responses to inactivated and split preparations. In contrast, children required two inoculations of the split vaccines to produce adequate antibody responses. While a similar result could be achieved with a single inoculation of whole virus vaccine, this was at the cost of side effects such as fever, headache, myalgia, and malaise. Antigen content in the vaccines at that time was standardized by a different and less accurate method than used today and it is difficult to compare the potency of these to current vaccines.

1.4 Safety

Inactivated influenza vaccine has been widely used for 60 years, and has been found to have an excellent safety profile. Aside from local tenderness and soreness, which may last for 1-2 days, vaccine-related side effects are uncommon for vaccine conforming to current international standards (27, 28, 29). Current vaccines are largely free of systemic effects; in some comparisons, there have been no significant differences between vaccine and placebo in terms of systemic symptoms. All current influenza vaccines contain egg protein, often at very low levels, but they should not be used in individuals with allergies to these proteins (30,31).

During a mass vaccination program in 1976, Guillian-Barré syndrome was reported in about 10 in 1 million recipients of vaccine containing swine influenza-like virus in the USA (32). Since then, there has been no statistically significant evidence for an association of this syndrome with influenza immunization (33,34) and the potential risk is thus considered to be considerably lower than the risk posed by influenza and its complications.

2. Production/Testing/Licencing

Vaccine viruses are egg isolates selected through surveillance activities, to have antigenic similarity to the WHO recommended strain and suitable growth properties. For influenza A viruses, a high growth genetic reassortant virus is usually produced which will substantially increase the yield of virus per egg. Ordinarily, the vaccine virus is cultivated in embryonated chickens' eggs and the harvested egg fluids are processed to concentrate, purify, and inactivate the virus from which a split or sub-unit vaccine is produced. The processes used include centrifugation and use of ether or detergents to disrupt the virus (2,3). Further steps of purification and formulation then follow.

Vaccine for pandemics will be produced by the same manufacturing facilities which produce influenza vaccine for interpandemic purposes. The availability of a safe high yielding vaccine virus may be a rate limiting factor and introduction of new reverse genetics technology may address this issue and should be evaluated. The development of libraries of vaccine viruses to represent all of the available haemagglutinin subtypes found in birds would also be of considerable benefit.

In some parts of the world, production of the interpandemic vaccine may be under way when the pandemic is declared and it is recommended that in such a situation, production of vaccine for the pandemic virus should supplant it. In other regions, production of vaccine may not be under way when the pandemic is declared. In such situations the supply of eggs will need to be re-established

as soon as possible. Unlike the situation in interpandemic years, in which three virus strains need to be contained in the vaccine, only the new pandemic strain will be required thus creating a monovalent vaccine. Given good growth characteristics, three times as many vaccine doses should therefore be available when compared to usual production. Production should be accelerated as much as possible, and consideration should be given to use of whole virus vaccines in the pandemic situation, for at least some segments of the population. Such a decision will decrease processing requirements and, given adequate supply of eggs, will further increase amounts of vaccine available. This pandemic vaccine may also eliminate the need for a booster inoculation and reduce the dose required to produce immunization. Whole virus vaccine may, however, produce side effects, which are undesirable in certain population groups, particularly children. Requirements, which will depend on the precise antigenic nature of the pandemic virus, are difficult to anticipate based on current knowledge. Recent studies with vaccine made from H5 and H9 subtypes have shown that the use of adjuvant systems may also enhance the antibody response significantly and hence reduce the amount of antigen required to produce immunity. Reactogenicity of such products needs further investigation.

Potency testing of reagents is required to standardize the haemagglutinin content of each strain in the vaccine and is developed and calibrated by regulatory authorities. Potency reagents already exist for H5 and H9 subtypes, but development is needed for other subtypes of haemagglutinin, which have not yet been involved in human disease.

3. Future developments

Severe delays in supply of vaccine strains and potency reagents are likely because of safety issues and the acknowledged difficulties in using conventional reassortment technology. Reverse genetics could be used to introduce attenuating mutations and to develop high growth reassortants and efforts should be made to ensure the availability of this technology.

Libraries of virus strains suitable for vaccine production and appropriate reagents for vaccine standardization should be developed for all avian HA subtypes. Although such reagents may not be an exact antigenic match with the pandemic strain, they are likely to provide a vaccine which will provide significant protection and they will be available immediately.

3.1 Use of cell culture derived vaccines

Eggs must be available for production of current inactivated vaccines. Although some companies are already in year-round production, eggs may well prove to be one of the factors limiting large-scale production. Development of cell culture-based vaccines is well advanced and is licensed in some countries. Although immunogenicity of cell culture-based vaccines is equivalent to conventional vaccines, their efficacy compared to egg derived vaccines is not well established. Further development and evaluation should be encouraged. Availability of both cell culture and egg derived vaccines would increase vaccine supply.

3.2 Role of live attenuated vaccines in a pandemic

Live vaccines are licensed in certain countries and may be available in others. They have certain advantages over inactivated vaccines in terms of breadth of immunity. However, they currently require specific pathogen-free eggs in order to be licensed in most jurisdictions. The role of live attenuated vaccine in a pandemic needs to be clarified, especially in terms of safety and the future ability to propagate the viruses in approved cell cultures for live vaccine production.

3.3 Vaccine type, dose and use of adjuvant

A great number of vaccines containing likely candidate haemagglutinin subtypes need to be produced and subsequently tested in humans to determine whether such factors as second doses and whole virus vaccine will give superior immune responses. Also, the frequency and severity of side effects need to be better determined. Various adjuvants have already been examined, and their place in vaccination plans needs to be determined. Internationally coordinated clinical trials are needed to evaluate such vaccination strategies and to support the development of the reagent libraries.

3.4 Other strategies for producing haemagglutinin antigens

Production of an A (H5N1) vaccine could not be carried out because of the embryo lethality of the virus in eggs and the need for biocontainment. One alternative strategy for vaccine preparation involved expression of H5 HA in baculovirus vectors. Although immunogenicity to date has not been very good, this work has potential and should be encouraged.

