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

Cancun, Mexico, 4-5 May 2011
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# Abbreviations and Acronyms

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<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>ASPR</td>
<td>Assistant Secretary for Preparedness and Response</td>
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<td>BARDA</td>
<td>The Biomedical Advanced Research Development Authority</td>
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<td>BIRMEX</td>
<td>The Laboratorios de Biologicos y Reactivos de México</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>Centers for Disease Control and Prevention</td>
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<tr>
<td>CHMP</td>
<td>Committee for Medicinal Products for Human Use (CHMP)</td>
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<td>DCVM</td>
<td>Developing Country Vaccine manufacturers</td>
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<td>FDA</td>
<td>Federal Drug Administration</td>
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<td>GADI</td>
<td>Global Adjuvant Development Initiative</td>
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<td>GAP</td>
<td>Global Action Plan</td>
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<td>GMP</td>
<td>Good Manufacturing Practice</td>
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<td>GPO</td>
<td>Governmental Pharmaceutical Organization (Thailand)</td>
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<td>HHS</td>
<td>US Department of Health &amp; Human Services</td>
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<td>IIV</td>
<td>Inactivated Influenza Vaccine</td>
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<td>IVAC</td>
<td>Institute of Vaccines and Medical Biologicals</td>
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<td>LAIV</td>
<td>Live Attenuated Influenza Vaccines</td>
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<td>MPLA</td>
<td>Monophosphoryl Lipid A</td>
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<tr>
<td>NIAID</td>
<td>National Institute of Allergy and Infectious Diseases</td>
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<td>NIH</td>
<td>National Institutes of Health</td>
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<td>NRA</td>
<td>National Regulatory Authorities</td>
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<td>NVI</td>
<td>Netherlands Vaccine Institute</td>
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<tr>
<td>PCAST</td>
<td>President's Council of Advisors on Science and Technology</td>
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<tr>
<td>QA</td>
<td>Quality Assurance</td>
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<td>QC</td>
<td>Quality Control</td>
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<td>PATH</td>
<td>Program for Appropriate Technology in Health</td>
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<td>PCR (PAGE 11)</td>
<td>Polymerase Chain Reaction</td>
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<tr>
<td>R&amp;D</td>
<td>Research and Development</td>
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<td>RIVM</td>
<td>National Institute for Public Health and the Environment</td>
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<td>SII</td>
<td>Serum Institute of India</td>
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<tr>
<td>SPF</td>
<td>Specific Pathogen Free</td>
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<td>WHO</td>
<td>World Health Organization</td>
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<tr>
<td>VLP</td>
<td>Virus-like Particle</td>
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1. Background

In 2006, the Global pandemic influenza action plan to increase vaccine supply (GAP) identified three principal strategies to reduce the anticipated gap between vaccine demand and supply during an influenza pandemic, i.e.

i) the promotion of seasonal vaccination programmes as a driver of increased market and production capacity;

ii) the expansion of manufacturing capabilities in both industrialized and developing countries; and

iii) the promotion of influenza vaccine research and development.

Directly related to strategy 2, the World Health Organization established a technology transfer initiative to provide financial and technical support to developing country manufacturers to establish influenza vaccine production capacity. To date, about US$ 28 million have been awarded to 11 developing country manufacturers in five of the six WHO Regions.

Regular meetings are convened to review progress of the technology transfer initiative and promote networking among the grantees and the GAP stakeholder and partners. Following the first meeting in Geneva, Switzerland (2007), the group has taken advantage of meeting at one of the grantee manufacturing sites (Pune, India, 2008; Nha Trang, Viet Nam, 2010).

In response to the 2009 A(H1N1) influenza threat pandemic, grantees were able to focus wherever feasible to the development, production and registration of a pandemic vaccine in the fastest possible time. This approach resulted in the successful licensing of two (A)H1N1 pandemic vaccines within one year, with several others in late stage clinical trials.

The last meeting of international partners (2010) reached consensus on the following points.

- WHO GAP-inspired technology transfer programme initiative is anticipated to increase production capacity in developing countries by 2015, which will have a significant impact on pandemic preparedness in the developing world.

- Demand for seasonal influenza vaccine will be crucial for the sustainability of both old and new production capacity.

- Technology hubs such as the National Institute for Public Health and the Environment (RIVM, formerly the Netherlands Vaccine Institute, NVI) and initiatives such as the Global Adjuvant Development Initiative (GADI) will be important for capacity building of developing country vaccine manufacturers.

- Strengthening of National Regulatory Authorities should be continued and extended to all countries intending to initiate vaccine production.
• Research and development of newer technologies should be encouraged.

• There is an urgent need to strengthen global communication on the benefits of influenza vaccination.
2. Introduction and objectives

The fourth meeting of International partners on influenza vaccine production technology transfer to developing countries was held on 4-5 May 2011 in Cancun, Mexico. The meeting was co-hosted by WHO and the Laboratorios de Biológicos y Reactivos de México (BIRMEX), one of the initial WHO capacity-building grantees. Professor Pathom Sawanpanyalert, chair of the meeting, thanked the organizers and the Mexican authorities for the preparation of the meeting, and welcomed participants (see List of Participants).

