Outcomes from the ‘Switch’ meetings
Switch June-July 2015: Switch 2 July 2016: Switch 3 June 2017

“Public health and practical considerations on switching from seasonal to pandemic vaccine production”

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Introduction
Switch 1 to 3 (2015 to 2017)  Scope and Purpose

- **Aim:** to develop a WHO guidance on pandemic vaccine protocols in response to a pandemic
  - in particular at the start of a pandemic when seasonal influenza may still be circulating and when seasonal influenza vaccine may be in the middle of its production cycle

- **Objectives:**
  - **Identify the challenges and bottlenecks** in vaccine production and develop a draft protocol of vaccine response at the beginning of an influenza pandemic
  - **Identify Challenges for developing countries**
  - **Identify the key principles in making a decision** to start pandemic vaccine production
Organization of each consultation

- Identify areas of concern, bring stakeholders together (Switch 1), Pandemic scenarios with increasing complexity.
- Decision algorithm, manufacturing bottlenecks, operational framework (Switch 1 & 2)
- Solutions and ownership; refinements and reality checks (Switch 3)
- Agreed key outcomes

2015 and 2016 Reports:

http://www.who.int/influenza/resources/publications/influenzavaccineresponse_meeting01/en/
http://www.who.int/influenza/resources/publications/influenzavaccineresponse_meeting02/en/
Mapping the pandemic vaccine production process

- Draft Operational Framework for Pandemic Vaccine Response – who?
- Timeline of pandemic vaccine production – when?
- Process for WHO pandemic vaccine response to pandemics – how?
- All to be an Annex to the PIRM places emphasis on a cooperative risk management approach

[Diagram showing phases of pandemic, interpandemic, alert, transition, and response phases with a risk assessment process.]
Timelines very tight - depend on interaction between many players

- GISRS, WHO CC, ERLs,
- Candidate Vaccine Virus (CVV) reassorting laboratories,
- Vaccine manufacturers,
- Regulatory agencies,
- Governments
- Clinical trial experts
- Vaccine program managers
# Timeline of Pandemic Vaccine Production

## Entities
1. Reassorting Labs
2. WHO CCs and Reassorting Labs
3. Manufacturers
4. Development
5. Clinical trials
6. Serology
7. ADR monitoring
8. Vaccine Production
9. Vaccine Formulation/Packaging/Distribution
10. ERLs
11. Production of reagents
12. Calibration and supply of reagents
13. Regulation
14. Emergency use approval
15. Registration process
16. Lot release
17. SRID and Endotoxin tests, cold chain review
18. Pharmacovigilence
19. Program managers

## Activities
- Reassortant development
- Reassortant evaluation
- Reassortant assessment
- Clinical trials
- Recruitment and Execution
- Serology
- ADR monitoring
- Antigen production
- Vaccine Formulation/Packaging/Distribution
- Preparation of purified HA (for sheep immunisation)
- Production of reagents
- Strain variation in mock dossier
- Emergency use approval
- Registration process
- SRID and Endotoxin tests, cold chain review
- AEFI monitoring
- Vaccine available for deployment

## Actions
- Development of CVVs for distribution
- CVVs characterization including safety and shipping
- CVVs Yield and growth characteristics
- Clinical lot production
- Recruitment and Execution
- Vaccine Formulation/Packaging/Distribution
- Preparation of purified HA (for sheep immunisation)
- Production of reagents
- Strain variation in mock dossier
- Emergency use approval
- Registration process
- SRID and Endotoxin tests, cold chain review
- AEFI monitoring
- Vaccine available for deployment

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("The when")
<table>
<thead>
<tr>
<th>Bottleneck</th>
<th>Data</th>
<th>Solutions</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Delay in making a risk assessment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• CVV production/availability</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Biocontainment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Yield and manufacturing of CVVs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Clinical trials for the first pandemic vaccines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Timing of SRID reagents for vaccine potency testing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Lack of mutual recognition of regulatory procedures leading to delays in vaccine supply</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Fill and finish capacity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bottleneck</td>
<td>Data needed</td>
<td>Solutions</td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| Delay in making a risk assessment whether or not to make a vaccine switch | • Assess potential impact of new virus versus that of seasonal virus, including:  
  o Epidemiology  
  o Severity  
  o Modelling  
  o Impact  
  o Ability to manufacture vaccine  
  • Update risk assessment as more data available | • WHO to prepare formal output from all risk assessments including rationale for decisions  
  • Review of risk assessment methodology  
    o Need to distinguish high and low risk  
  • Develop decision making tools |
## Bottlenecks

