

GLOBAL
HEALTH
SECURITY

EPIDEMIC
ALERT &
RESPONSE

WHO consultation on priority public health interventions before and during an influenza pandemic

Geneva, Switzerland
16–18 March 2004



World Health
Organization

Department of Communicable Disease
Surveillance and Response

© World Health Organization 2004

All rights reserved.

The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

The World Health Organization does not warrant that the information contained in this publication is complete and correct and shall not be liable for any damages incurred as a result of its use.

WHO consultation on priority public health interventions before and during an influenza pandemic

Geneva, Switzerland 16–18 March 2004

Department of Communicable Disease
Surveillance and Response

WHO consultation on priority public health interventions before and during an influenza pandemic

Contents

| | |
|---|----|
| Executive summary | 1 |
| Background | 1 |
| The consultation | 2 |
| Some general conclusions | 4 |
| Conclusions from the working groups | 5 |
| Surveillance for pandemic preparedness | 10 |
| Background | 10 |
| Underlying principles | 11 |
| Objectives and attributes of the surveillance system | 13 |
| Strengthening national and international surveillance activities | 13 |
| Recommendations and conclusions | 14 |
| Table 1: Recommended objectives, methods, and activities for surveillance at different phases | 16 |
| Public health interventions | 20 |
| Background | 20 |
| Assumptions and guiding principles | 21 |
| Sources of guidance | 23 |
| Limitations | 24 |
| Recommendations and conclusions | 25 |
| Table 1: Measures at the national level | 26 |
| Table 2: Measures at the international level | 29 |
| Antivirals – their use and availability | 31 |
| Background | 31 |
| An important role constrained by limited supplies | 32 |
| Use at different phases | 33 |
| Improving availability | 34 |
| Recommendations and conclusions | 35 |
| Better vaccines – better access | 37 |
| Background | 37 |
| Obstacles to development, production and licensing | 37 |
| Obstacles to effective and equitable delivery | 38 |
| Strategies and priority actions: expand and expedite production | 39 |
| Strategies and priority actions: increase equitable access | 40 |
| Recommendations and conclusions | 41 |
| Annexes | |
| 1 Phases in the progression towards a pandemic as a guide to levels of alert and preparedness | 43 |
| 2 Recent WHO documents on influenza and influenza pandemic preparedness | 44 |
| 3 Agenda | 45 |
| 4 List of participants | 54 |

WHO consultation on priority public health interventions before and during an influenza pandemic

Executive summary

Background

In January 2004, health authorities in Viet Nam and Thailand reported their first human cases of infection with avian influenza, caused by an H5N1 strain. The cases in humans are directly linked to outbreaks of highly pathogenic H5N1 avian influenza in poultry initially reported in the Republic of Korea in mid-December 2003 and subsequently confirmed in an additional seven Asian countries (Viet Nam, Japan, Thailand, Cambodia, China, Laos, and Indonesia). As at end-March 2004, no countries other than Viet Nam and Thailand had reported human cases. The number of human cases has remained small to date, but treatment has been largely ineffective and case fatality rates have been high. Moreover, the situation has several disturbing features, including the historically unprecedented scale of the outbreak in poultry.

Of foremost concern is the risk that conditions present in parts of Asia could give rise to an influenza pandemic. Pandemics, which recur at unpredictable intervals, invariably cause high morbidity and mortality and great social disruption and economic losses. Conservative estimates based on mathematical modelling suggest that the next pandemic could cause from 2 million to 7.4 million deaths.

Conditions favourable to the start of a pandemic are now much better understood than in the previous century, which witnessed three pandemics. Influenza research was greatly stimulated in 1997, when the world's first known cases of human infection with the H5N1 strain of avian influenza virus were documented in Hong Kong Special Administrative Region of China. Investigations launched by that outbreak, including studies in molecular biology and epidemiology, helped elucidate the mechanisms by which pandemic viruses could emerge and further clarified the conditions that favour such an event. These studies also demonstrated, for the first time, that the H5N1 strain can infect humans directly without prior adaptation in a mammalian host. On that occasion, the culling within three days of Hong Kong's poultry population, estimated at 1.5 million birds, is thought to have possibly averted a pandemic.

Some experts believe that this improved understanding, when combined with efficient surveillance and immediate and aggressive action, might make it possible to detect events with pandemic potential and delay – or even prevent – their escalation and global spread. Research has identified three essential prerequisites for the start of a pandemic. First, a novel influenza subtype must be transmitted to humans. Second, the new virus must be able to replicate in humans and cause disease. Third, the new virus must be efficiently transmitted from one human to another; efficient human-to-human transmission is expressed as sustained chains of transmission causing community-wide outbreaks. Since 1997, the first two prerequisites have been met on four occasions: Hong Kong in 1997 (H5N1), Hong Kong in 2003 (H5N1), the Netherlands in 2003

(H7N7), and Viet Nam and Thailand in 2004 (H5N1). Of these outbreaks, those caused by H5N1 are of particular concern because of their association with severe illness and a high case fatality. Of even greater concern is the uniqueness of the present H5N1 situation in Asia. Never before has an avian influenza virus with a documented ability to infect humans caused such widespread outbreaks in birds in so many countries. This unprecedented situation has significantly increased the risk for the emergence of an influenza pandemic.

A pandemic virus capable of efficient human-to-human transmission could arise via two mechanisms: virus reassortment (the swapping of genetic material between viruses) when humans or pigs are co-infected with H5N1 and a human influenza virus, and adaptive mutation during human infection. The risk that either event will occur remains so long as H5N1 is present in an animal reservoir, thus allowing continuing opportunities for human exposure and infection. The level of risk is determined most directly by the prevalence of the virus in poultry and the frequency of its transmission to humans. The risk also depends on the co-circulation of human and avian influenza viruses and the inherent propensity of these viruses to reassort. Most experts agree that control of the present outbreaks in poultry will take several months or even years; some believe that the virus may have already established endemicity in domestic poultry. The recent detection of highly pathogenic avian influenza in wild birds adds another layer of complexity to control.

The world may therefore remain on the verge of a pandemic for some time to come. At the same time, the unpredictability of influenza viruses and the speed with which transmissibility can improve mean that the time for preparedness planning is right now. Such a task takes on added urgency because of the prospects opened by recent research: good planning and preparedness might mitigate the enormous consequences of a pandemic, and this opportunity must not be missed.

The consultation

In response to these concerns, WHO convened a technical consultation on preparedness for an influenza pandemic from 16 to 18 March 2004. The consultation, attended by more than 100 experts from 33 countries, considered a wide range of measures that could be introduced, by WHO and national authorities, both before and during a pandemic. Three main objectives were identified: to forestall potential pandemics as they emerge, to slow national and international spread, and to reduce the usually high levels of morbidity, mortality, and social disruption. Participants agreed that the effectiveness of specific interventions would change over time in line with distinct phases, defined by epidemiological criteria, during the progression from an incipient pandemic situation to the declaration of a pandemic. Interventions were therefore discussed in terms of their objectives and likely impact at different phases as well as their feasibility in different resource settings. Epidemiological triggers for shifting objectives and adapting the recommended mix of measures were also identified. The consultation fully recognized that the best opportunity for mitigating the consequences of a pandemic would occur early on, and that planning and preparedness, at both national and global levels, would be needed to take full advantage of this opportunity.

Many key characteristics of a new pandemic virus – its pathogenicity, attack rate in different age groups, susceptibility to antivirals, and response to other treatments – would guide the selection of control measures, but could not be known with certainty in advance. In addition, many characteristics of normal human influenza, such as the role of asymptomatic transmission and the effectiveness of non-medical control measures, are poorly understood. During the chaos of a pandemic, health authorities would almost certainly need to make decisions, often with major social and economic consequences, in an atmosphere of considerable scientific uncertainty. To reduce some of this uncertainty, participants based their recommendations on relevant lessons from the recent SARS outbreak, knowledge about the epidemiology of previous influenza pandemics, and clinical data from outbreaks of H5N1 infection in Hong Kong in 1997 and Viet Nam and Thailand in 2004. Modelling of various scenarios for the emergence of a pandemic strain provided an especially useful planning tool.

Against this background, three main questions were addressed: what reporting and monitoring systems are needed to detect the start of a pandemic at the earliest possible stage and track its evolution, which interventions will be both feasible and effective at different phases and in different resource settings, and what policy options might best cope with the inevitable shortage of vaccines and antivirals. These questions were considered by four working groups focused on surveillance, public health interventions, antivirals, and vaccines. A more complete account of the deliberations and conclusions of each working group is provided in the main body of this report.

Some discussion centered on the question of whether – with better scientific knowledge, better control tools, and the international solidarity shown during the SARS response – something might be done to prevent the present situation from evolving towards a pandemic. In this regard, good surveillance in all countries experiencing outbreaks of highly pathogenic avian influenza in poultry was considered to be a fundamental prerequisite. Guarding against the start of a pandemic would also depend on rapid detection, prompt laboratory confirmation, and accurate reporting of human cases, and the transparent sharing of all relevant information with WHO.

Participants readily agreed that vaccines – the first line of defence for reducing morbidity and mortality – would not be available at the start of a pandemic and would remain in short supply throughout the first wave of international spread. For this reason, efforts to prevent or delay initial spread would have paramount importance. All countries would need to prioritize vaccine distribution and consider difficult ethical and practical questions of eligibility. Developing countries would face the most acute shortages, as manufacturing capacity is concentrated in Europe and North America, and countries can be expected to reserve scarce supplies for their own populations. In the absence of vaccines, antivirals would initially assume greater importance as a prophylactic and treatment tool for reducing morbidity and mortality. In practice, however, this potential role could be undermined by several problems, including high costs, uncertain efficacy, propensity to develop resistance, and extremely limited supplies, further constrained by the absence of any surge capacity for production.

With the first line of defence not a viable option at the start of a pandemic, participants looked at interventions that could forestall or delay national and international spread pending antiviral availability, the augmentation of vaccine supplies, and the implementation of mass vaccination strategies. This strategy of “buying time” was

linked to assumptions, partially based on modelling, that the first chains of human-to-human transmission might not reach the efficiency needed to initiate and sustain pandemic spread. In such a scenario, the first evidence of limited human-to-human transmission, most likely expressed as clusters of cases, would be the epidemiological trigger for intense international efforts aimed at interrupting further transmission or at least delaying further national and international spread. For this reason, surveillance systems in countries with outbreaks in animals caused by H5N1 or other influenza viruses of known human pathogenicity should be oriented towards early detection, reporting, and investigation of clusters of human cases, followed by aggressive containment measures, including tracing and management of contacts, targeted prophylactic use of antivirals, and travel-related measures. Participants recommended consideration of whether an international stockpile of antivirals should be established for use exclusively during this critical window of opportunity.

Should early containment fail, the consultation concluded that, once a certain level of efficient transmission was reached, no interventions could halt further spread, and priorities would need to shift to the reduction of morbidity and mortality. It was also recognized that a reassortment event could result in a virus fully equipped for efficient human-to-human transmission, thus immediately curtailing opportunities to “buy time” through measures aimed at preventing geographical spread. Should early surveillance fail, the detection of transmission would likely take place only after efficient transmission was established, again curtailing opportunities to intervene. However, in these cases as well, advance planning had much to offer. As the consequences of a pandemic became apparent, public health authorities would face great public and political pressure to maintain or introduce often drastic, costly, and disruptive protective measures (travel restrictions, screening measures at borders, contact tracing, isolation and quarantine) which, though useful at earlier stages, might have little or no impact once efficient transmission was established. By including provisions for stopping or adjusting measures in line with clear epidemiological criteria, preparedness plans would help public health authorities withstand this pressure and thus conserve resources for the next objectives: constraining transmission, preventing severe disease, and reducing case fatality.

When objectives shift, clear and frank public information and good communications systems would be essential in helping lower expectations and discouraging the continuation of personal protective measures no longer considered effective. Participants agreed that, once a pandemic begins, its overall management would move outside the public health sector and take on great political and economic significance. Good public information might also protect governments from accusations that extraordinary measures introduced at earlier phases – causing great economic costs and social disruption – failed and were therefore inappropriate. In addition, populations would need to be prepared for the even greater social disruption, linked to high morbidity and mortality, that could be expected as the pandemic progressed.

Some general conclusions

During the deliberations of the working groups and discussions in plenary session, the picture that emerged was one of a world inadequately prepared to respond to an

influenza pandemic. Response capacity was considered insufficient at levels ranging from vaccine manufacturing to the sensitivity of surveillance systems, the number of hospital beds, the affordability of diagnostic tests, and the supply of respirators and face masks. A recurring theme was the need to engage government departments beyond the health sector. At the same time, the urgency of the present situation was fully appreciated, and participants made a number of suggestions for improving capacity now. For example, better use of vaccines and antivirals during the inter-pandemic period would improve manufacturing capacity while also helping to reduce the estimated 250,000 to 500,000 deaths caused by seasonal influenza epidemics each year. The burden of influenza in developing countries, including its contribution to overall morbidity and mortality and economic impact, was virtually unknown in most cases. Studies of this burden would give national authorities a better foundation for making influenza a priority and bargaining for a share of resources. Establishment of vaccine manufacturing capacity in developing countries could be expected to improve access while reducing costs.

Moreover, most participants agreed that, under the pressures of an eminent or unfolding pandemic, innovative solutions to some problems would be found. For example, manufacturing capacity for vaccines might be augmented by decreasing the antigen quantity per dose or using adjuvants. Research on antivirals could determine whether reduced drug dose or shortened treatment course might still have a prophylactic or therapeutic effect, and whether administration later in the course of infection might influence transmission dynamics by reducing virus shedding.

As in all public health emergencies caused by an infectious agent, international mechanisms for alert and response can go only a certain way towards mitigating the consequences of an influenza pandemic. In the final analysis, each national health system will bear the burden of protecting populations and managing the emergency. The consultation concluded that international solidarity would have the greatest role to play at the start of human-to-human transmission, when an all-out effort would have the best chance of halting or at least delaying further national and international spread. Should that effort fail, inequities in capacity and the distribution of resources mean that the consequences of a pandemic would almost certainly be most severe in the developing world. Participants stressed the importance of addressing these inequalities now – before a pandemic makes the ethical implications of failing to do so both blatantly apparent and irrevocable.

Conclusions from the working groups

WORKING GROUP ONE: Surveillance for pandemic preparedness

1. One of the most important functions of surveillance is to ensure the detection of unusual clusters of cases and of the occurrence of human-to-human transmission at the earliest possible stage, when public health interventions have the greatest chance to prevent or delay further national and international spread. Once a pandemic is fully under way, no interventions are likely to halt further international spread during the first wave of infection.

2. Influenza pandemics are, by their very nature, matters of global concern. Prompt and transparent reporting of early cases and results from the investigation of clusters related to novel influenza viruses is essential for the protection of international public health.
3. The use of limited supplies of vaccines and antivirals will depend on the national situation and should consider the protection of essential community functions and the treatment of groups at highest risk of severe disease. Data from a national risk assessment and internationally coordinated epidemiological investigations will assist in the development of policies for vaccine and antiviral utilization. Data to inform policy decisions need to be produced as quickly and cost-effectively as possible.
4. As the origins of pandemic influenza viruses have historically involved animal species, surveillance activities surrounding the emergence of a potentially pandemic virus require intersectoral collaboration with veterinarians as well as with clinicians, virologists, epidemiologists, and public health professionals
5. Given resource constraints in many countries, strengthening existing systems to include a capacity to detect and investigate clusters of acute febrile respiratory disease may be the best value for money.
6. The objectives, methods, and attributes of an influenza surveillance system will vary according to different phases in the pre-pandemic and pandemic periods.
7. To assist in preparedness planning, the group set out recommended objectives for influenza surveillance and identified the corresponding methods and activities appropriate at different inter-pandemic, pre-pandemic, and pandemic phases. These recommendations appear as a table in the working group's report.