The objectives of the meeting were to:

- Review progress of the technology transfer initiative towards achieving the GAP goals.
- Consider lessons from the 2009 (A)H1N1 influenza pandemic in order to enhance global pandemic preparedness for a future outbreak.
- Discuss the potential of novel influenza vaccine technologies.
- Identify outstanding challenges.
- Propose priority avenues for the Initiative.
3. Overview of the WHO Initiative to Increase Capacity for Influenza Vaccine Production in Developing Countries

Dr Marie-Paule Kieny summarized the work of the WHO Technology Transfer Initiative to establish and sustain influenza vaccine manufacturing capability in developing countries, as part of the goals of the GAP. To date, the Initiative has provided financial and technical assistance to the following developing country vaccine manufacturers (DCVM).

1. Bio Farma, Indonesia
2. Birmex (Laboratorios de Biológicos y Reactivos de México), Mexico
3. Cantacuzino Institute, Romania
4. GPO (Government Pharmaceutical Organization), Thailand
5. Green Cross Corporation, Republic of Korea
6. Instituto Butantan, Brazil
7. IVAC (Institute of Vaccines and Medical Biologicals), Viet Nam
8. Razi Institute, Islamic Republic of Iran
9. Serum Institute of India, India
10. Torlak Institute, Serbia
11. Vacsera, Egypt

Six of these organizations have produced clinical lots of pandemic A/H1N1 2009 vaccine, four have completed pandemic vaccine clinical trials, and three have licensed pandemic vaccines for human use. A royalty-free licence for a live attenuated influenza vaccine (LAIV) technology was granted to two of the DCVMs, and further licences are being considered. It is estimated that the annual seasonal vaccine production capacity of the 11 manufacturers taken together will increase from 44 million doses in 2011 to around 200 million doses by 2015. This is a significant achievement in light of the global seasonal vaccine production capacity, which currently stands at 900 million doses.

It is essential that technical and financial support for these manufacturers is sustained until registration of their seasonal influenza vaccine. In parallel, support must also be extended to under-served regions, notably in sub-Saharan Africa and Central Asia. Building manufacturing capacity requires solid stakeholder involvement, particularly from policymakers and national regulatory authorities (NRA). In order to ensure sustainability, a business model should be developed with strategies that are flexible and tailored to local needs. Importantly, support to each capacity-building programme should include a component to strengthen the NRA.
4. 2009 H1N1 Pandemic Experience: What Did We Learn?

Overall, the WHO pandemic vaccine deployment during the 2009 A/H1N1 pandemic was considered a success. When pandemic vaccine demand ceased in 2010, 78 million doses had been provided to 77 countries.

However, a significant finding from the experience was the gap between manufacturers’ forecasted annual pandemic influenza vaccine production (5 billion doses) and actual number of doses produced (1.3 billion). Reasons for this drop relate to the suboptimal use of dose-sparing adjuvants, the continued production of seasonal vaccine, and the inferior yield of H1N1 against classical seasonal virus growth.

In addition, serious delays were experienced between pledge and delivery of the vaccine, largely due to absence of vaccine available to WHO for distribution to LMICs, as well as to the requirements of a ratified Letter of Intent, a legally-binding Letter of Agreement and a validated national delivery plan.

H1N1 vaccine use and population coverage showed significant variability among WHO regions and countries. At the regional level, vaccine use ranged from 15% to 73% and vaccine coverage in the general population from 0.6% to 24%. The WHO Region for the Americas had the highest average coverage at 24%.

Main lessons learnt:

• An influenza pandemic is complex and difficult to address using an ad hoc approach.
• The necessary frameworks and agreements should be put in place in advance.
• A research study should identify how to generate vaccine viruses that reliably generate high yields.
• A firm recommendation on when to interrupt seasonal vaccine production may significantly accelerate access to a pandemic vaccine.
• Different formulations of a vaccine should not be introduced in parallel in a country that has no experience of the technology.
• Public communication strategies should be prepared to ensure effective social marketing of pandemic vaccines.
• The global supply of pandemic vaccine could be significantly increased though the registration and use of LAIV and/or dose-sparing adjuvants.

Discussion
It was agreed that, while political commitment to an appropriate influenza pandemic response is critical, it is fruitless without an adequate supply of vaccine.
5. Capacity to Manufacture Influenza Vaccines – India

India’s experience in developing influenza vaccine capacity in response to the H1N1 pandemic was presented. The Government was committed to a rapid response following detection of the first case of H1N1 infection, as well as to the fast-track manufacture of an indigenous H1N1 vaccine. A two-pronged strategy comprised (i) timely consensus on a regulatory roadmap to allow immediate importation of an H1N1 vaccine in global use, to protect frontline health workers; and (ii) the parallel development of a vaccine by four Indian manufacturers (Serum Institute of India, Cadila Healthcare, Panacea Biotec, Bharat Biotech International). The technologies used by each company and their associated production capacity were described. In total, four H1N1 inactivated vaccines and one LAIV have been produced in India.

In conclusion, India underlined the invaluable role of each stakeholder, as follows.

