WHO Consultation for the Development of a Global Plan of Action to Increase Accessibility of Influenza Pandemic Vaccine

Working Group 2

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OVERALL OBJECTIVES OF THE MEETING

- **Working Group 1 Objective:**

Increasing production of influenza vaccine with Vaccine Industry

- **Working Group 2 Objective:**

Programmatic and Policy issues for increasing uptake of Influenza Vaccination

- **Working Group 3 Objective:**

Research and development for the development of a pandemic influenza vaccine

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Working Group 2: Programmatic and Policy issues for increasing uptake of Influenza Vaccination

i. **Executive Summary**

ii. **State of Issues/problems/obstacles**

iii. **Discussion Summary of Group's salient points and outstanding issues**

iv. **Statements of Major Challenges and Recommendations to be addressed short, medium, and long term time frames**

v. **Conclusions and Summary of Next steps**

WHO Consultation for the Development of a Global Plan of Action to Increase Accessibility of Influenza Pandemic Vaccine

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WORKING GROUP 2 SPECIFIC AIMS AND OUTLINE:

1. **Define strategies to increase seasonal influenza vaccine coverage as part of the yearly vaccination schedule in countries that already have season influenza vaccine programs.**
    1) Enhanced existing Strategies
    2) New Strategies
    3) Short, Medium, Long-term outcomes
    4) Major impediments

5) Recommendations and timeline for increasing doses for countries that are currently using a seasonal influenza vaccine

2. **Define conditions required by National Immunization Programs to introduce seasonal influenza vaccine into their yearly immunization schedule**
    1) Vaccine Supply
    2) Costs
    3) Disease Burden
    4) Short, Medium, Long-term outcomes
    5) Major impediments

3. **Define possible role (s) by developed countries and WHO to support developing countries with large populations and limited availability of influenza vaccine**
    1) Technical and epidemiologic support
    2) Vaccine Supply
    3) Alternative vaccination strategies with limited availability of vaccine
    4) Short, Medium, Long-term outcomes
    5) Possible role of H5N1 vaccine.

Acronyms

GAVI (Global Alliance Vaccine Initiative)

PAHO (Pan American Health Organization)

NIP (National Immunization Programme)

DALY (Disability-Adjusted Life Years)

i. Executive Summary

The rapid spread of H5N1 viruses, considered the influenza strain with the greatest pandemic potential suggests that the world is closer to an influenza pandemic than at anytime since 1968. Several manufacturers have active programmes to develop and evaluate vaccines against H5N1 influenza virus, as well as against the H9N2 and H2N2 subtypes, from which it is anticipated that valuable information can be obtained. It is not know how severe the next pandemic will be and also it is not know predictably which influenza virus will be responsible. However, given the alarming experience with human H5N1 influenza, it is considered prudent to prepare for the worst case scenario.

The objective of this position paper is to establish the possible strategies and define short, median, and long-term obstacles to promote the development of seasonal influenza vaccination policies in countries where there is not previously existent vaccination policy as well as to improve the uptake of seasonal influenza vaccination in countries with already existing influenza vaccination policies.

Immunization against influenza is considered the most important public health intervention to control both seasonal, epidemic, and pandemic influenza. There are marked differences between countries capacities, priorities, and resources to establish influenza vaccination policies and strategies. Moreover, major influenza vaccine producers operate and distribute almost exclusively in Europe, North America, and Asia. Most developing countries do not have the means to access, evaluate, and implement yearly seasonal influenza vaccination. This reality can have devastating consequences for resource-poor countries that cannot compete economically for expensive pandemic influenza countermeasures since vaccine production during a potential influenza pandemic will likely benefit primarily those with already existent influenza vaccination programs. Vaccination for an imminent pandemic requires a global

perspective and concerted effort not only for vaccine development but also for vaccine production and distribution. When a new pandemic virus emerges, vaccination will be central to pandemic response. Therefore, the development of seasonal influenza vaccination program in countries without existing influenza immunization policies and overcoming obstacles is a relevant priority. By strengthening of previously existing vaccination policies for seasonal influenza among countries with already existing vaccination programs will hopefully drive vaccine production during regular influenza seasons. Development of a global plan of action to increase accessibility to influenza pandemic vaccines by promoting seasonal vaccination policies will ultimately influence vaccine production by industry and will prime national immunization programs for influenza vaccination during pandemic influenza.

In 2003, more than 95% of the world's influenza vaccine supply was produced in only nine countries, and more than 65% of all doses came from five Western European Countries. Overall, the nine-vaccine producing countries used approximately 62% of world's vaccine, yet they accounted for only 12% of the world's population. The remaining 38% of all doses were used in countries that have little or no capacity to produce influenza vaccines on their own. Most of these countries relied on Western European companies for 99% of their available influenza vaccines. Current vaccine supply is estimated to be about 300 million doses of seasonal influenza vaccine per year. By 2009 the maximum installed capacity within current vaccine suppliers may permit a production around 600 million doses for a seasonal trivalent influenza at 15 ug per each strain with the current eggs based technology. The cost of a trivalent inactive influenza vaccine, under the best conditions has a price range of approximately $3-$7 dollars/dose. Access to influenza vaccine refers to the economic conditions present within countries to place and purchase influenza vaccine. Governments must create incentives by boosting demand of influenza vaccine through seasonal vaccine awareness programs, issuing

purchasing contracts, and providing price guarantees or subsidies. In some countries the feasibility of local production can be considered.

Identifying feasible strategies to increase seasonal influenza vaccine coverage as part of the yearly vaccination schedule in countries that already have seasonal influenza vaccine programs; as well as defining the conditions required by National Immunization Programs in countries with not existent seasonal influenza vaccine policies to introduce yearly seasonal influenza vaccination into their immunization schedule represent urgent global public health priorities. It is indispensable to define the possible role (s) by developed countries and WHO to support developing countries with large populations and limited availability of influenza vaccine during a potential influenza pandemic.

