Influenza Vaccine Response during the Start of a Pandemic
Report of a WHO Informal Consultation held in Geneva, Switzerland

29 June - 1 July 2015
# Influenza Vaccine Response during the Start of a Pandemic

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Executive Summary

Producing an influenza pandemic vaccine is very complex. It depends on the successful interaction between many different organizations in both the public and private sectors, and is performed under severe time constraints. Moreover, data on the epidemiology of the pandemic viruses and the local circulating seasonal viruses is critical but may be incomplete. The main focus of the WHO consultation was to better understand the complexities of the early stages of pandemic vaccine development during the start of a pandemic, to express any concerns about procedures that are either inefficient or may easily be compromised, and to recommend strategies for improvements.

The main areas of concern and outcomes of the meeting were:

- There was concern that the new “Pandemic Influenza Risk Management (PIRM) – WHO interim guidance” no longer identified clear pandemic phases which had in the past been widely used to guide the various stages of pandemic vaccine production. However, as a result of the meeting, different stakeholders became more aware of the need for risk assessments in initiating pandemic vaccine production. During the course of the meeting, a “draft operational framework for pandemic vaccine response” was prepared (see Annex 1) and it was felt that the inclusion of this framework brought the PIRM document closer to completion.

- A key decision is needed for the timing of the start of pandemic vaccine production. Global influenza vaccine manufacturers supply seasonal vaccine to many countries and are similarly likely to have multinational pandemic vaccine orders. If the decision to start pandemic vaccine production is left to national health agencies or even to vaccine manufacturers, it might lead to delays and shortages of pandemic vaccine and may compromise the production of seasonal vaccine with possibly significant public health consequences. There was agreement on the need for international leadership by WHO through its advisory bodies including the International Health Regulations (IHR) Emergency Committee and the Strategic Advisory Group of Experts (SAGE) on Immunization on recommending the start of pandemic vaccine production.

- Candidate Vaccine Viruses (CVVs) are crucial as the first step in the production of seasonal and pandemic vaccines. In 2009 there were some delays in their distribution and use. The WHO biosafety committee is urged to review and improve the procedures for assessment of biocontainment for CVVs and vaccine manufacturers are urged to have import permits in place in order to receive them.

During the course of the meeting, three guidance charts were prepared and they are included as annexes to this report:

- Draft operational framework for pandemic vaccine response.
- Timelines of pandemic vaccine production.
- Process of WHO vaccine response to an influenza pandemic or potential pandemic.
1. Introduction and Scope of the Meeting

Influenza pandemics are unpredictable but recurring events that can have significant consequences on human health and economic well-being worldwide. Advance planning and preparedness are vital to help mitigate the impact of a pandemic. In June 2013, WHO published a revision of the influenza preparedness and response guidance, entitled "Pandemic Influenza Risk Management (PIRM) – WHO interim guidance". This guidance was prepared following experience gained during the influenza A(H1N1) 2009 pandemic; experience with influenza A(H5N1) infections in poultry and humans; and advances in the development of antiviral medicines and pandemic vaccines. Two key lessons learned from the 2009 A(H1N1) pandemic were:

1. That countries experienced the influenza pandemic at different times and faced different levels of impact.
2. Member States had prepared for severe pandemics and found it difficult to react to a pandemic of moderate severity.

The WHO PIRM framework, through a cooperative risk management approach, thus allows more flexibility for countries and regions so that the declared global phases of a pandemic are not directly linked with national or regional actions and to also support local actions which are appropriate to the level of pandemic impact.

Influenza vaccines provide the main intervention for reducing morbidity and mortality of influenza. Although we have abundant experience with seasonal influenza vaccines, our experience with pandemic influenza vaccines is limited. The pandemic vaccine response is complicated due to the tight timeframe from virus detection to vaccine availability; complications associated with seasonal influenza, which may still be circulating in parts of the world; uneven production capacity in the world; and the enormous demands to vaccinate huge numbers of people. In the context of making pandemic vaccines more timely, widely and fairly available, three international activities have made important contributions:

1. The International Health Regulations (IHR) 2005 are legally binding for the 196 States Parties to prevent, control, or respond to public health risks that may spread between countries and within this remit is the declaration of a Public Health Emergency of International Concern (PHEIC) by the WHO Director General under guidance from the IHR Emergency Committee.

2. The Pandemic Influenza Preparedness (PIP) Framework for the sharing of influenza viruses and access to vaccines and other benefits was adopted in 2011. This important milestone event reflected growing recognition of the importance of the timely sharing and characterization of viruses and of the equitable provision of effective vaccines against pandemic influenza.

3. The WHO Global Action Plan for Influenza Vaccines (GAP) was launched in 2006 to increase global influenza production capacity and supply. It is based on increasing evidence-based use of seasonal influenza vaccines; increasing global pandemic vaccine production
Thirty-three participants from 18 countries were drawn from WHO Collaborating Centres (WHO CCs), WHO Essential Regulatory Laboratories (ERLs), the academic research community, National Regulatory Authorities (NRAs), national public health agencies, vaccine manufacturers, International Federation of Pharmaceutical Manufacturers & Associations (IFPMA), Developing Countries Vaccine Manufacturers Network (DCVMN) and other stakeholders.

2. Background Information

2.1 Challenges and timelines in producing a pandemic vaccine

The steps in production of seasonal vaccine for the northern and southern hemispheres are very complex and similar but are separated in time by about six months. The timelines for vaccine production are very tight and depend on close interaction between many different players, such as WHO CCs, ERLs, vaccine manufacturers, CVV reassorting laboratories, regulatory agencies and vaccine program managers. This is complicated further by some large vaccine manufacturers having contracts for supply of both northern and southern hemisphere vaccine, with the implication that they are essentially in year-round vaccine production. Three draft tables were presented to the meeting: “Draft operational framework for pandemic vaccine response”; “Timelines of pandemic vaccine production”; and “Process of the WHO vaccine response to influenza pandemic or potential pandemics”. As a result of discussions and experience gained during the meeting, these three tables were refined and the versions agreed to at the meeting are presented as Annexes 1, 2 and 3.

