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Influenza Vaccine Production Capacity Building in Developing Countries: Example of the Serum Institute of India

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Abstract

It is predicted that in case of an influenza pandemic, there will be a significant gap between potentially available vaccine supply and international demand. This paved the way for a WHO Global Pandemic Influenza Action Plan (GAP) aiming at increasing the world's production capacity for pandemic vaccine. In November 2006, six developing country manufacturers were awarded grants either to develop processes for production of inactivated or live attenuated seasonal and/or H5N1 influenza vaccines or for establishing filling facilities using imported antigens. In April 2009, spread of a new H1N1 influenza virus was identified which took a pandemic form. This paper gives an overview of influenza vaccine capacity building of developing country's manufacturers identified in WHO's GAP. Further, an account of developments at Serum Institute of India Limited (SIIL), one of recipients of WHO grant to develop pandemic influenza vaccine, are presented as a case study. Such initiatives have strengthened developing country vaccine manufacturers ability to respond to a pandemic situation in the future.

Keywords: Global Pandemic Influenza Action Plan; Pandemic Influenza Vaccine, H1N1; Swine flu vaccine; Serum Institute of India; Developing Countries

1. Introduction

The best tool for controlling a global influenza pandemic is the development of an effective vaccine. It is anticipated that given the current global annual production capacity of 600−700 million doses of vaccine, there would be a significant gap between potentially available vaccine supply and international demand. In order to strengthen pandemic influenza preparedness and response, the Fifty-eighth World Health Assembly in its WHA58.5 Resolution requested the World Health Organization (WHO) to seek solutions with partners to reduce the present global shortage of both seasonal and pandemic influenza vaccines [1]. This paved the way for a WHO Global Pandemic

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Influenza Action Plan (GAP) in November 2006 aiming at increasing the world's production capacity for pandemic vaccine [2]. GAP identified three major approaches: a) to increase the use of seasonal influenza vaccines; b) to increase the overall production capacity of influenza vaccines; and c) to encourage research and development of newer and better influenza vaccines. GAP was funded through Asian Development Bank, Bill & Melinda Gates Foundation, Public Heath Agency of Canada, Government of Japan, the United Kingdom Department of Health, the United States Department of Health and Human Services and United Nation Children's Fund (UNICEF).

Six developing country manufacturers were awarded grants in 2007 to either develop processes for production of inactivated or live attenuated seasonal and/or H5N1 influenza or to establish filling facilities using imported antigens. In 2008, many of these manufacturers were ready for Phase-I trials [3]. In April 2009, the new A/ H1N1 influenza virus was identified and on 11 June 2009, the influenza pandemic alert was raised by WHO to phase 6 [4]. Developing country grantees under GAP took a variety of steps towards early introduction of H1N1 vaccines in their respective countries.

This article will present an overview of capacity building of developing country manufacturers identified in GAP. Further, an account of developments at Serum Institute of India Limited (SIIL), one of the recipients of a WHO grant to develop pandemic vaccines, is presented as a case study of capacity building in developing countries.

2. GAP and Capacity Building of Developing Countries Manufacturers: Current status

Currently, 90 % of influenza vaccine production is located in Europe and North America, whose population represents only 10 % of the world population. Increasing and diversifying influenza vaccine production would ensure greater equity in the distribution of vaccines during the early months of a pandemic. In October 2006, WHO issued a call for proposals to developing country vaccine manufacturers willing to initiate domestic production of influenza vaccine. Technologies eligible for funding were inactivated split or whole virus vaccines, or live attenuated vaccines, using cell culture or egg-based production. Expectations were for large scale influenza vaccine production that would be rapidly operational, cost effective and sustainable.

Six developing countries manufacturers received grants of US$ 2-2.7 million each to develop processes for production of inactivated or live attenuated seasonal and/or H5N1 influenza vaccines or for establishing filling facilities using imported antigens. These included BioPharma, Indonesia; Birmex, Mexico; Butantan, Brazil; GPO, Thailand; IVAC, Vietnam and Serum Institute of India/ India. All projects were initiated between June and September 2007. The grantees made significant progress in capacity building and a few of them were ready for clinical trials during the summer of 2009 [**Table1**).

In 2009, GAP also met broad interest from other developing countries and manufacturers from Romania, Korea, Iran, Serbia and Egypt received grants for pandemic influenza vaccine development (**Table 1**).