The current inter-pandemic period provides a window of opportunity to maximize and harmonize global efforts to expedite vaccine development and to augment supplies. However, at this point in time most of these efforts have been conducted by many developed countries with already existent yearly seasonal influenza vaccination policies within their national immunization programmes. Therefore, the obstacles that need to be tackled are different from those countries where there is an existent yearly influenza vaccine schedule. Among these countries it is important to define the impediments to increase influenza vaccine uptake. Some of these issues include mostly programatic issues in the short-term, and education/information of the population to overcome myths and disbelief's associated to the use of influenza vaccine. Individuals in these countries need to understand that by increasing uptake of seasonal influenza vaccine, national immunization programs will have direct access to pandemic influenza vaccine. In developing countries without existent yearly seasonal influenza vaccination program the short, median, and long-term efforts include defining the burden of

influenza in the population as well as define the epidemiology of influenza at a country level, strengthening of laboratory surveillance data; estimate the need for influenza vaccine availability for each country without existing yearly seasonal influenza vaccine program; and define policy and programmatic issues for introduction of seasonal influenza vaccine into a yearly schedule by National Immunization Programmes.

An important strategy to increase the uptake of vaccine or initiate an influenza vaccination policy is to target particular high risk populations. In this regard, high risk groups include those individuals likely to develop serious complications associated to seasonal influenza may require to be hospitalized, or die from influenza or its complications. Countries need to define their high risk groups. However, it is recommended to include the following populations: pregnant women, health-care professionals, populations above the age of 60 years, chronically ill individuals, and immunodeficient populations as high risk groups to receive influenza seasonal vaccination. In addition, it is recommend introducing routine yearly seasonal vaccination programs for children from 6-23 months of age. Another potential strategy that is currently under scrutiny is the beneficial impact of vaccinating schoolchildren since this population has been determined in various settings to be the main spreader of influenza in the community (schools and households).

Therefore, countries planning to introduce seasonal influenza vaccine or those with already existent programs need to develop strong alliances and work closely with vaccine industry to increase capacity and production for seasonal influenza vaccine. Seasonal influenza vaccination programs in developing countries and increasing the uptake of seasonal influenza vaccination in countries with programs may have significant influence in the vaccine industry to increase vaccine production. Ideally this increase in influenza vaccine production in association

with a concomitant demand driven by the establishment of new vaccination programs or increase in the uptake with prime the vaccine industry to produce more seasonal vaccine and be in a better position to produce more pandemic influenza vaccine for both developed and developing countries.

Even if influenza vaccination supplies were adequate, distribution to the population is problematic. Developing and delivering vaccines, then, are by no means straightforward tasks. The progress in eliminating smallpox and drastically reducing cases of polio shows that, with will and concentrated efforts, immunization campaigns can be successful, but the momentum for mass immunization has stalled in recent years.

ii. Statement of Issues/problems/obstacles

The priority for pandemic influenza planning is to reduce morbidity and mortality associated with influenza; ensure continuation of essential medical services for the population; reduce economic and social impact; and ensure equitable distribution of resources nationwide. The Global burden of influenza on morbidity and mortality is considerable with an estimated 1 million annual deaths worldwide.

Approximately 2.6 billion people live in “low income” countries, with gross national income (GNI) per capita < US$765, and 2.2 billion people live in “lower middle income” countries, with GNI per capita of US$766-3,035 dollars. This single improvement in income is associated with a dramatic difference in the relative burden of disease caused by lung infections. The epidemiologic and biologic reasons for these differences may be inferred and may be due to malnutrition, crowding, poor living conditions, co-morbid illnesses and many other unmeasured factors. Whatever the numbers, the poor living in developing countries are especially likely to suffer from lung infections, and relatively modest income improvements or public health

measures may have a substantial impact in decreasing this burden of disease. The impact of influenza in these populations is unknown.

.An influenza pandemic would create an enormous burden not only for the public health and healthcare systems, but also for providers of essential services around the country and the globe. It is essential to have pandemic influenza preparedness plans in both developed and developing countries to address important issues: epidemiologic surveillance and laboratory diagnosis; medical care; supply and delivery of vaccines and drugs; isolation and quarantine; and communications.

In developing countries with existent seasonal influenza vaccine policies and programs, there are several factors that account for low coverage. Many influenza vaccination activities have not yet reached some populations or are individuals living in inaccessible areas, out of range of clinics and health services, or reluctant to be vaccinated or to vaccinate their children. Because these communities are more elusive, the average cost per vaccination has increased, and it may be that other apparently cheaper health interventions have become more attractive. Second, there are many practical problems impeding influenza vaccine delivery. Delivering vaccines to patients requires functioning freezers and refrigerators, which in turn require a constant supply of energy; good roads and reliable transport to move the vaccines from port to clinic; clinics with access to people who need to be immunized; parents who know the value of vaccination; trained medical staff to deliver the dose; and sterile syringes. The third factor behind the lack of progress in recent years is political. Political disruptions have affected coverage in some areas. Immunization campaigns do not operate in isolation; they are dependent on the prevailing political and social environment. The fourth reason for the lost momentum relates to public perceptions of vaccination. As coverage spreads through a

community, it reaches a point at which those who are unvaccinated are highly unlikely to catch a disease because herd immunity has set in. Much of the public perceptions of vaccinations, are related to vaccination scares and sometimes vaccine scares do not always lack foundation. More scientific estimates of the effects of vaccines tend to underplay the benefits, disregarding the broad economic impacts of immunization in favor of a predominant and narrow focus on the averted costs of medical treatment and health care.. Because of the narrow view of the policy-making community, policy emphasis on vaccination is weaker than it might be if the full range of benefits were taken into account.

iii. Discussion of group's salient points and outstanding issues

In the meantime, identifying feasible strategies to increase coverage seasonal influenza and defining the conditions required by National Immunization Programs to introduce seasonal influenza vaccination into their immunization schedule represent urgent global public health priorities.

