World Health Organization

Influenza Vaccine Response during the Start of a Pandemic

Report of a WHO Informal Consultation held in Geneva, Switzerland

29 June - 1 July 2015

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Contents

Executive Summary

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

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

- There was concern that the new "Pandemic Influenza Risk Management (PIRM) – WHO interim guidance" no longer identified clear pandemic phases which had in the past been widely used to guide the various stages of pandemic vaccine production. However, as a result of the meeting, different stakeholders became more aware of the need for risk assessments in initiating pandemic vaccine production. During the course of the meeting, a "draft operational framework for pandemic vaccine response" was prepared (see Annex 1) and it was felt that the inclusion of this framework brought the PIRM document closer to completion.
- A key decision is needed for the timing of the start of pandemic vaccine production. Global influenza vaccine manufacturers supply seasonal vaccine to many countries and are similarly likely to have multinational pandemic vaccine orders. If the decision to start pandemic vaccine production is left to national health agencies or even to vaccine manufacturers, it might lead to delays and shortages of pandemic vaccine and may compromise the production of seasonal vaccine with possibly significant public health consequences. There was agreement on the need for international leadership by WHO through its advisory bodies including the International Health Regulations (IHR) Emergency Committee and the Strategic Advisory Group of Experts (SAGE) on Immunization on recommending the start of pandemic vaccine production.
- Candidate Vaccine Viruses (CVVs) are crucial as the first step in the production of seasonal and pandemic vaccines. In 2009 there were some delays in their distribution and use. The WHO biosafety committee is urged to review and improve the procedures for assessment of biocontainment for CVVs and vaccine manufacturers are urged to have import permits in place in order to receive them.

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

- Draft operational framework for pandemic vaccine response.
- Timelines of pandemic vaccine production.
- Process of WHO vaccine response to an influenza pandemic or potential pandemic.

1. Introduction and Scope of the Meeting

Influenza pandemics are unpredictable but recurring events that can have significant consequences on human health and economic well-being worldwide. Advance planning and preparedness are vital to help mitigate the impact of a pandemic. In June 2013, WHO published a revision of the influenza preparedness and response guidance, entitled "Pandemic Influenza Risk Management (PIRM) – WHO interim guidance"[1]. This guidance was prepared following experience gained during the influenza A(H1N1) 2009 pandemic; experience with influenza A(H5N1) infections in poultry and humans; and advances in the development of antiviral medicines and pandemic vaccines. Two key lessons learned from the 2009 A(H1N1) pandemic were:

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

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

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

1. The International Health Regulations (IHR) 2005[2] are legally binding for the 196 States Parties to prevent, control, or respond to public health risks that may spread between countries and within this remit is the declaration of a Public Health Emergency of International Concern (PHEIC) by the WHO Director General under guidance from the IHR Emergency Committee.
2. The Pandemic Influenza Preparedness (PIP) Framework for the sharing of influenza viruses and access to vaccines and other benefits was adopted in 2011[3]. This important milestone event reflected growing recognition of the importance of the timely sharing and characterization of viruses and of the equitable provision of effective vaccines against pandemic influenza.
3. The WHO Global Action Plan for Influenza Vaccines (GAP) was launched in 2006 to increase global influenza production capacity and supply[4]. It is based on increasing evidence-based use of seasonal influenza vaccines; increasing global pandemic vaccine production

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

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

The main objectives of the meeting were to:

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

Thirty-three participants from 18 countries were drawn from WHO Collaborating Centres (WHO CCs)[5], WHO Essential Regulatory Laboratories (ERLs)[5], the academic research community, National Regulatory Authorities (NRAs), national public health agencies, vaccine manufacturers, International Federation of Pharmaceutical Manufacturers & Associations (IFPMA), Developing Countries Vaccine Manufacturers Network (DCVMN) and other stakeholders.

2. Background Information

2.1 Challenges and timelines in producing a pandemic vaccine

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

2.2 Issues associated with switching from seasonal vaccine to pandemic vaccine production

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

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

2.3 Development of Candidate Vaccine Viruses

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

2.4 Vaccine potency testing

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

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

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

2.5 Regulatory pathway for pandemic vaccines

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

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

2.6 Manufacturers' perspective on critical aspects of pandemic vaccine production

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

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

A recurring theme across the critical vaccine production factors is the need for a clear and unambiguous signal to start pandemic vaccine production.