WORKING GROUP TWO: Public health interventions

1. An influenza pandemic is a public health emergency that rapidly takes on significant political, social, and economic dimensions. A broad range of government departments apart from public health should be engaged in pandemic preparedness planning and will need to be involved in decisions regarding interventions having potentially broad impact outside the health sector.
2. Emergency decisions will need to be made in an atmosphere of scientific uncertainty. Health authorities may need to change recommended measures as data about the causative agent become available and the epidemiological situation evolves, and as interventions either succeed in containing transmission or lose their effectiveness. The basis for all interventions should be carefully explained to the public and professionals, as well as the fact that changes can be expected.
3. Non-medical interventions will be the principal control measures pending the availability of adequate supplies of an effective vaccine. Many will have their greatest potential impact in pre-pandemic phases while others will have a role after a pandemic has begun. In some resource-poor settings, non-medical interventions will be the only control measures available throughout the course of a pandemic.

4. Non-medical interventions considered by the consultation include public risk communication, isolation of cases, tracing and appropriate management of contacts, measures to “increase social distance” (such as cancellation of mass gatherings and closure of schools), limiting the spread of infection by domestic and international travel, and the targeted use of antiviral drugs. Certain measures are recommended for consideration based on a public health perspective, although it is recognized that other factors (such as availability of health resources, political, economic and social considerations) and a country’s special circumstances will legitimately influence national decisions regarding prioritization and implementation of the various options.
5. In general, providing information to domestic and international travellers (risks to avoid, symptoms to look for, when to seek care) is a better use of health resources than formal screening. Entry screening of travellers at international borders will incur considerable expense with a disproportionately small impact on international spread, although exit screening should be considered in some situations.
6. Emerging virus strains with pandemic potential require urgent and aggressive investigation to provide a stronger scientific basis for control recommendations and the strategic use of resources. Confirmation of early episodes of human-to-human transmission is especially important. Biological specimens as well as epidemiological and clinical data must be obtained and shared with extreme urgency, under the leadership of WHO. Advance planning is needed to take advantage of this narrow window of opportunity to contain or slow transmission, which will close quickly once a pandemic begins.
7. Health authorities may need to introduce extraordinary measures under emergency conditions. This is likely to require improvement of public health capacities and modernization of public health laws at national and international levels. The necessary legal authority for implementation of these measures must be in place before a pandemic begins. Respect for public health ethics and fundamental human rights is critical.
8. To assist in preparedness planning, the group assessed more than 30 public health interventions in terms of their feasibility and likely effectiveness at each of four phases in the progression from a pre-pandemic situation to the declaration of a pandemic. Recommended measures, at national and international level, appear as tables in the working group’s report.

WORKING GROUP THREE: Antivirals – their use and availability

1. Antivirals are expected to be effective against human illness caused by avian influenza and human pandemic strains. Pending the availability of vaccines, they will be the only influenza-specific medical intervention for use in a pandemic.
2. Inadequate supplies are a major constraint. Supplies are presently extremely limited and manufacturing capacity could not be augmented during the course of a pandemic. At current capacity, several years would be needed to increase supplies appreciably.

3. Most countries will have no access to antivirals throughout the course of a pandemic and will need to rely on public health measures and supportive care until vaccines become available.
4. Conditions of access will be best in countries that have manufacturing capacity, regularly purchase antivirals for seasonal use, or have stockpiled drugs in advance.
5. Stockpiling of drugs in advance is currently the only way to ensure sufficient supplies at the start of a pandemic. Governments with adequate resources should consider pursuing this option as a precautionary measure.
6. Establishment of an international stockpile of antivirals should be considered for use for specific objectives in the pre-pandemic period, when opportunities for averting a pandemic or delaying its further spread are likely to be greatest. An international stockpile could not be used to meet the needs of individual countries once a pandemic is fully under way.
7. Increased use of antivirals during the inter-pandemic years, based on better understanding of the medical and economic burden of annual influenza epidemics, is one strategy for augmenting production capacity.
8. Price is the second major constraint. Current costs for widespread use of even the shortest duration of treatment place these drugs outside health budgets in the vast majority of countries.
9. Additional obstacles to wide-scale use include side effects of certain agents (especially amantadine), the risk of drug resistance, and limited safety data in key sub-populations.
10. Early treatment is a more efficient use of resources than prophylaxis, which requires a prohibitively large stockpile.
11. Where available, the neuraminidase inhibitors are the preferred drugs for treatment. If the M2 inhibitors must be used for treatment, this should be done with a full awareness of their side effects and propensity to develop resistance.
12. Scarce supplies of an emergency intervention create ethical dilemmas of priority access both within and among countries. Ethical dilemmas regarding fair access and rationing of finite supplies will be difficult to resolve but must be addressed.

WORKING GROUP FOUR: Better vaccines – better access

1. Vaccines are the single most important intervention for preventing influenza-associated morbidity and mortality during both seasonal epidemics and pandemics.
2. No country will have adequate supplies of vaccine at the start of a pandemic. At least 4 to 6 months will be needed to produce the first doses of vaccine following isolation of a new pandemic virus. The subsequent augmentation of supplies will be progressive. Stockpiling in advance is not an option.

3. Global manufacturing capacity, which is driven by vaccine demand during the inter-pandemic years, is finite and inadequate. More than 90% of current production capacity is concentrated in countries in Europe and North America accounting for less than 10% of the world's population.
4. Equitable access will not be possible so long as global manufacturing capacity remains inadequate. Countries without manufacturing capacity will face the most acute vaccine shortages, as countries with manufacturing capacity can be expected to reserve scarce supplies for their own populations.
5. The production of a vaccine for a pandemic virus is a unique process that requires emergency procedures for its development, licensing, production, and delivery.
6. Important constraints to rapid and large-scale production of a pandemic vaccine include intellectual property rights, biosafety requirements for production facilities, and coordination and funding of clinical trials. A global effort to address these constraints is an efficient approach
7. Country-specific issues to be addressed by national authorities include procedures for licensing and testing and liability issues surrounding mass use of a new vaccine with an unknown safety profile.
8. Short-term solutions for augmenting supplies include the development of vaccines using a lower antigen content, use of adjuvants to improve immunogenicity, and outsourcing of certain production steps. Another strategy involves advance preparation of pilot lots of vaccine against virus subtypes with pandemic potential. To pursue this strategy, manufacturers may need financial or other incentives to support investments in a product that might never be used.
9. Public funding should give priority to research on cross-subtype vaccines conferring long-lasting protection. Development of vaccines protective against several candidate pandemic viruses is a particularly effective long-term solution, as it opens possibilities for stockpiling. If the vaccine confers long-lasting immunity, preventive vaccination for a future pandemic will be possible as a major step forward.
10. Increased vaccine use during the inter-pandemic years will increase production capacity, but depends upon the burden of influenza within individual countries compared with other health priorities. Regional production strategies and purchasing schemes should be explored as a strategy for increasing vaccine use during the inter-pandemic years.
11. All countries should decide in advance on priority groups for vaccination when supplies are limited and develop strategies for expanding coverage when supplies increase.
12. Vaccine manufacturers in developing countries should participate in the influenza vaccine supply task force of the International Federation of Pharmaceutical Manufacturers.

WORKING GROUP ONE: Surveillance for pandemic preparedness

Background

Comprehensive surveillance for pandemic preparedness should integrate data on disease occurrence with virological and clinical data. The WHO Global Influenza Surveillance Network, with its 110 national influenza centres and four collaborating centres for reference and research on influenza, is the overarching system for the virological surveillance of influenza. Collectively, the centres in this network offer strong monitoring and diagnostic support with a broad geographical reach. Over the years, the network has demonstrated its ability to keep the world alert to the emergence of influenza virus variants and novel strains with pandemic potential. Laboratories in the network also play an important role in the virological investigation of outbreaks and laboratory confirmation of cases, but very few perform epidemiological functions.

Within countries, infrastructures and capacities for conducting routine infectious disease surveillance and detecting unusual disease events vary considerably. Some countries have influenza-specific mechanisms, such as hospital-based surveillance and systematic virological sampling of patients, for monitoring influenza-like illness and detecting unusual trends, but the vast majority do not. Moreover, in countries where infectious diseases remain one of the leading causes of morbidity and mortality, influenza is usually considered a self-limiting disease and rarely given high priority. The challenges of improving influenza surveillance as a tool for pandemic preparedness are therefore great, but well worth considering.

Surveillance is the cornerstone of pandemic preparedness and response. A sensitive early warning system will pick up the first human cases related to the emergence of a novel influenza virus and signal the first instances of human-to-human transmission. Pandemic preparedness also relies on surveillance to signal the transition from limited human-to-human transmission to the efficient and sustainable transmission that marks the start of a pandemic. This function is especially important, as experts agree that control measures, other than vaccines and antivirals, will have their most significant impact prior to the start of a pandemic. In the pre-pandemic phases and as a pandemic unfolds, surveillance and epidemiological research contribute the data needed to assess transmission patterns and evaluate control efforts, supporting the adaptation of recommended measures to the changing epidemiological context.

The origins of pandemic influenza viruses have historically involved animal species. All mammalian influenza viruses, including those that affect humans, derive from the large pool of virus subtypes maintained in birds, the natural reservoir for influenza A viruses. Mammals, most notably pigs, can also play a role in the emergence of a virus with pandemic potential. Improving vigilance for indicators which may signal the start of a pandemic must therefore include a component for the monitoring of animal health,

which complements the human surveillance system. Surveillance for pandemic preparedness also requires the close collaboration of public health officials with the agricultural sector and veterinary services, keeping in mind the potential conflict of interest that can arise when measures for protecting public health have major economic consequences for agriculture.

Underlying principles

The working group on surveillance for pandemic preparedness first looked at the challenges confronting efforts to strengthen influenza surveillance. While better routine data on influenza incidence, impact and trends would be useful everywhere, this was not considered feasible in most countries due to resource constraints, weak public health infrastructures, and the competing demands of many other infectious diseases. Moreover, as participants noted, pandemic influenza is a rare event. In resource-poor settings, the development of an influenza-specific surveillance system was regarded as neither practicable nor wise, and was thus discouraged. Instead, the group looked for ways to augment surveillance capacity by building on existing systems and making better use of data already being collected. The most critical need for good surveillance data would come when epidemiological conditions were considered favourable for the emergence of a pandemic virus. Two questions were raised:

- What data would be most relevant and useful in a pre-pandemic situation?
- How could existing systems be adapted to collect these data?

In exploring these questions and seeking answers, the group identified three priority areas of activity: to build integrated surveillance systems, to concentrate on the inter-pandemic phase, and to focus on the detection of clusters of human cases.

Build integrated surveillance systems. The group recommended that surveillance for potentially pandemic influenza be built into existing systems, such as those for SARS or for the detection of other emerging and epidemic-prone diseases. Plans to enhance surveillance and response capacity should begin with a risk assessment, taking into consideration the local and regional risk that a novel influenza virus might emerge or be imported from a neighbouring high-risk area. Subsequent recommendations on the objectives of surveillance at different pandemic phases, as set out in the accompanying table, made a distinction between activities in countries with outbreaks of influenza in animals and countries where no such outbreaks had been detected. It was also recognized that a pandemic virus capable of efficient human-to-human transmission could emerge suddenly following a reassortment event, with no prior warning signalled by outbreaks of highly pathogenic avian influenza in poultry.

Participants saw a need to ensure that, if finite resources are used to shore up surveillance, sufficient funds remain to support response activities, especially during the emergency conditions at the start of a pandemic. In the early phases of a pandemic, surveillance activities should not compromise existing public health programmes, such as those for childhood immunization. However, once a pandemic was fully under way, overall priorities are likely to shift.

Concentrate on the inter-pandemic phase. Participants agreed that surveillance during the inter-pandemic phase, especially when concern was high that a pandemic virus might emerge, was more important than surveillance when a pandemic was fully under way. Several considerations supported this view. As pointed out in plenary presentations and other working groups, the greatest opportunity for preventing or delaying national and international spread will occur in the pre-pandemic phases or very early at the start of a pandemic. Certain resource-intensive activities, such as animal surveillance and the active detection, investigation and laboratory confirmation of human cases, make good sense under pre-pandemic conditions, but would not be sustainable or even necessary during a pandemic, when most resources would be absorbed by the emergency response. Finally, if surveillance activities have not been initiated prior to the start of a pandemic, it will be impossible to do so during the chaos of a pandemic.

Focus on the detection of clusters. As public health interventions are believed to have their maximum impact in the pre-pandemic phases, participants saw a need to ensure the ability of surveillance systems to detect unusual clusters of respiratory disease as an early warning function. For example, heightened surveillance for SARS-like illness in Viet Nam led to the detection and investigation of a cluster of unusual cases at a paediatric hospital in January 2004, which then aided the detection of rapidly spreading outbreaks of H5N1 avian influenza in poultry in that country and others. Surveillance systems also need to signal the transition from limited human-to-human transmission to efficient and sustained transmission at the earliest possible stage. A focus on the detection of clusters of cases was considered the best approach for achieving both objectives. As participants noted, achieving these objectives is a function of local capacity that has significant implications for international public health.

Several ways to improve surveillance for the clustering of health events were identified. Mobilizing communities to report unusual health events, including unexplained deaths, is the simplest form of cluster surveillance and will be most effective in smaller communities. Multidisciplinary teams for the investigation of clusters could be set up and trained and, when necessary, supported by international teams drawn from the Global Outbreak Alert and Response Network (GOARN). Investigations of clusters should be guided by well-defined questions set out in protocols. Intensive case investigations would be needed to gather early evidence of human-to-human transmission in household contacts and high-risk groups, such as health care workers, poultry workers, and cullers. Data on the spectrum of disease, key epidemiological indicators, and outcomes of illness in these initial cases also need to be collected and assessed. Applied research could help elicit answers to basic questions about the role of asymptomatic infection, patterns of virus shedding, and the effectiveness of contact tracing. In addition, as control measures following the detection of human-to-human transmission are likely to include the prophylactic and therapeutic use of antivirals, monitoring for the development of resistance would be another important surveillance function in countries with adequate capacity and resources.

Field investigations should be supported by targeted studies in molecular epidemiology; such studies can enhance understanding of the dynamics of human-to-human transmission, identify a reassortment event, and determine whether a virus is mutating. Laboratory studies can also provide evidence that differences in the severity of illness

and clinical outcomes are associated with different virus strains, and thus help to better target interventions.

The investigation of clusters of cases to determine the occurrence of human-to-human transmission has important international implications. Results must be promptly and transparently reported.

Objectives and attributes of the surveillance system

The attributes of the surveillance system will change over time in line with the evolving epidemiological context. During the pre-pandemic phase, the principal objective of surveillance is to maintain vigilance for conditions conducive to the start of a pandemic and provide an early warning. A highly sensitive system is needed to monitor disease in animals, detect human cases related to the emergence of a novel virus subtype, and look for evidence that the virus has increased its transmissibility or virulence. An early warning system includes the systematic monitoring and investigation of rumours of outbreaks as well as virological investigations to identify and characterize viruses with pandemic potential and support the first stages of vaccine development.

Once a pandemic is fully underway, the main aims of surveillance will be to identify priority groups for interventions such as vaccines and antivirals, to monitor the burden of disease, and to assess the impact on health and other essential services. These activities will mainly involve the collection of aggregate data; census data will provide the basis for final estimates of mortality.

During a pandemic, flexibility will be an especially important attribute of the surveillance system. Case definitions can be expected to change, and reporting requirements may need adjustment in line with reduced capacity in the health sector as the epidemic spreads. Surveillance systems therefore need to be simple and well-documented prior to the start of a pandemic; these attributes will also facilitate the continuity of functions when staff changes are needed because of illness or death. Automated data analysis and dissemination will streamline the process further.

Strengthening national and international surveillance activities

As most countries will not be able to invest in influenza-specific surveillance systems, the strengthening of surveillance is best viewed as part of initiatives to build overall capacity.

