

**INFLUENZA VACCINE RESPONSE DURING THE START OF A PANDEMIC**  
Report of the Third WHO informal consultation  
Geneva, Switzerland

7–9 June 2017



**World Health  
Organization**

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# 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

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

## 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 2<sup>nd</sup> 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 68<sup>th</sup> 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 CW 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<sup>1</sup> 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 CWs, 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.

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<sup>1</sup> 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.

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).

**Table 4.1. CVV production and distribution**

BOTTLENECK	DATA NEEDED	PROPOSED SOLUTION(S)	PROPOSED IMPLEMENTER(S)
Not enough laboratories producing CVVs, especially those from highly pathogenic viruses	<ul style="list-style-type: none"> <li>Review number and surge capacity of available laboratories</li> <li>Review requirement for laboratories to develop and test CVVs</li> </ul>	<ul style="list-style-type: none"> <li>Establish CVV development programme within DCVMN</li> </ul>	<ul style="list-style-type: none"> <li>CW laboratories</li> <li>WHO</li> <li>DCVMN</li> </ul>
Uncertainty of implications of Nagoya Protocol on pandemic virus sharing and CVV distribution	<ul style="list-style-type: none"> <li>Can PIP be considered an SII within the Nagoya Protocol?</li> <li>Explore the process in the Netherlands that waives the right to benefit from sharing viruses</li> </ul>	WHO to work with CBD for <ul style="list-style-type: none"> <li>PIP and GISRS to be considered as SII</li> <li>PIP and GISRS to be exempted from CBD</li> </ul>	<ul style="list-style-type: none"> <li>WHO</li> <li>CBD</li> <li>Environmental agencies</li> </ul>
Uncertainty about manufacturers' obligations to share CVVs and synthetic seeds	<ul style="list-style-type: none"> <li>Manufacturers with capacity for developing HGRs</li> </ul>	<ul style="list-style-type: none"> <li>Manufacturers agree to share HGRs and synthetic seed pandemic viruses, all including those produced with their own technology</li> </ul>	<ul style="list-style-type: none"> <li>WHO</li> <li>IFPMA</li> <li>DCVMN</li> </ul>
IP rights held by AstraZeneca / MedImmune for use of RG in producing pandemic CVVs	<ul style="list-style-type: none"> <li>Are non-US manufacturers exempt from IP in the event of a pandemic?</li> <li>Expiry dates of current IP rights</li> </ul>	<ul style="list-style-type: none"> <li>AstraZeneca/MedImmune agree on access to RG technology during a pandemic event</li> </ul>	<ul style="list-style-type: none"> <li>WHO CC US</li> <li>HHS/BARDA</li> <li>AstraZeneca / Medimmune</li> </ul>
Countries experience challenges in shipping wildtype IVPP to WHO CCs or CW laboratories	<ul style="list-style-type: none"> <li>Potential national and international barriers for international shipment of IVPP (PIP review report)</li> <li>Review national export and import permits</li> </ul>	<ul style="list-style-type: none"> <li>Align national import and export permits with national pandemic preparedness plan</li> </ul>	<ul style="list-style-type: none"> <li>WHO</li> </ul>
Variable yields from HGR and LAIV viruses	<ul style="list-style-type: none"> <li>Number of viruses needed to supply to HGR/LAIV laboratories</li> </ul>	<ul style="list-style-type: none"> <li>Ship multiple wildtype viruses to HGR/LAIV laboratories</li> </ul>	<ul style="list-style-type: none"> <li>WHO</li> <li>WHO CCs</li> <li>CW laboratories</li> </ul>
Use of CVVs, HGRs and LAIVs generated by RG techniques, because these are viewed as GMOs in some countries	<ul style="list-style-type: none"> <li>List of countries that consider RG products as GMO products</li> </ul>	<ul style="list-style-type: none"> <li>Manufacturers to confirm their readiness to work with GMOs, and the inclusion of GMOs in their pandemic plans</li> </ul>	<ul style="list-style-type: none"> <li>IFPMA</li> <li>DCVMN</li> <li>WHO</li> <li>MoH</li> </ul>
Problems in rescuing some RG viruses in qualified Vero cells		<ul style="list-style-type: none"> <li>Research to identify other cell lines</li> </ul>	<ul style="list-style-type: none"> <li>CW laboratories</li> <li>BARDA</li> </ul>

BARDA, 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**

BOTTLENECK	DATA NEEDED	PROPOSED SOLUTION(S)	PROPOSED IMPLEMENTER(S)
Uncertainty over what biosafety level is required for IVPP	<ul style="list-style-type: none"> <li>• Need for ferret safety tests</li> <li>• Criteria for attenuation and biosafety and utility of safety tests</li> </ul>	<ul style="list-style-type: none"> <li>• Guidance on safety testing of IVPP and CVVs</li> <li>• Guidance on biocontainment of IVPP and CVVs</li> </ul>	<ul style="list-style-type: none"> <li>• WHO ECBS</li> </ul>
Continued need for chicken pathogenicity test (i.e. IVPI) for testing HPAI CVVs	<ul style="list-style-type: none"> <li>• Data on IVPI testing, embryo lethality and trypsin dependence of CVVs</li> <li>• National biosafety guidelines</li> <li>• Biosafety guidance drafted by GHSA for poliovirus</li> </ul>	<ul style="list-style-type: none"> <li>• WHO position paper on need to relax requirement for IVPI</li> <li>• Revise TRS 941 in consultation with OIE and FAO</li> <li>• Review need for IVPI, to allow for downgrading of biocontainment levels for IVPP with ministry of agriculture</li> </ul>	<ul style="list-style-type: none"> <li>• WHO ECBS</li> </ul>
Restrictions accompanying CVV production and development, because of national regulations on selected or dual-use agents	<ul style="list-style-type: none"> <li>• Existing national guidelines</li> <li>• Template of manufacturer's CW certificate of release with CW laboratories</li> </ul>	<ul style="list-style-type: none"> <li>• Waiver of select agent status of IVPP once human-to-human transmission is confirmed</li> <li>• WHO CCs and CW laboratories to obtain permit for working with animal viruses</li> <li>• WHO to develop guidance on biosafety assessment</li> </ul>	<ul style="list-style-type: none"> <li>• WHO</li> <li>• OIE and FAO</li> <li>• Ministry of agriculture</li> <li>• IFPMA</li> </ul>