A serious consequence of recurring outbreaks of influenza is excess mortality during the influenza season among those with chronic medical conditions that place them at risk of the complications and among elderly persons. Control efforts have focused on the administration of inactivated influenza vaccine to target only these populations in many countries.. In virtually all developed countries, influenza vaccination is recommended for individuals 65 years old or older and those with chronic medical conditions. Recent cost-effectiveness analysis with influenza vaccination among the elderly in Mexico (those 65 of age and older) has shown that vaccination of this age group would result in saving per life per year well below the gross domestic product per capita. This suggests that even without examining alternative uses for these resources, that

this is a cost effective intervention in developing countries. Nonetheless, this analysis assumes a hypothetical elevated vaccination coverage and high acceptance of influenza vaccination in this particular age group. However, in many countries there are two important limitations to this immunization strategy: limited availability of influenza vaccine due to cost and production issues, as well as historical low acceptance rate of this kind of vaccination in this age group. However, despite all these efforts influenza continues to be a major cause of morbidity and mortality, despite intensive efforts to vaccinate persons at high risk in both developed and likely in developing countries.

The cost of a trivalent inactive influenza vaccine, under the best conditions has a price range of approximately $3-$7 dollars/dose. Access to influenza vaccine refers to the economic conditions present within countries to place and purchase influenza vaccine. Governments must create incentives by boosting demand of influenza vaccine through seasonal vaccine awareness programs, issuing purchasing contracts, and providing price guarantees or subsidies.

The current inter-pandemic period provides a window of opportunity to maximize and harmonize global efforts to expedite vaccine development and to augment supplies. However, at this point in time most of these efforts have been conducted by many developed countries with already existent yearly seasonal influenza vaccination policies within their national immunization programmes. Furthermore, influenza vaccine industry has indicated that any pandemic influenza vaccine production will be dependent on use of regular seasonal influenza vaccine use. In addition, availability of a pandemic influenza vaccine produced will go first to regular customers.

Moreover to the above influenza vaccine availability and access issues, recent publications have clearly shown that there are many research questions in developing regions such as the burden of influenza in these regions, where the severity of infections is likely compounded by malnutrition, limited supplies of antibiotics to treat secondary bacterial infections, and limited acces to outpatient and hospital care. Prevention of influenza through various vaccination strategies should be based on adequate surveillance data, and because these data is not available in many resource-limited countries establishment of sound influenza vaccination policies is cumbersome. Laboratory surveillance of influenza needs to be strengthened in many areas of the developing world. Estimating the burden of disease by surveillance of influenza like-illnesses is considered subjective since these data is non-specific. However, these issues need to be solved in order to develop prevention strategies that include cost-effective vaccination strategies to prevent morbidity and mortality associated to influenza.

iv. Statements of major challenges options and activities to be addressed

The obstacles that need to be tackled are different from those countries where there is an existent yearly influenza vaccine schedule. Among countries with existent yearly influenza vaccine, the reasons for persistent under-immunization of high risk critical populations are complex. Barriers to improving immunization rates include patient-specific factors and medical-care provider issues, as well as health care delivery systems features. Patient-centered determinants represent one of the most complex challenges to improve seasonal influenza uptake. Health care provider related factors, particularly a medical provider's recommendation to get a vaccine substantially affect immunization rates. Health care delivery system characteristics also substantially impact influenza immunization rates. A shortage of vaccine is considered an important direct and indirect cause of decrease vaccine coverage. Among these

countries it is important to define the impediments to increase influenza vaccine uptake. Some of these issues include mostly programatic issues in the short-term, and education/information of the population to overcome myths and disbelief's associated to the use of influenza vaccine. Individuals in these countries need to understand that by increasing uptake of seasonal influenza vaccine, national immunization programs will have direct access to pandemic influenza vaccine.

In developing countries without existent yearly seasonal influenza vaccination program the short, median, and long-term efforts include:

Short-term:

- Define burden of influenza in countries without existing yearly seasonal influenza vaccine programs. Prevention of influenza through various vaccination strategies should be based on adequate surveillance data, and because these data is not available in many resource-limited countries establishment of sound influenza vaccination policies is cumbersome. Laboratory surveillance of influenza needs to be strengthened to provide relevant data for developing countries to evaluate the introduction of a seasonal vaccination programme.

Medium-term:

- Define the need for influenza vaccine availability for each country without existing yearly seasonal influenza vaccine program. The overall goal of this issue is to define the installed capacity or to be created within or by the vaccine industry to produce influenza vaccine for a particular country.

- Define populations at higher risk of influenza complications to be targeted by influenza vaccination.
- Define the requirements for influenza vaccine acces for each country without existing yearly seasonal influenza vaccine program by establishing the economic conditions present within a country to place and purchase influenza vaccine.

Long-term:

- Define policy and programmatic issues for introduction of seasonal influenza vaccine into a yearly schedule by National Immunization Programmes.

The achievement of the above short, medium, and long-term objectives needs to be addressed by the following strategies:

A) Define strategies to increase seasonal influenza vaccine coverage as part of yearly vaccination schedule in countries that already have season influenza vaccine programs.

1. Enhanced existing Strategies

- Strengthening National surveillance system is key to identify vaccine strain and decide on the most effective trivalent combination in order to afford the highest possible level of protection against influenza in human populations.
- Development of Strategic alliances and partnerships with industry are essential to improving availability and access to influenza vaccine.
- Overcome barriers trough advertising campaigns to promote successful influenza vaccination to modify misperceptions about the need, effectiveness, and safety of

influenza vaccination. This important aspect remains an important impediment to immunization, especially among those most in need of vaccination.