National options. One option is to expand the role of national influenza centres within the larger context of the WHO Global Influenza Surveillance Network. An especially important role of the centres is to ensure the collection, testing, and timely transfer of clinical specimens to one of the four WHO collaborating centres for reference and research on influenza. This role should be strengthened. Additional options identified by the group for strengthening the function of national influenza centres include:

- Improvements in the representativeness and number of samples
- Establishment of centres in regions that are currently under-represented
- Closer networking nationally, sub-regionally and globally
- Integration of clinical, laboratory and epidemiological data
- Expansion of activities to include staff training, quality assurance, and laboratory biosafety

International options. Surveillance capacities and needs vary widely, often according to geographical area. Regional and sub-regional approaches, including training programmes and establishment of closer networking, could be used to strengthen influenza surveillance among countries with similar needs.

At the global level, FluNet should be further developed to serve as a platform for the real-time consolidation and dissemination of surveillance data and other information.

Options for improving technical tools and expertise. The group recommended that WHO develop a range of technical, administrative, and logistic protocols describing the mechanisms and agreed procedures for virological investigations at all phases during the pre-pandemic and pandemic periods. Consideration of the financial and human resource implications of virological surveillance should be part of the protocols. Other technical protocols should include criteria for the investigation of influenza outbreaks, assessment of the efficacy of vaccines and antivirals under field conditions, evaluation of public health interventions, and surveys of mortality, burden of disease, and impact on health services. Ideally, indicators and tools for the evaluation of public health interventions implemented during emergencies should be developed as part of preparedness planning. Evaluation is especially important for interventions for which the evidence of efficacy and cost-effectiveness is lacking.

Multidisciplinary teams, including clinicians, virologists, epidemiologists, and veterinarians, should be trained specifically to investigate clusters of cases and assess the risk that human-to-human transmission has occurred. When necessary, the teams could be deployed as part of international technical cooperation within the framework of GOARN. Surveillance would also benefit from wider availability of rapid tests which are subtype specific, supported by training in their use and quality assurance.

Recommendations and conclusions

1. One of the most important functions of surveillance is to ensure the detection of unusual clusters of cases and of the occurrence of human-to-human transmission at the earliest possible stage, when public health interventions have the greatest chance to prevent or delay further national and international spread. Once a pandemic is fully under way, no interventions are likely to halt further international spread during the first wave of infection.
2. Influenza pandemics are, by their very nature, matters of global concern. Prompt and transparent reporting of early cases and results from the investigation of clusters related to novel influenza viruses is essential for the protection of international public health.

3. The use of limited supplies of vaccines and antivirals will depend on the national situation and should consider the protection of essential community functions and the treatment of groups at highest risk of severe disease. Data from a national risk assessment and internationally coordinated epidemiological investigations will assist in the development of policies for vaccine and antiviral utilization. Data to inform policy decisions need to be produced as quickly and cost-effectively as possible.
4. As the origins of pandemic influenza viruses have historically involved animal species, surveillance activities surrounding the emergence of a potentially pandemic virus require intersectoral collaboration with veterinarians as well as with clinicians, virologists, epidemiologists, and public health professionals
5. Given resource constraints in many countries, strengthening existing systems to include a capacity to detect and investigate clusters of acute febrile respiratory disease may be the best value for money.
6. The objectives, methods, and attributes of an influenza surveillance system will vary according to different phases in the pre-pandemic and pandemic periods.

Recommended objectives, methods, and activities for influenza surveillance at different phases

| Objectives and rationale | Methods | Description, activities | Relevance according to phase | | | | | |
|--|---|---|------------------------------|------|--------------|-----|-----------|--|
| | | | Inter-pandemic | | Pre-pandemic | | Pan-demic | |
| | | | 0.0a | 0.0b | 0.1, 0.2 | 0.3 | 1.0 | |
| 1. Early warning | | | | | | | | |
| 0.1 To rapidly detect and investigate the initial cases of illness in humans compatible with infection caused by a novel influenza strain. | M.1.1 Rumour registers. | Rumour registers of outbreaks of acute respiratory illness of unknown etiology at local, national, regional, and global levels. | C | C+ | C+ | C+ | C+ | |
| | M.1.2 Detection and investigation of clusters of severe acute respiratory illness. | Surveillance (health care facilities) to detect clusters of severe acute respiratory illness. | C | C+ | C+ | C+ | C+ | |
| | M.1.3 Monitoring key parameters of cases of severe acute respiratory illness/pneumonia in patients admitted to/discharged from sentinel health care facilities. | Real-time analysis to detect unusual patterns of morbidity and mortality attributed to respiratory disease. | D | D+ | C+ | C+ | D+ | |
| | M.1.4. Monitoring of vital statistics. | Real-time analysis to detect unusual patterns of mortality related to acute respiratory illness. | D | D+ | D+ | D+ | D+ | |
| | M.1.5 Monitoring of circulating influenza strains in humans. | Characterization of circulating influenza viruses (subtyping, antigenic analysis, genetic analysis). | C | C+ | C+ | C+ | C+ | |
| | M.1.6 Monitoring of febrile illness and severe acute respiratory illness in individuals known to be at high risk of exposure. | Twice-daily self-monitoring of body temperature and self-referral to health care facilities. | | C | C | C | | |
| | M.1.7 Monitoring of febrile illness and severe acute respiratory illness in health care workers. | Twice-daily self-monitoring of body temperature and self-referral to health care facilities. | | | C | C | C | |

Phases:

0.0a = No indication of a new influenza virus subtype; no indications of highly pathogenic avian influenza activity in susceptible animal species.

0.0b = No indications of a new influenza virus subtype; evidence of highly pathogenic avian influenza in susceptible animal species is reported.

0.1 = A novel virus subtype is isolated from a single human case; no evidence of further spread or outbreak activity.

0.2 = Two or more human infections with the novel virus subtype are confirmed; no evidence of human-to-human transmission.

0.3 = Human-to-human transmission is confirmed.

1.0 = Onset of pandemic. Substantial transmission is confirmed. The new virus subtype causes several outbreaks in at least one country, shows international spread, and causes serious morbidity and mortality in at least one segment of the population.

C = Core activity; D = Desirable activity; + = Activity to be carried out in areas free of novel influenza strains in susceptible animal species or humans (does not apply to 0.0a, where all activities are routine).

| Objectives and rationale | Methods | Description, activities | Relevance according to phase | | | |
|---|--|--|------------------------------|---|---|---|
| | | | | | | |
| 2. Early case detection | | | | | | |
| 0.2 To implement appropriate case and contact management, initiate laboratory investigations, and define key epidemiological parameters (incubation period, infectious period). | M2.1 Identification of individuals early in the course of an illness compatible with infection caused by a novel influenza strain. | M2.1.a In areas where infection with a novel influenza strain in humans has been confirmed or with extensive animal outbreaks caused by a novel influenza strain with proven ability to infect humans elsewhere: enhanced hospital-based surveillance for cases of severe acute respiratory illness/pneumonia. | | C | C | C |
| | | M2.1.b In areas where no novel influenza strain has been isolated from animals or humans: enhanced hospital-based surveillance for cases of severe acute respiratory illness/pneumonia with a history of travel to areas where the burden of influenza disease due to a novel strain has reached a significant level. | | | C | C |
| 3. Human-to-human transmission | | | | | | |
| 0.3.1 To rapidly determine the occurrence of human-to-human transmission of a novel influenza strain. | M3.1.1 Case investigation including contact tracing and follow-up. In conjunction with surveillance activities described in 0.1.-M.1.2, 0.2-M.2.1, 0.3.2- M3.2.1, 0.3.2-M3.2.2. | M3.1.1.a Thorough field and laboratory investigations should be carried out to assess the likelihood of human-to-human transmission. Such investigations require appropriate laboratory, clinical and epidemiological skills. Ideally all confirmed cases should be investigated. Alternatively, cases with the most recent dates of onset, cases among health care workers and cases occurring in clusters within specific settings should be prioritized. In the event of a preceding avian or swine influenza outbreak, cases arising in individuals without a history of exposure to poultry, wild fowl or swine may provide the best evidence of human-to-human transmission. | | | C | C |
| | | M3.1.1.b Contacts of cases under investigation should be traced and followed up for fever and respiratory illness and similarly investigated as appropriate. | | | C | C |
| | M3.1.2 Retrospective seroprevalence studies. | Consideration should be given to retrospective seroprevalence studies within households or in specific settings where confirmed cases were identified. | | | D | D |

| Objectives and rationale | Methods | Description, activities | Relevance according to phase | | | | |
|---|---|---|------------------------------|----|----|----|----|
| | | | | | | | |
| 0.3.2 To determine whether the observed pattern of human-to-human transmission of a novel influenza strain is compatible with sustained human-to-human transmission in order to inform influenza preparedness planning and management at all levels. | M.3.2.1 Risk modelling In connection with surveillance activities described in 0.1-M.1.2, 0.3-M.3.1.1, 0.3.2-M.3.2.2. | Monitoring the size and geographical distribution of community clusters and the characteristics of well-defined transmission trees. | | | | C | |
| | M.3.2.2 (see 0.1-M.1.3) Monitoring key parameters of cases of severe acute respiratory illness/pneumonia in patients admitted to/discharged from sentinel health care facilities. In conjunction with surveillance activities described in 0.1-M.1.2, 0.3-M.3.1.1, 0.3.2-M.3.2.1. | Real-time trend analysis or other signalling of rapidly increasing numbers of hospital admissions for severe acute respiratory illness/pneumonia. | D | D+ | C+ | C+ | D+ |
| 4. Evolution of key clinical, epidemiological and laboratory parameters | | | | | | | |
| 0.4 To monitor the evolution of, and detect changes in, the pattern of key clinical, epidemiological and laboratory parameters in order to: - describe the characteristics of the epidemic/pandemic in terms of time, place and person - identify high-risk groups for severe disease - identify potential reassortment of circulating influenza strains - inform influenza preparedness planning and management at all levels (e.g. allocation of resources within the health care sector, prioritization of the use of vaccines and antivirals) | M.4.1 Sentinel surveillance for influenza-like illness. | Real-time analysis of data about cases of severe acute respiratory illness/pneumonia. | D | D+ | D+ | D+ | D+ |
| | M.4.2 (see 0.1-M.1.3) Monitoring of key parameters of cases of severe acute respiratory illness/pneumonia in patients admitted to/discharged from sentinel health care facilities. | | D | D+ | C+ | C+ | D+ |
| | M.4.3 (see 0.2-M.2.1) Identification of individuals early in the course of an illness compatible with infection caused by a novel influenza strain. | | | | C | C | |
| | M.4.4 (see 0.1-M.1.4) Monitoring of vital statistics. | | D | D+ | D+ | D+ | D+ |

| Objectives and rationale | Methods | Description, activities | Relevance according to phase | | | | |
|---|---|--|------------------------------|----|----|----|----|
| | M.4.5 Assessment of excess mortality | Ad hoc surveys to assess mortality in jurisdictions without timely registration of vital statistics (e.g. all-cause mortality and mortality attributed to severe acute respiratory illness/pneumonia/influenza-specific). | | | | D | D |
| 5: Allocation of and planning for health resources | | | | | | | |
| 0.5 To determine and forecast the burden of disease to inform influenza preparedness planning and management at all levels (e.g. to inform the rational utilization of health care services, to prioritize the utilization of available vaccines and antivirals). | M.5.1 Monitoring utilization of emergency services. | Real-time analysis of ambulance call-outs, number/demographics of staff outside the health sector re-deployed to assist in health-care related activities. | | | | D | D |
| | M.5.2 (see 0.1-M.1.3) Monitoring key parameters of cases of severe acute respiratory illness/pneumonia in patients admitted to/discharged from sentinel health care facilities. | Analysis of number of hospital admissions, number of admissions to intensive care unit, number of ventilated patients, number of intubated patients. Real-time analysis desirable during an influenza epidemic and during phase 1.0. | D | D | D | D | D |
| | M.5.3 (see 0.4-M.4.1) Sentinel surveillance for influenza-like illness. | | D | D+ | D+ | D+ | D+ |
| | M.5.4 Monitoring sales of drugs (e.g. antivirals, antimicrobials, decongestant drugs, antitussive drugs) in selected sites (e.g. pharmacies/outlets, retailers, manufacturers). | Analysis of pharmaceutical sales and distribution to signal rapidly increasing use of therapies for influenza-like illness and pneumonia in health care facilities and at a community level. | D | D | D | D | D |

WORKING GROUP TWO: Public health interventions

Background

Vaccines and, to a lesser extent, antivirals are the principal medical tools for mitigating the consequences of an influenza pandemic. Once a pandemic is fully under way, mass use of an effective vaccine is central to strategies for reducing morbidity and mortality. In addition, a wide range of non-medical interventions – from personal hygiene and the wearing of masks to quarantine and the screening of travellers – can potentially reduce opportunities for transmission and slow international spread. Although many of these non-medical interventions were tested during the emergency response to SARS, their use during the different conditions of an influenza pandemic has not been systematically evaluated. Consideration of their use during a pandemic is particularly important, as non-medical interventions will be the principal protective tools so long as supplies of effective vaccines and antivirals remain scarce. In countries unable to secure adequate supplies, non-medical measures may be the main line of defence throughout the course of a pandemic.

An influenza pandemic is a public health emergency that rapidly takes on significant political, social, and economic dimensions. As with other emerging infectious diseases, the course of its evolution is governed by factors – including the properties of a new causative agent – that cannot be known in advance and require some time to understand. In the phases moving from the pre-pandemic period to a full-fledged pandemic, health authorities will need to make a series of emergency decisions in an atmosphere of considerable scientific uncertainty and fragile public confidence. Prior guidance on which interventions are most likely to be effective and feasible at different phases is therefore greatly needed as part of preparedness planning. In addition, mathematical modelling suggests that early detection of the first chains of human-to-human transmission might provide a unique opportunity to prevent or at least delay further national and international spread. As this window of opportunity is expected to close quickly, prior guidance on the most appropriate interventions is particularly important.

The effectiveness of many interventions will depend on the behaviour of the virus as determined by its pathogenicity, principal mode of transmission (droplet or aerosol), attack rate in different age groups, duration of virus shedding, and susceptibility to antivirals. If, for example, it is known that children are the most severely affected age group, or play a major role in transmission, health authorities will be in a better position to make decisions about the effectiveness of school closure, travel measures (children travel less frequently than adults), and quarantine (children cannot be separated from their parents). Apart from questions of effectiveness, the selection of appropriate measures will be driven by questions of feasibility closely linked to costs, available resources, ease of implementation within existing infrastructures, the broader impact of possible interventions and likely acceptability to the public.

The many uncertainties surrounding the effectiveness and feasibility of interventions cannot be entirely resolved in advance, but they can be reduced in ways that facilitate rational preparedness planning. This was the task of the working group on public health interventions.

Assumptions and guiding principles

The working group assessed more than 30 public health interventions in terms of their feasibility and likely effectiveness in meeting different public health objectives. Interventions were considered separately for use at national and international levels during each of four phases in the progression from a pre-pandemic situation to the declaration of a pandemic. In developing recommendations, the group evaluated the likely protective effect of specific measures, but also considered the resource implications and the social and economic disruption they might cause. Although the emphasis was firmly placed on the use of non-medical interventions, the role of antivirals at different phases was also considered. The results of these assessments are set out in the tables below. Where appropriate, explanatory notes have been included to help health authorities assess the evidence base and decide whether a given measure will be suitable in a particular national setting.

Participants recognized that the effectiveness of specific interventions will vary according to epidemiological conditions at the different phases. Public health objectives will also shift in line with the evolving epidemiological situation, and these objectives should likewise guide the selection of interventions. Three objectives were identified:

- To prevent further human cases caused by a virus that has not yet established efficient human-to-human transmission
- To slow pandemic spread and thus gain time for strengthening preparedness measures, including the augmentation of vaccine supplies
- To reduce the impact of the first wave of a pandemic.

Particular attention was given to the confirmation of human-to-human transmissions as the epidemiological trigger for aggressive measures aimed at averting a pandemic (provided transmission is not yet efficient and sustained) or at least slowing further spread. Intense efforts, combined with vigilant surveillance for influenza viruses in animal and human populations, would be needed to prevent an emerging virus from improving its transmissibility. At this phase, local measures targeting settings where transmission is occurring were considered a more effective use of resources than more extensive measures in distant areas not yet experiencing cases.