The main objectives of the meeting were to:
- Better understand the complexities of pandemic vaccine response at the start of a pandemic.
- Discuss response strategies through different pandemic scenarios.
- Discuss mechanisms for the implementation of the above strategies, including the start of pandemic vaccine production and associated critical steps including switch from production of seasonal vaccine to pandemic vaccine.
- Draft an operational framework for a pandemic vaccine response.

capacity and strengthening regulatory competencies; and fostering development of new influenza vaccines that are not only higher-yielding and faster to produce, but also broader in protection and of longer duration.

The WHO PIRM Framework provides some interim guidance on development of pandemic vaccines, but few details are provided on the aspects of risk assessment and the practical issues associated with switching from seasonal to pandemic vaccines. It was thus timely to convene an expert consultation to develop a global strategy and operational mechanism for pandemic vaccine response at the start of a pandemic when seasonal influenza may still be circulating to a significant extent in many parts of the world and when seasonal influenza vaccine may still be needed.
2.2 Issues associated with switching from seasonal vaccine to pandemic vaccine production

It is encouraging that there has been a significant escalation of global influenza vaccine production capacity over the past few years as the capacity to produce seasonal vaccines is directly linked to pandemic vaccine production capacity. However, the decision to switch from seasonal to pandemic vaccine production involves multiple considerations, including:

- The seasonality of influenza in both hemispheres creates critical time constraints for both seasonal and pandemic vaccine production.
- A premature decision to switch to pandemic vaccine production may compromise the production of seasonal vaccine with possibly severe public health consequences. The time of year when such a switch has least impact is July to September for the northern hemisphere and December to January for the southern hemisphere.
- It is important to make the right vaccine available in the right place and at the right time to optimize the effectiveness of the vaccine.
- In the USA, production of 2009 pandemic vaccine was too late for the vaccine to be useful in combating the first wave of the pandemic. An earlier switch to pandemic vaccine production could have brought forward vaccine availability for some manufacturers.
- It is likely that a decision to switch will have to be made before all the information is available, so there is an element of risk involved.

- Most vaccine manufacturers have several contracts for seasonal and pandemic vaccine supply, often supplying countries in both northern and southern hemispheres. A decision by one company or country to switch to pandemic vaccine production would therefore affect vaccine supply in other countries.

2.3 Development of Candidate Vaccine Viruses

CVVs are crucial as the first step in the production of seasonal and pandemic vaccines. A CVV is an influenza virus that is appropriate according to the available epidemiological, antigenic and genetic data, has been optimized for high growth within the time constraints permitted, is stable, and is safe for work within production facilities. It may be a wild type virus, a conventional reassortant or one produced by reverse genetics (RG). There are at present seven laboratories producing CVVs and their output is closely coordinated by the WHO Global Influenza Programme (GIP) to ensure good collaboration. CVVs can be produced within three weeks from a virus specimen, but more time is needed if they are produced from highly pathogenic viruses where safety tests are needed. In the case of influenza A(H1N1)pdm09 virus, a CVV was available in less than a month from detection and confirmation of the novel virus strain, although higher yielding CVVs were produced at a later date. In the case of influenza A(H7N9) virus, despite many attempts there is still no suitable conventional reassortant CVV available. This illustrates that research is needed to optimize CVV production.
2.4 Vaccine potency testing

The Single Radial Immunodiffusion (SRID) assay is globally accepted for estimation of vaccine potency and accepted by NRAs worldwide. Thus the SRID reagents (calibrated antigen and specific antiserum) are critical components in the vaccine production pathway. SRID reagents are produced and standardized by the four ERLs of WHO GISRS that work closely together to ensure that availability and standardization is optimal within the following constraints:

- Sheep antiserum reagents may take up to twelve weeks to produce.
- Antigen reagents are dependent on supply of antigen from a vaccine manufacturer.
- International calibration of antigen reagents can take up to one month.

It is clear that the availability of pandemic vaccine reagents may be problematic. In 2009, alternative potency assays were used during the early stages of pandemic vaccine production. This is an area for considerable research and WHO has provided guidance on the key characteristics for improved potency assays.6

2.5 Regulatory pathway for pandemic vaccines

Procedures to license pandemic vaccines during a pandemic need to ensure that vaccines are safe and effective, but should not be so cumbersome that they create unnecessary delays in vaccine availability nor cause poor public acceptance of vaccine due to the perception that short cuts have been taken.

For example, in the USA a pandemic vaccine licensing strategy, with clinical trials performed during the inter-pandemic period, offers a clear pathway for implementation of virus-specific pandemic vaccine, with the proviso that clinical trials of a pandemic vaccine may be needed to establish formulation, schedule and corresponding targeted populations. See Annex 5.

2.6 Manufacturers’ perspective on critical aspects of pandemic vaccine production

There are several key factors for an effective response from manufacturers, where delays or inadequate response would be a bottleneck. The impact of most of these factors depends on the timing of the WHO pandemic declaration and whether the seasonal vaccine is well underway. These factors include:

- Clear and timely communication, particularly on the need to switch to pandemic vaccine production.
- Collaboration between all stakeholders, particularly when problems arise.
- Prompt provision of CVVs.
- Lowering of biological containment level to BSL2+.
- Yields from CVVs.
- For egg-produced vaccines, a secure and reliable provision of eggs.
- Prompt provision of vaccine potency reagents.
- The existence of suitable alternative vaccine potency assays.
- Prompt production of a clinical trial vaccine.
- Clear and efficient regulatory pathway for pandemic vaccine release.
A recurring theme across the critical vaccine production factors is the need for a clear and unambiguous signal to start pandemic vaccine production.

3. Organization of the Consultation

After hearing the background information described above and in order to stimulate discussion, participants were provided with three different scenarios for a pandemic vaccine response during the early stages of a pandemic. The issues arising from the three scenarios (Annex 6) were discussed by participants and were designed to generate a greater understanding of work performed by different organizations; highlight problems and concerns that could delay or prevent pandemic vaccine production; and highlight gaps that would need filling before improvements could be made in pandemic vaccine response. The discussions were enriched by the varied backgrounds and experiences of the participants and, notably representatives from vaccine manufacturers were invited to take part as full participants not just as observers. In addition, and for the first time at a WHO consultation on influenza, the discussions at this consultation were aided by the services of an external facilitator. The output of the pandemic scenario discussions during the meeting were organized into different topics under the general heading of “areas of concern”.