CC, collaborating centre; CW, candidate vaccine virus; ECBS, WHO Expert Committee on Biological Standardization; FAO, Food and Agriculture Organization of the United Nations; GHSA, Global Health Security Agenda; HPAI, highly pathogenic avian influenza; IFPMA, International Federation of Pharmaceutical Manufacturers & Associations; IVPI, in-vitro pathogenicity index; IVPP, influenza viruses with pandemic potential; OIE, World Organisation for Animal Health; TRS, Technical Report Series; WHO, World Health Organization

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

BOTTLENECK	DATA NEEDED	PROPOSED SOLUTION(S)	PROPOSED IMPLEMENTER(S)
Low-yield CWVs	<ul style="list-style-type: none"> <li>GMP models established by manufacturers for highly pathogenic H1, H3, H5 and H7</li> <li>Do GMP models work for different subtypes?</li> </ul>	<ul style="list-style-type: none"> <li>All manufacturers to establish small-scale GMP model for harvest of pilot-scale production (e.g. HPLC and sucrose mini-gradients)</li> <li>Timely sharing of yield information by manufacturers</li> <li>Research to evaluate high-yield donor backbones provided by CVV laboratories</li> <li>Research to evaluate the latest time point when change could be made to a CWV to improve yield</li> <li>Research to evaluate potential to use non homologous reagents</li> <li>Establish a yield assessment group</li> </ul>	<ul style="list-style-type: none"> <li>IFPMA</li> <li>DCVMN</li> <li>CVV laboratories</li> <li>ERLs</li> </ul>
Slow evaluation of CVV yield	<ul style="list-style-type: none"> <li>Yield data</li> </ul>	<ul style="list-style-type: none"> <li>CVV laboratories to indicate yield based on rapid analytic methods (HPLC and sucrose mini-gradients) in information package</li> <li>Standardize release information package</li> <li>Early sharing of preliminary yield data by CVV laboratories</li> <li>Early shipping of CWVs pending concurrent tests</li> </ul>	<ul style="list-style-type: none"> <li>CVV laboratories</li> </ul>
SRID potency reagents delayed if too many CWVs	<ul style="list-style-type: none"> <li>CVV yield information</li> </ul>	<ul style="list-style-type: none"> <li>Rapid evaluation and elimination of low-yield or low-quality CWVs</li> <li>Maximum of three CWVs to be used for vaccine development</li> </ul>	<ul style="list-style-type: none"> <li>CVV laboratories</li> <li>IFPMA</li> <li>DCVMN</li> </ul>
Low downstream yield from CWVs	<ul style="list-style-type: none"> <li>Established CVV manufacturing practices</li> <li>Adaptation and consequences of manufacturing practices for low-yield CWVs</li> </ul>	<ul style="list-style-type: none"> <li>Small-scale pilot GMP facility to develop improved characterization and processes for optimization and application of rapid yield assessment</li> </ul>	<ul style="list-style-type: none"> <li>IFPMA</li> <li>DCVMN</li> </ul>
Lack of high-yield CWVs	<ul style="list-style-type: none"> <li>IP rights of optimized high-yield donor backbone(s)</li> </ul>	<ul style="list-style-type: none"> <li>Identify and share optimized high-yield donor backbone(s)</li> <li>Research for alternative combinations to 6:2 reassortants</li> </ul>	<ul style="list-style-type: none"> <li>CVV laboratories</li> </ul>
Genetic or protein instability during replication, passaging or downstream processing: <ul style="list-style-type: none"> <li>retention of antigenic match</li> <li>no reversions of LAIVs</li> </ul>	<ul style="list-style-type: none"> <li>Antigenic analysis; sequencing at RNA and amino acid level</li> <li>RNA sequencing to confirm genetic stability with respect to mutations</li> <li>Results of antigenic analysis</li> </ul>	<ul style="list-style-type: none"> <li>Testing by manufacturers or NRA: <ul style="list-style-type: none"> <li>optimize sequencing techniques and use the information to improve yields and stability</li> <li>rapid antigenic and possibly genetic analysis</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>IFPMA</li> <li>DCVMN</li> <li>WHO CCs</li> </ul>

**Table 4.3. Candidate vaccine virus yield and manufacture [continued]**

BOTTLENECK	DATA NEEDED	PROPOSED SOLUTION(S)	PROPOSED IMPLEMENTER(S)
Generation of antisera or antibodies to be used for antigenic analysis	<ul style="list-style-type: none"> <li>Data on feasibility of using monoclonal antibodies</li> </ul>	<ul style="list-style-type: none"> <li>Establish a library of monoclonal antibodies for faster and improved antigenic analysis</li> </ul>	<ul style="list-style-type: none"> <li>WHO CCs</li> </ul>

CC, collaborating centre; CWV, 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**

BOTTLENECK	DATA NEEDED	PROPOSED SOLUTION(S)	PROPOSED IMPLEMENTER(S)
Permits not being in place to allow formulation and fill of LAIVs		Facilities are audited, and permits issued in a timely manner	<ul style="list-style-type: none"> <li>IFPMA</li> <li>DCVMN</li> </ul>
Equipment (e.g. vials, stoppers, syringes and sprayers) not available	<ul style="list-style-type: none"> <li>A review of contracts and supplies with manufacturers</li> </ul>	Ensure contracts with suppliers	<ul style="list-style-type: none"> <li>IFPMA</li> <li>DCVMN</li> </ul>
Availability of production facility depends on contractual requirements to fill pandemic vaccine, and is affected by the uncertainty of when to switch	<ul style="list-style-type: none"> <li>A review of current contractual obligations between manufacturers and countries or consumers</li> </ul>	<ul style="list-style-type: none"> <li>Clear signal to switch by WHO</li> <li>All contracts are triggered on this switch recommendation</li> </ul>	<ul style="list-style-type: none"> <li>WHO</li> <li>IFPMA</li> <li>DCVMN</li> </ul>
Lack of stability data	<ul style="list-style-type: none"> <li>Stability data</li> </ul>	<ul style="list-style-type: none"> <li>Use historical data and then extrapolate from in-parallel stability studies after formulation and fill</li> </ul>	<ul style="list-style-type: none"> <li>IFPMA</li> <li>DCVMN</li> </ul>
Delayed availability of SRID reagents for formulation	<ul style="list-style-type: none"> <li>Calibration data</li> </ul>	<ul style="list-style-type: none"> <li>Timely donations of antigen from manufacturers</li> <li>Early start of antiserum production</li> <li>Timely sharing of information with other manufacturers, WHO CCs, ERLs</li> </ul>	<ul style="list-style-type: none"> <li>IFPMA</li> <li>DCVMN</li> <li>ERLs</li> </ul>
Limitations of pre-filled syringes (e.g. filling is slower and more antigen used), multidose vials (include thiomersal, which limits use)	<ul style="list-style-type: none"> <li>What delivery mode do countries prefer? What criteria do countries use to make choice?</li> <li>What is the shelf life of each delivery mode?</li> <li>Is pre-filled syringe preferred for pregnant women and children?</li> <li>Evaluation of US model of fill-and-finish network to optimize global filling capacity</li> </ul>	<ul style="list-style-type: none"> <li>Model of a fill-and-finish network to optimize global filling capacity</li> </ul>	

