Influenza Vaccine Response during the Start of a Pandemic


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Executive Summary

In June 2015, the World Health Organization (WHO) held an Informal Consultation to bring together key stakeholders to address questions associated with vaccine response at the start of an influenza pandemic and, in particular, the strategic problems associated with switching from seasonal influenza vaccine production to pandemic vaccine production (switch). The 2015 Consultation clarified some of the complexities associated with the switch and identified key actions and challenges. However, several gaps remained in both knowledge and planning.

A second Informal Consultation was held by WHO in June 2016. The main goal of the 2016 consultation was to work to bridge these gaps by better understanding the complexities of the early stages of pandemic vaccine development; elaborating the principles that could guide the decision to switch; obtaining a better understanding of the evidence or data needed to support the decision-making process; and prioritizing the technical actions needed to overcome any bottlenecks in pandemic vaccine production.

The main outcomes of the meeting were:

- The decision to switch is complex and multifaceted and will involve nearly all parts of the influenza community. An integrated approach could be achieved by establishing an international expert group tasked with making such a recommendation to WHO.

- Greater clarity and transparency is needed in the decision-making process, which will be enhanced by elaborating the principles involved in making such a decision. Several principles were proposed during the Consultation.

- National and international decision makers should be made aware of the complex issues associated with the decision to switch.

- As identified during the first consultation, there are several potential technical bottlenecks which could severely interfere with pandemic vaccine development. These were discussed and solutions were proposed. The next steps would be to convene expert groups in order to address potential solutions in greater depth.

- The feasibility of establishing a publicly funded small scale GMP pilot lot vaccine production facility should be explored. The facility could be used in the early stages of pandemic vaccine development by assessing CVV yield; assessing biosafety; producing pilot lots of vaccine for evaluation of process yield and for clinical evaluation; supplying antigen for potency reagents; and establishing diagnostic capacity.

- Three charts were finalized during the consultation (the operational framework for pandemic vaccine response; timelines of pandemic vaccine production; process of the WHO vaccine response to an influenza pandemic or a potential pandemic). These are intended for inclusion in the final version of the PIRM Framework document.
1. Introduction and Scope of the Meeting

In June 2013, WHO published a revision of the pandemic influenza preparedness and response guidance entitled Pandemic Influenza Risk Management (PIRM) — WHO interim guidance (ref 1). The WHO PIRM framework provides flexibility to countries for risk-based national response, including pandemic influenza vaccine response. In order to ensure rapid and adequate production and deployment of pandemic influenza vaccines, taking into consideration seasonal epidemics which may be severe and occur concurrently at the start of a pandemic, there is a pressing need to review the whole process from identification of the pandemic virus through to vaccines being available for use.

In June 2015, the first WHO Informal Consultation was held (http://www.who.int/influenza/resources/publications/influenzavaccineresponse_meeting01/en/) in order to bring together key stakeholders to address questions associated with pandemic vaccine response at the start of an influenza pandemic and to identify and discuss the strategic problems around switching from seasonal influenza vaccine production to pandemic vaccine production.

The Consultation clarified some of the enormous complexities at national, regional and global levels with the various public and private partners involved and an “operational framework for pandemic vaccine response was drafted”. While a common understanding of an effective pandemic vaccine response was established at the first Consultation, key challenges were also identified including: risk assessment; availability of candidate vaccine viruses (CVVs) and reagents; clinical trials; regulatory procedures; bottlenecks involved in production of seasonal vaccines and in the switch to pandemic vaccine production; and programmatic issues involved in vaccine “roll out”. Also adding to the complexity was the possible need for the use of seasonal vaccines at the start of a pandemic.

One of the key recommendations from the first WHO Consultation was that WHO, through its advisory bodies, shall recommend the start of pandemic influenza vaccine production based on risk assessment. It was also recommended that the PIRM be updated from the earlier “interim” 2013 version and finalized based on the outcome of the WHO Consultation.

The Second Informal Consultation was held in June 2016. Its main objectives were to:

- Better understand the complexities and strategies for pandemic vaccine response at the start of a pandemic through discussion of different pandemic scenarios;
- Elaborate the principles that will guide the decision to switch from production of seasonal vaccine to pandemic vaccine;
- Better understand the evidence or data needed to support the decision-making process;
- Prioritize the technical actions needed to overcome any bottlenecks in pandemic vaccine production; and
- Finalize the draft “operational framework for a pandemic vaccine response” and use this to finalize the WHO PIRM Framework.
It was emphasized that both the first and the second consultations were designed specifically to address issues and difficulties in producing pandemic vaccines at the start of a pandemic and not to address other different but possibly related issues surrounding pandemic vaccine production and use.

Thirty-eight participants from 24 countries were drawn from WHO Collaborating Centres (WHO CCs), National Influenza Centers (NICs), WHO Essential Regulatory Laboratories (ERLs), academic research community, National Regulatory Authorities (NRAs), national/regional public health agencies, vaccine manufacturers, International Federation of Pharmaceutical Manufacturers & Associations (IFPMA), Developing Countries Vaccine Manufacturers Network (DVVMN) and other stakeholders.

2. **Reports of key international pandemic influenza preparedness activities**

At the start of the first consultation, background information was provided to bring all participants up to date on some key international pandemic influenza preparedness activities:

- WHO Pandemic Influenza Risk Management (PIRM) Framework *(ref 1)*
- The International Health Regulations (IHR) 2005 *(ref 2)*
- The Pandemic Influenza Preparedness (PIP) Framework *(ref 3)*
- The WHO Global Action Plan for Influenza Vaccines (GAP) *(ref 4)*

This information considerably helped the discussions in 2015, but needed updating for the second consultation in 2016. In addition there were other activities that need some explanation in order that participants could fully contribute to the second consultation.

### 2.1 The key players in WHO decision-making at the start of pandemic influenza vaccine production

WHO will engage all expertise inside and outside of the organization needed for the decision making, including but not limited to the following WHO programmes and advisory bodies:

- Global Influenza Programme including WHO Global Influenza Surveillance and Response System (GISRS) and PIP Framework Secretariat
- Initiative for Vaccine Research including GAP
- Technologies Standards and Norms including vaccine regulation
- Global Capacities, Alert and Response including IHR
- Strategic Advisory Group of Experts (SAGE) on Immunization
- IHR Emergency Committee

### 2.2 Pandemic Influenza Risk Management (PIRM)

As reported in the first consultation, the WHO published in 2013 a revision of the influenza preparedness and response guidance, entitled “Pandemic Influenza Risk Management (PIRM) – WHO interim guidance”. The PIRM Framework provides high-level guidance on risk management of pandemic influenza, but
the section on pandemic influenza vaccines still needs completion. The two WHO consultations on Influenza Vaccine Response during the Start of a Pandemic should enable the PIRM Framework to be completed with the inclusion of the operational framework and the practical issues associated with pandemic vaccine development and, in particular, those associated with switching from seasonal vaccine to pandemic vaccine production.