3.5 Other approaches to vaccination

Use of non-haemagglutinin/neuraminidase based vaccines has been explored for some time, e.g. DNA vaccines and vaccines containing other antigens such as the M2 protein. This work should be encouraged for its long-term potential.

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Annex 5 - Considerations for the Use of Antivirals during an Influenza pandemic⁶

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⁶ This paper was prepared by Dr Frederick Hayden (see list of participants) with inclusion of comments from the participants in the WHO Guidelines on the Use of Vaccines and Antivirals during Influenza Pandemics, Geneva 2-4 October 2002.

1. Abstract

Antiviral drugs are effective for both prevention (chemoprophylaxis) and early treatment of influenza. Wide-scale use could reduce influenza-related morbidity, complications, hospitalizations and other demands on the health care system during a pandemic and might possibly reduce mortality. Current supplies are very limited and production surge capacity is negligible, so that stockpiling of drugs is essential to establish adequate availability in a pandemic or major epidemic. The available agents can be administered once daily for prophylaxis and twice daily for treatment, but they have important differences in mechanism of action, pharmacology and ease of administration, side effect profiles, cost, and potential emergence of drug resistance. The two M2 ion channel inhibitors (amantadine, rimantadine) and one neuraminidase inhibitor (oseltamivir) are taken orally, whereas the other neuraminidase inhibitor (zanamivir) is self-administered by oral inhalation and requires a specific delivery device. The M2 inhibitors are associated with central nervous system and gastrointestinal side effects (amantadine more often than rimantadine), oseltamivir with gastrointestinal side effects, and zanamivir infrequently with bronchospasm. The neuraminidase inhibitors and rimantadine are superior to amantadine in regard to need for individual prescribing, tolerance monitoring, and frequency of serious side effects (Table 1). The M2 inhibitors are more likely than the neuraminidase inhibitors to have clinically significant issues with emergence and spread of drug-resistant influenza viruses. Few current national or other plans address the specific issues of advance stockpiling, selection of appropriate agents, rapid distribution of drugs, and monitoring of resistance.

2. Introduction

Improvements in medical care and the introduction of new anti-influenza antiviral drugs since the last pandemic offer the potential of reducing the impact of the next one.

If available in sufficient supply, antiviral agents could potentially play a valuable role in the initial response to pandemic influenza, particularly in the likelihood that an effective vaccine is unavailable. Depending on available supply, they might reduce morbidity, hospitalizations and other demands on the health care system, and possibly mortality. The choice if and which influenza antivirals to stockpile before a pandemic and their effective use during a pandemic would depend on multiple factors including characteristics of the specific agent (efficacy, tolerability, and pharmacology), chemical stability of raw materials or formulated drug, and potential for antiviral drug resistance, as well as practical considerations such as drug costs and their reimbursement, rapid access to drugs, and the rationing or distribution of limited drug supplies. **At present the overarching limitation to antiviral use in a pandemic is inadequate availability.** The high demand over the short period anticipated during the initial wave or waves of a pandemic would likely deplete supplies of antivirals unless stockpiles were in place or markedly enhanced surge production capacity were possible. Ethical dilemmas regarding fair access and rationing of available resources need to be addressed both within and between countries.

Three separate manufacturers produce rimantadine, oseltamivir, and zanamivir; amantadine is made by several different companies. Raw materials for production are procured internationally. Amantadine and rimantadine are stable at ambient temperatures for 25 years or longer (Scholtisseck and Webster, 1998). Published findings regarding shelf lives of neuraminidase inhibitors are unavailable. Anecdotal, M2 inhibitors have been shown to exhibit in vitro efficacy over a decade after manufacture. In addition, M2 inhibitor manufacturers report that the shelf life of raw material is substantial, making stockpiling of these

materials, or the agents themselves, a viable option. Published data are lacking on raw and formulated material shelf life for the neuraminidase inhibitors.

By manufacturers' reports, currently available supplies of these drug are modest and only a minimal increase in current production of both M2 and neuraminidase inhibitors would be possible with short notice, so that surge capacity is very limited. The extent of antiviral use during the interpandemic period will affect availability for a pandemic response, such that increasing use would enhance overall supplies.

3. Characteristics of available agents

Currently, four antivirals have proven efficacy in treatment and prophylaxis of influenza A infections, and most developed countries have access to one M2 inhibitor (amantadine) and two neuraminidase inhibitors (zanamivir, oseltamivir). In the United States and Russian Federation the M2 inhibitor rimantadine is also available. Ribavirin is available in certain countries for influenza treatment, but low doses are ineffective (Smith et al, 1980) and the efficacy of high-dose oral ribavirin in influenza treatment is modest (Stein et al, 1987) and requires further research and documentation. Aerosolized ribavirin is a very costly therapeutic intervention possible only in a hospital setting.

All of these agents are effective for chemoprophylaxis of influenza A infections and do not impair immune responses to inactivated vaccine. Data regarding actual use in pandemic influenza are only available with the M2 inhibitors, and the comparative efficacies of M2 and neuraminidase inhibitors have received very limited study. However, clinical testing of the neuraminidase inhibitors in interpandemic influenza suggests that they would be effective in a pandemic setting. The therapeutic efficacies of all of these agents have received study principally in ambulatory adults and children who received treatment within two days of symptom onset, and very limited controlled data are available from higher risk populations (serious cardiopulmonary disorders, hospitalized, immunocompromised).

Furthermore, the selection of an antiviral agent for potential wide-scale use also depends heavily on its pharmacology, which in turn influences the complexity of dose regimens, route of administration, need for therapeutic monitoring, and the potential for drug-drug or drug-disease interactions (Hayden, 2001). Important differences exist among the M2 inhibitors (reviewed in Hayden and Aoki, 1999) and the neuraminidase inhibitors (reviewed in Gubareva & Hayden, 2000) with regard to their pharmacology and tolerability. Although dosing recommendations vary, data from clinical trials indicate that each of the available agents can be administered once daily for prevention and once (rimantadine) or twice daily for treatment. However, the clinical pharmacology and adverse drug effect profiles of the neuraminidase inhibitors and rimantadine are superior to amantadine in regard to need for individual prescribing, tolerance monitoring, and seriousness of side effects (Table 1).

