Report of the Eighth Meeting with International Partners on Prospects for Influenza Vaccine Technology Transfer to Developing Country Vaccine Manufacturers

Sao Paulo, Brazil, 17–18 March 2015
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# ABBREVIATIONS AND ACRONYMS

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<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>ACIP</td>
<td>Advisory Committee on Immunization Practices</td>
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<td>BAA</td>
<td>broad agency announcement</td>
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<tr>
<td>BARDA</td>
<td>US Biomedical Advanced Research Development Authority</td>
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<td>BMGF</td>
<td>Bill &amp; Melinda Gates Foundation</td>
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<tr>
<td>BSL</td>
<td>biosafety level</td>
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<tr>
<td>CBER</td>
<td>Center for Biologics Evaluation and Research</td>
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<td>CDC</td>
<td>US Centers for Disease Control and Prevention</td>
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<tr>
<td>CFR</td>
<td>Case Fatality Rate</td>
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<td>cGMP</td>
<td>current Good Manufacturing Practice</td>
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<td>CRO</td>
<td>contract research organization</td>
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<td>CVV</td>
<td>candidate vaccine virus</td>
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<td>DCVMN</td>
<td>developing country vaccine manufacturers network</td>
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<tr>
<td>DNA</td>
<td>deoxyribonucleic acid</td>
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<td>DSMB</td>
<td>Data and Safety Monitoring Board</td>
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<td>ECBS</td>
<td>Expert Committee on Biological Standardization</td>
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<tr>
<td>ELISA/EIA</td>
<td>enzyme-linked immunosorbent assay/enzyme immunoassay</td>
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<td>EMA</td>
<td>European Medicines Agency</td>
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<tr>
<td>ERL</td>
<td>Essential Regulatory Laboratory</td>
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<td>FDA</td>
<td>United States Food and Drug Administration</td>
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<td>GAP</td>
<td>Global Action Plan for Influenza Vaccines</td>
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<td>GAVI</td>
<td>Gavi, the Vaccine Alliance</td>
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<tr>
<td>GCP</td>
<td>good clinical practice</td>
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<td>GISRS</td>
<td>Global Influenza Surveillance and Response System</td>
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<td>GLP</td>
<td>good laboratory practice</td>
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<td>GMP</td>
<td>good manufacturing practice</td>
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<tr>
<td>HA</td>
<td>haemagglutinin</td>
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<td>HAI</td>
<td>haemagglutination inhibition (assay)</td>
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<td>HHS</td>
<td>Health &amp; Human Services</td>
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<td>HI</td>
<td>haemagglutination inhibition</td>
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<tr>
<td>HPLC</td>
<td>high-performance liquid chromatography</td>
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<td>ICH</td>
<td>International Council for Harmonisation</td>
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<tr>
<td>IC-IDMS</td>
<td>immunoaffinity capture-immunocapture isotope dilution mass spectrometry</td>
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<tr>
<td>IDRI</td>
<td>Infectious Disease Research Institute</td>
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<td>IFPMA</td>
<td>International Federation of Pharmaceutical Manufacturers &amp; Associations</td>
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<td>IgA</td>
<td>immunoglobulin A</td>
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<td>IHR</td>
<td>International Health Regulations</td>
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<td>IIV</td>
<td>inactivated influenza vaccine</td>
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<td>ILI</td>
<td>influenza-like illness</td>
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<td>IRAT</td>
<td>Influenza Risk Assessment Tool</td>
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<td>IVS</td>
<td>IFPMA Influenza Vaccine Supply</td>
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<td>LAIV</td>
<td>live attenuated influenza vaccine</td>
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<td>MMWR</td>
<td>Morbidity and Mortality Weekly Report</td>
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<tr>
<td>MN</td>
<td>microneutralization</td>
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<tr>
<td>NA</td>
<td>neuraminidase</td>
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<tr>
<td>NCL</td>
<td>National Control Laboratory</td>
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<td>NIBSC</td>
<td>National Institute for Biological Standards and Control</td>
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<td>NIC</td>
<td>National Influenza Centre</td>
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<td>NITAG</td>
<td>national immunization technical advisory group</td>
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<td>NRA</td>
<td>national regulatory authority</td>
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<tr>
<td>OGA</td>
<td>US/HHS Office of Global Affairs</td>
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<td>PAHO</td>
<td>Pan American Health Organization (WHO Office for the Americas)</td>
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<tr>
<td>PATH</td>
<td>Appropriate Technology in Health Program</td>
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<tr>
<td>PCR</td>
<td>polymerase chain reaction</td>
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<tr>
<td>Acronym</td>
<td>Description</td>
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<tr>
<td>PIP</td>
<td>Pandemic Influenza Preparedness Framework</td>
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<td>QALY</td>
<td>quality-adjusted life year</td>
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<td>QIV</td>
<td>quadrivalent influenza vaccine</td>
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<tr>
<td>R&amp;D</td>
<td>research and development</td>
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<tr>
<td>RACI</td>
<td>responsible, accountable, consulted and informed</td>
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<tr>
<td>RT-PCR</td>
<td>reverse transcription polymerase chain reaction</td>
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<tr>
<td>SAE</td>
<td>severe adverse event</td>
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<td>SAGE</td>
<td>Strategic Advisory Group of Experts on Immunization</td>
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<td>SARI</td>
<td>severe acute respiratory infection</td>
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<tr>
<td>SARS</td>
<td>severe acute respiratory syndrome</td>
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<tr>
<td>SDS-PAGE</td>
<td>sodium dodecyl sulfate polyacrylamide gel electrophoresis</td>
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<td>SII</td>
<td>Serum Institute of India</td>
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<td>SOP</td>
<td>standard operating procedures</td>
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<tr>
<td>SPR</td>
<td>Surface plasmon resonance</td>
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<td>SRID</td>
<td>single radial immunodiffusion</td>
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<td>TAG</td>
<td>Technical Advisory Group</td>
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<td>TIV</td>
<td>trivalent influenza vaccine</td>
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<td>TSE</td>
<td>transmissible spongiform encephalopathy</td>
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<td>TTi</td>
<td>Technology Transfer initiative</td>
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<td>US</td>
<td>United States</td>
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<td>USA</td>
<td>United States of America</td>
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<td>WHO</td>
<td>World Health Organization</td>
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SESSION 1. INTRODUCTION

The Eighth Meeting of International Partners on Prospects for Influenza Vaccine Technology Transfer to Developing Country Vaccine Manufacturers was held on 17–18 March 2015 in Sao Paulo, Brazil. The agenda, list of participants and presentations are available on the World Health Organization (WHO) website (www.who.int/phi/8th_Partners_Mtg/en/). The meeting was chaired by Dr Gary Grohmann.

1.1 Welcome address and opening remarks
The meeting was opened by Dr Martin Friede on behalf of Dr Marie-Paule Kieny. He presented an overview of the Global Action Plan for Influenza Vaccines (GAP) which was created in 2006 as a 10-year action plan. The ending of the GAP in 2016 also marks the end of financial support to manufacturers in the WHO Technology Transfer initiative (TTi).

The original target for the GAP was to increase global influenza vaccine production to vaccinate 100% of the world with two doses of pandemic vaccine within six months of availability of the pandemic strain, i.e. to produce 14 billion doses within six months. At the GAP II meeting in 2011, factoring in herd immunity led to a revision of this target to vaccinate 70% of the population, i.e. 10 billion doses within six months. While much progress has been made, the world is still short on achieving this goal.

By 2016, global annual vaccine supply is expected to reach 1.7 billion doses of seasonal (trivalent) vaccine, which corresponds to 5.1 billion doses of pandemic vaccine (assuming the same yield and that 15 µg of monovalent antigen would be sufficient). This level of production does not meet the long-term GAP targets, but would provide two doses for 1.3 billion people within the first six months. Dose sparing technologies could overcome this shortfall. By 2016 the number of countries producing influenza vaccine is estimated to increase from 17 to 25, and several more should be on their way to producing vaccine within the forthcoming years.

In order to meet this GAP target, three conditions need to be met. First, the 1.7 billion dose capacity needs to be sustained. Second all the planned capacity must be brought on line. Third, it is important that the best case scenario is met, i.e. that all manufacturers have access to dose-sparing technologies along with the necessary approvals for the vaccines using these technologies.

Dr Friede provided an overview of recent changes in the influenza vaccine production landscape, including the recent acquisition by bioCSL of the Novartis influenza vaccine franchise, the withdrawal from the market of Baxter and Crucell and the various new vaccine technologies entering the market such as Protein Sciences’ baculovirus-based recombinant vaccine.

The first objective of the GAP, which is critical for sustainable production capacity, is to increase the use of seasonal vaccine. Dr Friede stressed that seasonal influenza continued to kill hundreds of thousands of people each year and gave examples from India and the United States which were currently experiencing severe epidemics. With regard to the threat of pandemic influenza, human cases of H5N1 had been reported in Egypt, and avian influenza outbreaks were becoming more widespread, making influenza pandemic preparedness just as relevant, or even more so, than in 2016.

In conclusion, global production capacity was still short of need in the event of a pandemic. Developing country vaccine manufacturers have an important role to play in both national and regional health security. In order to achieve sustainable production, manufacturers and their governments must work together. While some manufacturers in the programme were well advanced with licensed products, others had a long way to go. The purpose of this meeting was to help manufacturers reach product licensure and sustainable production; to this end, dedicated sessions were scheduled on clinical trial management and vaccine approval; ensuring sustainability and market issues; and options for dose-sparing and regulatory pathways.

1.2 WHO Technology Transfer Initiative: progress to date
Mr Guido Torelli presented an update on progress on the Technology Transfer initiative for Influenza Vaccine Production. Over the previous year, successful clinical trials of H7N9 live attenuated
influenza vaccine (LAIV) had been completed in the Russian Federation; a prime boost clinical study of H5N1 LAIV completed in Thailand; and a Phase I H5N1 study completed in Viet Nam. More production facilities were completed and more manufacturers were ready to take their vaccines into clinical trials, five of which planned to conduct clinical trials in 2015.

Technical support was being provided to manufacturers in the planning and conduct of these trials through WHO and PATH. In 2014, WHO convened a workshop in Bangkok on clinical trial design with participation from manufacturers and their national regulatory authorities (NRA), prior to which template protocols and summary guidance documents had been shared with participants.

Through collaboration with the United States Biomedical Advanced Research Development Authority (BARDA), WHO will issue a final year of grants to manufacturers for 2015–2016 and will continue to provide support through site visits and technical advice. WHO has also established an adjuvant advisory group to assist manufacturers in the selection of appropriate adjuvants. Through collaboration with the US Health & Human Services Office of Global Affairs (OGA) and the US Centers for Disease Control and Prevention (CDC), WHO will continue work on sustainability assessments and building communication capacity. WHO country offices are increasingly involved, especially with regards to engagement with ministries of health. TTi coordinates with the WHO Pandemic Influenza Preparedness Framework (PIP), the Global Influenza Programme, and many others with a specific focus, for example on NRA strengthening.

The target of the TTi is to have as many vaccines as possible approved or in late-stage development by 2016. Although the programme has already enabled a capacity of more than 300 million additional doses of pandemic vaccine from GAP grantee manufacturers, efforts are needed to bring more candidates to approval and to add an additional 300 million doses of pandemic capacity. Major challenges include navigating the complex approval pathways for both seasonal and pandemic vaccines, and ensuring that new production capacity is sustainable in the long term. Manufacturers are urged to take advantage of the expertise and technical support available through this network.

1.3 GAP: progress and issues

Dr Bruce Gellin, Chair of the GAP Advisory Group, stressed that as 2016 approached there was still a lot to be done to achieve the targets set forth in the plan. He reminded participants of the three objectives of the GAP (www.who.int/influenza_vaccines_plan/en/) he underlined that: (i) increase the evidence based use of seasonal vaccines; (ii) increase production and regulatory capacity for influenza vaccines; and (iii) Develop improved influenza vaccines that are not only higher-yielding and faster to produce, but also broader in protection and of longer duration.

To assist in reaching the goals of the GAP, partnership offices have been established in the USA at BARDA and CDC and a new office is being established within the Pasteur Institute in France.

Dr Gellin reminded participants of the recommendations of the Strategic Advisory Group of Experts on Immunization (SAGE) for risk groups for influenza vaccination. Notably, SAGE recommends that, while countries should decide which risk groups to prioritize based on burden of disease, cost-effectiveness, feasibility and other appropriate considerations, influenza vaccination programmes should prioritize pregnant women.

GAVI, the Vaccine Alliance, considered influenza vaccination for maternal immunization in its 2013 investment strategy. However, influenza was not selected due to uncertainty of its impact and potential complications with year-round supply and low country demand. The Alliance plans to re-evaluate influenza vaccines for maternal immunization in its next investment strategy and is currently addressing uncertainties surrounding burden of disease, safety, effectiveness, cost, implementation, regulation and manufacturing/supply.

Dr Gellin also provided an overview of the PIP framework and its relation to the GAP. PIP recognizes the need for a fair, transparent, equitable and efficient framework for the sharing of H5N1 and other influenza viruses with human pandemic potential. It also promotes the sharing of benefits, including access to and distribution of affordable diagnostics and treatments, including vaccines, to those in
need, especially in developing countries, in a timely manner. In parallel, the GAP aims to build sustainable vaccine production capacity to enhance equitable and timely access to pandemic influenza vaccines.

The threat of a pandemic is very real, and circulating influenza viruses need to be closely monitored. For seasonal influenza, vaccine strain selection is still based on best predictions; mismatches between the circulating and the vaccine strains can have a negative impact on vaccine effectiveness, which in turn will influence public confidence in the vaccine.

With regard to progress, the previous GAP Advisory Group meeting in 2014 considered that the objectives of Pillars 2 and 3 were being met, but called for more attention to Pillar 1. Reasons for concern included weak implementation of the 2012 SAGE recommendations on seasonal influenza vaccination of priority groups. While efforts were improving preparedness for a future pandemic, they would be insufficient to protect the world’s population. Furthermore, regional differences in production capacity remained, especially the relative paucity of influenza vaccine manufacturing in the Middle East and Africa. Without reliable and growing demand for seasonal influenza vaccine, the sustainability of even the current production capacity remains uncertain.