2.3 Tool for Pandemic Influenza Risk Assessment (TIPRA)
(http://www.who.int/influenza/areas_of_work/human_animal_interface/tipra/en/)

One of the main components of the PIRM Framework is the country-specific risk assessment of the pandemic potential of a newly detected influenza virus, taking into account the global risk assessment conducted by WHO. TIPRA provides the means by which countries, regions and WHO (at a global level) can conduct standardized hazard assessment. TIPRA attempts to answer questions such as, “what is the risk of sustained human-to-human transmission of the virus; specifically, what is the likelihood and what is the likely impact?”

There are 11 steps in the TIPRA process and during its development, it has been tested several times in simulation exercises before Version 1 was launched in May 2016 (http://apps.who.int/iris/bitstream/10665/250126/1/WHO-OHE-PED-GIP-2016.3.pdf).

2.4 Global Action Plan for Influenza Vaccines (GAP)

As reported during the first consultation, the Global Action Plan for Influenza Vaccines (GAP) is a comprehensive strategy to reduce the global shortage of influenza vaccines for seasonal epidemics and pandemic influenza in all countries through three major approaches:
1. Increase in seasonal vaccine use.
2. Increase in vaccine production capacity.
3. Research into more effective vaccines.

Another important component is sustainability of any improvements made.

GAP started in 2006 and there has been considerable progress since then, with nine approved new vaccines (6 pandemic and 3 seasonal vaccines) with some of the vaccines being prequalified for possible UN use. GAP will end in 2016, when there will be a review taking account of opinions from stakeholders around the world (http://www.who.int/influenza_vaccines_plan/en/).

2.5 Standard Material Transfer Agreements 2 (SMTA2)
(http://www.who.int/influenza/pip/benefit_sharing/smta2/en/)

Under the PIP Framework, a non-GISRS institution that receives PIP biological materials from a GISRS laboratory is required to complete a Standard Material Transfer Agreement 2 (SMTA2) with WHO. The SMTA2 is a legally-binding contract to ensure that manufacturers of vaccines, antivirals and diagnostic products and research institutions that receive PIP biological materials share with WHO some of the benefits arising from their access to the PIP biological materials. Possible benefits include pandemic influenza vaccines, antiviral medicines and other pandemic related products or technologies.

In terms of vaccine manufacturers, WHO strategy was first to reach agreement with manufacturers that had prequalified vaccines and had export experience. At the
time of the second consultation, WHO had concluded or was in formal negotiation with seven large vaccine manufacturers and was in informal negotiations with two other manufacturers having prequalified vaccines. For manufacturers of diagnostic materials, WHO was in formal negotiations with two large manufacturers and a number of smaller manufacturers. Forty-seven academic and research institutions from around the world had already signed SMTA2s and 19 had agreed to provide some benefits. In addition, WHO will be consulting widely to examine the various options for effective deployment of influenza vaccines.

2.6 The IFPMA perspective on the initiation of pandemic vaccine production

Before the PIRM Framework was adopted, vaccine manufacturers had a clear signal to start pandemic vaccine production when WHO had declared pandemic phase 6 of the former WHO pandemic guidance was declared by WHO. At present, the PIRM Framework gives responsibility to countries and regions for pandemic response based on its own risk assessment, but the World Health Assembly clearly noted that the initiation of pandemic vaccine production is the responsibility of vaccine manufacturers (ref 6), leading to considerable uncertainty surrounding the decision to initiate pandemic vaccine production. Given the interconnected nature of vaccine manufacturers and countries, they need:

• A clear international signal of when to switch from seasonal to pandemic vaccine production;
• Clear identification of roles and responsibilities of key stakeholders involved in the decision-making process; and
• Clarity and transparency in the decision-making process.

2.7 The USA plan to mitigate vaccine mismatch risk

During the 2014-2015 northern hemisphere influenza season, there was late emergence of an influenza A (H3N2) virus which led to a vaccine mismatch and reduction in vaccine effectiveness (http://ecdc.europa.eu/en/publications/Publications/RRA-InfluenzaA-H3N2-Dec-2014.pdf http://www.nature.com/articles/srep15279). As a result of a USA government enquiry, the HHS organized an interagency consultation to try to develop a plan to mitigate the risk of a vaccine mismatch. There are elements of this plan that have synergy with improving the decision-making process for a pandemic vaccine switch, e.g. improving CVV and reagent availability and improving the yield of high-growth reassortants. The proposal from the consultation is that the USA decision on seasonal vaccine strains could be in stages, with the possibility of one vaccine strain decision being delayed until April 15th.

The most relevant message from the USA consultation is to take steps to be better prepared to make a vaccine strain change, whether it be seasonal or pandemic.
3. **Organization of the Consultation**

After hearing the progress reports described above and in order to stimulate discussion to address the main objectives of the consultation, participants were provided with two different scenarios (Annex 1) for initiating a pandemic vaccine response during the early stages of a pandemic. Participants were tasked with assessing the type of data needs and the principles involved in making decisions about vaccine production following the emergence of a pandemic virus while seasonal influenza virus was still circulating and causing illness.

The discussions were enriched by the varied backgrounds and experiences of the participants and representatives from vaccine manufacturers. In addition, as with the first consultation, the discussions were aided by an external facilitator. The pandemic scenario discussions were invaluable for formulating ideas as participants moved on to the next tasks during the meeting and for different stakeholders to understand the challenges involved of various players. It was noticeable that during the second consultation, participants had a clearer understanding of the need for risk assessment and the procedures for producing a pandemic vaccine than they had one year earlier. Consequently, one of the tasks identified for participants during the second consultation was to identify the key principles and the data required for a decision to recommend the start of pandemic vaccine production so that key stakeholders will also be able to understand and follow the recommendation with more ease and with greater transparency.

The second focus of the consultation was to refine the description of the pandemic vaccine process, which was drafted during the first consultation. Three tables outlining the process were finalized by input from all participants.

The third activity was to build on earlier experience from the first consultation and identify principles that should be applied to decisions made to switch from seasonal to pandemic vaccine production and to address the various technical bottlenecks in pandemic vaccine production so that possible solutions could be identified.

During the first consultation, areas of concern that were outside the scope of the meeting but still needed attention were listed in a “parking lot”. Supplementary items identified during the second consultation were added to the list. (Annex 5).

Finally, the key outcomes and next steps were identified.

4. **Refinement of the process for pandemic vaccine response**

As noted above, three pandemic vaccine process charts were finalized during the consultation:

- Operational framework for pandemic vaccine response (i.e. who takes the actions?). (Annex 2)
- Timelines of pandemic vaccine production (i.e. when are actions taken?). (Annex 3)
- Process of the WHO vaccine response to influenza pandemic or potential pandemics (i.e. how are actions taken?). (Annex 4)
The outcomes of the consultation will be referenced in the PIRM Framework document in order to better describe the complexities and interactions of different stakeholders in making a pandemic vaccine available.