- **WHO**
  - guidance documents, notably for the regulatory roadmap; assistance in obtaining H1N1 influenza strains and reagents; facilitating coordination among all stakeholders; and close cooperation and technical and financial support.

- **Ministry of Health**
  - encouraging and financing the production of indigenous H1N1 vaccines; facilitating interaction between manufacturers, regulators, clinicians and academia. In this respect, the support and trust of senior politicians was critical for public acceptance.

- **Regulators/manufacturers**
  - the rapid preparation of the regulatory roadmap; continual close collaboration to allow the seamless review of dossiers.

**Discussion**
It was noted that India’s potential influenza vaccine production capacity would allow the country to meet future challenges in the shortest possible time.
6. Presentations by WHO grantees

6.1. First Round 2006-2010

6.1.1. Institute of Vaccines and Medical Biologicals, Viet Nam

The State-owned Institute of Vaccines and Medical Biologicals (IVAC) first initiated research into avian influenza vaccines in the early 1990s. The current influenza vaccine production capacity in Viet Nam is 2 million doses per year. The goal of IVAC is to manufacture 500,000 doses of monovalent influenza vaccine per year under current Good Manufacturing Practice (cGMP) conditions, with the potential for expansion to more than 1 million doses. In order to achieve this, a small-scale manufacturing facility has been established to produce egg-derived inactivated whole virus, alum-adjuvanted influenza vaccine for pandemic use, along with a waste treatment system and a chicken farm to secure supplies of qualified clean eggs. With regard to the latter, IVAC eventually plans to make 3 million eggs per year available for export, pending the acquisition of additional equipment.

As at May 2011, all validation documentation for the facility had been reviewed and approved, and the performance qualification for both building and manufacturing systems reviewed and accepted by WHO experts. Production-scale lots in full GMP compliance have been produced. IVAC is now preparing for vaccine manufacturing validation lots and clinical material. Clinical trials are planned to start in early 2012. A three-year consultancy agreement has been signed with the National Institute for Public Health and the Environment (RIVM) in the Netherlands to cover the production process.

Twenty per cent of IVAC training relates to influenza vaccines. All levels of staff are covered by the training strategy, half of which takes place overseas.

Discussion
It was agreed that IVAC had made impressive progress. The WHO seed grant was pivotal in attracting funding from other agencies. In addition, the WHO external inspections were highly beneficial.

6.1.2. Government Pharmaceutical Organization, Thailand

The Government Pharmaceutical Organization (GPO) presented its progress since 2007 towards sustainable capacity to develop and produce influenza vaccines. The strategy for national self-reliance, and the ability to respond effectively in the event of an influenza pandemic, focuses on the development of LAIV as well as industrial-scale production of an inactivated influenza vaccine (IIV).

An industrial-scale IIV plant is due for completion in 2012. To meet the need for technical support and training, a memorandum of understanding was signed in 2009 with the Japanese company Kaketsuken, which includes support to potential GPO egg suppliers. Laboratory-scale production will test the new production systems before pilot production of lots for clinical testing in late 2012. Once the vaccine is licensed, GPO will start small-scale production in 2013 with full-scale production expected by early 2014. The initial annual capacity of 2 million doses will
rise progressively to 10 million doses of seasonal IIV or 30 million doses of pandemic influenza vaccine per year.

A ferret study carried out using GPO’s H1N1 pandemic LAIV found the vaccine to be safe, highly immunogenic and highly protective. Results of the first part of a pandemic LAIV clinical trial showed the vaccine to be safe in a small number of healthy adults (n=24) with little virus shedding. The second part of the study, involving 324 subjects from three different age groups, found the vaccine to be safe with no serious adverse reactions. An interim analysis also showed promising immunogenicity. The study should be completed in June 2011.

H5N2 pandemic LAIV toxicity testing in mice has been performed at GPO, in parallel with the ferret study at RIVM. A two-part clinical trial involving adult subjects is expected to start later in 2011, with the results available by 2012.

Finally, scaling-up production is planned for the development and production of a seasonal LAIV, initiated in early 2011.

The following challenges remained for GPO.

- Strengthening new staff and management teams over the next five years, including technical support.
- Since LAIV technology is new, further capacity development of the Thai NRA and epidemiology unit.
- Securing an adequate supply of specific pathogen free (SPF) and clean eggs.
- Increased public confidence in influenza vaccines.
- Sustainable supply of pre-master seeds, diagnostic kits, and essential laboratory products.

**Discussion**

Public confidence in influenza vaccines in Thailand is higher than that for vaccines in general, and has improved since the H1N1 outbreak, despite setbacks due to media coverage and irregular supply. It is hoped that local vaccine manufacture, along with better matching of supply to demand, will further increase this.

6.1.3. **Serum Institute of India, India**

The Serum Institute of India (SII) presented its initial development of a seasonal influenza A(H1N1)/ A(H3N2)/type B vaccine and pandemic A(H5N1) whole and subunit vaccines. However, at the onset of the H1N1 pandemic, SII turned its focus to the rapid development, manufacture and licensing of an H1N1 pandemic IIV (for pregnant women, children under 3 years of age and immunocompromised individuals) and an H1N1 pandemic LAIV for the general population, given its dose-sparing capacity.