The second focus of the meeting was to provide a better description of the pandemic vaccine process as earlier presented in draft form in one of the introductory talks. The participants divided into groups of specialties and populated or modified the table “Draft operational framework for pandemic vaccine response” (i.e. who takes the actions?). The agreed version of the framework is shown in Annex 1.

*During the course of the meeting, three further activities were carried out:*

- Modification of the table “Timelines of pandemic vaccine production” (i.e. when are actions taken?) (Annex 2).

- Modification of the table “Process of the WHO vaccine response to influenza pandemic or potential pandemics” (i.e. how are actions taken?) (Annex 3).

- Identification of areas of concern that were outside the scope of the meeting, but which nevertheless needed some attention. These items were listed in a “parking lot” (Annex 4).
4. Areas of Concern Raised during the Consultation

4.1 Declaration of pandemic phases

In 2009, at the onset of the A(H1N1) pandemic, the WHO pandemic guidance was directed towards six distinct pandemic phases. Countries were advised to develop their own national influenza preparedness and response plans that addressed the recommendations in the guidance. The designation of a global pandemic phase (Phase 6) was made by the Director-General of WHO after a series of consultations with internal and external entities. After the 2009 pandemic, as described in Section 1 of this report, the WHO pandemic guidance was revised to place greater emphasis on a cooperative risk management approach to allow more country and region flexibility.

Although this approach is understandable and logical, there are concerns that could affect supply of pandemic vaccine:

- Previously, national or regional pandemic activities were clearly linked to WHO pandemic phases. In the absence of these pandemic phases, countries and regions and possibly vaccine manufacturers need to develop their own phases of pandemic response. For many low and lower-middle income countries, this is challenging and there is need for greater guidance.
- There is some confusion whether WHO will declare a pandemic or not. If there is no clear signal, this could create confusion for countries with insufficient pandemic response plans and in communicating with the media and the general public. This could have an impact on supply of pandemic vaccine.

4.2 Switching from production of seasonal to pandemic vaccines

The representatives from influenza vaccine manufacturers emphasized that their production facilities could not be used to produce seasonal and pandemic vaccines at the same time. Therefore, if pandemic vaccine is needed, it would be necessary to stop seasonal vaccine production and switch to pandemic vaccine production. Influenza vaccine production to meet seasonal demand is a year-round activity for some large vaccine manufacturers to meet orders for both northern and southern hemisphere countries. Therefore, for these manufacturers there is no time of the year when a switch to pandemic vaccine production will not affect the supply of seasonal vaccine. Depending on when the switch is made, there may or may not be seasonal vaccine already made and ready for final filling, packaging and distribution. Decisions will be needed as to whether and how this seasonal vaccine should be used.

There are different elements to the initiation of a switch: epidemiology of pandemic influenza virus and possible co-circulating seasonal influenza viruses; the assessment of risk by WHO surveillance activities, governments or regional authorities; and the activation of orders for pandemic vaccine from governments. The risk assessment by various agencies would involve not only the virological, epidemiological and clinical aspects of the emerging pandemic but also the risk of stopping seasonal vaccine production and not having enough seasonal vaccine for vulnerable people. At present the responsibility for switching to pandemic vaccine production lies principally with national governments.
This requires governments to have revised their pandemic preparedness plans so they have risk assessment procedures in place to make such a key decision. There was comment at the meeting that very few countries have such a revision in place. In countries with dedicated vaccine manufacturers (e.g. Japan), it would be necessary for manufacturers to react to country demands, but many vaccine manufacturers had contracts with several governments and private organizations for supply of seasonal and pandemic vaccine, so it would be impossible for a vaccine manufacturer to meet the demands of a country requesting pandemic vaccine and another country which still needed seasonal vaccine.

The identified needs were:

- International leadership in recommending that pandemic vaccine production commence, based on evidence of need.

- Revision of national pandemic preparedness plans to identify the process for a pandemic vaccine switch, including the risks of stopping seasonal vaccine versus the risks of not going ahead with pandemic vaccine.

- Based on current knowledge, the pandemic vaccine component should not be incorporated into seasonal vaccine until its safety profile is well understood. There were some adverse reactions to a 2010 seasonal vaccine in children in Australia and it was difficult to evaluate whether they were due to the newly introduced A(H1N1)pdm09 vaccine component or not.⁷⁸

- Although some low and lower-middle income countries needed international leadership in taking decisions, all countries should make as much pandemic preparation as possible, e.g. an updated inventory of their healthcare capacity.

- A flowchart of the multi-factorial decision-making process that will generate greater transparency and trust, which may in turn translate into greater public acceptance of pandemic vaccination.

After much discussion, it was agreed that the recommendation on the start of pandemic vaccine production should be made by WHO through its advisory bodies including the IHR Emergency Committee and SAGE. This recommendation should then be translated into national responses.

4.3 Preparation and communication

Although a large amount of preparation for pandemic vaccine production has already taken place and communication between different organizations has greatly improved, there was a recurring theme during the discussions that further improvements could be made.

In terms of preparedness, the main concerns were:

- Vaccine manufacturers should ensure that they have import permits in place for receipt of CVVs. This should include wild-type viruses, conventional reassortants and reassortants generated by RG, which in some countries are judged to be genetically modified organisms (GMOs).
In 2009 there were delays in assessing and recommending appropriate biocontainment for CVVs, which led to delays in distributing CVVs to manufacturers. This needs to be more timely and efficient.

There was concern from vaccine manufacturers that vaccine potency reagents became available at different times across the world. It is desirable that all vaccine manufacturers use the first available reagents thus saving time and also generating better global vaccine standardization.

Although WHO CCs, ERLs and vaccine manufacturers have some capacity for preliminary work on potential pandemic viruses before a pandemic begins (e.g. preparing CVVs; preparing vaccine seed viruses; preparing pilot vaccine lots), there are no facilities or funding to prepare pilot lots of potential pandemic vaccine under Good Manufacturing Practice (GMP) conditions for the vaccine to be evaluated clinically. Such research could be performed well in advance of a pandemic for influenza subtypes, which are assessed by WHO to pose the most serious pandemic threat, and could also serve as a model for rapid clinical assessment in the early stages of pandemic vaccine production. This would provide invaluable experience for solving production problems that could delay vaccine availability. It could also generate antigen for pilot vaccine potency reagents and help to generate confidence in making orders for pandemic vaccine by governments, health professionals and the general public and the need to promote the use the vaccine. Vaccine regulators should be involved with this research to evaluate and give advice on how broadly applicable such data can become. It was stressed that in the USA and the EU, if a vaccine manufacturer had a licence for a pre-pandemic vaccine for a certain influenza virus subtype, it would not be necessary to do further clinical trials for vaccines prepared from the same subtype. This emphasized how important it was to conduct vaccine clinical trials as early as possible. Research funding would be needed for this preparatory work.

