INFLUENZA VACCINE RESPONSE DURING THE START OF A PANDEMIC

Report of the Third WHO informal consultation
Geneva, Switzerland — 7–9 June 2017

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### Abbreviations and acronyms

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<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>BARDA</td>
<td>United States Biomedical Advanced Research and Development Authority</td>
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<tr>
<td>CC</td>
<td>Collaborating Centre</td>
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<td>CDCs</td>
<td>United States Centers for Disease Control and Prevention</td>
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<tr>
<td>CVV</td>
<td>candidate vaccine virus</td>
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<tr>
<td>DCVMN</td>
<td>Developing Countries Vaccine Manufacturers Network</td>
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<tr>
<td>ECBS</td>
<td>Expert Committee on Biological Standardization (WHO)</td>
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<tr>
<td>ERL</td>
<td>Essential Regulatory Laboratory</td>
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<td>EU</td>
<td>European Union</td>
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<td>GAP</td>
<td>WHO Global Action Plan for Influenza Vaccines</td>
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<td>GISRS</td>
<td>WHO Global Influenza Surveillance and Response System</td>
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<tr>
<td>GMP</td>
<td>good manufacturing practice</td>
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<tr>
<td>HHS</td>
<td>United States Department of Health and Human Services</td>
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<td>HPAI</td>
<td>highly pathogenic avian influenza</td>
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<tr>
<td>IFPMA</td>
<td>International Federation of Pharmaceutical Manufacturers &amp; Associations</td>
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<tr>
<td>IIV</td>
<td>inactivated influenza vaccine</td>
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<tr>
<td>IRAT</td>
<td>influenza risk assessment tool</td>
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<tr>
<td>LAIV</td>
<td>live attenuated influenza vaccine</td>
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<td>LMICs</td>
<td>low- and middle-income countries</td>
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<td>LPAI</td>
<td>low pathogenic avian influenza</td>
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<td>NCL</td>
<td>national control laboratory</td>
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<tr>
<td>NIBSC</td>
<td>United Kingdom National Institute for Biological Standards and Control</td>
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<tr>
<td>NIC</td>
<td>National Influenza Centre</td>
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<td>NRAs</td>
<td>national regulatory authorities</td>
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<tr>
<td>PHEIC</td>
<td>public health emergency of international concern</td>
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<td>PIP</td>
<td>pandemic influenza preparedness</td>
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<td>PIRM</td>
<td>pandemic influenza risk management</td>
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<tr>
<td>PPE</td>
<td>personal protective equipment</td>
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<tr>
<td>PPCs</td>
<td>preferred product characteristics</td>
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<tr>
<td>R&amp;D</td>
<td>research and development</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 assessment</td>
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<tr>
<td>TRS</td>
<td>WHO Technical Report Series</td>
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<tr>
<td>VCM</td>
<td>WHO Influenza Vaccine Composition Meeting</td>
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<td>WHO</td>
<td>World Health Organization</td>
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Executive Summary

This meeting report provides an overview of discussions and outcomes from the third WHO informal consultation on influenza vaccine response during the start of a pandemic, held in June 2017. The aim of the meeting was to address challenges and bottlenecks in vaccine response at the start of an influenza pandemic, including issues associated with the decision to start the pandemic vaccine production which might entail the switch from seasonal to pandemic vaccine production.

The first WHO informal consultation on this topic, which took place in 2015, analysed the complexities of vaccine response at the start of an influenza pandemic and provided clarity and understanding among key players on roles and responsibilities of the response. The 2nd WHO informal consultation in 2016 furthered the discussion to developing principles and processes of decision making of the start of pandemic vaccine production and addressing bottlenecks surrounding the switch. Based on the outcome from the two consultations, the 2013 interim WHO pandemic guidance WHO Pandemic Risk Management Framework (PIRM) was finalized in 2017.

The third informal consultation developed operationalization of the outcomes from the previous two consultations jointly with influenza experts, public health officials, and other stakeholders to address vaccine response at the start of an influenza pandemic, in particular, issues surrounding the potential switch from seasonal to pandemic vaccine production. In addition, the specific challenges for low- and middle-income countries were discussed. During the consultation, participants drafted an operational framework for pandemic vaccine response, developed a common understanding of an effective pandemic vaccine response, and identified key challenges and potential bottlenecks that would interfere with switching from seasonal to pandemic vaccine production. Guiding principles of technical, ethical and political aspects involved in making the decision to start pandemic vaccine production were also elaborated.

Key outcomes from the third informal consultation included the following:

- A clear, transparent and integrated approach to initiating pandemic vaccine production was proposed; this proposed approach will be further developed by WHO working groups.
- At the start of a pandemic, WHO will issue recommendations on pandemic vaccine composition and use which will be based on a variety of criteria clearly communicated to all stakeholders involved in the pandemic vaccine response. Such criteria will be based on risk assessment and to be developed by WHO working groups. These will inform the vaccine production decisions.
- Solutions to potential bottlenecks in the pandemic vaccine response at the start of a pandemic should be further prioritized, addressed or operationalized through WHO working groups.
- Communication to clarify the critical responses – including the declaration of a public health emergency of international concern (PHEIC), the declaration of an influenza pandemic, the recommendation to start pandemic vaccine production and subsequent availability of pandemic vaccines should be comprehensively incorporated into global and national pandemic preparedness planning.

These informal consultations clarified critical complexities at national, regional and global levels, and the need for WHO coordinated global response especially the decision to commence the start of pandemic vaccine production based on risk assessment.
1. **Scope and expected outcomes**

The first two WHO informal consultations on the influenza vaccine response during the start of a pandemic, held in June 2015 and July 2016, addressed pending questions in the 2013 publication *Pandemic influenza risk management (PIRM): WHO interim guidance* (1). The third informal consultation, held in June 2017, endeavoured to operationalize the process for making WHO recommendations on the influenza vaccine response at the start of a pandemic. Thus, the objectives of the third WHO informal consultation were to:

- discuss the challenges and bottlenecks in vaccine production, and develop a draft protocol of the vaccine response at the beginning of an influenza pandemic;
- identify challenges for developing countries; and
- identify and finalize the key principles in making a decision to start pandemic vaccine production.

Participants included representatives from the WHO Collaborating Centres (WHO CCs), National Influenza Centres (NICs) and WHO Essential Regulatory Laboratories (ERLs) of the Global Influenza Surveillance and Response System (GISRS), the academic research community, national regulatory authorities (NRAs), national public health agencies, vaccine manufacturers, the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA), the Developing Countries Vaccine Manufacturers Network (DCVMN) and other stakeholders. A full list of participants is given in Annex 5. This report summarizes the discussions in the meeting.

2. **Organization of the Third WHO informal consultation**

Building on the first two informal consultations, participants of the third consultation were briefed on key international pandemic influenza preparedness activities and updated on additional relevant activities, to ensure that all participants were up to date. A summary of the updates is provided in Section 3. Participants were then divided into working groups to address two tasks:

- Review and refine the bottlenecks developed from the two previous informal consultations, proposing solutions and an implementation plan:
  - candidate vaccine virus (CVV) production and distribution;
  - biocontainment for wild type pandemic virus and CVV;
  - yield and manufacturing of CVVs; and fill and finish capacity;
  - timing of single radial immunodiffusion (SRID) reagents for vaccine potency; regulatory harmonization; and alternative potency assays;
  - clinical trials for the first pandemic vaccines; and
  - risk assessment.

- Finalize the key principles and data needs for decision-making related to the start of pandemic vaccine production (to help key stakeholders understand and follow the recommendation with more ease and with greater confidence); refine the decision matrix and propose an implementation plan.
A further focus of the informal consultation was to refine the description of the pandemic vaccine process developed from the two previous consultations (Annexes 1, 2 and 3). Finally, the key outcomes and next steps were identified. This report presents the summary of discussions in the meeting.

3. Updates on relevant international pandemic influenza preparedness activities

3.1 Global Action Plan for Influenza Vaccines and new vaccine development

The Global Action Plan for Influenza Vaccines (GAP) was a 10-year strategy to reduce the predicted global shortage of and inequitable access to vaccines in the event of a pandemic. The GAP promoted three projects: increasing the evidence-based use of seasonal vaccines, expanding vaccine production capacity and regulatory capacity, and research and development (R&D) for better vaccines. At the final GAP consultation in 2016, the 10-year progress and lessons learned for the three GAP objectives were reviewed and remaining gaps and options for future work were identified (2).

During the 10 years of the GAP, the number of countries with seasonal vaccination policies has increased from 74 to 115, and dose distribution has increased from 350 to 490 million, although in some areas it is plateauing or decreasing. More information is needed on the country-specific impact of influenza infections and of different vaccination strategies. The potential global production capacity for pandemic vaccines has increased from 1.5 to 6.4 billion doses. Also, 14 low- and middle-income countries (LMICs) have received technology transfer by GAP, resulting in eight pandemic influenza vaccines and three seasonal influenza vaccines licensed in six countries, with five more vaccines in the late stage of development. This is expected to contribute more than 1 billion doses to the global capacity (3). The newly established capacity must be sustainable; hence, the NRAs should continue to strengthen their collaboration, and vaccine production should be optimized (e.g. by decreasing reliance on eggs, optimizing yields and exploring new technologies).