- More difficult to overcome are those obstacles that include socioeconomic status, access to vaccine, racial disparities and missed vaccination opportunities. Nevertheless, there are existing and well-functioning programs that promotes access to influenza vaccine, reaching underserved communities to counsel and promote the use of influenza vaccine.
- Assessment of missed vaccination opportunities at different levels: community-based, outpatient, inpatient, emergency room and any other possible contact with the health-care environment. The identification of missed opportunities for influenza vaccination will allow the development of vaccination programs and strategies to decrease the gap of missed opportunities to provide yearly seasonal influenza vaccination.

2. New Strategies

- Seasonal influenza programs could target the vaccination of high risk groups. These groups could include individuals from 6-23 months, and expand vaccination to commencing with persons over 55 years of age, and those individuals with chronic medical comorbidities.
- Vaccination at school-age children may be an alternative strategy for countries with limited availability of influenza vaccine. Only Japan has ever based its policy for controlling influenza on a strategy of vaccinating school-children rather that elderly persons. This decision was based on the influenza epidemic of 1957 where some schools were closed due to attack rates of more than 60% in school-age children. It was then decided to start a nationwide vaccination campaign for school-children since

children were considered major disseminators of influenza in the community. After this policy was instituted, it has been estimated that vaccination of Japanese schoolchildren have prevented more that 40,000 deaths per year or about 1 death for every 420 children vaccinated. The number of excess deaths during the winter season in Japan decreased from 1962 until 1987, despite a large increase in the number of elderly people. The number of excess deaths began to rise after 1987, and the increase became significant after 1994. The most likely explanation for this changing pattern of seasonal mortality is that the herd immunity produced by the mass immunization of schoolchildren protected elderly persons. The fact that there was a rapid increase in excess deaths after 1994, the year in which mass immunization formally ended, supports the conclusion that the effects observed in earlier years were due to vaccine-induced herd immunity and rules out economic and social improvements as the sole reason for this unique epidemiologic pattern.

- A combination of vaccinating schoolchildren and older adults would be most effective for reducing influenza associated deaths during seasonal and pandemic influenza. However, limited availability of resources, particularly in resource-poor settings, calls for alternative cost-effective vaccination strategies. In this regard, aside from reducing community-wide transmission of seasonal influenza, vaccinating schoolchildren against influenza pandemic would probably be the most efficient approach to reducing the impact of influenza during a pandemic.

3. Major impediments

- Because of co-payments for influenza vaccine are high in countries with private health insurance schemes persons do not have financial access to get vaccinated unless yearly seasonal influenza vaccine is available at no cost.

- Even if its offered at no cost, some individuals find it difficult to identify the location of clinics offering influenza vaccine at no cost.
- In addition to the well-recognized barriers to successful influenza vaccination such as socioeconomic status, access to vaccine, racial disparities and missed vaccination opportunities, misperceptions about the need, effectiveness, and safety of influenza vaccination remain an important impediment to immunization, especially among those most in need of vaccination.

4. Short, Medium, Long-term activities

- The key steps for introducing seasonal influenza vaccine include identify stakeholders of the immunization programme; identify funding sources (governments or donors); establishment of task forces to bring together all parties; and elaborate policy and programmatic issues by reviewing existing evidence.
- The driving force to consider the introduction of influenza vaccine might come from different sources.
- Development of a national comprehensive influenza vaccination multi-year plan that includes the rationale, strategies, and activities needed for introducing influenza vaccine which includes:
    - Public health importance and public demand of influenza vaccination programs.
    - Experience from previous vaccine introductions that could be use as an extrapolation for the introduction of seasonal influenza vaccine.
    - Disease burden of influenza and cost-effectiveness analyses of influenza vaccination
    - Surveillance data on influenza and influenza trends
    - Programatic objectives:

- Expected influenza vaccine coverage
- Influenza reduction goals.

5. Outcomes from discussion

B) Define conditions required by National Immunization Programs to introduce seasonal influenza vaccine into their yearly immunization schedule

1. Vaccine Supply

In 2003, more than 95% of the world's influenza vaccines were produced in only nine countries, and more than 65% of all doses came from five Western European Countries. Overall, the nine-vaccine producing countries used approximately 62% of world's vaccine, yet they accounted for only 12% of the world's population. The remaining 38% of all doses were used in countries that have little or no capacity to produce influenza vaccines on their own. Most of these countries relied on Western European companies for 99% of their available influenza vaccines. Because influenza vaccination is increasing rapidly in these countries, it is expected that hopefully these countries will account for most of the global use of seasonal vaccines. It is an utmost priority to ensure that effective vaccines are developed and that they can be quickly produced and equitably distributed to all countries.

2. Costs

The cost of a trivalent inactive influenza vaccine, under the best conditions has a price range of approximately $3-$7 dollars/dose. Access to influenza vaccine refers to the economic conditions present within countries to place and purchase influenza vaccine. Governments must create

incentives by boosting demand of influenza vaccine through seasonal vaccine awareness programs, issuing purchasing contracts, and providing price guarantees or subsidies. Assessing the economic and financial implications of introducing influenza vaccine into their national immunization schedule can provide valuable information for decision-making for both governments and their partners taking into account 4 different issues:

- Cost-effectiveness of introducing influenza vaccine as a yearly seasonal immunization policy
- Long-term resources required with regards to budget to introduce influenza vaccine
- Magnitude of potential funding gap (mobilization of external vs. internal funding)
- Identify potential prospects for financial sustainability of influenza vaccine, once introduced into yearly seasonal influenza schedules.

3. Disease Burden

The burden of influenza in more developed countries such as the US is adequately defined, the burden of disease in developing countries is not well established. The current practice in developing countries is either no surveillance or passive surveillance or sentinel surveillance activities that are insufficient to estimate the burden of influenza in developing countries. Furthermore, estimating the burden of disease among different age groups and with various associated risk factors for complications may be critical to optimize resource allocation of influenza vaccine and antivirals, given the limited availability in many developing countries.