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**

BOTTLENECK	DATA NEEDED	SOLUTIONS	IMPLEMENTATION
Delays in development and supply of SRID potency assay reagents	<ul style="list-style-type: none"> <li>Which CVVs are used?</li> <li>How much antigen and antisera are available for reagent production?</li> <li>Are existing reagents suitable?</li> <li>Can heterologous reagents be used?</li> <li>Is early supply of small lots of reagents better than later supply of large lots?</li> </ul>	<ul style="list-style-type: none"> <li>Timely and secured donation of antigen</li> <li>Agreements with manufacturers</li> <li>Use of small-scale GMP pilot facility to produce potency reagents</li> <li>Continued sharing of amount of reagents by manufacturers and ERLs</li> <li>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</li> <li>Create library of reagents at risk similar to CVV library, using the small-scale GMP pilot facility</li> </ul>	<ul style="list-style-type: none"> <li>IFPMA</li> <li>DCVMN</li> <li>ERLs</li> </ul>
SRID potency assay as the only option	<ul style="list-style-type: none"> <li>Validation results of different assays</li> </ul>	<ul style="list-style-type: none"> <li>Use alternate potency assays</li> </ul>	<ul style="list-style-type: none"> <li>BARDA</li> <li>ERLs</li> <li>HHS</li> <li>IFPMA</li> </ul>

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**

BOTTLENECK	DATA NEEDED	SOLUTIONS	IMPLEMENTATION
Limited mutual recognition of regulatory procedures, leading to delays in vaccine supply	<ul style="list-style-type: none"> <li>Criteria for seasonal and pandemic vaccine PQ</li> <li>VE data</li> <li>Review of national requirements and NRA capability for labelling and lot release for emergency use of pandemic vaccine</li> </ul>	<ul style="list-style-type: none"> <li>WHO guidelines on regulatory preparedness for provision of marketing authorization of pandemic vaccines in non-vaccine-producing countries</li> <li>Strengthen capabilities of NRA and PQ for seasonal and pandemic vaccine for market authorization, and for pharmacovigilance</li> <li>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</li> </ul>	<ul style="list-style-type: none"> <li>WHO ECBS</li> <li>NRAs</li> </ul>
Deployment (import and export) of vaccine, reagents and CVVs (GMO issues)	<ul style="list-style-type: none"> <li>Barriers, if any, to rapid shipping of pandemic vaccines</li> </ul>	<ul style="list-style-type: none"> <li>Export–import permits with all manufacturers</li> <li>Agreements with all shippers</li> </ul>	<ul style="list-style-type: none"> <li>IFPMA</li> <li>DCVMN</li> </ul>

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**

BOTTLENECK	DATA NEEDED	PROPOSED SOLUTION(S)	PROPOSED IMPLEMENTER(S)
Delay in availability of clinical trial vaccine lots and vaccine potency assays due to GMO issues	<ul style="list-style-type: none"> <li>Environmental risk assessment</li> </ul>		<ul style="list-style-type: none"> <li>IFPMA</li> </ul>
Delay due to country-specific vaccine lot release	<ul style="list-style-type: none"> <li>National and regional regulatory requirements for lot release</li> </ul>	<ul style="list-style-type: none"> <li>NRA waiver for lot release for pandemic vaccine trials</li> </ul>	<ul style="list-style-type: none"> <li>WHO</li> </ul>
Global lack of consistency for conduct of clinical trials, leading to delays in clinical trial protocol review	<ul style="list-style-type: none"> <li>Clinical trial protocols</li> <li>Human and ferret challenge studies to show reduced or prevention of shedding</li> </ul>	<ul style="list-style-type: none"> <li>Establish clinical end-points (e.g. safety and immunogenicity) to determine dose</li> <li>Establish immunological correlates of protection</li> <li>Develop and test clinical development plan with a series of protocols</li> </ul>	<ul style="list-style-type: none"> <li>WHO Norms and Standards group</li> <li>CONSISE</li> <li>Academic community</li> <li>Public health institutes</li> <li>IFPMA/DCVMN</li> </ul>
Delays due to supply of adjuvants (not all manufacturers have access to an adjuvant)	<ul style="list-style-type: none"> <li>Review of licensed adjuvants</li> <li>Data from "mix and match" studies</li> </ul>	<ul style="list-style-type: none"> <li>Improve access to adjuvants</li> <li>If too little access, use adjuvants for 1<sup>st</sup> dose and unadjuvanted vaccine for 2<sup>nd</sup> dose</li> <li>Use alum adjuvant for A(H7N9) vaccine</li> </ul>	<ul style="list-style-type: none"> <li>IFPMA</li> <li>WHO</li> </ul>
Uncertainty of safety of pandemic vaccine	<ul style="list-style-type: none"> <li>Identify who is likely to need or not need (prior immunity) pandemic vaccine</li> <li>Safety data from pre-clinical safety studies (DART studies)</li> <li>Pharmacovigilance data on AEs</li> <li>Epidemiological studies of background AEFI rates</li> </ul>	<ul style="list-style-type: none"> <li>Establish national serum banks ready for testing when needed</li> <li>Strengthen pharmacovigilance</li> <li>Develop a risk management plan</li> </ul>	<ul style="list-style-type: none"> <li>WHO</li> <li>MoH</li> <li>WHO Norms and Standards group</li> </ul>