WHO has developed preferred product characteristics (PPCs) (4) for the next generation of influenza vaccines. It is important to continue to develop new vaccine technologies and accompanying regulatory guidance, standardize clinical trial design and identify funding opportunities.

3.2 Pandemic influenza risk management

Since the publication in 2013 of the WHO pandemic influenza risk management (PIRM) – WHO interim guidance (1), there have been considerable discussions with the key stakeholders. The PIRM framework was finalized in 2017 (5). It is based on the outcomes of the first and second informal consultations and provides greater clarity about the role of WHO in developing recommendations related to the start of production of pandemic influenza vaccines based on the risk assessment.

3.3 Revision of the WHO Technical Report Series

Guidance on the biosafety requirements for production and quality control of pandemic vaccines is provided by the WHO Technical Report Series 941 (TRS 941), which was published in 2007 (6). Nevertheless, at the onset of the 2009 pandemic, delays in the provision of WHO recommendations on biocontainment level led to delays in the start of influenza vaccine production.
The first and second WHO informal consultations identified uncertainty surrounding biocontainment levels of CVVs as a potential bottleneck during the early stages of pandemic vaccine production. Consequently, a working group to revise TRS 941 was convened on 9–10 May 2017; Annex 5 of the report of the meeting dealt with risk assessment and guidelines for influenza pandemic vaccines (7). The revision aimed to update TRS 941 to make it more flexible and the safety-testing procedures more consistent. It is intended that the first draft revision will be presented to the 68th WHO Expert Committee on Biological Standardization (ECBS) in October 2018.

3.4 Alternative vaccine potency assays

The SRID assay is accepted globally for potency testing of inactivated influenza vaccines. However, this assay depends on timely provision of antigenically matched and carefully calibrated reagents. This takes at least 12 weeks, and if problems arise it can take much longer. There are also limitations on the use of SRID for some adjuvanted vaccines. This uncertainty was recognized as a potential bottleneck in the previous informal consultations.

In 2011, the ECBS published a guidance on the characteristics needed for an alternative potency assay. Following the guidance, a “core group” was established to evaluate new assays. The group comprises representatives of the United Kingdom National Institute for Biological Standards and Control (NIBSC), the United States (US) Department of Health and Human Services (HHS), and the IFPMA. This group has compared new assays for influenza A(H1N1)pdm09, A(H3N2) and B viruses with SRID assay with preliminary results showing good comparison for some assays. However, if an alternative assay is found to be suitable and is selected, it is likely to be a biological assay that also depends on timely availability of reagents. Therefore, this may not completely address the bottleneck. A likely interim solution is to adopt a physicochemical assay for emergency use in the first stages of a pandemic, with subsequent use of a biological assay when reagents are available. More work on this issue is needed.

3.5 Current zoonotic pandemic threats

Any of the influenza viruses belonging to the 16 haemagglutinin (HA) subtypes that circulate in wild waterfowl have pandemic potential; however, most attention is given to those subtypes that have either caused zoonotic human infections or have resulted in past pandemics (e.g. H1, H2, H3, H5, H7 and H9). Apart from a large number of highly pathogenic avian influenza (HPAI) A(H5N1) cases in Egypt in 2014, there has been a gradual decrease in human A(H5N1) cases in recent years and currently most human H5 cases are due to A(H5N6) viruses. From 2004 to July 2017, there were 859 human H5 cases, of which 453 were fatal (8). Low pathogenic avian influenza (LPAI) A(H7N9) viruses have caused outbreaks of human infections in China since 2013, with the 2017 peak being the largest; a total of 1564 human cases have been recorded to date (9). Recent human cases of HPAI (H7N9) virus infections are a worrying development, prompting WHO to recommend and develop new vaccine candidates (10). The availability of the WHO tool for influenza pandemic assessment (TIPRA) has standardized the risk assessment process, and has made it possible to compare assessments of the likelihood of emergence of a virus with human-to-human transmissibility, and the likely impact on public health should such human-to-human transmission occur.
3.6 BARDA pandemic preparedness

The US Biomedical Advanced Research and Development Authority (BARDA) has an active pandemic preparedness programme that focuses primarily on vaccines, but also antiviral drugs, diagnostic tools and personal protective equipment (PPE). BARDA has an active pandemic vaccine stockpiling programme, based on risk assessment using tools such as the influenza risk assessment tool (IRAT) of the US Centers for Disease Control and Prevention (CDCs).

Stockpiles of vaccines or bulk antigen were created for A(H5N1) virus in 2005, pandemic A(H1N1) virus in 2009, and A(H7N9) virus in 2013 and 2017. In addition, clinical trials were conducted for A(H3N2)v virus in 2012 and for A(H7N9) virus in 2013, and adjuvants were stockpiled in 2009. Many different vaccine strategies (e.g. egg-based inactivated, cell-based inactivated and live attenuated vaccines) have been used to prepare vaccines using CVVs prepared from different virus subtypes and clades. Adjuvants and prime-boost regimens are potential strategies to broaden the immune responses to stockpiled vaccine, to address a potential antigenic mismatch between a stockpiled pandemic vaccine and an emerging virus.

3.7 Investigation into a pilot facility for pandemic influenza vaccine preparedness

One of the proposals from the previous consultations was to investigate the potential role in pandemic preparedness of a small-scale pilot-lot vaccine facility with good manufacturing practice (GMP). Such a facility would address some of the important bottlenecks by undertaking pre-pandemic and pandemic influenza R&D of novel candidate vaccine viruses, and by serving all influenza vaccine manufacturers involved in the pandemic vaccine response. The facility would potentially:

- provide biosafety level 3 or higher GMP laboratories for early and small-scale pandemic influenza CVV development;
- enable evaluation and optimization of CVV biosafety, pathogenicity and yields;
- produce GMP vaccine lots for human clinical trials;
- supply pandemic influenza antigens for vaccine assay reagents and supporting preclinical and clinical studies; and
- provide training.

In addition, because there are scientific and technical synergies between pandemic influenza vaccine development and vaccine development for other pathogens, the facility could be used for vaccines against other pathogens of public health significance.

The next steps are to conduct a detailed needs assessment and feasibility analysis, gain global interest in the proposal, assemble global collaborative partners and investors, and develop an investment plan for a small-scale pilot-lot GMP vaccine facility.

3.8 An IFPMA appraisal on the key issues and challenges for vaccine manufacturers

IFPMA considered that satisfactory progress has been made on:

- revision of TRS 941 for biocontainment of CVVs, which may allow vaccine manufacturers to speed up production of the first lots of pandemic vaccine;
- clarification by WHO that the PIRM statement – that WHO "may" recommend that production of pandemic vaccine
commence – refers to the risk assessment based approach; once the risk assessment outcome warrants the start of the production of pandemic influenza vaccines, WHO will issue related information; and
- the concept of a small-scale pilot plant that could help with supply of antigen for vaccine potency reagents and for clinical study.

However, some concerns remain:

- There is a lack of clarity about WHO’s role and the process followed in declaring a pandemic, and the related implications for the pandemic vaccine response.
- IFPMA noted that vaccine manufacturers have contracts with national governments, and, without more definitive advices from WHO, the execution of contracts will largely be led by different national needs for pandemic vaccine, which may be impossible for manufacturers to accommodate.
- Uncertainty remains about the utility of the “mock-up dossier” concept for pandemic vaccine licensing that has been adopted in the European Union (EU) and by some other licensing authorities (11). This concept was developed and used for licensing of H5N1 vaccines, but not for the 2009 H1N1 pandemic vaccines.
- There is a lack of mutually recognized regulatory pathways between national regulatory agencies.

3.9 The Nagoya Protocol

The participants were briefed on the Nagoya Protocol (12), and its potential implications for the pandemic influenza vaccines in the context of the pandemic influenza preparedness (PIP) framework and the GISRS.

3.10 The WHO decision-making process

In June 2013, WHO published a revision of the pandemic preparedness and response guidance entitled Pandemic influenza risk management (PIRM) — WHO interim guidance (1). The WHO PIRM framework gives flexibility to countries for risk-based national responses, including pandemic influenza vaccine response. To ensure rapid and adequate production and deployment of pandemic influenza vaccines – taking into consideration of seasonal epidemics that may be severe and occur at the same time as 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.

The previous two informal consultations identified three key decision points, depending on how the situation progresses: the need for CVV development from a novel virus of public health concern; production and use of pandemic or pre-pandemic vaccines; and the need for further vaccine development, licensing or stockpiling (13).