During the preparation of a seasonal influenza vaccine, most activities are undertaken by several organizations working closely together to achieve a common goal. An example of this is the preparation and evaluation of CVVs where WHO CCs, reassorting laboratories, RG laboratories, ERLs, vaccine manufacturers and the WHO expert group on biocontainment collaborate closely. Currently such activities are conducted harmoniously by good collaboration without a single coordinating entity in charge. There was some concern that in a pandemic emergency situation, this spontaneous process may not work efficiently and a single coordinating entity should be identified.

There were concerns that regulatory procedures for fast track approval of pandemic vaccines were not harmonized globally and there was no global mutual recognition process of regulatory approval, which could lead to delays and inconsistencies in pandemic response.
vaccine availability. It was pointed out that regulatory agencies can now share information and there is movement towards a common regulatory approach in Member States, which is a significant improvement. It was considered that this was outside the scope of the meeting, but this issue was retained in the “parking lot” (Annex 4).

- Similarly, pandemic vaccine release is not harmonized globally and there is no global mutual recognition process for lot release. There are some very effective mutual recognition procedures in place within the EU and some other countries and these could be models for strengthening and extending the network of lot release agencies. Again, this was considered to be outside the scope of the meeting and it was retained in the “parking lot”.

In terms of communication, the main concerns were:

- If data are available on cross-protection afforded by seasonal vaccine, this should be communicated as quickly as possible.

- There should be efficient communication from WHO to national governments on the epidemiology of pandemic and seasonal co-circulating viruses and the severity of pandemic virus infections.

- Some participants at the meeting expressed surprise at the many facets of pandemic vaccine production, the number of organizations involved and the different strands of communication required. It was felt that a map of the communication network for pandemic vaccine production should be made.

5. Draft Operational Framework for Pandemic Vaccine Response

One of the key outputs of the meeting was to develop and improve the “Draft operational framework for pandemic vaccine response”, which serves to identify who will play a role in the various aspects of delivering a pandemic vaccine. This draft framework (Annex 1) will be further refined by WHO and external advisors so that eventually it will be included in the PIRM document to better describe the complexities and interactions of different stakeholders in making a pandemic vaccine available.
6. Key Outcomes of the Meeting and Next Steps

Within the scope of the meeting, the main outcomes were:

- Better understanding of the complexities of pandemic vaccine production during the start of a pandemic, especially in describing the roles and responsibilities of different stakeholders. This should lead to improved levels of communication between all stakeholders.

- Agreement on the need for international leadership by WHO through its advisory bodies, including the IHR Emergency Committee and SAGE, on recommending that production of pandemic vaccine commence based on risk assessment. This may entail critical steps including switching from production of seasonal vaccine to pandemic vaccine.

- In preparing the “Draft operational framework for pandemic vaccine response”, it was felt that this brought the PIRM document closer to completion.

- Different stakeholders are now more aware of the need for risk assessments in initiating pandemic vaccine production.

- There is increased awareness of the need to review and improve the procedures for assessment of biocontainment for CVVs.

In terms of the next steps, the priority actions were agreed as:

- Finalize the WHO risk assessment tool (TIPRA).

- Complete the “Draft operational framework for pandemic vaccine response” and then the PIRM document. After this, further consultations with Member States would be needed.

- The identified coordinators in the various activities of the “Draft operational framework for pandemic vaccine response” should examine their roles further so that improvements can be made and hence better information can be provided to WHO.

- The procedures for assessment of biocontainment for CVVs need to be reviewed and improved by the WHO biosafety committee.

The above priority activities and further activities recognized at the meeting are listed in the “parking lot” (Annex 4).
7. References

1. **Pandemic Influenza Risk Management (PIRM) – WHO interim guidance**

2. **The International Health Regulations (IHR) 2005**
   http://whqlibdoc.who.int/publications/2008/9789241580410_eng.pdf?ua=1

3. **The Pandemic Influenza Preparedness (PIP) Framework for the sharing of influenza viruses and access to vaccines and other benefits**

4. **Global Action Plan for Influenza Vaccines (GAP) to increase global influenza production capacity and supply**
   http://whqlibdoc.who.int/hq/2006/WHO_IVB_06.13_eng.pdf

5. **WHO Collaborating Centres for influenza and Essential Regulatory Laboratories**
   http://www.who.int/influenza/gisrs_laboratory/collaborating_centres/list/en/

6. **Recommendations for the production and control of influenza vaccine (inactivated)**
   http://www.who.int/biologicals/publications/trs/areas/vaccines/influenza/ANNEX%203%20InfluenzaP99-134.pdf

7. **Systematic review of fever, febrile convulsions and serious adverse events following administration of inactivated trivalent influenza vaccines in children**