3. Organization of the Consultation

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

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

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

- Modification of the table "Timelines of pandemic vaccine production" (i.e. when are actions taken?) (Annex 2).
- Modification of the table "Process of the WHO vaccine response to influenza pandemic or potential pandemics" (i.e. how are actions taken?) (Annex 3).
- Identification of areas of concern that were outside the scope of the meeting, but which nevertheless needed some attention. These items were listed in a "parking lot" (Annex 4).

4. Areas of Concern Raised during the Consultation

4.1 Declaration of pandemic phases

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

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

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

4.2 Switching from production of seasonal to pandemic vaccines

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

There are different elements to the initiation of a switch: epidemiology of pandemic influenza virus and possible co-circulating seasonal influenza viruses; the assessment of risk by WHO surveillance activities, governments or regional authorities; and the activation of orders for pandemic vaccine from governments. The risk assessment by various agencies would involve not only the virological, epidemiological and clinical aspects of the emerging pandemic but also the risk of stopping seasonal vaccine production and not having enough seasonal vaccine for vulnerable people. At present the responsibility for switching to pandemic vaccine production lies principally with national governments.

This requires governments to have revised their pandemic preparedness plans so they have risk assessment procedures in place to make such a key decision. There was comment at the meeting that very few countries have such a revision in place. In countries with dedicated vaccine manufacturers (e.g. Japan), it would be necessary for manufacturers to react to country demands, but many vaccine manufacturers had contracts with several governments and private organizations for supply of seasonal and pandemic vaccine, so it would be impossible for a vaccine manufacturer to meet the demands of a country requesting pandemic vaccine and another country which still needed seasonal vaccine.

The identified needs were:

- International leadership in recommending that pandemic vaccine production commence, based on evidence of need.
- Revision of national pandemic preparedness plans to identify the process for a pandemic vaccine switch, including the risks of stopping seasonal vaccine versus the risks of not going ahead with pandemic vaccine.
- Based on current knowledge, the pandemic vaccine component should not be incorporated into seasonal vaccine until its safety profile is well understood. There were some adverse reactions to a 2010 seasonal vaccine in children in Australia and it was difficult to evaluate whether they were due to the newly introduced A(H1N1)pdm09 vaccine component or not.[7,8]
- Although some low and lower-middle income countries needed international leadership in taking decisions, all countries should make as much pandemic preparation as possible, e.g. an updated inventory of their healthcare capacity.
- A flowchart of the multi-factorial decision-making process that will generate greater transparency and trust, which may in turn translate into greater public acceptance of pandemic vaccination.

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

4.3 Preparation and communication

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

In terms of preparedness, the main concerns were:

- Vaccine manufacturers should ensure that they have import permits in place for receipt of CVVs. This should include wild-type viruses, conventional reassortants and reassortants generated by RG, which in some countries are judged to be genetically modified organisms (GMOs).

- In 2009 there were delays in assessing and recommending appropriate biocontainment for CVVs, which led to delays in distributing CVVs to manufacturers. This needs to be more timely and efficient.

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

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

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

- There were concerns that regulatory procedures for fast track approval of pandemic vaccines were not harmonized globally and there was no global mutual recognition process of regulatory approval, which could lead to delays and inconsistencies in pandemic

vaccine availability. It was pointed out that regulatory agencies can now share information and there is movement towards a common regulatory approach in Member States, which is a significant improvement. It was considered that this was outside the scope of the meeting, but this issue was retained in the "parking lot" (Annex 4).

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

In terms of communication, the main concerns were:

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

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

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

5. Draft Operational Framework for Pandemic Vaccine Response

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

6. Key Outcomes of the Meeting and Next Steps

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

- Better understanding of the complexities of pandemic vaccine production during the start of a pandemic, especially in describing the roles and responsibilities of different stakeholders. This should lead to improved levels of communication between all stakeholders.
- Agreement on the need for international leadership by WHO through its advisory bodies, including the IHR Emergency Committee and SAGE, on recommending that production of pandemic vaccine commence based on risk assessment. This may entail critical steps including switching from production of seasonal vaccine to pandemic vaccine.
- In preparing the "Draft operational framework for pandemic vaccine response", it was felt that this brought the PIRM document closer to completion.
- Different stakeholders are now more aware of the need for risk assessments in initiating pandemic vaccine production.
- There is increased awareness of the need to review and improve the procedures for assessment of biocontainment for CVVs.