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**

BOTTLENECK	DATA NEEDED	SOLUTIONS	IMPLEMENTATION
Delay in making a risk assessment about whether or not to make a vaccine switch	<ul style="list-style-type: none"> <li>Epidemiology, virology, severity, serology, modelling and impact data on the IVPP</li> </ul>	<ul style="list-style-type: none"> <li>Develop a decision-making process that includes what data are needed, data sources, data-collecting protocols and channels, analytical methods and communication channels</li> <li>Develop simulation exercises to determine, for example, the type of data needed, speed of collection, resources needed, output format and communication</li> <li>Review risk assessment methodology in terms of how to integrate it at regional and international levels</li> </ul>	<ul style="list-style-type: none"> <li>WHO</li> <li>Modellers</li> <li>CONCISE</li> <li>IFPMA/DCVMN</li> </ul>
Lack of clarity on what data exists, whether data can be collected rapidly and how to integrate all streams	<ul style="list-style-type: none"> <li>Systems existing for data collection and analysis</li> </ul>	<ul style="list-style-type: none"> <li>Develop a scheme for data collection, risk assessment and mode of operation</li> </ul>	<ul style="list-style-type: none"> <li>WHO</li> </ul>

CONCISE, Consortium for the Standardization of Influenza Seroepidemiology; DCVMN, Developing Countries Vaccine Manufacturers Network; IFPMA, International Federation of Pharmaceutical Manufacturers & Associations; IVPP, influenza viruses with pandemic potential; WHO, World Health Organization

## 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 CWV 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 CWVs 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,

- ❖ inclusion of the perspective of LMICs in the outcome of the informal consultation.

***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.

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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

## ANNEX I: Table A1. RISK ASSESSMENT & COMMUNICATIONS

1

go forward or not with the production of pandemic vaccine



Activities	Participating Entities	Coordinating Entities	Deliverables or Outputs	Channels to Communicate the Outcomes
Virological risk assessment <sup>a</sup>	WHO, GISRS, affected countries, OFFLU, animal sectors, academic institutions	WHO	Updated risk assessment based on virus characterization and special studies	WHO website, scientific publications as appropriate
Epidemiological monitoring and risk assessment	WHO, GISRS and associated epidemiologic institutions in affected countries, regional coordinating entities, (e.g. ECDC)	WHO	Early descriptions of the emerging epidemiological pattern of the pandemic virus  Progression of the pandemic  Identification of risk groups  Estimates of the likely impact on health care services  Public health advice on measures to be taken	WHO website, regional and national websites, scientific publications as appropriate
Severity assessment <sup>a</sup>	WHO, affected countries, regional coordinating entities (e.g. ECDC)	WHO	Updated severity assessment	WHO website, regional and national websites, scientific publications as appropriate
Declaration of PHEIC	WHO, IHR EC, GISRS, and other subject experts	WHO	WHO DG's declaration of PHEIC and issuance of temporary recommendations	WHO website, other media channels as appropriate
Declaration of a pandemic	WHO, IHR EC, GISRS, and other subject experts	WHO	Declaration of a Pandemic	WHO website, other media channels as appropriate
Composition of pandemic vaccine	WHO, Emergency VCM,	WHO	Composition of pandemic vaccine (recommendation to switch)	WHO website, other media channels as appropriate

Risk Assessment & Communications – whether to go forward with the production of pandemic vaccine

### ABBREVIATIONS

- ADR** Adverse Drug Reaction
- AEFI** Adverse Event Following Immunization
- BLA** Biologics 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
- 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**s 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

<sup>a</sup> Using appropriate modelling tools, such as the tool for influenza pandemic assessment (TIPRA) and the pandemic influenza severity assessment (PISA).  
 DG, Director General; EC, European Commission; ECDC, European Centre for Disease Prevention and Control; GISRS, Global Influenza Surveillance and Response System; IHR, International Health Regulations (2005); OFFLU, World Organisation for Animal Health (OIE) and 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

2

	Activities	Participating Entities	Coordinating Entities	Outcomes	Channels to Communicate the Outcomes
CVV development	Classical reassortant <sup>a</sup>	WHO CCs and reassorting laboratories	WHO CCs and reassorting laboratories	Potential CVVs	WHO website, WHO email distribution, IFPMA teleconferences and other channels as appropriate <sup>b</sup>
	RG reassortant <sup>a,c</sup>	WHO CCs and reassorting laboratories	WHO CCs and reassorting laboratories	Potential CVVs	WHO website, WHO email distribution, IFPMA teleconferences and other channels as appropriate <sup>b</sup>
	Wildtype virus	WHO CCs and reassorting laboratories	WHO CCs and reassorting laboratories	Potential CVVs	WHO website, WHO email distribution, IFPMA teleconferences and other channels as appropriate
CW assessment and evaluation	Characterization	WHO CCs	WHO CCs	Characterized CVVs	WHO website, WHO email distribution, IFPMA teleconferences and other channels, (e.g. customer specific ) as appropriate
	Safety testing	WHO CCs and specialist labs	WHO CCs	CVVs that are safe for manufacturing	WHO website, WHO email distribution, IFPMA teleconferences and other channels, (e.g. customer specific) as appropriate
	Yield evaluation	WHO CCs, ERLs, manufacturers	WHO with ERLs, IFPMA and manufacturers	Appropriateness of the CVVs for manufacturing	Teleconferences of WHO, IFPMA and involved manufacturers and other entities as appropriate
Bio-containment	Assessment of biosafety level for large scale production	WHO Expert Group on Bio-containment OIE/FAO	WHO	Required containment levels	WHO website, teleconferences of WHO, IFPMA, NRA, involved manufacturers and other entities as appropriate

<sup>a</sup> Includes CVVs for LAIVs.  
<sup>b</sup> Includes communication about CVVs for LAIVs by WHO.  
<sup>c</sup> Includes the use of synthetic viruses.