It was particularly challenging to develop accurate and realistic timelines for pandemic vaccine production as so many of the activities had an impact on other activities. For example, if there are delays in producing a CVV, there will also be delays in vaccine clinical trials, vaccine production and ultimately in vaccine availability. The timelines developed during the two consultations therefore reflect pandemic vaccine production during ideal circumstances. If some activities do not go well, they may take longer and this is indicated in the hatched areas of the chart.

5. Principles and bottlenecks in making the switch from seasonal to pandemic vaccine production

Participants were invited to discuss and make proposals for the types of evidence, expertise and principles needed to make a decision to switch from producing seasonal vaccine to pandemic vaccine. Inevitably there are some aspects of the vaccine production process which could cause potential bottlenecks and delay vaccine availability and some of these were raised during the first consultation.

At the second consultation, participants were encouraged to develop proposals for solutions to the bottlenecks and identify who should be responsible for taking each issue forward.

It was noted, however, that these proposals only reflect the opinions of the participants during the consultation and the actual solutions may be different after further discussed among expert groups drawn together by WHO.

5.1 Principles

There are many challenges in switching from production of seasonal vaccine to pandemic vaccine and, as elaborated during the first consultation, they are:

- A switch that is too early may compromise the production of seasonal vaccine with possibly severe public health consequences.
- A switch that is too late could have significant public health consequences, particularly if the pandemic is severe.
- Influenza vaccine production facilities cannot produce seasonal and pandemic vaccines at the same time. If the decision to start pandemic vaccine production is made when a facility is in the middle of producing seasonal vaccine, the facility has to stop seasonal vaccine production and switch to pandemic vaccine production. In addition, many areas lack influenza vaccine production capacity.
- Risk assessment involves the virological, epidemiological and clinical aspects of the emerging pandemic as well as assessment of the risk of stopping seasonal vaccine production potentially resulting in not having enough seasonal vaccine for vulnerable people.
• Few countries have a revised pandemic preparedness plan in place that includes country-specific risk assessment, risk management and vaccine response procedures.

With these challenges in mind, participants identified the following key principles in making a decision to start pandemic vaccine production:

• Any decision will be made on incomplete data. The amount and quality of data available in the early stages of a pandemic are likely to be different from those available in the later stages.

• There should be some built-in flexibility in order to review the decision to switch or not to switch as new data arise. But once the decision to switch is made, it will not be realistic to switch back immediately.

• There are different components to the advice and evidence needed:
  o Technical (e.g. evidence, data).
  o Philosophical (e.g. ethics, transparency).
  o Structural (e.g. governance, expert advice).

• The declaration of a pandemic does not automatically trigger a switch to pandemic vaccine production. For example, a pandemic vaccine may be produced against the threat from a newly emerging, highly pathogenic virus, although it may not have reached pandemic proportions. Conversely, it may not be considered appropriate to produce a pandemic vaccine if a pandemic has been declared, yet the virus causes only mild infections while ongoing seasonal influenza infections are severe and widespread. Considerations such as time of year, the geography of seasonal and pandemic virus circulation, and availability of CVVs will also play a role.

• The WHO recommendation should maximize global health and be guided by expert opinion.
  o The risks of mortality, morbidity and economic consequences should be considered in order to minimize serious impact.
  o The impact of not having enough seasonal vaccine available in case of a switch should be considered.

• Any decision or recommendation should be evidence-based and the process should be transparent and defensible.
  o There should be clarity of roles and responsibilities for individuals and organizations making decisions.
  o The information assessed should include a global map of influenza manufacturing capacity and relevant timelines for vaccine production.

• Different vaccine formulations should be an option (e.g. monovalent pandemic and monovalent seasonal vaccine; monovalent pandemic and bivalent seasonal vaccine) and these options should be evaluated by experts.

• The structure of the WHO Expert committee tasked with making recommendations on the start of
pandemic vaccine production should be representative and include groups such as manufacturers.

- There should be clear, understandable and rapid communication of any decision or recommendation, equally accessible by all stakeholders.

### 5.2 Bottlenecks

As identified during the first consultation, there are several potential technical bottlenecks that could severely interfere with pandemic vaccine development. Each bottleneck was discussed by participants with a view to identifying the data needed to solve the problems and, where possible, to identify how the problem could be solved and by whom.

#### CVV Production/Availability

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<tr>
<th>BOTTLENECK</th>
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<tbody>
<tr>
<td>Lack of suitable BSL3/GMP laboratories for early small scale work</td>
<td>• Review number of suitable labs available</td>
<td>• Dedicated publicly funded pilot BSL3/GMP labs</td>
</tr>
<tr>
<td>Not enough labs producing CVVs especially from highly pathogenic (hp) viruses</td>
<td>• None identified</td>
<td>• WHO to identify and establish more pandemic CVV labs</td>
</tr>
<tr>
<td>Not enough high containment labs for making LAIV CVVs</td>
<td>• Review number of suitable labs available</td>
<td>• Dedicated publicly funded pilot BSL3/GMP labs</td>
</tr>
<tr>
<td>Uncertainty of CVV status in terms of implications related to the Nagoya Protocol or PIP Framework*</td>
<td>• None identified</td>
<td>• WHO to obtain clarification</td>
</tr>
<tr>
<td>Uncertainty about manufacturers’ obligations to share synthetic seed viruses and shipping requirements</td>
<td>• None identified</td>
<td>• Manufacturers to start dialogue with WHO</td>
</tr>
<tr>
<td>Delays in access to CVVs</td>
<td>• None identified</td>
<td>• Manufacturers to obtain import permits (including GMO CVV) in advance; obtain agreement(s) with courier(s)</td>
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* After the Consultation, clarification has been obtained that CVVs are included within PIP Framework, i.e. not covered by Nagoya Protocol
### Biocontainment for Wild Type Pandemic Virus and CVV

<table>
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| Identification of the type of safety tests needed; availability of WT virus comparator; the need for ferret safety tests | • WT virus risk assessment  
• Criteria for attenuation and biosafety and utility of safety tests | • WHO to review guidance on safety testing of CVVs                          |
| Continued need for chicken pathogenicity tests of CVVs derived from hp viruses | • Historical review of chicken test data  
• Review in vitro test data | • USDA to remove requirement for chicken pathogenicity test or remove hp influenza viruses from Select Agent status |
| Slow decision on biosafety and USDA Select Agent status; biosafety status could be country-specific | • Information on pathogenicity  
• Sequence especially HA/NA gene segments and including both egg and cell isolates | • All CVV labs aiming to work with hp viruses should register with USDA in advance  
• WHO to lead and coordinate bio-safety assessment and to speed up assessment  
• WHO to provide feedback on IFPMA ‘white paper’ on CVV biocontainment  
• Better coordination of CVV labs  
• Better communication between CVV labs and manufacturers  
• CVV labs to standardize release documents for CVVs  
• Future use of synthetic HA/NA CVVs |
| Uncertainty about biosafety status of synthetic CVVs especially with USDA Select Agent status | • Information on pathogenicity  
• Sequence especially HA/NA gene segments and including both egg and cell isolates | • Manufacturers to clarify status with human and agricultural safety authorities  
• WHO to coordinate accumulation of data and liaison with human and agricultural safety authorities |
### Yield and Manufacturing of CVVs