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

- Finalize the WHO risk assessment tool (TIPRA).
- Complete the "Draft operational framework for pandemic vaccine response" and then the PIRM document. After this, further consultations with Member States would be needed.
- The identified coordinators in the various activities of the "Draft operational framework for pandemic vaccine response" should examine their roles further so that improvements can be made and hence better information can be provided to WHO.
- The procedures for assessment of biocontainment for CVVs need to be reviewed and improved by the WHO biosafety committee.

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

7. References

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

   http://www.who.int/influenza/preparedness/pandemic/GIP_PandemicInfluenzaRiskManagementInterimGuidance_Jun2013.pdf

2. The International Health Regulations (IHR) 2005

   http://whqlibdoc.who.int/publications/2008/9789241580410_eng.pdf?ua=1

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

   http://whqlibdoc.who.int/publications/2011/9789241503082_eng.pdf

4. Global Action Plan for Influenza Vaccines (GAP) to increase global influenza production capacity and supply

   http://whqlibdoc.who.int/hq/2006/WHO_IVB_06.13_eng.pdf

5. WHO Collaborating Centres for influenza and Essential Regulatory Laboratories

   http://www.who.int/influenza/gisrs_laboratory/collaborating_centres/list/en/

6. Recommendations for the production and control of influenza vaccine (inactivated)

   http://www.who.int/biologicals/publications/trs/areas/vaccines/influenza/ANNEX%203%20InfluenzaP99-134.pdf

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

   http://www.eurosurveillance.org/images/dynamic/EE/V20N24/art21159.pdf

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

   http://www.sciencedirect.com/science/article/pii/S0264410X14003831

8. Abbreviations

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

9. Acknowledgements

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10. Annexes

1. **Draft operational framework for pandemic vaccine response**
2. **Timelines of pandemic vaccine production**
3. **Process of the WHO vaccine response to an influenza pandemic or a potential pandemic**
4. **Further activities: the "parking lot"**
5. **Regulatory pathways for pandemic vaccines in the USA**
6. **List of Participants**
7. **Scenario Worksheets**

OPERATIONAL FRAMEWORK FOR PANDEMIC VACCINE RESPONSE

RISK ASSESSMENT & COMMUNICATIONS

1 — *to go forward or not with the production of pandemic vaccine*

	Activities	Participating Entities	Coordinating Entities	Deliverables or Outputs	Channels to Communicate the Outcomes
Risk Assessment & Communications – – to go forward or not with the production of pandemic vaccine	Virological Risk Assessment	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 healthcare services Public health advice on measures to be taken	WHO website, scientific publications as appropriate
	Severity Assessment	WHO, affected countries, regional coordinating entities, e.g. ECDC	WHO	Updated severity assessment	WHO website, scientific publications as appropriate
	Declaration of PHEIC	WHO, IHR Emergency Committee (EC), GISRS and other subject experts'	WHO	Declaration of PHEIC or EC 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

REASSORTANT DEVELOPMENT

2

	Activities	Participating Entities	Coordinating Entities	Outcomes	Channels to Communicate the Outcomes
Reassortant Development	Classical Reassortant	WHO CCs, Reassorting Labs	WHO CCs, Reassorting Labs	Potential CVVs	WHO website, WHO emailing, IFPMA teleconferences and other channels as appropriate
	RG Reassortant	WHO CCs, Reassorting Labs	WHO CCs, Reassorting Labs	Potential CVVs	WHO website, WHO emailing, IFPMA teleconferences and other channels as appropriate
CVV Assessment and Evaluation	Characterization	WHO CCs	WHO CCs	Characterized CVVs	WHO website, WHO emailing, 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 emailing, IFPMA teleconferences and other channels, e.g. customer specific as appropriate
	Yield Evaluation	WHO CCs, ERLs, manufacturers	WHO with WHO CCs, IFPMA, and manufacturers	Appropriateness of the CVVs for manufacturing	Teleconferences of WHO, IFPMA and involved manufacturers and other entities as appropriate
Biocontainment	Assessment of BSL Level for Large Scale Production	WHO Expert Group on Biocontainment	WHO	Required containment levels	WHO website, teleconferences of WHO, IFPMA, National Regulatory Authority (NRA), involved manufacturers and other entities