3. Capacity building of DCVM manufacturer: Case study of the Serum Institute of India

Infectious diseases are present in almost all parts of the world but they appear to be more severe in poor and developing countries. Avian influenza, caused by A (H5N1 influenza virus, continues to cause outbreaks and has spread from Asia to other regions, including Europe, the Middle East, and Africa. India has also been affected and significant cases of bird infection were reported. It is now clear that in case of an influenza pandemic, all countries worldwide will inevitably be affected. However, the impact may differ between high and low income countries. For instance, estimations from various countries shows that mortality rates during the 1918-1920 flu pandemic was significantly lower in Europe and North America than in Asia, Sub-Saharan Africa, and Latin America [6]. Furthermore, it has been estimated that 96% of the deaths occurring in a future influenza pandemic (estimated at 62 million deaths) would occur in developing countries [7].

Country/Institute	Technology	Main achievements at end of 2008[3]
Brazil: Instituto Butantan	Egg-based inactivated split virus and whole-virion H5N1 vaccines with adjuvant.	New pandemic pilot plant established.
India:Serum Institute of India	Cell-based inactivated split virus and egg-based LAIV	H1N1 and H3N2 strains successfully grown. QC system in place.
Indonesia:BioFarma	Fill/finish for egg-based split seasonal vaccine.	Facility established, three clinical grade lots produced and a clinical trial completed.
Mexico:Birmex	Fill/finish egg-based inactivated split seasonal vaccine.	Product specific equipment for QC laboratory purchased. Construction and engineering plans for blending facility under validation.
Thailand:Government Pharmaceutical Organization (GPO)	Egg-based split inactivated vaccine and LAIV, depending on access to live attenuated strain.	Successful laboratory scale production of trivalent seasonal vaccine with QC confirmation. Technology ready to test under pilot plant conditions.
Viet Nam:IVAC	Egg-derived whole-virion, alum adjuvanted vaccine.	Facility under construction. Three rH5N1 experimental lots sent to NIBSC for confirmatory testing for antigen content.
Year 2009		
• WHO continued the grants in aid for those manufacturers who were already awarded the Pandemic Vaccine Development Project. • Romania, Korea, Iran, Serbia & Egypt have received grant for PIV Development Project. • USD 3.6 Million was awarded to Russia through WHO and USD 7.9 Million to Vietnam through PATH. Funding through PATH will be used for Phase I and Phase II human clinical trials of the vaccine produced in Vietnam.		

Table 1: Update on activities under the Global Pandemic Influenza Action Plan (GAP) (2006-2009)

. These disparities are anticipated owing to socioeconomic conditions, weak public health infrastructures and co-existing medical conditions in developing countries. Thus, the severity of an epidemic caused by an influenza pandemic would be enormous in developing countries, which would be further worsened in the absence of an effective vaccine.

Vaccines for subtype H5N1 viruses are currently being developed. However, the majority of manufacturing units are in Europe or North America as constituent countries have huge uptake of seasonal influenza vaccines. In developing countries such as India where there is no capacity unless the demand for seasonal influenza vaccine increases , vaccine manufacturers are understandably reluctant to invest in production in their routine immunization programs (**Figure 1**).