4. Major impediments

- When deciding about the priority of a particular vaccine, in this case inactivated influenza vaccine through yearly seasonal influenza vaccination programs through the auspices of National Immunization Programmes, it is important to consider other vaccines that would

become available in the near future. Other vaccines which may also provide important public health benefits and that will become available in the near future for resource-limited countries include rotavirus vaccines. It is relevant to compare in detail the trade offs between introducing one vaccine versus another, in this case inactivated influenza vaccine vs. rotavirus vaccine. In these decision-making processes, important consideration include burden of disease estimated in terms of DALY's ideally, but individual measures of frequency such as incidence rate, prevalence rate, hospitalizations, disability, and mortality are also very relevant. However, since the burden of disease associated to influenza has not been well defined in resource-limited settings compared to that caused by viral gastroenteritis including rotavirus may turn out to provide a difficult comparison. Vaccine efficacy, quality and safety are also important factors to consider in deciding introducing inactivated influenza vaccine programs versus rotavirus or other newly available vaccines.

- Economic and financial issues: No existing budget or cost for the introduction of inactivated influenza vaccine as part of the yearly seasonal influenza vaccination programs. However, it is recommended that assessing the economic and financial implications of introducing inactivated influenza vaccination programs can provide important information for decision-making for both governments and their developing partners as to:
    - Whether influenza vaccine is cost-effective relative to other uses of scarce resources
    - What are the long-term resource requirements of the influenza vaccine will be and how this compares with government budgets in order to assure its sustainability.
    - Define the magnitude of the potential funding gap for influenza vaccine and whether additional domestic or external funding could be mobilized to fill this gap.

- The potential prospects for financial sustainability of influenza vaccine, once it is introduced in countries without existent previous yearly seasonal influenza vaccine policies.

- Programatic issues such as:
  - Influenza vaccine presentations: presentations of vaccines include issues such as multi-dose vs. single-dose, prepared vs. need to be reconstituted. In addition, countries may not have a chance to introduce the most preferred influenza vaccine option because of high cost or lack of availability.
  - Supply and availability of influenza vaccine: the main purpose of introducing influenza vaccine into yearly seasonal influenza vaccine programs is to reduce influenza mobility and mortality. This strategy is also intended to foster increased influenza vaccine availability for both developed and developing countries. In some developing countries local production could be considered. Having a confirmed demand for seasonal influenza vaccine provide the industry with a better planning forecasting for assessing the production of pandemic vaccine
  - Programatic strength to introduce influenza vaccine: it is relevant to assess the overall performance of national immunization programmes ahead of introduction of seasonal influenza vaccination policies. If the influenza vaccine is already being used in the private sector, this may have implications for influenza vaccine impact, advocacy, and communication. In assessing programatic strength prior to introduction of yearly seasonal influenza vaccination some criteria are useful such as a NIP that obtains full benefit from existing routine vaccinations; financial sustainability of the program; existing functional col-chain; well management of vaccine stock; existence of adverse events monitoring systems; and quality of disease surveillance.

5. Short, Medium, Long-term activities

- Development of Strategic alliances and partnerships with industry are essential to improving availability and access to influenza vaccine.
- Development of a national comprehensive influenza vaccination multi-year plan that includes the rationale, strategies, and activities needed for introducing influenza vaccine and which includes;
    - Public health importance and public demand of influenza vaccination programs.
    - Experience from previous vaccine introductions that could be use as an extrapolation for the introduction of seasonal influenza vaccine.
    - Disease burden of influenza and cost-effectiveness analyses of influenza vaccination
    - Surveillance data on influenza and influenza trends
    - Programatic objectives:
        - Influenza immunization target population (s); influenza immunization schedule; cold-storage space, vaccine wastage, injection safety equipment; staff training and supervision; recording and reporting mechanisms of influenza vaccination.
        - Expected influenza vaccine coverage
        - Influenza reduction goals.

6) Outcomes of the discussion

C) Role of developed countries and WHO to support developing countries to access to a potential pandemic vaccine

1. Technical and epidemiologic support

- Development of Regional Influenza Technical Support Groups
- Supportive Supervision
- Advocacy and Communication
- Information Systems
- Development of Adverse Events Monitoring Systems

2. Vaccine Supply

- Development of a Regional Influenza Vaccine Stockpile.
- Use of Vaccine Revolving Funds by Region to Procure Influenza Vaccine for Countries with limited resources for procurement at lowest possible price.

3. Alternative vaccination strategies with limited availability of vaccine

- Yearly seasonal influenza programs should target to vaccinate mostly high risk groups. These groups should include individuals from 6-23 months, persons over 55 years of age, and those individuals with chronic medical comorbidities.
- Vaccination school-age children may be an alternative strategy for countries with limited availability of influenza vaccine. In order to reduce transmission to the elderly.
- WHO should provide technical assistance to assess and recommend the above mentioned alternative

4. Short, Medium, Long-term activities

- Development of strategic alliances and partnerships with industry are essential to improving availability and access to influenza vaccine.
- Development of a national comprehensive influenza vaccination multi-year plan that includes the rationale, strategies, and activities needed for introducing influenza vaccine and which includes:
    - Public health importance and public demand of influenza vaccination programs.
    - Experience from previous vaccine introductions that could be use as an extrapolation for the introduction of seasonal influenza vaccine.
    - Disease burden of influenza and cost-effectiveness analyses of influenza vaccination
    - Surveillance data on influenza and influenza trends
    - Programatic objectives:
        - Influenza immunization target population (s); influenza immunization schedule; cold-storage space, vaccine wastage, injection safety equipment; staff training and supervision; recording and reporting mechanisms of influenza vaccination.
        - Expected influenza vaccine coverage and expected influenza reduction.