8. **Role of viral RNA and lipid in the adverse events associated with the 2010 Southern Hemisphere trivalent influenza vaccine**
8. Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>BLA</td>
<td>Biologics License Application (USA regulatory mechanism)</td>
</tr>
<tr>
<td>BSL2+</td>
<td>Biosafety level 2+</td>
</tr>
<tr>
<td>CVV</td>
<td>Candidate Vaccine Virus</td>
</tr>
<tr>
<td>DCVMN</td>
<td>Developing Countries Vaccine Manufacturers Network</td>
</tr>
<tr>
<td>EUA</td>
<td>Emergency Use Authorization (USA regulatory mechanism)</td>
</tr>
<tr>
<td>GAP</td>
<td>WHO Global Action Plan for Influenza Vaccines</td>
</tr>
<tr>
<td>GIP</td>
<td>WHO Global Influenza Programme</td>
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<tr>
<td>GMO</td>
<td>Genetically Modified Organism</td>
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<tr>
<td>GMP</td>
<td>Good Manufacturing Practice</td>
</tr>
<tr>
<td>IHR</td>
<td>International Health Regulations</td>
</tr>
<tr>
<td>IFPMA</td>
<td>International Federation of Pharmaceutical Manufacturers &amp; Associations</td>
</tr>
<tr>
<td>IND</td>
<td>Investigational New Drug (USA regulatory mechanism)</td>
</tr>
<tr>
<td>NRAAs</td>
<td>National Regulatory Authorities</td>
</tr>
<tr>
<td>PHEIC</td>
<td>Public Health Emergency of International Concern</td>
</tr>
<tr>
<td>PIP</td>
<td>Pandemic Influenza Preparedness</td>
</tr>
<tr>
<td>PIRM</td>
<td>Pandemic Influenza Risk Management</td>
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<tr>
<td>RG</td>
<td>Reverse Genetics</td>
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<tr>
<td>SAGE</td>
<td>Strategic Advisory Group of Experts on Immunization</td>
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<tr>
<td>SRID</td>
<td>Single Radial Immunodiffusion</td>
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<tr>
<td>TIPRA</td>
<td>Tool for Influenza Pandemic Risk Assessment</td>
</tr>
<tr>
<td>VRBPAC</td>
<td>US Vaccines and Related Biological Products Advisory Committee</td>
</tr>
<tr>
<td>WHO CCs</td>
<td>WHO Collaborating Centres</td>
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<tr>
<td>WHO ERLs</td>
<td>WHO Essential Regulatory Laboratory</td>
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</table>

9. Acknowledgements

The World Health Organization (WHO) wishes to acknowledge the contributions of experts who participated in the preparation and peer review of this report:

Derek Ellis (Canada), Gary Grohmann (Australia), Susan Perry (Canada), John Wood (United Kingdom).

WHO staff were involved in the development and review of this document and their contribution is gratefully acknowledged.

10. Annexes

1. Draft operational framework for pandemic vaccine response
2. Timelines of pandemic vaccine production
3. Process of the WHO vaccine response to an influenza pandemic or a potential pandemic
4. Further activities: the “parking lot”
5. Regulatory pathways for pandemic vaccines in the USA
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## Timeline of Pandemic Vaccine Production

<table>
<thead>
<tr>
<th>Week Number Since Virus Detection (Genetic Sequence Upload)</th>
<th>Comments and Potential Issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-4</td>
<td>CVVs are selected by the WHO CCs. If govt. scientists take about 3-4 days. Clinical volunteers about 31 days. Synthesis takes about six weeks. Safety testing (TB) and genotyping takes about 1 month. Stability test completion often takes a few days if the virus is in stable conditions. Vaccine production takes about 21 days. Classical reassortants take about 21 days. Synthetic seeds may also be an option. Safety testing TBD.</td>
</tr>
<tr>
<td>5-8</td>
<td>ADRs need to be monitored. A rapid test can be done at the first part of the clinical trial and then in the field depending on the WHO. This would occur before the 14th week mark.</td>
</tr>
<tr>
<td>9</td>
<td>Regulatory Agencies must inform the WHO on the status of the vaccine.</td>
</tr>
<tr>
<td>10</td>
<td>ERLs need to inform the WHO on the status of the vaccine.</td>
</tr>
<tr>
<td>11</td>
<td>Serology and endotoxin tests must be completed.</td>
</tr>
<tr>
<td>12</td>
<td>Immunization managers must inform the WHO on the status of the vaccine.</td>
</tr>
<tr>
<td>13</td>
<td>Lot release must be informed.</td>
</tr>
<tr>
<td>14</td>
<td>Vaccine roll-out must be informed.</td>
</tr>
<tr>
<td>15</td>
<td>Vaccine available for use.</td>
</tr>
<tr>
<td>16</td>
<td>Vaccine available for use.</td>
</tr>
<tr>
<td>17</td>
<td>Vaccine available for use.</td>
</tr>
<tr>
<td>18</td>
<td>Vaccine available for use.</td>
</tr>
</tbody>
</table>

### Activities

1. **Reassorting Labs**
   - Reassortment development
   - Development of CVVs for distribution
2. **WHO CCs and Reassorting Labs**
   - Reassortment evaluation
   - CVVs characterization including safety and sterility
3. **Manufacturers**
   - Reassortment assessment
   - CVVs yield and growth characteristics
4. **Development**
   - Clinical lot production
5. **Clinical Trials**
   - Recruitment
6. **Serology**
7. **ADR monitoring**
8. **Vaccine Production**
   - Antigen production
9. **Vaccine Formulation/ Packaging/ Distribution**
   - Vaccine available for use

### Comments and Potential Issues

1. CVVs are selected by the WHO CCs. If govt. scientists take about 3-4 days. Clinical volunteers about 31 days. Synthesis takes about six weeks. Safety testing (TB) and genotyping takes about 1 month. Stability test completion often takes a few days if the virus is in stable conditions. Vaccine production takes about 21 days. Classical reassortants take about 21 days. Synthetic seeds may also be an option. Safety testing TBD.
2. ADRs need to be monitored. A rapid test can be done at the first part of the clinical trial and then in the field depending on the WHO. This would occur before the 14th week mark.
3. Regulatory Agencies must inform the WHO on the status of the vaccine.
4. ERLs need to inform the WHO on the status of the vaccine.
5. Serology and endotoxin tests must be completed.
6. Immunization managers must inform the WHO on the status of the vaccine.
7. Lot release must be informed.
8. Vaccine roll-out must be informed.
10. Vaccine available for use.
11. Vaccine available for use.
12. Vaccine available for use.
13. Vaccine available for use.
15. Vaccine available for use.
17. Vaccine available for use.
18. Vaccine available for use.
ANNEX 3 – Process of the WHO vaccine response to an influenza pandemic or a potential pandemic

PROCESS FOR WHO PANDEMIC VACCINE RESPONSE TO INFLUENZA PANDEMICS/ POTENTIAL PANDEMICS

DETECTION OF A NOVEL VIRUS IN HUMANS

Preliminary global RA by GISRS including epidemiology, transmissibility and severity of the disease associated with the virus

Potentially significant to public health?