Dr Gellin presented a schematic diagram of the various elements surrounding vaccination from disease surveillance, vaccine development, market, price/procurement, effectiveness through to uptake and achieving coverage rates to protect the population from disease. Regarding the H1N1 pandemic, the major issues encountered were timely vaccine distribution and use, due to a shortfall in global production capacity; distribution and donations; liability and legal agreements; navigating NRA requirements for importing countries; and limited capacity to transport, store and administer vaccines.

In conclusion, the end of the GAP was fast approaching and the coming year would serve to: review progress, challenges and opportunities; identify and prioritize remaining gaps; discuss options for continued progress; and learn from lessons/commonalities with other outbreak response challenges.

**SESSION 2. ADDRESSING BOTTLENECKS**

**2.1 Experiences with H7N9: time from announcement of strain to availability of candidate vaccine viruses and assays**

Dr James Robertson presented the recent experience on the development of candidate vaccine viruses (CVVs) and assays for H7N9 influenza. Following reports of severe human influenza infection with H7N9 in the People’s Republic of China from February to March 2013, WHO requested the preparation of CCVs and reagents. The virus was received at the National Institute for Biological Standards and Control (NIBSC) on 10 April 2013, and the first CVV (NIBRG-267) was available 23 days later for dispatch to laboratories/manufacturers with biosafety level (BSL) 3 in place. Development of the first CVV at CDC took 20 days and, while their availability was announced on the WHO website on 10 May, they had not yet been fully safety tested to confirm attenuation in the ferret model. However, partial safety testing (knowing the sequence and attenuation through passage and survival in embryonated eggs) allows handling at BSL3 conditions, which saves 2–3 weeks waiting for the ferret data to allow handling at BSL2.

As of 26 May 2014 (the most up-to-date information on the WHO website), four CVVs based on A/Shanghai/2/13 and four CVVs based on A/Anhui/1/2013 were available from WHO Essential Regulatory Laboratories (ERLs). All have undergone full safety testing to allow handling at BSL2 conditions. Of note is that all available CVVs for H7N9 were produced through reverse genetics since attempts to produce them through classical reassortance were unsuccessful.

In addition, the protein yield for these CVVs is not optimal. Wild type A/Anhui/1/13 gave a yield of 15.7 mg per 100 eggs, but the two CVVs were much lower at 3.7 and 2.3 mg/100 eggs. Normally the opposite occurs and CVVs give a higher yield than wild type virus. This is because with H7N9, wild type grows so well that it is difficult to extract the desired reassortants.
Another important aspect is the availability of reagents to conduct potency testing through single radial immunodiffusion (SRID) which requires both reference antiserum and antigen. At NIBSC, antiserum made against N9 and H7 was available on 14 August and 20 September 2013 respectively. This is time-consuming because sheep cannot be bled until they have built up immunity following immunization. ERLs cannot easily prepare the large quantity of reference antigen required and must rely on industry to do this. In the case of H7N9, since no manufacturer took it on, NIBSC assumed this task. In November 2013, the US Center for Biologics Evaluation and Research (CBER) made small lots of antisera and antigen which were sent to NIBSC for distribution to ERLs that required them.

In summary, the main bottlenecks for H7N9 CVV development were unsuccessful classical reassortment; delays in the dispatch of CVVs once available; and suboptimal yield. On a positive note, obtaining the starting virus, sequencing haemagglutinin/neuraminidase (HA/NA), developing synthetic deoxyribonucleic acid (DNA), rescuing the virus and conducting safety testing were all relatively rapid.

As a final note, it is important to remember that each influenza virus is unique and bottlenecks may be technical or bureaucratic.

2.2 Alternatives to SRID for potency testing

Dr Othmar Engelhardt described alternative potency assays for influenza vaccines. Potency testing of inactivated influenza vaccine (IIV) is currently conducted through SRID, which has been used since its development in the 1970s. Overall, the test is reliable and reproducible, and influenza vaccines that have been standardized using SRID have performed well.

The principle of SRID is simple, comprising an agar matrix containing a specific antiserum with wells into which the antigen/standard is pipetted. The antigen is allowed to diffuse into the agar matrix and react with the antibody to form a precipitant ring which can be stained and its size measured. Since the size of the ring is proportional to the amount of antigen present, the quantity of HA in an unknown sample can be determined if there is a standard.

The SRID assay requires two types of reagents, a calibrated antigen and a specific antiserum. The antigen reagent which is calibrated in micrograms of HA is specific for a particular CVV or reassortant. For instance, if there are several CVVs for a particular H3N2 virus, there is a specific antigen reagent for each one. The antiserum reagent, by contrast, is broadly reactive for one specific antigenic group, so for one H3N2 recommendation, one antiserum can be used to test vaccines produced with different CVVs. These reagents are currently made, calibrated and distributed by the four WHO ERLs.

During the 2009 H1N1 pandemic, many jurisdictions required clinical trials. This created huge pressure to release clinical trial lots early, some of which were released using alternative potency assays and later retested by SRID when the reagents became available. The result was a new interest in the development and testing of alternative potency assays.

There are two major types of assays: physicochemical assays such as high-performance liquid chromatography (HPLC), sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) and mass-spectrometry; and biological assays such as enzyme-linked immunoabsorbent assay/enzyme immunoassay (ELISA/EIA), titre on a chip, surface plasmon resonance (SPR), and immunocapture isotope dilution mass spectrometry.

Generally, physicochemical assays measure the total amount of HA present in the sample regardless of conformation of HA. In essence, they do not distinguish between native and denatured forms of HA and are thus unlikely to indicate stability, although it may be possible to estimate conformation of HA by combining various methods to see whether it is native or denatured. The advantages of some physicochemical methods are that they may be rapid, automatable and even lend themselves to high through-put assays, and reproducible (yet to be shown in collaborative studies). Disadvantages are that the HA is measured regardless of its conformation, immunogenicity or antigenicity. Some of
these assays may still require reference reagents and some methods are not going to work for trivalent vaccines such as SDS-PAGE. Certain methods are quite expensive, technically challenging and quite difficult to implement, such as mass-spectrometry.

Biological assays measure biological activity or reactivity and are often antibody-based. If they are, then the antigen must be in a conformation that is recognized by the antibody/antibodies. Therefore, depending on the choice of antibody, these assays have the potential to distinguish native from denatured HA. This means they can also be stability-indicating because denatured or degraded HA can be monitored. Some of these assays can be combined with physicochemical methods; the immunocapture isotope dilution mass spectrometry (IC-IDMS) and immunocapture mass spectrometry methods, for instance, have been described by CDC.

Additional advantages of biological assays are that some of the proposed assay formats are well known and well established, making them easy to implement. Disadvantages are the need for calibrated reference reagents, and some assays are expensive and technically complex.

NIBSC compared some of these assays in forced degradation studies to see how they determine the amount of HA in samples to monitor degradation or the loss of stability in a vaccine. The physicochemical assays (HPLC and SDS-PAGE) tested showed no difference in potency in the untreated and treated vaccines, whereas the biological assays (SRID and competition ELISA) that were tested did. The difference in potency of the vaccines were confirmed in mouse immunogenicity studies.

With regard to evaluating new potency assays, Dr Englehardt summarized a document developed by WHO ERLs, WHO collaborating centres and industry which was presented to the WHO Expert Committee on Biological Standardization (ECBS) in 2011. The document defines the essential characteristics required by improved or alternative potency assays for IIV as: the biological relevance of the analyte, accuracy and robustness of the assay, subtype specificity, flexibility and maximum practicability. The “nice to have” features were listed as applicability to existing and novel vaccines, and robustness of reference reagents.

In order to advance the availability of new potency assays, international coordination and sharing of information and data are needed. SRID is a globally standardized assay in general use; while the development of new assays offers great opportunities, it also poses a risk for this global standardization of influenza vaccines. In the meantime, efforts are ongoing to improve the SRID potency assay, some of which are spearheaded by the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) with the involvement of ERLs.

Down-selection will be needed in the growing field of assays under development, with various publications describing alternative potency assays. While they cannot all be evaluated in depth, shortlisted promising assays should be evaluated, not just by the laboratories that develop them but in a collaborative study with other laboratories. In an initiative led by BARDA, WHO/ERLs and IFPMA have formed a steering group comprising members of BARDA, CBER, NIBSC and IFPMA. The group plans to compare the most promising alternative potency assays. A questionnaire has been issued to gauge the interest of manufacturers and others to identify and evaluate tests, and a consultant has been hired to advance this study.

2.3 Improving the strain selection process

Dr Wenqing Zhang presented the work being undertaken to improve the global influenza vaccine strain selection process, coordinated by WHO. She reminded participants that, because influenza viruses are constantly evolving/mutating and have the potential to rapidly spread, surveillance and control measures need to be conducted in a timely and continuous way on a global scale.

WHO issued its first formal recommendation on influenza vaccine composition in 1973. In 1986, the first documented WHO annual consultation on the composition of influenza vaccines with influenza vaccine manufacturers was held in Geneva. Since 1998, WHO holds biannual meetings and issues recommendations on the composition of influenza vaccines for northern and southern hemispheres.
The Global Influenza Surveillance and Response System (GISRS) was founded by WHO in 1952 and now includes 6 WHO collaborating centres and 142 national influenza centres (NICs) in 112 countries. GISRS monitors circulating viruses, and conducts risk assessments and laboratory diagnostics to support the vaccine strain selection process.

In addition to influenza vaccine composition recommendations, this network is a global mechanism for surveillance of influenza and other emerging respiratory pathogens. For example, the network identified the severe acute respiratory syndrome (SARS) coronavirus in China in 2003, and responded to the A(H1N1) pandemic in 2009: following laboratory confirmation and gene sequencing of the virus on 25 April 2009, the first diagnostic protocol was available within three days, and within seven days the first reverse transcription polymerase chain reaction (RT-PCR) kits were sent out. This led to the recommendation for the pandemic virus on 26 May, and on 27 May the first CVV was available.

Dr Zhang presented a schematic diagram of the process of influenza vaccine virus selection and development. She stressed that the process was highly technical and complicated, using various assays and tools. Because of its prominent role in protective immunity, HA remains the focus, although there is also interest in the role of NA for its protective immunity and antiviral use. Assays currently used to support the process include haemagglutination inhibition (HAI), neuraminidase inhibition, neutralization assays, as well as genome sequencing. Human vaccine serology is also conducted twice a year using sero panels from vaccinees, vaccinated with the most recently available vaccine. Since September 2004 antigenetic cartography has also been used to visualize antigenic properties as well as the antigenic relationship of viruses. All these data are used as a base for the WHO selection of vaccine viruses, in addition to available epidemiological and clinical data. Information on the growth of viruses in eggs and cells is also used to support this process.

Improving the vaccine virus selection process, beyond the initial HA criteria, has been ongoing for a number of years. WHO has organized three global consultations on this process since 2010, and is planning a fourth consultation in 2015 to include all key stakeholders. Main areas in this process that are under continuous review are:

**Global surveillance**
GISRS currently covers 91% of the global population and 51% of countries in the world. Projects related to the quality and efficiency of virus sharing within WHO include the External Quality Assessment Project and the Shipment Fund Project. Regarding the scale of surveillance, more than 1.9 million clinical specimens were tested by this network in 2014. Capacity-building for global surveillance is ongoing, in particular since 2011 under the PIP framework, which includes support to improve an understanding of disease burden, contributing to Pillar 1 of the GAP. The PIP framework also supports the strengthening of regulatory and vaccine deployment capacities.

Capacity is also being strengthened for epidemiology and disease surveillance for influenza-like illness (ILI) and severe acute respiratory infections (SARI) as well as surveillance systems. This will ensure that specimens sent to GISRS are of high quality. Efforts are ongoing with WHO collaborating centres to address issues such as egg versus cell isolates, the low HA titres of some recent H3N2 viruses, and adapting assays to understand the antigenicity and antigenic relationships of recent viruses. On the pandemic preparedness side, WHO is collaborating with OFFLU (network of expertise on animal influenza) on the human–animal interface side of influenza. Another collaboration with vaccine manufacturers focuses on the provision of sera from vaccinees, use of isolates from qualified cell lines and communication up to the vaccine composition announcement.

While WHO recommendations have focused since 1973 on the northern and southern hemispheres, WHO is now looking at the vaccine composition for the tropics. An informal working group will review the needs in this area to enhance surveillance and policy. The many challenges include timeliness, representativeness and quality of viruses and information sharing.

**Characterization of antigenicity and antibody response**
HAI is a surrogate for virus neutralization; it is widely used and is the current basis for the vaccine composition recommendation. Efforts are being made in WHO collaborating centres to overcome HAI
challenges. In order to address the current limitations of traditional HAIs, focus is on developing synthetic bead- and non bead-based technologies using recombinant proteins. Despite this, no viable alternatives yet exist to the traditional HAI.

While NA antibodies contribute to immunity, there is no regulatory requirement or precise determination and standardization of the NA content in influenza vaccines. Current studies aim to understand better the pattern of antigenic drift of NA and its impact on influenza vaccine virus selection.

To analyse antibody responses, an “antibody landscape” approach is used. For example, antigenic mapping tries to understand the quality and breadth of antibody response to HA and NA and the influence of prior immunity on vaccination responses. In a study in Viet Nam, it was observed that increasing immunity over time seems to have a “back-boost” effect. This approach is advancing the prediction of virus evolution, which may be a potential for selecting “optimum vaccine viruses”.

**Technologies and tools**

Whole genome sequences can be mapped very quickly, which assists outbreak investigations as well as risk assessments. However, use of these comprehensive datasets requires a high level of expertise and significant resources. Synthetic genomics technology has already demonstrated its potential in the response to H7N9, where the first CVV was developed using synthetic HA and NA. Reverse genetics technology has been applied to develop CVVs, in particular for zoonotic influenza viruses.