Adapting measures to the epidemiological context. Participants agreed that opportunities for averting a pandemic or appreciably slowing its spread would end once efficient and sustained human-to-human transmission was established, as the containment of influenza at this stage is considered virtually impossible. At some point, efforts to prevent international spread through travel-related measures would also become ineffective. As levels of morbidity and mortality mount during a pandemic, measures that made good sense at earlier phases – such as isolation of patients, contact tracing, and voluntary quarantine of contacts – would cease to be effective or feasible

because of the large number of cases. The prophylactic treatment of contacts with antivirals, which are expected to be extremely scarce, would likewise be rendered impractical, as noted by the working group on antivirals. These varying phase-specific recommendations are reflected in the tables.

On a more positive note, the group agreed that some measures might be stopped following successful achievement of their objectives. All interventions come at a cost; a phase-wise halt to interventions, whether because of their success or the loss of their effectiveness, is ethically justified to conserve resources for addressing the main public health objective during a full-fledged pandemic: reducing the number of cases and deaths.

The group recommended that interventions be introduced as packages, as it was considered unlikely that any single measure would have sufficient impact on its own. Some interventions are interdependent. For example, the prophylactic use of antivirals as a measure for reducing transmission depends on rapid and efficient case detection and contact tracing. The predictable need to change the recommended mix of interventions over time necessitates careful advance preparation and explanation to the public, policy-makers, and health care staff. The group felt that risk communication would be crucial at all phases, but most especially so following the declaration of a pandemic, as the public would need to understand that certain public health measures were no longer effective and that others could at best delay rather than prevent further spread.

Ethical and legal concerns. In recommending interventions, participants recognized that opportunities for responding to a pandemic have been strengthened by recent research, technological advances, and evidence of the power of international collaboration demonstrated during the SARS outbreak. At the same time, it was recognized that translation of these developments into public health benefits will require the improvement of public health capacity and modernization of public health laws at both national and international levels. Faced with a pandemic, authorities may need to introduce unusual public health measures, for example closing schools or curtailing certain non-essential work and services. The legal authority and procedures for doing so must be established and understood by key personnel, such as those in the public health, judicial, and law enforcement systems, before a pandemic begins. It will also be critical to ensure that, as far as possible, such measures respect fundamental human rights as well as public health ethics.

Changes following the declaration of a pandemic. Participants noted that objectives would shift most dramatically following the declaration of a pandemic, but agreed that several measures would remain beneficial at that phase and would be particularly important in the absence of adequate supplies of vaccines and antivirals. Based on patterns seen in previous pandemics, all parts of the world are unlikely to be affected simultaneously during the first wave of infection; opportunities for protecting geographical areas or population groups will probably remain open even after a pandemic is declared. Even during severe pandemics not everyone is affected, opening opportunities to maximize the proportion who remain uninfected. In this phase, measures such as simple hand washing and the use of masks and voluntary quarantine for symptomatic persons could help reduce transmission, while travel-related measures,

such as exit screening for persons departing from affected areas, might dampen or delay international spread.

When faced with a pandemic situation, the general public would probably be strongly motivated to adopt personal protective measures and behaviours, some of which may have limited effectiveness. The group felt that these measures should be permitted provided they caused no harm and did not have major resource implications. One challenge would be to persuade populations to change behaviours in line with sound public health policy. Some behaviours, such as avoidance of travel to affected areas, would probably take place regardless of official recommendations. The group strongly recommended that authorities openly inform the public whenever new evidence warranted a change of policy.

Judging from past pandemics, a point would likely be reached when the political and economic dimensions of the pandemic become so great that decisions are no longer left to the health sector alone. Members of the group raised the possibility that decisions made by health ministers might be counterbalanced by other considerations. Arguments for reducing internal travel would have to be balanced against the need to move essential goods such as foodstuffs around a country. Entry screening of travellers at international borders, which was not considered effective, provided one example of a resource-intensive intervention that might nonetheless be introduced in response to public and political pressure. Good preparedness plans, agreed on in advance, might protect against this possibility.

Antivirals as an adjunct to public health interventions. The group considered the role of antivirals, in combination with other measures, at each epidemiological phase, giving particular attention to their targeted use when the first instances of human-to-human transmission are confirmed. As supplies would be limited, the group recommended that the use of antivirals be prioritized, as indicated in the tables. The group cited strong ethical reasons for offering antivirals to contacts, but recommended aggressive antiviral prophylaxis of contacts only during the pre-pandemic phase. The use of antivirals without clear objectives and target groups, which could lead to drug resistance, was cited as an example of how the inappropriate use of an intervention can do more harm than good. Good preparedness plans could help prevent this problem from arising.

Sources of guidance

When evaluating measures and making recommendations, the working group took into account lessons from the recent SARS outbreak, historical data from previous pandemics, and experiences during the 1997 outbreak of human cases of H5N1 infection in Hong Kong. The SARS outbreak was considered informative, as it tested the feasibility and to some extent the effectiveness, under emergency conditions, of non-medical public health interventions. In addition, SARS was one of the first severe new diseases to spread rapidly along the routes of international air travel. Compared with pandemics during the previous century, which began in 1918, 1957, and 1968, experiences in the control of SARS may be more relevant to the behaviour of an infectious disease in a world where airlines now carry an estimated 1.6 billion travellers every year.

The group agreed that the characteristics of a pandemic virus would differ in significant ways from that of a normal influenza virus, but felt that certain key characteristics of influenza viruses, such as the incubation period and patterns of virus shedding, would likely be similar. Pandemic influenza was considered far more difficult to control than SARS for several reasons. The incubation period for influenza (2 to 3 days) is much shorter than that for SARS (10 days); contact tracing would therefore need to be much more rapid. Infectivity for influenza may begin up to 24 hours before symptoms and is believed to peak during early symptoms. Children can play a significant role in influenza transmission and may shed influenza virus longer than adults. Immunocompromised persons may shed influenza virus for very long periods. As with SARS, droplet spread is most important epidemiologically for normal influenza. Influenza can, however, also spread by the aerosol route,.

The concentration of SARS in hospital settings, placing health care workers at particular risk, facilitated case detection and contact tracing. Epidemiological indicators will be less helpful for influenza, which has no well-defined risk group. As influenza has a shorter serial interval than SARS, the number of secondary cases will grow much faster; a community-wide outbreak of pandemic influenza cannot be prevented once efficient human-to-human transmission is established. Influenza has non-specific symptoms, differential diagnosis is difficult, and laboratory diagnosis is complex and costly. The group felt that these difficulties would be most important during the pre-pandemic phases when cases are few and the diagnosis and investigation of each yields useful information.

Limitations

The tables were prepared with the understanding that they are based on incomplete scientific data and do not constitute WHO recommendations. They should be adapted by countries taking into account their special circumstances, and are not intended to supplant national sovereignty and decision-making. Equally the group agreed that individual countries should generally not be taking decisions in isolation since decisions and actions in one country will frequently have implications elsewhere.

The tables list a series of measures as options that were considered most likely to be effective by public health experts, based on the limited scientific data available and experiences in the control of other epidemic-prone diseases of international concern. However, the effectiveness of most measures for the control of influenza has not been evaluated in scientific studies. An analysis of available research suggests that a number of the epidemiological characteristics of influenza, important for designing an effective control strategy, remain poorly understood. For measures of uncertain effectiveness, an effort was made to balance expected effectiveness against potential costs and likely harm. Measures considered ineffective were generally discouraged but permitted in a few exceptional cases.

Recommendations are based on public health considerations; the decisions of policy-makers and practitioners will understandably take into account other factors, such as available resources, political concerns, and economic and social consequences. Some countries may have special characteristics (status as an island, or long and porous land borders) that may likewise lead to adaptation of recommended measures.

Recommendations and conclusions

1. An influenza pandemic is a public health emergency that rapidly takes on significant political, social, and economic dimensions. A broad range of government departments apart from public health should be engaged in pandemic preparedness planning and will need to be involved in decisions regarding interventions having potentially broad impact outside the health sector.
2. Emergency decisions will need to be made in an atmosphere of scientific uncertainty. Health authorities may need to change recommended measures as data about the causative agent become available and the epidemiological situation evolves, and as interventions either succeed in containing transmission or lose their effectiveness. The basis for all interventions should be carefully explained to the public and professionals, as well as the fact that changes can be expected.
3. Non-medical interventions will be the principal control measures pending the availability of adequate supplies of an effective vaccine. Many will have their greatest potential impact in pre-pandemic phases while others will have a role after a pandemic has begun. In some resource-poor settings, non-medical interventions will be the only control measures available throughout the course of a pandemic.
4. Non-medical interventions considered by the consultation include public risk communication, isolation of cases, tracing and appropriate management of contacts, measures to “increase social distance” (such as cancellation of mass gatherings and closure of schools), limiting the spread of infection by domestic and international travel, and the targeted use of antiviral drugs. Certain measures are recommended for consideration based on a public health perspective, although it is recognized that other factors (such as availability of health resources, political, economic and social considerations) and a country’s special circumstances will legitimately influence national decisions regarding prioritization and implementation of the various options.
5. In general, providing information to domestic and international travellers (risks to avoid, symptoms to look for, when to seek care) is a better use of health resources than formal screening. Entry screening of travellers at international borders will incur considerable expense with a disproportionately small impact on international spread, although exit screening should be considered in some situations.
6. Emerging virus strains with pandemic potential require urgent and aggressive investigation to provide a stronger scientific basis for control recommendations and the strategic use of resources. Confirmation of early episodes of human-to-human transmission is especially important. Biological specimens as well as epidemiological and clinical data must be obtained and shared with extreme urgency, under the leadership of WHO. Advance planning is needed to take advantage of this narrow window of opportunity to contain or slow transmission, which will close quickly once a pandemic begins.
7. Health authorities may need to introduce extraordinary measures under emergency conditions. This is likely to require improvement of public health capacities and modernization of public health laws at national and international levels. The necessary legal authority for implementation of these measures must be in place before a pandemic begins. Respect for public health ethics and fundamental human rights is critical.

Measures at the national level
(for persons living or travelling within an affected country)

| Measures | Phases* | | | | Comments |
|---|--------------|-----|-----|-----|--|
| | Pre-pandemic | | | | |
| | 0.1 | 0.2 | 0.3 | 1.0 | |
| Public health information, communication | | | | | |
| Information for public on risks and risk avoidance (tailored to target population) | Y | Y | Y | Y | |
| Information for professionals | Y | Y | Y | Y | |
| Advice on universal hygiene behaviour | Y | Y | Y | Y | |
| Preparatory information on next phase | Y | Y | Y | Y | |
| Measures to reduce risk that cases transmit infection | | | | | |
| Confinement – Confine cases (mild and severe) as appropriate to local situation; provide medical and social care | Y | Y | Y | Y | Need to plan for large numbers of severe cases. |
| Face masks ¹ – Symptomatic persons | Y | Y | Y | Y | Logistics need to be considered. |
| – Exposed person: undertake risk assessment considering: evidence of human-to-human transmission; closeness of contact; frequency of exposure | C | C | C | C | Consider recommending masks based on risk assessment. |
| – Persons seeking care (respiratory illness) in risk area (waiting room) | Y | Y | Y | Y | Need more data, especially on use by well persons. |
| Measures to reduce risk that contacts transmit infection | | | | | |
| Tracing and follow-up of contacts | Y | Y | Y | N | Not feasible once pandemic starts. |
| Self-health monitoring and reporting if ill | Y | Y | N | Y | |
| Voluntary quarantine (home confinement) of healthy contacts; provide medical and social care | N | N | Y | N | Home confinement should also apply to persons undergoing antiviral prophylaxis, as efficacy not known. |
| Advise contacts to reduce social interaction | N | N | NR | N | Not relevant for contacts in quarantine; see also measures to increase social distance. |
| Advise contacts to defer travel to unaffected areas | N | Y | NR | Y | Precautionary principle when unclear whether human-to-human transmission is occurring; see also travel measures. |

Y = Yes, should be done at this phase; N = No, not necessary at this phase; C = Should be considered; NR = Not relevant

¹Quality and type of mask depend on risk group. Cases: surgical mask; health care workers: N95 or equivalent; others: depends on risk.

| Measures | Phases* | | | | Comments |
|--|---------|-----|-----|-----|--|
| | 0.1 | 0.2 | 0.3 | 1.0 | |
| Provide contacts with antiviral prophylaxis ² | Y | Y | Y | N | Principle of early aggressive measures to avert pandemic. |
| Measures to increase social distance | | | | | |
| Voluntary home confinement of symptomatic persons | Y | Y | Y | Y | Measures needed to reduce risk of transmission to other household members. |
| Closure of schools (including pre-school, higher education) in conjunction with other measures (limiting after-school activities) to reduce mixing of children | N | N | C | C | Depends on epidemiological context – extent to which these settings contribute to transmission. |
| Population-wide measures to reduce mixing of adults (furlough non-essential workers, close workplaces, discourage mass gatherings) ³ | N | N | C | C | Consider in certain circumstances – extent to which unlinked community transmission and transmission in workplaces occurs. |
| Masks in public places | N | N | N | N | Not known to be effective; permitted but not encouraged. |
| Measures to decrease interval between symptom onset and patient isolation | | | | | |
| Public campaign to encourage prompt self-diagnosis | Y | Y | Y | Y | |
| Urge entire population (affected area) to check for fever at least once daily | N | N | N | N | |
| Set up fever telephone hotlines with ambulance response | N | N | C | N | |
| Set up fever clinics with appropriate infection control | N | N | C | N | |
| Introduce thermal scanning in public places | N | N | N | N | Not effective based on experience; also requires individual and public health action for identified febrile persons. |
| Disinfection measures | | | | | |
| Hand washing | Y | Y | Y | Y | |
| Household disinfection of potentially contaminated surfaces | Y | Y | Y | Y | |
| Widespread environmental disinfection | N | N | N | N | |
| Air disinfection | N | N | N | N | |

²Implementation depends on adequate supplies and may require a global stockpile with a pre-negotiated targeting and delivery strategy to ensure availability in the area where a potential pandemic virus emerges. Prophylactic use will depend on evidence of effectiveness. Targeted use required because of potential for drug resistance, side effects and limited supplies. Targeted use might consider: public prevention; protection of health care workers; protection of other essential service providers; individual treatment.

³Given a pandemic strain causing significant morbidity and mortality in all age groups and the absence of a vaccine, authorities should seriously consider introducing population-wide measures to reduce the number of cases and deaths. Decisions can be guided by mathematical and economic modelling. If modelling indicates a reduction in the absolute numbers of cases and deaths, decisions to introduce measures, involving multiple government sectors, will then need to balance the protection of priority functions against the risk of social and economic disruption.

| Measures | Phases* | | | | Comments |
|--|---------|-----|-----|-----|--|
| | 0.1 | 0.2 | 0.3 | 1.0 | |
| Measures for persons entering or exiting an infected area within the country | | | | | |
| Advise to avoid contact with high-risk environments (infected poultry farms, live poultry markets) | Y | Y | Y | Y | |
| Recommended deference of non-essential travel to affected areas | N | N | Y | Y | If significant areas of country remain unaffected. |
| Restrict travel to and from affected areas | N | N | N | N | Enforcement of travel restrictions considered impractical in most countries but likely to occur voluntarily when risk appreciated by the public. |
| Cordon sanitaire | N | N | N | N | Enforcement considered impractical. |
| Disinfection of clothing, shoes, or other objects of persons exiting affected areas | N | N | N | N | Not recommended for public health purposes, but may be required by veterinary authorities to prevent spread of infection in animals. |

*Phases

0.1 = A novel virus subtype is isolated from a single human case. No evidence of further spread or outbreak activity.

0.2 = Two or more human infections with the novel virus subtype are confirmed. No evidence of human-to-human transmission.

0.3 = Human-to-human transmission is confirmed.

1.0 = Onset of pandemic. The new virus subtype causes several outbreaks in at least one country, shows international spread, and causes serious morbidity and mortality in at least one segment of the population.

