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WHO initiative to increase global and equitable access to influenza vaccine in the event of a pandemic: Supporting developing country production capacity through technology transfer

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ABSTRACT

Should a highly pathogenic avian influenza virus, such as the H5N1 virus type currently circulating in birds, become transmissible among humans, an effective vaccine, rapidly available in vast quantities, would be the best tool to prevent high case-fatalities and the breakdown of health and social services. The number of vaccine doses that could be produced on demand has risen sharply over the last few years; however, it is still alarmingly short of the 13 billion doses that would be needed if two doses were required to protect fully the world's population. Most developing countries would be last in the queue to benefit from a pandemic vaccine. The World Health Organization, together with governments, the pharmaceutical industry and other stakeholders, has been implementing the global pandemic influenza action plan to increase vaccine supply since 2006. Building capacity in developing countries to manufacture influenza vaccine is an integral part of this plan, as well as research and development into more efficacious technologies, e.g. those that allow significant dose-sparing. To this end, the influenza vaccine technology transfer initiative was launched in 2007 and, to date, vaccine manufacturers in 11 developing countries have received grants to acquire the capacity to produce inactivated or live attenuated influenza vaccine for their populations. In addition, a centralized 'hub' has been established to facilitate training in the new technologies for scientists and regulators in the countries. This supplement of *Vaccine* is devoted to showcasing the interim results of the WHO initiative and the impressive progress made by the developing country manufacturers.

1. Introduction

The world has been on its guard against avian influenza (A)H5N1 ever since 1997, when a highly pathogenic virus crossed the species barrier to affect humans working in close contact with infected poultry in the Hong Kong Special Administrative Region, People's Republic of China. Between February 2003 and December 2010, the World Health Organization (WHO) received reports of 516 human H5N1 influenza cases, of whom 306 died, representing a case-fatality rate of over 59%. This, and the threat of an imminent, severe pandemic led the Fifty-eighth World Health Assembly in 2005 (resolution WHA58.5) to urge countries to strengthen their pandemic influenza preparedness and response. The WHO Secretariat was requested to seek solutions to increase global capacity to produce epidemic and pandemic influenza vaccines, and to encourage research and development (R&D) into new and improved vaccines, particularly those that required a lower antigen content per dose. This recommendation was based on awareness that containment measures, although critical, may delay but cannot alone prevent the spread of a deadly influenza virus.

In November 2005, WHO convened the first of a series of meetings on the development and clinical evaluation of influenza vaccines targeting viral strains with pandemic potential [1], during which researchers, manufacturers and regulators review safety and efficacy standards, antigen-sparing strategies, and priority research needs. These meetings complement those organized by WHO since 2004 on the development of influenza vaccines that induce broad spectrum and long-lasting immune responses. It was considered that vaccines with these characteristics could protect against anti-

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genic variants within a subtype and, at least partially, against infection by novel viruses with the potential to cause a pandemic.

2. Global action plan to increase vaccine supply

In order to address a central concern of the World Health Assembly – reducing the anticipated gap between influenza vaccine supply and demand in a pandemic situation – WHO organized a landmark consultation to identify the most promising approaches to enable the immunization of the world's 6.7 billion population within the shortest possible time. Thus, in May 2006, the global pandemic influenza action plan to increase vaccine supply (GAP) [2] was agreed upon by a broad range of stakeholders representing policy makers, national immunization programmes, regulatory authorities, vaccine manufacturers and the research community. To achieve the overarching goal, three mutually reinforcing strategies were considered urgent and essential: the promotion of seasonal vaccination programmes to increase market demand and drive production capacity; the expansion of manufacturing capability, particularly in developing countries; and enhanced influenza vaccine R&D.

In 2006, global production capacity for seasonal influenza vaccine was estimated at 350 million doses. Although annual capacity had reached nearly 900 million doses in 2009 [3], this still falls alarmingly short of 13.4 billion pandemic doses, should two doses be required to elicit immunity in the entire world population within six months of a pandemic alert. Moreover, in 2006, 90% of influenza vaccine production was located in nine countries (largely in Europe and North America) that represented only 10% of the global population. Other countries, notably those in Africa, the Middle East and Asia, could witness a staggering death toll and a severe strain on their health services while waiting for producing countries and regions to have vaccinated their own populations.

