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WHO Report

Report on eighth WHO meeting on development of influenza vaccines that induce broadly protective and long-lasting immune responses: Chicago, USA, 23–24 August 2016

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ABSTRACT

In August 2016, the World Health Organization (WHO) convened the "Eighth meeting on development of influenza vaccines that induce broadly protective and long-lasting immune responses" to discuss the regulatory requirements and pathways for licensure of next-generation influenza vaccines, and to identify areas where WHO can promote the development of such vaccines. Participants included approximately 120 representatives of academia, the vaccine industry, research and development funders, and regulatory and public health agencies. They reviewed the draft WHO preferred product characteristics (PPCs) of vaccines that could address prioritized unmet public health needs and discussed the challenges facing the development of such vaccines, especially for low- and middle-income countries (LMIC). They defined the data desired by public-health decision makers globally and explored how to support the progression of promising candidates into late-stage clinical trials and for all countries. This report highlights the major discussions of the meeting.

1. Introduction

1.1. Need for next-generation vaccines

Influenza causes a substantial amount of death and suffering annually, and it is responsible for considerable economic losses due to the cost of care and lost productivity [1]. The World Health Organization (WHO) has determined that "*Safe and well-tolerated influenza vaccines that prevent severe influenza illness, provide protection beyond a single year, and are suitable for programmatic use, are needed for low- and middle-income countries (LMICs)* [2,3]." This global health need is not

Abbreviations: ADCC, Antibody-dependent cell-mediated cytotoxicity; AE, Adverse event; CMI, cell-mediated immunity; CONSISE, Consortium for the Standardization of Influenza Seroepidemiology; CoP, Immune correlate of protection; EMA, European Medicines Agency; EU, European Union; HA, Influenza haemagglutinin protein; HI, Haemagglutination inhibition; Hib, *Haemophilus influenzae* type b; HICs, High-income countries; IIV, Inactivated influenza vaccine; LAIV, Live-attenuated influenza vaccine; LMICs, Low- and middle-income countries; M2e, Ectodomain of influenza matrix 2 protein; NA, Influenza neuraminidase protein; PDVAC, WHO Product Development for Vaccines Advisory Committee; PPC, Preferred product characteristic; PPP, Public-private partnerships; WHO, World Health Organization.

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addressed sufficiently by current influenza vaccine products and evidence.

Current influenza vaccines have limited duration of protection and must be updated annually to match the rapid evolution of circulating influenza viruses. This regular reformulation of influenza vaccines addresses two challenges, "antigenic drift" and "antigenic shift." Antigenic drift results from mutations within viral proteins. New vaccines that can provide broad protection against drifted strains could decrease the need for frequent formulation change and greatly facilitate prevention of seasonal influenza disease in LMICs. Antigenic shift refers to major changes in the influenza type A hemagglutinin (HA) antigen caused by reassortment between different influenza A subtypes. This can result in viruses to which most of the population has no protective immunity and lead to a global pandemic. If new vaccines with broad activity against influenza A were available before the emergence of an influenza pandemic, they could be rapidly deployed to all countries to prevent pandemic illness or to decrease transmission within the population. Collectively, such new vaccines are referred to as "next-generation" vaccines.

The WHO Product Development for Vaccines Advisory Committee (PDVAC) has concluded that, "Development of improved seasonal vaccines may represent lower hanging fruit in terms of regulatory acceptability, compared to the timelines for a truly universal influenza vaccine [4]." PDVAC has noted that, "Development of universal influenza vaccines will be challenging and protracted," and recommended that, "There should be a focus on the definition of, and the collection of data to support implementation of 'improved' seasonal [influenza]vaccines that would offer more immediate impact in LMICs [5]." PDVAC also advised WHO to, "Develop strategic public health goals and preferred product characteristics (PPCs) for improved seasonal [influenza] vaccines and to provide guidance on data that would be needed to establish improved performance of such vaccines [5]."

In response, this meeting was convened to discuss the regulatory requirements and pathways for licensure of next-generation influenza vaccines, and to identify areas where WHO can promote the development of such vaccines. While solutions to both seasonal and pandemic influenza are likely to share technologies and delivery systems, the meeting focused on prevention of seasonal influenza through routine immunization programs. The last WHO meeting on development of next-generation influenza vaccines was in 2014 [6].