### CVV production/availability

<table>
<thead>
<tr>
<th>Bottleneck</th>
<th>Data needed</th>
<th>Solutions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of suitable BSL3/GMP laboratories for early small scale work</td>
<td>• Review number of suitable labs available</td>
<td>• Dedicated pilot BSL3/GMP labs</td>
</tr>
<tr>
<td>Not enough labs producing CVVs especially from highly pathogenic viruses</td>
<td>• None identified</td>
<td>• WHO to identify and establish more pandemic CVV labs</td>
</tr>
<tr>
<td>Not enough high containment labs for making LAIV CVVs</td>
<td>• Review number of suitable labs available</td>
<td>• Dedicated publically-funded pilot BSL3/GMP labs</td>
</tr>
<tr>
<td>Slow decision on CVV status for Nagoya Protocol or SMTA2</td>
<td>• Prepare a review of the type of CVVs to be produced and their use</td>
<td>• WHO to obtain clarification</td>
</tr>
<tr>
<td>Uncertainty about manufacturers’ obligations to share synthetic seed viruses and shipping requirements</td>
<td>• None identified</td>
<td>• Manufacturers to start dialogue with WHO</td>
</tr>
<tr>
<td>Delays in shipping</td>
<td>• None identified</td>
<td>• Manufacturers to obtain import permits (including GMO CVV) in advance; obtain agreement(s) with courier(s)</td>
</tr>
</tbody>
</table>
Draft Operational Framework for Pandemic Vaccine Response – The who?
<table>
<thead>
<tr>
<th>Activities</th>
<th>Participating Entities</th>
<th>Coordinating Entities</th>
<th>Outcomes</th>
<th>Channels to Communicate the Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reagent Preparation &amp; Supply</td>
<td>WHO ERLs and manufacturers</td>
<td>WHO ERLs</td>
<td>Availability of calibrated reagents</td>
<td>WHO ERL websites and WHO website, and WHO chaired teleconferences</td>
</tr>
<tr>
<td>Production of Antigen</td>
<td>WHO ERLs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Production of Antiserum</td>
<td>WHO ERLs, NRAs</td>
<td>WHO ERLs, manufacturers</td>
<td>Calibrated reagents</td>
<td>WHO ERLs via TCs or email or other channels, reagent tracking table and other channels as appropriate</td>
</tr>
<tr>
<td>International calibration studies</td>
<td>WHO ERLs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Structured feedback from manufacturers</td>
<td>WHO ERLs, National Authorities, and manufacturers</td>
<td>WHO ERLs, and manufacturers</td>
<td>Calibrated reagents</td>
<td></td>
</tr>
<tr>
<td>Potential intensification of seasonal production</td>
<td>Manufacturers</td>
<td>Individual manufacturers</td>
<td>Potentially increased volume of seasonal vaccines</td>
<td>Direct communication from manufacturers to customer countries, updates to WHO</td>
</tr>
<tr>
<td>Cessation of seasonal vaccine production</td>
<td>WHO, National Authorities, and manufacturers</td>
<td>WHO, National Authorities, and manufacturers</td>
<td>Readiness for pandemic vaccine manufacturing</td>
<td>Direct communication from manufacturers to customer countries, updates to WHO</td>
</tr>
<tr>
<td>Ongoing risk assessment on the need for pandemic vaccine</td>
<td>WHO, IHR EC, GISRS, SAGE and other subject experts</td>
<td>WHO</td>
<td>Recommendation on the transition from seasonal vaccine production to pandemic vaccine production</td>
<td>WHO website, other media channels as appropriate</td>
</tr>
<tr>
<td>Start of pandemic vaccine production</td>
<td>WHO, manufacturers</td>
<td>Manufacturers and regulators</td>
<td>Initiation of pandemic vaccine production</td>
<td>IFPMA to WHO (updates with proprietary protections); manufacturers to customer countries</td>
</tr>
<tr>
<td>Vaccine production</td>
<td>Manufacturers</td>
<td>Manufacturers</td>
<td>Build monobulk stock of pandemic strain</td>
<td>Updates from IFPMA to WHO, and manufacturers to customer countries</td>
</tr>
<tr>
<td>Vaccine formulation</td>
<td>Manufacturers, WHO</td>
<td>Manufacturers</td>
<td>Pandemic Vaccine</td>
<td>Updates from IFPMA to WHO, and manufacturers to customer countries</td>
</tr>
<tr>
<td>Filling/Packaging</td>
<td>Manufacturers, customer countries</td>
<td>Manufacturers, customer countries and WHO</td>
<td>Correct proportions of multidose vials, syringes, etc.</td>
<td>IFPMA to WHO Industry to Customer</td>
</tr>
</tbody>
</table>
Principles to guide Decision Making

- The WHO recommendation should maximise global health and be guided by expert opinion
  - The risks of mortality, morbidity and economic consequences should be considered (minimising serious impact, minimising spread, risk reduction)

- The consequences and health implications of the switch, or not switching, should be considered.
  - Impact of not having seasonal vaccine available.

- Any decision or recommendation should be evidence based
  - The process should be transparent
  - Any recommendation should be defensible

- There should be clarity of roles and activities (Operational Plan)
Principles to guide Decision Making

- Any decision will be made on incomplete data. Early data may not be the same over time.
- Needs to be flexibility to review the decision/recommendation to switch as new data arises, if no switch is recommended.
- Pandemic and Switch not co-dependant.
  - A Pandemic does not trigger a switch automatically; A switch to pandemic or novel vaccine is different to declaring a pandemic. Time. geography. CVV.
Key Outcomes of the Meetings and Next Steps

- There are many components of the decision to switch and they will involve nearly all aspects of the influenza community.

- Such an integrated approach could be achieved by bringing together an international expert group tasked with making such a decision. EPIC (Expert Pandemic Influenza Committee)
Some Key Outcomes

- Investigation continuing into small scale GMP pilot plant for lot vaccine production
  - Training, Clinical trials, CVVs evaluation, reagents, support for developing countries?

- PIRM Framework Finalized; Switch 1 and 2 reports published

- RA tools finalized ..TIPRA, PISA

- Biocontainment issues being addressed with WHO and Industry (TRS941)

- Issues around reagents and regulation are being addressed

- Participants were now much better informed
Some remaining considerations

- The timing of a switch to pandemic vaccine production has implications for manufacturers, program managers.
  - The switch cannot be immediate
  - Contract implications
  - The decision by countries to stop seasonal vaccine manufacturing has potential public health implications
  - Clinical trial, dose, adjuvant, adverse events, etc. are unknown
  - Developing country manufacturers and non-producing countries will need guidance from WHO
  - The implications of the Nagoya protocol?
  - Further efforts towards Regulatory Harmonisation
  - Communications within and without WHO need improvement
Acknowledgements

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- Derek Ellis (Rapporteur)
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- WHO colleagues from IVB/IVR, and Health Systems and Innovation