Another important issue is the potential for emergence and spread of drug-resistant influenza A viruses that cause antiviral drugs to lose their clinical effectiveness. The M2 and neuraminidase inhibitors also have important differences with respect to the frequency and biologic properties of resistant variants. In addition to selection of drug-resistant variants during antiviral use, the possibility of primary or de novo drug resistance in a pandemic strain warrants consideration.

4. M2 Inhibitors (amantadine, rimantadine)

4.1 Efficacy for prophylaxis

Amantadine and rimantadine have comparable antiviral and clinical activities when used for chemoprophylaxis or treatment of influenza A illness (reviewed in Hayden and Aoki, 1999). Placebo-controlled, prospective studies of seasonal prophylaxis with amantadine and rimantadine during the 1968 H3N2 pandemic and 1977 H1N1 reappearance established that these agents are effective for chemoprophylaxis in immunologically naïve adult populations. The level of protection against illness averaged approximately 60-70% but was variable across studies in both 1968 (59-100%) and 1977 (31-71%) (Table 2). One of the reasons for differences in protection could have related to delayed initiation of prophylaxis in some studies. In general, these levels of protection against influenza illness are lower than the 80-90% levels found in studies of interpandemic influenza. Further, the relationship between dose and protection has not been adequately characterized. One study in the former Soviet Union which utilized amantadine doses of 100 mg daily for prophylaxis found approximately 63% protection against confirmed influenza illness. As found in interpandemic influenza, the levels of protection against laboratory proven influenza infection irrespective of illness were lower in both 1968 (28-52%) and 1977 (18-39%) (Table 2). Such observations are indicative of subclinical infections that created adequate protective host immune responses during long-term chemoprophylaxis. In contrast, during the 1968 pandemic one study of short-term, post-exposure amantadine prophylaxis in families, in which treatment of the index case was combined with 10 day prophylaxis of household contacts, found low protective efficacy against influenza illness (6%) and none against infection (Galbraith et al, 1969), perhaps in part related to emergence and transmission of M2 inhibitor resistant virus (see below).

4.2 Efficacy for treatment

Early treatment reduces symptom duration and the time to functional recovery by one to two days in adults and children with acute uncomplicated influenza. Several placebo-controlled, prospective studies during the 1968 H3N2 pandemic and 1977 H1N1 reappearance showed that amantadine and rimantadine provided therapeutic benefit in uncomplicated illness in previously healthy adults with reductions in fever, symptom severity, and time to resuming usual activities (Galbraith et al 1971; Van Voris et al 1981). These and most other M2 inhibitor treatment studies during interpandemic periods have enrolled relatively few patients, and no prospective trials to date have documented reductions in complications, antibiotic use, or hospitalizations. Rimantadine provided no beneficial effects on earache or presumed otitis media risk following influenza in children (Hall et al, 1987), otologic changes after *experimental influenza* in adults (Doyle et al, 1998), or pulmonary complications in elderly nursing home patients with influenza (Betts et al, 1987). Recent uncontrolled studies have reported reduced lower respiratory complications with early treatment in nursing home patients (Bowles et al, 2002) and immunocompromised hosts (LaRosa et al, 2001). Pediatric treatment studies have found variable clinical benefits relative to acetaminophen controls and document the frequent emergence of drug-resistant variants.

4.3 Pharmacology and administration

Both amantadine and rimantadine are well absorbed (80% or more) following oral administration and have prolonged plasma elimination half-lives, which average 12-16 hours for amantadine and 24-36 hours for rimantadine. Amantadine is excreted largely unchanged in the urine by glomerular filtration and tubular secretion, whereas rimantadine undergoes extensive hepatic metabolism prior to renal excretion of the parent and metabolites. Because amantadine depends directly on renal excretion for elimination and

has a narrow therapeutic index, dose adjustments are required for relatively small decrements in renal function (creatinine clearance <50-80 ml/min), including those typically observed with aging. The dose of both drugs needs to be decreased in adults aged 65 years and older in order to reduce the risk of side effects. Furthermore, amantadine has several recognized drug interactions that increase the likelihood of side effects (Table 1) and need for close clinical monitoring in certain patient groups. Drugs which delay amantadine excretion or also affect the CNS may increase the risk of adverse CNS events. The need for individual prescribing of amantadine based on knowledge of renal function is a significant limitation to wide-scale use. No clinically important drug interactions have been recognized with rimantadine, but specific studies with immunosuppressive agents and anti-retrovirals have not been reported.

4.4 Tolerability and safety

Amantadine has the narrowest toxic to therapeutic ratio among the available agents and is commonly associated with dose-related minor central nervous system (CNS) side effects (anxiousness, difficulty concentrating, insomnia, lightheadedness) and less often severe CNS toxicities (including delirium, hallucinosis, acute psychosis, seizures, coma) (Aoki and Sitar, 1988). The latter occur most often in those with high plasma concentrations resulting from impaired renal excretion and are observed most often in older persons on higher doses (200 mg/day) and those with pre-existing renal insufficiency, seizure disorders, or psychiatric illness. When used for chemoprophylaxis of pandemic influenza at doses of 200 mg daily, amantadine is associated with excess drug cessation rates of 2-9% compared to placebo (Table 2). Administration of this dose in divided doses appears to lessen the risk of CNS adverse events.