Administrative and technical challenges included preparing and equipping separate facilities for the two technologies; formulation and administration strategies; and safety and immunogenicity in relation to licensing.

Following promising preclinical challenge studies of the H1N1 LAIV in BALB/c mice and ferrets, the absence of observable toxicity in rats or mice, and successful Phase I, II and III studies, the SII LAIV vaccine was launched in India in July 2010. More than 2.5 million doses of pandemic
LAIV were distributed within India. Approximately 1.7 million doses are currently in stock, supported by a production capacity of 20 million doses per year with a possible augmentation to 40 million doses per year. Post-marketing surveillance found the vaccine to be safe and well-tolerated, and SII has now applied for WHO prequalification status.

The development and licensing pathway of an H1N1 IIV was also presented. Results showed strong seroconversion in clinical trials with no reported severe adverse events.

Finally, the work plans for a seasonal LAIV, an H5N1 LAIV and an H5N1 IIV were described.

**Discussion**

Regarding the decision to licence the 15 µg instead of the 10 µg dose, SII explained that despite lower seroconversion in the elderly, the 15 µg dose had been tested in many more volunteers, and this had guided the licensing of the higher dose. SII also confirmed that the Indian NRA decided to licence the vaccine based on the LAIV seroconversion data, given the progression of the H1N1 pandemic. Furthermore, the distribution of 2.5 million doses has shown good immune responses and high levels of protection and safety. It was too early to know how the vaccine will react with novel H1N1 strains.

It was noted that SII’s LAIV production capacity would only need to be reviewed if demand exceeded 40 million doses per year.

6.1.4. Butantan Institute, Brazil

The Butantan Institute is a not-for-profit, public foundation and a major producer of vaccines in Latin America. The influenza vaccine plant has now been validated by sanofi-pasteur. An agreement was reached with the technology transfer partner to supply vaccine bulk until the Institute reaches self-sufficiency. The plant is designed to produce 20 million doses per year, sufficient to vaccinate the >60 group. Capacity will soon be needed to cover pregnant women and children. Butantan also wishes to provide surplus vaccine to protect neighbouring countries.

A smaller pilot-plant facility is dedicated to vaccine production, where Butantan is preparing to start its own seasonal vaccine production with a potential capacity of 120 000 doses per day. The Institute demonstrated its capability to prepare 20 000 H5N1 doses as part of a study funded by the US Centers for Disease Control and Prevention (CDC) and the Brazilian Government, and plans to prepare both northern and southern seasonal influenza vaccines in the same facility in order to ensure year-long use of the plant.

Data presented showed that H1N1 vaccine, formulated using a proprietary combination adjuvant – MPLA (monophosphoryl lipid A), a squalene-based emulsion and an aluminium salt – indicated promising seroconversion rates with 3.75 µg antigen.

**Discussion**

In response to queries regarding the use of aluminium adjuvants in combination with squalene and MPLA to formulate pandemic vaccines, Butantan stated that the combination of the three adjuvants induced a different immune response and that the combination adjuvant’s safety data showed only minor local reactions.
6.1.5. Birmex, Mexico

Birmex, established in 1895, is a non-profit company of the Mexican Ministry of Health that develops, produces and commercializes vaccines for human health. Within the influenza vaccine sphere, Birmex guarantees influenza vaccine availability to the Mexican population, acquires and produces seasonal and pandemic influenza vaccines, and distributes vaccines and antiviral drugs nationally. Birmex’s seasonal influenza vaccine production rose from 430 000 doses in 2003 to 21 million in 2010.

To address the 2009 H1N1 pandemic in Mexico, Birmex initiated production of pandemic vaccine in June 2009. This experience highlighted the need for more production sites with technology to prepare pandemic vaccines more rapidly. The cooperative strategy between Birmex and sanofi-pasteur entailed bulk production and quality control (QC) by the technology transfer partner before blending, filling, packing and final product QC at Birmex. Remodelling of the Cuautitlan facility to be able to produce 30 million doses of seasonal vaccine and at least 60 million doses of pandemic vaccine per year, is likely to start in 2014.

6.1.6. Bio Farma, Indonesia

Bio Farma is a state-funded company and a WHO-prequalified manufacturer. Its work with egg-based whole IIV parallels is being carried out in parallel to the development of adjuvants, cell-based and split vaccines. Between 2007 and 2010, technology transfer was received for the formulation, filling, QC, as well as bulk production, purification and inactivation of a seasonal influenza vaccine. Bio Farma’s current strain – H1N1 NYMC X-179A (whole virion and split) – will be complemented by a recently acquired H5N1 Indo 05/PR8-RG2, to be used with whole/split and adjuvanted/non-adjuvanted strategies.

In 2011, WHO seed funding supported the development of cell-based, pandemic influenza vaccine production using MDCK-modified cell culture. The five-year project starts by scaling up the cell line from laboratory- to larger scale (2L cultures). Characterization of the cell line has already been successfully completed. A new manufacturing and egg facility, with an operational capacity of 4 million doses per year (and a maximum capacity of 20 million doses per year) is due to be completed in 2012.