5. Possible role of H5N1 vaccine. (as tetravalent seasonal vaccine or a monovalent)

- Currently there are no licensed vaccines against avian influenza Nevertheless, there are numerous clinical field trials ongoing testing a prototype vaccine. In a recent study, serum collected from healthy volunteers before and after administration of non-

adjuvanted or MF59-adjuvanted H5N3 vaccines were tested to assess the breadth of antibody responses to H5N1 viruses. The addition of MF59 as an adjuvant induced cross-reactive neutralizing antibody responses to various H5N1 variants isolated from humans and increased titers compared to non-adjuvanted vaccine.

- So far, there is insufficient data to support the use of H5N1 for priming the population:
- Despite these important limitations, the potential use of H5N1 vaccines in a pre-pandemic period (in seasonal vaccine formulation or as separate vaccine) should be discussed in the WG2. Production of about 8 million H5N1 doses will be ready on hand in the US by mid-2006 (to cover approximately 4 million people).

V. Conclusions and summary of next steps

The perception of the public and the medical community about the importance of influenza vaccine is a significant factor to identify its introduction as a priority. The more important and visible is the disease and its complications, and the safer and more effective the vaccine is perceived to be, the better the acceptance and uptake of any new vaccine including inactivated influenza vaccine. A major challenge in developing countries is that in some of these countries influenza vaccine may have already entered in the private market and the challenge is to extend access and availability of the vaccine to the public sector raising equity considerations. The introduction of yearly seasonal influenza vaccine in countries with limited resources present numerous issues in prioritizing investments of a national immunization programme. These issues should be tackled systematically and providing the best available strategies in a cost-effective manner. **Figure 1.** summarizes the policy and programatic issues with regards to introducing influenza vaccine into a national immunization program and the required steps to be

tackled in order to introduce influenza vaccine through national immunization programs in countries without previously existent yearly seasonal influenza vaccination policies..

Figure 1: Key Issues on Introduction of Seasonal Influenza Vaccine into National Immunization Programs and Its Impact in Pandemic Influenza Preparedness

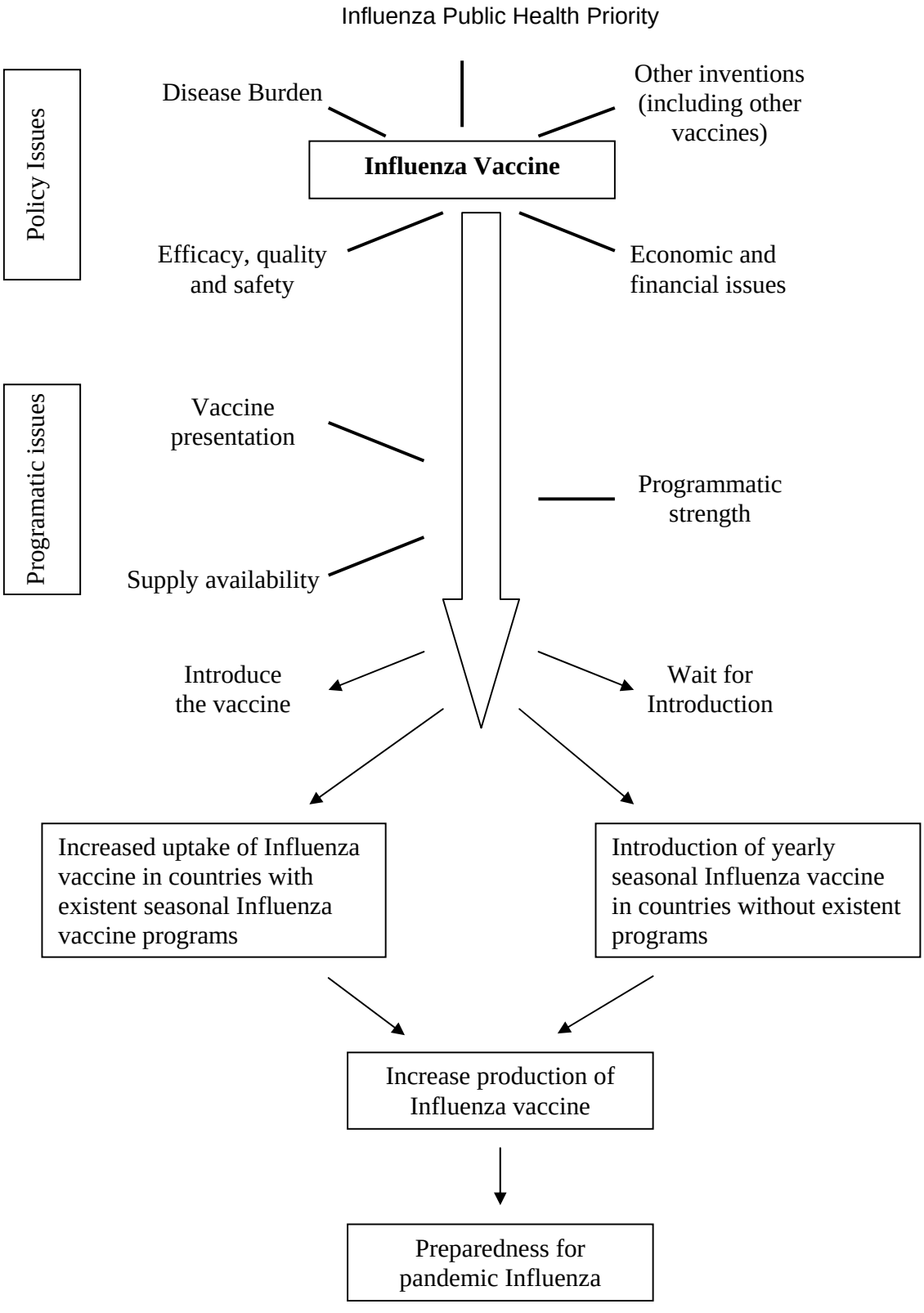

Table 1. Major issues/impediments/challenges; Strategies/activities; Timeframe for the Increase uptake of Influenza vaccine among countries with already existing influenza vaccination programs; and to introduce yearly seasonal influenza vaccine in countries without existent seasonal influenza programs