1.1.1. Potential to facilitate vaccine delivery

Influenza vaccines are reformulated up to twice yearly for use in the Northern and Southern Hemispheres [7]. Some countries, however, have more than one epidemic period per year [8] or prolonged circulation of influenza virus, including different influenza types and subtypes, for many months of the year [7,9]. The production of influenza vaccines is timed to ensure vaccine availability before the anticipated influenza season in temperate countries, and the expiration date is determined to prevent use of an outdated formulation during the subsequent influenza season [10]. There are gaps in influenza vaccine availability when a prior formulation has expired and when the next formulation is not yet available. Theoretically, disruption can be minimized with a country alternating between different hemisphere formulations of influenza vaccine when they become available, or by extending the vaccine expiration date 2–3 months to complete vaccination campaigns [10].

For several reasons, protection after vaccination might not last for more than about six months [9], leading to the suggestion that strategies could include year-round vaccination in settings where influenza virus circulation is perennial [10]. Such a strategy could also potentially better respond to drifted circulating viruses with the use of the most up-to-date influenza vaccine formulation [10]. Year-round vaccination programs may have the strongest usefulness for maternal immunization, as vaccine can protect a woman during her pregnancy when she is at high risk for influenza morbidity and it can protect her infant for the first months of life when influenza vaccines are not approved for use [11]. Scenarios of year-long use of influenza vaccines introduce many complexities in vaccine procurement, stock rotations, and waste removal. An influenza vaccine providing longer protection after vaccination would simplify this situation.

1.1.2. Potential to increase demand and improve equity of coverage

WHO's influenza vaccine policy recommendations aim to protect vulnerable high-risk groups against severe influenza disease and death [1]. While many LMICs are anticipated to prioritize vaccines indicated for the prevention of severe influenza illness, additional considerations including maintaining a healthy work force and the cost-effectiveness of vaccines may drive vaccine policy decisions in high-income countries (HICs). There is a predictable demand in some, but not all HICs, for seasonal influenza vaccines [12]. In addition, countries want access to a vaccine to protect against a future influenza pandemic [13,14].

A recent study [15] showed that 59% of WHO Member States reported having an influenza vaccine policy; however, many countries and, some whole WHO regions, do not purchase and use influenza vaccines for most of their populations [12]. While this could be seen as a failure to establish a convincing value proposition [2], there are many reasons for this serious health inequity of access to influenza vaccines, especially in low-resource settings [12,15]. These include competing priorities for scarce resources; the perception, or reality, that vaccines are unaffordable; lack of data on local burden of influenza-associated disease; logistical difficulties of vaccinating the populations at risk; availability and timing of the appropriate vaccine formulation [16] and short vaccine shelf-life with need for annual stock replacement [10]. While comprehensive studies have not been conducted to determine why low-resource countries are not adopting influenza vaccines, one survey indicated that low recognition of influenza as a severe disease among immunization program and policy leaders may play a role [17]. Additionally, policy makers from low-resource countries are expected to place higher value on vaccines with demonstrated impact on severe illness – and such data for influenza are limited, particularly in such settings [2,3].

The unmet need for influenza vaccines in LMICs may be addressed by using current vaccines in different ways and not just by using novel products. Several attendees thought that vaccine price will also remain a key consideration.

Many of the improvements in influenza vaccines would be valued in both LMICs and HICs markets. This would provide a commercial rationale for developing products that can be used in both markets, even if the vaccine presentation and packaging might be different [18]. For example, multi-dose vials are recommended for LMICs due to the relatively low cost and cold-chain storage volume per dose [19], whereas pre-filled syringe presentations are preferred in HICs due to their convenience.

1.2. Unaddressed evidence needs among specific target groups

In 2012, WHO recommendations for the use of seasonal influenza vaccines were published [1]. Pregnant women were listed as the highest priority group in countries starting or expanding their influenza vaccine programs because they have increased risk of influenza morbidity, antenatal services in most countries could facilitate the delivery of influenza vaccines during pregnancy, and influenza vaccines are effective in this group [20]. Other risk

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