Biofarma is receiving technology transfer for oil-in-water emulsion adjuvant from the University of Lausanne, under a programme funded by BARDA. Progress was presented, including training activities.

**Discussion**

Bio Farma indicated that the Indo H5N1 would be licensed for use in Indonesia as a prepandemic vaccine. It was also confirmed that there was no national programme for seasonal vaccine in Indonesia, and any change in the annual 200 000 doses produced for Hajj pilgrims will be decided by the Arabic governments.

It was agreed that Bio Farma had made good progress with egg-based vaccines. The company will also work in partnership with manufacturers from Japan on a suitable cell line as part of its R&D activities.
6.1.7. **End of Session Discussion**

Regarding the ready-outs and end-points of clinical trials to support approval of LAIV, it was generally agreed that virus titre may be more appropriate given existing data on licensed LAIV. The clinical studies carried out in India aimed at confirming the safety and immunogenicity in the numerous population groups in India, although more data from vaccine use need to be acquired to confirm this.

The following are responses from WHO grantees to a request for comments on potential policy barriers (beyond regulatory and national policy on immunization); the need for further support to the Ministry of Health; and any research and development activities to improve seed strain production for increased yields.

Thailand considered the following elements to significantly influence the inclusion of a vaccine in its national immunization programme: demonstrated efficacy, safety, availability, affordability, and deliverable; proven public acceptance; burden of disease data; a cost-benefit analysis of vaccine use; health technology assessment, as well as Ministry of Health support in public communication strategies. Top priority is making production capacity sustainable. Research to increase supply must be accompanied by work to increase demand.

India had experienced some reluctance on the part of health workers to take up the pandemic vaccine. The Government provided seed funding to manufacturers. It also promised to purchase their vaccines, although once prepared bulk H1N1, this was no longer needed. Regarding new technologies, VLP has been transferred to Cadila Pharmaceuticals who intends to develop a seasonal vaccine using this technology.

The Viet Nam Ministry of Health and regulatory authority faced unprecedented demand for vaccine from the general public, who perceived the H1N1 pandemic as a high risk. The country depended on technical guidance from WHO to compile its manufacturing data in a standardized format, and suffered certain delays in registering and licensing the vaccine, given the lack of management experience in handling such a novel dossier. While IVAC agreed that R&D is important, it felt that focus on currently available vaccine technologies remains the priority.

In Mexico, the Ministry of Health system for budget allocation is complex. For Birmex, effective technology transfer has been essential, and R&D in cell-based vaccine production is now under way, as well as exploration of other novel systems to produce vaccines.

Butantan stated that the most challenging aspect is the funding of new technologies.

Finally, participants discussed where responsibility should lie for decisions on how many doses to produce.

6.2. **Second Round 2009-2011**

6.2.1. **Cantacuzino Institute, Romania**

The Cantacuzino Institute, sole seasonal influenza vaccine producer in Romania since 1971, aims to enhance national capacity to prepare for an influenza pandemic, and to distribute vaccine to neighbouring countries.
Upgrading of preclinical testing facilities and the establishment of a functional influenza vaccine production site are almost completed. Preclinical studies using H5N1 and H1N1 vaccines in mice and ferrets were presented along with H1N1 pandemic vaccine clinical trials in adults and children. A 15 µg haemagglutinin (HA) dose of “Cantgrip” was shown to be immunogenic after a single dose, and met all three Committee for Medicinal Products for Human Use (CHMP) criteria.

For the seasonal influenza vaccine, the immune response after a single dose depended on the virus strain: two of three CHMP criteria were fulfilled by a purified trivalent IIV containing 45 µg HA. Clinical trial results presented no safety concerns and none of the reported adverse events led to the discontinuation of a subject.

The Institute’s current capacity is 25 000 eggs daily, with five lots per week.

**Discussion**

Two million doses of H1N1 have been produced in the Cantacuzino Institute. Given low acceptance of vaccine by the population, the Cantacuzino Institute switched to production of H1N1 pandemic vaccine in bulk only, for inclusion in a seasonal vaccine. Regarding the high level of vaccine efficacy noted from year to year, and whether this efficacy was the same for all respiratory diseases, the Cantacuzino Institute had participated in a three-year study, supported by the European Center for Disease Control, to measure the effectiveness of influenza vaccines. In this way, Cantacuzino has had access to case-control data, with a history of vaccination and hospitalization as well as laboratory results.

6.2.2. **Green Cross Corporation, Republic of Korea**

The Green Cross Corporation first focused on pilot-scale process optimization and validation of an H5N1 influenza vaccine, and is now concentrating on preparing the vaccine for testing in clinical trials. Lot release testing and analysis, as well as evaluation of the final vaccine product were presented. The results of preclinical studies in mice and ferrets, and Phase I clinical trials showed no issues of concern although larger cohorts are needed to confirm the data. The next steps include the characterization and analysis of the H5N1 vaccine in a Phase II clinical study.