The factors influencing the WHO consideration to recommend the start of pandemic vaccine production, with the potential implication of ceasing ongoing seasonal influenza vaccine production, include epidemiology, virology, biosafety, status of seasonal vaccine, readiness to produce pandemic vaccine, modelling estimates of risk to public health, and impact on health systems. There has been progress in defining the sources of data needed to make the decision, and the principles to be used to guide data analysis and decision-making. However, more work is needed to clarify how the data collection can be standardized to facilitate global
analysis, what the trigger to start data collection should be, what format and methodologies should be used for the modelling, and what approach should be used for the high-level risk assessment. One of the proposals from the informal consultation was to establish a WHO expert advisory group\textsuperscript{1} to advise WHO on the vaccine response at the start of an influenza pandemic.

Some activities can be initiated in the period between pandemics. Such activities include standardizing methods and formulating channels for collecting data, convening modellers, ensuring that national pandemic plans are updated to be consistent with PIRM, and establishing a strategy for communication.

4. Bottlenecks in pandemic vaccine development: proposing solutions

The bottlenecks were grouped into eight thematic areas: CVV production and distribution, biocontainment of wildtype viruses and CVVs, CVV manufacturing and yield, fill-and-finish capacity, SRID reagents for testing vaccine potency, regulatory harmonization, clinical trials of the first available pandemic vaccines, and assessment of risks associated with the switch from seasonal to pandemic vaccine production.

It was proposed that three multidisciplinary working groups be established to follow up on the outcomes from the informal consultation.

Activities recognized but not considered directly within the scope of the informal consultations are listed in the “parking lot” (Annex 4).

\textsuperscript{1} Further discussions on the establishment of an advisory group and its terms of reference are needed within WHO, to ensure alignment with WHO rules and practices, and the existing mechanisms for pandemic and other emergency responses.
**Table 4.1. CVV production and distribution**

<table>
<thead>
<tr>
<th>BOTTLENECK</th>
<th>DATA NEEDED</th>
<th>PROPOSED SOLUTION(S)</th>
<th>PROPOSED IMPLEMENTER(S)</th>
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</thead>
</table>
| Not enough laboratories producing CVVs, especially those from highly pathogenic viruses | • Review number and surge capacity of available laboratories  
• Review requirement for laboratories to develop and test CVVs | • Establish CVV development programme within DCVMN | • CVV laboratories  
• WHO  
• DCVMN |
| Uncertainty of implications of Nagoya Protocol on pandemic virus sharing and CVV distribution | • Can PIP be considered an SII within the Nagoya Protocol?  
• Explore the process in the Netherlands that waives the right to benefit from sharing viruses | WHO to work with CBD for  
• PIP and GISRS to be considered as SIs  
• PIP and GISRS to be exempted from CBD | • WHO  
• CBD  
• Environmental agencies |
| Uncertainty about manufacturers’ obligations to share CVVs and synthetic seeds | • Manufacturers with capacity for developing HGRs | Manufacturers agree to share HGRs and synthetic seed pandemic viruses, all including those produced with their own technology | • WHO  
• IFPMA  
• DCVMN |
| IP rights held by AstraZeneca / MedImmune for use of RG in producing pandemic CVVs | • Are non-US manufacturers exempt from IP in the event of a pandemic?  
• Expiry dates of current IP rights | AstraZeneca/MedImmune agree on access to RG technology during a pandemic event | • WHO CC US  
• HHS/BARDA  
• AstraZeneca / Medimmune |
| Countries experience challenges in shipping wildtype IVPP to WHO CCs or CVV laboratories | • Potential national and international barriers for international shipment of IVPP (PIP review report)  
• Review national export and import permits | Align national import and export permits with national pandemic preparedness plan | • WHO |
| Variable yields from HGR and LAIV viruses | • Number of viruses needed to supply to HGR/LAIV laboratories | Ship multiple wildtype viruses to HGR/LAIV laboratories | • WHO  
• WHO CCs  
• CVV laboratories |
| Use of CVVs, HGRs and LAIVs generated by RG techniques, because these are viewed as GMOs in some countries | • List of countries that consider RG products as GMO products | Manufacturers to confirm their readiness to work with GMOs, and the inclusion of GMOs in their pandemic plans | • IFPMA  
• DCVMN  
• WHO  
• MoH |
| Problems in rescuing some RG viruses in qualified Vero cells | • Research to identify other cell lines | | • CVV laboratories  
• BARDA |

BARDÁ, US Biomedical Advanced Research and Development Authority; CBD, Convention for Biological Biodiversity (1992); CC, collaborating centre; CVV, candidate vaccine virus; DCVMN, Developing Countries Vaccine Manufacturers Network; GISRS, Global Influenza Surveillance and Response System; GMO, genetically modified organism; HGR, high-growth reassortant; HHS, US Department of Health and Human Services; IFPMA, International Federation of Pharmaceutical Manufacturers & Associations; IP, intellectual property; IVPP, influenza viruses with pandemic potential; LAIV, live attenuated influenza vaccine; MoH, ministry of health; PIP, pandemic influenza preparedness; RG, reverse genetics; SII, specialized international access and benefit-sharing instrument under article 4(4) of the Nagoya Protocol; US, United States; WHO, World Health Organization.
### Table 4.2. Biocontainment of wildtype viruses and CVVs

<table>
<thead>
<tr>
<th>BOTTLENECK</th>
<th>DATA NEEDED</th>
<th>PROPOSED SOLUTION(S)</th>
<th>PROPOSED IMPLEMENTER(S)</th>
</tr>
</thead>
</table>
| Uncertainty over what biosafety level is required for IVPP | • Need for ferret safety tests  
• Criteria for attenuation and biosafety and utility of safety tests | • Guidance on safety testing of IVPP and CVVs  
• Guidance on biocontainment of IVPP and CVVs | • WHO ECBS |
| Continued need for chicken pathogenicity test (i.e. IVPI) for testing HPAI CVVs | • Data on IVPI testing, embryo lethality and trypsin dependence of CVVs  
• National biosafety guidelines  
• Biosafety guidance drafted by GHSA for poliovirus | • WHO position paper on need to relax requirement for IVPI  
• Revise TRS 941 in consultation with OIE and FAO  
• Review need for IVPI, to allow for downgrading of biocontainment levels for IVPP with ministry of agriculture | • WHO ECBS |
| Restrictions accompanying CVV production and development, because of national regulations on selected or dual-use agents | • Existing national guidelines  
• Template of manufacturer’s CVV certificate of release with CVV laboratories | • Waiver of select agent status of IVPP once human-to-human transmission is confirmed  
• WHO CCs and CVV laboratories to obtain permit for working with animal viruses  
• WHO to develop guidance on biosafety assessment | • WHO  
• OIE and FAO  
• Ministry of agriculture  
• IFPMA |

**Table 4.3. Candidate vaccine virus yield and manufacture**

<table>
<thead>
<tr>
<th>BOTTLENECK</th>
<th>DATA NEEDED</th>
<th>PROPOSED SOLUTION(S)</th>
<th>PROPOSED IMPLEMENTER(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-yield CVVs</td>
<td>• GMP models established by manufacturers for highly pathogenic H1, H3, H5 and H7 • Do GMP models work for different subtypes?</td>
<td>• All manufacturers to establish small-scale GMP model for harvest of pilot-scale production (e.g. HPLC and sucrose mini-gradients) • Timely sharing of yield information by manufacturers • Research to evaluate high-yield donor backbones provided by CVV laboratories • Research to evaluate the latest time point when change could be made to a CVV to improve yield • Research to evaluate potential to use non homologous reagents • Establish a yield assessment group</td>
<td>• IFPMA • DCVMN • CVV laboratories • ERLs</td>
</tr>
<tr>
<td>Slow evaluation of CVV yield</td>
<td>• Yield data</td>
<td>• CVV laboratories to indicate yield based on rapid analytic methods (HPLC and sucrose mini-gradients) in information package • Standardize release information package • Early sharing of preliminary yield data by CVV laboratories • Early shipping of CVVs pending concurrent tests</td>
<td>• CVV laboratories</td>
</tr>
<tr>
<td>SRID potency reagents delayed if too many CVVs</td>
<td>• CVV yield information</td>
<td>• Rapid evaluation and elimination of low-yield or low-quality CVVs • Maximum of three CVVs to be used for vaccine development</td>
<td>• CVV laboratories • IFPMA • DCVMN</td>
</tr>
<tr>
<td>Low downstream yield from CVVs</td>
<td>• Established CVV manufacturing practices • Adaptation and consequences of manufacturing practices for low-yield CVVs</td>
<td>• Small-scale pilot GMP facility to develop improved characterization and processes for optimization and application of rapid yield assessment</td>
<td>• IFPMA • DCVMN</td>
</tr>
<tr>
<td>Lack of high-yield CVVs</td>
<td>• IP rights of optimized high-yield donor backbone(s)</td>
<td>• Identify and share optimized high-yield donor backbone(s) • Research for alternative combinations to 6:2 reassortants</td>
<td>• CVV laboratories</td>
</tr>
<tr>
<td>Genetic or protein instability during replication, passaging or downstream processing: • retention of antigenic match • no reversions of LAIVs</td>
<td>• Antigenic analysis; sequencing at RNA and amino acid level • RNA sequencing to confirm genetic stability with respect to mutations • Results of antigenic analysis</td>
<td>• Testing by manufacturers or NRA: • optimize sequencing techniques and use the information to improve yields and stability • rapid antigenic and possibly genetic analysis</td>
<td>• IFPMA • DCVMN • WHO CCs</td>
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### Table 4.3. Candidate vaccine virus yield and manufacture [continued]