In May 2007, the Sixtieth World Health Assembly, noting the objectives and strategies of the GAP, requested the Secretariat in resolution WHA60.28 to seek ways to ensure the equitable sharing of benefits of influenza vaccine R&D, including the development of capacity for influenza vaccine production in developing countries. Indeed, domestic or regional production was considered one of the most effective strategies for vulnerable countries and regions to have access to an influenza vaccine in the event of a pandemic. The general consensus to increase global access to drugs, vaccines and diagnostics was significantly promoted through adoption of the global strategy and plan of action on public health, innovation and intellectual property (GSPA-PHI) by the Sixty-first World Health Assembly in May 2008 (resolution WHA61.21). Two elements highlighted by the GSPA-PHI were the need to build and improve capacity in developing countries, and to facilitate the transfer of health-related technologies. The GSPA-PHI thus provided further legitimacy to the WHO strategy of enhancing influenza vaccine production through technology transfer to developing countries.

Progress by WHO, its global partners and developing countries towards this strategy is the focus of this special edition of *Vaccine*.

3. WHO influenza vaccine technology transfer initiative

In 2007, WHO embarked on an ambitious initiative to increase the capacity for influenza vaccine production in developing countries. To date, more than US$ 25 million have been awarded to 11 developing country manufacturers to establish or enhance this capacity. Grants have also enabled the establishment of a centre of excellence for training and transfer of influenza vaccine production technologies to new manufacturers. In addition, WHO has negotiated a non-exclusive licence for a live attenuated influenza vaccine (LAIV) technology. A summary of the rationale behind the choice of the technologies and the selection process for the awards under the aegis of the WHO influenza vaccine technology transfer initiative is provided in this Section.

3.1. Selection of technologies

In order to assist developing country vaccine manufacturers to identify technologies most suited to their needs, WHO commissioned in 2006 a review of the technologies used to produce the currently registered influenza vaccines [4]. The review considered whole-virion, split and subunit inactivated, as well as live attenuated vaccines, produced either in eggs or cell culture. It also considered the capital investment required to establish a manufacturing facility, the time needed for product approval, and the relative cost of vaccine produced by each method. The review concluded that the egg-based inactivated influenza vaccine (IIV) production process was potentially the easiest to establish as it is used to produce more than 90% of vaccines available on the market and presents few unknowns in the path to regulatory approval. In contrast, tissue-culture based production of IIV requires much greater financial investment and, at the time of the review, faced numerous regulatory questions.

For pandemic surge capacity, egg-based LAIV requires smaller capital investment than IIV and offers significantly higher yield, faster quality control and release and, importantly, needle-free administration. This made LAIV an attractive option, particularly for developing countries with very large populations and limited numbers of health-care workers able to administer injectable IIV in a short period of time. However, while the LAIV manufacturing process is simple and potentially easier to transfer to developing countries than IIV, the production and distribution of LAIV requires a licence agreement with one of the two technology owners (see Section 3.3 below).

The review did not evaluate in detail upstream vaccine technologies such as recombinant antigens, viral vector- or DNA-based vaccines. Although promising, none of these technologies were licensed at that time, and it was therefore premature for WHO to recommend them to developing countries. The review did, however, point out that the addition of adjuvants, particularly oil-in-water emulsions, to IIV permitted significant dose reduction and could therefore be very useful for surge production in the event of a pandemic.

3.2. Selection of manufacturers

Following a first public call for proposals via the WHO web site in 2007, six developing country vaccine manufacturers were awarded grants (out of nine who applied) to establish or expand influenza vaccine manufacturing capacity, and a further five were selected subsequent to a second call in 2009. The 11 vaccine manufacturers (Table 1) have received grants of between US$ 0.5–4.27 million. All proposals were evaluated against mandatory criteria, technical merit, public health value and potential domestic and regional impact by an independent external Technical Advisory Group. In addition, each manufacturer was required to demonstrate government support for its proposal – a critical element to ensuring that manufacturing plans are in line with immunization plans.

One mandatory criterion was that a manufacturer was producing at least one human vaccine approved by the national regulatory agency. Given the complexity of influenza vaccine production, this helped ensure the transfer of technology to experienced manufacturers, and contributed to the success of the project. However, the criterion eliminated emerging manufacturers that were keen to establish local influenza vaccine production but had not (yet) registered a vaccine for human use. In order to address the urgent need for regions such as sub-Saharan Africa to be able to produce