Measures at the international level

| Measures | Phases* | | | | Comments |
|---|--------------------------------|-----|-----|-----|--|
| | Pre-pandemic | | | | |
| | 0.1 | 0.2 | 0.3 | 1.0 | |
| Measures at borders for persons entering or exiting a country | | | | | Message must be tailored to phase. While travel would remain matter of personal choice, transparency must be assured in order to allow for informed decision-making. Consequences for the traveller may include personal risk to health and economic harm. |
| Information to travellers – Outbreak notice | Y | Y | Y | Y | |
| – Recommend that travellers to areas experiencing outbreaks of highly pathogenic avian influenza avoid contact with poultry farms and live animal markets | Y | Y | N | N | |
| – Recommend deference of non-essential international travel to affected areas | N | N | Y | Y | |
| – Recommend deference of non-essential international travel from affected areas | <i>See screening measures.</i> | | | | |
| Measures at borders for international travellers coming from or going to affected areas | | | | | |
| Health alert notices to travellers to and from affected areas | N | N | Y | Y | WHO negotiates with IATA to ensure that airlines distribute health alert notices; WHO facilitates shared notice formats among countries. |
| Medical surveillance | | | | | |
| – Daily self-checking for fever | | | | | |
| Travellers from affected area | N | N | Y | Y | |
| Travellers to affected area | N | N | N | Y | |
| – Self-reporting if symptoms appear in travellers from affected areas | Y | Y | Y | Y | Contacts of confirmed cases should be encouraged to monitor health. Quarantine may be indicated. Persons on affected conveyance should be traced and similarly advised. |
| – Advice on how to behave if ill after travel in affected areas (seek health care, give travel history, receive influenza lab test); if pandemic virus detected, patient should be isolated and public health officials, including WHO, notified. | Y | Y | Y | Y | |
| Entry screening for travellers coming from affected areas | | | | | Due to lack of proven health benefit, practice should be permitted (for political reasons, to promote public confidence) but not encouraged. Travellers should receive health alert notices instead. |
| – Screening for symptoms (visual detection of symptoms) | N | N | N | N | Entry screening may be considered where host country suspects exit screening (see below) at traveller's point of embarkation is suboptimal. |
| – Screening for at-risk travellers (health declaration, questionnaire) | N | N | N | N | |

Y = Yes, should be done at this phase; N = No, not necessary at this phase; C = Should be considered; NR = Not relevant

| | | | | | |
|--|---|---|---|---|---|
| – Thermal screening | N | N | N | N | |
| – Medical examination | N | N | N | N | |
| Entry screening options for geographically isolated infection-free areas (islands) | N | N | Y | Y | Feasible, may prevent entrance of pandemic virus. May also be relevant where country's internal surveillance capacity is limited. |
| Exit screening for all travellers from areas with human infection | N | N | Y | Y | More feasible than entry screening for detecting early cases. |
| – Screening for symptoms (visual detection of symptoms) | N | N | N | N | Not feasible due to passenger volume. |
| – Screening for at-risk travellers (health declaration, questionnaire) | N | N | Y | Y | |
| – Thermal scanning or ear-temperature measurement | N | N | Y | Y | Thermal scanning less sensitive and specific but may be more practical than ear-temperature scanning. |
| – Stop list of isolated or quarantined persons | N | N | N | N | May be feasible in certain countries, but generally not encouraged. |
| – Recommend that ill persons postpone travel | Y | Y | Y | Y | |
| – Medical examination for travellers at risk or with fever | N | N | N | N | Not feasible to implement at borders. |
| Measures for countries with porous borders (including informal or illegal crossing points) adjoining affected areas | | | | | |
| Raise awareness among health care providers and general public to facilitate "informal" surveillance and response measures, such as social distancing, quarantine or isolation | N | N | Y | Y | WHO to post relevant guidelines on web for use by countries in developing posters, mass media messages, and similar measures. Possible benefits include rumour control. |
| Measures for travellers on board international conveyances from affected areas | | | | | |
| Recommend self-reporting if influenza-like symptoms appear | N | N | Y | Y | |
| Separate sick travellers (if possible) on board | N | N | Y | Y | On flights from affected areas, masks should be offered to all passengers upon boarding. |
| Advise health authority at countries of traveller's embarkation, destination and transit that a person on board is ill (airline is responsible for destination only) | Y | Y | Y | Y | Established requirement for destination, but not uniformly observed in practice. |
| Share epidemiological information for contact tracing with national public health authorities | N | N | Y | Y | Countries to share this information directly with others, as appropriate. |

*Phases

0.1 = A novel virus subtype is isolated from a single human case. No evidence of further spread or outbreak activity.

0.2 = Two or more human infections with the novel virus subtype are confirmed. No evidence of human-to-human transmission.

0.3 = Human-to-human transmission is confirmed.

1.0 = Onset of pandemic. The new virus subtype causes several outbreaks in at least one country, shows international spread, and causes serious morbidity and mortality in at least one segment of the population.

WORKING GROUP THREE: Antivirals – their use and availability

Background

Research has shown that antiviral drugs are effective for both the prevention (chemoprophylaxis) and early treatment of influenza, if administered within 48 hours following the onset of illness. During normal seasonal epidemics, antivirals are considered an important adjunct to vaccination as a strategy for reducing the medical and economic burden of influenza. Their use can reduce the duration of uncomplicated disease and the likelihood of complications requiring antimicrobial treatment and possibly hospitalization. Less certain, due to lack of studies, is their ability to reduce serious complications and mortality in groups at highest risk, including the elderly and persons with underlying disease.

Many questions surround the most appropriate use and expected impact of antivirals during a pandemic. Under pandemic conditions, their importance is elevated during the first wave of infection, when vaccines – unquestionably the most useful medical tool for reducing morbidity and mortality – are not yet available. In the absence of vaccines, antivirals are the only medical intervention for providing both protection against disease and therapeutic benefit in persons who are ill. Moreover, unlike pandemic vaccines, antivirals can be stockpiled in advance and have the added advantage of being immediately effective. Antivirals may also have an important role during the early response to the emergence of a new virus with pandemic potential. During that phase, aggressive prophylactic use of antivirals in the outbreak foci, supported by rapid case detection and contact tracing, could reduce opportunities for adaptive mutation and reassortment between avian and human viruses and thus possibly prevent the virus from establishing efficient human-to-human transmission.

At the same time, however, the role of antivirals in mitigating the impact of a pandemic faces several obstacles. Foremost among these are the extremely limited supplies, determined by low use of antivirals during the inter-pandemic period, and negligible surge capacity for production. Price is another major obstacle. Current costs for even the shortest duration of treatment place these drugs outside health budgets in the vast majority of countries. These limitations make it highly unlikely that antivirals could be used to delay progression of a pandemic once efficient transmission is established, as doing so might require extensive population coverage. Limited supplies also constrain the use of antivirals as a strategy for reducing the burden of illness on a large scale and thus protecting health services from being rapidly overwhelmed. Their use to reduce social disruption by preserving essential services will require difficult decisions about priority groups, supported by strong public communications to explain why access is limited and to help keep expectations realistic.

Decisions about the use of antivirals during a pandemic also need to consider the properties of individual drugs. Four antivirals are available in two drug classes: the M2 ion channel inhibitors (amantadine and rimantadine) and the neuraminidase inhibitors (oseltamivir and zanamivir). Although influenza vaccine is included in the *WHO model list of essential medicines*, these antivirals are not; access in most developing countries is non-existent. Apart from limited supplies, uneven access, and high costs, the major obstacles to the wide-scale use of these drugs include side effects for certain agents, the risk of drug resistance, and limited safety data in key sub-populations, including infants, young children, and pregnant women.

The M2 inhibitors have a long shelf life (at least two decades and possibly more), which facilitates stockpiling, but are associated with side effects in the central nervous system and gastrointestinal tract. Side effects are particularly important for amantadine, which also has several recognized drug interactions. The need for individual prescribing of this agent is a significant limitation to its wide-scale use. In addition, abundant evidence points to the rapid emergence of drug resistance to both M2 inhibitors.

The neuraminidase inhibitors are newer drugs but are also much more expensive. They are known to be effective for chemoprophylaxis against illness caused by epidemic influenza. They are registered in around 65 countries for treatment and in around 13 countries for prophylaxis. Based on current knowledge, the neuraminidase inhibitors are the preferred drugs for treatment during a pandemic because of their lower risk of adverse events, decreased evidence of drug resistance, and therapeutic value in decreasing lower respiratory tract complications. Evidence shows that treatment with neuraminidase inhibitors reduces virus shedding; the impact on transmission during a pandemic requires further investigation. While scientific data support the use of oseltamivir for reducing influenza-related morbidity, its impact on mortality has not been adequately studied. For zanamivir, wide-scale application in a pandemic response is limited by poor bioavailability and administration via an inhaler device as well as by the shortage of supplies.

The formulation of national strategies for using antivirals thus faces significant constraints linked most importantly to the inadequacy of supplies and high price, especially for the newer drugs. Scarce supplies of an emergency intervention create ethical dilemmas of priority access both within and among countries. Options for using antivirals are further governed by public health objectives at different pandemic phases, the scale of use needed to reach these objectives, the adequacy of distribution systems, and the properties of individual drugs, including their costs, performance characteristics, and side effects. The capacity of antivirals to reduce mortality is yet another area of uncertainty that hinders rational preparedness planning. All of these issues were considered by the working group on the use and availability of antivirals.

An important role constrained by limited supplies

The working group benefited from participation by drug manufacturers and by clinicians from Thailand and Viet Nam with experience in the management of human cases of H5N1 infection. Results from mathematical modelling were used to assess the likely burden of a pandemic in terms of mortality, severe illness resulting in

hospitalization, and health-seeking behaviour, which would also be a burden on services. This information was considered useful in both forecasting the quantities of antivirals needed to meet specific objectives and balancing costs against likely benefits.

One conclusion of the group was straightforward: supplies of antivirals are presently extremely limited and could not be augmented during the course of a pandemic. The production of antivirals is a multistage process necessitating a lead time of one year. Production capacity is driven by the inter-pandemic demand for antivirals, which – like the priority given to influenza – is low in most countries. Manufacturers estimate that five years would be needed to increase supplies to an adequate level. Although bulk ingredients can be produced within a month and are less expensive, this option was noted to raise significant regulatory, legal, and logistic challenges. As production capacity cannot be increased, stockpiling in advance becomes the only option for ensuring adequate supplies during a pandemic. Advance orders are understandably the preferred option for manufacturers. For all these reasons, the group recommended that governments consider the stockpiling of antivirals as a precautionary measure.

In general, the group felt that prophylaxis is more likely to prevent serious complications than treatment, as it prevents disease from occurring in the first place. However, the use of antivirals for prophylactic purposes would require a prohibitively large stockpile. The group concluded that early treatment is a more efficient use of resources than prophylaxis. The group further recommended that, where available, the neuraminidase inhibitors should be the preferred drugs for treatment. If the M2 inhibitors must be used for treatment, this should be done with a full awareness of their side effects and propensity to develop resistance.

Use at different phases

With these considerations in mind, the group looked at the role of antivirals and indicators for their use during the different phases of a pre-pandemic situation and after a pandemic has been declared. In a key innovation, the group recommended that the establishment of an international stockpile of antivirals be considered for use at distinct phases and for specific objectives in the pre-pandemic period. Antivirals are expected to be effective for the treatment of human illness caused by avian influenza.

No human-to-human transmission. At the phase when no human-to-human transmission has been documented, a stockpile would allow a rapid response aimed at preventing human infections. At this phase, antivirals would be used for the prophylaxis of persons, such as poultry cullers, at high risk of exposure, the protection of teams investigating the outbreak, and the early treatment of symptomatic persons. Prophylaxis of groups at high risk should be combined with administration of vaccine protective against circulating strains of influenza virus to reduce the risk of reassortment following human co-infection with avian and human viruses.

Limited human-to-human transmission. At the next phase, when limited human-to-human transmission has been confirmed, the use of antivirals would be driven by a focus on clusters of cases with the objective of reducing further human cases and thus preventing or at least delaying further spread. Should these clusters be caused by a virus that has not yet established efficient human-to-human transmission, targeted and

aggressive use of antivirals might also limit opportunities for the virus to improve its transmissibility through adaptive mutation during continuing chains of transmission. Antivirals would be used for the early treatment of suspected cases, prophylaxis of contacts, including health care workers, and may be considered for intense (“saturation”) prophylaxis around a limited number of small, well-defined clusters.

In both phases, however, the group cautioned against the raising of unrealistic expectations, as no one knows whether the spread of a pandemic can be prevented or delayed. Attempts to do so rely on two main assumptions: that the drugs will be effective against an emerging pandemic virus (which is considered likely), and that surveillance systems in the affected country are sufficiently strong to detect the earliest cases and clusters, identify contacts, and deliver drugs during a very short incubation period.

Pandemic declared. The objectives for antiviral use would shift dramatically following the declaration of a pandemic. One conclusion was clear: an international stockpile could not be used to meet the needs of individual countries once the virus has established efficient transmission and a pandemic has been declared. In addition, contact tracing and management, considered important for antiviral use at earlier stages, would no longer be feasible once a pandemic is fully under way. Prioritized national distribution, supported by public education, would be the likely strategy with two objectives: to reduce morbidity and mortality in patients and to buy time for the augmentation of vaccine stocks and limiting spread in the initial months of a pandemic. Some degree of social disruption in countries might be initially mitigated by prioritizing distribution to protect essential services. Priority groups would need to be defined by national authorities, but might include health workers and first responders and workers providing essential municipal services. Advice on factors to consider when making these decisions is contained in *WHO Guidelines on the Use of Vaccines and Antivirals during Influenza Pandemics*. For treatment, priority might go to patients considered at high risk of severe disease. For this purpose, clinical predictors of serious outcomes would be needed to better target the use of limited supplies.

Improving availability

On the issue of antiviral availability, the group reached several stark conclusions: global supplies at the start of a pandemic will be extremely limited; most countries will have no access to antivirals throughout the course of a pandemic; stockpiling of drugs in advance is the only strategy for ensuring sufficient supplies. Participants agreed that conditions of access would be best in countries that have manufacturing capacity, regularly purchase antivirals for seasonal use, or have stockpiled drugs in advance. The group saw little hope that antivirals would be available in developing countries, where the pandemic response would have to rely on public health measures until vaccines became available. Increased use of antivirals during the inter-pandemic years, based on better understanding of the medical and economic burden of annual influenza epidemics, was seen as the main way to improve production capacity. Moreover, given the unpredictable nature of influenza pandemics, participants recognized the difficulty of persuading countries facing other immediate and urgent health problems to invest in drugs for a potential future emergency, however great its projected impact might be.

The group gave particular attention to the ethical dilemmas regarding fair access and rationing of limited and finite supplies. Participants agreed that a solution to this problem will be hard to find; much work needs to be done on the part of WHO, national authorities, donor agencies, and manufacturers. Another problem was the present absence of agreement on national and international priorities and use strategies for finite supplies. It was not considered realistic to ask countries that have invested in their own protective stockpile to share it with others once a pandemic is fully under way.

Other options explored ranged from a radical change in the production infrastructure, possibly involving purchase of the manufacturing license and production by another manufacturer, to questions of whether a shorter course, reduced dose, and later treatment might alter patterns of virus shedding and thus have an impact on transmission. Monitoring for the emergence of drug resistance was considered important, as was the theoretical possibility that wide-scale use of antivirals might exert selective pressure on the virus, resulting in its modification. The group also cited the need for operational research to better determine the logistics of wide-scale administration of antivirals. Possibilities opened by the rapid production and lower price of bulk ingredients should be explored together with national regulatory authorities and manufacturers.

Finally, participants stressed the need to help policy-makers better understand the benefits of antivirals, when used as an adjunct to vaccination, during seasonal influenza epidemics, and their limitations as well as benefits during a future pandemic. The group equally stressed the need to guard against public perceptions that antivirals are a panacea for protecting populations during a pandemic. Vaccines are unquestionably the most important tool for doing so. Pending their availability, antivirals would have an important, but limited role to play.