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 that can begrown to high yields	WHO platforms, e.g. website, press release, 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/ global coordinating entities, e.g. BARDA (Biomedical Advanced Research & Development Authority) to do/fund/ coordinate extra trials	Manufacturers and Regulators	Approval from relevant regulator	WHO platforms, e.g. website, press release, teleconferences – regular and emergency as appropriate Rapid communications with manufacturers, funders, customer countries and other entities as appropriate
Clinical Trials	Preclinical studies Ethics committee approvals Studies in adults Paediatric studies Regulatory evaluation of vaccine safety	Manufacturers, academia, commercial clinical trial units, national/ international entities, such as US NIH/CDC	Manufacturers, regulators, national/ international entities such as US NIH/CDC	Evaluation of vaccine safety	Communication at global platform to all stakeholders, including regulators and other national authorities, modellers and other entities as appropriate
	Serology with appropriate expert advice and oversight at all stages	Ethics committee, regulatory authorities, manufacturers, academia, commercial clinical trial units, national/ international entities, such as US NIH/CDC	Funders, commercial laboratories involved in clinical trials, manufacturers	Correlates of protection; vaccine formulation; vaccination strategy	Communication at global platform including website, press releases, and teleconferences. Rapid direct communication with manufacturers and funders

PRODUCTION

4

	Activities	Participating Entities	Coordinating Entities	Outcomes	Channels to Communicate the Outcomes
Reagent Preparation	Production of Antigen Production of Antigenum	WHO ERLs and manufacturers	WHO ERLs	Availability of calibrated reagents	WHO ERL websites and WHO website, and WHO chaired teleconferences
Reagent Calibration & Supply	International calibration studies	WHO ERLs	WHO ERLs	Calibrated reagents	WHO ERLs via TCs or 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, IHREC, GISRS, SAGE and other subject experts**	**WHO**	**Recommend that production of pandemic vaccine commence, based on risk assessment. This may entail critical steps including switching from production of seasonal vaccine to pandemic vaccine**	**WHO website, other media channel as appropriate**
	Start of pandemic vaccine production	WHO, manufacturers	Manufacturers and regulators	Initiation of pandemic vaccine production	IFPMA to WHO (updates with proprietary protections); manufacturers to customer countries
	Vaccine production	Manufacturers	Manufacturers	Build monobulk stock of pandemic strain	Updates from IFPMA to WHO, and manufacturers to customer countries
	Vaccine formulation	Manufacturers, WHO	Manufacturers	Pandemic Vaccine	Updates from IFPMA to WHO, and manufacturers to customer countries
	Filling/Packaging	Manufacturers, customer countries	Manufacturers, customer countries and WHO	Correct proportions of multidose vials, syringes, etc.	IFPMA to WHO Industry to Customer

REGISTRATION

5

	Activities	Participating Entities	Coordinating Entities	Outcomes	Channels to Communicate the Outcomes
Registration Process & Pre-qualification Process	Dossier route	WHO, manufacturers, national and regional (e.g. EMA) regulating authorities	WHO, Regulators	Approval/no approval Enhanced/fast-tracked approval process See #1 below	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 See #2 below	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 NRA labs	Regulatory Network/WHO	Development of a formal network of release laboratories to enhance availability of pandemic vaccine Clear set of assays to streamline process See #3 below	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	National Regulatory Authorities	Improved safety assessment and monitoring system Increased use of tools (models, etc.) See #4 below	HCW, public health organizations, manufacturers
Vaccine Rollout	Distribution and communications Pandemic Vaccine Deployment Plan	Health authorities SAGE	Health and local authorities SAGE	Distribution, availability, early ADRs	Health authorities and NRAs ERLs via TCs or email or other channels

Notes

1. Forward looking outcomes would be establishment of Global guidelines and common regulatory processes to support fast tracking/cheaper development costs.
2. Clear process, transparent, mutual recognition, faster access.
3. Each WHO region should have such laboratories. Mutual recognition procedures to be developed. Recognized standards and inspections are needed, EU can be seen as as a model.
4. Increased confidence among HCW and Public. Ensure case definitions are available for AEFIs.