<table>
<thead>
<tr>
<th>BOTTLENECK</th>
<th>DATA NEEDED</th>
<th>PROPOSED SOLUTION(S)</th>
<th>PROPOSED IMPLEMENTER(S)</th>
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<tbody>
<tr>
<td>Generation of antisera or antibodies to be used for antigenic analysis</td>
<td>• Data on feasibility of using monoclonal antibodies</td>
<td>• Establish a library of monoclonal antibodies for faster and improved antigenic analysis</td>
<td>• WHO CCs</td>
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</tbody>
</table>

**CC, collaborating centre; CVV, candidate vaccine virus; DCVMN, Developing Countries Vaccine Manufacturers Network; ERL, essential regulatory laboratory; GMP, good manufacturing practice; HPLC, high-performance liquid chromatography; IFPMA, International Federation of Pharmaceutical Manufacturers & Associations; IP, intellectual property; LAIV, live attenuated influenza vaccine; NRA, national regulatory authority; RNA, ribonucleic acid; SRID, single radial immunodiffusion; WHO, World Health Organization**

### Table 4.4. Fill-and-finish capacity

<table>
<thead>
<tr>
<th>BOTTLENECK</th>
<th>DATA NEEDED</th>
<th>PROPOSED SOLUTION(S)</th>
<th>PROPOSED IMPLEMENTER(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Permits not being in place to allow formulation and fill of LAIVs</td>
<td></td>
<td>Facilities are audited, and permits issued in a timely manner</td>
<td>• IFPMA • DCVMN</td>
</tr>
<tr>
<td>Equipment (e.g. vials, stoppers, syringes and sprayers) not available</td>
<td>• A review of contracts and supplies with manufacturers</td>
<td>Ensure contracts with suppliers</td>
<td>• IFPMA • DCVMN</td>
</tr>
<tr>
<td>Availability of production facility depends on contractual requirements to fill pandemic vaccine, and is affected by the uncertainty of when to switch</td>
<td>• A review of current contractual obligations between manufacturers and countries or consumers</td>
<td>• Clear signal to switch by WHO • All contracts are triggered on this switch recommendation</td>
<td>• WHO • IFPMA • DCVMN</td>
</tr>
<tr>
<td>Lack of stability data</td>
<td>• Stability data</td>
<td>• Use historical data and then extrapolate from in-parallel stability studies after formulation and fill</td>
<td>• IFPMA • DCVMN</td>
</tr>
<tr>
<td>Delayed availability of SRID reagents for formulation</td>
<td>• Calibration data</td>
<td>• Timely donations of antigen from manufacturers • Early start of antiserum production • Timely sharing of information with other manufacturers, WHO CCs, ERLs</td>
<td>• IFPMA • DCVMN • ERLs</td>
</tr>
<tr>
<td>Limitations of pre-filled syringes (e.g. filling is slower and more antigen used), multidose vials (include thiomersal, which limits use)</td>
<td>• What delivery mode do countries prefer? What criteria do countries use to make choice? • What is the shelf life of each delivery mode? • Is prefilled syringe preferred for pregnant women and children? • Evaluation of US model of fill-and-finish network to optimize global filling capacity</td>
<td>• Model of a fill-and-finish network to optimize global filling capacity</td>
<td>• IFPMA • DCVMN • ERLs</td>
</tr>
</tbody>
</table>

**CC, collaborating centre; DCVMN, Developing Countries Vaccine Manufacturers Network; ERL, essential regulatory laboratory; IFPMA, International Federation of Pharmaceutical Manufacturers & Associations; LAIV, live attenuated influenza vaccine; SRID, single radial immunodiffusion; WHO, World Health Organization**
### Table 4.5. Single radial immunodiffusion potency assay reagents

<table>
<thead>
<tr>
<th>BOTTLENECK</th>
<th>DATA NEEDED</th>
<th>SOLUTIONS</th>
<th>IMPLEMENTATION</th>
</tr>
</thead>
</table>
| Delays in development and supply of SRID potency assay reagents | - Which CVVs are used?  
- How much antigen and antisera are available for reagent production?  
- Are existing reagents suitable?  
- Can heterologous reagents be used?  
- Is early supply of small lots of reagents better than later supply of large lots? | - Timely and secured donation of antigen  
- Agreements with manufacturers  
- Use of small-scale GMP pilot facility to produce potency reagents  
- Continued sharing of amount of reagents by manufacturers and ERLs  
- Strategies to speed up antisera availability; for example, use of alternate immunogens (e.g. recombinant HA and DNA vaccines), production of wildtype IVPP under containment for early purification of HA, and production of antisera at risk  
- Create library of reagents at risk similar to CVV library, using the small-scale GMP pilot facility | - IFPMA  
- DCVMN  
- ERLs |
| SRID potency assay as the only option | - Validation results of different assays | - Use alternate potency assays | - BARDA  
- ERLs  
- HHS  
- IFPMA |

BARDA, US Biomedical Advanced Research and Development Authority; CVV, candidate vaccine virus; DCVMN, Developing Countries Vaccine Manufacturers Network; DNA, deoxyribonucleic acid; ERL, essential regulatory laboratory; GMP, good manufacturing practice; HA, haemagglutinin; HHS, US Department of Health and Human Services; IFPMA, International Federation of Pharmaceutical Manufacturers & Associations; IVPP, influenza viruses with pandemic potential; SRID, single radial immunodiffusion; US, United States; WHO, World Health Organization

### Table 4.6. Regulatory harmonization

<table>
<thead>
<tr>
<th>BOTTLENECK</th>
<th>DATA NEEDED</th>
<th>SOLUTIONS</th>
<th>IMPLEMENTATION</th>
</tr>
</thead>
</table>
| Limited mutual recognition of regulatory procedures, leading to delays in vaccine supply | - Criteria for seasonal and pandemic vaccine PQ  
- VE data  
- Review of national requirements and NRA capability for labelling and lot release for emergency use of pandemic vaccine | - WHO guidelines on regulatory preparedness for provision of marketing authorization of pandemic vaccines in non-vaccine-producing countries  
- Strengthen capabilities of NRA and PQ for seasonal and pandemic vaccine for market authorization, and for pharmacovigilance  
- Support regional harmonization of labels, package inserts and lot release; and improve traceability (bar coding), emergency use authorization and criteria for VE assessment of pandemic vaccines in LMIC | - WHO ECBS  
- NRAs |
| Deployment (import and export) of vaccine, reagents and CVVs (GMO issues) | - Barriers, if any, to rapid shipping of pandemic vaccines | - Export–import permits with all manufacturers  
- Agreements with all shippers | - IFPMA  
- DCVMN |

CVV, candidate vaccine virus; DCVMN, Developing Countries Vaccine Manufacturers Network; ECBS, Expert Committee on Biological Standardization (WHO); GMO, genetically modified organism; IFPMA, International Federation of Pharmaceutical Manufacturers & Associations; LMIC, low- and middle-income countries; NRA, national regulatory authority; PQ, prequalification; US, United States; VE, vaccine effectiveness; WHO, World Health Organization
### Table 4.7. Clinical trials for the first pandemic vaccines