Recommendations and conclusions

1. Antivirals are expected to be effective against human illness caused by avian influenza and human pandemic strains. Pending the availability of vaccines, they will be the only influenza-specific medical intervention for use in a pandemic.
2. Inadequate supplies are a major constraint. Supplies are presently extremely limited and manufacturing capacity could not be augmented during the course of a pandemic. At current capacity, several years would be needed to increase supplies appreciably.
3. Most countries will have no access to antivirals throughout the course of a pandemic and will need to rely on public health measures and supportive care until vaccines become available.
4. Conditions of access will be best in countries that have manufacturing capacity, regularly purchase antivirals for seasonal use, or have stockpiled drugs in advance.
5. Stockpiling of drugs in advance is currently the only way to ensure sufficient supplies at the start of a pandemic. Governments with adequate resources should consider pursuing this option as a precautionary measure.

6. Establishment of an international stockpile of antivirals should be considered for use for specific objectives in the pre-pandemic period, when opportunities for averting a pandemic or delaying its further spread are likely to be greatest. An international stockpile could not be used to meet the needs of individual countries once a pandemic is fully under way.
7. Increased use of antivirals during the inter-pandemic years, based on better understanding of the medical and economic burden of annual influenza epidemics, is one strategy for augmenting production capacity.
8. Price is the second major constraint. Current costs for widespread use of even the shortest duration of treatment place these drugs outside health budgets in the vast majority of countries.
9. Additional obstacles to wide-scale use include side effects of certain agents (especially amantadine), the risk of drug resistance, and limited safety data in key sub-populations.
10. Early treatment is a more efficient use of resources than prophylaxis, which requires a prohibitively large stockpile.
11. Where available, the neuraminidase inhibitors are the preferred drugs for treatment. If the M2 inhibitors must be used for treatment, this should be done with a full awareness of their side effects and propensity to develop resistance.
12. Scarce supplies of an emergency intervention create ethical dilemmas of priority access both within and among countries. Ethical dilemmas regarding fair access and rationing of finite supplies will be difficult to resolve but must be addressed.

WORKING GROUP FOUR: Better vaccines – better access

Background

Vaccines are the single most important intervention for preventing influenza-associated morbidity and mortality during both seasonal epidemics and pandemics. Manufacturers, supported by laboratories in the WHO Global Influenza Surveillance Network, have considerable experience in the production of annual vaccines to match each season's circulating strains. Global manufacturing capacity for influenza vaccines is finite and currently estimated at 260 million doses of trivalent vaccine per year. More than 90% of this production capacity is concentrated in countries accounting for only 10% of the world's population.

An influenza pandemic is one of the few disease events in which all populations will be fully susceptible to infection. A mass vaccination strategy is therefore required, and all countries will need rapid access to large supplies of pandemic vaccine. This need will not be met: current manufacturing capacity is sufficient to cover less than 5% of the world's population. The demand for vaccines will be sudden, and distribution is certain to be unequal, as the few countries with manufacturing capacity can be expected to reserve supplies for their own populations.

No country will have adequate supplies at the start of a pandemic. The production of a vaccine for a pandemic virus is a unique process that requires emergency procedures for its development, licensing, production, and delivery. Stockpiling of vaccine in preparation for a pandemic is not an option, as vaccine composition needs to match the unique genetic and antigenic characteristics of the new virus. Production must therefore await the emergence and characterization of the virus. After a new pandemic virus has been isolated, at least 4 to 6 months will be needed to produce the first doses of vaccine. The subsequent augmentation of supplies will be progressive.

A common characteristic of pandemics is the occurrence of successive waves of infection. Although global vaccine supplies will almost certainly remain inadequate throughout the first wave of infection, their availability for subsequent waves should be greatly beneficial.

Obstacles to development, production and licensing

Industry has little incentive to build additional manufacturing capacity, which requires very large long-term investments for an event that occurs only rarely and unpredictably. An estimated 3 to 5 years would be needed to develop and validate a new production line. The rapid and large-scale manufacturing of pandemic vaccines faces several

barriers in addition to limited facilities. Rapid production requires access to patented technologies, such as reverse genetics for strain development and adjuvants for improved immunogenicity. Although patent issues are manageable for the larger vaccine companies, other manufacturers may have difficulty securing access to these technologies.

Another constraint is the required production of pandemic vaccines in facilities with a high level of biosafety. Only a few facilities are presently equipped to meet the enhanced biosafety level 2 conditions needed for safe manufacturing of pandemic vaccines, as recommended by WHO (*Production of pilot lots of inactivated influenza vaccine from reassortants derived from avian influenza viruses*).

If the reverse genetics technology is used, the pandemic strain would be classified under European Union regulations as a genetically modified organism, meaning that, in some important manufacturing countries, biosafety level 3 facilities would be required for vaccine production. To initiate large-scale production of a pandemic vaccine, industry will need support to implement a production environment at the required biosafety level. A less costly alternative would be the revision of legislation to provide for the exemption of pandemic vaccine production using reverse genetics technology from constraints pertaining to work with genetically modified organisms.

Several technical options could be used to increase capacity. A pandemic vaccine will most likely be a monovalent vaccine as opposed to the trivalent vaccines currently used in seasonal epidemics, thus increasing annual production capacity from 260 million doses to an estimated 750 million doses. Other options for increasing capacity include decreasing the antigen quantity per dose and using adjuvants to improve immunogenicity. If a monovalent adjuvanted vaccine is produced, annual production capacity could rise to an estimated 6 billion doses. However, two doses of vaccine may be needed to confer adequate protection in fully susceptible populations. If the vaccine is produced in the traditional way, using embryonated eggs instead of cell-culture, advance efforts to secure an adequate egg supply could avoid delays in production.

Some work on the development of a pandemic vaccine can be done in a pre-pandemic situation. However, given the unpredictability of pandemics, industry needs a strong incentive to invest in a product that may never be needed. For example, work currently under way to define the profile of an H5N1 pandemic vaccine incurs high production costs to produce small clinical batches that may never see a commercial return.

Obstacles to effective and equitable delivery

Questions of equitable delivery within and between countries are not easily resolved as the demand for pandemic vaccines will be sudden and supplies will become available only progressively. Furthermore, as manufacturing capacity is concentrated in Europe and North America, and producing countries can be expected to reserve scarce supplies for their own populations, non-producing countries are likely to face the most acute shortages.

Manufacturing capacity is driven by the demand for vaccines during the inter-pandemic years. Increased demand for seasonal vaccines would increase capacity to manufacture

pandemic vaccines. Increased vaccine use during the inter-pandemic years also gives countries experience in the logistics of vaccine administration. Participants agreed, however, that limited resources and competing health priorities will preclude any investment in influenza immunization programmes in some countries.

Many countries have considerable experience with mass immunization programmes for childhood diseases and during emergency situations, such as those caused by outbreaks of yellow fever and epidemic meningitis. The implementation of mass immunization strategies during a pandemic could draw on existing infrastructures and experiences and should not be an impediment to effective and equitable vaccine delivery.

Strategies and priority actions: expand and expedite production

A global approach to the sharing of intellectual property rights should be adopted to encourage vaccine production by more manufacturers, including those located in developing countries. Such an approach could extend access to important production technologies, notably reverse genetics and the use of adjuvants. The need for uniform biosafety requirements – another urgent concern during the emergency of a pandemic – should be addressed by WHO. International coordination of clinical trials of candidate vaccines could accelerate the availability of a pandemic vaccine, when needed. Clinical trials, though essential, are expensive and may require support from the international community.

WHO should convene a technical meeting of influenza vaccine manufacturers to define existing pandemic vaccine capacity, identify specific impediments to improved capacity, and work out short- and long-term technical solutions. Possible short-term solutions include the development of vaccines using a lower antigen content and the use of adjuvants to improve immunogenicity. The outsourcing of certain production steps, such as filling and packaging, could be another option. Such outsourcing should preferably involve countries that do not have national vaccine manufacturing capacity. Outsourcing can be expected to reduce vaccine prices, possibly stimulating the demand for seasonal vaccines in developing countries. The group regarded technology exchange between industrialized and developing countries, supported by manufacturers, as another important option, and recommended that vaccine manufacturers in developing countries participate in the influenza vaccine supply task force of the International Federation of Pharmaceutical Manufacturers Associations.

Several other potential obstacles to vaccine availability can also be addressed in advance. For example, national authorities can address liability issues likely to arise with mass immunization using a new pandemic vaccine with an unknown profile of side effects. National authorities can also develop fast track procedures for licensing and testing of pandemic vaccines and new delivery formats, such as multidose vials.

Long-term solutions include the production of vaccines using cell-culture technology and the expansion of capacity based on more extensive vaccine use during the inter-pandemic years. Another strategy is the advance preparation of pilot lots of vaccine against virus subtypes considered likely to develop pandemic potential, such as the H5, H7, H9 and H2 subtypes. For example, H5, H7, and H9 subtypes are all known to have crossed the species barrier from birds to humans in recent years. WHO should explore

the advisability of establishing a limited stockpile of vaccines for these candidate viruses for the exclusive purpose of preventing an emerging pandemic virus from establishing efficient human-to-human transmission or at least delaying its further spread. In these and other activities, manufacturers would need financial or other incentives to support investments that might not bring a commercial return.

A particularly effective long-term solution would be to develop vaccines that protect against several candidate pandemic viruses, as such vaccines could be produced and, depending on their shelf-life, probably stockpiled in advance. If the vaccine also induces long-lasting immunity, this would open a unique opportunity for preventive vaccination against a future pandemic during the inter-pandemic years rather than during the chaos of a pandemic. Participants urged public funding agencies to support research on cross-subtype, long-lasting vaccines.

Strategies and priority actions: increase equitable access

Equitable access will not be possible so long as global manufacturing capacity remains inadequate. Improved vaccine use during the inter-pandemic years is one way to increase capacity. This is, however, a long-term strategy that depends on the higher positioning of influenza among the many other infectious diseases that compete for attention and funds. In May 2003, the World Health Assembly agreed on vaccination coverage targets for those countries with influenza vaccination policies already in place. Countries without such policies were urged to assess the disease burden and economic impact of seasonal epidemics as a basis for framing policies in the context of other national health priorities.¹ Reports to WHO on progress in reaching these objectives would be welcome.

During a pandemic, vaccines become a precious commodity, and countries should anticipate a sudden demand for limited supplies. As a preparedness measure, all countries should define in advance the groups that should be protected first, using the existing *WHO Guidelines on the use of vaccines and antivirals during influenza pandemics*, while also considering the need to protect supplies by guarding against hoarding and the growth of a black market. As supplies increase, the strategy of targeted vaccination is replaced by mass vaccination. Preparedness for mass vaccination includes plans for the expansion and training of staff, logistics, communications, vaccination safety, and the monitoring of adverse reactions. WHO can assist by preparing protocols for safety monitoring and guidelines for mass vaccination based on considerable experience with other diseases under both routine and emergency conditions.

Regional production strategies should be explored as an option for increasing vaccine use during the inter-pandemic years. One example of a regional purchasing scheme is a revolving fund maintained by PAHO for bulk purchasing of influenza vaccines, with local filling, for some Latin American countries. The wider use of such schemes could make prices more affordable for developing countries and possibly increase vaccine use. The many countries that do not have national manufacturing capacity should also consider bilateral and multilateral arrangements with countries that do have this capacity. However, while countries are urged not to nationalize manufacturing capacity during a pandemic, governments are likely to face great pressure to do so.

Recommendations and conclusions

1. Vaccines are the single most important intervention for preventing influenza-associated morbidity and mortality during both seasonal epidemics and pandemics.
2. No country will have adequate supplies of vaccine at the start of a pandemic. At least 4 to 6 months will be needed to produce the first doses of vaccine following isolation of a new pandemic virus. The subsequent augmentation of supplies will be progressive. Stockpiling in advance is not an option.
3. Global manufacturing capacity, which is driven by vaccine demand during the inter-pandemic years, is finite and inadequate. More than 90% of current production capacity is concentrated in countries in Europe and North America accounting for less than 10% of the world's population.
4. Equitable access will not be possible so long as global manufacturing capacity remains inadequate. Countries without manufacturing capacity will face the most acute vaccine shortages, as countries with manufacturing capacity can be expected to reserve scarce supplies for their own populations.
5. The production of a vaccine for a pandemic virus is a unique process that requires emergency procedures for its development, licensing, production, and delivery.
6. Important constraints to rapid and large-scale production of a pandemic vaccine include intellectual property rights, biosafety requirements for production facilities, and coordination and funding of clinical trials. A global effort to address these constraints is an efficient approach
7. Country-specific issues to be addressed by national authorities include procedures for licensing and testing and liability issues surrounding mass use of a new vaccine with an unknown safety profile.
8. Short-term solutions for augmenting supplies include the development of vaccines using a lower antigen content, use of adjuvants to improve immunogenicity, and outsourcing of certain production steps. Another strategy involves advance preparation of pilot lots of vaccine against virus subtypes with pandemic potential. To pursue this strategy, manufacturers may need financial or other incentives to support investments in a product that might never be used.
9. Public funding should give priority to research on cross-subtype vaccines conferring long-lasting protection. Development of vaccines protective against several candidate pandemic viruses is a particularly effective long-term solution, as it opens possibilities for stockpiling. If the vaccine confers long-lasting immunity, preventive vaccination for a future pandemic will be possible as a major step forward.
10. Increased vaccine use during the inter-pandemic years will increase production capacity, but depends upon the burden of influenza within individual countries compared with other health priorities. Regional production strategies and

purchasing schemes should be explored as a strategy for increasing vaccine use during the inter-pandemic years.

11. All countries should decide in advance on priority groups for vaccination when supplies are limited and develop strategies for expanding coverage when supplies increase.
12. Vaccine manufacturers in developing countries should participate in the influenza vaccine supply task force of the International Federation of Pharmaceutical Manufacturer

¹Prevention and control of influenza pandemics and annual epidemics. World Health Assembly Resolution [WHA56.19](#). Geneva: World Health Organization, 2003

ANNEX ONE: Phases in the progression towards a pandemic as a guide to levels of alert and preparedness

Phase 0.0

(inter-pandemic phase, preparedness level 0)

No indications of a new influenza virus subtype are reported.

Phase 0.1

(inter-pandemic phase, preparedness level 1)

A novel virus subtype is isolated from a single human case.

No evidence of further spread or outbreak activity.

Phase 0.2

(inter-pandemic phase, preparedness level 2)

Two or more human infections with the novel virus subtype are confirmed.

No evidence of human-to-human transmission.

Phase 0.3

(inter-pandemic phase, preparedness level 3)

Human-to-human transmission is confirmed.

Phase 1

(onset of pandemic)

Substantial transmission is confirmed.

The new virus subtype causes several outbreaks in at least one country, shows international spread, and causes serious morbidity and mortality in at least one segment of the population.

Note: The phases are described in more detail in the WHO *Influenza Pandemic Preparedness Plan*. The plan, developed in 1999, spells out some of the roles of WHO and national authorities. Parts of the document are now being revised to take account of recent events with pandemic potential and the recommendations and conclusions of the March 2004 consultation.