CC, collaborating centre; CVV, candidate vaccine virus; ERL, essential regulatory laboratory; FAO, Food and Agriculture Organization of the United Nations; IFPMA, International Federation of Pharmaceutical Manufacturers & Associations; NRA, national regulatory authority; OIE, World Organisation for Animal Health; WHO, World Health Organization



### ABBREVIATIONS

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

\* USA regulatory mechanism

# OPERATIONAL FRAMEWORK FOR PANDEMIC VACCINE RESPONSE

## ANNEX 1: Table A3.

### CLINICAL EVALUATION

3

	Activities	Participating Entities	Coordinating Entities	Outcomes	Channels to Communicate the Outcomes
Clinical lot production	Start with CVVs and seed lot	Manufacturers, regulators, relevant national authority	Manufacturers and regulators	Influenza vaccine lots suitable for human use produced from CVVs or seed lots that can be grown to higher yield	WHO platforms, such as website, press releases and teleconferences (regular and emergency) as appropriate
	Evaluate growth properties	Manufacturers	Manufacturers and regulators	Yield data	Teleconferences of WHO, IFPMA and involved manufacturers and other entities as appropriate
	Animal studies	Manufacturers' senior management, national and global coordinating entities, e.g. BARDA to do/fund/coordinate extra trials	Manufacturers and regulators	Approval from relevant regulator	WHO platforms, such as website, press releases and teleconferences (regular and emergency), as appropriate  Rapid communications with manufacturers, funders, customer countries and other entities, as appropriate
Clinical Trials	Preclinical studies	Manufacturers, academia, commercial clinical trial units, national / international entities such as US NIH/CDCs, ethics committees, regulatory authorities	Manufacturers, regulators, national / international entities such as US NIH/CDCs	Evaluation of vaccine safety	Communication at global platform to all stakeholders, including regulators and other national authorities, modellers and other entities as appropriate
	Ethics committee approvals				
	Studies in adults				
Paediatric studies					
Regulatory evaluation of vaccine safety					
Sharing of baseline safety data					
Serology with appropriate expert advice and oversight at all stages	Ethics committee, regulatory authorities, manufacturers, academia, commercial clinical trial units, national/international entities, (e.g. US NIH/CDC) and research entities (e.g. FLUCOP <sup>a</sup> )	Funders, commercial laboratories involved in clinical trials, manufacturers, regulators	Immunogenicity that is consistent with previously defined correlates of protection, vaccine formulation and vaccination strategy	Communication through global platform including website, press releases, and teleconferences.  Rapid direct communication with manufacturers and funders	



### ABBREVIATIONS

<b>ADR</b>	Adverse Drug Reaction
<b>AEFI</b>	Adverse Event Following Immunization
<b>BLA</b>	Biologics License Application*
<b>BSL2+</b>	Biosafety level 2+
<b>CVV</b>	Candidate Vaccine Virus
<b>DCVMN</b>	Developing Countries Vaccine Manufacturers Network
<b>EMA</b>	European Medicines Agency
<b>EPIC</b>	Expert Pandemic Influenza Committee
<b>EUA</b>	Emergency Use Authorization*
<b>GAP</b>	WHO Global Action Plan for Influenza Vaccines
<b>GISRS</b>	Global Influenza Surveillance & Response System
<b>GMO</b>	Genetically Modified Organism
<b>GMP</b>	Good Manufacturing Practice
<b>HCW</b>	Health Care Worker
<b>IHR</b>	International Health Regulations
<b>IFPMA</b>	International Federation of Pharmaceutical Manufacturers & Associations
<b>LAIV</b>	Live Attenuated Influenza Vaccine
<b>IND</b>	Investigational New Drug*
<b>NRA</b>	National Regulatory Authorities
<b>PHEIC</b>	Public Health Emergency of International Concern
<b>PIP</b>	Pandemic Influenza Preparedness
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<b>VCM</b>	Vaccine Composition Meeting
<b>VRBPAC</b>	US Vaccines and Related Biological Products Advisory Committee
<b>US NIH/CDC</b>	US National Institutes of Health/Centres for Disease Control
<b>WHO CCs</b>	WHO Collaborating Centres
<b>WHO ERLs</b>	WHO Essential Regulatory Laboratory

\* USA regulatory mechanism

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

BARDA, US Biomedical Advanced Research and Development Authority; CDC, US Centers for Disease Control and Prevention; CVV, candidate vaccine virus; IFPMA, International Federation of Pharmaceutical Manufacturers & Associations; NIH, National Institutes of Health; US, United States; WHO, World Health Organization a FLUCOP is a collaborative research project that aims to standardize and develop assays for the assessment of influenza vaccine correlates of protection.

# OPERATIONAL FRAMEWORK FOR PANDEMIC VACCINE RESPONSE

## ANNEX I: Table A4. PRODUCTION

4

	Activities	Participating Entities	Coordinating Entities	Outcomes	Channels to Communicate the Outcomes
Reagent preparation	Production of antigen	WHO ERLs and manufacturers	WHO ERLs	Availability of calibrated reagents	WHO ERL websites and WHO website, and WHO-chaired teleconferences
	Production of antiserum				
Reagent calibration & supply	International calibration studies	WHO ERLs	WHO ERLs	Calibrated reagents	WHO ERLs via teleconferences, email or other channels, reagent-tracking table and other channels, as appropriate
	Structured feedback from manufacturers on use of reagents	WHO ERLs NRAs	WHO ERLs, and manufacturers		
Seasonal vaccine production	Potential intensification of seasonal production prior to the potential start of pandemic vaccine production	Manufacturers	Individual manufacturers	Potentially increased volume of seasonal vaccines	Direct communication from manufacturers to customer countries, updates to WHO
	Cessation of seasonal vaccine production	WHO, national authorities, and manufacturers	WHO, national authorities, and manufacturers	Readiness for pandemic vaccine manufacturing	Direct communication from manufacturers to customer countries, updates to WHO
Pandemic vaccine production	Ongoing risk assessment on the need for pandemic vaccine	WHO, IHR EC, GISRS, SAGE, Emergency VCM and other subject experts	WHO	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.	WHO website, other media channels as appropriate
	Start of pandemic vaccine production	WHO, manufacturers, NCLs	Manufacturers and regulators	Initiation of pandemic vaccine production	IFPMA to WHO (updates with proprietary protections); manufacturers to customer countries
	Vaccine production	Manufacturers, NCLs	Manufacturers	Build mono-bulk stock of pandemic strain	Updates from IFPMA to WHO, and manufacturers to customer countries
	Vaccine formulation	Manufacturers, WHO, NCLs	Manufacturers	Pandemic Vaccine	Updates from IFPMA to WHO, and manufacturers to customer countries
	Filling/Packaging	Manufacturers, customer countries, NCLs	Manufacturers, customer countries and WHO	Correct proportions of multidose vials, syringes, etc.	IFPMA to WHO Industry to Customer