Mathematical modelling is another important tool, and efforts are focussing on integrating data in order to identify factors determining antigenic drifts. A concept called “viral fitness” aims to predict the evolution of HA sequence clades. However, in general, these mathematical efforts have been retrospective and based on genetic sequence information. Their predictive value at the phenotypic level and their actual use in the real world, i.e. their prospective use, have yet to be demonstrated.

The synthetic genomics, genetics and system biology concept has the potential to identify specific host-susceptibility genes and diagnostic and prognostic markers. This technology may help to understand pathogenic and virulence mechanisms, evaluate vaccine performance and response, and to understand at the molecular level the correlates of immune response and immunogenicity.

“Big data” is another concept of interest, the future of which depends on many advances that need to be developed, for example, data generation, integration, analysis and distribution.

**Manufacturing and regulatory perspectives**

In the context of influenza vaccine virus selection, manufacturers are under extremely tight timeframes, many start producing, at risk, before WHO recommendation. In parallel to increasing regulatory demands on new types of vaccines, BARDA is working to optimize backbones for faster development and higher yield.

In summary:

- Challenges exist in predicting which viruses are likely to be circulating in the next 6–8 months; current tools are retrospective, hypothetical and experimental.
- Measuring vaccine effectiveness through current correlates of protection such as HI is suboptimal. Identifying better correlates of protection should be a research priority.
- Better vaccine technologies could shorten the vaccine production cycle. Recommendations from WHO would allow more virus circulation information to be used for decision-making.
- Better vaccines with a broader spectrum of protection would eliminate the need for seasonal strain changes.
- WHO is committed to provide global platforms to move this area forward in collaboration with partners.
2.4 Panel discussion: Reducing the time from start of a pandemic to availability of a vaccine
(Panellists: Othmar Engelhardt, James Robertson, Larisa Rudenko, Julie Villanueva, Paulo Lee Ho)

Dr Larisa Rudenko emphasized the need to include LAIV candidate vaccine preparations when presenting timelines for CVV production. In the case of LAIV, reverse genetics was not needed to generate H7N9 CVV and these were rapidly developed. Reverse genetics is a significant issue for developing country vaccine manufacturers, as a license is required for a vaccine intended for commercial purposes. Regarding the WHO seasonal influenza vaccine strain selection process, Dr Rudenko asked if it was possible to obtain potential CVVs in advance of the announcement, so that manufacturers could already work on the virus and be ready to produce the reassortants as soon as the announcement is made.

- Dr Zhang responded that teleconferences with WHO collaborating centres and ERLs are always organized before the WHO vaccine composition consultation, summaries of which are shared with manufacturers through IFPMA and the Developing Countries Vaccine Manufacturers Network (DCVMN). If a manufacturer is not member of either association, Dr Zhang would be happy to add it to the distribution list. The summaries provide information on the priority viruses being evaluated by WHO, and the CCVs being developed by WHO collaborating centres and ERLs. It is possible to request such viruses for development in advance of the strain announcement.

- Responding to a query, Dr Rudenko confirmed that the yields for H7N9 LAIV were very good and a Phase 1 clinical trial of the candidate had been completed. The results showed this to be the best potential candidate compared with H1, H5 and H7N3 because one dose of vaccine elicited very good immune response to H7N9 LAIV. Data from a ferret challenge study of H7N9 LAIV of the Serum Institute of India (SII) also showed protection after a single dose.

- Paulo Lee Ho commented that Butantan experienced good yield for H7N9 but the vaccine itself was poorly immunogenic, demonstrating the need for an adjuvant.

- Regarding H7N9 timelines, Dr Friede noted that while CVVs were available quite quickly, import permits delayed getting them into countries by up to several months. Furthermore, it took several months to develop the reagents for manufacturers to conduct potency testing on candidate vaccines. If this had been a real pandemic this would be a serious barrier to the timely availability of vaccine. These two issues (import permits and reagent development) need to be addressed now outside of a pandemic situation.

- Othmar Engelhardt agreed that permits and reagents were barriers to the timely development of H7N9 vaccines. However, the timeline to develop reagents cannot be compared with that in a real pandemic situation. The pandemic vaccine reagents would be available much earlier because manufacturers all over the world would produce antigens and ship them to ERLs to make the reagents. The antiserum will always take time and vary from strain to strain. For example, a recent antiserum against a new H5N1 CVV was ready in 5 weeks, but some take 12–13 weeks.

- Dr Julie Villanueva added that import and shipping issues were big bottlenecks which countries should work to resolve now. CDC is working closely with the US Food and Drug Administration (FDA) to move this forward. Identifying courier services willing to ship CVVs of prepandemic strains and other samples in a pandemic is also a major issue. Communication channels with couriers should be opened now to ensure their rapid shipment in such an event.

Another concern, raised by Larisa Rudenko, was the need for safety data from ferrets to confirm attenuation of prepandemic CVVs to ship and use under BSL2+ conditions. A CVV can be made and fully characterized quickly, but if a ferret study is required to confirm safety, this can delay the shipment by several months.
Dr Paulo Lee Ho noted that, besides the availability of strains and reagents, communication channels need to be improved. Butantan waited a long time for a response from CDC with regard to H7N9. Another major barrier is that, to ensure that eggs are available in time of need, the plant needs to be functional all year round.

- Dr Rick Bright (BARDA) commented that, despite the bottlenecks for H7N9, the world was much better prepared for a pandemic than in the past, especially with regard to technologies. For example, Novartis used synthetic biology to make a seed virus in 8–10 days. LAIV seeds were made quickly, and again, as seen in 2009 with H1N1, LAIV were the first candidates available. The recombinant based-technologies as well as the Novavax virus-like particle vaccine came out very quickly. Thus, technologies are now more poised and ready for a pandemic. However, regulatory and shipping issues do need to be solved.

- Martin Friede agreed that significant advances in technologies had been made and most barriers to the timely availability of CVVs resolved. Focus should be on getting the processes in place for shipment and importation of CVVs. Transfer of reagents could be done while awaiting ferret data.

- Dr Parikshit Tyagi (SII) added that a mechanism needs to be agreed with governments in advance. In India, a system exists for automatic endorsement of seasonal influenza CVV strain import and strain change. Such a system will reduce the time to import seed virus in a pandemic event.

- Dr Jinchang Wu (Changchun BCHT Biotechnology Co.) confirmed this was an issue in China, and urged that action be taken and country experiences shared to identify mechanisms that work. WHO could issue guidance or work closely with local administrations to develop a formalized process, not only for pandemic but also for seasonal CVVs.

- Jim Robertson felt that the most profound issue was bureaucracy in terms of permits/import. The issue of yield for H7N9 CVVs was clearly unique to H7N9 and needs to be overcome. He explained that, while the wild type yields for H7N9 were remarkable, this was not so for attenuated CVVs. When a virus is not circulating, authorities do not want manufacturers to use a wild type virus for vaccine development due to the potential risk to communities; initial vaccine batches therefore use attenuated CVVs. Once a pandemic is declared and the virus is in the community, wild type may be used although there may still be issues with its potential pathogenicity for humans.

Wenqing Zhang noted that since countries have their own pandemic preparedness plans, certain mechanisms need to be in place in all countries to receive viruses from the WHO system. Before ferret safety testing is done, viruses have to be shipped under category A, i.e. infectious substances, which requires more administrative work than for category B. Countries should plan for this.

Dr Han van den Bosch asked the panel whether any alternative assays to SRID were planned. If physicochemical assays were not going to be feasible, what was the future of potency testing?

- Othmar Engelhardt responded that a number of promising tests were being researched and a group has been established to compare some of these assays across laboratories. While physicochemical methods may be problematic, they can be a temporary solution in a pandemic when the first clinical trial lots are tested; since these are not multivalent and there is no need to distinguish between subtypes, it is easier to use assays such as SDS-PAGE. Ultimately, a new biological assay will hopefully be faster with a more robust and rapidly available supply of reagents. Issues also need to be resolved in comparing different vaccine types such as a split, subunit or whole.

Dr Alex Precioso asked whether current potency testing for adjuvanted vaccines was suitable or whether new tests would need to be developed for adjuvanted vaccines.
Martin Friede noted that the choice of adjuvant will affect the readout of antigen yield from a SRID assay. In an oil-in-water emulsion, the SRID needs to be modified to enable the antigen to migrate within the emulsion, or an alternative in-house procedure found. Aluminium can be very complex because the alum has to desorb from the antigen in order to carry out the SRID. However, bulk antigen can at least be released using SRID and independent methods used to confirm the potency once formulated with adjuvant, such as a mouse study.

Gary Grohmann confirmed that any regulatory lot release laboratory will take the results of the bulk and project what might occur with an adjuvanted vaccine in an assay. This will require a little research on the manufacturing and regulatory side, and both sides must agree on the assay system. Such systems have been agreed for MF59 and ASO3. While it might work for physico-chemical assays, most regulators will insist on a biological assay, particularly an immunological assay such as an ELISA.

SESSION 3. MANAGEMENT AND CONDUCT OF CLINICAL TRIALS

3.1 Resources available for planning clinical trials
Ms Erin Sparrow presented WHO materials available for planning clinical trials which were provided to GAP manufacturers and their regulatory agencies at a Workshop on the regulatory requirements for the preclinical and clinical evaluation of influenza vaccines held in Bangkok in July 2014. The workshop was attended by over 100 participants including 55 representatives from NRAs, 30 representatives from the DCVMN and WHO staff and experts in influenza vaccine evaluation and regulation.

The purpose of the workshop was to enhance the capacity of developing countries to manufacture and license seasonal and pandemic influenza vaccines through training on design and regulatory review of preclinical and clinical studies. All preclinical and clinical requirements for vaccine approval were covered, as well as studies for annual strain change or process modification. Postmarket surveillance and requirements for WHO vaccine prequalification were also reviewed.

A secondary purpose of the workshop was to enhance the capacity of non-producing countries to evaluate, register and conduct postmarket surveillance of influenza vaccines. As the workshop was held in Thailand, non-producing countries from that region were invited, including regulators from Bangladesh, Cambodia, Lao People’s Democratic Republic and Sri Lanka. Prior to the workshop, WHO commissioned a package of supporting materials, including examples of preclinical study plans, template protocols for Phase I and II clinical trials and generic templates of clinical trial study instruments. These documents covered IIV, LAIV, seasonal, pandemic, and adjuvanted vaccine types. Participants also received summaries of European Medicines Agency (EMA), FDA and WHO guidance on clinical trial requirements for seasonal/pandemic vaccines including special considerations for Phase III trials. It was stressed that the templates for the design of preclinical and clinical trials were only a guide; manufactures should always engage early in clinical trial planning with their NRA, who will confirm whether or not the plans meet the national requirements.

3.2 Common challenges in conduct of clinical trials
Dr Rahnuma Wahid presented some of the planning processes and challenges that might be encountered in implementing a clinical trial. Although the following list was not exhaustive, it outlined many parallel and competing factors:

- Coordination of manufacturing activities
- Clarity of trial protocol and case report forms
- Ethical/regulatory review(s)
- Site capacity, management, and experience
- Management of different partners
- Contracting and agreements
- Trial timeline
- Overlapping/parallel activities.
The starting point should be the development of a realistic timeline/plan to prepare and implement the clinical trial. It is important to identify overlapping activities and how to sequence them. The first is the manufacturing of the product and its readiness, preclinical studies, and the length of time for review and approval of the protocol dossier. The time needed for contract negotiation and finalization should be included here as well as adequate time to develop and roll out the data capture system and site start-up activities. Adequate time also needs to be planned for clinical site preparation, trial recruitment/enrolment and implementation. Allowing adequate time to complete the clinical study report following database lock is also important.

Dr Wahid detailed the key steps needed for the areas mentioned above. She highlighted the importance of understanding preclinical studies and the various regulatory requirements at the local and international level. Expiry dates and stability data are a key factor as a clinical trial can take longer than anticipated.

The development of the clinical trial protocol should start early with sharing the protocol synopsis with partners during site and contract research organization (CRO) assessments. After this, the full proposal and trial documents should be developed, using the required regulatory formats if needed, understanding the various regulatory requirements, and those related to study and recruiting instruments. Examples were given of situations where advertising for clinical trials is not allowed, requiring innovative ways that are acceptable for recruitment. Appropriate informed consent, adapted to the target population, is essential, ascertaining the need for parental consent or local language/dialect. A final step in the planning process is to ensure that all partners are fully trained on the protocol and study-related documents.

Dr Wahid then discussed clinical site assessments and evaluation of their capacity and infrastructure, including the safety of laboratories. Assessment factors included staff training, accreditation, and adherence to quality assurance systems and good clinical practice (GCP).

CROs ensure data safety and quality, compliance of their system with the NRA, appropriate statistical support and timely reporting. Working with the CRO also ensures that the case report form design is appropriate for data entry at the site.

Regarding trial monitoring and the role of a CRO, it is critical that health and safety plans include the ability to identify and treat any adverse or serious adverse event (SAE) and report these immediately to relevant parties. An important step is to set up a safety review committee or a Data and Safety Monitoring Board (DSMB) for trial safety oversight. A trial monitoring plan would ensure that all related documents are completed correctly, comply with GCP and local regulations, and adhere to the trial protocol.

Once the partners, trial sites and CROs and have been selected, and all approvals are in place, the clinical trial can start. However, challenges happen, and it is important to know how to handle them, e.g. out-of-range lab results, toxicity tables, or grade 1 or 2 lab results. The key is to discuss issues at length if needed with partners and CROs to ensure that the data received are accurate and clear.

In summary, the main points about challenge mitigation are: clear communication, consistent follow-up with all partners, predefined roles and responsibilities for activities associated with the clinical trial and, of course, appropriate planning and timeline management.
3.3 Tools for conduct of early phase clinical trials
Noting that there are many other tools available for project planning, Rahnuma Wahid presented a simple Excel Gantt chart for clinical trial planning and activity tracking, looking at some high-level items and their sub-items. The first items concerned all the manufacturing activities and preclinical studies that need to take place and the timelines required for each. These included: process development; release assay development; validation steps (if required); formulation and filling; lot release at the company and the national lab level; stability studies; preclinical studies such as immunogenicity and toxicology studies. All these steps take time and should be prepared and in place to start immediately after the product release.