GLOSSARY

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
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
IND	Investigational New Drug*
NRAs	National Regulatory Authorities
PHEIC	Public Health Emergency of International Concern
PIP	Pandemic Influenza Preparedness
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
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

VERSION 16.05.2016

TIMELINE OF PANDEMIC VACCINE PRODUCTION

VERSION 16.05.2016

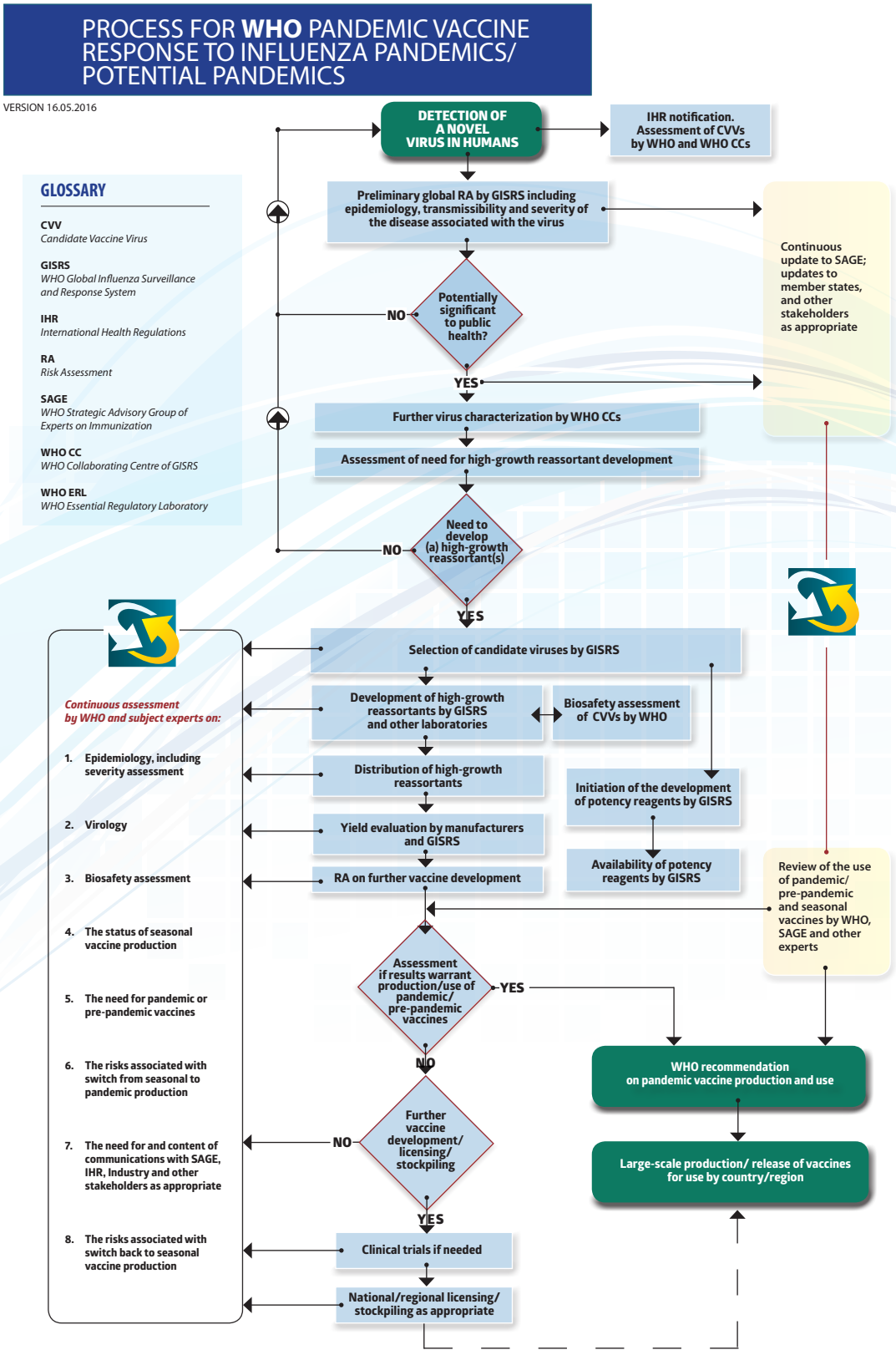
	ENTITIES	ACTIVITIES	ACTIONS	WEEK NUMBER SINCE VIRUS DETECTION (genetic sequence upload)																			
				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
1	Reassorting Labs	Reassortant development	Development of CVVs for distribution	■	■	■																	
2	WHO CCs and Reassorting Labs	Reassortant evaluation	CVVs characterization including safety and sterility				■	■	■														
3	Manufacturers	Reassortant assessment	CVVs Yield and growth characteristics						■	■													
4		Development	Clinical lot production						■	■	■												
5		Clinical trials	Recruitment						■	■	■												
6			Serology								■			■		■							
7			ADR monitoring								■	■	■	■	■	■	■	■	■	■	■	■	■
8		Vaccine Production	Antigen production								■	■	■	■	■	■	■	■	■	■	■	■	■
9			Vaccine Formulation/Packaging/Distribution																	■	■	■	■
10	ERLs	Reagents	Preparation of purified HA (for sheep immunisation)			■	■	■															
11			Production of reagents								■	■	■	■	■	■	■	■					
12			Calibrations and supply of reagents														■	■	■	■	■		
13	Regulatory Agencies	Regulation	Mock dossier approval	■	■																		
14			Emergency use approval														■	■					
15			Registration process					■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	
16		Lot release	SRID and Endotoxin tests, cold chain review																	■	■	■	■
17		Pharmacovigilence	ADR monitoring																	■	■	■	■
18	Immunization managers	Vaccine roll-out	Vaccine available for use																	■	■	■	■