6.2.3. **RAZI Institute, Islamic Republic of Iran**

The RAZI Institute, established in 1925, joined the WHO technology transfer project in 2009. The company manufactures numerous veterinary and human vaccines at eight production plants throughout Iran, including a veterinary influenza vaccine. The Institute has experience with live vaccines through the measles-mumps-rubella and polio programmes. RAZI possesses an excellent egg farm facility.

A final decision on the technology to develop and produce a human influenza vaccine has not yet been made. Laboratory-scale production of an H1N1 vaccine has been completed. Difficulties encountered in accessing zonal centrifuges have hindered the production of whole IIV, pointing to the possible production of LAIV as a more attractive option. RAZI is currently preparing to design a new building, initiate technology transfer and complement the staff training already received from RIVM. WHO has been facilitating discussions with SII and RIVM to assist RAZI access new technologies.
**Discussion**

Although more challenging, consideration should be given to manufacturing IIV using chromatography instead of ultracentrifugation. RAZI is trying to secure further funding to accelerate its activities.

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6.2.4. **Torlak Institute, Serbia**

The Torlak Institute has been producing whole IIV since 1960. The Institute presented the progress made since 2006 in building and equipping its new facility. Regarding the manufacture of influenza vaccines for the Serbian market, Torlak plans to complete clinical studies in 2011 and start production runs in 2012.

6.2.5. **Vacsera, Egypt**

Vacsera aims to establish, test and prepare documentation for an egg-based influenza vaccine production facility, construction of which is under way. Initial capacity will be 500 000 doses of trivalent vaccine per year, with possible expansion to 1.5 million doses of seasonal and 20 million doses of pandemic vaccine per year. Numerous regulatory documents have been prepared and several technology transfer consultants and contractors arranged. Staff have been trained in laboratory and QC techniques, and production processes. Once construction of the production facility is completed and production initiated, further staff training will be organized and a marketing plan prepared.

6.2.6. **End of Session Discussion**

Participants discussed why so few manufacturers are working with LAIV since the technology is cost-effective and well adapted for delivery in resource-poor settings. IIV may have a more robust safety database, and there are currently limitations in age range for LAIV. Whichever technology is selected, the importance of determining disease burden was reiterated.

It was mentioned that multi-use vaccine plants, i.e. those that can switch from regular production of a vaccine such as duck-egg rabies to an influenza vaccine, had tremendous pandemic preparedness potential. Maintaining more than one technology, e.g. both egg and cell-based technologies, to offset inadequate performance was also discussed.

The need to map supply against expected demand was critical and will determine investment requirements in each country. This is especially important in Africa and central Asia where local supply may not exist. However, effectively predicting demand and supply is very difficult, and stated as one of the most challenging part of UNICEF’s yearly forecasting for childhood vaccines. It may be beneficial for WHO and UNICEF to liaise on this issue.

Other comments included:

- the importance of seasonal vaccine production to ensure pandemic capacity;
- the difficulty of applying single strategies to different countries; each site needs its own realistic business model;
- the importance of government commitment, and agreement to purchase the vaccine;
- the significant public health benefit that can be achieved from relatively small funding.
7. Keynote address by Dr Jose Angel Cordova Villalobos, Secretary of Health of Mexico

Dr Jose Angel Cordova, Secretary of Health of Mexico, gave an insightful intervention on the need for global commitment to pandemic influenza preparedness, based on the successful implementation of the influenza programme in Mexico. A summary of his address is provided below.

In welcoming participants, Dr Cordova recalled the pivotal meeting hosted by Mexico in 2009, when health ministers and key international partners prioritized the need to strengthen influenza vaccine production in countries without access to the vaccine. This fourth meeting of international partners on influenza vaccine technology transfer, held in the same Mayan Riviera, celebrates the continuity of that encounter.

The effectiveness of vaccines to reduce morbidity and mortality from seasonal influenza is well known. However, novel influenza viruses can and do emerge without warning, requiring health systems to consolidate their strengths, first to identify the outbreak and thereafter to address it with drugs and vaccines.

Dr Cordova presented an overview of the vaccination programme in Mexico, which is based on nationwide epidemiological needs and scientific criteria, without direct costs to vaccinees. Indeed, Mexico was proud to have one of the most complete vaccine schedules in the world, covering polio, measles, rubella, as well as diseases caused by rotavirus, pneumococcus, hepatitis B, tuberculosis and influenza.

Birmex supplies 67% of national demand for biologicals, representing 135 million vaccines per year. Vaccines are administered throughout the year across the country, and intensively during campaigns in February, May and October. Despite geographical, logistic and ideological hurdles, Mexico’s vaccine coverage was up to 90%.

Annual seasonal influenza vaccination was introduced in Mexico in 2004 for children under five years old, adults over 60 and persons with underlying conditions. Vaccine acceptance has been very good, and the number of doses produced has increased to 20 million this season.

Dr Cordova emphasized that Mexico’s seasonal influenza vaccination campaigns were the best preparation for a solid pandemic response. A vaccine candidate and associated material were obtained in record time, allowing 28 millions pandemic doses to be produced and administered safely and effectively. Only 34 temporary vaccine-related serious events had been reported.