The various activities and their timelines associated with preparing for the clinical trial were then presented, including: site and CRO assessments; clinical plan and study design; and development of the protocol and the trial documents. Engaging with the CRO early is critical for the development of the case report forms which can take months to finalize. In addition, time should be set aside to develop the manual of procedures which encompasses three different documents (vaccine and sample handling, laboratory manual and the pharmacy manual).

After the documentation is place, the trial can be submitted for approval. The activities involved include submission to the local ethics committees, Ministry of Health or NRA and, if working with WHO, to its Ethics Review Committee. Many of these activities occur in parallel so they should be assigned to different people. Integrating time for negotiation of contracts was also important, not only with the clinical trial site and the CRO, but with all partners involved. One of the most important documents is the clinical trial agreement, usually between the sponsor and the trial site, which must be in place before the clinical trial can move forward. Site preparation can take time, ensuring that standard operating procedures (SOPs) are in place and any training required is provided.

Dr Wahid described the post-approval activities, i.e. from the start of the clinical trial, including the site initiation visit, audits, training and recruitment. Key activities to note in the Gantt chart are the first subject in, the actual implementation time and the last subject out. Generally the trial itself may last 90 days, but its actual duration may last up to 5–6 months depending on various factors.

The last set of activities presented focused on data management, report writing and report dissemination, which can take another 6–8 months to complete. Dr Wahid closed with a RACI chart that outlined, for each activity, the “responsible party” the “approver”, the “consulted person” and the “informed Person”.

Discussion
In response to a question on Ebola vaccine trials, countries should have a clear plan to present to regulators; for multi-country trials, it is simpler if regulators can review submissions jointly for the same product as this avoids the need to submit different formats to different countries; and finally, early engagement of the CROs and investigators is key.

Regarding the use of a secondary laboratory for confirmatory testing (when the serology assay might not be validated in early trials) and what to do if there is a discrepancy in the results between laboratories, Dr Wahid suggested that one way was to have the lab performing the confirmatory testing only work on a subset of samples.

Regarding the use of a secondary laboratory for confirmatory testing (when the serology assay might not be validated in early trials) and what to do if there is a discrepancy in the results between laboratories, Dr Wahid suggested that one way was to have the lab performing the confirmatory testing only work on a subset of samples.

A query was raised about the clinical trial requirements for switching from trivalent to quadrivalent influenza vaccines. Depending on the regulators they may require a small Phase I or II trial to show immunogenicity to ensure that the three antigens are not competing in any way with the fourth, and to ensure there is no obvious safety signal.

A question was also raised about the acceptance of accelerated stability study data when real-time stability data are unavailable. Again, this was dependent on the regulatory agency.
3.4 Late phase clinical development of influenza vaccines

Dr Martine Denis presented specific aspects related to late stage development of influenza vaccines and the generation of clinical efficacy data. The organization of efficacy trials for influenza vaccines can be particularly challenging and she presented some key aspects of efficacy study designs.

The first example provided was a placebo-controlled efficacy trial to demonstrate protection against influenza. Subjects are randomized to receive either vaccine or placebo before the influenza season starts. Follow-up takes place throughout the influenza season, whereby each time a subject experiences influenza-like symptoms a sample is collected and laboratory confirmation is done. At the end of the trial, the study is unblinded and the number of cases that occurred in each of the two groups helps calculate the vaccine efficacy.

It is challenging to define an influenza case as there is no widely accepted definition. ILI definitions exist but since they are not specific for influenza, laboratory confirmation is required. Two different methods exist: PCR which is an easy and convenient, and virus isolation by culture, which allows for antigenic characterization of the virus to confirm matching or miss-matching to the vaccine strains. However, sensitivity and specificity of influenza diagnosis will impact vaccine efficacy. For example, if the method classifies some non-real cases, this may reduce the vaccine efficacy measured.

Another way of impacting vaccine efficacy is the selection of outcomes/endpoints for the trial. The results of a meta-analysis of influenza vaccines efficacy demonstrated that when the endpoint aimed to match the virus to the vaccine virus, the efficacy observed was significantly higher than when it was measured against any influenza strain. However, while it may appear advantageous to use this type of endpoint, in practice the situation is more complex. This is because the attack rate of the disease will be lower than in the second situation, and if fewer cases are identified in the trial, there is a risk that statistical significance will not be reached.

Another key aspect to address when planning an efficacy trial is the population to select. In practice, the target groups are typically elderly subjects, children and persons at risk, while in the literature today, most placebo-controlled trials that have data have been conducted in young adults. Recently a number of clinical trials have been organized or planned in children. The reasons to do this include the fact that cases of influenza are relatively frequent in this group and the symptoms of the disease are quite standard. However, specific issues need to be considered when including children. First, it is more expensive as such trials are more complex to organize. The number of subjects that can be enrolled per centre are lower, and ethical issues exist related to efficacy trials in children. Safety data in adults are required before moving into trials in children and ideally there should be no recommendation for vaccinating children against influenza in the country where the trial is conducted.

Dr Denis then discussed comparators and how to carry out randomization. While placebo is acceptable in young adults, there may be ethical reasons to prefer using an active vaccine comparator in children. With regard to the randomization ratio, most trials use a 1:1 ratio which is the most “effective” approach in terms of biostatistics. However, recent trials have used a 2:1 ratio, where twice as many subjects receive the vaccine compared with the control.

Regarding sample size, two situations were presented with different sample sizes, attack rates observed, and endpoints (matched versus any case). Vaccine efficacy calculated in each situation varied significantly: while typically one looks at point estimates, it is also critical to look at the lower level of confidence intervals which will be of interest to regulators. This is taken into account when biostatisticians calculate the sample size, as they will make assumptions on the attack rate of the disease and true vaccine efficacy associated with the vaccine. Obviously, the higher the attack rate, the higher the vaccine efficacy, and the lower the number of subjects needed in the trial.

With regard to attack rates, the epidemiology of influenza is highly variable and difficult to predict. All data available need to be reviewed, and assumptions made on vaccine efficacy, e.g. the degree of matching between the virus that will circulate in the coming year and the virus included in the
composition of the vaccine. To avoid non-significant data, Dr Denis recommended a conservative assumption, although this would increase the cost of the trial. For late stage development of a novel influenza vaccine where efficacy is measured by influenza outcome, several thousand persons need to be enrolled. This may only be feasible in large pharmaceutical organizations as it may require a multicentre or even multi-country trial, which is complex and costly to organize.

An efficacy trial will typically last about six months, the duration of an influenza season. However, enrolling all subjects before the influenza season can be a challenge. Another option is to plan the trial across two or more influenza seasons to reach the target enrolment for the study, although this would significantly impact the budget of the trial. Another possibility is to conduct the trial in both the northern and southern hemispheres, if the vaccine being manufactured can be delivered for both hemispheres.

Regarding the selection of clinical trial sites and CROs, an efficacy trial requires a large number of centres with a high enrolment capacity, posing a potential challenge as competition exists for access to the best study sites. The best investigators and sites are well known and all sponsors want to work with them. When dealing with very large trials, working with a CRO cannot be avoided for site training and monitoring, regulatory submissions, etc. There are two different options for working with CROs: selecting a large international CRO and contracting out the entire conduct of the study; or using more restricted support from a local, smaller CRO. The first option is more expensive. For smaller companies, coordination or project leadership of the trial should be retained within the company, relying on the local CRO for the support required.

Issues related to the role of the laboratory in these types of trials were presented. Confirmation of cases is key to success as it defines the level of efficacy measured in the trial. Lab confirmation must be performed as quickly as possible after onset of symptoms as the period of viral shedding can be quite short. A specific process will be needed to obtain the sample rapidly, for example a nurse that visits the house of any suspected case. A process for shipment to an ERL will also be required. If cases are confirmed by viral culture, the virus should be alive when it reaches the laboratory. Validated methods and a laboratory certified for good laboratory practice (GLP) are needed. If multiple laboratories are used, similar methods and performance should be ensured.

Dr Denis’ final point related to the difficulty in applying GCP in a multi-country trial, particularly when planning a late phase trial. Fraud is very rare but exists. A major objective in a trial is to track and resolve any compliance issue as quickly as possible. The CRO has its own monitoring plan and should help identify any compliance issue. However, the sponsor can take additional measures, for example, to look at the results (blinded) as they arrive and analyse them per centre and per investigator. There is then an opportunity to review the outlier values, e.g. an analysis of each centre, the number of suspected cases observed, and the ratio of confirmed versus suspected cases.

To conclude, Martine Denis again raised the issue that large efficacy trials on influenza incidence may only be feasible by the largest pharma organizations, since they have to balance the low selling price of the vaccine. For non-novel influenza vaccines, immunogenicity by a correlate of protection (i.e. HI) may be a more feasible endpoint.

**Discussion**

Regarding efficacy trials on vaccines against viruses that are not circulating (potential pandemic viruses), Martine Denis noted that a number of approaches/mechanisms had been described by regulatory authorities from different regions. Outside of a pandemic, a number of methods can be used, including immunogenicity by HAI with generation of safety data. During a pandemic, effectiveness results can be generated. All these issues need to be discussed with the NRAs.

Using HAI as a correlate of protection for inactivated seasonal influenza vaccines is an option that regulators may accept or even prefer. Effectiveness data can be gathered under postmarket surveillance. HAI is not a good correlate of protection for LAIV. For LAIV vaccines, when efficacy through influenza outcomes cannot be measured, micronucleus test, HAI and IgA are considered. Many correlates have been explored but it will take time for investigators and regulators to agree on one that is appropriate and achievable.
3.5 **Quiz: Managing and conducting influenza vaccine clinical trials**

Participants were presented with a list of multiple choice questions to answer in a self-assessment. A panel session reviewed the correct answers, followed by time for discussion.

**Q** **What is the closest definition of the sponsor?**

A The institution/individual that takes responsibility for the initiation and management of the trial (definition from the WHO Technical Report Series No. 924). The sponsor may or may not also fund the clinical study. This definition differs a lot from country to country.

**Q** **Should preclinical studies be conducted under GLP?**

A It depends. Safety testing in animals should have a clear rationale and should be performed in compliance with national and international laws for the protection of laboratory animals, under GLP. However, in situations where full compliance with GLP is not possible, areas of noncompliance should be defined and a statement of the reason for noncompliance drawn up.

**Q** **Following an SAE, which of the following pieces information should be recorded?**

A All of them. (A: Patient study number, study identification, type of adverse event; B: Patient characteristics, including underlying diseases, concomitant vaccinations or drugs; C: How long after vaccination the adverse event occurred and action taken; D: Duration and outcome of the adverse event and investigator assessment of causality.)

**Q** **According to WHO, when should a trial be registered; and when must the results be made publicly available?**

A Before the first subject receives the intervention; and within 30 months of completion. This follows the Declaration of Helsinki that states that all negative and positive results should be published or otherwise made publicly available. if it is not possible to publish in a peer review journal, the following is a WHO statement on this issue:

> Clinical trial results are to be reported within 30 months of study completion date. Reporting to occur in BOTH of the following modalities:

1. Main findings to be submitted for publication in a peer reviewed journal within 18 months of study completion and published through open access or made available publicly at most within 30 months of completion.

2. Key outcomes to be made publicly available in the results section of the primary clinical trial registry. Where a registry is used without a results database available, the results should be posted on a free-to-access, publicly available, searchable institutional website of the Regulatory Sponsor, Funder or Principal Investigator.

This must be kept in mind after completion of the trial and has been added by WHO to letters of agreement when it is involved in supporting clinical studies.

**Q** **According to the International Council for Harmonisation (ICH) GCP, where should ORIGINAL completed case report form pages be filed?**

A In the sponsor files.

**Q** **What are the absolute minimum requirements for essential documents at site before vaccine can be sent to the site?**

A Clinical Trial Agreement and Ethics Committee Approval.

**Q** **According to ICH GCP, clinical trials should be _____, and described in a clear, detailed protocol.**

A Scientifically sound.

**Q** **In ICH GCP, who is responsible for providing the Ethics Committee with the Investigators Brochure?**

A The investigator.
Q What is the most common correlate of protection used to measure inactivated influenza vaccine efficacy?
A HI antibody titre.

Q For influenza vaccines, what is the seroprotection level correlating to protection?
A Antibody titre $\geq 1:40$.

Seminar: International Proficiency Study of the Single Radial Immunodiffusion Test for Influenza Vaccine Manufacturers and Regulators from Developing Countries

Dr Laszlo Palkonyay presented a study to evaluate the effectiveness of WHO training workshops carried out under the umbrella of GAP on quality control of seasonal IIV through a proficiency study on SRID for vaccine manufacturers and national vaccine regulators from developing countries.

Since 2007, WHO has provided grants, in collaboration with international donors, for developing country manufacturers to establish domestic influenza vaccine production. These grants have been complemented with concrete technical support, including hands-on training, offered not only to manufacturers but their domestic NRA and National Control Laboratories (NCL). Since 2008, many workshops have been organized on the theory and practice of SRID testing.

In order to evaluate the effectiveness of the training, WHO contracted NIBSC, through an agreement between WHO and CBER, to carry out a proficiency study. This will provide an objective, internationally comparable measurement tool to assess the effectiveness of numerous WHO-funded SRID training courses carried out over the last five years. The results also explain how the SRID test was introduced and implemented at the national level in the grant recipient countries. WHO aims to include some 22 participants in the study.

IFPMA will provide the test antigen for this process. The preparation of reference antigens and sera has been completed. The next steps are to: distribute test antigens, reagents and study protocol to participants; perform the tests; submit the study results to NIBSC; draft the report; and make the report available to participants. In addition, presentations are expected to be given at international meetings and, hopefully, an article in a peer reviewed journal.

Details presented of the study protocol included: types/numbers of samples to be obtained from manufacturers; tests to be undertaken on materials before shipping to the participants; the protocol to be used; the types of reagents that labs would receive; and the assays expected to be performed.