### ABBREVIATIONS

<b>ADR</b>	Adverse Drug Reaction
<b>AEFI</b>	Adverse Event Following Immunization
<b>BLA</b>	Biologics License Application*
<b>BSL2+</b>	Biosafety level 2+
<b>CVV</b>	Candidate Vaccine Virus
<b>DCVMN</b>	Developing Countries Vaccine Manufacturers Network
<b>EMA</b>	European Medicines Agency
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<b>EUA</b>	Emergency Use Authorization*
<b>GAP</b>	WHO Global Action Plan for Influenza Vaccines
<b>GISRS</b>	Global Influenza Surveillance & Response System
<b>GMO</b>	Genetically Modified Organism
<b>GMP</b>	Good Manufacturing Practice
<b>HCW</b>	Health Care Worker
<b>IHR</b>	International Health Regulations
<b>IFPMA</b>	International Federation of Pharmaceutical Manufacturers & Associations
<b>LAIV</b>	Live Attenuated Influenza Vaccine
<b>IND</b>	Investigational New Drug*
<b>NRA</b>	National Regulatory Authorities
<b>PHEIC</b>	Public Health Emergency of International Concern
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<b>US NIH/CDC</b>	US National Institutes of Health/Centres for Disease Control
<b>WHO CCs</b>	WHO Collaborating Centres
<b>WHO ERLs</b>	WHO Essential Regulatory Laboratory

\* USA regulatory mechanism

EC, European Commission; ERL, essential regulatory laboratory; GISRS, Global Influenza Surveillance and Response System; IFPMA, International Federation of Pharmaceutical Manufacturers & Associations; IHR, International Health Regulations (2005); NCL, national control laboratory; NRA, national regulatory authority; SAGE, WHO Strategic Advisory Group of Experts on Immunization; VCM, WHO Influenza Vaccine Composition Meeting; WHO, World Health Organization

# OPERATIONAL FRAMEWORK FOR PANDEMIC VACCINE RESPONSE

## ANNEX I: Table A5. REGISTRATION

	5 Activities	Participating Entities	Coordinating Entities	Outcomes	Channels to Communicate the Outcomes
Registration process & prequalification process	Dossier route <sup>a</sup>	WHO, manufacturers, national and regional (e.g. EMA) regulating authorities	WHO, regulators	Approval/no approval Enhanced/fast-tracked approval process <sup>b</sup>	Guidelines Website Workshops to create understanding of the processes
	Emergency route	WHO, manufacturers, national and regional (e.g. EMA) regulating authorities	WHO, regulators	Approval/no approval Enhanced/fast-tracked approval process <sup>c</sup>	Guidelines Website Workshops to create understanding of the processes
Lot release	Regulatory oversight to assure the quality of pandemic vaccines.	Existing lot release labs including WHO ERLs and NCLs	Regulatory network/WHO	Development of a formal network of release laboratories to enhance availability of pandemic vaccine  Clear set of assays to streamline process <sup>d</sup>	Websites, workshops, written standards, membership criteria
Pharmacovigilance	Risk management, safety monitoring, signal detection  Vaccine effectiveness quantification of adverse effects, exposure data  Benefit / risk assessment	Health-care workers, regulators, public health immunization programs, manufacturers	NRA, WHO	Improved safety assessment and monitoring system  Improved vaccine effectiveness monitoring in key target populations  Increased use of tools (models, etc.) <sup>e</sup>	Health-care workers, public health organizations, manufacturers, international exchange of safety data or signals via WHO, SAGE or GACVS
Vaccine rollout	Distribution and communications  Pandemic Vaccine Deployment Plan	Health authorities  SAGE	Health and local authorities  SAGE	Distribution, availability and early adverse drug reactions	Health authorities, and NCLs and ERLs via teleconferences, email or other channels



### GLOSSARY

<b>ADR</b>	Adverse Drug Reaction
<b>AEFI</b>	Adverse Event Following Immunization
<b>BLA</b>	Biologics License Application*
<b>BSL2+</b>	Biosafety level 2+
<b>CVV</b>	Candidate Vaccine Virus
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<b>WHO CCs</b>	WHO Collaborating Centres
<b>WHO ERLs</b>	WHO Essential Regulatory Laboratory

\* USA regulatory mechanism

EMA, European Medicines Agency; ERL, essential regulatory laboratory; GACVS, WHO Global Advisory Committee on Vaccine Safety; NCL, national control laboratory; NRA, national regulatory authority; SAGE, WHO Strategic Advisory Group of Experts on Immunization; WHO, World Health Organization

#### Notes

<sup>a</sup> Manufacturers are encouraged to license vaccines approved for emergency use. WHO has provided guidance on the options for registration of pandemic vaccines [http://www.who.int/biologicals/vaccines/Annex\\_2\\_WHO\\_TRS\\_963-3.pdf?ua=1](http://www.who.int/biologicals/vaccines/Annex_2_WHO_TRS_963-3.pdf?ua=1)

<sup>b</sup> Forward-looking outcomes would be establishment of global guidelines and common regulatory processes to support fast tracking/cheaper development costs.

<sup>c</sup> Approval process principles to include: clarity, transparency, mutual recognition, rapid access.

<sup>d</sup> 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.