ANNEX TWO: Recent WHO documents on influenza and pandemic preparedness

- Avian influenza fact sheet
http://www.who.int/mediacentre/factsheets/avian_influenza/en/
- Global agenda for influenza surveillance and control
<http://www.who.int/csr/disease/influenza/globalagenda/en/>
- Influenza pandemic preparedness plan. The role of WHO and guidelines for national or regional planning. Geneva, Switzerland, April 1999 (under revision)
http://www.who.int/csr/resources/publications/influenza/WHO_CDS_CSR_EDC_99_1/en/
- Production of pilot lots of inactivated influenza vaccines from reassortants derived from avian influenza viruses. Interim biosafety risk assessment
http://www.who.int/csr/resources/publications/influenza/WHO_CDS_CSR_RMD_2003_5/en/
- WHO guidelines for global surveillance of influenza A/H5
http://www.who.int/csr/disease/avian_influenza/guidelines/globalsurveillance/en/
- WHO guidelines on the use of vaccines and antivirals during influenza pandemics
http://www.who.int/csr/resources/publications/influenza/WHO_CDS_CSR_RMD_2004_8/en/

ANNEX THREE: Agenda

Plenary morning session

Tuesday 16 March

| | | |
|----------------------|---|--------------------------------|
| 08:30 – 09:00 | Registration | |
| 09:00 – 09:15 | Welcome address | Dr A. Asamoah-Baah, ADG/CDS |
| 09:15 – 09:20 | Election of Chairpersons | |
| 09:20 – 09:30 | Introduction of Objectives and Programme | Dr M. Esveld, WHO/HQ |
| 09:30 – 10:00 | Global response to the current avian flu outbreak in Asia | Dr H. Oshitani, WHO/WPRO |
| 10:00 – 10:30 | Influenza Pandemics: challenges and issues | Dr K. Stöhr, WHO/HQ |
| 10:30 – 11:00 | COFFEE BREAK | |
| 11:00 – 11:30 | Development and use of influenza vaccine: issues and challenges | Dr A. Monto, USA |
| 11:30 – 12:00 | Role of antivirals in an influenza pandemic | Professor K. Nicholson, UK |
| 12:00 – 12:30 | Public health interventions for an influenza pandemic | Dr P. Horby, WHO Viet Nam |
| 12:30 – 12:45 | Introduction of working groups | |
| 12:45 – 14:00 | LUNCH BREAK (Group chairs and rapporteurs to meet) | |

Working group 1: Surveillance for pandemic preparedness

Dr R. Andraghetti, Dr T. Azad, Dr A. Bosman, Dr A. Chaieb, Mr R. Dietz, Dr A. Ellis, Professor N. Ferguson, Dr N. Gay, Dr T. Grein, Dr W. Hanshaoworakul, Dr H. Hollmeyer, Dr C. Ihekweazu, Dr K. Jebara, Dr Z. Jing, Dr T. Kiedrzyński, (Rapporteur), Dr S. Krishnan, Dr S. Lazzari, Dr W. Lim, Dr D. Levy-Bruhl, Professor H. Thuy Long, Dr J. Macey, Mr M. Malimbo, Dr A. Merianos, Dr F. Meslin, Dr A. Moen, Professor A. Plant, (Chair) Dr C. Roces, Dr Y. Soares, Dr I. Sow, Dr N. Teleb, Dr O. Uez, Dr M. Valenciano, Mr T. Waddell, Dr J. Watson, Dr D. Werker, Dr W. Zhang

| | | |
|----------------------|---|------------------------|
| 14:00 – 14:10 | Registration Introduction – goals of the group – selection of Chair and Rapporteur | |
| 14:15 – 14:30 | Welcome ad Experience of countries affected by avian influenza A (H5N1) – Thailand | Dr W Hanshaoworakul |
| 14:30 – 14:45 | Experience of countries affected by avian influenza A (H5N1) – Viet Nam | Professor H. Thuy Long |
| 14:45 – 15:00 | Experience of countries affected by avian influenza A (H7N7) – the Netherlands | Dr A. Bosman |
| 15:00 – 15:25 | Implementation of WHO Guidelines for Global Surveillance of Influenza A/H5 – national, regional and global issues | Dr C. Roces |
| 15:25 – 15:45 | Animal influenza surveillance | Dr K. B. Jebara |
| 15:45 – 16:00 | TEA BREAK | |
| 16:00 – 16:20 | Mathematical modelling of early influenza transmission: transition from pre-pandemic to pandemic phase | Dr N. Gay |
| 16:20 – 16:35 | Country perspective on epidemic influenza surveillance systems and plans for the pandemic – Canada | Dr J.Macey |
| 16:35 – 16:50 | Country perspective on epidemic influenza surveillance systems and plans for the pandemic – Uganda | Mr M. Malimbo |
| 16:50 – 17:05 | Country perspective on epidemic influenza surveillance systems and plans for the pandemic – India | Dr S. K. Krishnan |
| 17:05 – 17:20 | Influenza surveillance systems adaptability to a pandemic at national, regional and global levels | Dr C. Ihekweazu |
| 17:20 – 18:00 | Discussion | |

Working group 2: Public health interventions

Dr J. Beigel, Dr D. Bell, Dr I. Bonmarin, Dr M. Cetron, Ms M. Cheng, Ms P. Creese, Mr K. Dobby, Dr J. Eiros, Dr M. Etchegorry, Mr D. Gamper, Dr B. Ganter, Dr N. Gay, Professor L. Gostin, Dr C. Gonzales, Dr P. Guglielmetti, Dr M. Hardiman, Dr P. Horby, Prof J. Horvath, Dr R. Ichhpujani, Ms M. Kindhauser, Dr R. Lam, Dr M. Lixin, Dr M. Machala, Professor Angus Nicoll, (Chair) Professor P. Ndumbe, Dr N. Okabe, Ms C. Poncé, Dr P. Prempre, Dr G. Rodier, Dr C. Roth, Mr D. Rutz, (Rapporteur) Dr R. St. John, Dr K. Vandemaele, Dr L. Zhengmao

| | | |
|----------------------|--|------------|
| 14:00 – 14:15 | Introduction – goals of the group – selection of Chair and Rapporteur | |
| 14:15 – 14:45 | Mathematical modelling of early influenza transmission, including considerations regarding further subdivision of pandemic phase 0, preparedness level 3 | Dr N. Gay |
| 14:45 – 15:15 | Effectiveness of public health interventions during the SARS epidemic of 2003 | Dr D. Bell |

Practical aspects of implementing possible interventions

| | | |
|----------------------|---|----------------|
| 15:15 – 16:00 | Local and national measures: <ul style="list-style-type: none">• Public awareness• Management of cases and contacts• Measures to increase social distance• Travel restrictions | Dr R. Lam |
| 16:00 – 16:15 | TEA BREAK | |
| 16:15 – 16:45 | Local and national measures continued Role of antivirals as adjunct measures | Dr I. Bonmarin |
| 16:45 – 17:15 | Measures regarding conveyances (e.g., aircraft) | Mr K. Dobby |
| 17:15 – 18:00 | International measures: <ul style="list-style-type: none">• Information for travellers• Measures at borders | Dr N. Okabe |
| 18:00 | Adjourn | |

Working group 3: Antivirals – their use and availability

Dr M. Al-Jeffri, (Chair), Dr J. Beigel, Dr P. Brown, Ms E. Chatigny, Dr T. Chotpitayasunondh, professor C. Ciufecu, Dr P. v. Dalen, Ms G. v. Dijk, Dr M. Everard, Ms E. Fitzpatrick, Dr K. Fukuda, Dr T. Hien, Dr K. Jalava, Mr H. Khenniche, Dr S. Lambert, Dr K. Leitmeyer, Mr T. Leuenberger, Professor P. Littlejohns, Dr E. Luna, Dr S. Mardel, Dr H. Matter, Dr M. Meltzer, Dr K. Nakajima, Professor K. Nicholson, Dr M. Ossi, Professor S. Park, Dr N. Shindo, Dr R. Snacken, Dr T. Tam, (Rapporteur) Professor S. Tswana, Dr E. Wilkins, Professor X. Xiaoyuan

| | | |
|----------------------|--|---------------|
| 14:00 – 14:10 | Introduction – goals of the group – selection of Chair and Rapporteur | |
| 14:10 – 14:30 | Overview of the use of influenza antivirals during pandemics (WHO Guidelines) | Dr T. Tam |
| 14:30 – 14:45 | Clinical profile of pandemic influenza | |
| 14:45 - 15:25 | Antiviral production – Representatives from pharmaceutical companies: <ul style="list-style-type: none">• Capacities and possibilities during the different phases of a pandemic• Factors which influence production capacities and possibilities• Models of antiviral production• Hurdles to timely and equitable access to influenza antivirals | |
| 15:25 – 15:50 | Questions and discussion on production capacity | |
| 15:50 – 16:20 | TEA BREAK | |
| 16:20 – 16:40 | Distribution of antiviral drugs during an influenza pandemic: <ul style="list-style-type: none">• Antiviral distribution scenarios• Antiviral demand models | Dr M. Meltzer |
| 16:40 – 17:00 | Accessibility of antivirals <ul style="list-style-type: none">• Access in countries with/without production• Factors that will influence access | Dr M. Everard |
| 17:00 – 17:15 | Summary from the GHSAG Technical Working Group on Pandemic Influenza | Dr J. Leese |
| 17:15 – 18:00 | Discussion and summary – Chair | |

Working group 4: Better vaccines – better access

Dr S. Chunsuttiwat, (Chair), Dr T. Colegate, Dr T. Digneffe, Dr M. Esveld, Dr D. Fedson, Dr D. O’Flanagan, Dr B. Gellin, Dr C. Gerdil-Lacroix, Dr I. Gust, Dr N. Hanh, Dr J. Hendriks, Dr L. Hessel, B. Hersh, Dr L. Jennings, Dr L. Kant, Dr A. King, (Rapporteur) Dr Y. Kino, Dr S. Lambert, Mr C. Maher, Dr O. Oliva, Dr M. Orkhan, Dr A. Palache, Dr Pervikov, Dr C. Rota, Dr L. Schaade, Mr J. Sigurdson, Dr K. Stöhr, Dr S. Tamblyn, Dr M. Tashiro, Mr D. Thompson, Professor H. Yin, Dr K. Young-taek, Dr G. Yuangi

| | | |
|----------------------|--|----------------|
| 14:00 – 14:10 | Introduction – goals of the group – selection of Chair and Rapporteur | |
| 14:10 – 14:30 | Overview on options for the use of influenza vaccines during pandemics (WHO Guidelines) | Dr L. Jennings |
| | Vaccine production capacities and possibilities | |
| 14:30 – 15:00 | Challenges in pandemic vaccine development – WHO secretariat | |
| 15:00 – 15:30 | Current realities for vaccine production during various phases of pandemic | Dr L. Hessel |
| 15:30 – 16:00 | TEA BREAK | |
| 16:00 – 16:30 | Factors which influence production capacities and possibilities | Dr D. Fedson |
| 16:30 – 17:30 | Discussion on vaccine development and production capacity (based on questions provided by the WHO secretariat) | |

Wednesday 17 March

Working group 1: Surveillance for pandemic preparedness

| | | |
|----------------------|--|------------|
| 08:30 – 08:45 | Briefing session | Rapporteur |
| 08:45 – 09:00 | Setting the tasks for the session | Chair |
| 09:00 – 10:00 | Group Work | |
| 10:30 – 12:30 | Group Work | |
| 12:30 – 14:00 | LUNCH BREAK (Group chairs and rapporteurs to meet) | |
| 14:00 – 15:30 | Group Work | |
| 15:30 – 16:00 | TEA BREAK | |
| 16:00 – 18:00 | Review and harmonization of group report | |

Working group 2: Public health interventions

| | | |
|----------------------|---|---------------------|
| 08:30 – 09:00 | International Health Regulations Issues | Dr M. Hardiman |
| 09:00 – 09:30 | Issues for national legal systems | Professor L. Gostin |
| 09:30 – 10:00 | Divide into two sub-groups: (1) Local and national measures and (2) International measures to discuss measures to be considered | |
| 10:00 – 10:30 | COFFEE BREAK | |
| 10:30 – 12:30 | Sub-group discussions continued | |
| 12:30 – 14:00 | LUNCH BREAK (Group chairs and rapporteurs to meet) | |
| 14:00 – 15:30 | Sub-group discussions continued | |
| 15:30 – 16:00 | TEA BREAK | |
| 16:00 – 17:00 | Presentation of sub-group reports | |
| 17:00 – 18:00 | Review and harmonization of sub-group reports | |

Working group 3: Antivirals their use and availability

| | | |
|----------------------|---|----------------------|
| 09:00 – 09:30 | Feedback from Rapporteur — identifying of the gaps | |
| 09:30 – 10:00 | Use of antiviral during a pandemic — possible scenario and mathematical modelling | Dr Y. Ohkusa |
| 10:00 – 10:30 | COFFEE BREAK | |
| 11:00 – 12:30 | Continuation of above discussion | |
| 12:30 – 14:00 | LUNCH BREAK (Group chairs and rapporteurs to meet) | |
| 14:00 – 14:30 | Summary of morning discussion | Rapporteur |
| 14:30 – 15:30 | Discussion — Exploring the contribution of various partners and stakeholders in improving timely and equitable access to influenza antivirals | |
| 15:30 – 16:00 | TEA BREAK | |
| 16:00 – 17:00 | Continuation of above discussion | |
| 17:30 – 18:00 | Summary and proposals for plenary feedback | Chair and Rapporteur |

Working group 4: Better vaccines - better access

Beyond technical solution

| | | |
|----------------------|---|--------------------------|
| 09:00 – 09:15 | Access to influenza vaccines — perspective of country with production facilities | Dr C. Rota (Italy) |
| 09:15 – 09:30 | Access to influenza vaccines — perspective of country without production facilities | Dr K. Young-taek (Korea) |
| 09:30 – 10:00 | Factors that will influence access | Dr S. Tamblyn |
| 10:00 – 10:30 | Discussion on factors that will influence access | |
| 10:30 – 11:00 | COFFEE BREAK | |

Learning from experience

| | | |
|----------------------|--|-----------------|
| 11:00 – 11:30 | Management of emergency vaccine campaigns | WHO secretariat |
| | Exchange of experience regarding access to vaccine | |
| 12:30 – 14:00 | LUNCH BREAK (Group chairs and rapporteurs to meet) | |

Action points, roles and responsibilities

| | | |
|----------------------|--|----------------------|
| 14:00 – 14:30 | Summary on identified hurdles and possibilities | Chair and Rapporteur |
| 14:30 – 15:30 | Discussion on priority actions by various stakeholders to increase production capacities and access | |
| 15:30 – 16:00 | TEA BREAK | |
| 16:00 – 17:30 | Discussion on roles and responsibilities (including WHO, national authorities, NGOs, and pharmaceutical companies) | |
| 17:30 – 18:00 | Summary and proposals for plenary feedback | Chair and Rapporteur |

Plenary morning session

Thursday 18 March

| | | |
|----------------------|--|--|
| | Address by the Director-General | Dr Jong-wook LEE |
| 09:00 – 09:15 | Report of Working Group 1 (Surveillance) | Rapporteur of Working Group 1 (Dr T. Kiedrzyński) |
| 09:15 – 09:45 | Discussion | |
| 09:45 – 10:00 | Report of Working Group 2 (Public health measures) | Rapporteur of Working Group 2 (Dr D. Rutz) |
| 10:00 – 10:30 | Discussion | |
| 10:30 – 10:45 | Report of Working Group 3 (Antivirals) | Rapporteur of Working Group 3 (Dr T. Tam) |
| 10:45 – 11:15 | Discussion | |
| 11:15 – 11:45 | COFFEE BREAK | |
| 11:45 – 12:00 | Report of Working Group 4 (Vaccines) | Rapporteur of Working Group 4 (Dr A. King) |
| 12:00 – 12:30 | Discussion | |
| 12:30 – 12:50 | Summary presentation of final conclusions | Chairperson (Dr I. Gust) |
| 12:50 – 13:00 | Closing | Dr A. Asamoah-Baah, ADG/CDS |

ANNEX FOUR: List of participants

Dr M. H. Al-Jeffri, Infectious and Parasitic Diseases, Ministry of Health, Airport Road, Riyadh 11176, Saudi Arabia

Dr T. M. Azad, Teheran University, 16 Street, Enghelab Ave., Teheran, Islamic Republic of Iran

Dr J. Beigel, National Institutes of Health, Bldg 10 Rm 7043, 10 Center Dr, Bethesda, MD 20892, USA

Dr I. Bonmarin, Département Maladies Infectieuses, Institut de Veille Sanitaire, 12 rue du Val d'Osne, 94415 Saint-Maurice, France