The data will be analysed by NIBSC as described in the study protocol and an anonymized report will be generated. All participants will have a code number so they can trace their own results and compare them with the general outcome. The report is expected to be completed in 2016.

Laszlo Palkonyay finished by informing participants that an email would be sent to potential participants, and that any specific queries could be sent to him directly.
SESSION 4. SUSTAINABILITY OF PANDEMIC INFLUENZA VACCINE PREPAREDNESS

4.1 Creating the environment for sustainable production

Claudia Nannei and Chris Chadwick discussed a parallel between investing in vaccine manufacturing from a pure business perspective, and investing in local production of influenza vaccines from a governmental perspective as a means to ensure sustainable influenza preparedness. The presenters started with an overview of how to generate a business plan from a purely business perspective. A graph showed four quadrants and key considerations for each as follows:

1. **Market analysis**: potential and actual demand; competitors and market share; national and international trade; and regulations
2. **Production process**: know-how; technologies; goods and services; stocks; workforce
3. **Financial requirements**: investment; cash flow; capital requirements; return on investment
4. **Marketing strategy**: pricing; market penetration; product distribution; product life cycle.

The presenters expanded on the four quadrants to look at the public health investment from a governmental perspective. The environment changes, with health-care services considered as common goods, the right to health taken into consideration, and population health corresponding to national security. Economic development is also important: in addition to the stakeholders, the Ministry of Finance (which needs to allocate national budget for the initial investment), health-care workers, donors, the insurance system, patient associations etc., need to be involved. For the business analysis, and since the issue is public health policies, the government has a role in discussing its strategic partnerships and ensuring sustainable procurement strategies.

Regarding marketing strategy, the first consideration is that the product should be accessible. It needs to be affordable for the target population and for the manufacturer’s budget. And it needs to correspond to local needs. The return on investment goes beyond profitability of the business to include health indicators such as national security and population protection. It includes economic development and the spill-over effect that local manufacturing can bring, i.e. generating employment and reducing hospital costs through prevention, and potentially expanding production to include exports. These are the considerations from a governmental perspective in investing in local manufacturing of IIV with sustainable pandemic preparedness in mind.

A figure was shown depicting the interactions between population/market size, vaccine price, production scale/capacity and infrastructure, and policy and communication. If a population or a market is small, the price of the vaccine can be high, and therefore the target market needs to be expanded and/or the government needs to invest in seasonal influenza vaccination to ensure capacity is in place if a pandemic hits. The environment in which this investment takes place is complex, and
sustainability is essential to protect the investment. The government has a key role in driving this process ahead.

Both presenters stressed the importance of a procurement policy whereby the local manufacturer has a continuous demand. This is part of the government’s responsibility: governments should be in charge of their procurement strategy as they should know what is circulating within their borders.

To support governments in their investment choices, an easy-to-use, high-level checklist was being developed to guide them through all areas related to local production that influence sustainable pandemic influenza preparedness. The checklist assesses the following themes and topics: the policy environment for both health-specific and other policies, influenza-specific evidence, product development and manufacturing, approval and regulations, and the national communication system.

Furthermore, the WHO document *Local production for access to medical products: Developing a framework to improve public health* shows the relationship between health and industrial policies.

Participants were briefed on the key aspects of the checklist. These cover whether the political will exists to ensure that influenza is both a national and regional priority, and whether it is always a part of the agenda. The checklist also ascertains whether or not national influenza recommendations are utilized to support local policy development, and looks at coherence among the relevant policies and programmes. Stakeholder understanding is also sought on the fact that seasonal vaccination not only supports the population but also strengthens national security and pandemic preparedness because the vaccine system is in place in the event of a pandemic. Finally, the checklist looks at the vaccine delivery infrastructure to identify gaps and opportunities that can help planning and possible prioritization of investments.

In addition to health-specific policies, the checklist assesses related policies such as industrial policy, procurement policy and practice, national and international trade, and workforce. For example, it assesses whether existing policies overcome possible bureaucratic obstacles to establish vaccine manufacturing, and whether the national and regional procurement and distribution policies promote in-country production and sourcing of materials.

The checklist addresses influenza-specific evidence generated from the surveillance system. The existing system must be able to detect the circulating seasonal strains and emerging strains. It must look at the reporting and collection of data, how these are aggregated, how they support disease burden in cost-effectiveness studies, and how they are translated to support the priorities of policymakers.

The next section of the checklist addresses sustainability from the manufacturing perspective and whether a sound business plan is in place. This is the most extensive part of the checklist, which assesses components including supply chain, reimbursement of revenues, R&D, technology selection, compliance with GMP, clinical trial design and administration, public–private partnerships, workforce, and participation in manufacturer associations.

The checklist then covers product approval and NRA regulations, and specifically whether the regulatory authority is minimally functional. First, manufacturers are assessed on how they perform postmarket surveillance, approve clinical trials, etc. Second, the working relationship between the NRA and the manufacturers is assessed, including the understanding of the manufacturer of both national regulatory as well as WHO prequalification requirements. Finally and most importantly, the checklist assesses whether there is regional harmonization and integration of regulatory approvals.

The final section of the checklist assesses the national vaccination communication system. This is critical for a fully effective system for both influenza prevention and pandemic preparedness and, most importantly, helps build confidence in vaccination.
Claudia Nannei and Chris Chadwick concluded by informing participants of the steps currently being undertaken to pilot test the checklist in Mexico and Indonesia. It will then be utilized in other countries as part of the GAP and lead to the development of a compendium of adaptable policy options available to policy-makers and vaccine manufacturers to ensure sustainability.

Discussion

In response to a query about potential countries to pilot test the checklist, it was clarified that contact had been initiated with Serbia, South Africa and Brazil.

A comment noted that the main challenge was to coordinate all relevant departments and stakeholders, who often work independently. This was indeed why this single checklist had been developed.

4.2 Local vaccine production in middle-income countries: an economic evaluation of cost

Dr Lisa Munira presented the findings of a recent study that looked at establishing local vaccine production in middle-income countries from a cost-per-dose view. The study reviewed vaccines in general and was conducted through a questionnaire to DCVMs.

Few studies have looked at local vaccine production and the issue of costs. A landmark study, conducted in 1997 by Julie Milstien and colleagues, looked at the viability of local vaccine manufacture in which they identified seven factors for viability: (1) economics/scale and product portfolio; (2) GMP and consistency of production; (3) historical ability and systems in place to access new technologies; (4) historical performance to meet demand and to scale up production; (5) credibility of quality and the power of the National Control Authority; (6) management structure; and (7) legal status and adequate autonomy. More interestingly, the study refuted two general assumptions for local vaccine production: the first being that the main barrier of viability is the lack of funds, and the second that a large captive market is necessary for a viable producer. Their study concluded that the most important element is total GMP or national wealth as well as government commitment to invest in local vaccine production.

Other studies conducted by Richard Mahoney and colleagues looked specifically at the cost of vaccine production. The first study in 1990 reviewed the cost of plasma-derived hepatitis B vaccines and the second, in 2012, estimated the potential market of dengue vaccines. The studies presented an interesting economic analysis of vaccine production costs, and found that vaccines could be made available at prices affordable to developing markets. The findings seem to support that fixed costs make up a large proportion of vaccine production costs and that scale plays an important role in the final cost of a vaccine.

Indeed, Dr Munira showed a graph on monovalent influenza vaccines showing that, in general, production costs are strongly linked to the size of the manufacturing capacity: as manufacturing capacity goes down, the cost of production goes up. Thus for small manufacturers, the cost of a trivalent influenza vaccine is estimated at US$ 5–7 compared with US$ 2.5–3 for large manufacturers. It is assumed that these costs do not necessarily represent amortization of capital, R&D, etc., but materials and labour costs. It suggests that the cost of influenza vaccine manufacturing depends on volume and therefore on the market it needs to gain.

Dr Munira presented the findings of her recent study based on a questionnaire. The first question divided the costs into four different scenarios based on capital cost to build a new facility with different production scales. The second question concerned the R&D costs of bringing a product to market, and the third question related to the average failure or success rate of such a development. The final question looked at the costs associated with filling. A graph presented the average cost per dose stratified by the scale of production according to the presentation of the vaccine (i.e. multi dose, single dose, pre-filled syringe etc.); and the type of vaccine (bacterial, viral, traditional, new).
The preliminary findings suggest that capital expenditure plays a big role in determining the cost per dose. Production costs of new vaccines are consistently higher than that of traditional vaccines. The findings, while only estimates, suggest that bacterial vaccines in small volume are relatively more expensive than the same volume for viral vaccines. The analysis includes an economic opportunity cost where attrition costs or failure rates are considered as well as an amortization of capital costs.

The second part of the study looked at the economic benefit of procuring antigens and then filling locally as opposed to procuring finished vaccines. The responses show that the economic benefit is not the same across manufacturers, although the economic benefit of a fill-finish model is relatively higher than a new vaccine at a larger scale.

Dr Munira concluded with an overview of the next steps in the study: to engage more respondents to verify the consistency of the findings; to engage with an individual manufacturer for a more in-depth cost–benefit analysis as the methodology; and to do a regression analysis to identify factors that contribute to, or inhibit success of local production in middle-income countries.

Discussion
A suggestion was to look at affordable costs of vaccines as the target for manufacturers beyond production costs.

4.3 Establishing local production of influenza vaccines in Nicaragua
Dr Igor Krasilnikov provided an overview of the St Petersburg Scientific Research Institute of Vaccines and Sera and its influenza vaccine technology programme, and a joint project between the Institute and Nicaragua for technology transfer of influenza vaccine.

The project is supported by the Government of Nicaragua and the Ministry of Health of the Russian Federation. The technology from Russia will be transferred to the Institute in Nicaragua where a facility is being built. Efforts are being carried out to build the capacity of the Nicaraguan NRA to be recognized as functional by WHO, together with regional reference centres in Cuba and Argentina. The WHO Office for the Americas (PAHO) is also supporting this project.

Dr Krasilnikov described the specific activities such as training that would be conducted. His colleague, Vitaly Granovskiy informed participants of the current stage of developing the design of the facility. The fill-finish facility should be constructed by the end of 2015 and commissioned in 2016. At the same time, the vaccine produced in St Petersburg will be registered in Cuba because the Cuban regulatory authority is considered the reference centre for biologicals at the PAHO level. They then intend to become a supplier to the revolving fund of PAHO. The second stage will be to construct full-scale production in Nicaragua with the antigens production facility.

Discussion
It was noted that the WHO prequalification programme was a prerequisite to use the United Nations agency system. The manufacturer should engage with the WHO prequalification department early in the development. While PAHO currently has a separate system for vaccines purchased through the revolving fund, it is moving towards the WHO system.

4.4 Overview of seasonal market and procurement
Atika Abelin, Claudia Nannei and Julie Villanueva presented different aspects of seasonal markets and procurement.

Dr Abelin presented an overview of the IFPMA Influenza Vaccine Supply (IVS), an industry association comprising 19 vaccine manufacturers around the world, and the outcome of a dose distribution survey conducted by the IVS Task Force. The lack of global data on vaccination coverage worldwide led IVS to start this exercise in 2004 with the objective to gather data from its members about vaccine dose distribution worldwide. Data from 2010-2011 were published in *Vaccine* in 2014.
The methodology consisted of a survey sent to members to ascertain the number of doses distributed in 157 WHO Member States. Data were gathered over a calendar year, rather than during northern and southern hemisphere seasons. A graph of consolidated data from 2004–2011 broken down by WHO region showed an overall increase in the doses of influenza vaccine distributed, and that this increase was mostly located in the Americas. However, Dr Abelin pointed out that in the WHO regions of Africa, the Eastern Mediterranean, and South-East Asia, which represent 47% of the world’s population, only 3.7% of the population is vaccinated against influenza, if doses distributed are used as a proxy for coverage.

These data also show a decrease in the usage of influenza vaccine in the European Region as well as in the Eastern Mediterranean Region since the H1N1 influenza pandemic. This was a worrying trend for both companies and health authorities in their need to meet their targets for seasonal influenza vaccination. Thus, while there is an overall increase in influenza vaccine use on a global scale, there is disparity when this is broken down between the different WHO regions. This also means that few countries are reaching 75% coverage of elderly and at risk populations as recommended by the WHO Strategic Advisory Group of Experts on immunization (SAGE).

Dr Abelin suggested that more data need to be generated through surveillance in WHO regions to generate disease burden and health economics studies, as well as to document seasonal influenza cases in order to strengthen policies. She also pointed out that vaccination coverage of health workers remained unsatisfactory; IVS had initiated collaboration with the World Medical Association to advocate the importance of seasonal influenza vaccination. She finished by stating that seasonal influenza vaccination was an essential link in maintaining production capacity for pandemic preparedness and that countries should be encouraged to promote this by generating the right data and documenting the importance of prevention.

Ms Claudia Nannei shared data provided by the PAHO revolving fund, a procurement mechanism for vaccines and other health technologies in the Latin American region. The distribution between northern and southern hemisphere vaccine use was illustrated, along with expected changes in hemisphere for some central American countries. Annual purchase of vaccines by the PAHO revolving fund from 2006 to 2014 show that influenza vaccine procurement increased significantly, to 95 million doses in 2014. The price paid by the revolving fund was US$ 1.42–4.6 per dose for both the southern and northern hemispheres. The pooled procurement has clearly enabled PAHO to lower the price of the vaccine. Currently 30 of the 35 countries in the PAHO region use the PAHO revolving fund to procure their vaccines. Only the USA, Canada, Mexico, Brazil and Argentina do not participate in this Fund.