Target countries	Major issues /impedimens/ challenges	**Strategies/activities**	Timeframe **(short, medium and long term)**
A) Define strategies to increase seasonal influenza vaccine coverage as part of yearly vaccination schedule in countries that already have season influenza vaccine programs.			
B)Define conditions required by National Immunization Programs to introduce seasonal influenza vaccine into their yearly immunization schedule			
C) Role of developed countries and WHO to support developing countries to access to a potential pandemic vaccine			

ANNEX I

a) Seasonal Influenza

A vital factor in evaluating the impact of influenza vaccination is the accurate diagnosis of influenza. Some countries determine influenza incidence by measuring nonspecific case definitions, such as pneumonia and influenza-like illness. However, if virologic confirmation of a random sample of influenza-like cases is performed, the proportion of confirmed influenza positive cases can then be used to estimate the proportion of the nonspecific influenza-like cases that were in fact truly influenza.

Influenza A viruses are classified on the basis of the characteristics of two surface glycoproteins, hemagglutinin (H1 to H16) and neuraminidase (N1 to N9). All subtypes of these two proteins have been detected in viruses recovered from aquatic birds which are the natural reservoir for influenza viruses. So far, only H1, H2, H3 and N1 and N2 are associated with large-scale influenza outbreaks among humans. The hemagglutinin protein attaches to specific sialic acid receptors on respiratory epithelial cells and is considered the major antigenic determinant to which vaccine-induced neutralizing antibody is directed. The neuraminidase protein cleaves enzymatically glycosidic linkages to sialic acid so that progeny virions can leave infected cells. This protein is the target of the antiviral medications termed neuraminidase inhibitors such as oseltamivir (Tamiflu®). A hallmark of influenza viruses is their capacity to evolve in a short time frame. New strains emerge each year as a consequence of antigenic drift through point mutations in the surface glycopeptides in order to have the ability to enter into

susceptible populations. The constant emergence of new strains is the reason for a new trivalent influenza vaccine each year.

Because of the presence of specific sialic acid receptors on human respiratory tract epithelium, only 3 H (H1 to H3) and 2 N (N1 and N2) subtypes of the 16 distinct H and 9 distinct N antigenic subtypes typically infect humans. All antigenic subtypes may occur in any combinations in waterfowl or migratory birds (i.e. wild ducks), the primary reservoirs of influenza A virus. Waterfowl carry influenza A virus asymptomatically and may excrete large amounts of the virus in feces for extended periods. A wide range of animals may become infected with influenza A virus, including pigs, domestic fowl, and humans. Domestic fowl (most notably chickens) are usually infected with avian viruses such as the H5 or H7 subtypes. Such viruses have preferred binding to avian-specific respiratory tract receptors. Poultry with avian influenza may demonstrate a spectrum of symptoms, from asymptomatic infection to cough, sneezing, excessive lacrimation, ruffled feathers, diarrhea, and decreased egg production, and may die of secondary to this infection. Large outbreaks of avian influenza within the domestic poultry industry can have devastating economic effects.

The mechanism responsible for the morbidity and mortality associated with infection and disease due to influenza viruses starts with the entry, adhesion, and subsequent replication of the virus inside ciliated columnar respiratory epithelium, especially in large airways. Influenza virions produced within these cells are then transmitted from person to person through exposure to droplets generated by coughing and sneezing and through indirect contact with contaminated fomites. The incubation period ranges from one to four days. Compared to other infectious diseases in which the transmission occurs after the onset of symptoms, people infected with influenza are usually infectious from the day before the onset of symptoms to about three to five days after symptoms appear. Close to 50% of infected persons have no symptoms but may be

infectious. Therefore, during the spread of seasonal or pandemic influenza this short incubation period and the ability of the virus to be transmitted before the occurrence of symptoms are considered important obstacles to limiting spread. Children and individuals of any age group with immunosuppression may remain infectious much longer than normal adults. Influenza has a striking seasonal occurrence in temperate climates, but it occurs year-round in the tropics. The onset of the flu season is highly variable and difficult to predict. In the northern hemisphere, it usually starts in November or December and subsides before May. In the Southern Hemisphere, the season usually begins in May and subsides by October. From the global perspective, strains of influenza are always circulating somewhere in the world and always challenging the capability to produce adequate quantities of antigenically matched vaccines. The most severe effects of influenza are felt most at both ends of the age spectrum; the very young and the elderly although younger populations, such as school children may have the highest attack rates. Persons with certain underlying chronic illnesses are also at higher risk of serious complications from influenza compared to the general population.

b) Pandemic Influenza

Pandemic influenza becomes possible when there is a shift in the hemagglutinin of influenza A viruses to a completely new type to which virtually the entire population lacks immunity. These changes occur either by reassortment when human and avian viruses infect a host simultaneously and the progeny contain a new hemagglutinin with many of the remaining genes contributed by human adapted strains or by genetic mutation of an avian strain such that it becomes efficiently transmitted from human to human. Three criteria are needed for a global influenza pandemic to occur: 1) a new virus emerges with a new hemagglutinin to which there is

almost universal susceptibility, 2) the virus is capable of causing significant disease in humans, and 3) the virus is efficiently transmitted from human to human. While reassortment appears to be the mechanism that accounts for the 1957-58 and 1968-69 pandemics, direct mutation of an avian strain to make it adaptable to humans appears to be the cause of the 1918-19 pandemic