WHO’s leadership and guidance in pandemic influenza preparedness was applauded, for it facilitated effective action worldwide. At the same time, the global community was now in a position to take stock of the successes and pitfalls of the H1N1 pandemic. Following its experience, Mexico now has:

- a network of laboratories across each State to match the world’s best;
• a strategic stockpile of antiviral drugs (future stockpiles will include more patient-care material);
• increased hospital infrastructure and specially trained human resources;
• a new pandemic preparedness manual;
• a medical disaster response system, including hospital and response teams in each state; and,
• good hygiene measures, respiratory etiquette, antibiotics control and no self-medication campaigns.

Dr Cordova considered the WHO technology transfer initiative as a significant, long-term effort to guarantee access to influenza vaccines in developing countries. Birmex, one of the first grantees of the initiative, has used the support to enhance its influenza vaccine filling and packing plant. Achievements in Mexico mirror those of other grantees and corroborate the effectiveness of the initiative.

In conclusion, Dr Cordova urged all partners to persevere in their efforts to improve influenza vaccine production capacity so that safe and effective vaccines against both seasonal and pandemic influenza are available to all. He thanked WHO and Birmex for organizing this important meeting, which would reinforce global preparedness to achieve this goal.

**Discussion**

The results of the government policy in Mexico to increase production capacity, build demand and ensure sustainability were impressive. The most important influence was considered to be a demonstrable threat to national security. Although unpredictable, this threat is real and autonomous influenza vaccine production is essential to stem the spread of an influenza pandemic.
8. Other WHO Activities Relevant to Influenza Vaccine Technology Transfer

8.1. International Technology Platform for Pandemic Influenza Vaccines, 2008-2010

The former Netherlands Vaccine Institute (NVI) has been reorganized into two entities: the National Institute for Public Health and the Environment (RIVM), and Bilthoven Biologicals. RIVM will continue to serve as a “hub” for the transfer of a generic production process for influenza vaccines. Through these activities, WHO grantees have access to technical advice, process and production technology, documentation, assays, and (pre)clinical support.

The production process was presented as well as data from preclinical studies with whole IIV H3N2 and H5N1. Both vaccines were shown to be immunogenic, safe and suitable for technology transfer activities. From 2009 to 2011, 53 trainees from 18 institutes participated in training courses on influenza held in Bilthoven.

Future activities will include general process development (including split vaccines), additional processes – possibly for LAIV and cell culture – as well as identifying new trainees, preparing new courses and acquiring new partners.

8.2. The Adjuvant Hub: Increasing Global Access to Vaccine Adjuvants

The creation of an Adjuvant Hub at the University of Lausanne, Switzerland, was presented. The “Vaccine Formulation Laboratory” is a platform providing access to vaccine adjuvants, vaccine formulation services, training on adjuvants, and transfer of adjuvant technologies. Notably, a BARDA-funded programme for transferring oil-in-water technology to developing countries enabled Bio Farma to be the first recipient of the technology transfer in 2010.

Technology transfer packages for the manufacture and QC of oil-in-water adjuvants include the provision of:

- GMP-compatible process suitable for industry partners
- Full set of manufacturing and QC equipment (GMP pilot and laboratory scale)
- Relevant documentation (standard operating procedures, user requirement specifications, process development reports etc.)
- General advice and support
- Hands-on training in adjuvant manufacture, QC and vaccine formulation.
Discussion
The long-term strategy for the technology transfer hubs was discussed. WHO has a five-year agreement with RIVM until the end of 2012. The Vaccine Formulation Laboratory hub is currently self-sustaining and growing rapidly. It was recommended that on the one hand, all grantees consider using the services of these global assets, which will help sustain them; and on the other, the costs of the services remain accessible, ideally on a non-profit basis. It was noted that increased production capacity will reduce the cost per vaccine, and thus encourage demand. Moreover, once established, squalene-based oil-in-water emulsions will only add marginally to the price of vaccine.

Two BARDA-funded programmes provide advanced biomanufacturing training for DCVMs. The experience will be evaluated to improve future courses and overcome practical obstacles such as language barriers.

Finally, participants would welcome more information from grantees on the specific challenges they are facing.

8.3. Live Attenuated Influenza Vaccine Strains for Developing Countries

The generation of reassortants of A/Mallard/NL/12/00 (H7N3) with Len/17 MDV, and of H5N1–PR with Len/17 MDV were presented. Safety, immunogenicity and protection studies in mice, as well as toxicity studies in mice and guinea pigs showed the vaccine viruses to have low pathogenicity, with excellent safety profiles in mice and chickens. Immunogenicity and challenge studies using H5N1 indicated complete protection in vaccinated mice. The efficacy of H5N1 pandemic influenza LAIV in a ferret challenge model also showed encouraging protection. Preparations are under way to test H7N3 and H5N1 vaccines in clinical trials.

8.4. Progress in regulatory preparedness for human influenza vaccines

The WHO influenza vaccine capacity-building programme in developing countries has increased its focus on regulatory issues, including expedited procedures for evaluating both seasonal and pandemic influenza vaccines for prequalification.