Dr Julie Villanueva gave an overview of data available on the CDC web site (www.cdc.gov/flu/). In the USA, around 21 different vaccine formulations are approved by seven different manufacturers. CDC receives data on the total number of influenza vaccine doses distributed in the USA by week. However, it was underlined that CDC does not get product specific data by vaccine manufacturer and distributor. The site shows weekly how many vaccines have been distributed. Another feature is the ability to compare the total number of doses distributed over time, even comparing retroactively. Coverage data can also be estimated utilizing data from four different nationally recognized surveys. As data are collected, they will be available on this website.
4.5 Cost effectiveness and budget impact of quadrivalent vs trivalent vaccine in developing countries

Jan Hendriks presented an overview of a recent study commissioned by WHO to look at the cost-effectiveness of TIV versus QIV. The question posed by the study is “under which scenario’s will QIVs be cost-effective compared to TIVs in low and middle income countries from a societal perspective?”

The study was a modelling simulation study conducted in collaboration with the University of Western Australia, the National Institute of Communicable Diseases in South Africa and the University of Groningen in the Netherlands.

The method employed is called a community model. A simulation is done where real communities are mimicked by individual-based multi strain influenza simulation models. The comparisons that are made are: what happens if you do no vaccination versus TIV vaccination versus QIV vaccination? This information is then put into an economic analysis model to determine cost and cost-effectiveness.

Methodologically speaking, the perspective is from the societal public health perspective, the costs analysed are vaccine procurement and delivery costs, treatment, hospitalization and also the costs due to losses of productivity when a person get ill due to influenza. The benefits are expressed in quality of life loss related to influenza, also called QALYS, Quality Adjusted Life Years. A short budget impact analysis was also performed.

Three “communities” were studied in the model: one community in a high income country (Australia); one community in an upper middle income country (South Africa) and one community in a lower middle-income country (Viet Nam).

He presented some preliminary results to participants but warned them of study limitations and that the model was still being finalized.

4.6 Vaccination in pregnancy

Dr Joachim Hombach reiterated the importance of cost-effectiveness with regards to maternal immunization as well as other at-risk groups. WHO will soon provide an update to SAGE on its activities on maternal immunization. Dr Hombach also highlighted a recent conference convened by

Discussion

In response to a question on whether a decrease had been observed in the European region after 2011, Atika responded that this was indeed the case and that data from the European CDC showed that only the United Kingdom and the Netherlands were achieving the coverage objective of the European Commission recommendations. She also pointed out the wide gap in coverage between western and eastern European countries, and noted that a meeting in Luxemburg would be held in April 2015 for a high-level stakeholders discussion on this issue. Part of the meeting would focus on issues related to seasonal influenza vaccination to identify problems, drivers, bottlenecks for vaccination, and to encourage countries to share best practices. In addition, given that the influenza market in Europe is being commoditized, it is increasingly a tender market for most countries, which are under pressure to decrease prices. Some manufacturers have started to exit the European market which is not a good sign for the international community and for influenza preparedness. It is hoped that the Luxemburg meeting will result in commitments from Member States.

It was suggested that a more in-depth analysis was needed to identify problems at a country-by-country level, starting from whether countries had a goal. Atika agreed, adding that IVS was updating the data published last year. Among follow-up actions, it was decided to visit some countries performing well and others having problems. Interviews would be run with some leaders and policy-makers in order to understand the problems and what triggers would be necessary for a successful vaccination policy. The outcomes will serve for future discussion on these issues.
the Bill & Melinda Gates Foundation (BMGF) on maternal immunization, which included influenza and other vaccines in the pipeline with a focus on implementation.

He reiterated the difficulties in precisely describing the burden of disease due to influenza in both young children and pregnant women. Estimates exist for pregnant woman in terms of the increased risk of seasonal flu hospitalization, although hospitalization does not necessarily indicate severe disease. WHO was holding a consultation the following week to carefully review these disease burden data.

Joachim Hombach reminded participants of the WHO recommendations issued in 2012 that encouraged countries introducing or expanding vaccine coverage to prioritize pregnant women. One reason for this is that it is considered operationally more feasible, particularly in low-income settings, than reaching out to other priority groups for flu vaccination, even though it may require significant investment in education, communication, etc. It is operationally more feasible because the vaccine can be delivered through antenatal care as has been demonstrated through maternal and neonatal tetanus programmes.

Recent data were then presented showing countries that have influenza vaccination policies. Recommendations are in place in the Americas and Europe, whereas most of the African and Asian regions have no recommendations. Data from the Joint Reporting Form on reported immunization of pregnant women, including coverage, were also described.

With regards to evidence, some key BMGF-sponsored maternal influenza immunization trials were outlined. Following the proof-of-concept trial in Bangladesh, which showed a significant impact in preventing influenza illness of the mothers and on birth outcomes, BMGF sponsored three larger randomized studies in Nepal, Mali and South Africa to corroborate these findings. On overview was provided of the data available from the South African study, which looked at HIV-infected and non-infected mothers. The uninfected study showed a very high influenza attack rate in the placebo group of 3.6% versus 1.8–1.9% in the vaccinated group. Vaccine efficacy was 55% among the women and 46% among the infants. Interestingly and contrary to what was described in the Bangladesh study, there was no difference in newborn weight or prematurity. In the HIV-infected cohort, vaccine efficacy was high at 71%. The influenza attack rate was 17% in the placebo versus 7% in the vaccinated group. There were too few outcomes to look at children. The vaccine was safe for both groups. These are very encouraging data and more data from the studies in Nepal and Mali are expected to become available this year.

Dr Hombach then outlined some of the key activities being conducted on maternal influenza immunization across WHO departments including work on burden of disease, vaccine safety and performance, impact and economics, implementation, regulation, manufacturing and data review and synthesis.

Following the GAVI vaccine investment strategy review of influenza and the call for better data, WHO has conducted reviews on a variety of subjects: burden of disease, impact of other pregnancy interventions on birth outcomes, methodological issues related to vaccine studies in pregnancy, and a maternal immunization vaccine effectiveness assessment.

WHO has also started to work on creating a manual to estimate the economic burden and on providing guidance for economic evaluation to support countries to generate evidence.

With regards to vaccine safety, a major review conducted by the Global Advisory Committee on Vaccine Safety was published which found no safety concerns.1 WHO has also initiated an effort to harmonize adverse events following immunization in relation to maternal immunization in collaboration with the Brighton Collaboration.

With regards to policy and implementation WHO has started to draft implementation guidance for maternal immunization programmes. Detailed data are being gathered on best practices for maternal immunization from case studies, and work is ongoing to integrate maternal immunization into new WHO antenatal care guidance documents. Work is also ongoing to strengthen national immunization technical advisory groups (NITAGs) to generate a database and information that they can use for decision-making.

WHO is also working to create a more favourable regulatory environment. A consultation was held in July 2014 on flu vaccines for pregnant and lactating women around questions on clinical data requirements for product labelling. Language in these sections may discourage general practitioners to use the vaccine. The discussion therefore sought to identify tools to promote more permissive language and any data needed to support this. Efforts are also under way to update WHO’s general guidance on clinical evaluation of vaccines and to strengthen them in terms of the rationale for running clinical studies in pregnant women.

Another activity at WHO focuses on ensuring an all-year supply of vaccine, which is particularly important for pregnant women. The vaccine should be made available before the peak of the season and hopefully also whenever pregnant women present for antenatal care. WHO has held discussions on this issue with experts in regulation, manufacturing, public health, and epidemiology. A key outcome of the discussions was that a relatively modest increase in shelf life could actually close the gap when vaccine is not available. Another simple option is to do a late filling to extend the period. These are relatively straightforward options that now need to be discussed and put into practice.

Dr Hombach concluded his presentation by thanking his colleagues involved in these projects.

4.7 Vaccinating children < 2 years: LAIV age de-escalation and the use of adjuvants

Dr Gary Grohmann presented the outcomes of a WHO meeting held in December 2014 to assess LAIV to prevent paediatric influenza disease in low- and middle-income countries. The meeting also reviewed relevant data on influenza vaccines in children to identify gaps and see how LAIV might be used in paediatric immunization programmes.

A brief overview was given of two LAIVs, one from MedImmune that was evaluated in children under the age of 2 showing wheezing as a safety signal; and another from SII that has been evaluated for safety and efficacy in children aged 2–5 years in Bangladesh and Senegal.

Dr Grohmann reminded participants that the highest burden of severe influenza disease is in children under the age of 2 and that no licensed vaccine exists in children under the age of 6 months. Licensed IIV in infants 6 months and above are often suboptimally immunogenic, and currently LAIV is only available for children > 2 years of age. Until 2014, LAIV from Medimmune had superior efficacy in children to IIV in clinical trials. In 2014, Canada, Germany, Israel, the United Kingdom and the USA preferentially recommended LAIV for children. However, important developments have taken place since the meeting in December 2014: the ACIP (Advisory Committee on Immunization Practices) removed in February 2015 its preferential recommendation for LAIV in the USA for the next season; a recent study in the United Kingdom has shown that LAIV is safe for children > 2 years of age with either egg allergies or asthma; and an adjuvanted inactivated influenza vaccine (Fluad) was licensed in Canada in January 2015 for the use in children 6 months to 2 years of age.

The meeting aimed to discuss evaluating effectiveness and safety of LAIV in children < 2 years of age. Wheezing is the safety signal of most concern. With regards to efficacy, Dr Grohmann noted that the efficacy estimates for H1N1 virus between Bangladesh and Senegal varied from very significant to not significant respectively. The investigators were unable to identify a cause for this discrepancy and numerous explanations offer no conclusive answer. Some unexpected effectiveness findings with MedImmune’s LAIV in US studies also yield unexpectedly low effectiveness against the H1N1, for which there is no clear explanation bar some explanations by the manufacturer. It cannot be assumed that the MedImmune and SII LAIVs have identical efficacy and safety profiles. Recent work from David Wentworth from CDC was presented to explain these issues related to MedImmune’s LAIV.
With regards to age de-escalation of LAIV, the meeting suggested using the lessons from rotavirus vaccine development with regards to risk–benefit by location, and noted that post-licensure surveillance would be critical for vaccination below the age of 2.

During the December meeting, PATH proposed to conduct a Phase II safety trial in 300 children from 12 to 23 months of age with investigation of wheezing outcomes, SAEs, hospitalizations and solicited and unsolicited adverse reactions. After a review of safety data, the study would proceed to a Phase III efficacy and safety trial among 2000 children aged 12–23 months. Depending on the results, a larger study might assess wheezing in children before proceeding to even younger children, the evidence of which may even allow studies to proceed cautiously in the 6–11 months age group.

The meeting recognized the overall unmet need for influenza prevention in young children, especially those under 2. A cautious stepwise age de-escalation study with LAIV in the <2 age group is certainly needed, and a small safety study of 300 would be a prudent first step. There was general agreement that a study in children between 12 and 23 months old should be performed before those <1 year of age. To measure the benefit of the vaccine, 300 subjects were unlikely to identify any significant safety signal or a sufficient number of influenza cases. It was also noted, although not discussed in detail, that adjuvants for IIV may also prevent influenza in children <2 years of age.

Dr Grohmann concluded by pointing participants to the summary of the meeting on the GAP website.

**Discussion**

Age de-escalation studies would be conducted using LAIV produced by SII, as studies carried out on MedImmune’s LAIV showed wheezing as a safety signal. The vaccines have a different backbone with a different attenuation.

**4.8 Panel discussion: efficient use of resources, including human resources, throughout the year**

*Panellists: P. Lee Ho, B. Taylor, P. Tyagi, G. Zettlmeissl*

The following key points were raised relative to how manufacturers manage their facilities and human resources when influenza vaccine production activities are inactive.

- Some manufacturers only experience a small downtime because they supply vaccines for both the northern and southern hemispheres.
- During downtime, revalidation of processes and equipment is required in some areas. Essential maintenance is carried out in both manufacturing and lab areas, as well as any process improvement projects that have been identified.
- Some companies have multi-use facilities that produce other antigens while they are not producing influenza vaccine. However, this requires significant capital investment.
- Some companies produce animal flu vaccines that can be of commercial benefit, e.g. flu vaccine for horses and, although expensive, provides training for the human manufacturing season.
- Opportunities exist to conduct formulation and fill-finish activities for a third party.
- Some manufacturers have considered that the cost of keeping employees year round is not economically feasible.
- Many companies use a system called “annualized hours”, basically buying hours from employees and paying them back based on actual hours manufacturing influenza vaccine.
- Regarding human resources, temporary staff can be recruited during the manufacturing season, although if a pandemic occurs off-season, trained staff may not be readily available.
- The 2009 pandemic showed the importance of keeping facilities alive throughout the year, especially for egg supply, in order to address the pandemic situation.
- The exact strategy will vary from manufacturer to manufacturer depending on its situation.
SESSION 5. ADJUVANTS FOR PANDEMIC PREPAREDNESS

5.1 Sustainable influenza vaccine manufacturing capacity worldwide: establishing an adjuvant hub

Ms Julie Schafer presented an overview of the adjuvant hub created by BARDA in collaboration with the Infectious Disease Research Institute (IDRI) in Seattle. The Hub could supply adjuvant as well as expertise in preclinical and clinical trials with adjuvanted influenza vaccines. BARDA sees this hub as an opportunity to make adjuvants available to manufacturers for dose sparing in a pandemic response. Ms Shafer handed the floor to Dr Chris Fox for further details on the hub at IDRI.

Dr Chris Fox described IDRI and its adjuvant programme, a stable oil-in-water emulsion adjuvant designed for 1:1 mix by volume with vaccine prior to immunization. The adjuvant is manufactured under current GMP (cGMP) conditions by microfluidization which has stability for at least five years under refrigeration. It has produced multiple cGMP batches, and Phase 3 clinical testing is planned within the year. Data showed significant dose sparing from ferret studies and a Phase 2 clinical trial with the Protein Sciences pandemic vaccine antigen.

IDRI has extensive experience with influenza, since two of its scientists were formerly employed in preclinical and clinical testing in the influenza division of CDC. Dr Fox presented a list of clinical trials in which IDRI had been involved in various adjuvants.