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<tr>
<td>Low yielding CVV; slow evaluation of CVV yield</td>
<td>• Small scale yield in eggs and cells</td>
<td>• CVV labs and manufacturers to optimize rapid small scale yield assessment techniques</td>
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<tr>
<td></td>
<td></td>
<td>• Better high yield donor viruses</td>
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<td></td>
<td></td>
<td>• Dedicated publicly funded pilot BSL3/GLP labs</td>
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<tr>
<td>Low downstream yield from CVV (i.e. vaccine processing)</td>
<td>• Small scale processing yield</td>
<td>• CVV labs and manufacturer to optimize rapid small scale yield and processing assessment techniques</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Dedicated publicly funded pilot BSL3/GMP labs</td>
</tr>
<tr>
<td>Not enough CVVs to select one with high yield</td>
<td>• None identified</td>
<td>• WHO to identify and establish more possible pandemic CVV labs</td>
</tr>
<tr>
<td>Genetic/protein instability during downstream processing</td>
<td>• Genetic/amino acid sequencing</td>
<td>• Sequence optimization to improve yield and stability</td>
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### Clinical Trials for the First Pandemic Vaccines

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<tr>
<td>Delay in availability of clinical trial vaccine lots, specifically related</td>
<td>• Data from SRID and alternative potency assays</td>
<td>• WHO and ERLs to review and recommend alternative potency assays</td>
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<tr>
<td>to vaccine potency assays</td>
<td></td>
<td>-----------------------------------------------------------------------------------------------------</td>
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<tr>
<td>Delay due to GMO issues</td>
<td>• Certificate of analysis</td>
<td>• None identified</td>
</tr>
<tr>
<td>Delay due to country-specific vaccine lot release</td>
<td>• Lot release data</td>
<td>• WHO ERLs to coordinate pandemic vaccine lot release globally</td>
</tr>
<tr>
<td>Delay in clinical trial protocol review</td>
<td>• None identified</td>
<td>• Harmonize clinical trial procedures</td>
</tr>
<tr>
<td>Delay in serology assays</td>
<td>• Robustness and reproducibility of assays</td>
<td>• Improvement, standardization and acceptance of assays</td>
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### Timing of SRID Reagents for Vaccine Potency Testing

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| Delays in reagent supply will delay vaccine lot release and vaccine supply | • Availability of antigen and antiserum for use in reagent production  
• Biosafety status of antigen  
• Which CVV is being used?  
• Suitability of existing reagents, i.e. are new ones really needed? | • Reagent supply needs better coordination and harmonization  
• Alternative validated potency tests  
• Early start of antiserum production (before CVV availability)  
• Allow use of heterologous reagent  
• Consider making panel of reagents at risk |

### Regulatory Harmonization

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| Lack of mutual recognition of regulatory procedures leading to delays in vaccine supply | • Review of regulatory requirements in different countries  
• A basic set of criteria for seasonal and pandemic vaccine prequalification  
• Requirements for donated vaccines in an emergency  
• Confirmation of whether country NRAs meet published criteria for functionality  
• Robustness of pandemic vaccine capability in countries  
• Review of data on vaccine effectiveness  
• Labelling requirements for emergency use of pandemic vaccine  
• Review of pandemic vaccine lot release requirement in different countries | • Cross communication between regulatory authorities  
• WHO to introduce prequalification for seasonal and pandemic influenza vaccines  
• Continue to support regional regulatory harmonization in low and middle income countries  
• MS to establish or strengthen NRAs:  
  o Regulatory systems  
  o Marketing Authorization  
• Agreement on criteria for assessment of vaccine effectiveness  
• Harmonization of labels and package inserts for pandemic vaccines  
• Harmonization of pandemic vaccine lot release |
### Risk Assessment

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| Delay in making a risk assessment of whether or not to make a vaccine switch | • Potential impact of new virus versus that of seasonal virus, including:  
  - Epidemiology  
  - Severity  
  - Modelling  
  - Impact  
  - Ability to manufacture vaccine  
  • Update of risk assessment as more data becomes available | • Develop decision-making process including data, data source, data collecting channels, analytical methods, and communication channels.  
  • WHO to prepare formal output from risk assessments  
  • Review of risk assessment methodology |

### Fill and Finish Capacity

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| If pre-filled syringes are used, filling is slower and uses more antigen; if multidose vials are used, thiomersal will be used and this limits its use | • Criteria used by countries for selecting final presentation  
  • Formulation requirements to ensure required shelf life  
  • An understanding of the need for prefilled syringes for some groups, e.g. pregnant women, children | • Evaluate different delivery methods  
  • Education on benefits of use of multidose vials  
  • Use USA model of a fill/finish network to optimize global filling capacity |
### 6. Key Outcomes of the Consultation and Next Steps

**The main outcomes of the second consultation were:**

- There is a need for an integrated approach to the decision to switch or not to switch as there are many components to the decision process and they will involve nearly all parts of the influenza community. Such an integrated approach could be achieved by bringing together an international expert group tasked with making such a recommendation. The expert group should follow the principles as outlined during this consultation and should meet occasionally to work through switch scenarios in order to establish an effective working relationship.

- There is a need for greater clarity and transparency in the decision-making process and the elaboration during this consultation of the principles involved in making the decision will be a considerable help.

- As a result of the scenario exercises and resulting discussions, participants were now much better informed about the complex nature of the switch process and thus would be better equipped to make a recommendation and implement the decision. However, it is less likely that key national and international decision makers are fully aware of these issues. A critical outcome of the two consultations is to bring this information to key decision makers both within and outside of WHO.

- A main focus of the second consultation was to propose solutions to bottlenecks and problems that would interfere with making a timely switch and making pandemic vaccine available quickly. The next steps would be to follow up these proposals including identifying leading entities and convening expert groups in order to bring solutions closer. It was agreed at the consultation that small working groups, organized by WHO, would take this forward.

- One important outcome was the identification of solutions to the potential bottleneck where manufacturers are uncertain about clear signals being received concerning the need to escalate pandemic vaccine production (Bottleneck: Risk Assessment; Operational Flowchart: 1 Risk Assessment and Communications).

- One proposal that was placed in the “parking lot” during the first consultation was to establish a publicly funded small scale GMP pilot lot vaccine production facility. This proposal was repeated several times during the second consultation so that it was now regarded as one of the key outcomes. The facility could be used to assess CVV yield, assess biosafety, produce pilot lots of vaccine for evaluation of process yield, assess supply of antigen for potency reagent, establish diagnostic capacity and for training purposes. The facility would need to be in continuous use, e.g. as a training facility in non-pandemic period. Then in a pandemic emergency it would be used for influenza vaccine evaluation.
Following finalization of the operational framework for pandemic vaccine response, it will now be possible to finalize the PIRM Framework document. Following that, there should be consultation with member states on its implementation and periodically it should be reviewed and updated.