<table>
<thead>
<tr>
<th>BOTTLENECK</th>
<th>DATA NEEDED</th>
<th>PROPOSED SOLUTION(S)</th>
<th>PROPOSED IMPLEMENTER(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delay in availability of clinical trial vaccine lots and vaccine potency</td>
<td>- Environmental risk assessment</td>
<td>- Establish clinical end-points (e.g., safety and immunogenicity) to determine dose</td>
<td>• IFPMA</td>
</tr>
<tr>
<td>assays due to GMO issues</td>
<td></td>
<td>- Establish immunological correlates of protection</td>
<td></td>
</tr>
<tr>
<td>Delay due to country-specific vaccine lot release</td>
<td>- National and regional regulatory requirements for lot release</td>
<td>- Develop and test clinical development plan with a series of protocols</td>
<td>• WHO</td>
</tr>
<tr>
<td>Global lack of consistency for conduct of clinical trials, leading to</td>
<td>- Clinical trial protocols</td>
<td></td>
<td></td>
</tr>
<tr>
<td>delays in clinical trial protocol review</td>
<td>- Human and ferret challenge studies to show reduced or prevention of</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delays due to supply of adjuvants (not all manufacturers have access</td>
<td>- Review of licensed adjuvants</td>
<td>- Improve access to adjuvants</td>
<td>• IFPMA</td>
</tr>
<tr>
<td>to an adjuvant)</td>
<td>- Data from “mix and match” studies</td>
<td>- If too little access, use adjuvants for 1st dose and unadjuvanted vaccine for</td>
<td>• WHO</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2nd dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Use alum adjuvant for A(H7N9) vaccine</td>
<td></td>
</tr>
<tr>
<td>Uncertainty of safety of pandemic vaccine</td>
<td>- Identify who is likely to need or not need (prior immunity) pandemic</td>
<td>- Establish national serum banks ready for testing when needed</td>
<td>• WHO</td>
</tr>
<tr>
<td></td>
<td>vaccine</td>
<td>- Strengthen pharmacovigilance</td>
<td>• MoH</td>
</tr>
<tr>
<td></td>
<td>Safety data from pre-clinical safety studies (DART studies)</td>
<td>- Develop a risk management plan</td>
<td>• WHO Norms and Standards group</td>
</tr>
<tr>
<td></td>
<td>Pharmacovigilance data on AEs</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Epidemiological studies of background AEFI rates</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AE, adverse event; AEFI, adverse events following immunisation; CONSISE, Consortium for the Standardization of Influenza Seroepidemiology; DART, developmental and reproductive toxicology; DCVMN, Developing Countries Vaccine Manufacturers Network; GMO, genetically modified organism; IFPMA, International Federation of Pharmaceutical Manufacturers & Associations; MoH, Ministry of Health; NRA, national regulatory authority; WHO, World Health Organization
### Table 4.8. Risk assessment

<table>
<thead>
<tr>
<th>BOTTLENECK</th>
<th>DATA NEEDED</th>
<th>SOLUTIONS</th>
<th>IMPLEMENTATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delay in making a risk assessment about whether or not to make a vaccine switch</td>
<td>• Epidemiology, virology, severity, serology, modelling and impact data on the IVPP</td>
<td>• Develop a decision-making process that includes what data are needed, data sources, data-collecting protocols and channels, analytical methods and communication channels</td>
<td>• WHO&lt;br&gt;• Modellers&lt;br&gt;• CONCISE&lt;br&gt;• IFPMA/DCVMN</td>
</tr>
<tr>
<td>Lack of clarity on what data exists, whether data can be collected rapidly and how to integrate all streams</td>
<td>• Systems existing for data collection and analysis</td>
<td>• Develop a scheme for data collection, risk assessment and mode of operation</td>
<td>• WHO</td>
</tr>
</tbody>
</table>

5. **Challenges and principles in making the decision to start pandemic vaccine production**

Participants at the meeting re-examined and further refined the challenges and principles identified in the previous informal consultations, in particular, the challenges in switching from seasonal vaccine to pandemic vaccine and the principles in making a decision to start pandemic vaccine production. These challenges and principles are discussed below.

5.1 **Challenges**

One challenge is that 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 in order to produce pandemic vaccines. Therefore:

- a switch that is too early may compromise the production of seasonal vaccine, with possibly severe public health consequences; and
- a switch that is too late could have significant public health consequences, particularly if the pandemic is severe.

Another challenge is the mitigation of risks associated with a too-early or too-late decision to switch from seasonal to pandemic vaccine production.

Finally, few countries have updated their national pandemic preparedness plan to stipulate country-specific risk assessment, risk management and vaccine response procedures.

5.2 **Principles**

The principles developed at the meeting are listed below.

- Any decision or recommendation should be evidence-based and the process should be rapid, direct, transparent, data driven, flexible,
well documented and defensible. Any individuals and organizations advising WHO should have clear roles and responsibilities.

- Any decision made will be based 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 to review the decision as new data arise; however, once the decision to start pandemic vaccine production is made, it will not be realistic to take it back.

- The advice and evidence needed will include different components:
  - technical (e.g. availability of CVV and high-growth reassortants);
  - ethical; and,
  - political (e.g. governance and expert advice).

- A public health emergency of international concern (PHEIC) could be declared without declaring a pandemic or deciding to start pandemic vaccine production.

- An influenza pandemic can be declared without recommending the start of pandemic vaccine production. A decision to defer the start of pandemic vaccine production will be reviewed periodically as the pandemic evolves and more data become available.

- No recommendation to start pandemic vaccine production will be made unless a pandemic has been declared.

- Considerations such as time of year, the geography of seasonal and pandemic virus circulation, and the availability of CVVs will play a role in the decision on whether to start pandemic vaccine production.

- The WHO recommendation should always maximize global health and be guided by evidence-based risk assessment:
  - the risks of mortality, morbidity and economic consequences should be considered in order to minimize serious impact, and
  - the impact of not having enough seasonal vaccine available in case of a switch should be considered.

- The information assessed should include global mapping of influenza manufacturing capacity, seasonal and pandemic vaccines, and projection with relevant timelines.

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

- Different strategies for vaccine formulations may be considered (e.g. monovalent pandemic and monovalent seasonal vaccine, or monovalent pandemic and bivalent seasonal vaccine), and these options should be evaluated by experts.
6. Refinement of the process for pandemic vaccine response

Three pandemic vaccine process charts were revised, as follows:

- The operational framework for pandemic vaccine response (i.e. Who takes the actions?) (Annex 1).
- The timelines for pandemic vaccine production (i.e. When are actions taken?) (Annex 2). A further timelines chart was added, to include the actions needed to prepare both inactivated influenza vaccine (IIV) and live attenuated influenza vaccine (LAIV).
- The process of the WHO vaccine response to an influenza pandemic or potential pandemics (i.e. How are actions taken?) (Annex 3). The description of the decision-making process was improved to better illustrate the type of data assessed, how they are gathered and interpreted, and, in particular, what role the working groups play. In addition, the types of data and available tools (i.e. the data packages in the lower left-hand side of the chart) that are required to make key decisions were also revised. Specifically:
  - additions were made to the descriptions of the “data packages”, especially for modelling, to determine whether there are scenarios for which more lives will be saved if the switch to pandemic influenza production occurs earlier rather than later; and
  - references to the use of pre-pandemic vaccines and vaccine stockpiles were removed for the sake of clarity, because these are national resources.

7. Key outcomes of the informal consultation and next steps

7.1 Key outcomes

The key outcomes of the third informal consultation were as follows:

- identification of a clear, transparent and integrated process to influenza vaccine response at the start of a pandemic which considers the associated challenges and is based on the principles developed in the WHO informal consultations;
- identification of bottlenecks and potential solutions to overcome obstacles surrounding the switch from seasonal to pandemic vaccine production;
- establishment of three multidisciplinary working groups to work on the proposed solutions to bottlenecks and the risk assessment required for making a decision to start pandemic vaccine production;
- an option for issuing the WHO recommendation can be an emergency influenza Vaccine Composition Meeting (VCM) convened by WHO to recommend the composition of a pandemic vaccine;
- further refinement and confirmation of the principles for guiding the decision-making on recommending the start of pandemic vaccine production which might entail cessation of the ongoing seasonal influenza vaccine production and switch to pandemic vaccine production;
- finalization of the three pandemic vaccine process charts; and,
Participants agreed that the next steps should be to:

- establish WHO working groups to continue the work identified in the informal consultation;
- evaluate, along with the work of the working groups, whether there are other unmet resource needs (e.g., serum panels for seroprevalence studies);
- develop an overarching communication strategy and implement the part appropriate in the inter-pandemic period. The strategy should include implementation plans covering essential steps of pandemic vaccine response process, to augment the element of communication specific to defined activities in the process charts, targeting audience of not only the scientific community, but also policy-makers, decision-makers and the general public.

Acknowledgements

WHO wishes to acknowledge the technical contributions of the experts who participated in the WHO informal consultations, and in the development and peer review of this report: Derek Ellis (Canada), Susan Perry (Canada) and John Wood (United Kingdom).

WHO also wishes to thank its staff in the regional offices and headquarters involved in the process of developing this report.