YES

Further virus characterization by WHO CCs

Assessment of need for high-growth reassortant development

Need to develop (a) high-growth reassortant(s)

NO

Selection of candidate viruses by GISRS

YES

Development of high-growth reassortants by GISRS and other laboratories

Biosafety assessment of CVVs by WHO

Initiation of the development of potency reagents by GISRS

Availability of potency reagents by GISRS

RA on further vaccine development

Further vaccine development/licensing/stockpiling

Clinical trials if needed

National/regional licensing/stockpiling as appropriate

WHO recommendation on pandemic vaccine production and use

Large-scale production/release of vaccines for use by country/region

Continuous assessment by WHO and subject experts on:

1. Epidemiology, including severity assessment
2. Virology
3. Biosafety assessment
4. The status of seasonal vaccine production
5. The need for pandemic or pre-pandemic vaccines
6. The risks associated with switch from seasonal to pandemic production
7. The need for and content of communications with SAGE, IHR, Industry and other stakeholders as appropriate
8. The risks associated with switch back to seasonal vaccine production

Continuous update to SAGE; updates to member states, and other stakeholders as appropriate

Glossary

CVV
Candidate Vaccine Virus

GISRS
WHO Global Influenza Surveillance and Response System

IHR
International Health Regulations

RA
Risk Assessment

SAGE
WHO Strategic Advisory Group of Experts on Immunization

WHO CC
WHO Collaborating Centre of GISRS

WHO ERL
WHO Essential Regulatory Laboratory

Review of the use of pandemic/pre-pandemic and seasonal vaccines by WHO, SAGE and other experts

Influenza Vaccine Response during the Start of a Pandemic – WHO Informal Consultation REPORT

VERSION 16.05.2016
ANNEX 4
Further Activities: the “Parking Lot”

The “parking lot” was a list of comments relevant to the informal consultation but not considered in depth. Some of these comments and proposals could be considered as part of forward agendas in future meetings.

Key proposals

Communication
• Improve sharing of information including genetic and epidemiological data.
• Review procedures to announce that pandemic vaccine production should be considered.
• Review how WHO communicates to stakeholders in an influenza pandemic emergency.

Research
• Review issues related to Gain of Function research.
• Further surveillance information on the spread of pandemic viruses and seasonal viruses concurrently. What is the likelihood of a pandemic virus displacing seasonal viruses?

Future meetings
• Hold follow-up consultations with this group of experts and enlarge to include other stakeholders if necessary, especially those from developing countries. The consultation should include pandemic vaccine strategies.
• Hold specific consultations on research and development of current and future pandemic vaccines.

Other activities
• Finalize the risk assessment tool (TIPRA).
• Review and improve the procedures for assessment of biocontainment for CVVs by the WHO biosafety committee.
• Finalize the PIRM.
• Update national pandemic preparedness plans.
• Revise biosafety criteria for CVV release (attenuation) including those for wild type viruses.
• Consider WHO prequalification of pandemic vaccines.
• Confirm that the Nagoya protocol will not apply to pandemic viruses.

Further proposals
• Synchronize regulatory procedures worldwide.
• Streamline vaccine lot release.
• Harmonize vaccine distribution, shipping, logistics, and cold chain.
• Include recombinant, cell based and live vaccines in future consultations on pandemic vaccine response.
• Review new technology platforms to speed up production of current vaccines.
• Review the need and progress of potentially more effective vaccine, including adjuvanted and universal vaccines.
• Post-release observational vaccine effectiveness studies, especially among elderly vaccines, should be undertaken.
• Behavioural analysis: how do people, e.g. politicians, medical profession and the public, actually behave in a pandemic and its implications to pandemic response.
• Regulators should consider the acceptance and use of the first available set of SRID reagents in all regions.
• Explore a central pilot facility (GMP) to produce clinical material for pandemic studies.
• Manufacturers should try to obtain preapproval for the import and use of RG material.

ANNEX 5
Regulatory pathways for pandemic vaccines in the USA

Procedures to license pandemic vaccines during a pandemic need to ensure that vaccines are safe and effective, but should not be so cumbersome that they create unnecessary delays in vaccine availability nor cause poor public acceptance of vaccine due to the perception that short cuts have been taken. In the USA, three regulatory mechanisms exist for making influenza vaccine available during a pandemic:

- **Biologics License Application (BLA).** This is based on data that demonstrate that the vaccine meets prescribed requirements for safety, purity and potency and can be used as a basis for Accelerated Approval whereby adequate and well-controlled clinical trials establish that the vaccine has an effect on a surrogate endpoint which is likely to predict a clinical benefit.

- **Investigational New Drug (IND).** This is for an unapproved vaccine with limited safety and efficacy data, where informed consent is required.

- **Emergency Use Authorization (EUA).** This is for an unapproved vaccine, or unapproved use of an approved vaccine, in response to a public health emergency or the potential for a public health emergency. Important criteria of an EUA are that the known and potential benefits of the use of the product outweigh its known and potential risks and there is no adequate, approved, and available alternative to the product.

In 2009, pandemic vaccines were licensed in the USA by means of strain change supplements to the seasonal influenza virus vaccine BLAs. However, in contrast to annual strain change supplements, clinical trials were required for 2009 pandemic vaccines. There are two influenza A(H5N1) vaccines licensed in the USA and this was done by the BLA route following advice from the US Vaccines and Related Biological Products Advisory Committee (VRBPAC). As a consequence, these licenses can be updated with other A(H5N1) viruses following WHO and VRBPAC advice.

A pandemic vaccine licensing strategy, with clinical trials performed during the inter-pandemic period, offers a clear pathway for implementation of virus-specific pandemic vaccine, with the proviso that clinical trials of a pandemic vaccine may be needed to establish formulation, schedule and corresponding targeted populations.
ANNEX 6
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ANNEX 7 – Scenario Worksheets

WHO Influenza Vaccine Response during the Start of a Pandemic

WORKSHEET - SCENARIO 1: PART 1

FROM THE "BURLINGTON NEWS": “A severe unknown influenza virus kills 4”

(Note: In discussing this scenario, note that the WHO GRISS network is continuously assessing and responding to the risk of existing and emerging influenza viruses and that the WHO mechanisms including HR and SAGE are functioning efficiently.)

WEEK 1

A local physician reported a cluster of 12 cases of severe acute respiratory infections (SARI) in a country called “Burlington”. Most patients needed respirators and 4 patients died. Preliminary laboratory tests confirmed the presence of influenza type A. Samples were sent to the NIC, arriving 2 weeks after the initial cluster was detected.