Rimantadine has a significantly lower potential for causing CNS adverse effects, in part related to lower plasma drug concentrations (Hayden and Aoki, 1999). One prospective comparative study of long-term prophylaxis at 200 mg daily doses in younger adults found CNS side effects in 13% of amantadine, 6% of rimantadine, and 4.5% of placebo recipients (Dolin et al, 1982). A retrospective cross-over study in an elderly nursing home population compared prolonged amantadine and rimantadine chemoprophylaxis at the doses of 100 mg/day, further adjusted for renal function, and found approximately 10-fold higher frequencies of CNS adverse events, including confusion and hallucinosis, and drug cessation (18%) during amantadine administration (Keyser et al, 2000). Both amantadine and rimantadine can cause gastrointestinal side effects (anorexia, nausea) in approximately 1-3% of recipients. In most instances the adverse effects associated with these drugs are readily reversible after cessation of administration.

Another concern with regard to extensive community use of antivirals during pandemic influenza is their potential for adverse effects during pregnancy. All four drugs are classified as category C agents and have not been adequately studied in pregnant women, so that their potential risk to the fetus needs to be justified by benefit to the mother. All cross the placenta and are excreted in breast milk. Amantadine and rimantadine are teratogenic and embryotoxic in rodents at high doses, and there have been several case reports of congenital anomalies in humans associated with amantadine use early in pregnancy. Consequently, the use of amantadine is relatively contraindicated in pregnancy unless the potential clinical benefit justifies the risk to the fetus.

4.5 Antiviral resistance

High-level cross-resistance to the M2 inhibitors results from point mutations in the M gene with corresponding single amino acid changes in the transmembrane domain of the M2 protein (reviewed in Hay, 1996). Resistant variants exist as subpopulations and readily emerge under selective drug pressure in vitro and in vivo. Most resistant variants show no obvious loss of virulence or transmissibility in animal models or humans (reviewed in Hayden, 1996) and have been shown to effectively compete with wild-type virus for transmission in the absence of selective drug pressure in an avian model (Bean et al, 1989).

Primary resistance to the M2 inhibitors occurs in clinical isolates and has been documented to spread from person-to-person and from swine-to-person. The most common resistance mutation in M2 (Ser31Asn) was described in swine influenza viruses of the H1N1 subtype in the 1930s in the absence of selective drug pressure. More recently, swine viruses in Europe and North America and isolates from several zoonotically infected humans with H1N1 and H3N2 subtypes have shown primary resistance. Amantadine resistance has also been found in a small portion (<1%) of field isolates from untreated persons (Ziegler et al, 1999) and from nursing home residents, some of whom were receiving the drug for parkinsonian symptoms (Houck et al, 1995; Iwahashi et al, 2001). A recent Japanese survey found a 28% frequency of detecting resistant variants in homes where residents with influenza were treated with amantadine and a 16% frequency in homes where amantadine was used only in some for Parkinson's disease (Saito et al, 2002). Approximately 80% of patients with amantadine resistant virus detected did not have a history of drug administration. Such observations indicate that amantadine resistant variants might circulate naturally under certain conditions and that viruses infecting swine, which could serve as the source of the next pandemic virus, are often M2 inhibitor resistant. In addition, the use of amantadine for influenza management in China also increases the potential that a pandemic strain might develop resistance to amantadine and rimantadine.

The M2 inhibitors have been associated with rapid emergence of high-level resistant variants during treatment (reviewed in Hayden 1996). The frequency of recovering resistant variants averages about 30% in treated adults and children but may be higher in immunocompromised hosts (Englund et al, 1998). Resistant variants can replace susceptible strains within 2-4 days of starting therapy. Emergence of resistance during treatment is usually not associated with rebound in illness in immunocompetent persons but may be in some children (Hall et al, 1987) and immunocompromised hosts (Englund et al, 1998).

The emergence of resistance is associated with transmission and failures of M2 inhibitor chemoprophylaxis under close contact conditions in households and nursing homes. When rimantadine was used for index case treatment and post-exposure prophylaxis in families, negligible prophylactic efficacy (3%) was observed due to high rates of resistance emergence and transmission (Hayden et al, 1989). A similar study with amantadine during the 1968 pandemic also found low prophylactic efficacy, although resistance was not studied (Galbraith et al, 1969). A recent nursing home-based study comparing two weeks of prophylaxis with oral rimantadine or inhaled zanamivir after recognized outbreaks found 61% higher protection in zanamivir recipients, in part due to high frequencies of rimantadine prophylaxis failures due to resistant viruses (Gravenstein et al, 2000). The extensive use of rimantadine for prophylaxis and treatment of non-study participants on the same wards may have contributed to the observed prophylaxis failures. Such experiences highlight the potential for emergence of amantadine-resistant influenza A viruses and spread under close contact conditions.

Mathematical models can be used to assess the potential for spread of drug-resistant influenza viruses under both epidemic and pandemic circumstances (Stilianakis et al, 1998). For example, one such study examined the effect of different approaches using amantadine or rimantadine in a closed population during a theoretical pandemic outbreak in which all residents were assumed to be susceptible and become infected. The model, based on studies with amantadine and rimantadine, predicted that treatment alone would minimally affect the epidemic curve, whereas chemoprophylaxis alone or a combination of treatment and chemoprophylaxis both reduce the number of symptomatic cases. However, the observed outcomes depended heavily on the transmissibility of drug-resistant virus relative to wild-type, susceptible virus. When transmissibility of the resistant variant was comparable to wild-type, prophylaxis failures due to resistant virus were common, particularly with the combined approach for which one-half of illnesses were due to resistant virus. A relatively modest five-fold reduction in transmissibility was associated with substantial reductions in the impact of resistant virus and improved effectiveness for both the prophylaxis alone or combined intervention approaches. Another recently described model examining effects of resistance emergence also predicts that decreases in biologic fitness and associated transmissibility of

drug-resistant virus, as observed with neuraminidase inhibitor-resistant variants, would lead to negligible community spread of such variants (Ferguson and Mallett, 2001).