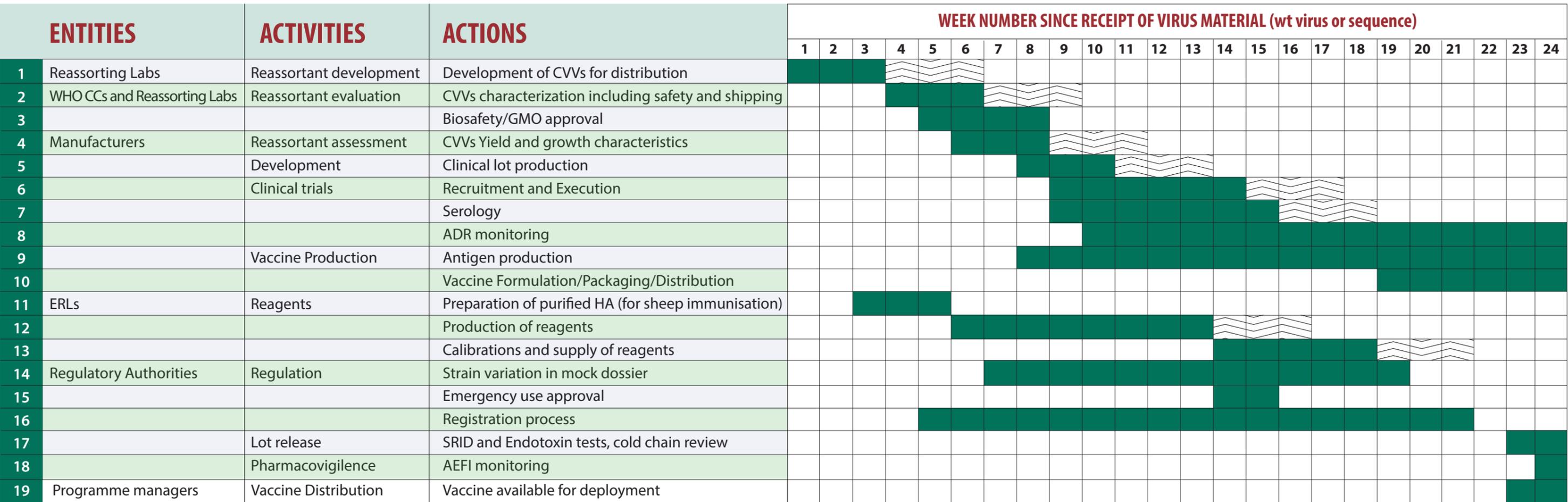
<sup>e</sup> Increased confidence among health-care workers and the public. Ensure case definitions are available for adverse events following immunization.

# TIMELINE OF PANDEMIC VACCINE PRODUCTION

## ANNEX 2: Timelines of pandemic vaccine production

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.

### A2.1. Inactivated influenza vaccine scheme



#### Line COMMENTS AND POTENTIAL ISSUES

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#### Line COMMENTS AND POTENTIAL ISSUES

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.

**1, 2, 3 and 4** CVVs are selected by the WHO CCs. RG 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 Sterility 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.

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

**5** 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. 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.

**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** 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.

**9** 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.

**11/12** The production of sheep sera is critical and a major bottleneck in the process.

**13** Ideally the 4 WHO ERLs would calibrate the reagents. But if time is of the essence, the reagent can be calibrated locally to save time, e.g., between the ERL and the manufacturer or another competent laboratory, the option to prepare and calibrate one set of reagents to reduce the workload of cross calibration, and alternative tests such as ELISA tests to be considered pending relevant NRA approval.

**14** 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.

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

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

**17** 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.

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

**19** Distribution by programme managers to sites. Roll-out priority to be determined according to the pandemic plan. To continue beyond the week 14 mark.

ADR, adverse drug reaction; AEFI, adverse events following immunization; CC, collaborating centre; CVV, candidate vaccine virus; ELISA, enzyme-linked immunosorbent assay; EMA, European Medicines Agency; ERL, essential regulatory laboratory; EU, European Union; GMO, genetically modified organism; HA, haemagglutinin; HI, haemagglutination inhibition; NRA, national regulatory authority; RG, reverse genetics; SRID, single radial immunodiffusion; TBD, to be determined; WHO, World Health Organization; wt, wild type

# TIMELINE OF PANDEMIC VACCINE PRODUCTION

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

	ACTIVITIES	ACTIONS	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	Reassort/clone & rescue LAIV, initial characterisation in include in vivo BSL testing	█	█	█	█	█	█	█	█	█	█	█	█	█	█	█	█	█	█	█	█	█	█	█	█
2	Approval and BSL change	Confirm lower BSL handling																								
3	LAIV assessment	Biocharacterisation and manufacturability (yield and growth)																								
4	Reagents	Antigen preparation for sheep/ferret immunisation																								
5		Production and calibration of assays reagents																								
6	Development	Master seed production and intial release for CT vial filling/bulk manufacture (1) (4)																								
7	Vaccine production	LAIV bulk production and initial release (2) (4)																								
8	Regulatory Authorities	Vaccine formulation/packaging/distribution																								

BSL, biosafety level; CT, cycle threshold; IIL, 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