As the expert working group progresses as mentioned above, WHO may consider organizing a third consultation on the same topic.

Further activities recognized during the first and second consultations and not considered directly within the scope of the consultations are listed in the “parking lot” (Annex 5).

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. Standard Material Transfer Agreement 2 (SMTA2) outside the WHO global influenza surveillance and response system (GISRS)
   http://www.who.int/influenza/pip/smta2_eng.pdf?ua=1

   http://apps.who.int/gb/ebwha/pdf_files/WHA64/A64_10-en.pdf

8. Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<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>ERL</td>
<td>WHO Essential Regulatory Laboratory</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>GISRS</td>
<td>WHO Global Influenza Surveillance and Response System</td>
</tr>
</tbody>
</table>
Annexes

1. Scenarios
2. Draft operational framework for pandemic vaccine response
3. Timelines of pandemic vaccine production
4. Process of the WHO vaccine response to an influenza pandemic or a potential pandemic
5. Further activities: the “parking lot”
6. List of Participants

9. Acknowledgements

The World Health Organization (WHO) wishes to acknowledge the contributions of all experts who participated in the preparation and in particular:

Derek Ellis (Canada), Susan Perry (Canada) and John Wood (United Kingdom) for peer review of the report.
ANNEX 1 – Scenarios

Scenario 1
(Note: In discussing this scenario, note that the WHO GISRS network is continuously assessing and responding to the risk of existing and emerging influenza viruses and that the WHO mechanisms including IHR and SAGE are functioning efficiently).

Week 1
GISRS has detected 12 human cases of H6N9 infection in the Netherlands during the month of December. The virus, originally detected in aquatic birds has acquired mutations in HA usually associated with mammalian adaptation.

Question 1
a) Do any additional communications need to be made?
b) Do any additional actions need to be taken and by whom?

Week 2
One hundred further cases of human H6N9 infection have been detected within the same region. All infections are clinically not as severe as those associated with seasonal H3N2 virus that is causing widespread human infection. An H6N9 CVV was prepared by GISRS one year earlier.

Question 2
a) Do extra CVVs need to be made?
b) Do any additional actions need to be taken and by whom?

Week 6
Within a month over 800 cases of H6N9 human infection have occurred across several countries. Cases were across all age groups.

Question 3
a) Is there a need to advance the development for a pandemic vaccine now? And if so, how far down the development pathway should it go and by whom?
b) Will national/regional contracts of seasonal vaccines be affected by activating pandemic APAs; if so, how?
c) When should pandemic vaccine production start? For all manufacturers or some - if only some, what are the principles or assumption to consider when making this decision. Who decides what?
d) Are there issues around seasonal versus pandemic vaccine availability? Are there any implications for those needing seasonal vaccine?

Question 4 (Concluding Question):
a) In this scenario, what would you recommend with regard to pandemic vaccine production vs. seasonal vaccine production?
b) On what basis is this recommendation to be made? Who are the stakeholders making the recommendation? How should the recommendations be communicated?
ANNEX 1 – Scenarios

Scenario 2
(Note: In discussing this scenario, note that WHO GISRS network is continuously assessing influenza isolates and novel viruses and that IHR and WHO expert committees such as SAGE are regularly informed).

Week 1
GISRS has detected the emergence of an antigenically drifted H3N2 in New Guinea.

Week 5
The drifted H3N2 virus has spread to Fiji and Northern Australia, and the WHO VCM for the Southern Hemisphere has recommended the inclusion of the drifted H3N2 virus in the seasonal vaccine. There is evidence that infections are clinically severe with many patients being hospitalized.

Question 1
a) Do any additional communications need to be made?
b) Do any additional actions need to be taken and by whom?

Week 6
GISRS has detected 10 human cases of H10N2 virus in New Guinea. One patient was hospitalised.

Week 7
There is evidence of spread of H10N2 virus within the region but infections are clinically not as severe as the variant H3N2 virus infections. All age groups are affected.

Question 2
WHO (GISRS) is now ready to distribute CVVs to vaccine manufacturers for pandemic vaccine preparatory activities.
a) When are manufacturers able to work with these CVVs to produce clinical lots?
b) Does working with CVVs and the production of clinical lots interfere with the production of seasonal vaccine?

Week 10
Within a month 1500 cases of H10N2 human infection have occurred across several countries and H3N2 infections continue to occur. All age groups were affected by both viruses.

Question 3
a) Should countries and stakeholders be informed on the progress of developing pandemic vaccine; and if so, how?
b) How does WHO communicate with countries, industry and regulators?
c) Would the presence of the N2 in the southern hemisphere vaccine provide any cross protective immunity and how would this influence any decision to produce H10N2 vaccine?

Question 4
a) Is there a need to advance the development for a pandemic vaccine now? And if so, how far down the development pathway should it go and by whom?
b) Will national/regional contracts of seasonal vaccines be affected by activating pandemic APAs; if so, how?
c) When should pandemic vaccine production start? For all manufacturers or some - if only some, what are the principles or assumption to consider when making this decision. Who decides what?
d) Are there issues around seasonal versus pandemic vaccine availability? Are there any implications for those needing seasonal vaccine?
e) If both the H3 and H10 viruses were resistant to neuraminidase inhibitors, would this affect any of your decisions?

Weeks 12 - 15
Within 3 months over 49 countries reported the spread of influenza, with many patients needing medical attention and some needing intensive care. Over 100,000 cases were reported with a 0.4% mortality rate. There were reports of severe challenges for the health care systems in most countries. There was also an increase in reports of absenteeism in front line health care workers. Laboratory tests on some 9200 samples showed that about 50% were of the new novel type A virus and nearly 50% were the new variant H3.

Question 5 (Concluding Question):
a) In this scenario, what would you recommend with regard to pandemic vaccine production vs. seasonal vaccine production?
b) Would your recommendation change in the face of increased morbidity and mortality which was over and above the normal seasonal expectation.
c) On what basis is this recommendation to be made? Who are the stakeholders making the recommendation? How should the recommendations be communicated?
d) In the situation of H3 dominating in some regions and H10 in others, what would your recommendations be?
### Operational Framework for Pandemic Vaccine Response

#### Risk Assessment & Communications

**Activities**
- Virological Risk Assessment
- Epidemiological Monitoring and Risk Assessment
- Severity Assessment
- Declaration of PHEDC
- Declaration of a Pandemic

**Participating Entities**
- WHO, GISS, affected countries, OFFL, animal sector, academic institutions
- WHO, GISS, and associated epidemiologic institutions in affected countries, regional coordinating entities, e.g., ECDC
- WHO, affected countries, regional coordinating entities, e.g., ECDC
- WHO, IHR Emergency Committee (EC), GISS, and other subject experts
- WHO, IHR EC, GISS, and other subject experts