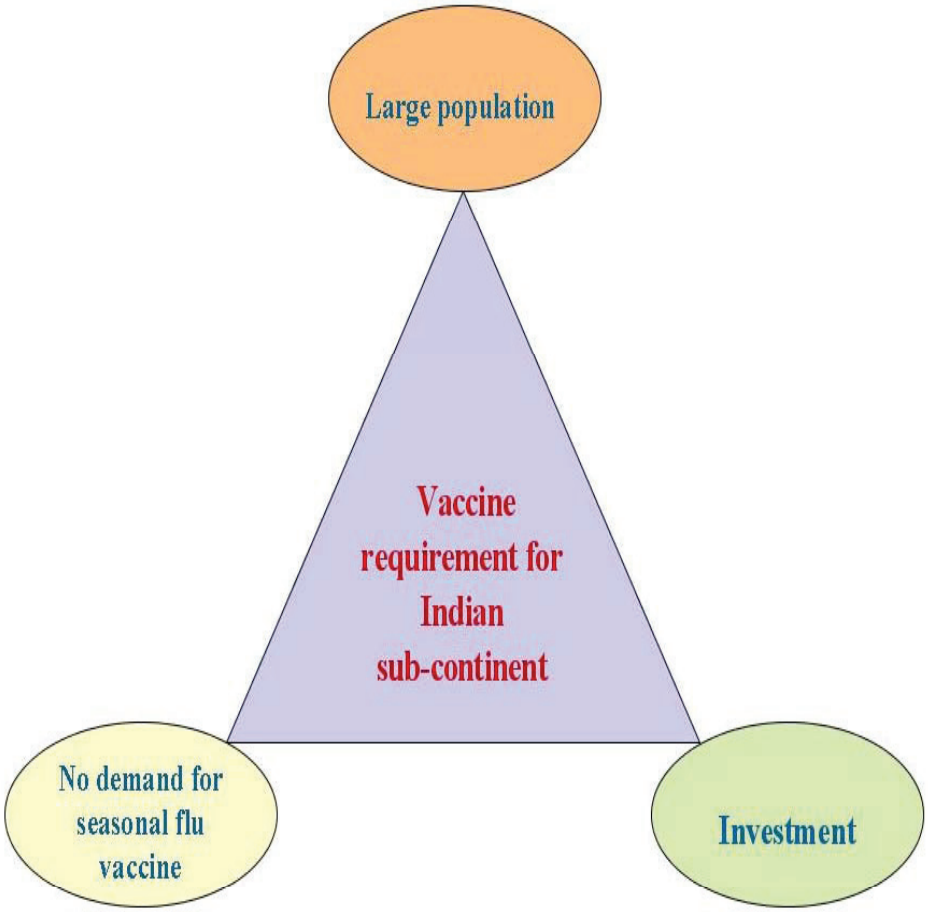

Figure 1: Production challenges for pandemic vaccine development in developing countries such as India

Serum Institute of India Ltd. (SIIL) has been one of the largest vaccine manufacturers and has contributed immensely in making country self-sufficient for DTP (Diphtheria, Tetanus and Pertussis), MMR (Measles, Mumps and Rubella), *Haemophilus influenzae* (type-b), BCG and Hepatitis-B vaccines. SIIL could not undertake capacity building exercise for flu vaccines for an obvious lack of market demand.

Therefore, when the WHO approached SIIL for capacity building, SIIL decided to work on a pandemic vaccine with the aim of contributing to the capacity building and stockpiling approach of WHO. A special team was created to support the activity of development of pandemic flu vaccine. The activity went through handling of simple flu virus strains like APR8, seasonal vaccine strains and subsequently H5N1 virus. A suitable system for growing, inactivating and purifying viruses was developed which could be tailored to facilitate handling of any strain of flu virus to produce a vaccine. Different approaches of subunit and whole virion (inactivated) vaccines were followed and formulation studies in view of defining doses, adjuvants and route of administrations were undertaken. The studies indicated higher immunogenicity of whole virus vaccine as compared to sub-unit vaccine. A marked increase in immunogenicity of whole virus vaccine as compared to subunit vaccine was observed with aluminium-based adjuvants (**Figure 2**). This was consistent with previous reports on superior immunogenicity of alum adjuvanted

whole virus vaccine [8]. Furthermore, the use of alum based adjuvants was attractive due to few IP barriers and moreover studies on adjuvanted H5N1 vaccines have yielded modest evidence for dose sparing or broadened immune responses [9].

Based on this, use of adjuvanted whole virion vaccine was finalized and a generic procedure of formulation and adjuvantation was followed. SIIL was able to develop an inactivated adjuvanted H5N1 whole virus vaccine for animal toxicity studies in the record time of 18 to 20 months (December 2008).

In April/May 2009, reports of a possible swine flu pandemic appeared and WHO requested SIIL to undertake the development of an H1N1 vaccine. It was anticipated that a stockpile approach alone might not be adequate for countries like India, which will require at least 1.2 billion doses if the whole population needs to be immunized.