Line	COMMENTS AND POTENTIAL ISSUES
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. 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.
3	Poor yields might result in delays in vaccine supply to large populations.
4	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.
5	Recruitment will need to begin early for the clinical trial.
6	Base line serology and then at 2 and 4 weeks after injection.

Line	COMMENTS AND POTENTIAL ISSUES
7	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.
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.
10/11	The production of sheep sera is critical and a major bottleneck in the process.
12	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.
13	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.

Line	COMMENTS AND POTENTIAL ISSUES
14	Emergency use approval may be given prior to final registration. Early discussions with NRA essential.
15	All manufacturers should ideally seek registration of the vaccine not only mock dossier approval and/or emergency use.
16	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.
17	ADRs monitoring by the NRA and other specialist groups, web-based reporting and sentinel monitoring. This would occur beyond the 14 week mark.
18	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 3 – Process of the WHO vaccine response to an influenza pandemic or a potential pandemic



ANNEX 4
Further Activities: the "Parking Lot"

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

Key proposals

Communication

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

Research

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

Future meetings

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

Other activities

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

Further proposals

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

- Explore a central pilot facility (GMP) to produce clinical material for pandemic studies.
- Manufacturers should try to obtain preapproval for the import and use of RG material.

ANNEX 5
Regulatory pathways for pandemic vaccines in the USA

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

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

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

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

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

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

ANNEX 6
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ANNEX 7 – Scenario Worksheets

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

WORKSHEET - SCENARIO 1: PART 1

FROM THE *"BUNGALY NEWS": "A severe unknown influenza virus kills 4"*

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

WEEK 1

A local physician reported a cluster of 12 cases of severe acute respiratory infections (SARI) in a country called "Bungaly". Most patients needed respirators and 4 patients died. Preliminary laboratory tests confirmed the presence of influenza type A. Samples were sent to the NIC arriving about 1 week after the initial cluster was detected.

WEEKS 2-4

Within 2 weeks the NIC confirmed the presence of influenza type A but could not confirm a known subtype in specimens from 9 of the 12 cases. Meanwhile several clusters of SARI were reported in other parts of the country involving 32 cases and 5 deaths. In a neighboring country 54 SARI cases including 13 deaths were reported together with the detection of an unsubtypable influenza A virus in 39 SARI cases.

Cases were across all age groups.

(Note: WHO IHR mechanisms are fully functional. Outbreak information is being reported through IHR channels and on the WHO website. The WHO GISRS network is alerted and following up with immediate actions among CCs/ERLs/NICs on the possible emergence of novel influenza viruses. WHO at all levels is alerted and countries are informed through IHR mechanisms.)

QUESTION 1

a) Do any additional communications need to be made?

b) Do any additional actions need to be made and by whom?

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

WORKSHEET - SCENARIO 1: PART 2

WEEK 4-7 Within a month, over 800 unsubtypable influenza A positive samples are detected in NICs in several countries and over 100 are received in WHO CCs of GISRS. Five weeks after the initial cluster is detected, a novel influenza virus type A, subtype H8N9 virus, was confirmed in most of the specimens received. There is now worldwide awareness of the new influenza virus.