**Coordinating Entities**
- WHO

**Deliverables or Outputs**
- Updated risk assessment based on virus characterization and special studies
- Early descriptions of the emerging epidemiological pattern of the pandemic virus
- Progression of the pandemic
- Identification of risk groups
- Estimation of the likely impact on healthcare services
- Public health advice on measures to be taken
- WHO D-Cs declaration of PHEDC and issuance of temporary recommendations
- Declaration of a Pandemic

**Channels to Communicate the Outcomes**
- WHO website, scientific publications as appropriate
- WHO website, scientific publications as appropriate
- WHO website, other media channels as appropriate
- WHO website, other media channels as appropriate

#### GLOSSARY

- **ADR**: Adverse Drug Reaction
- **AEFI**: Adverse Event Following Immunization
- **BLA**: Biologic License Application*
- **CVV**: Candidate Vaccine Virus
- **DCVMN**: Developing Countries Vaccine Manufacturers Network
- **ECDC**: European Centre for Disease Prevention and Control
- **EMA**: European Medicines Agency
- **EUA**: Emergency Use Authorization*
- **FAO**: Food and Agriculture Organization of the UN
- **FLUCOP**: EU research consortium http://www.flucop.eu/
- **GACVS**: WHO Global Advisory Committee on Vaccine Safety
- **GAP**: WHO Global Action Plan for Influenza Vaccines
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- **GMO**: Genetically Modified Organisms
- **GMP**: Good Manufacturing Practice
- **HCW**: Health Care Worker
- **IHR**: International Health Regulations (2005)
- **IFPMA**: International Federation of Pharmaceutical Manufacturers & Associations
- **IND**: Investigational New Drug*
- **NCs**: National Control Laboratories
- **OE**: World Organization for Animal Health
- **PHEIC**: Public Health Emergency of International Concern
- **PIP**: Pandemic Influenza Preparedness
- **PIRM**: Pandemic Influenza Risk Management
- **RG**: Reverse Genetics
- **STRG**: Strategic Advisory Group of Experts on Immunization
- **SRID**: Single Radial Immunodiffusion
- **TIPRA**: Tool for Influenza Pandemic Risk Assessment
- **VRBPAC**: US Vaccines and Related Biological Products Advisory Committee
- **US NIH/CDC**: US National Institutes of Health/Centres for Disease Control and Prevention
- **WHO CCs**: WHO Collaborating Centres
- **WHO ERIs**: WHO Essential Regulatory Laboratory

* USA regulatory mechanism
## OPERATIONAL FRAMEWORK FOR PANDEMIC VACCINE RESPONSE

### CVV DEVELOPMENT

<table>
<thead>
<tr>
<th>Activities</th>
<th>Participating Entities</th>
<th>Coordinating Entities</th>
<th>Outcomes</th>
<th>Channels to Communicate the Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classical Reassortant</td>
<td>WHO CCs, Reassorting Labs</td>
<td>WHO CCs, Reassorting Labs</td>
<td>Potential CVVs</td>
<td>WHO website, WHO email distribution, IFPMA teleconferences and other channels as appropriate</td>
</tr>
<tr>
<td>RG Reassortant</td>
<td>WHO CCs, Reassorting Labs</td>
<td>WHO CCs, Reassorting Labs</td>
<td>Potential CVVs</td>
<td>WHO website, WHO email distribution, IFPMA teleconferences and other channels as appropriate</td>
</tr>
<tr>
<td>Wild Type Virus</td>
<td>WHO CCs, Reassorting Labs</td>
<td>WHO CCs, Reassorting Labs</td>
<td>Potential CVVs</td>
<td>WHO website, WHO email distribution, IFPMA teleconferences and other channels as appropriate</td>
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</tbody>
</table>

### CVV Assessment and Evaluation

<table>
<thead>
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<th>Activities</th>
<th>Participating Entities</th>
<th>Coordinating Entities</th>
<th>Outcomes</th>
<th>Channels to Communicate the Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characterization</td>
<td>WHO CCs</td>
<td>WHO CCs</td>
<td>Characterized CVVs</td>
<td>WHO website, WHO email distribution, IFPMA teleconferences and other channels, e.g. customer specific as appropriate</td>
</tr>
<tr>
<td>Safety Testing</td>
<td>WHO CCs and Specialist Labs</td>
<td>WHO CCs</td>
<td>CVVs that are safe for manufacturing</td>
<td>WHO website, WHO email distribution, IFPMA teleconferences and other channels, e.g. customer specific as appropriate</td>
</tr>
<tr>
<td>Yield Evaluation</td>
<td>WHO CCs, ERLs, manufacturers</td>
<td>WHO with WHO CCs, IFPMA, and manufacturers</td>
<td>Appropriateness of the CVVs for manufacturing</td>
<td>Teleconferences of WHO, IFPMA and involved manufacturers and other entities as appropriate</td>
</tr>
</tbody>
</table>

### Biocontainment

<table>
<thead>
<tr>
<th>Activities</th>
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<th>Coordinating Entities</th>
<th>Outcomes</th>
<th>Channels to Communicate the Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assessment of BSL Level for Large Scale Production</td>
<td>WHO Expert Group on Biopreparations OIE/FAO</td>
<td>WHO</td>
<td>Required containment levels</td>
<td>WHO website, teleconferences of WHO, IFPMA, National Regulatory Authority (NRA) involved manufacturers and other entities as appropriate</td>
</tr>
</tbody>
</table>
### CLINICAL EVALUATION

#### Activities
- Start with CVVs and Seed Lot
  - Manufacturers, regulators, relevant national authority
  - Influenza vaccine lots suitable for human use that can be grown to high yields
  - WHO platforms, e.g. website, press release, teleconferences – regular and emergency as appropriate

- Evaluate Growth Properties
  - Manufactures and Regulators
  - Manufacturers
  - Yield data
  - Teleconferences of WHO, IFPMA, and involved manufacturers and other entities as appropriate

- Animal Studies
  - Manufacturers’ senior management, national/global coordinating entities, e.g. BARDA (Biomedical Advanced Research & Development Authority) to identify/ coordinate extra trials
  - Approval from relevant regulator
  - WHO platforms, e.g. website, press release, teleconferences – regular and emergency as appropriate
  - Rapid communications with manufacturers, funders, customer countries and other entities as appropriate

- Preclinical studies
  - Manufacturere, academia, commercial clinical trial units, national/international entities such as US NIH/CDC, ethics committees
  - Manufacturers, regulators, national/international entities such as US NIH/CDC
  - Evaluation of vaccine safety
  - Communication at global platform to all stakeholders, including regulators and other national authorities, modellers and other entities as appropriate

- Serology
  - Ethics committee, regulatory authorities, manufacturers, academia, commercial clinical trial units, national/international entities, such as US NIH/CDC, research entities, e.g. FLUCOP
  - Funders, commercial laboratories involved in clinical trials, manufacturers regulation
  - Correlates of protection; vaccine formulation; vaccination strategy
  - Communication at global platform to all stakeholders, including regulators and other national authorities, modellers and other entities as appropriate