5. Neuraminidase inhibitors (oseltamivir, zanamivir)

5.1 Efficacy for prophylaxis

Inhaled zanamivir, although not approved in most countries for this indication, and oral oseltamivir are highly effective for chemoprophylaxis against epidemic influenza in studies assessing seasonal prophylaxis in unimmunized adults with protective efficacies against febrile influenza illness of 84% and 82%, respectively (Monto et al, 1999; Hayden et al, 1999). Long-term oseltamivir is protective in immunized nursing home residents (efficacy 92%)(Peters et al, 2001), and both agents are effective for post-exposure prophylaxis in families (Hayden et al, 2000; Welliever et al, 2001). Several uncontrolled studies have reported that inhaled zanamivir or oral oseltamivir (Bowles et al, 2002) have been effective at terminating outbreaks in nursing homes that were continuing despite amantadine use. The single study comparing the prophylactic efficacy of an M2 to a neuraminidase inhibitor found that inhaled zanamivir was superior to oral rimantadine for short-term influenza prophylaxis (2 weeks) in nursing home outbreaks largely because of frequent rimantadine prophylaxis failures secondary to resistant virus (Gravenstein et al, 2000). Such results would predict that the neuraminidase inhibitors would also be effective for prophylaxis of pandemic influenza.

5.2 Efficacy for treatment

The antiviral and clinical benefits of early antiviral treatment have not been compared directly between an M2 and a neuraminidase inhibitor. Several large placebo-controlled, blinded studies have shown that treatment with either inhaled zanamivir or oral oseltamivir reduces illness duration by approximately 1-2 days, time to resuming usual activities, and the likelihood of physician-diagnosed lower respiratory complications leading to antibiotic use by 40-50% in adults (Monto et al, 1999; Kaiser et al, 2000; Treanor et al, 2000; Nicholson et al 2000; Kaiser et al, 2003). Efficacy has been established only in febrile influenza patients treated within 36-48 hours of symptom onset. For example, in one trial of otherwise healthy adults with acute influenza, inhaled zanamivir provided a decrease of approximately one day in time to alleviation of major symptoms, whereas a decrease of three days was found in those with febrile illness or those treated within 30 hours of symptom onset (Hayden et al, 1997). Clinical benefits have been found in zanamivir treatment studies involving patients with mild-moderate asthma or chronic obstructive airways disease (Murphy et al, 2000) and in oseltamivir treatment studies involving children aged 1-12 years, in whom new otitis media diagnoses were reduced by over 40% (Whitley et al, 2001). Furthermore, preliminary analysis of the aggregated clinical trials experience with oseltamivir indicates that early treatment is also associated with reductions in hospitalizations (Kaiser et al, 2003). However, published data from treatment of elderly and other persons at high-risk for influenza complications are limited.

5.3 Pharmacology and administration

Due to poor oral bioavailability in humans (estimated less than 5%), zanamivir has been formulated as a dry powder in a lactose carrier for delivery to the respiratory tract. Following oral inhalation with the

proprietary Diskhaler device, 7 to 21% of the inhaled drug reaches the tracheobronchial tree and lungs and about 80 to 90% deposits in the oropharynx. Zanamivir remains detectable in expectorated sputum up to 24 hours after dosing. The bioavailability of zanamivir delivered by inhalation is approximately 10 to 20%, and low serum concentrations decline with a half-life of about 2.5 to 5 hours. Zanamivir is excreted unchanged by the kidney, but dose adjustments are not necessary in renal insufficiency.

Oseltamivir is an ethyl ester prodrug of the antivirally active carboxylate form. Oral absorption of prodrug is high, and following deesterification by esterases in the gut, liver, and blood, the bioavailability of the carboxylate is approximately 80%. The active drug has a serum half-life of 8-10 hours and, like the prodrug, is excreted unchanged by the kidney. Consequently, oseltamivir dose frequency needs to be reduced when creatinine clearance falls below 30 ml/min. Probenicid reduces the clearance of oseltamivir carboxylate by 50% and increases plasma levels correspondingly. No clinically important drug interactions have been recognized with oseltamivir, but specific studies with immunosuppressive agents and anti-retrovirals have not been reported.

No age-related adjustments are required for the neuraminidase inhibitors. The inhaler device used for zanamivir dosing is also an obstacle with respect to ease of administration and to wide-scale application in a pandemic response. The current delivery system requires a cooperative, informed patient who is able to make an adequate inspiratory effort. Demonstration of the correct use of the device is beneficial for inexperienced persons. Elderly hospitalized patients often have problems using the delivery system effectively (Diggory et al, 2001), and the current device is not appropriate for use in young children (below 5 years of age) or those with cognitive impairment or marked frailty.

5.4 Safety and tolerability

Controlled studies found no differences in adverse events between inhaled zanamivir and placebo (lactose) or significant end-organ toxicity. Nasal and throat discomfort may occur in some persons. Inhaled zanamivir treatment has been very infrequently described to cause bronchospasm, sometimes severe or associated with fatal outcome, in acute influenza sufferers with pre-existing airways disease. Influenza itself often causes severe exacerbations in such patients, so that the possible causal relationship to zanamivir administration is uncertain, as is the actual frequency of such events. One large placebo-controlled study of influenza-infected patients with underlying mild-moderate asthma or less often chronic obstructive airways disease found no excess of serious respiratory adverse events and more rapid clinical recovery including peak expiratory flow rates in zanamivir recipients compared to its lactose carrier (Murphy et al, 2000). Approximately one in seven zanamivir or placebo participants in this trial experienced a 20% or greater fall in forced expiratory volume in one second (FEV1) after treatment. Consequently, zanamivir use in risk patients with underlying airways disease requires close clinical monitoring, including the availability of a fast-acting bronchodilator. Possible allergic reactions with oropharyngeal or facial edema have been reported postmarketing.