Annexes

Annex 1: Draft operational framework for a pandemic vaccine response

Annex 2: Timelines of pandemic vaccine production
   A2.1. Inactivated influenza vaccine scheme
   A2.2. Live attenuated influenza vaccine scheme

Annex 3: Process of WHO vaccine response to an influenza pandemic or a potential pandemic

Annex 4: Activities: the “parking lot”

Annex 5: List of participants
**OPERATIONAL FRAMEWORK FOR PANDEMIC VACCINE RESPONSE**

### RISK ASSESSMENT & COMMUNICATIONS

<table>
<thead>
<tr>
<th>Activities</th>
<th>Participating Entities</th>
<th>Coordinating Entities</th>
<th>Deliverables or Outputs</th>
<th>Channels to Communicate the Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virological risk assessment*</td>
<td>WHO, GSRS, affected countries, OFFLU, animal sectors, academic institutions</td>
<td>WHO</td>
<td>Updated risk assessment based on virus characterization and special studies</td>
<td>WHO website, scientific publications as appropriate</td>
</tr>
<tr>
<td>Epidemiological monitoring and risk assessment</td>
<td>WHO, GSRS and associated epidemiologic institutions in affected countries, regional coordinating entities, (e.g. ECDC)</td>
<td>WHO</td>
<td>Early descriptions of the emerging epidemiological pattern of the pandemic virus</td>
<td>WHO website, regional and national websites, scientific publications as appropriate</td>
</tr>
<tr>
<td>Severity assessment*</td>
<td>WHO, affected countries, regional coordinating entities (e.g. ECDC)</td>
<td>WHO</td>
<td>Updated severity assessment</td>
<td>WHO website, regional and national websites, scientific publications as appropriate</td>
</tr>
<tr>
<td>Declaration of PHEIC</td>
<td>WHO, HR EC, GSRS, and other subject experts</td>
<td>WHO</td>
<td>WHO DG’s declaration of PHEIC and issuance of temporary recommendations</td>
<td>WHO website, other media channels as appropriate</td>
</tr>
<tr>
<td>Declaration of a pandemic</td>
<td>WHO, HR EC, GSRS, and other subject experts</td>
<td>WHO</td>
<td>Declaration of a Pandemic</td>
<td>WHO website, other media channels as appropriate</td>
</tr>
<tr>
<td>Composition of pandemic vaccine</td>
<td>WHO, Emergency VCM,</td>
<td>WHO</td>
<td>Composition of pandemic vaccine (recommendation to switch)</td>
<td>WHO website, other media channels as appropriate</td>
</tr>
</tbody>
</table>

* Using appropriate modelling tools, such as the tool for influenza pandemic assessment (TIPRA) and the pandemic influenza severity assessment (PISA).

**ABBREVIATIONS**

- ADR: Adverse Drug Reaction
- AEFI: Adverse Event Following Immunization
- BLA: Biologics License Application*
- BSL2+: Biosafety level 2+
- CVV: Candidate Vaccine Virus
- DCMVN: Developing Countries Vaccine Manufacturers Network
- EMA: European Medicines Agency
- EPIC: Expert Pandemic Influenza Committee
- EUA: Emergency Use Authorization*
- GAP: WHO Global Action Plan for Influenza Vaccines
- GISRS: Global Influenza Surveillance & Response System
- GMO: Genetically Modified Organism
- GMP: Good Manufacturing Practice
- HCW: Health Care Worker
- IHR: International Health Regulations
- IFPMA: International Federation of Pharmaceutical Manufacturers & Associations
- LAIV: Live Attenuated Influenza Vaccine
- IND: Investigational New Drug*
- NRAs: National Regulatory Authorities
- PHEIC: Public Health Emergency of International Concern
- PIP: Pandemic Influenza Preparedness
- PISA: Pandemic Influenza Severity Assessment
- PIRM: Pandemic Influenza Risk Management
- RG: Reverse Genetics
- SAGE: Strategic Advisory Group of Experts
- SRID: Single Radial Immunodiffusion
- TIPRA: Tool for Influenza Pandemic Risk Assessment
- VCM: Vaccine Composition Meeting
- VRBPAC: US Vaccines and Related Biological Products Advisory Committee
- US NIH/CDC: US National Institutes of Health/Centres for Disease Control
- WHO CCs: WHO Collaborating Centres
- WHO ERLs: WHO Essential Regulatory Laboratory
- * USA regulatory mechanism

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**Annex I: Draft operational framework for a pandemic vaccine response**

**ANNEX 1: Table A1.**

| Influenza vaccine response during the start of a pandemic – REPORT of the Third WHO informal consultation | 18 | 18 |

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**DG, Director General; EC, European Commissions EDCO, European Centre for Disease Prevention and Control; GSRS, Global Influenza Surveillance and Response System; HR, International Health Regulations (2005); OFFLU, World Organisation for Animal Health (OIE) Network of Expertise on Animal Influenza, FAO, Food and Agriculture Organization of the United Nations (FAO) Network of Expertise on Animal Influenza, PHEIC, public health emergency of International concern; VCM, WHO Influenza Vaccine Composition Meeting; WHO, World Health Organization**
## OPERATIONAL FRAMEWORK FOR PANDEMIC VACCINE RESPONSE

### ANNEX 1: Table A2.

### CANDIDATE VACCINE VIRUS 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 and reassorting laboratories</td>
<td>WHO CCs and reassorting laboratories</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 and reassorting laboratories</td>
<td>WHO CCs and reassorting laboratories</td>
<td>Potential CVVs</td>
<td>WHO website, WHO email distribution, IFPMA teleconferences and other channels as appropriate</td>
</tr>
<tr>
<td>Wildtype virus</td>
<td>WHO CCs and reassorting laboratories</td>
<td>WHO CCs and reassorting laboratories</td>
<td>Potential CVVs</td>
<td>WHO website, WHO email distribution, IFPMA teleconferences and other channels as appropriate</td>
</tr>
<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 ERLs, 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>

### ABBREVIATIONS

- ADR: Adverse Drug Reaction
- AEFI: Adverse Event Following Immunization
- BLA: Biologics License Application
- BSL2+: Biosafety level 2+
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- EPIC: Expert Pandemic Influenza Committee
- EUA: Emergency Use Authorization
- GAP: Global Action Plan for Influenza Vaccines
- GISRS: Global Influenza Surveillance & Response System
- GMO: Genetically Modified Organism
- GMP: Good Manufacturing Practice
- HCW: Health Care Worker
- IHR: International Health Regulations
- IFPMA: International Federation of Pharmaceutical Manufacturers & Associations
- LAIV: Live Attenuated Influenza Vaccine
- IND: Investigational New Drug
- NRA: National Regulatory Authority
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- PISA: Pandemic Influenza Severity Assessment
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- SRID: Single Radial Immunodiffusion
- TIPRA: Tool for Influenza Pandemic Risk Assessment
- VCM: Vaccine Composition Meeting
- VRBPAC: US Vaccines and Related Biological Products Advisory Committee
- US NIH/CDC: US National Institutes of Health/Centres for Disease Control and Prevention

Influenza vaccine response during the start of a pandemic – REPORT of the Third WHO informal consultation

* USA regulatory mechanism
### Table A3.

<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>Start with CVVs and seed lot</td>
<td>Manufacturers, regulators, relevant national authority</td>
<td>Manufacturers and regulators</td>
<td>Influenza vaccine lots suitable for human use produced from CVVs or seed lots that can be grown to higher yield</td>
<td>WHO platforms, such as website, press releases and teleconferences (regular and emergency) as appropriate</td>
</tr>
<tr>
<td>Evaluate growth properties</td>
<td>Manufacturers</td>
<td>Manufacturers and regulators</td>
<td>Yield data</td>
<td>Teleconferences of WHO, IFPMA and involved manufacturers and other entities as appropriate</td>
</tr>
<tr>
<td>Animal studies</td>
<td>Manufacturers’ senior management, national and global coordinating entities, e.g. BARDA to do/fund/coordinate extra trials</td>
<td>Manufacturers and regulators</td>
<td>Approval from relevant regulator</td>
<td>WHO platforms, such as website, press releases and teleconferences (regular and emergency), as appropriate</td>
</tr>
<tr>
<td>Preclinical studies</td>
<td>Manufacturers, academia, commercial clinical trial units, national / international entities such as US NIH/CDCs, ethics committees, regulatory authorities</td>
<td>Manufacturers, regulators, national / international entities such as US NIH/CDCs</td>
<td>Evaluation of vaccine safety</td>
<td>Communication at global platform to all stakeholders, including regulators and other national authorities, modelers and other entities as appropriate</td>
</tr>
<tr>
<td>Clinical Trials</td>
<td>Ethics committee approvals</td>
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<td></td>
</tr>
<tr>
<td>Studies in adults</td>
<td>Studies in adults</td>
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<td></td>
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<tr>
<td>Paediatric studies</td>
<td>Regulatory evaluation of vaccine safety</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sharing of baseline safety data</td>
<td>Serology with appropriate expert advice and oversight at all stages</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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- LAIV: Live Attenuated Influenza Vaccine
- IND: Investigational New Drug
- NRAs: National Regulatory Authorities
- PHEIC: Public Health Emergency of International Concern
- PIP: Pandemic Influenza Preparedness
- PISA: Pandemic Influenza Severity Assessment
- PIRM: Pandemic Influenza Risk Management
- RG: Reverse Genetics
- SAGE: Strategic Advisory Group of Experts
- SRID: Single Radial Immunodiffusion
- TIPRA: Tool for Influenza Pandemic Risk Assessment
- VCM: Vaccine Composition Meeting
- VRBPAC: US Vaccines and Related Biological Products Advisory Committee
- WHO CCs: WHO Collaborating Centres
- WHO ERLs: WHO Essential Regulatory Laboratory
- WHO, World Health Organization
- USNIH/CDC: US National Institutes of Health/Centers for Disease Control

* FLUCOP is a collaborative research project that aims to standardize and develop assays for the assessment of influenza vaccine correlates of protection.

