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WHO Report

Data and product needs for influenza immunization programs in low- and middle-income countries: Rationale and main conclusions of the WHO preferred product characteristics for next-generation influenza vaccines

Kathleen M. Neuzil [a], Joseph S. Bresee [b], Fernando de la Hoz [c], Kari Johansen [d], Ruth A. Karron [e], Anand Krishnan [f], Shabir A. Madhi [g], Punam Mangtani [h], David J. Spiro [i], Justin R. Ortiz [j,*], On behalf of the WHO Preferred Product Characteristics for Next-Generation Influenza Vaccines Advisory Group

[a] University of Maryland, Center for Vaccine Development, Baltimore, MD, USA
[b] Centers for Disease Control and Prevention, Atlanta, GA, USA
[c] Colombian National Institute of Health, Bogotá, Colombia
[d] European Centre for Disease Prevention and Control, Stockholm, Sweden
[e] Center for Immunization Research, Johns Hopkins University, Baltimore, MD, USA
[f] Centre for Community Medicine, All India Institute of Medical Sciences, New Delhi, India
[g] Medical Research Council: Respiratory and Meningeal Pathogens Research Unit, University of the Witwatersrand, Faculty of Health Sciences, Parktown, South Africa
[h] Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK
[i] National Institutes of Health, Bethesda, MD, USA
[j] World Health Organization, Geneva, Switzerland

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ABSTRACT

In 2017, WHO convened a working group of global experts to develop the Preferred Product Characteristics (PPC) for Next-Generation Influenza Vaccines. PPCs are intended to encourage innovation in vaccine development. They describe WHO preferences for parameters of vaccines, in particular their indications, target groups, implementation strategies, and clinical data needed for assessment of safety and efficacy. PPCs are shaped by the global unmet public health need in a priority disease area for which WHO encourages vaccine development. These preferences reflect WHO's mandate to promote the development of vaccines with high public health impact and suitability in Low- and Middle-Income Countries (LMIC). The target audience is all entities intending to develop or to achieve widespread adoption of a specific influenza vaccine product in these settings. The working group determined that existing influenza vaccines are not well suited for LMIC use. While many developed country manufactures and research funders prioritize influenza vaccine products for use in adults and the elderly, most LMICs do not have sufficiently strong health systems to deliver vaccines to these groups. Policy makers from LMICs are expected to place higher value on vaccines indicated for prevention of severe illness, however the clinical development of influenza vaccines focuses on demonstrating prevention of any influenza illness. Many influenza vaccine products do not meet WHO standards for programmatic suitability of vaccines, which introduces challenges when vaccines are used in low-resource settings. And finally, current vaccines do not integrate well with routine immunization programs in LMICs, given age of vaccine licensure, arbitrary expiration dates timed for temperate country markets, and the need for year-round immunization in countries with prolonged influenza seasonality. While all interested parties should refer to the full PPC document for details, in this article we highlight data needs for new influenza vaccines to better demonstrate the value proposition in LMICs.

* Corresponding author at: Initiative for Vaccine Research, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland.
E-mail addresses: kneuzil@som.umaryland.edu (K.M. Neuzil), jsb6@cdc.gov (J.S. Bresee), fpdelahozr@unal.edu.co (F. de la Hoz), Kari.Johansen@ecdc.europa.eu (K. Johansen), rkarron@jhu.edu (R.A. Karron), kanand@aiims.ac.in (A. Krishnan), ShabirM@nicd.ac.za (S.A. Madhi), Punam.Mangtani@lshtm.ac.uk (P. Mangtani), david.spiro@nih.gov (D.J. Spiro), influenzavaccine@who.int (J.R. Ortiz).

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1. Background

Influenza causes substantial death and suffering and has significant socioeconomic implications [1]. The World Health Organization (WHO) recommends that countries use influenza vaccine in high risk individuals, including pregnant women, children aged 6–59 months, elderly adults, individuals with specific chronic medical conditions, and health-care workers to prevent severe illness and death [1]. Influenza vaccines are reformulated up to twice yearly and are of modest effectiveness against influenza illness. The continuous mutations of circulating influenza viruses and the limited duration of vaccine protection necessitate that high-risk persons be vaccinated annually. High-income countries use most of the influenza vaccines that are distributed globally [2,3], while many low- and middle-income countries (LMICs) do not have national influenza vaccine programs [3]. Available influenza vaccines may not meet the expectations or programmatic needs of LMICs, and the data in support of their use may be insufficient for LMIC policy makers.

2. WHO preferred product characteristics

Improved influenza vaccines that meet the needs of LMICs are critically needed. In 2017, WHO developed *Preferred Product Characteristics for Next-Generation Influenza Vaccines* to encourage innovation in influenza vaccine development [4]. Preferred product characteristics (PPCs) describe WHO preferences for vaccine indications, target groups, implementation strategies, and clinical data needed for assessment of product safety and efficacy [5].

PPCs are shaped by the global unmet public health need in a priority disease area for which WHO encourages vaccine development. These preferences reflect WHO's mandate to promote the development of vaccines with high public health impact and suitability in LMICs. The target audience is all entities intending to develop or to achieve widespread adoption of a specific influenza vaccine product in these settings.