Oseltamivir is associated with mild-moderate gastrointestinal upset in the form of nausea and emesis each occurring in about 10-15% of adults treated for acute influenza. Diarrhea occurs less often than with placebo. Gastrointestinal symptoms occur less often when oseltamivir is administered with food and are usually not dose-limiting. About 1-2% of recipients stop taking the drug because of adverse events. Headache has also been reported in older adults, and cases of hypersensitivity reactions, rash, hepatotoxicity, and thrombocytopenia have also been reported rarely, although the relationship to oseltamivir is uncertain.

5.5 Antiviral resistance

Primary resistance to the neuraminidase inhibitors among clinical isolates has not been described in enzyme inhibition assays, and these agents are active against all of the nine neuraminidase subtypes recognized in avian influenza viruses (reviewed in Tisdale, 2000; McKimm-Breschkin, 2000). Two major mechanisms of resistance to neuraminidase inhibitors have been recognized following *in vitro* passage of influenza virus in the presence of the drugs: hemagglutinin mutations that reduce viral dependence on neuraminidase activity and neuraminidase variants that alter inhibition of the enzyme by the drugs. *In vitro* selection of variants with neuraminidase resistance usually requires prolonged passage prior to acquisition of associated mutations, whereas hemagglutinin variants arise readily *in vitro* but usually retain drug susceptibility in experimental animal models of influenza. Neuraminidase variants generally show reduced enzyme activity or stability and infectiousness in animal models compared to parental virus. The commonest variant selected *in vivo* by oseltamivir (position 292) shows reduced transmissibility in a ferret model (Carr et al, 2001). Because these agents have different binding sites for the enzyme, cross-resistance is variable between zanamivir and oseltamivir carboxylate. In general, catalytic site mutations (eg, position 152) confer cross-resistance, whereas framework mutations (eg, positions 292, 274) do not.

Treatment with the neuraminidase inhibitors is associated with a low frequency of resistance emergence due to neuraminidase mutations (reviewed in McKimm-Breschkin, 2000 and Tisdale, 2000). To date only one instance of zanamivir resistance in an immunocompromised host has been documented (Gubareva et al, 1998), and no resistance has been found in immunocompetent persons receiving treatment (Boivin et al, 2000; Hayden et al, 2000). The frequency of recovering resistant variants appears to be higher with oseltamivir therapy, in that variants exhibiting neuraminidase resistance have been recovered from about 1.8% of treated persons (Jackson et al, 2000). The likelihood appears to be higher in children (8.6% of posttreatment isolates) than adults (1.3% of posttreatment isolates) (Whitley et al, 2001). However, clinical variants are generally detected late in therapy and are not associated with clinical deterioration. The most commonly recognized mutations following oseltamivir therapy are 292 in H3N2 viruses and 274 in H1N1 viruses. These variants retain susceptibility to zanamivir *in vitro*. In contrast to the experience with M2 inhibitors, either inhaled zanamivir or oral oseltamivir used for both treatment and post-exposure prophylaxis in families are highly effective and not associated with resistance emergence (Hayden et al, 2000; Belshe et al, 2001). Antiviral resistance due to neuraminidase resistance appears to alter the fitness of influenza viruses and their transmissibility, which suggests that resistance will be much less likely to be a threat during drug use in pandemic influenza. Post-marketing surveillance of resistance to neuraminidase inhibitors is being conducted (Zambon and Hayden, 2001).

6. Strategies for use

The overall goals of vaccine and antiviral interventions during pandemic influenza are to limit the burden of disease, minimize social disruption, and reduce economic impact. Vaccine is the preferred intervention for prophylaxis. However, vaccine is unlikely to be available for the first and possibly subsequent waves of the next pandemic, and antivirals could have a significant beneficial impact on these outcomes. The principle, inter-related challenges with regard to effective antiviral use are selection of the strategies for use, ranking of priority groups, and supply/distribution. To be effective, all of these strategies would require supplemental supplies of drug(s) and a controlled distribution system.

6.1 Long-term prophylaxis

Long-term prophylaxis has been shown to be effective in partially protecting against pandemic influenza illness, by decreasing the risk of illness, by reducing influenza-related complications, hospitalizations,

mortality, and by reducing morbidity in particular risk populations. This approach requires large amounts of drug and has a high cost per individual treated or prophylaxed, so that its applicability is limited. For seasonal prophylaxis (4-8 weeks), the highest priority groups for protection would be different from those for immunization programmes during interpandemic influenza. In the absence of adequate vaccine supplies, chemoprophylaxis would be essential for protection of essential personnel (eg. laboratory and vaccine production personnel working directly with the pandemic strain, health care providers, key emergency service personnel), in order to minimize disruption of critical health care and community services. Depending on drug availability and the characteristics of the pandemic, seasonal chemoprophylaxis of high-risk persons, and perhaps their immediate contacts, could be considered. Although mass chemoprophylaxis in school-attending children might reduce their burden of disease and theoretically limit the spread of virus, it is extremely unlikely that antiviral prophylaxis could delay the progression of a pandemic because of the need for extensive coverage and inadequate availability of the drugs.

For greatest cost effectiveness, the drugs should be utilized only during the peak period of activity in a community. Prior pandemic waves have generally lasted approximately 4 weeks in particular communities. Unless subclinical infection had taken place, the risk of infection would resume shortly after cessation of administration, so that seasonal prophylaxis would need to extend for at least 4 weeks during a particular pandemic wave. Constraints on prolonged prophylactic administration include restricted availability, drug costs, risks of adverse effects, and potential emergence of drug resistance. The M2 inhibitors and neuraminidase inhibitors appear to have broadly comparable prophylactic efficacy against interpandemic influenza, but resistance is a more significant issue for M2 inhibitors, particularly if they are used concurrently for treatment.

6.2 Short-term prophylaxis

Antiviral agents have the advantage, relative to immunization, of providing rapid onset of protection. Short-term antiviral prophylaxis (10-21 days) could be effectively utilized in a number of ways: control of institutional or semi-closed community outbreaks, protection during the immune response period after inactivated vaccine administration, or post-exposure (eg, households, travelers). These drugs do not interfere with the response to inactivated vaccines, so that chemoprophylaxis could provide protection during periods until immunization responses have been completed. However, the combined use of antiviral prophylaxis with live-attenuated vaccines would likely blunt replication and immune responses to such vaccines. As for seasonal prophylaxis, the risk of infection would resume shortly after cessation unless combined with immunization.