QUESTION 2:
(Line 7 & 8 of Chart 1 & Chart 2)

WHO (GISRS) is now ready to distribute CVVs to vaccine manufacturers for pandemic vaccine preparatory activities.

a) **When are manufacturers able to work with these CVV's to produce clinical lots?** (see Week 6/7 of scenario / Line 8 of Chart 1)

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

- What are the implications for all stakeholders if the decision on pandemic vaccine production is made in **February** (Northern Hemisphere) or in **September** (Southern Hemisphere) when seasonal vaccine production has just started? (see chart 3)
- What are the implications for all stakeholders if the decision on pandemic vaccine production is made in **May** (Northern Hemisphere) or in **December** (Southern Hemisphere) when seasonal vaccine production is running at full capacity?

QUESTION 3:

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

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

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

WORKSHEET - SCENARIO 1: PART 3

WEEKS 8-12

Within 3 months over 40 countries reported the spread of influenza with the vast majority needing urgent medical attention and intensive care. Over 100,000 cases were reported with a 6% mortality rate. There were reports of overstressed health care systems in most countries. Laboratory tests on some 5000 samples showed that about 80% were of the new novel virus.

QUESTION 4:

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

b) **Will national/regional contracts of seasonal vaccines be affected by activating pandemic APAs; if so, how?**

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

QUESTION 5: (concluding question)

a) **In this scenario, what would you recommend with regard to pandemic vaccine production vs. seasonal vaccine production?**

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

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

WORKSHEET - SCENARIO 2: PART 1

From the *"Bungaly News": "Unusual and possibly dangerous Influenza virus detected"*

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

WEEK 1

A local physician reports a cluster of 14 cases of influenza like illness (ILI) associated with unexpected symptoms including conjunctivitis and diarrhea in some patients in a country called Bungaly. Two patients needed hospitalization and respirators. No deaths were reported. Laboratory tests confirmed the presence of Influenza type A but could not confirm a known subtype. Samples were sent to a WHO NIC laboratory arriving about 2 weeks after the initial cluster of influenza like illness was reported.

Meanwhile, from sentinel surveillance data, 79 cases of influenza like illness were reported within a week of the first cluster in another part of the country. Five patients were hospitalized with severe illness and there was 1 death reported. This was followed by another report of 142 cases, in a neighboring country and all cases were laboratory confirmed as influenza type A. Seven patients were hospitalized and 2 deaths were reported. All age groups were affected.

WEEKS 2-6

Within a month, over 900 samples arrived from sentinel sites at the regional WHO NICs and over 100 were sent to a WHOcc. Six weeks after the initial reports, a novel influenza virus type A, subtype H13N2 virus was identified in all clusters of cases. The higher frequency of these reported cases has alerted WHO and local public health authorities resulting in increased awareness of the outbreak. There is now also worldwide awareness of the new virus and it becomes clear that the rates of morbidity and mortality are no higher than that of seasonal viruses.

(Note: WHO IHR mechanisms are fully functional. Outbreak information is being reported through IHR channels and on the WHO website. The WHO GISRS network is alerted and following up with immediate actions among CCs/ERLs/NICs on the possible emergence of novel influenza viruses. WHO at all levels is alerted and countries are informed through IHR mechanisms.)

QUESTION 1:

a) **Do any additional communications need to be made?**

b) **Do any additional actions need to be made and by whom?**

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ANNEX 7 – Scenario Worksheets

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

WORKSHEET - SCENARIO 2: PART 1

QUESTION 2:
(see Line 7 & 8 of Chart 1 and Chart 2)

WHO (GISRS) **is now ready to distribute CVVs to vaccine manufacturers for pandemic vaccine preparatory activities.**

a) **When are manufacturers able to work with these CVV's to produce clinical lots?** (Week 6/7 of scenario / Line 8 of Chart 1):

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

- What are the implications for all stakeholders if the decision on pandemic vaccine production is made in **February** (Northern Hemisphere) or in **September** (Southern Hemisphere) when seasonal vaccine production has just started? (see chart 3)
- What are the implications for all stakeholders if the decision on pandemic vaccine production is made in **May** (Northern Hemisphere) or in **December** (Southern Hemisphere) when seasonal vaccine production is running at full capacity?