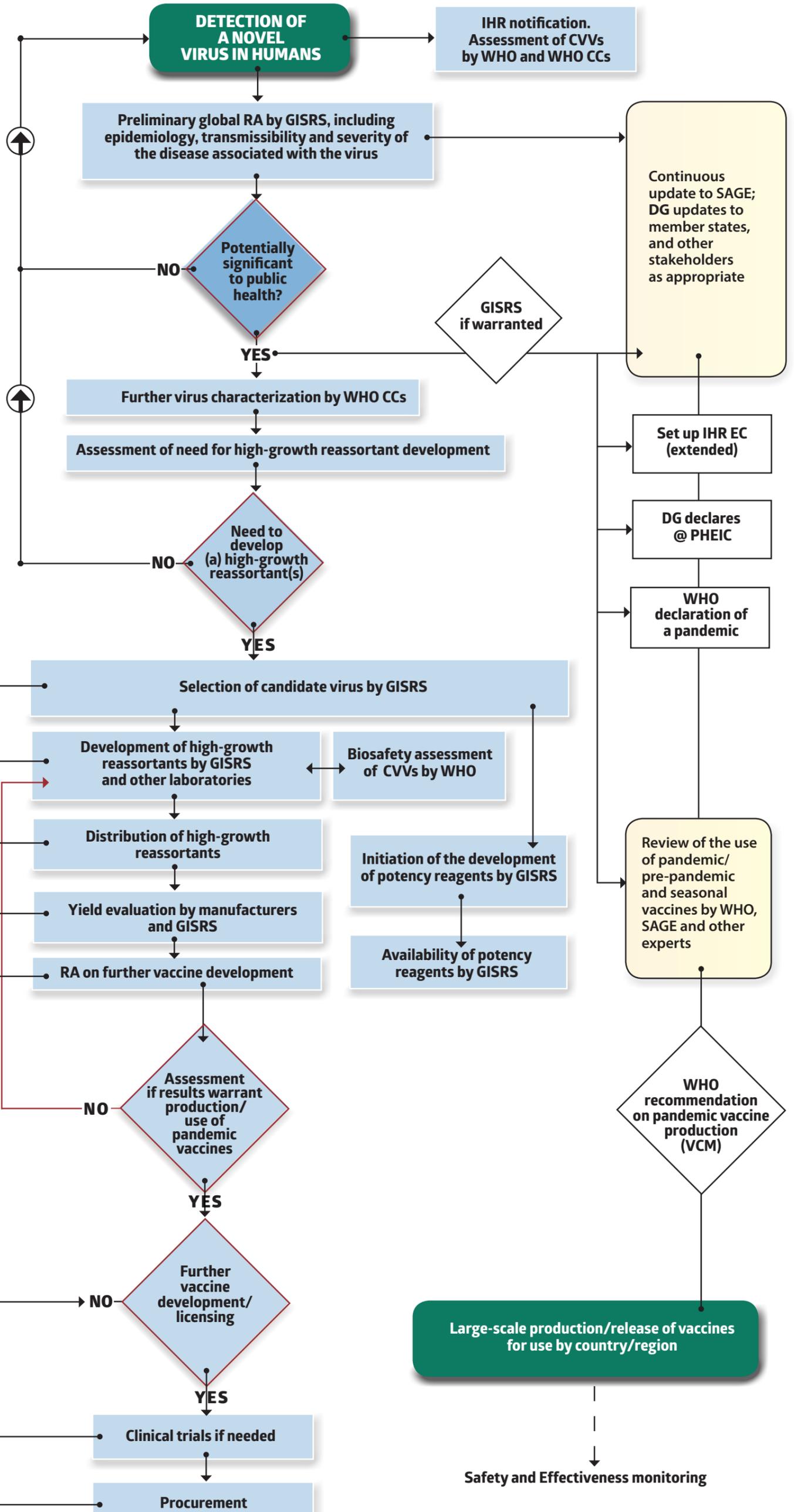
The timing for LAIV clinical trials, regulatory authorities, Pharmacovigilance and Program Managers topics are similar to those for IIV and they are synchronized with Clinical Lot Vaccine and bulk vaccine being available

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

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

### 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



*Continuous risk assessment by WHO's IHR, SAGE and subject experts as well as industry and stakeholders on:*

### DATA PACKAGES

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

## 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*

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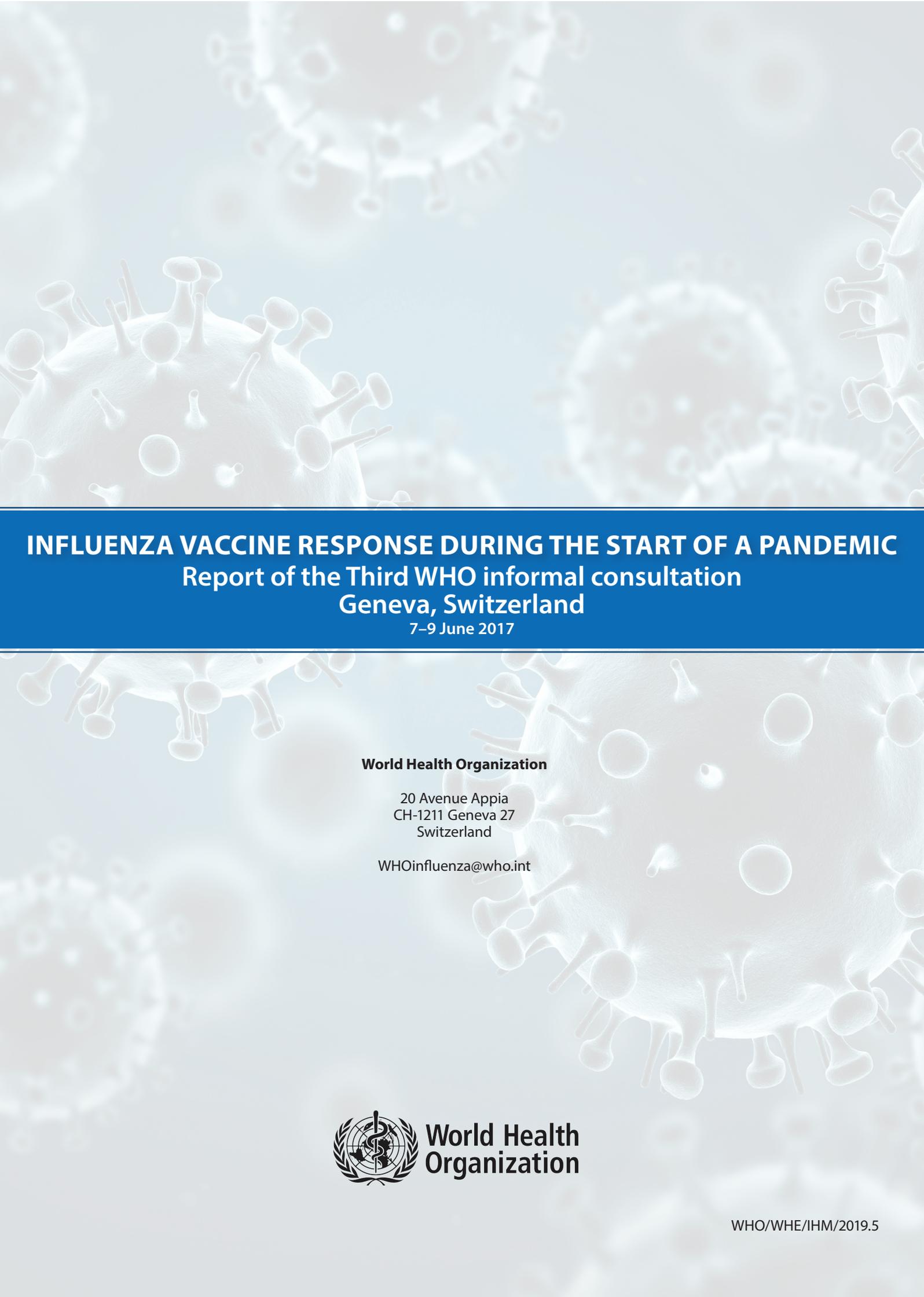
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