Requests for prequalification have been received, and new submissions are expected, including from the WHO grantees. The regulatory strengthening aspects of the WHO initiative are now integrated into the WHO NRA assessment system, since prequalification depends on a functioning domestic authority. Lessons learnt from the pandemic influenza vaccine prequalification process have been incorporated into the new evaluation procedure. The integration of influenza vaccines into the main prequalification procedure in 2012 is thus timely.

Discussion
As there are no specific correlates of protection for LAIV, their prequalification must be based either on efficacy trials or clinical data and bridging studies.

It was noted that once a vaccine is prequalified, issues related to strain changes are handled by the NRA.
9. International Partner Initiatives
US Department of Health and Human Services

9.1. Biomedical Advanced Research and Development Authority

The mission of the Biomedical Advanced Research and Development Authority (BARDA) is to provide to the US government countermeasures for chemical, biological, radiological and nuclear threats, pandemic influenza, and emerging infectious diseases. To do this, BARDA engages in product requirement setting, product development, stockpile acquisition/building, manufacturing infrastructure building, and product innovation. An overview of the PCAST (President’s Council of Advisors on Science and Technology) recommendations was presented.

The BARDA International Influenza Programme capacity building programme has supported since 2005 clinical evaluation of vaccine candidates (PATH/Vietnam), capacity building for local production under the GAP programme (WHO), development and technology transfer of adjuvants, advanced biomanufacturing training for DCVMN, and surveillance using new diagnostic tools. BARDA’s activities have shown that building manufacturing capacity will not succeed without the concomitant technical, regulatory, clinical and policy capacity development. Also critical are a business model to support sustainability, strong local government support, close collaboration and communication among partners, and flexibility in approach, models, pace, and funding.

In the future, BARDA will continue its partnerships with WHO and PATH. Support will continue for oil-in-water adjuvant technology transfer activities, biomanufacturing training, workshops on regulatory and workforce development, and LAIV clinical studies performed by DCVMs. In addition, the feasibility of establishing manufacturing facilities in developing countries capable of producing multiple types of vaccines will be investigated.

9.2. US Department of Health and Human Services Initiatives to Accelerate Influenza Vaccine Manufacturing

Subsequent to the 2009 H1N1 pandemic, HHS plans include:

- Optimizing influenza virus vaccine strains for high production yields: develop methods to rapidly produce vaccine candidate viruses that replicate to higher titre and yield larger amounts of HA; and prepare and stockpile a library of high yielding vaccine candidates of protective value against all potential influenza pandemic threats. Implementation will involve NIH/NIAID, CDC/ID, FDA/CBER and ASPR/BARDA.

- Developing faster potency and sterility assays: vaccine release assays will use new methods to circumvent the need for current reagents. One alternative method in advanced development is isotopic dilution mass spectrometry (IDMS). Implementation will involve NIH/NIAID, FDA/CBER and ASPR/BARDA. The rapid sterility assay (reducing analysis time from 14 to approximately 6 days) is being evaluated by FDA/CBER and ASPR/BARDA.
9.3. Influenza Vaccine Technologies

The global status of influenza vaccine development was presented, including that of LAIV, recombinant VLP, cell- and plant-based vaccines. Priority challenges comprised safety, immunogenicity, scalability, formulation and potency determination, developing clear regulatory pathways and acquiring adequate funding. It was noted that influenza vaccine development was active and rapidly evolving, most remarkably with the emergence of several DCVMs.

WHO should continue to support DCVMs and new technology development/transfers to support global capacity building. DCVMs should carefully consider the developmental stages of any new technology before they agree to form partnerships.

Discussion
Cell-based, live attenuated and insect cell-based technologies, and vaccines formulated with adjuvants were considered the most promising. Licensing new technologies remains a major issue: criteria need to be developed, e.g. for registration of LAIV. BARDA is interested in improving live and inactivated reassortants, and is investigating alternatives/strategies for reverse genetic technologies.
10. Concluding Remarks

The WHO influenza vaccine technology initiative was considered an excellent example of how countries can work together to improve global health. However, future funding of the initiative must be broadened, and partners agreed to develop an advocacy plan to attract new funders to support technology transfer to DCVMs.

There is a need to determine how to accelerate the improvement of production and quality. The new technology for rapid potency and sterility tests was very encouraging. Sustainability is also important and should be described in a business plan. However, this is not sufficient unless there is a demand for vaccine and government support.

The DCVM group is largely focused on technical aspects and it is important to remember the enormous and complex challenges for regulatory and workforce development aspects. It will also be important to provide guidance to new DCVMs, and WHO needs to consider how to communicate the numerous vaccine technology options (and their pros and cons) in light of individual cases and prevailing funds.

It was suggested that at the next meeting, challenging issues should be prepared and presented by each grantee. These meetings encourage strong networking of manufacturers and should consider workshops and/or side sessions.

The importance of support and guidance from WHO, CDC, NIH and HSS regarding new technologies was highly appreciated.

Close of Meeting
The Chair and WHO thanked the committees, participants and hosts before closing the meeting.
11. List of Participants

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