#### Participating Entities
- Manufacturers
- Regulators
- Relevant national authority

#### Coordinating Entities
- Manufacturers and Regulation
- Manufacturers

#### Outcomes
- Influenza vaccine lots suitable for human use that can be grown to high yields
- Approval from relevant regulator
- Evaluation of vaccine safety
- Correlates of protection; vaccine formulation; vaccination strategy
- Communication at global platform to all stakeholders, including regulators and other national authorities, modellers and other entities as appropriate

#### Channels to Communicate the Outcomes
- WHO platforms, e.g. website, press release, teleconferences – regular and emergency as appropriate
- Rapid communications with manufacturers, funders, customer countries and other entities as appropriate

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### Glossary

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</tr>
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<td>Investigational New Drug*</td>
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<tr>
<td>NCLs</td>
<td>National Control Laboratories</td>
</tr>
<tr>
<td>NRAs</td>
<td>National Regulatory Authorities</td>
</tr>
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</tr>
<tr>
<td>WHO CCs</td>
<td>WHOCollaborating Centres</td>
</tr>
<tr>
<td>WHO ERLs</td>
<td>WHOEssential Regulatory Laboratory</td>
</tr>
</tbody>
</table>

* USA regulatory mechanism
### Operational Framework for Pandemic Vaccine Response

**PRODUCTION**

<table>
<thead>
<tr>
<th>Activities</th>
<th>Participating Entities</th>
<th>Coordinating Entities</th>
<th>Outcomes</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Antigen Production</strong></td>
<td>WHO ERLs and manufacturers</td>
<td>WHO ERLs</td>
<td>Availability of calibrated reagents</td>
<td>WHO ERL websites and WHO website, and WHO chaired teleconferences (TCs)</td>
</tr>
<tr>
<td><strong>Antiserum Production</strong></td>
<td>International calibration studies</td>
<td>WHO ERLs</td>
<td>Calibrated reagents</td>
<td>WHO ERLs via TCs or email or other channels, reagent tracking table and other channels as appropriate</td>
</tr>
<tr>
<td><strong>Potential intensification of seasonal production</strong></td>
<td>Manufacturers</td>
<td>Individual manufacturers</td>
<td>Potentially increased volume of seasonal vaccines</td>
<td>Direct communication from manufacturers to customer countries, updates to WHO</td>
</tr>
<tr>
<td><strong>Gessation of seasonal vaccine production</strong></td>
<td>WHO, National Authorities, and manufacturers</td>
<td>WHO, National Authorities, and manufacturers</td>
<td>Readiness for pandemic vaccine manufacture</td>
<td>Direct communication from manufacturers to customer countries, updates to WHO</td>
</tr>
<tr>
<td><strong>Ongoing risk assessment on the need for pandemic vaccine</strong></td>
<td>WHO, JHRC, GERS, SAGE, and other subject experts</td>
<td>WHO</td>
<td>Recommendation of pandemic vaccine commence, based on risk assessment. This may entail critical steps including switching from production of seasonal vaccine to pandemic vaccine</td>
<td>WHO website, other media channels as appropriate</td>
</tr>
<tr>
<td><strong>Start of pandemic vaccine production</strong></td>
<td>WHO, manufacturers, NCLs</td>
<td>Manufacturers and regulators</td>
<td>Initiation of pandemic vaccine production</td>
<td>IFPMA to WHO, updates with proprietary protections; manufacturers to customer countries</td>
</tr>
<tr>
<td><strong>Vaccine production</strong></td>
<td>Manufacturers, NCLs</td>
<td>Manufacturers</td>
<td>Build monobulk stock of pandemic strain</td>
<td>Updates from IFPMA to WHO, and manufacturers to customer countries</td>
</tr>
<tr>
<td><strong>Vaccine formulation</strong></td>
<td>Manufacturers, WHO, NCLs</td>
<td>Manufacturers</td>
<td>Pandemic Vaccine</td>
<td>Updates from IFPMA to WHO, and manufacturers to customer countries</td>
</tr>
<tr>
<td><strong>Filling/Packaging</strong></td>
<td>Manufacturers, customer countries, and WHO</td>
<td>Manufacturers, customer countries and WHO</td>
<td>Correct proportions of multidose vials, syringes, etc.</td>
<td>IFPMA to WHO Industry to Customer</td>
</tr>
</tbody>
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*USA regulatory mechanism*
OPERATIONAL FRAMEWORK FOR PANDEMIC VACCINE RESPONSE

REGISTRATION

Activities: Dossier route
Participating Entities: WHO, manufacturers, national and regional (e.g. EMA) regulating authorities
Coordinating Entities: WHO, Regulators
Outcomes: Approval/no approval, enhanced/fast-tracked approval process
Channels to Communicate the Outcomes: Guidelines Website, Workshops to create understanding of the processes

Activities: Emergency route
Participating Entities: WHO, manufacturers, national and regional (e.g. EMA) regulating authorities
Coordinating Entities: WHO, Regulators
Outcomes: Approval/no approval, enhanced/fast-tracked approval process
Channels to Communicate the Outcomes: Guidelines Website, Workshops to create understanding of the processes

Activities: Regulatory oversight to assure the quality of pandemic vaccines
Participating Entities: Exiting lot release labs including WHO ERLs and NCLs
Coordinating Entities: Regulatory Network/WHO
Outcomes: Development of formal network of release laboratories to enhance availability of pandemic vaccine, Clear set of assays to streamline process
Channels to Communicate the Outcomes: Webistes, workshops, written standards, membership criteria

Activities: Risk management, safety monitoring, signal detection
Participating Entities: Health care workers, regulators, public health
Coordinating Entities: National Regulatory Authorities, WHO
Outcomes: Improved safety assessment and monitoring system, Increased use of tools (models, etc.)
Channels to Communicate the Outcomes: HCW, public health organizations, manufacturers, international exchange of safety data/signals via WHO/GAP/GACVS

Activities: Distribution and communications
Participating Entities: Health authorities
Coordinating Entities: Health and local authorities
Outcomes: Distribution, availability, early ADRs
Channels to Communicate the Outcomes: Health authorities and NCLs/ERLs, email or other channels

**Glossary**

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* USA regulatory mechanism

**Notes**
1. Manufacturers are encouraged to license vaccines approved for emergency use.
2. For forward tracking outcomes would be establishment of guidelines and common regulatory processes to support fast-tracking cheaper development costs.
3. Approval process principles to include: clarity, transparency, mutual recognition, rapid access.
4. Each WHO region should have such laboratories. Mutual recognition procedures to be developed.
5. Increased confidence among HCWs and public. Ensures case definitions are available for AEFI.
6. EU can be seen as a model.
# TIMELINE OF PANDEMIC VACCINE PRODUCTION