The adjuvant hub was presented, whereby IDRI supplies cGMP- and research-grade adjuvant to manufacturers for preclinical and clinical development. This includes technical support for physicochemical and biological assays such as SRID, particle size, deglycosylated SDS-PAGE, and visual appearance. These are designed to include adjuvants and to avoid associated effects in some of these assays. Technical support for preclinical and clinical development is also be provided. IDRI has HI and microneutralization (MN) assay expertise as well as expertise in animal studies (mice, ferrets, toxicology), clinical trial operational and technical support. Data from a modified SRID assay demonstrated that for at least 24 hours the formulation with adjuvant remained stable.

Manufacturers interested in collaborating with the IDRI adjuvant hub need to be at the appropriate development stage for their vaccine, and preferably not in the major optimization stages of vaccine manufacture. Scientists from IDRI can train manufacturers at their facility in Seattle and then on-site at the manufacturer’s facility to support assay development to adapt assays to account for adjuvant inclusion. Minimum equipment necessary on site includes a particle sizer, dynamic light scattering instrument to measure the size of the adjuvant, in addition to standardized assay equipment.

5.2 Critical steps for approval of adjuvanted pandemic vaccines

Gary Grohmann highlighted the potential of adjuvants for developing country vaccine manufacturers. They are good immune potentiators or immunomodulators and have been used for decades to improve the immune response to vaccine antigens. Adjuvants aim to enhance, accelerate and prolong the specific immune response of vaccine antigens. They are also used to optimize immune response to the induction of cytotoxic or helper T-lymphocyte responses and obviously to promote antibody responses.

A diagram presented the characteristics of an ideal adjuvant, i.e. its ability to increase antibody responses, memory helper T-cells and cytotoxic T-cells; to promote cross-talk between innate and acquired immune systems, and to prevent autoimmune diseases and induce non-pathological inflammatory responses. In addition to discussing safety, stability, bioavailability and cost-effectiveness, Dr Grohmann reviewed the landscape of adjuvants in use or used in the past: mineral salts, like aluminium hydroxide or calcium phosphate gels; oil emulsions such as MF59 or AS03; particulate adjuvants such as virosomes; microbial derivatives; endogenous human immunomodulators and inert vehicles like gold particles.

The preclinical stage for adjuvants is of prime importance. Registration occurs when all data are available on quality, non-clinical and clinical data for safety and efficacy. A Phase 4 study is often
required, as well as a post-registration study usually involving passive surveillance, pregnancy
registers, lot testing and so on. An overview of guidelines available from the EMA, FDA and WHO
on vaccines in general, as well as on adjuvants, was presented. Anyone starting an adjuvant
programme should be familiar with the guidelines and communicate regularly with the relevant NRA.

A complete chemical description of the adjuvant is required, together with a detailed plan for
manufacture of the adjuvant, including source material. Local guidelines need to be followed, e.g. on
minimizing the risk of transmissible spongiform encephalopathy (TSE) agents. Critical parameters
should be defined to confer the correct physical, biochemical, biological or adsorptive properties of
the adjuvant and generate some stability data.

For preclinical studies, the increased/modified immune response with the adjuvanted vaccine should
be demonstrated in a relevant animal model. Toxicity studies would be required for adjuvants with no
existing toxicology data, and/or in an adjuvanted vaccine repeat-dose toxicity study. Markers of
inflammation, toxicity information on pivotal organs, and local tolerance should be studied. If the
adjuvant is immunogenic, an appropriate test for hypersensitivity may be anaphylaxis assays or
immunoglobulin E (IgE). The adjuvant should also be tested for pyrogenicity. Non-clinical
immunogenicity data are expected by regulators. Other important studies are dose-response and
comparative studies to assess the effect of the adjuvant compared to vaccine alone. Studies in two
different animal models are also useful.

Regarding clinical study requirements, Dr Grohmann underlined that the inclusion of an adjuvant in a
vaccine must always be justified, especially the amount of adjuvant appropriate to enhance the
immune response to the antigen(s). A comprehensive study may be need if there is more than one
antigen, and if the adjuvant itself is immunogenic.

Assessment of the humoral immune response should include the detection and titration of functional
antibodies and, if possible, some subclasses, along with other properties of the antibody response like
avidity. Other important issues are the assessment of cell responses, the generation of dose-finding
studies, and sufficient data to demonstrate that the amounts of adjuvant and antigen chosen for further
study represent an acceptable balance between immune responses and the risk of adverse events.
These studies should also be performed in the target population for the vaccine.

Clinical trials should be randomized and double-blind, and performed in the final target population.
Conservative stopping rules, particularly when a new adjuvant is involved, also need to be in place.

The safety data should show the likely rates of reactions that may be expected based on the known
properties of the adjuvants and antigens. In some cases, it may be appropriate that the data focus on
immune mediated reactions. The risk–benefit relationship for the adjuvanted product should be at
least as favourable as that for the non-adjuvanted product. A postmarket surveillance programme
should also be in place.

Dr Grohmann finished by reiterating the importance of communication with the NRA and
understanding the relevant guidelines. While clinical studies and clinical safety assessments are
essential, non-clinical safety assessments are equally important, along with pharmacology and toxicity
studies. The added value of the adjuvant in any formulation must be demonstrated and there must be a
risk–benefit assessment.
Discussion
In response to whether an adjuvant needed to be approved as a standalone product, it was clarified that an adjuvant has to be approved with the vaccine.

Regarding the use of adjuvants in seasonal vaccines and the data needed, this depends on the adjuvant to be used and whether the seasonal vaccine is already licensed. If safety data for the adjuvant exist with other influenza antigens, a move to Phase III may be relatively rapid, although a Phase IV study would definitely be required.

In response to a question on the supply conditions of adjuvant from the hub at IDRI, it was clarified that, while these were still being reviewed, it was likely to be on a case-by-case basis, to respect the different DCVMN relationships with their respective governments and rules and regulations.

It was asked whether the manufacture of an MF59-like adjuvant is considered a new product. In most cases it would indeed be considered an entirely new product and preclinical studies would be needed. However, if the preclinical data are good along with other evidence, a manufacturer might be able to forgo a Phase I clinical trial, regulators might allow a modified Phase II trial and then go from there. Safety, and thus preclinical studies are extremely important.

It was noted that the use of adjuvants in seasonal vaccines may help overcome reluctance in the general population towards adjuvants. It will be interesting to see what data are generated from an ongoing Phase IV clinical trial of an adjuvanted seasonal influenza vaccine licensed in Canada for children under 2.

SESSION 6. INNOVATION AND VACCINES

6.1 Global vaccine development pipeline and universal vaccines
Rick Bright started by congratulating the partners and manufacturers for progress made towards establishing local production of influenza vaccines. He highlighted the burden of influenza infection for both seasonal epidemics and pandemics, stating that the mission is to stop morbidity and mortality caused by influenza virus. Influenza is particularly difficult to control due to the mutating nature of the virus and new subtypes are constantly emerging. This is why it is so important to build capability to respond to a pandemic. The influenza programme at BARDA started in 2006, prior to which there was no cohesive national strategy for influenza pandemic preparedness in the USA or other parts of the world. There was no prepandemic vaccine or antiviral stockpile programme and the USA had limited domestic manufacturing capabilities for seasonal vaccine or pandemic response. At that time, global vaccine supply was limited, and all licensed vaccines in the USA used egg-based technology. Today, there are cell-based, recombinant and adjuvant technologies.

BARDA understands the value that components other than vaccines play in halting and reducing the threat of influenza such as therapeutics, antiviral drugs, monoclonal antibodies, immunotherapeutics, respiratory devices, masks and diagnostics. As well as building capacity in the USA, BARDA has supported the GAP and capacity-building in low- and middle-income countries.

In addition to supporting egg-based factories, BARDA also supports capacity to produce cell-based influenza vaccines. It has partnered with Novartis to build the first cell-based vaccine production facility in the USA with the capacity to produce over 250 million doses as well as MF59 adjuvant for antigen sparing in a pandemic. BARDA has also launched three centres in the USA for advanced development and manufacturing of a number of vaccines for biodefense threats; in a pandemic situation, each of these centres will be made available to produce over 50 million doses of pandemic influenza vaccine within four months of the start of the pandemic.
He then presented a timeline showing the situation in 2005-2018 with regards to domestic vaccine manufacturing capacity. In 2014 the USA has about 500 million doses capacity and by 2018 they hope to be close to 700 million doses capacity, recognizing that 2 doses of vaccine might be required, the 700 million doses would be enough vaccine to immunize the entire US population.

Rick Bright then reviewed the technologies available for seasonal influenza. A number of suppliers use egg-based technologies and some use cell- and recombinant-based technologies. Many manufacturers are moving to the quadrivalent vaccine to have the second B strain included. One technology with transdermal or intradermal delivery is practically needle-free; a LAIV nasal spray is available; and a high-dose vaccine has been shown to be much more effective in older populations.

BARDA is working on faster development of influenza vaccine in the event of a pandemic. Recombinant-based vaccines will help because they do not rely on eggs, in some cases do not rely on traditional potency assays, and can span from sequence to vaccine lot release in about 12 weeks, as demonstrated during the response to the 2013 H7N9 outbreak in China. BARDA is also looking at backbones of seed viruses that can produce higher growth and higher yield vaccine. It supports the development of a number of alternative potency assays to SRID, which can be time consuming. In 2013 when many manufacturers made H7N9 vaccines, HPLC was used as an assay to release vaccine lots. Focus is also on an improved rapid sterility assay as it currently takes two weeks to conduct traditional sterility assays.

A presentation was made on BARDA activities to improve current vaccines that are vulnerable to virus change and shifting, provide minimal-cross protection to other sub-types and need to be updated each year. A graph on vaccine effectiveness as measured by CDC over the last 10 years showed an average efficacy of 46% over this period. Despite this, uptake of the vaccine has been increasing in the USA. A slide illustrated that about 90 new influenza vaccine technologies are under development in addition to the various new vaccines approved in the USA and in other countries. The next big focus at BARDA is the development of a universal flu vaccine, defined as a vaccine that provides safe, effective and long-lasting immunity against a broad spectrum of antigenically divergent influenza viruses in all age groups and people in high-risk groups. BARDA believes that progress towards this goal can be made by encompassing the information learnt over the last decade or two about influenza and about vaccine development. Potential targets for investigation were to identify epitopes that are conservative and cross protective; whether to use vectors; to include adjuvants; or evaluate different immunization schedules such as priming and boosting. A slide showed companies that are focusing solely on technologies to bring about a broader immune response.

There are many challenges in developing more effective influenza vaccines both on the scientific and regulatory side. New markers of immunity and new potency assays will be required. These may have to be produced in different ways, using different analytical methods and will probably require large-scale clinical studies. This will be a lot more expensive than for traditional vaccines. New partnerships must be created. Public/private partnerships will be formed in different consortiums on different technologies. Funding is a big challenge, as a new vaccine candidate is expected to cost over US$ 1 billion. BARDA is preparing to support a portfolio of these new technologies over the next 5–10 years towards licensure, and has two funding mechanisms available which can be found on the BARDA website (https://www.medicalcountermeasures.gov/).

1. A broad agency announcement (BAA) for the advanced development of a novel influenza vaccine candidate with the potential to stimulate broader and more effective immune responses than can currently available products. Proposals can be submitted to BARDA provided that a Phase I clinical study has been completed. The BAA is an ongoing submission opportunity that has already been open for three years, and is expected to be renewed in July 2015.
2. Requests for proposals for technologies that may be useful for development of these improved influenza vaccines, also depending on a Phase I completion.
BARDA is looking for a transformative approach in technologies or ways of using vaccines. As well as demonstrating safety, candidates should show 20% or greater efficacy above a licensed influenza vaccine comparator measured by clinical or surrogate endpoints. Another requirement is that the vaccine follows a US Investigational New Drug Application. All available preclinical and clinical data must be included in the BAA or request for proposals. Long duration immunity is sought with the immediate goal to provide protection for two or more years. Ideal candidate vaccines will also provide a prime before a pandemic, so that during a pandemic two doses of pandemic vaccine would no longer be needed.

**Discussion**

Some discussion was held about the significant financing that has gone into and will be needed for R&D for influenza vaccines. BARDA alone has invested about US$ 4–5 billion in this area since 2006, plus another US$ 2 billion on the stockpile. BARDA estimates that a further US$ 1 billion over the next 5–6 years will be needed to develop next generation immunotherapeutics such as monoclonal antibodies that would expand the treatment window for people infected with influenza. BARDA also believes that, to develop a more effective influenza vaccine, a portfolio of 5 to 7 candidates needs to be built, each of which will need US$ 300–500 million. While its financing is not guaranteed in the coming years, BARDA hopes to be able to provide some funds to advance the programme.

### 6.2 Barriers to development of next generation vaccines

Joachim Hombach presented the outcomes of several WHO consultations that had touched on broad-based and long-lasting influenza vaccines. While WHO has no active portfolio in this area for the time being, it is monitoring the field and has recently conducted reviews. The most recent WHO consultation on this topic was held in May 2014.¹ WHO also convened the first meeting of the WHO Product development for vaccines advisory group in September 2014² to advise on advancing priority vaccines in preclinical development. In addition, influenza was discussed at the first Global Vaccine and Immunization Research Forum held in March 2014, which tracks progress on vaccine and implementation research issues in conjunction with the global vaccine action plan.³ This action plan has a few indicators related to R&D. One of these indicators is to monitor progress towards a universal flu vaccine in protecting against drift and shift, with the target of having at least one vaccine providing broad spectrum protection against influenza A virus licensed by 2020.

The meeting on influenza vaccines that induce broadly protective and long-lasting immune responses discussed mechanisms of protection in natural influenza-virus infection and vaccine-induced immunity; antigens for humoral and cellular responses; new approaches to vaccine design; vaccine production; and novel routes of administration. Different perspectives on the definition of a universal flu vaccine were also discussed. For example, whether the aim is to look for a product that is really protective against shifts, or limited to the most common subtypes; whether to include influenza B; and how long the multi-year immunity should last. Is it reasonable to assume incremental developments towards more broadly protective vaccines without the type of transformational technologies referred to by Rick Bright?

