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Universal influenza vaccines: Shifting to better vaccines

Francesco Berlanda Scorza*, Vadim Tsvetnitsky[1], John J. Donnelly

PATH, 2201 Westlake Avenue Suite 200, Seattle, WA 98121, USA

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ABSTRACT

Influenza virus causes acute upper and lower respiratory infections and is the most likely, among known pathogens, to cause a large epidemic in humans. Influenza virus mutates rapidly, enabling it to evade natural and vaccine-induced immunity. Furthermore, influenza viruses can cross from animals to humans, generating novel, potentially pandemic strains. Currently available influenza vaccines induce a strain specific response and may be ineffective against new influenza viruses. The difficulty in predicting circulating strains has frequently resulted in mismatch between the annual vaccine and circulating viruses. Low-resource countries remain mostly unprotected against seasonal influenza and are particularly vulnerable to future pandemics, in part, because investments in vaccine manufacturing and stockpiling are concentrated in high-resource countries. Antibodies that target conserved sites in the hemagglutinin stalk have been isolated from humans and shown to confer protection in animal models, suggesting that broadly protective immunity may be possible. Several innovative influenza vaccine candidates are currently in preclinical or early clinical development. New technologies include adjuvants, synthetic peptides, virus-like particles (VLPs), DNA vectors, messenger RNA, viral vectors, and attenuated or inactivated influenza viruses. Other approaches target the conserved exposed epitope of the surface exposed membrane matrix protein M2e. Well-conserved influenza proteins, such as nucleoprotein and matrix protein, are mainly targeted for developing strong cross-protective T cell responses. With multiple vaccine candidates moving along the testing and development pipeline, the field is steadily moving toward a product that is more potent, durable, and broadly protective than previously licensed vaccines.

Influenza viruses circulate globally and affect all age groups. Vaccines are the best tools available for preventing influenza illness and are recommended annually by the World Health Organization (WHO) for groups at high risk of mortality or significant morbidity, including pregnant women, children six months to five years of age, elderly individuals (65 years of age and older), individuals with chronic medical conditions and health care workers. The US Centers for Disease Control and Prevention (CDC) have broadened the WHO recommendation for influenza vaccination to all persons older than six months of age, with two doses for children between six months and eight years old who are receiving influenza vaccine for the first time.

Human influenza viruses are classified into three types (A, B, C) based on the following highly conserved internal proteins: matrix protein 1 (M1), membrane matrix protein (M2), and nucleoprotein (NP). Type A influenza viruses are further sub-divided into subtypes based on the antigenicity of their hemagglutinin (HA) and neuraminidase (NA) surface glycoproteins. Currently, 18 HA and 9 NA subtypes of influenza A are known and all exist in aquatic birds, their natural reservoirs. Influenza B viruses infect only humans, but two antigenically and phylogenetically distinct lineages co-circulate. Type C influenza viruses are known to infect humans and pigs but infections are rare. Species tropism, particularly of influenza A, is determined by the presence, anatomic location and structure of terminal sialic acid residues that mediate viral attachment and entry. Influenza's antigenic variation, which has limited the development of a broadly protective vaccine, manifests as either antigenic drift or antigenic shift. Antigenic drift is the ability of the virus to escape pre-existing immunity through point mutations in the genes encoding HA and NA, making circulating strain prediction difficult and antigenic mismatch likely. Antigenic shift is defined by the recombination of HA genes that results in the generation of a novel influenza A strain to which a large proportion of the human population has no pre-existing immunity, therefore increasing the potential for a pandemic, as occurred during the shift from H1 to H2 in 1957 and H2 to H3 in 1968.

The 2009 influenza A/H1N1 pandemic (a new strain of A/H1N1), the highly pathogenic avian influenza strains (A/H5N1 and

* Corresponding author. Tel.: +1 2069414873.
E-mail address: fberlanda-scorza@path.org (F. Berlanda Scorza).
[1] Present address: International AIDS Vaccine Initiative, 125 Broad Street, 9th Floor, New York, NY 10004, USA.

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A/H7N9), and past experiences with seasonal influenza vaccine mismatch have all illustrated the unpredictability of the virus and the challenges to mounting a global response against newly emerging virus strains. Currently, influenza A H1 and H3 subtypes co-circulate. The direct transmission of highly pathogenic avian strains to humans (such as influenza A/H5N1 and, more recently, influenza A/H7N9) presents an additional threat, but such strains have not yet demonstrated the capacity for efficient transmission in humans. Vaccination remains the preferred approach toward controlling influenza; however, the challenge of annual large-scale immunizations is currently beyond the capacities of low-resource countries, which need to improve vaccine delivery across all age groups, with a special focus on children. For such immunizations to become a reality, a vaccine that induces broadly cross-protective and durable immunity would need to be developed.

