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Advancing new vaccines against pandemic influenza in low-resource countries

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ABSTRACT

With the support of the Biomedical Advanced Research and Development Authority (BARDA), PATH is working with governments and vaccine manufacturers to strengthen their influenza vaccine manufacturing capacity and improve their ability to respond to emerging pandemic influenza viruses. Vaccines directed against influenza A/H5N1 and A/H7N9 strains are a particular focus, given the potential for these viruses to acquire properties that may lead to a pandemic. This paper will review influenza vaccine development from a developing country perspective and PATH's support of this effort. Several vaccines are currently in preclinical and clinical development at our partners for seasonal and pandemic influenza in Vietnam (IVAC and VABIOTECH), Serbia (Torlak), China (BCHT), Brazil (Butantan), and India (SII). Products in development include split, whole-virus inactivated and live attenuated influenza vaccines (LAIVs). Additionally, while most manufacturers propagate the virus in eggs, PATH is supporting the development of cell-based processes that could substantially increase global manufacturing capacity and flexibility. We review recent data from clinical trials of pandemic influenza vaccines manufactured in developing countries. An important discussion is on the role of whole virion vaccines for H5N1, given the poor immunogenicity of split vaccines and the complexity involved in developing potent adjuvants.

1. Licensed seasonal influenza vaccines and their limitations

Public health leaders agree that vaccines are the best way to control the spread of influenza. Globally, influenza results in 3–5 million cases of severe illness and up to 500,000 deaths each year. People at high risk of serious influenza complications include children younger than 5 years of age, adults 65 years of age and older, pregnant women, and people with certain medical conditions. A recent study showed that in 2008, 2–7% of deaths globally from acute lower respiratory infections in children younger than 5 years of age were associated with seasonal influenza. This represents 28,000–111,500 deaths, 99% of which occurred in developing countries [1,2].

Several licensed influenza vaccines are available in the United States for the 2016–2017 influenza season. These included: inactivated, quadrivalent (IIV4), standard dose, FLUARIX® (GSK) and FLULAVAL® (ID Biomedical Corporation of Quebec); Fluzone® and Fluzone®, intradermal (Sanofi Pasteur); inactivated, quadrivalent, cell culture-based (ccIIV4), standard dose, FLUCELVAX® (Seqirus); inactivated, trivalent (IIV3), standard dose, AFLURIA® and FLUVIRIN® (Seqirus); adjuvanted inactivated, (aIIV3) trivalent, standard dose, FLUAD™ (Seqirus); inactivated, trivalent (IIV3), high dose, Fluzone® (Sanofi Pasteur); recombinant, trivalent (RIV3), Flublok® (Protein Sciences) [3]. Trivalent influenza vaccines (TIV) target 2 circulating influenza A viruses and 1 influenza B virus, and quadrivalent vaccines target an additional B virus.

Vaccine effectiveness (VE) is a yearly concern, and antigenic drift and antigenic shift are important causes for vaccine failure (Fig. 1). Seasonal influenza vaccine mismatch, in which the circulating strains do not match well with the vaccine, has occurred multiple times over the last several years due to antigenic drift. In 2014–2015, the drifted influenza A/Switzerland/9715293/2013 (H3N2) virus became the prevalent circulating strain and the vaccine available in fall 2014 (influenza A/Texas/50/2012) offered poor protection against the mismatch (VE 18%). In 2012–2013, a mismatch was caused by a mutation of the seed virus (IVR-165) due to adaptation to growth in eggs. During the 2007–2008 influenza season, the dominant circulating strain was A/Brisbane/10/2007 (H3N2), which was antigenically different from the strain included

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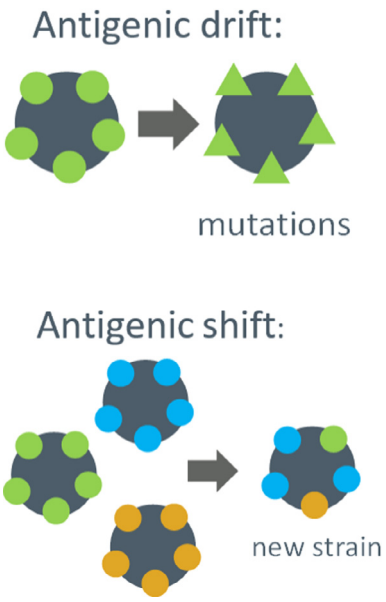

Fig. 1. Antigenic drifts are generated by mutations in the viral genome and small changes to antigenic sites on the viral surface. Antigenic shift occurs when 2 or more different strains combine to form a new virus.

in the vaccine (A/Wisconsin/67/2005) and led to a severe influenza season. In 2003–2004, there was a mismatch due to the circulation of A/Fujian/411/2002, a new unanticipated antigenic variant of influenza A/H3N2 [4,5]. These recent influenza seasons exemplify the unpredictability of seasonal influenza epidemics and the challenges facing current generation vaccines, which can only follow changes in circulating viruses.