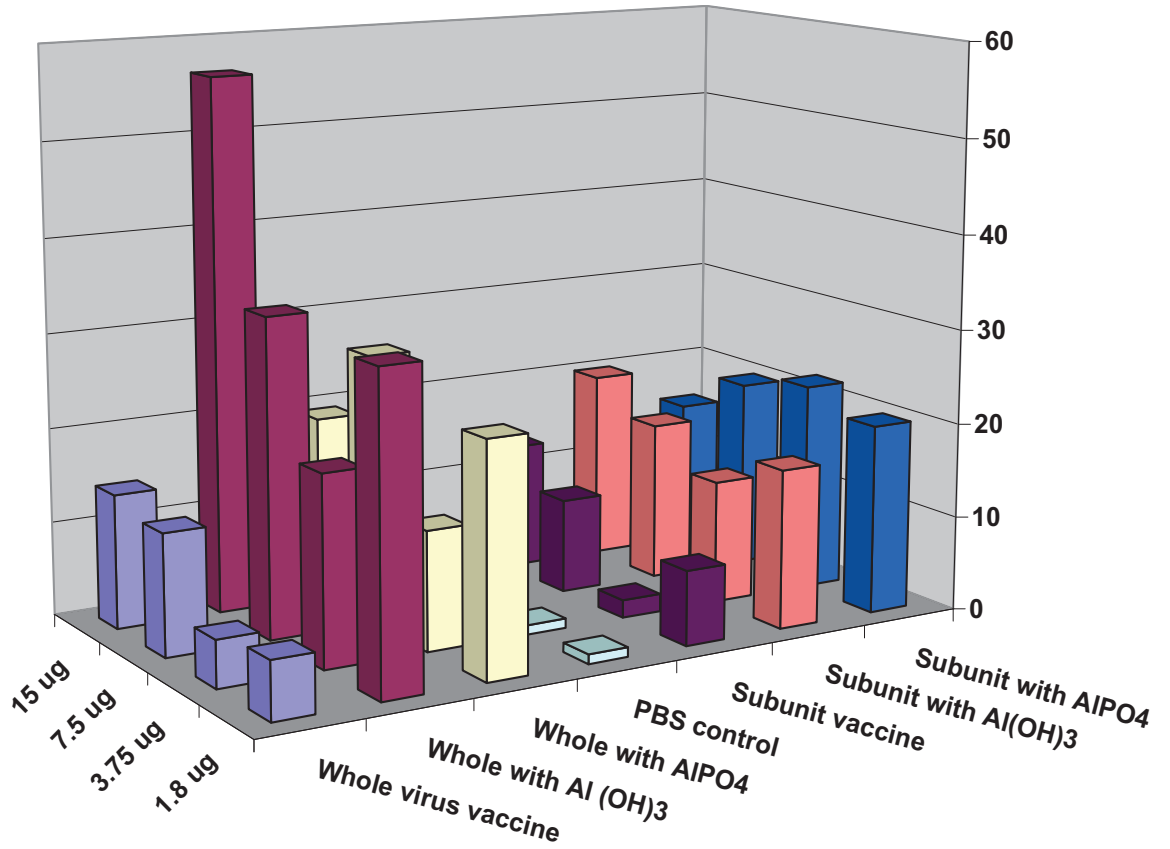

Figure 2 : Comparative immune response to H5N1-NIBRG-14 whole virus vaccine and subunit vaccine

SIIL looked for acquisition of technology which would be highly scalable and offer ease of delivery. A successful agreement was reached between WHO, Nobilon, BioDiem & SIIL, by which SIIL obtained the license to use the cold-adapted virus strain for developing an intranasal live attenuated influenza vaccine. In August 2009, the cold-adapted strain was received and SIIL developed LAIV vaccine at a fast speed. The vaccine is currently in Phase-I clinical trials. With current set up, SIIL expects to reach a production capacity of about 50 million doses/year.

Based on experience with the inactivated H5N1 vaccine, development of an inactivated, alum adjuvanted whole virion H1N1 vaccine was also undertaken using in-house technology. In July 2009, the strain for manufacturing an inactivated vaccine was received and a vaccine was developed for intramuscular administration. Regulatory approvals for human Phase-I clinical trials have been obtained and studies were to begin in January 2010. SIIL expects to reach a production capacity of about 1.5 million doses/year.

After successful completion of these trials, SIIL will have the required production capacity to position itself as a large-scale manufacturer of both LAIV & IIV vaccines. This entire exercise will lay the foundation for pandemic as well as seasonal flu production which will cater to needs for people in India as well as for people outside India who have no access to these vaccines.

4. Conclusion

Capacity building has been an excellent international public heath initiative to support the development and production of pandemic influenza vaccines. Such initiatives will definitely result in more equitable distribution of production capacities globally. The success of this initiative is also attributed to whole hearted support of international agencies including national and international Regulatory Agencies, for which product development was completed in the shortest possible time. Such initiatives have also prepared and strengthened developing country vaccine manufacturers to tackle a pandemic situation in the future, as the capacity to develop a vaccine in the shortest possible time can be extended to any influenza virus strain.

5. Acknowledgements

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