It is clear that broader-based vaccines will require a broader array of antigens and different parts of the antigens, for instance a move towards the conserved regions of the HA and other epitopes and to elicit different immune responses. Obviously, these different immune responses need to be measured, which will require assay development. There was much discussion about vaccine platforms and

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¹ The Second WHO integrated meeting on development and clinical trials of influenza vaccines that induce broadly protective and long-lasting immune responses, 5–7 May 2014, Geneva. Selected presentations (www.who.int/immunization/research/meetings_workshops/2nd_influenzamtg_geneva_may14/en/).

² WHO Product development for vaccines advisory committee meeting, 7–9 September 2015, Geneva. Summary and presentations (www.who.int/immunization/research/meetings_workshops/pdvac/en/).

delivery technologies. Also important is the potential of prime-boost technologies and for instance the viral vectors that might actually benefit in a prime-boost strategy even with conventional inactivated flu vaccines.

General considerations discussed related to the assessment of heterosubtypic immunity. It appeared that no real consensus was reached on what would constitute a primary clinical benefit, from the public health side, of a universal flu vaccine. Would there be success, for instance, if severe illness could be prevented versus only lab confirmed illness of any severity. This is a significant challenge: no current vaccine has been licensed on the basis of prevention of severe disease. This may be considered a disadvantage if a vaccine just works against severe diseases while transmission is still maintained.

The ability to compare the efficacy of one vaccine to another should be developed, hopefully avoiding the need for large-scale efficacy studies in each case, which of course calls for correlates of protection. However, these will likely differ according to the type of vaccine. A further challenge is how to demonstrate cross-strain protection: will large, multi-year studies or other avenues be needed, and will the issue of prior history of influenza infection in conjunction with clinical efficacy trials be addressed?

The meeting also raised questions related to the usefulness of animal studies as well as regulatory pathways to facilitate licensure of successful candidate vaccines. How would these vaccine be evaluated, compared with traditional vaccines? Would different vaccines be needed for different population groups? A major conclusion of the meeting was the need for a “roadmap” with a better definition of these new vaccines, and a basic definition of study endpoints. It was believed that the costs for full development of a universal flu vaccine would be very high.

With regard to the role of WHO in this field, the Product development for vaccines advisory committee recommended that WHO create preferred product characteristics to develop desirable target products profiles that would guide manufacturers/developers in their product development as well as to coordinate the standardization of endpoints and consensus on regulatory pathways.

**Discussion**

It was queried whether a broad or universal flu vaccine would be licensed in a gradual way to show protection against different strains. A developer of a universal flu vaccine could spend a long time showing broad-spectrum against a number of different strains before applying for licensure. Or could they show that their vaccine is as good as or better than an existing traditional vaccine, obtain licensure and then progressively show that it is effective year upon year?

It was noted that, as part of the European consortium, a workshop would be held in June at NIBSC to discuss assays and harmonization. The European Commission is also putting research funding into the development of broadly reactive influenza vaccines. Currently five projects have been financed, averaging 5 million euros per project and involving European regulators from the beginning.

**6.3 Epidemiology of new potentially pandemic strains**

Wenqing Zhang presented an overview of the current situation at the human/animal interface for influenza. She reminded participants that minor changes in the virus leads to antigenic drift which requires adaptation of influenza vaccine viruses for the vaccine to be effective and that major changes in influenza A viruses can cause pandemics.

She presented a snapshot of zoonotic influenza infections. For H5N1, since 2003 there were 794 cases with an overall Case Fatality Rate (CFR) of 55%. Since 2014, there were 3 human cases of H5N6 recorded in China. Since 2013, there are a total of 631 cases of H7N9 with a CFR of 32%. There are also non-seasonal zoonotic influenza infections reported since 2014, for example H9N2, H10N8 and variant virus H3N2 and variant H1N2. She then presented more detailed slides by subtypes.
She started with Influenza A(H5) and presented a map of outbreaks in animals since 2014, showing that the H5 virus was spreading from South Eastern Asia to North America and that there was also re-emergence of H5N1 virus in Nigeria. She presented detailed genetic clade information and epidemiology data for H5 outbreaks in animals and in humans showing the geographic spread. She also presented a list of H5 candidate vaccine viruses that had been developed.

She then moved on to H7N9 and showed the epidemiologic curve and map of human cases since March 2013. The majority of cases of H7N9 were in older age groups with a median age of 57 years, 74% of cases were severe, critical or fatal (with CFR of 32%). With regards to risk factors, 72% reported having history of exposure to poultry or poultry markets. She also presented the phylogenetic tree of HA genes which showed that H7N9 viruses were clustered into two different sub-clades. She showed the candidate vaccine viruses for H7N9 and noted that they had not been successful in producing CVVs through classical reasortment but that efforts were still ongoing.

She then presented on other zoonotic influenza viruses circulating including H9N2 and H3N1, for which candidate vaccine viruses are available or under development.

She informed participants that these candidate vaccines viruses are available free of charge to all the manufacturers upon request.

In summary, Dr Zhang noted that the pandemic threat was still present and could hit at any moment. The response strategy to an influenza pandemic needs to be rapid and efforts on R&D need to be sped up.

**Discussion**

Several comments were made about the current outbreak of H1N1 influenza in India. WHO has been working with the country office to assess the situation. The outbreak which demonstrates that seasonal epidemics can be very severe and the need to increase seasonal vaccination in countries such as India.

**6.4 Panel discussion : are we ready to deal with new potentially pandemic strains?**

Rick Bright introduced a comprehensive risk assessment process used in the US department of health and human services to understand pandemic preparedness activities. The process uses a tool called the Influenza Risk Assessment Tool (IRAT) which assesses the potential pandemic risk posed by novel emerging viruses. The risk is assessed based on two scenarios: 1) the risk of a virus mutating to acquire an ability to spread easily and efficiently in people and 2) what the public health impact might be in terms of the potential severity of human disease. Through a working group of key stakeholders, the CDC has identified variables that should be considered when assessing the risk of potential viruses including whether genomic variation is occurring, transmission in animals, particular receptor binding properties, susceptibility or resistance to current drugs, disease severity and pathogenesis, existing population immunity and antigenic relationship to current vaccine candidates. Through this process, each viral strain is given a number and heat maps are generated showing which viruses are of most concern. Because the timeline to make influenza vaccines is several months, this risk assessment tool helps to prioritize which viruses pose the greatest threat and enables candidate vaccine viruses to be prepared in advance which can shave of 4-6 weeks if needed. If a virus is assessed to be an even higher risk, clinical lots of that vaccine can be made. This gives the manufacturers critical experience with these newly emerging strains and information can be gathered on what the dose might be and whether one or two doses would be required. This can shave off about 12 to 14 weeks on the response. If a super-high threat is identified then the US Government might ask manufacturers to make full scale lots and stockpile those lots.

Julie Villanueva added that the risk assessment through IRAT is re-run whenever new data becomes available. She also added that in September 2014, there was a Morbidity and Mortality Weekly Report (MMWR) called the updated preparedness and response framework for influenza pandemics. This MMWR provides much greater detail and clarity regarding any potential timing of key decisions or
actions which need to happen to help slow the spread of disease or mitigate the impact of a pandemic. It also provides information on the IRAT. The document is also in alignment with WHO pandemic phases which were restructured in 2013. She mentioned through collaboration with BARDA, CDC is continuing to increase its capacity for gene sequencing and synthesis. With this technology CDC can now obtain and synthesize these sequences very quickly and share internationally. CDC have bilateral grants with over 40 countries across the globe to understand disease burden and to establish and strengthen surveillance. Rapid detection is incredibly important across the globe and we need to ensure that we all have the tools and the training to be able to detect an emerging influenza virus.

Larisa Rudenko reiterated that the two key factors for a virus to cause a pandemic is “no immunity” and “human-to-human transmission”. From her point of view, there are two viruses of key concern: H2N2 - because people younger than 60 years old have no immunity and H7N9 - because with one or two mutations this virus could become transmissible from human-to-human. She then stressed the importance of preparing a full collection of potential candidates for inactivated and for LAIV vaccines and taken these through preclinical and phase I clinical studies so that in the event of a pandemic this collection would be available for any manufacturer to produce vaccine in a more timely way.

Bruce Gellin agreed with the points raised by the former panelists and added that beyond the risk assessment and preparation of CVVs we need to consider the deployment and use of vaccine in the event of a pandemic. Ensuring public confidence in the vaccines through clear communication is critical.

Wenqing Zhang described some of the findings of the IHR review committee with regards to the response to H1N1 pandemic. The review committee made a long list recommendations to make the world better prepared for the next pandemic and WHO currently is following up those recommendations. In collaboration with CDC and the European Commission, WHO is developing a flu risk tool to be used by countries similar to the IRAT used by the USA. The tool is being pilot tested during this Northern Hemisphere influenza season and will continue to be pilot tested each season and updated as necessary so it will be ready to use in the event of a pandemic. She also provided a brief overview of the PIP framework which was adopted in 2011. The framework has mobilized resources to support pandemic preparedness. Among other areas, resources are being directed towards regulatory system strengthening, laboratory surveillance and burden of disease studies in developing countries. WHO also continues to work on CVV issues, and issues recommendations for the development of new CVVs when required. This allows manufacturers to gain experience in production of these new subtype CVVs and allows stockpiling of vaccines in case the next pandemic virus is antigenically the same or similar.

Othmar Engelhardt added some points regarding the work done by the WHO ERLs on CVV and reagents preparation. While we are better prepared than we were several years ago, influenza viruses are constantly evolving. Some of these emerging viruses are genetically unstable when you put them into eggs. There is still quite a lot of work to do to improve CVV production, such as to improve yields and obtain high growth reassortants as well as potency testing and reagent development which can take time to develop. Another issue is safety testing of CVVs, the current models for the safety testing aren’t ideal and there have been examples where the ferret model is not sensitive enough to detect the attenuation of a reassortant. So we need to work on refining these models. He also stressed the importance of surveillance in detecting these emerging viruses.

**Meeting Wrap-Up**
The chair acknowledged the extraordinary progress made as a result of this programme. He thanked the manufacturers and all partners involved for their efforts. He then thanks participants and presenters and panelists for their active participation in the meeting.
Concluding remarks
Marie-Paule Kieny thanked the chair and attendees for their participation. She stressed the importance of the coming years with only a small window left of availability for continued financial and technical support for manufacturers. Once the GAP programme closes in 2016, WHO will continue to support manufacturers looking at policy and sustainability. Technical support from PATH and WHO will also continue for a short time to assist manufacturers with vaccines in clinical development to get their vaccines to licensure.

She acknowledged the great strides that had been made over the last 10 years under objective 2 of the GAP and technology transfer to build influenza vaccine production capacity in developing countries. In particular she thanked BARDA for their support and the TAG for their continued guidance.
ANNEX 1: PROGRAMME
Chair: Dr Gary Grohmann

Tuesday, 17 March

SESSION 1: INTRODUCTION
9:30 – 10:10 Welcome address and opening remarks (Dr Marie-Paule Kieny)
WHO Technology Transfer Initiative: progress to date (Mr Guido Torelli)
GAP: progress and issues (Dr Bruce Gellin)

SESSION 2: ADDRESSING BOTTLENECKS
10:10 – 11:10 Experiences with H7N9: time from announcement of strain to availability of CVVs and assays (Dr James Robertson)
Alternatives to SRID for potency testing (Dr Othmar Engelhardt)
Improving the strain selection process (Dr Wenqing Zhang)
11:45 – 12:15 Panel Discussion: reducing the time from start of a pandemic to availability of a vaccine

SESSION 3: MANAGEMENT AND CONDUCT OF CLINICAL TRIALS
12:15 – 12:45 Resources available for planning clinical trials (Ms Erin Sparrow)
Common challenges for the sponsor in the conduct of clinical trials (Dr Rahnuma Wahid)
Conducting clinical trials: training session for manufacturers specialists
14:15 – 15:45 Early phase clinical trials (Dr Rahnuma Wahid)
Late phase clinical trials (Dr Martine Denis)
16:15 – 16:50 Quiz: managing and conducting influenza vaccine clinical trials
Wrap-up

Seminar
17:15 – 17:45 International proficiency study of the SRD test for manufacturers and regulators from developing countries (Dr Laszlo Palkonyay)
19:00 – 20:00 Networking cocktail

Wednesday, 18 March

SESSION 4: SUSTAINABILITY OF PANDEMIC INFLUENZA VACCINE PREPAREDNESS
9:00 – 10:15 Creating the environment for sustainable production (Mr Christopher Chadwick and Ms Claudia Nannei)
Cost of production (Ms Liza Munira)
Establishing local production of influenza vaccines in Nicaragua (Dr Igor Krasilnikov)
Overview of seasonal market and procurement (Dr Atika Abelin, Dr Julie Villanueva, and Ms Claudia Nannei)

Expected changes in seasonal uptake
10:45 – 11:45 Cost effectiveness and budget impact of Quadrivalent vs Trivalent vaccine (LAIV and IIV) in developing countries (Mr Jan Hendriks)
Vaccination in pregnancy (Dr Joachim Hombach)
Vaccinating children <2 years – LAIV age de-escalation and the use of adjuvants (Dr Gary Grohmann)

Use of resources
11:45 – 12:15 Panel Discussion: efficient use of resources (including human resources) throughout the year
SESSION 5: ADJUVANTS FOR PANDEMIC PREPAREDNESS
13:45  14:30  BARDA adjuvant supply hub (Ms Julie Schafer)
       Critical steps for approval of adjuvanted pandemic vaccines (Dr Gary Grohmann)
       Discussion

SESSION 6: INNOVATION AND VACCINES
14:30 – 15:20  Global vaccine development pipeline and universal vaccines (Dr Rick Bright)
       Barriers to development of next generation vaccines (Dr Joachim Hombach)
       Epidemiology of new potentially pandemic strains (Dr Wenqing Zhang)
15:00 – 16:20  Panel discussion: are we ready to deal with new potentially pandemic strains?
16:20 – 16:30  Wrap up
16:30 – 16:35  Concluding remarks
ANNEX 2: LIST OF PARTICIPANTS

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