The combined use of antiviral treatment of ill persons and chemoprophylaxis of contacts would be appropriate under certain circumstances, such as institutional outbreaks or perhaps household introductions. Prior studies have shown that this approach is often ineffective with M2 inhibitors, likely because of resistance emergence and transmission. In contrast to negative studies of combined treatment and post-exposure prophylaxis with M2 inhibitors (Galbraith et al, 1969; Hayden et al, 1989), this approach has succeeded with inhaled zanamivir and oral oseltamivir in family-based studies (Hayden et al, 2000; Belshe et al, 2001). Similarly, neuraminidase inhibitors have been reported to terminate some nursing home outbreaks continuing in the face of amantadine use (Bowles et al, 2002). Consequently, neuraminidase inhibitors would be the optimal choice in these situations or used as second-line treatment in the case of M2 inhibitor failure. If an institutional outbreak continues in the face of M2 inhibitor prophylaxis, resistance transmission is a distinct possibility, and substitution of a neuraminidase inhibitor (eg, oseltamivir) would be warranted.

6.3 Treatment

Optimal treatment of afflicted persons should focus on distribution of available drug to those most likely to benefit. Efficacy has been proven only with early administration (within 2 days of illness onset), so that rapid access is essential. In most countries, treatment is likely to be given to those presenting first and lead to rapid depletion of available antiviral supplies. Restriction of treatment to only high-risk persons would extend available supplies but miss an opportunity to reduce morbidity in otherwise healthy persons. Although not yet validated, it is likely that earlier intervention with patient-initiated therapy, as contrasted with delayed therapy due to clinic or office-based prescribing, would provide greater antiviral effects, faster recovery and potentially higher likelihood of reducing complications. The current agents have been studied in dosing schedules usually lasting 5 days, and it remains to be determined whether shorter therapy, which could extend the supply, would be as effective and avoid rebound in viral replication or illness. A similar uncertainty applies to the use of lower daily doses, particularly in pandemic influenza.

Pandemic influenza will be associated with increased hospitalizations of patients with viral or mixed viral-bacterial pneumonias and lower respiratory tract complications. Although no controlled data have proven the effectiveness of antiviral therapy in such patients, antivirals are likely to be used in such patients. Combinations of M2 and neuraminidase inhibitors show enhanced antiviral activity in vitro and animal models of influenza and might be considered for use in such circumstances.

Based on current knowledge, the preferred drugs for treatment would be neuraminidase inhibitors because of lower risk of adverse events (compared historically to amantadine), decreased evidence of clinically significant drug resistance, and therapeutic value in decreasing lower respiratory tract complications leading to antibiotic use and perhaps hospitalizations (Kaiser et al, 2000; Kaiser et al, 2003). It is uncertain whether treatment reduces the likelihood of transmission, although one modelling study of M2 inhibitor use in an institutional outbreak setting did not find that treatment alone significantly affected the course of the outbreak (Stilianakis et al, 1998).

7. Cost considerations

Per capita costs of antiviral administration are generally higher than for vaccines, except possibly for short courses of amantadine. Procurement costs of neuraminidase inhibitors are substantially higher than for M2 inhibitors for interpandemic use, but the costs of bulk purchases for stockpiling may vary from current circumstances.

Formal pharmacoeconomics analyses of antiviral interventions are needed to guide selection of the appropriate strategies and target populations for antiviral use. The results of such analyses and decisions regarding priority groups for antivirals (or vaccines) will depend on the particular outcome measure analyzed (eg, death, direct medical burden and hospitalizations, societal economic impact) and their projected costs, on the age-related morbidity and mortality of the next pandemic, side effect profile, and the assumed effectiveness of the intervention. Although experiences from prior pandemics and the interpandemic period can be used for modelling purposes, the age-specific attack rates for illness and death are unpredictable in the next pandemic. Based on prior experiences, the risk of death can be mitigated to the greatest extent by targeting high-risk older adults (65 years and older) and the healthy

elderly with effective prophylaxis interventions (Meltzer et al, 1999) and possibly antiviral treatment. In contrast, reductions in economic costs are likely to be greatest by targeting high-risk and healthy younger adults.

Through use of the economic model developed by Meltzer et al (1999) and assumptions regarding drug effectiveness derived from recent therapeutic trials with oseltamivir, preliminary assessment of the economic impact of using antivirals for treatment during an influenza pandemic have been made (Hayden, 2001). These analyses indicate that wide-scale therapeutic use would be projected to reduce lost work days, out-patient visits for presumed complications, and, particularly in older adults, hospitalizations. By assigning direct and indirect costs to particular outcomes, it is possible to project that treatment of adults older than 20 years would result in cost savings. If it were possible to extend early treatment to those who would not seek medical care, savings in indirect costs due to days off work/school could be achieved across all age groups. Such economic models can help guide decisions about the potential benefits of antiviral treatment or prophylaxis in different populations groups.

8. Future studies

A number of questions remain unanswered with regard to potential antiviral use during the next pandemic. Some of these can be addressed in trials during the interpandemic era. For example, the minimally effective doses and durations of therapy or prophylaxis need careful study in interpandemic influenza before recommendations might be considered for the pandemic situation.