1. Licensed influenza vaccines and their limitations

In general, influenza vaccines have an excellent safety record, but their efficacy varies significantly in various age groups and against different strains. Rare exceptions to the safety profile have emerged in association to the use of specific adjuvants, as discussed later. Strain mismatch and pandemics are frequent causes for vaccine failure and, over the last few years, several mismatches and one pandemic have occurred. The development and deployment of an H1N1 pdm2009 vaccine was relatively rapid, but the vaccine still became available too late to provide timely protection to vulnerable populations during the pandemic (Fig. 1, yellow line). Vaccine mismatch with seasonal influenza strains also has occurred multiple times, for example during the 2003/2004 season when an A/Fujian/411/2002 virus emerged as a new and unanticipated antigenic variant of influenza A/H3N2 (Fig. 1, orange line). Of 326 influenza A/H3N2 isolates characterized, only 25% were antigenically similar to the widely used vaccine strain A/Panama/2007/99 (H3N2). During the 2007/2008 influenza season, A/Wisconsin/67/2005 (H3N2) was included in the vaccine, but A/Brisbane/10/2007 (H3N2) was the dominant circulating strain, resulting in a particularly severe influenza season (Fig. 1, gray line). A mismatch of the vaccine to the recent 2012/2013 influenza season resulted in only 46% efficacy in adults 18 through 49 years and 9% efficacy in people older than 65 years of age (Fig. 1, green line). In this case, the circulating strain prediction was correct, but the mismatch was caused by a mutation in the egg-adapted seed virus (IVR-165) that was sent to vaccine manufacturers. The mutation was not present in the WHO-recommended strain but occurred during strain adaptation to growth in eggs.

Influenza vaccine mismatch also occurred during the 2014/2015 influenza season (Fig. 1, brown line). The influenza A/H3N2 strain included in the vaccine (A/Texas/50/2012) was selected based on the most common circulating influenza A/H3N2 virus in February 2014. The drifted influenza A/Switzerland/9715293/2013 virus was first detected in the United States in March 2014 in a small number of samples. Before the end of the year, it became the prevalent circulating strain and the vaccine available in the fall of 2014 offered poor protection against the mismatch, with an efficacy estimated around 18% for influenza A/H3N2. As a result, the influenza-associated hospitalization rate among people 65 years of age and older in the 2014/2015 season was the highest recorded since the CDC began tracking those data in 2005. In February 2015, WHO recommended that the new A/Switzerland/9715293/2013 (H3N2)-like virus to be included in the vaccine for the 2015/2016 season.

In the case of live-attenuated influenza vaccines (LAIVs), the efficacy of Flumist® in randomized clinical trials was tempered by limited effectiveness against influenza A (H1N1) pdm09 in children during the 2013/2014 influenza season. These results may be specific to the influenza A/H1N1 component of the vaccine since the original A/California strain has been found to be more susceptible to thermal degradation due to a unique HA stalk sequence [1]. The full reason for its lack of effectiveness, however, is not entirely understood and is the subject of ongoing investigation. The past and current seasons exemplify the unpredictability of seasonal influenza epidemics and the challenge for current-generation vaccines that can only follow changes in circulating viruses. They also highlight opportunities for a universal vaccine that would induce broadly protective immunity.

2. General approaches for low- and middle-income country (LMIC) markets

While availability of data on disease burden in LIMIC remains limited, a recent study has shown that, during year 2008, seasonal influenza was associated globally with 2–7% of deaths from acute lower respiratory infections (ALRI) in children younger than 5 years and resulted in 28,000–111,500 deaths, of which 99% occurred in developing countries. Influenza A, particularly H3N2 subtype, caused higher morbidity and mortality than influenza B [2]. As for pandemic outbreaks, models based on the 1918–1920 influenza pandemic estimate that up to 62 million people could die if a similar pandemic occurred today, and approximately 96% of the deaths would occur in the developing world [3]. Despite these figures, investments for improved seasonal and pandemic vaccine manufacturing and stockpiles are concentrated in high-resource countries. More than 80% of seasonal influenza vaccine doses produced between 2009 and 2010 originated from seven large manufacturers located in the United States, Canada, Australia, western Europe, Russia, China, and Japan. Moreover, no pandemic influenza A/H1N1 vaccine was available in the majority of low-resource countries before January 2010, more than eight months after the WHO declared a pandemic. Many low-resource countries do not have a full picture of their influenza disease burden due to limited surveillance. In some tropical settings, influenza circulates year-round, making influenza-related morbidity substantial, especially as a major contributor to childhood pneumonia [4].

Five companies currently offer WHO-prequalified split virion inactivated trivalent or quadrivalent seasonal influenza vaccines (GlaxoSmithKline, Green Cross Corp., Hualan Bio, Novartis, and Sanofi Pasteur) or seasonal trivalent LAIV (Serum Institute of India). Several companies (CSL, Green Cross Corp., MedImmune, Novartis, Sanofi Pasteur and Serum Institute of India) obtained prequalification of their pandemic influenza vaccines only for the 2009 pandemic influenza A/H1N1 virus. Despite sufficient influenza vaccine production capacity for annual needs in high-resource countries, influenza vaccination coverage rates among high-risk groups are below the targets set by national governments and recommended by WHO in these settings. In LMICs, differing health priorities and constraints on health budgets primarily limit influenza vaccine use to private markets, with the possible exception of Pan-American Health Organization countries. Expanding influenza vaccine coverage to public markets in LMICs is unlikely to happen in the absence of data from cost-benefit studies. Local production is expected to reduce cost and improve availability of vaccines in some LMICs, but the lack of local recommendations and government funding for vaccine use remains a limiting factor. Limited regional manufacturing capacity for seasonal vaccines also results in limited capacity to respond to pandemic outbreaks. The use of LAIVs may contribute to improved coverage rates in children since they cost less than IIVs to produce and administer, particularly if the age indication for current LAIV, currently two years of age, can be safely extended to a younger population.

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