**FLUCOP** is a collaborative research project that aims to standardize and develop assays for the assessment of influenza vaccine correlates of protection.
## PRODUCTION

### ANNEX 1: Table A4.

<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>Production of antigen</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</td>
</tr>
<tr>
<td>Production of antiserum</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>International calibration studies</td>
<td>WHO ERLs</td>
<td>WHO ERLs</td>
<td>Calibrated reagents</td>
<td>WHO ERLs via teleconferences, email or other channels, reagent-tracking table and other channels, as appropriate</td>
</tr>
<tr>
<td>Structured feedback from manufacturers on use of reagents</td>
<td>WHO ERLs, NRAs</td>
<td>WHO ERLs, and manufacturers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potential intensification of seasonal production prior to the potential start of pandemic vaccine production</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>Cessation of seasonal vaccine production</td>
<td>WHO, national authorities, and manufacturers</td>
<td>WHO, national authorities, and manufacturers</td>
<td>Readiness for pandemic vaccine manufacturing</td>
<td>Direct communication from manufacturers to customer countries, updates to WHO</td>
</tr>
<tr>
<td>Ongoing risk assessment on the need for pandemic vaccine</td>
<td>WHO, IHR EC, GISRS, SAGE, Emergency VCM and other subject experts</td>
<td>WHO</td>
<td>Recommend that production of pandemic vaccine commence based on risk assessment. This may entail critical steps including recommendation for composition of pandemic vaccine and switching from production of seasonal vaccine to pandemic vaccine.</td>
<td>WHO website, other media channels as appropriate</td>
</tr>
<tr>
<td>Start of pandemic vaccine production</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>Vaccine production</td>
<td>Manufacturers, NCLs</td>
<td>Manufacturers</td>
<td>Build mono-bulk stock of pandemic strain</td>
<td>Updates from IFPMA to WHO, and manufacturers to customer countries</td>
</tr>
<tr>
<td>Vaccine formulation</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>Filling/Packaging</td>
<td>Manufacturers, customer countries, NCLs</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>
</table>

### ABBREVIATIONS

- ADR: Adverse Drug Reaction
- AEFI: Adverse Event Following Immunization
- BLA: Biologics License Application
- BSL2+: Biosafety level 2+
- CVV: Candidate Vaccine Virus
- DCV MN: Developing Countries Vaccine Manufacturers Network
- EMA: European Medicines Agency
- EPIC: Expert Pandemic Influenza Committee
- EUA: Emergency Use Authorization
- GAP: WHO Global Action Plan for Influenza Vaccines
- GEMR: Global Influenza Surveillance & Response System
- GMID: Genetically Modified Organism
- GMP: Good Manufacturing Practice
- HCW: Health Care Worker
- IHR: International Health Regulations
- IFPMA: International Federation of Pharmaceutical Manufacturers & Associations
- LAIV: Live Attenuated Influenza Vaccine
- IND: Investigational New Drug
- NRAs: National Regulatory Authorities
- PHEIC: Public Health Emergency of International Concern
- PIP: Pandemic Influenza Preparedness
- PISA: Pandemic Influenza Severity Assessment
- PIRM: Pandemic Influenza Risk Management
- RG: Reverse Genetics
- SAGE: Strategic Advisory Group of Experts
- SRR: Single Radial Immunodiffusion
- TIPRA: Tool for Influenza Pandemic Risk Assessment
- VCM: Vaccine Composition Meeting
- VRBPAC: US Vaccines and Related Biological Products Advisory Committee
- US NIH/CDC: US National Institutes of Health/Centers for Disease Control
- WHO CCs: WHO Collaborating Centres
- WHO ERLs: WHO Essential Regulatory Laboratory
- *USA regulatory mechanism
### ANNEX 1: Table A5. REGISTRATION

<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>Dossier route</td>
<td>WHO, manufacturers, national and regional (e.g. EMA) regulating authorities</td>
<td>WHO, regulators</td>
<td>Approval/no approval</td>
<td>Guidelines Website</td>
</tr>
<tr>
<td>Emergency route</td>
<td>WHO, manufacturers, national and regional (e.g. EMA) regulating authorities</td>
<td>WHO, regulators</td>
<td>Approval/no approval</td>
<td>Guidelines Website</td>
</tr>
<tr>
<td>Regulatory oversight to assure the quality of pandemic vaccines</td>
<td>Exiting lot release labs including WHO ERLs and NCLs</td>
<td>Regulatory network/WHO</td>
<td>Development of a formal network of release laboratories to enhance availability of pandemic vaccine Clear set of assays to streamline process</td>
<td>Websites, workshops, written standards, membership criteria</td>
</tr>
<tr>
<td>Risk management, safety monitoring, signal detection</td>
<td>Health-care workers, regulators, public health immunization programs, manufacturers</td>
<td>NRAs, WHO</td>
<td>Improved safety assessment and monitoring system Improved vaccine effectiveness monitoring in key target populations Increased use of tools (models, etc.)</td>
<td>Health-care workers, public health organizations, manufacturers, international exchange of safety data or signals via WHO, SAGE or GACVS</td>
</tr>
<tr>
<td>Vaccine effectiveness quantity of adverse effects, exposure data Benefit / risk assessment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distribution and rollout</td>
<td>Health authorities</td>
<td>Health and local authorities SAGE</td>
<td>Distribution, availability and early adverse drug reactions</td>
<td>Health authorities, and NCLs and ERLs via teleconferences, email or other channels</td>
</tr>
</tbody>
</table>

**Notes:**
- Forward-looking outcomes would be establishment of global guidelines and common regulatory processes to support fast tracking/cheaper development costs.
- Approval process principles to include: clarity, transparency, mutual recognition, rapid access.
- Each WHO region should have such laboratories. Mutual recognition procedures need to be developed. Recognized standards and inspections are needed, EU can be seen as a model.
- Increased confidence among health-care workers and the public. Ensure case definitions are available for adverse events following immunization.

**Glossary:**
- ADR: Adverse Drug Reaction
- AEFI: Adverse Event Following Immunization
- BLA: Biologies License Application*
- BSL2+: Biosafety level 2+
- CVV: Candidate Vaccine Virus
- DCVMN: Developing Countries Vaccine Manufacturers Network
- EMA: European Medicines Agency
- EPIC: Expert Pandemic Influenza Committee
- EUA: Emergency Use Authorization*
- GAP: WHO Global Action Plan for Influenza Vaccines
- GISSR: Global Influenza Surveillance & Response System
- GMDO: Genetically Modified Organism
- GMP: Good Manufacturing Practice
- HGW: Health Care Worker
- IHR: International Health Regulations
- IFPMA: International Federation of Pharmaceutical Manufacturers & Associations
- LAIV: Live Attenuated Influenza Vaccine
- IND: Investigational New Drug*
- NRAs: National Regulatory Authorities
- PMH: Public Health Emergency of International Concern
- PIP: Pandemic Influenza Preparedness
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- RG: Reverse Genetics
- SAGE: Strategic Advisory Group of Experts
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- TIPRA: Tool for Influenza Pandemic Risk Assessment
- VCM: Vaccine Composition Meeting
- VRB PAC: US Vaccines and Related Biological Products Advisory Committee
- US NIH/CDC: US National Institutes of Health/Centres for Disease Control
- WHO CCs: WHO Collaborating Centres
- WHO ERLs: WHO Essential Regulatory Laboratory
- WHO: World Health Organization

* USA regulatory mechanism
The following timelines represent ideal circumstances, when all staff, facilities, reagents, equipment and process stages are in place and function optimally. If some activities do not go well, they may take longer and this is indicated by the hatched areas of the chart. Due to the interrelatedness of many of the activities, a delay in one activity would delay others in the timeline.

A21. Inactivated influenza vaccine scheme

<table>
<thead>
<tr>
<th>ENTITIES</th>
<th>ACTIVITIES</th>
<th>ACTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Reassorting Labs</td>
<td>Reassortant development</td>
</tr>
<tr>
<td>2</td>
<td>WHO CCs and Reassorting Labs</td>
<td>Reassortant evaluation</td>
</tr>
<tr>
<td>3</td>
<td>Manufacturers</td>
<td>Reassortant assessment</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>Development</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>Clinical trials</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>Serology</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>Vaccine Production</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>ERLs</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>Regulatory Authorities</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td></td>
<td></td>
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<tr>
<td>12</td>
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<td>13</td>
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<tr>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td></td>
<td>Programme managers</td>
</tr>
</tbody>
</table>

This timeline is in ideal circumstances when everything goes well. If some activities do not go well, they may take longer and this is indicated in the hatched 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.