1. Determine minimal effective dose and duration of administration. One proposed mechanism for extending the availability of limited antiviral drug supplies during pandemic influenza involves reductions in either dose level or, in the case of treatment, the duration of therapy. Short course therapy of 1-3 days might sufficiently reduce viral loads to provide clinical benefit. However, concerns exist about the rebound in viral replication and symptoms after cessation of administration and the subsequent fostering emergence of drug resistance. The risks of these events would likely be higher in pandemic influenza than in interpandemic disease because of the lack of specific immunity to an antigenically novel strain and potential for higher or more protracted levels of viral replication in affected persons. Studies in infants and young children experiencing their first influenza infection would be of particular interest.
2. Compare directly the effectiveness of antiviral therapy with M2 or neuraminidase inhibitors with regard to reduction of complications, tolerance, and emergence of resistance. Specific populations of interest include children, adults with high-risk conditions, elderly adults, and otherwise healthy adults.
3. Compare the effectiveness of monotherapy with combination therapy in patients hospitalized with serious lower respiratory manifestations of influenza or immunocompromised hosts (e.g., transplant recipients) with regard to clinical outcomes and the emergence of antiviral resistance.
4. Determine the tolerability and appropriate doses for antiviral use in selected high-risk populations where data are limited or lacking (eg, infants, pregnant women, immunocompromised hosts, high-risk elderly). For example, inhaled zanamivir, which produces low blood levels, may be the more appropriate agent for use during pregnancy.
5. Determine whether antiviral administration blunts the response to live-attenuated influenza vaccines. Since inhaled zanamivir, in contrast to intranasal delivery, does not significantly reduce nasal influenza virus replication, one specific combination of interest would be intranasal live-attenuated vaccine with inhaled zanamivir intranasal.

6. Examine mechanisms for antiviral resistance to both classes of agents and assess the biological consequences (infectiousness, virulence) of resistance in relevant models.
7. Expand surveillance for antiviral resistance within the context of the existing WHO Influenza Surveillance Network and in dedicated community or institution-based clinical studies.

9. Summary

In the event of delayed availability of an effective influenza vaccine, antiviral drugs could provide both protection against influenza and therapeutic benefit in those with acute illness. Wide-scale use could reduce influenza-related morbidity, complications, hospitalizations and other demands on the health care system, as well as potentially reducing mortality in the event of a pandemic or major drift variant. The major obstacles to effective use at present are inadequate supply, side effects for certain agents, cost, limited safety data in certain subpopulations, and potential emergence of drug resistance. The clinical pharmacology and adverse drug effect profiles of the neuraminidase inhibitors and rimantadine are superior to amantadine in regard to need for individual prescribing, tolerance monitoring, and seriousness of side effects (Table 1). Few current national or other plans address the specific issues of advance stockpiling, selection of appropriate agents, rapid distribution of drugs, and monitoring of resistance. The latter could be a particular concern for widespread use of amantadine or related M2 inhibitors, such that initial testing of new strains and on-going monitoring are required.

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Table 1. Adverse drug reaction profiles of currently available anti-influenza agents

Agent	Brand name	Route	Dose adjustment	Adverse drug interactions	Adverse reaction	Severity	Frequency during treatment
Amantadine	Symmetrel	Oral	CC < 50-70 age > 65 years	CNS stimulants, anticholinergics, antihistamines, and certain diuretics	CNS CNS gastrointestinal	mild-moderate severe mild	10-30% uncommon common
Rimantadine	Flumadine	Oral	CC < 10 age > 65 years hepatic disease	not reported	CNS gastrointestinal	mild-moderate mild	< 10% common
Oseltamivir	Tamiflu	oral	CC < 30	not reported	gastrointestinal	mild-moderate	common (5 –15%)
Zanamivir	Relenza	inhalation	no	not reported	bronchospasm	mild-severe	very uncommon

CC = Creatinine clearance in ml/min, CNS = Central nervous system

Table 2. Studies of amantadine and rimantadine prophylaxis during pandemic influenza

Pandemic	Setting (N)	Drug	Daily Dose (adults)	Duration	Percent reduction (attack rate)*		Comment
					Influenza illness	Influenza infection	
A/Hong Kong/68 (H3N2) (Smorodintsev et al, 1970){227}	Young adults (6,383)	A	100 mg	12-30 days	49% (4.0% vs 7.8%)	28% (42.1% vs 58.4%)	Efficacy estimated at 63% for confirmed influenza A illness
A/Hong Kong/68 (H3N2) (Galbraith et al, 1970){220}	Household contacts > 2yrs (176)	A	200 mg (divided doses)	10 days	6% (13.8% vs 14.6%)	-35% (35.4% vs 26.2%)	Index case treated Dose of 100 mg/d for ages 10 – 15 yrs. No serious AEs
A/Hong Kong/68 (H3N2) (Nafta et al, 1970){228}	Adults & children (215)	A	200 mg (divided doses)	20 days	100% (0 vs 17.6%)	49% (10.4% vs 20.3%)	No significant AEs
A/Hong Kong/68 (H3N2) (Oker-Blom et al, 1970){224}	Young adults (391)	A	200 mg (divided doses)	30 days	58% (11.3% vs 27.0%)	52% (14.1% vs 29.6%)	Headache: A 8.7%, P 3.4%; CNS complaints: A 7.3%
A/USSR/77 (H1N1) (Quarles et al, 1981){89}	Young adults (308)	A	200 mg (divided doses)	6 weeks	31% (14.0% vs 20.2%)	19% (26% vs 32%)	Cessation due to AEs: A 5.6%, R 2.0%, P 4.0%
		R	200 mg (divided doses)		27% (14.7% vs 20.2%)	9% (29% vs 32%)	
A/USSR/77 (H1N1) (Monto et al, 1979){246}	Young adults (286)	A	200 mg	6 weeks	71% (5.9% vs 20.1%)	39% (18.3% vs 30.2%)	Cessation due to AEs: A 8.3%, P 2.1%
A/USSR/77 (H1N1) (Petterson et al, 1980){245}	Young adults (military) (225)	A	200 mg (divided doses)	3 or 5 weeks	42% (34.7% vs 60.1%)	37% (47.4% vs 75.3%)	Cessation due to AEs: A 18.8%, P 10.2%

A = amantadine, R = rimantadine, P = placebo

*Attack rate (M2 inhibitor versus placebo)