WEEKS 2-4

Within 2 weeks the NIC confirmed the presence of influenza type A but could not confirm the strain subtype in SARI cases. Meanwhile, several clusters of SARI were reported in other parts of the country involving 32 cases and 5 deaths. In a neighboring country, 54 SARI cases including 12 deaths were reported together with the detection of an unsubtypable influenza A virus in 19 SARI cases.

Cases were across all age groups.

(Note: WHO HR mechanisms are fully functional. Outbreak information is being reported through the network and on the WHO website. The WHO GRISS network is started and following up with immediate action among GRISS/PMIS on the possible emergence of novel influenza viruses. WHO all levels are notified and countries are informed through HR mechanisms.)

QUESTION 1

a) Do any additional communications need to be made?

b) Do any additional actions need to be taken?

QUESTION 2: “Is a novel influenza virus type A, subtype H9N2, confirmed in most of the specimens received. There is now worldwide awareness of the new influenza virus.”

a) When are manufacturers able to work with these CVVs to produce clinical trials (Chart 1) and (Chart 2)?

b) Does work with CVVs and production of clinical lots interface with the production of seasonal vaccine?

- What are the implications for all stakeholders if the decision on pandemic vaccine production is made in February (recommended) or in September (recommended but allows some vaccine production has started) (chart 3)?

- What are the implications for all stakeholders if the decision on pandemic vaccine production is made in May (recommended) or in December (recommended but allows some vaccine production has started) (chart 4)?

QUESTION 3

a) Should countries and stakeholders be informed on the progress of developed pandemic vaccine and if so, how?

b) How does WHO communicate with countries, industry and regulators?

WHO Influenza Vaccine Response during the Start of a Pandemic

WORKSHEET - SCENARIO 1: PART 3

WEEKS 5-12

Within 3 months, over 40 countries reported the spread of influenza with the vast majority needing urgent medical attention and intensive care. Over 100,000 cases were reported with a 4% mortality rate. There were reports of overwhelmed health-care systems in many countries. Laboratory tests on some 5000 samples showed that about 80% were of the new novel virus.

QUESTION 4

a) Is there need for pandemic vaccine now? On what basis is that need established?

b) Will national and regional contracts of seasonal vaccine be affected by activating pandemic APCs if so, how?

c) When should pandemic vaccine production start? Are there issues around seasonal versus pandemic vaccine availability? Are there any implications for those needing seasonal vaccine?

QUESTION 5 (concluding question)

a) In this context, what advice do you recommend with regard to pandemic vaccine production versus seasonal vaccine production?

b) On what basis is this recommendation made? What are the stakeholders needing the recommendation? How should the recommendations be communicated?

WHO Influenza Vaccine Response during the Start of a Pandemic

WORKSHEET - SCENARIO 2: PART 1

From the "Burlington News": “Unusual and possibly dangerous influenza virus detected”

(Note: In discussing this scenario, note that WHO GRISS network is continuously assessing influenza isolates and novel viruses and that HR and SAGE are regularly informed.)

WEEK 1

A local physician reports a cluster of 14 cases of influenza-like illness (ILI) associated with associated symptoms including conjunctivitis and diarrhea in five patients in a country called Burlington. Two patients were hospitalised and one died. Samples were sent to a WHO NIC laboratory and 7 weeks after the initial cluster was reported.

Must Be: From historical surveillance data, 79 cases of influenza-like illness were reported within a week of the first cluster in another country. Three patients were hospitalised with severe illness and there was 1 death reported. This was followed by a further report of 142 cases, in a neighboring country and all cases were laboratory confirmed as influenza type A. Seven patients were hospitalised and 2 deaths were reported. All age groups were affected.

WEEKS 4-6

Within a month, over 500 samples arrived in sentinel sites at the regional WHO/WHO. Over 100 were sent to a WHO/WHO. Within 6 weeks after the initial reports, a novel influenza type A, subtype H1N2 virus was identified in all studies of cases. The higher frequency of these reported cases has raised WHO and local public health authorities resulting in increased awareness of the outbreak. There is now widespread awareness of the new virus and it becomes clear that the rates of mortality and morbidity are no higher than that of seasonal viruses.

(Note: WHO HR mechanisms are fully functional. Outbreak information is being reported through the network and on the WHO website. The WHO/WHO network is started and following up with immediate action among GRISS/PMIS on the possible emergence of novel influenza viruses. WHO all levels are notified and countries are informed through HR mechanisms.)

QUESTION 3

a) Do any additional communications need to be made?

b) Do any additional actions need to be taken by whom?
ANNEX 7 – Scenario Worksheets

WHO Informal Consultation on Influenza Vaccine Response during the Start of a Pandemic

WORKSHEET – SCENARIO 2: PART 1

QUESTION 1:
(a) When are manufacturers able to work with WHO to produce (doses) of seasonal vaccine in a country?
(b) Does work with countries on production of clinical trials have started?

QUESTION 2:
(a) Is there a need for pandemic vaccine now or in the near future?
(b) Will national/region clinics be affected by vaccine production?
(c) How should vaccine production be maintained?

QUESTION 3:
(a) How does WHO communicate with countries, industry and regulators?

WORKSHEET – SCENARIO 3: PART 1

From the "Bungy News": "Flu has arrived!!"

Week 1

A local influenza report of a cluster of 10 cases of severe influenza-like illness (ILI) in a country named "Bungy". Most patients needed hospitalization and 2 other deaths were reported. Laboratory tests confirmed the presence of influenza type A virus and death certificates were sent to WHO/IVS laboratory arriving about 3 weeks after the initial case of influenza-like illness was reported.

Week 3

Influenza-like illness is confirmed and being reported in 8 neighboring countries and WHO has been asked to look into the emergence of severe influenza. WHO and the local authorities are collaborating on the investigation through the WHO website.

Week 4

WHO (and other) experts have raised concern over the emergence of severe influenza. WHO has been collaborating with countries and the situation has been monitored through the WHO website.

WORKSHEET – SCENARIO 3: PART 2

WHO Informal Consultation on Influenza Vaccine Response during the Start of a Pandemic

WORKSHEET – SCENARIO 2: PART 2

WEEKS 9-10

An influenza pandemic is declared and WHO is asked to distribute vaccines to all countries to ensure that all adults are vaccinated. The WHO has been asked to work closely with countries to ensure that all health care workers receive vaccines to protect them from the virus. WHO has been working with countries to ensure that the vaccine is distributed to all adults and that all adults receive vaccines to protect them from the virus.