**COMMENTS AND POTENTIAL ISSUES**

1. CVVs are selected by the WHO CCs. RS reassortants will take about 19 days, classical reassortants about 21 days. Synthetic seeds may also be an option. Safety testing TBD, but if the CVV is derived from a highly pathogenic virus, it will need to be evaluated for exclusion from “Select Agent” status in the USA and if the CVV is derived by reverse genetics it will need to comply with EU GMO regulations. CVVs are generally NOT distributed until Serology Test complete & at least a 1-way HI but in a pandemic situation they could be distributed pending HI and sterility data. WHO will give clear guidance on biocontainment and a risk assessment of severity, transmissibility and epidemiology associated with the emerging virus.

2. Checking gene sequences, gene constellation and performing one and two way tests.

3. Poor yields might result in delays in vaccine supply to large populations.

4. Essential to begin a clinical trial if required (phase 3). Some countries will require a clinical trial if the emerging pandemic subtype has little or no clinical data. HA content and dosing schedule will not be known for a new subtype. Adults and older adults should be included in the trial. It is expected that a half dose x 2 would be given to children as for seasonal vaccine.

5. ADRs need to be monitored especially in the first part of the clinical trial and then in the field as a pharmacovigilance study depending on the NRA. This would occur beyond the 14 week mark.

6. The early stages of planning and recruitment will have taken place earlier than this.

7. Base line serology and then at 2 and 4 weeks after injection.

8. The production of a monovalent vaccine can take place early with expected lot release later. Manufacturers need to supply antigen to ERLs as soon as possible for reagent preparation.

9. The production of sheep sera is critical and a major bottleneck in the process.

10. Used by EU and countries/NRAs that follow the EMA. Assumes that the manufacturing process for the emerging pandemic virus will be the same as that for seasonal vaccine viruses. Early discussions with NRA essential.

11. Emergency use approval may be given prior to final registration. Early discussions with NRA essential.

12. All manufacturers should ideally seek registration of the vaccine not only mock dossier approval and/or emergency use.

13. This is the batch release process. Faster alternative tests such as ELISA tests could also be used in addition to SRID to assess potency. Endotoxin tests are essential as are other lot release requirements. About 4 to 6 days are needed.

14. AEFI monitoring by the NRA and other specialist groups, web-based reporting and sentinel monitoring. This would occur beyond the 14 week mark.

15. Distribution by programme managers to sites. Roll-out priority to be determined according to the pandemic plan. To continue beyond the week 14 mark.
ANNEX 2: Timelines of pandemic vaccine production

**A2.2: Live attenuated influenza vaccine scheme**

<table>
<thead>
<tr>
<th>ACTIVITIES</th>
<th>ACTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prepare LAIV reassortant vaccine variant/s</td>
<td>Reassort/clone &amp; rescue LAIV, initial characterisation in include in vivo BSL testing</td>
</tr>
<tr>
<td>Approval and BSL change</td>
<td>Confirm lower BSL handling</td>
</tr>
<tr>
<td>LAIV assessment</td>
<td>Biocharacterisation and manufacturability (yield and growth)</td>
</tr>
<tr>
<td>Reagents</td>
<td>Antigen preparation for sheep/ferret immunisation</td>
</tr>
<tr>
<td>Production and calibration of assays reagents</td>
<td>Production and calibration of assays reagents</td>
</tr>
<tr>
<td>Development</td>
<td>Master seed production and initial release for CT vial filling/bulk manufacture (1) (4)</td>
</tr>
<tr>
<td>Vaccine production</td>
<td>LAIV bulk production and initial release (2) (4)</td>
</tr>
<tr>
<td>Regulatory Authorities</td>
<td>Vaccine formulation/packaging/distribution</td>
</tr>
</tbody>
</table>

**TIMELINE OF PANDEMIC VACCINE PRODUCTION**

| WEEK NUMBER SINCE RECEIPT OF VIRUS MATERIAL (wt virus or sequence) | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 |
|--------------------------------------------------------------------|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| 1. Prepare LAIV reassortant vaccine variant/s                     |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 2. Approval and BSL change                                        |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 3. LAIV assessment                                                 |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 4. Reagents                                                       |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 5. Production and calibration of assays reagents                  |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 6. Development                                                    |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 7. Vaccine production                                             |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |

BSL, biosafety level; CT, cycle threshold; IIV, inactivated influenza vaccine; LAIV, live attenuated influenza vaccine

6. Assuming 1-2 batches of master seed produced.

6,7. Final release and issuing of the certificate of analysis will be circa 8-10 weeks later from week 16 or 20, respectively.

7. Assuming 2-3 batches produced per week to generate 18 batches per IIVs below.

The timing for LAIV clinical trials, regulatory authorities, Pharmacovigilance and Program Managers topics are similar to those for RV and they are synchronized with Clinical Lot Vaccine and bulk vaccine being available.

Influenza vaccine response during the start of a pandemic – REPORT of the third WHO informal consultation
**ANNEX 3: Process of WHO vaccine response to an influenza pandemic or a potential pandemic**

**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

**DATA PACKAGES**
- Continuous risk assessment by WHO’s IHR, SAGE and subject experts as well as industry and stakeholders on:
  1. Epidemiology, including risk severity assessment PISA
  2. Virology, including sero prevalence TIPRA
  3. Forecasting/modelling of vaccine implementation scenarios (e.g. impact on health systems)
  4. The status of seasonal vaccine production – modelling of current production capacities
  5. Status of CVV development
  6. Risks and benefits associated with switch from seasonal to pandemic production (health economic modelling) and/or back

**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
  - Potential for significant impact to public health? (GISRS if warranted)
  - Further virus characterization by WHO CCs
  - Assessment of need for high-growth reassortant development
  - Need to develop (a) high-growth reassortant(s)? (GISRS if warranted)

- **Selection of candidate virus by GISRS**
  - Development of high-growth reassortants by GISRS and other laboratories
  - Distribution of high-growth reassortants
  - Yield evaluation by manufacturers and GISRS
  - RA on further vaccine development

- **Assessment if results warrant production/use of pandemic vaccines**
  - YES
  - Further vaccine development/licensing
    - Clinical trials if needed
    - Procurement
  - NO
  - NO

- **Biosafety assessment of CVVs by WHO**
  - Initiation of the development of potency reagents by GISRS
  - Availability of potency reagents by GISRS

- **WHO recommendation on pandemic vaccine production (VCM)**
  - Large-scale production/release of vaccines for use by country/region
  - Safety and Effectiveness monitoring

- **Continuous update to SAGE; DG updates to member states, and other stakeholders as appropriate**
  - Set up IHR EC (extended)
  - DG declares @ PHEIC
  - WHO declaration of a pandemic
  - 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 – REPORT of the Third WHO informal consultation**
Annex 4: Activities: the “parking lot”

The “parking lot” is a list of comments and proposals that are relevant to the informal consultation but were not considered in depth. Some of these comments and proposals from the first two informal consultations have now been incorporated into Section 4 of this report. The remaining items could be considered as part of forward agendas in future meetings. Comments and proposals from the 2017 informal consultation are in italics.

Communication
- Strategy for WHO to communicate to stakeholders and key decision-makers in Member States.
  - A concise compilation of information from all three informal consultations to be distributed to national authorities.

Research
- Gain-of-function research.
- Further surveillance information on the concurrent spread of pandemic viruses and seasonal viruses. 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
- Update national pandemic preparedness plans.
- Consider including administration procedures in pandemic plans.
- What are the liability issues for switching?
- What is the resilience of production facilities to make the switch?
- What preservatives are to be recommended for pandemic vaccines?
- If an adjuvant is needed for a pandemic vaccine and not all manufacturers have access to an effective adjuvant, what plans are in place to share adjuvants?
- What is the process for stopping pandemic vaccine production and administration?
- Harmonize vaccine distribution, shipping, logistics and cold chain.
- Review new technology platforms to speed up production of current vaccines.
- Review the use of alternative non-vaccine strategies, including antiviral drugs.
  - Review the need for and progress of potentially more effective vaccines, including adjuvanted and universal vaccines.
- Review whether a seasonal vaccine has any effectiveness against a pandemic influenza.
- Conduct post-release observational vaccine effectiveness studies, especially among elderly vaccines.
- Behavioural analysis: how do people actually behave in a pandemic (e.g. politicians, the medical profession and the public)?
- Strengthen pharmacovigilance globally.
Annex 5: List of participants

Third WHO informal consultation on influenza vaccine response during the start of a pandemic, 7–9 June 2017

**Ampofo**, William Kwabena, Noguchi Memorial Institute for Medical Research, Legon, Accra, Ghana

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Kistner, Otfried, Independent Vaccine Expert, Vienna, Austria

Koopmans, Marion, Virosciences Department, Erasmus MC, Rotterdam, Netherlands

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McCauley, John, The Francis Crick Institute, London, United Kingdom of Great Britain & Northern Ireland

Meyer, Heidi, Paul-Ehrlich Institute, Langen, Germany

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References