Antigenic shift occurs less frequently than antigenic drift, but is a potential cause for global pandemic outbreaks. The most recent case is the pandemic A/H1N1/California in 2009. The virus was first detected in mid-April 2009; laboratory testing immediately confirmed it was an entirely new virus that appeared to be a unique combination of North American swine-lineage H1N1 and Eurasian lineage swine-origin H1N1 influenza viruses. A vaccine for the virus was first administered in the United States in early October 2009 to individuals at highest risk of complications, and by late December 2009, vaccination was made available to everyone. The epidemic peaked in late October, then quickly declined to below baseline levels in January 2010. Though the response was quick, the vaccine was not available to provide timely protection, and highlighted the need for alternative production platforms or a different paradigm [6].

2. Influenza A/H5N1

Influenza A viruses circulating among poultry have the potential to recombine with human influenza A viruses and become transmissible among humans. The highly pathogenic Asian avian influenza A virus H5N1, in particular, poses a significant public health threat. Influenza A/H5N1 was first detected in humans in 1997 during a poultry outbreak in Hong Kong and is often referred to as avian influenza or bird flu. In birds, this virus is highly infectious and causes severe respiratory disease. Though it can spread to people, the virus does not easily infect humans and there is no evidence of significant transmission between humans. As of July 2016, 854 confirmed human cases and 450 deaths had been reported to the World Health Organization (WHO) [7]. If the influenza A/H5N1 virus were to change and become easily transmissible from person to person while retaining its capacity to cause severe disease, the public health consequences could be very serious.

3. HHS/BARDA and PATH: Influenza vaccine development and international capacity building

With a gap of billions of doses between today's global influenza vaccine production capacity and what is needed to protect the world's population, health leaders recognize that the participation of many vaccine suppliers is vital to meeting needs for annual and pandemic influenza control worldwide. Supporting the availability of additional manufacturers to enter the market and produce high-quality, lifesaving influenza vaccines at a lower cost is critical to ensuring preparedness against seasonal influenza and pandemic influenza outbreaks [8].

Pandemic influenza outbreaks could lead to mortality rates significantly greater than those of seasonal influenza. Models based on the 1918–1920 influenza pandemic estimate that up to 62 million people could die if a similar pandemic were to occur today, with approximately 96% of those deaths taking place in the developing world [9]. The 2009 influenza A/H1N1 pandemic (a new strain of A/H1N1), the highly pathogenic avian influenza strains (A/H5N1 and A/H7N9), and past experiences with seasonal influenza vaccine mismatch have all illustrated the unpredictability of the virus and the challenges of generating a global response to newly emerging virus strains.

With funding from the Biomedical Advanced Research and Development Authority (BARDA) of the US Department of Health and Human Services, PATH is helping to improve sustainable influenza vaccine production capacity by supporting vaccine manufacturers in Brazil, China, India, Serbia, and Vietnam. This project is an important step toward increasing local and regional seasonal influenza vaccine supplies and improving real-time response in the case of pandemic outbreaks [10].

In Vietnam, we are supporting the state-run vaccine developer Institute of Vaccines and Medical Biologicals (IVAC), to advance the clinical development of an inactivated, whole virion, alum adjuvanted influenza A/H5N1 pandemic vaccine candidate and a low-cost seasonal, inactivated split trivalent inactivated vaccine (TIV) candidate. This work builds on previous work in which PATH and WHO helped IVAC ready its vaccine production facility to manufacture influenza vaccines and advance influenza vaccine candidates into clinical development, including the conduct of a clinical trial for IVAC's monovalent inactivated influenza A/H1N1 whole virion vaccine candidate in healthy adults. We also worked in partnership with Vietnam's Ministry of Health to support the establishment of policies and guidelines for the development, production, and use of influenza vaccines in Vietnam [11–13].

We are also supporting the production of cell culture-based inactivated influenza vaccines at VABIOTECH, a state-owned vaccine and biological production company in Vietnam. Such vaccines could be promising options in a pandemic given their potential to be produced efficiently, at large-scale, and without reliance on egg supplies. To date, PATH has helped VABIOTECH obtain a manufacturing license for cell lines, conducted technical training, and purchased equipment and supplies.

In Serbia, we are providing technical assistance to help the Institute of Virology, Vaccines, and Sera (Torlak) in Belgrade advance an affordable seasonal influenza vaccine candidate through clinical development. The institute has produced a split seasonal, inactivated TIV candidate that has been evaluated in preclinical and Phase 1 studies, and is currently in a Phase 3 clinical trial — the culmination of a long collaboration between Torlak and WHO and, more recently, PATH. We are providing in-depth advice on process development and manufacturing, regulatory

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