The 20th Century witnessed three pandemics of influenza: the “Spanish influenza” (1918-19) caused by the H1N1 virus, the “Asian influenza” (1957-58) caused by the H2N2 strain, and the “Hong Kong flu” (1968-69) caused by the H3N2 virus met the above criteria. These viruses spread rapidly worldwide but only the 1918 was associated with many millions of deaths, almost doubling the number killed on the battlefields of Europe during World War 1. More than 500,000 deaths occurred in the United States. Influenza A (H1) strains continued to cause seasonal outbreaks until 1957, when influenza A (H2N2) emerged. Since most of the population was not immune to new H2 antigen, another pandemic developed, causing about 70,000 deaths in the United States. In 1968, influenza A (H3) caused a third pandemic, which resulted in approximately 50,000 deaths in the United States. In 1977, H1 reappeared as the dominant hemagglutinin subtype, but a true pandemic did not occur, since most people more than 20 years of age had prior exposure to this subtype antigen and had residual immune protection. Since 1997, influenza A H3 and H1 subtypes as well as influenza B strains have been in circulation.

The occurrence of human influenza A (H5N1) in Southeast Asia has paralleled large outbreaks of avian influenza A (H5N1), although the avian epidemics in 2004 and 2005 have only rarely led to disease in humans. The largest number of cases has occurred in Vietnam, particularly during the third ongoing wave of disease. The expanding geographic distribution of avian influenza A (H5N1) infections, with recent outbreaks in Kazakhstan, Mongolia, and Russia, indicates that more human populations are at risk.

Since 1997, at least 6 distinct avian influenza outbreaks affecting humans have occurred:

- Hong Kong 1997 (H5N1) with 18 cases and 6 deaths
- Hong Kong 1999 (H9N2) with 2 cases and 0 deaths
- Hong Kong 2003 (H5N1) with 2 cases and 1 death
- The Netherlands 2003 (H7N7) with 83 cases and 1 death
- Canada 2004 (H7N undefined) with 2 cases and 0 deaths
- Egypt 2004 (H10N7) with 2 cases and 0 deaths
- Current outbreak in Southeast Asia (Vietnam, Thailand, Indonesia and Cambodia (H5N1) with 112 cases and 57 deaths (as of early December 2005)

The complete nucleotide sequence of the 1918 influenza virus genome has been determined from preserved tissue samples from military personnel in the United States who succumbed to influenza during those years and also from the frozen cadaver of a victim buried in the Alaskan permafrost. Phylogenetic analysis of the 1918 virus genome sequence indicates that the 1918 H1N1 virus was derived entirely from an avian source. Thus two mechanisms exist for the H5N1 strain to become a pandemic strain – simultaneous infection of a host, pig, human or other, with a human adapted strain and the H5N1 viruses leading to reassortment or by repeated mutations that make it more fit to infect and be transmitted from human to human. When the 1918-19 viruses were reconstructed by reverse genetic techniques it was shown to be aggressive. In two days the mice injected with it lost 13% of their body weight, whereas mice infected with contemporary H1N1 virus did not lose weight. The mouse lung produced 39,000-fold more virus than contemporary H1N1 human virus and human lung cells released 50 times more 1918 particles than contemporary H1N1 virus. The 1918 influenza virus caused deep lung pathology:

necrotizing bronchiolitis, severe alveolitis, severe alveolar edema and important lung inflammation.

Although vaccination is the primary strategy for the prevention and control of influenza outbreaks, there are a number of scenarios for which vaccination is inadequate and administration of effective antiviral drugs would be important. In the course of a pandemic, vaccine supplies would likely be inadequate. Vaccine production by current methods cannot be carried out with the speed required to halt the progress of a new strain of influenza virus and hence it is likely that vaccine would not be available for the first wave of the pandemic virus. Antiviral drugs that target influenza virus form an important part of a rational approach to pandemic influenza. In addition, in the absence of a vaccine, countries will likely turn first to antiviral medications in the face of a pandemic. These medications may be stockpiled in anticipation of a possible event, and if found to be effective, will likely be instrumental in the initial response. Antiviral medications can be both preventive and curative. They may be used to treat people who have already been infected or, perhaps more importantly, provided to the contacts of sick individuals as a means of warding off the illness. Treatment with an antiviral may help alleviate symptoms and reduce the potential for serious complications resulting from the infection. Although they may help reduce morbidity and mortality from a pandemic, it is unlikely that antivirals would greatly diminish the spread of pandemic influenza.

An influenza pandemic, however, could be far more serious and widespread than a seasonal outbreak. The consequences of the introduction of a new hemagglutinin into human influenza viruses are usually a pandemic, or a worldwide epidemic, resulting in hundreds of thousands of influenza-related deaths. Pandemic viruses occur when a new influenza virus emerges or an existing one undergoes a major transformation. In order to cause a pandemic, this virus must cause serious illness and have the capacity to spread easily from person to person. The entire

global community would be susceptible to pandemic influenza, as the ease of international travel could quickly introduce the virus around the world. A pandemic virus has either never circulated among people, or has not circulated for a long period of time, leaving the majority of individuals with few natural defenses to ward off illness.

For centuries, a flu pandemic is believed to have emerged every 25 to 30 years.
It is widely believed that a flu pandemic virus would inevitably affect populations around the globe, rapidly traveling through the international transportation system. Many professionals in public health, medicine and science believe that another flu pandemic is inevitable. Though it is impossible to predict the exact timing or nature of a future pandemic, some modeling studies suggest that the impact could substantially affect both the physical and financial health of countries.

Because influenza is frequently transmitted before a specific diagnosis is possible and there is a dearth of global and vaccine stores, aggressive transmission reducing measures such as isolation of cases and contacts will probably be required as demonstrated by recent mathematical models.

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