**ENTITIES** | **ACTIVITIES** | **ACTIONS** | **WEEK NUMBER SINCE WHO RECOMMENDATION OF PANDEMIC VIRUS**
--- | --- | --- | ---
1 | Reassorting Labs | Reassortant development | Development of CVVs for distribution
2 | WHO CCs and Reassorting Labs | Reassortant evaluation | CVVs characterization including safety and shipping
3 | | Biosafety/GMO approval | 1, 2, 3
4 | Manufacturers | Reassortant assessment | CVVs Yield and growth characteristics
5 | | Development | Clinical lot production
6 | | Clinical trials | Recruitment and Execution
7 | | Serology | 5, 6, 7, 8
8 | | ADR monitoring | 9, 10, 11, 12
9 | Vaccine Production | Antigen production | 13, 14, 15, 16
10 | ERLs | Vaccine Formulation/Packaging/Distribution | 17, 18
11 | Regulatory Authorities | Reagents | Preparation of purified HA (for sheep immunisation)
12 | | Production of reagents | 19
13 | | Calibrations and supply of reagents | 20
14 | | Regulatory Authorities | 21, 22, 23, 24
15 | | Lot release | SRID and Endotoxin tests, cold chain review
16 | | Pharmacovigilence | AEFI monitoring
17 | Programme managers | Vaccine Distribution | Vaccine available for deployment

**COMMENTS AND POTENTIAL ISSUES**

- This timeline is ideal circumstances when everything goes well. If some activities do not go well, they may take longer and this is indicated in the shaded areas of the chart. Due to the inter-relatedness of many of the activities, a delay in one activity would delay others in the timeline.

- CVVs are selected by the WHO CCs. Reassortants will take about 19 days, as trials are usually about 21 days. Synthetic vaccines may be an option. Safety testing (BTLD) is essential but may be added at the last moment. If the CVVs are derived from a highly pathogenic virus, it will need to be evaluated. Evaluation from "Select Agent" status in the USA will be delayed, and if the CVVs derived from reassortants, they will need to comply with the EU's regulations. CVVs are generally not distributed until they first complete at least 2 weeks but in a pandemic situation they could be distributed pending H1N1 data. WHO will give clear guidance on the initial containment and reassortment at the early development stage. Antigen and associated dose will only be known with virus isolation and antigen production. The production of a monovalent vaccine can take place early with some lot release later. Therefore, vaccine production needs to be started early for peak production.

- Poor yields might result in delays in vaccine supply for large populations. The early stages of planning and recruitment will have taken place earlier than this. Base line serology and then further antigen production at 2 and 4 weeks after injection. Early discussions with NRA essential.

- Calibrations and supply of reagents are essential to begin a clinical trial if required (phase 1). Some countries will require a clinical trial if the emerging pandemic subtype has little or no clinical data. The production of sheep sera is critical and a major bottleneck in the process. Ideally the 4 WHO ERLs would calibrate the reagents. But given the nature of the vaccine, the reagent can be calibrated locally, e.g., between the ERL and the manufacturer or another competent laboratory, the option to prepare and calibrate sets of reagents could be considered pending the workload of cross calibration, and alternative tests such as ELISA tests to be considered pending WHO approval. A pharmacovigilance study depending on the NRA. This would occur beyond the 14 week mark.

- Distributions by programme managers’ workplaces. Roll-out priority to be determined according to the pandemic plan. To continue beyond the Week 14 mark.

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**ANNEX 3 – Timelines of pandemic vaccine production**

**COMMENTS AND POTENTIAL ISSUES**

- This timeline is ideal circumstances when everything goes well. If some activities do not go well, they may take longer and this is indicated in the shaded areas of the chart. Due to the inter-relatedness of many of the activities, a delay in one activity would delay others in the timeline.

- CVVs are selected by the WHO CCs. Reassortants will take about 19 days, as trials are usually about 21 days. Synthetic vaccines may be an option. Safety testing (BTLD) is essential but may be added at the last moment. If the CVVs are derived from a highly pathogenic virus, it will need to be evaluated. Evaluation from "Select Agent" status in the USA will be delayed, and if the CVVs derived from reassortants, they will need to comply with the EU's regulations. CVVs are generally not distributed until they first complete at least 2 weeks but in a pandemic situation they could be distributed pending H1N1 data. WHO will give clear guidance on the initial containment and reassortment at the early development stage. Antigen and associated dose will only be known with virus isolation and antigen production. The production of a monovalent vaccine can take place early with some lot release later. Therefore, vaccine production needs to be started early for peak production.

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- Distributions by programme managers’ workplaces. Roll-out priority to be determined according to the pandemic plan. To continue beyond the Week 14 mark.
ANNEX 4 – 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?

NO

Further virus characterization by WHO CCs

Assessment of need for HGR development

YES

Need to develop (a) HGR(s) or (b) alternative vaccine viruses?

NO

Selection of candidate viruses by GISRS

Development of high-growth reassortants by GISRS and other laboratories

Biosafety assessment of CVVs by WHO

Distribution of high-growth reassortants

Initiation of the development of potency reagents by GISRS

Availability of potency reagents by GISRS

RA on further vaccine development

Assessment if results warrant production/use of pandemic/pre-pandemic vaccines

YES

Further vaccine development/licensing/stockpiling

NO

Clinical trials if needed

National/regional licensing/stockpiling as appropriate

YES

WHO recommendation on pandemic vaccine production and use

WHO declaration of pandemic

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

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

Continuous assessment by WHOs IHR, SAGE and subject experts, as well as industry and stakeholders 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 risks associated with switch back to seasonal vaccine production

*a decision whether CVV is covered by Nagoya Protocol

GLOSSARY

CVV  Candidate Vaccine Virus
GISRS WHO Global Influenza Surveillance and Response System
HGR High growth reassortant
IHR International Health Regulations (2005)
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

Influenza Vaccine Response during the Start of a Pandemic – 2nd WHO Informal Consultation REPORT
ANNEX 5
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 the Parking Lot comments and proposals from the first Consultation have now been incorporated into Section 5.2 Bottlenecks of this report. The remaining Parking Lot items could be considered as part of forward agendas in future meetings. New proposals from the 2016 consultation are in italics.

Key proposals

Communication
• Improve sharing of information including genetic, sequence and epidemiological data.
• Review how WHO communicates to stakeholders in an emergency.

Research
• Promote 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 a specific consultation on research and development of current and future pandemic vaccines.

Other activities
• Finalize the risk assessment tool (TIPRA).
• Update national pandemic preparedness plans.
• Consider adding administration procedures in pandemic plans.

• What preservatives are to be recommended for pandemic vaccines?
• If an adjuvant is needed for pandemic vaccine and not all manufacturers have access to an effective adjuvant, what plans are in place to share adjuvants?
• What is the process to stop pandemic vaccine production?

Further proposals
• 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 actually behave in a pandemic? E.g., politicians, medical profession and the public.
• Pharmacovigilence should be strengthened globally.
ANNEX 6
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