WEEKS 11-12

WHO has asked all countries to distribute vaccines to all adults to ensure that all adults receive vaccines to protect them from the virus. WHO has been working closely with countries to ensure that the vaccine is distributed to all adults and that all adults receive vaccines to protect them from the virus.

WEEKS 13-14

WHO has asked all countries to distribute vaccines to all adults to ensure that all adults receive vaccines to protect them from the virus. WHO has been working closely with countries to ensure that the vaccine is distributed to all adults and that all adults receive vaccines to protect them from the virus.

WEEKS 15-16

WHO has asked all countries to distribute vaccines to all adults to ensure that all adults receive vaccines to protect them from the virus. WHO has been working closely with countries to ensure that the vaccine is distributed to all adults and that all adults receive vaccines to protect them from the virus.

WEEKS 17-18

WHO has asked all countries to distribute vaccines to all adults to ensure that all adults receive vaccines to protect them from the virus. WHO has been working closely with countries to ensure that the vaccine is distributed to all adults and that all adults receive vaccines to protect them from the virus.

WEEKS 19-20

WHO has asked all countries to distribute vaccines to all adults to ensure that all adults receive vaccines to protect them from the virus. WHO has been working closely with countries to ensure that the vaccine is distributed to all adults and that all adults receive vaccines to protect them from the virus.

WEEKS 21-22

WHO has asked all countries to distribute vaccines to all adults to ensure that all adults receive vaccines to protect them from the virus. WHO has been working closely with countries to ensure that the vaccine is distributed to all adults and that all adults receive vaccines to protect them from the virus.

WEEKS 23-24

WHO has asked all countries to distribute vaccines to all adults to ensure that all adults receive vaccines to protect them from the virus. WHO has been working closely with countries to ensure that the vaccine is distributed to all adults and that all adults receive vaccines to protect them from the virus.

WEEKS 25-26

WHO has asked all countries to distribute vaccines to all adults to ensure that all adults receive vaccines to protect them from the virus. WHO has been working closely with countries to ensure that the vaccine is distributed to all adults and that all adults receive vaccines to protect them from the virus.

WEEKS 27-28

WHO has asked all countries to distribute vaccines to all adults to ensure that all adults receive vaccines to protect them from the virus. WHO has been working closely with countries to ensure that the vaccine is distributed to all adults and that all adults receive vaccines to protect them from the virus.

WEEKS 29-30

WHO has asked all countries to distribute vaccines to all adults to ensure that all adults receive vaccines to protect them from the virus. WHO has been working closely with countries to ensure that the vaccine is distributed to all adults and that all adults receive vaccines to protect them from the virus.

WEEKS 31-32

WHO has asked all countries to distribute vaccines to all adults to ensure that all adults receive vaccines to protect them from the virus. WHO has been working closely with countries to ensure that the vaccine is distributed to all adults and that all adults receive vaccines to protect them from the virus.

WEEKS 33-34

WHO has asked all countries to distribute vaccines to all adults to ensure that all adults receive vaccines to protect them from the virus. WHO has been working closely with countries to ensure that the vaccine is distributed to all adults and that all adults receive vaccines to protect them from the virus.

WEEKS 35-36

WHO has asked all countries to distribute vaccines to all adults to ensure that all adults receive vaccines to protect them from the virus. WHO has been working closely with countries to ensure that the vaccine is distributed to all adults and that all adults receive vaccines to protect them from the virus.

WEEKS 37-38

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WEEKS 39-40

WHO has asked all countries to distribute vaccines to all adults to ensure that all adults receive vaccines to protect them from the virus. WHO has been working closely with countries to ensure that the vaccine is distributed to all adults and that all adults receive vaccines to protect them from the virus.

WEEKS 41-42

WHO has asked all countries to distribute vaccines to all adults to ensure that all adults receive vaccines to protect them from the virus. WHO has been working closely with countries to ensure that the vaccine is distributed to all adults and that all adults receive vaccines to protect them from the virus.

WEEKS 43-44

WHO has asked all countries to distribute vaccines to all adults to ensure that all adults receive vaccines to protect them from the virus. WHO has been working closely with countries to ensure that the vaccine is distributed to all adults and that all adults receive vaccines to protect them from the virus.

WEEKS 45-46

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WEEKS 47-48

WHO has asked all countries to distribute vaccines to all adults to ensure that all adults receive vaccines to protect them from the virus. WHO has been working closely with countries to ensure that the vaccine is distributed to all adults and that all adults receive vaccines to protect them from the virus.

WEEKS 49-50

WHO has asked all countries to distribute vaccines to all adults to ensure that all adults receive vaccines to protect them from the virus. WHO has been working closely with countries to ensure that the vaccine is distributed to all adults and that all adults receive vaccines to protect them from the virus.

WEEKS 51-52

WHO has asked all countries to distribute vaccines to all adults to ensure that all adults receive vaccines to protect them from the virus. WHO has been working closely with countries to ensure that the vaccine is distributed to all adults and that all adults receive vaccines to protect them from the virus.
ANNEX 7 – Scenario Worksheets

WHO Informal Consultation on Influenza Vaccine Response during the Start of a Pandemic:

WORKSHEET - SCENARIO 3: PART 2

WEEKS 12-26

Within a 6-month period, 35 samples arrived at the NIs and 30 were sent to a WHO lab. 2 months after the initial reports, a novel influenza virus type A, subtype H1N1, virus was identified in all clusters of cases.

**QUESTION 4:**

a) Is there a need for pandemic vaccine now? On what basis is the need established? What are the implications for those needing seasonal vaccine?

b) Will national/regional contracts of seasonal vaccine be affected by actively procuring pandemic APVs if so, how?

c) What should pandemic vaccine production start? (i.e., seasonal or pandemic vaccine availability)

6-12 MONTHS

Within 12 months, 9 countries in two different WHO regions, reported the spread of influenza with the vast majority needing urgent medical attention and intensive care. The case-fatality rate was 30%.

**QUESTION 5:** (concluding question)

a) Based on the evidence provided in the scenario, what would you recommend with regard to pandemic vaccine production vs. seasonal vaccine production?

b) On what basis is this recommendation made? Who are the stakeholders making this recommendation? How should the recommendations be communicated?