Dr A. Bosman, Department of Infectious Diseases Epidemiology, National Institute of Public Health and the Environment (RIVM), PO Box 1, 3720 BA Bilthoven, The Netherlands

Dr M. Cetron, Division of Global Migration and Quarantine, National Center for Infectious Diseases (E-03), Centers for Disease Control and Prevention, Atlanta, GA 30333, USA

Ms E. Chatigny, Horizontal Coordination Division, Health Canada, Tunney's Pasture, Ottawa, Ontario K1A 0K9, Canada

Dr T. Chotpitayasunondh, Queen Sirikit National Institute of Child Health, 420/8 Rajvithi Road Payathai, Bangkok 10400, Thailand

Dr S. Chunsuttiwat, Department of Disease Control, Ministry of Public Health, Tiwanond Road 11000, Nonthaburi, Thailand

Professor C. Ciufecu, Cantacuzino Institute, Splaiul Independentei 103, Sector 5, Bucharest 70100, Romania

Dr P. v. Dalen, Ministry of Health, P.O. Box 20350, 2500 EJ The Hague, The Netherlands

Mr R. K. Dietz, Communications/Media relations, 40 Southern Way, Princeton, NJ 08540, USA

Ms G. v. Dijk, Ministry of Health, P.O. Box 20350, 2500 EJ The Hague, The Netherlands

Mr K. Dobby, International Air Transport Association (IATA), 33 Route de l'Aéroport, P.O. Box 416, 1215 Geneva 15 Airport, Switzerland

Dr J. Eiros, Microbiology National Centre, Ctra Majadahonda a Pozuelo km 2, 28220 Majadahonda, Madrid, Spain

Dr M. G. Etchegorry, Chargé de mission à la Direction générale de la Santé (DGS), 8 rue de Segur, 75007 Paris, France

Dr D. Fedson, 57 Chemin du Lavoir, 01630 Sergy Haute, France

Professor N. Ferguson, Department of Infectious Disease Epidemiology, Imperial College Faculty of Medicine, St Mary's Campus, Norfolk Place, London W2 1PG, United Kingdom

Dr D. O'Flanagan, National Disease Surveillance Centre, 25 –27 Middle Gardiner Street, Dublin 1, Ireland

Dr K. Fukuda, Epidemiology Unit, Influenza Branch, Centers for Disease Control and Prevention, 1600 Clifton Road, GA 30333 Atlanta, USA

Mr D. Gamper, Airports Council International (ACI HQ), Facilitation & Technical/Safety, P.O. Box 16, CH-1215 Geneva Airport, Switzerland

Dr N. Gay, Communicable Disease Surveillance Centre, Health Protection Agency, 61 Colindale Avenue, London NW9 5EQ, United Kingdom

Dr B. Gellin, Hubert H. Humphrey Building, 200 Independence Ave, SW-Room 736E, Washington, D. C., USA

Dr C. Gonzales, Departamento de Epidemiologia, Ministerio de Salud, Mac Iver 541, Casilla:50979, Santiago, Chile

Professor L. Gostin, The John Hopkins University, 600 New Jersey Avenue, N.W. Washington, D.C. 20001-2075, USA

Dr P. Guglielmetti, Health Threats, Euro, Rue Alcide de Gasperi, L-2920 Luxembourg

Dr I. Gust, Department of Microbiology and Immunology, University of Melbourne, Parkville, Melbourne, Victoria 3010, Australia

Dr N. T. H. Hanh, National Institute of Hygiene and Epidemiology Office: No. 1, Yersin Sar, Hai Batrung Dist., Hanoi, Viet Nam

Dr W. Hanshaoworakul, Surveillance and Outbreak Response Department, Bureau of Epidemiology, Ministry of Public Health, Nonthaburi 11000, Thailand

Dr J. Hendriks, Health and Consumer Protection, European Commission, Euroforum bldg.10, rue Robert Stumper, Luxembourg L-2557

Dr T. T. Hien, Hospital for Tropical Diseases in Ho Chi Minh City, 190 Ben Ham Tu St. Dist. 5, Ho Chi Minh City, Viet Nam

Professor J. Horvath, Australian Government Dept. of Health and Ageing, 7th floor Alexander Building, Furzer St Woden ACT 2606, Canberra, Australia

Dr R. L. Ichhpujani, Division of Zoonoses, National Institute of Communicable Diseases, Directorate General of Health Services, Government of India, 22 Sham Nath Marg, 110 054 New Delhi, India

Dr K. B. Jebara, Animal Health Information Department, Office International des Epizooties, World Organization for Animal Health (OIE), 12 rue de Prony, 75017 Paris, France

Dr L. Jennings, Canterbury Health Laboratories, P.O. Box 151, Christchurch, New Zealand

Dr Z. Jing, Office of Disease Control and Emergency Response, Chinese CDC, Nanwei Road, Xuanwu District, Beijing 100050, People's Republic of China

Dr R. St. John, Centre for Emergency Preparedness and Response, Health Canada, 100 Colonnade Rd., Ottawa, Ontario K1A 0K9, Canada

Dr L. Kant, Division of Epidemiology & Communicable Diseases, Indian Council of Medical Research, Ansari Nagar, 110-029 New Delhi, India

Dr T. Kiedrzyński, Public Health Surveillance & Communicable Disease Control Section, Public Health Programme, Secretariat of the Pacific Community, B.P. D5, 98848 Noumea, New Caledonia

Dr A. King, Laboratory Centre for Disease Control, Tunney's Pasture 0603 E1, Edifice LCCM, Ottawa, Ontario K1A 0L2, Canada

Dr R. Lam, Disease Prevention & Control Division, Department of Health, 18/F Wu Chung House, 213 Queen's Road East, Wanchai, Hong Kong SAR, People's Republic of China

Dr J. Leese, Department of Health, Room 605A, 80 London Road, London SE16LH, United Kingdom

Dr K. Leitmeyer, Robert Koch-Institut, Zentrum für Infektionsepidemiologie, Seestr. 10, 13353 Berlin, Germany

Dr D. Levy-Bruhl, Institut de Veille Sanitaire, 12 rue du Val d'Osne , 94415 Saint-Maurice cedex, France

Ms. W. Lim, Government Virus Unit, 9/F Public Health Laboratory Centre, 382 Nam Cheong Street, Shek Kip Mei, Kowloon, Hong Kong, SAR , People's Republic of China

Professor A. Linde, Department of Virology, Swedish Institute for Infectious Disease Control, Department of Virology, SE 17182 Solna, Sweden

Professor P. Littlejohns, National Institute for Clinical Excellence (NICE), Midcity Place, 71 High Holborn, WC1V 6NA London, United Kingdom

Dr M. Lixin, Department of Supervision on Health Quarantine, AQSIC, No 9 Madiandonglu, Haidian District, Beijing 100088, People's Republic of China

Professor H. T. Long, National Institute of Hygiene and Epidemiology (NIHE), 1 Yersin St. Ha Noi, Viet Nam

Dr E. Luna, Department of Epidemiologic Surveillance, Ministry of Health, Esplanada dos Ministérios bloco G sala 155, Brasília DF 70.058-900, Brazil

Dr J. Macey, Respiratory Infections Section, Centre for Infectious Diseases Prevention and Control, Population and Public Health Branch, Health Canada, AL: 06023E1, Tunney's Pasture, Ottawa ON K1A 0L2, Canada

Ms M. Machala, National Influenza Centre, National Institute of Hygiene, Ul. Chocimska 24, 00-791 Warsaw, Poland

Dr M. Malimbo, Epidemiological Surveillance Division, Ministry of Health, P.O. Box 7272 Kampala, Uganda

Dr H. Matter, Division of Epidemiology and Infectious Diseases, Swiss Federal Office of Public Health, P.O. Box, Hess Strasse 27 E, 3097 Liebefeld, Switzerland

Dr M. I. Meltzer, NCID/OD/OS, Centers for Disease Control and Prevention, 1600 Clifton Road, Atlanta, GA 30333, USA

Dr A. Moen, Influenza Branch, Centers for Disease Control and Prevention (CDC), 1600 Clifton Road, Atlanta, GA 30333, USA

Dr K. Nakajima, Infectious Disease Control Division, Ministry of Health Labour and Welfare, Kasumigaseki 1-2-1 Chiyoda-ku, Tokyo 100-8916, Japan

Professor K. G. Nicholson, Leicester Royal Infirmary, Department of Infectious Disease & Tropical Medicine, Infirmary Square, Leicester LE1 5WW, United Kingdom

Professor A. Nicoll, Communicable Disease Surveillance Centre (CDSC), Public Health Protection Agency, 61 Colindale Avenue, London NW9 5EQ, United Kingdom

Professor P. M. Ndumbe, Centre for the Study and Control of Communicable Diseases (CSCCD), Faculty of Medicine and Biomedical Sciences, University of Yaoundé 1, BP 8445, Yaoundé, Cameroon

Dr Y. Ohkusa, Infectious Disease Surveillance Center, National Institute of Infectious Disease, Toyama 1-23-1 Shinjuku-ku, JP-162-8640 Tokyo, Japan

Dr N. Okabe, National Institute of Infectious Diseases (NIID), Toyama 1-23-1 Shinjuku, Tokyo 162-8640, Japan

Professor S. C. Park, Seoul Veterans Hospital, 6-2 Dunchon2-dong, Guandong-gu, Seoul 134-791, Republic of Korea

Professor A. Plant, International Health Division of Health Sciences, Curtin University of Technology, GPO Box U1987, Perth, Western Australia 6845, Australia

Dr. C. Rota, Centro Nazionale di Epidemiologia, Sorveglianza e Promozione della Salute, Istituto Superiore di Sanità, Viale Regina Elena 299, 00161 Rome, Italy

Mr D. Rutz, Centers for Disease Control and Prevention (CDC), 1600 Clifton Rd, MS-C1 Atlanta GA 30333, USA

Dr. L. Schaade, Bundesministerium für Gesundheit und Soziale Sicherung, Postfach 500, D-53108 Bonn, Germany

Dr R. Snacken, Department of Epidemiology, Toxicology Scientific Institute of Public Health, Rue J. Wytsman 16, 1050 Brussels, Belgium

Dr Y. Souares, Caribbean Epidemiology Centre (CAREC), 16-18 Jamaica Boulevard, Federation Park, P.O Box 164, Port of Spain, Trinidad and Tobago

Dr T. Tam, Division of Immunization and Respiratory Diseases, Health Canada, Tunney's Pasture 0603 E1, Edifice LLMC, Ottawa, Ontario K1A 0L2, Canada

Dr S. Tamblyn, Perth District Health Unit, 653 West Gore Street, Stratford, Ontario N5A 1L4, Canada

Dr M. Tashiro, WHO Collaborating Centre for Reference and Research on Influenza, National Institute of Infectious Diseases, Gakuen 4-7-1, Musashi-Murayama, Tokyo 208-0011, Japan

Professor S. Tswana, Bindura University of Science Education, P. B. 1020 Bindura, Zimbabwe

Dr O. Uez, Instituto Nacional de Epidemiología "J.H.Jara", Ituzaingo 3520, 7600 Mar del Plata, Argentina

Dr J. Watson, Health Protection Agency (HPA), Communicable Disease Surveillance Centre, 61 Colindale Avenue, London NW9 5EQ, United Kingdom

Dr E. Wilkins, North Manchester General Hospital, Delaunays Road, Manchester M8 5RB, United Kingdom

Professor X. Xiaoyuan, The First Affiliated Hospital of Beijing University, No. 1 Da Hon Lou Chan street, West Cheng district, Beijing 100034, People's Republic of China

Professor Hongzhang Yin, State Drug Administration, A 38 Beilishilu, Beijing 100810, People's Republic of China

Dr K. Young-taek, Division of VPD control and NIP Korea, Center for Disease Control and Prevention, National Institute of Health, 5 Nokbun-Dong, Eunpyung-Gu, Seoul 122-701, Republic of Korea

Dr Guo Yuangi, Virological Institute, Chinese CDC, 100 Ying Xin Jie, Xuan Wu Qu, Beijing 100052, People's Republic of China

Dr L. Zhengmao, Department of Disease Control, Ministry of Health, 1 Nanlu Xizhimenwai, Xicheng District, Beijing 100044, People's Republic of China

Pharmaceutical companies representatives

Dr P. Brown, F. Hoffmann-La Roche, Grenzacherstrasse 124 P.O. Box, Building 74, Room 40.100, CH-4070 Basel, Switzerland

Dr T. Colegate, Influenza Technical Affairs, Chiron Vaccines, Gaskill Road, Speke, Liverpool L24 99R, United Kingdom

Dr T. Digneffe, Government Affairs & Public Policy, Baxter, Boulevard de la Plaine, 5 Pleinlaan, B - 1050 Bruxelles, Belgium

Dr C. Gardil-Lacroix, Influenza Industrial Product, Aventis Pasteur SA, 1541 Avenue Marcel Mérieux, F-69280 Macy l'Etoile, 69007 Lyon, France

Dr L. Hessel, Medical and Public Affairs, Europe Aventis Pasteur MSD, 8 Rue Jonas Salk, F-69367 Lyon, Cedex 07, France

Dr Y. Kino, Division 1, Second Research Department Kaketsuken, Kikuchi Research Center Kyokushi, Kikuchi, Kumamoto 869-1298, Japan

Mr Th. Leuenberger, F. Hoffmann-La Roche, Grenzacherstrasse 124, P.O. Box, Building 74 / 4W.220, CH-4070 Basel, Switzerland

Dr M. H. Orkhan, Egyptian Organisation for Biological Products and Vaccines, 51 Sh. Wezarat, El Zeraa, Agouza, Cairo, Egypt

Dr M. J. Ossi, Infectious Diseases Medicine Development Centre (ID MDC), Glaxo Smith Kline, 5 Moore Drive, 54624 RTP, NC 27709, USA

Dr A.M. Palache, Solvay Pharmaceuticals, C.J.van Houtenlaan 36, 1381 Cp Weesp, The Netherlands

WHO Secretariat (HQ, Regional and Country Offices)

Dr A. Asamoah-Baah, ADG/CDS

Dr G. Rodier, Director CSR/HQ

Dr R. Andraghetti, CSR/HQ

Dr D. Bell, CSR/HQ

Dr J. Beigel, CSR/HQ

Ms P. Creese, CSR/HQ

Dr A. Chaieb, CSR/HQ

Ms M. Cheng, CDS/HQ

Dr A. Ellis, CPE/HQ

Dr M. Esveld, CSR/HQ

Dr M. Everard, EDM/HQ

Ms E. Fitzpatrick, CSR/HQ

Dr B. Ganter, EURO

Dr T. Grein, CSR/HQ

Dr M. Hardiman, CSR/HQ

Dr B. Hersh, IVB/HQ

Dr P. Horby, WHO/Viet Nam

Dr H. Hollmeyer, CSR/HQ

Dr C. Ihekweazu, CSR/HQ

Dr K. Jalava, CSR/HQ

Ms M. K. Kindhauser, CDS/HQ

Mr H. Khenniche, CSR/LYO

Dr S. K. Krishnan, WHO/India

Dr S. Lambert, VAB/HQ

Dr S. Lazzari, CSR/HQ

Mr C. Maher, DGR/HQ

Dr A. Merianos, CSR/HQ

Dr F. Meslin, CPE/HQ

Dr O. Oliva, PAHO

Dr H. Oshitani, CSR/WPRO

Dr Y. Pervikov, IVB/HQ

Ms C. Poncé, CSR/HQ

Dr P. Prempee, WHO/Thailand

Dr C. Roces, CSR/WPRO

Dr C. Roth, CSR/HQ

Dr N. Shindo CSR/HQ

Mr J. Sigurdson, SDE/HQ

Dr I. Sow, CSR/AFRO

Dr K. Stöhr, CSR/HQ

Dr N. Teleb, VPI/EMRO

Mr D. Thompson, CDS/HQ

Dr M. Valenciano, CSR/HQ

Dr K. Vandemaele, CSR/LYO

Mr T. Waddell, CSR/HQ

Dr D. Werker, CSR/HQ

Dr W. Zhang, CSR/HQ