QUESTION 3:

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

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

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

WORKSHEET - SCENARIO 2: PART 2

WEEKS 8-12

Within 3 months over 49 countries reported the spread of influenza with many needing medical attention and some needing intensive care. Over 100,000 cases were reported with a 0.4% mortality rate. There were reports of severe challenges for the health care systems in most countries. Laboratory tests on some 1200 samples showed that about 80% were of the new novel type A virus.

QUESTION 4:

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

b) **Will national/regional contracts of seasonal vaccines be affected by activating pandemic APAs; if so, how?**

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

QUESTION 5:
(concluding question)

a) **In this scenario, what would you recommend with regard to pandemic vaccine production vs. seasonal vaccine production?**

b) **Would your recommendation change in the face of increased morbidity and mortality which was over and above the normal seasonal expectation.**

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

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

WORKSHEET - SCENARIO 3: PART 1

From the *"Bungaly News": "Killer flu detected"*

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

WEEK 1

A local physician reports a cluster of 10 cases of severe influenza like illness (SARI) in a country called 'Bungaly'. Most patients needed respirators and 2 otherwise healthy young patients died. Laboratory tests confirmed the presence of Influenza type A but could not confirm a known subtype. Samples were sent to a WHO NIC laboratory arriving about 1 week after the initial cluster of influenza like illness was reported.

(Note: WHO IHR mechanisms are fully functional. Outbreak information is being reported through IHR channels and on the WHO website. The WHO GISRS network is alerted and following up with immediate actions among CCs/ERLs/NICs on the emergence of novel influenza viruses. WHO at all levels is alerted and countries are informed through IHR mechanisms.)

QUESTION 1:

a) **Do any additional communications need to be made?**

b) **Do any additional actions need to be made and by whom?**

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

WORKSHEET - SCENARIO 3: PART 2

WEEKS 8-16

2 months after the initial reports, a novel influenza virus type A, subtype H4N7 virus was identified in all clusters of cases. Three months after the initial report another 8 cases of influenza like illness were reported in another part of the country. All patients were hospitalized with severe illness and 3 died. This was followed by another report of 10 cases, in a neighboring country one month later and all cases were laboratory confirmed as influenza type A. All were hospitalized and 3 persons died. All age groups were affected.

QUESTION 2:
(Line 7 & 8 of Chart 1 and Chart 2):

WHO (GISRS) **is ready to distribute CVVs to vaccine manufacturers for pandemic vaccine preparatory activities.**

a) **When are manufacturers able to work with these CVV's?** (see Week 6/7 of scenario / Line 8 of Chart 1)

b) **At what time are manufacturers able to produce clinical lots?**

c) **Does working with CVVs and the production of clinical lots interfere with the production of seasonal vaccine?**

- What are the implications for all stake holders if the decision on pandemic vaccine production is made in **February** (Northern Hemisphere) or in **September** (Southern Hemisphere) when seasonal vaccine production has just started? (see chart 3)
- What are the implications for all stakeholders if the decision on pandemic vaccine production is made in **May** (Northern Hemisphere) or in **December** (Southern Hemisphere) when seasonal vaccine production is running at full capacity?

QUESTION 3:

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

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

ANNEX 7 – Scenario Worksheets

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

WORKSHEET - SCENARIO 3: PART 2

WEEKS 12-26

Within a 6 month period, 35 samples arrived at the NICs and 30 were sent to a WHOcc. 2 months after the initial reports, a novel influenza virus type A, subtype H4N7 virus was identified in all clusters of cases.

QUESTION 4:	☑
a) **Is there a need for pandemic vaccine now? On what basis is the need established? What are the implications for those needing seasonal vaccine?**	
	☑
	☑
b) **Will national/regional contracts of seasonal vaccines be affected by activating pandemic APAs; if so, how?**	
	☑
c) **When should pandemic vaccine production start?** (i.e. seasonal vs. pandemic vaccine availability)	☑

6-12 MONTHS

Within 12 months, 9 countries in two different WHO regions, reported the spread of influenza with the vast majority needing urgent medical attention and intensive care. The case-fatality rate was 20%.

QUESTION 5: (concluding question)	☑
a) **Based on the evidence provided in the scenario, what would you recommend with regard to pandemic vaccine production vs. seasonal vaccine production?**	☑
	☑
b) **On what basis is this recommendation made? Who are the stakeholders making the recommendation? How should the recommendations be communicated?**	
	☑
	☑