3. Unmet global public health need and use case

WHO convened an advisory group of international experts on influenza vaccines and public health to develop the PPC document. The PPC Advisory Group developed a consensus statement on the global public health need for improved influenza vaccines:

> *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.*

The WHO position on influenza vaccines and the global unmet public health need define a use case that is prioritized – the prevention of severe seasonal influenza illness through routine immunization of high-risk groups in LMICs which have existing systems for vaccine delivery. The high risk groups for which improved influenza vaccines are most needed are young children and older adults, as influenza vaccine effectiveness is suboptimal in these groups [6]. The PPC Advisory Group considered immunization strategies timed with existing immunization contacts, such as the routine childhood vaccination schedule or antenatal care. Given the limitations in immunization systems for adults in low-resource settings [7], the priority target group of the PPC document therefore is young children, defined as those younger than five years of age, with immunization of other risk groups as a secondary target.

4. Strategic goals

The PPC defines strategic goals for five- and ten-year time horizons and the preferred vaccine characteristics to address each strategic goal. The document development was guided by evidence-based assumptions with regard to vaccine research and development as well as availability of immunization services within these time horizons. The strategic goals take into account burden of disease, likelihood of product availability, and the practical realities of immunization systems in LMICs. The first strategic goal specifies vaccine improvements by 2022:

> *By 2022, greater protection against vaccine-matched or drifted influenza strains than provided by currently prequalified non-adjuvanted non-replicating influenza vaccines, and protection against severe influenza for at least one year, will have been demonstrated for seasonal influenza vaccines that are suitable for high-risk groups in low- and middle-income countries.*

This strategic goal promotes the evaluation of currently available vaccines and vaccine technologies to demonstrate product characteristics and feasibility of use that would align with the global unmet public health need. A second strategic goal specifies vaccine improvements by 2027:

> *By 2027, influenza vaccines that have the potential to provide protection against severe influenza A virus illness for at least five years, and are suitable for high-risk groups in low- and middle-income countries, will be in advanced clinical development.*

This strategic goal promotes research and development of products that are aligned with the global unmet public health need.

5. Key findings of the advisory group

The full PPC document is available on the WHO website [8]. It includes an expanded rationale, procedures followed, assumptions, and vaccine characteristic parameters for each strategic goal. Specific product parameters include indication, target population, safety, co-administration with other vaccines, duration of protection, outcome measures and efficacy, immunogenicity, registration, prequalification for procurement by United Nations agencies, programmatic suitability, and value proposition. The document highlights gaps in data needed by LMIC policy makers. Fully addressing certain gaps, such as the ten-year goal of development of an influenza vaccine that can prevent illness up to five years after a primary series, will likely require more extensive research and additional product development. Other gaps, such as age de-escalation studies to facilitate integration of influenza vaccination into routine pediatric immunization schedules, can be pursued already with existing products. While all interested parties should refer to the full PPC document for details, key conclusions are highlighted below.

5.1. Vaccine delivery systems are limited in many countries

While scant information is available regarding the burden of severe influenza in high-risk groups in most LMIC settings, data from high-income countries indicate that adults with chronic medical illness and older adults bear the highest burden of influenza mortality [9]. However, these age groups do not have established vaccine delivery systems in many LMICs. In these countries, health systems are typically able to provide vaccination through national childhood immunization programs which target children <2 years of age, antenatal care programs, and HPV vaccination programs targeting girls from 9 years of age. While providing vaccination across the entire life course is a global priority [7], more work is

needed to strengthen adult immunization systems. Any entity advocating influenza vaccine use in LMICs must be aware of the limitations of health systems to deliver immunization services to adults.

5.2. Data on the impact of influenza vaccination on severe illness are needed

Policy makers from LMICs are expected to place higher value on vaccines indicated for prevention of severe illness. High quality data on the impact of influenza vaccines on severe illness in these settings are extremely limited. Severe illness clinical endpoints should be developed which are generalizable, feasibly applicable in studies conducted in LMIC settings, and reproducible. Well-designed studies demonstrating influenza vaccine impact on important public health outcomes would strengthen the case for their use globally. An influenza vaccine clinical trial in LMICs with demonstration of vaccine efficacy against severe illness would substantially influence how influenza vaccines are used globally [10].

5.3. Influenza vaccines must meet the programmatic needs of immunization programs

Vaccine developers should be aware of the call from immunization programs in resource-poor settings that innovation related to programmatic suitability, such as ease of administration and thermostability, would lead to major public health benefits. Advances that are achievable in the next decade include greater availability of needle-free administration for vaccine delivery and improved thermostability to obviate the need for a refrigerated cold chain. Widespread integration of influenza vaccines into routine pediatric programs in LMICs will require decreased age for licensure and possibly changes in vaccine presentation and packaging to adhere to current WHO guidelines for programmatic suitability [11]. For immunization programs in countries with prolonged or atypical influenza seasons, addressing the gaps in vaccine availability caused by fixed expiration dates and manufacturing schedules designed for temperate countries could be transformative.

5.4. Existing options should be tested and utilized

Although broad-spectrum influenza vaccines which confer long-lasting immunity may not be licensed for many years [12], much can be done in the short term to ensure evaluation and optimal use of existing vaccines and to adapt or modify current influenza vaccine technologies and vaccination strategies. Available influenza vaccine technologies including adjuvanted, live-attenuated, intradermal, microneedle patches, or high-dose vaccines may meet some or all of the PPC criteria and should be evaluated for use in LMICs.

6. Conclusion

The PPC document describes preferences for parameters of influenza vaccines to prevent severe influenza illness in LMICs. To date, the evidence in support of influenza vaccine program impact has not sufficiently demonstrated the value proposition of their routine use in LMIC settings. Data on additional clinical outcomes, including severe illness, are needed if influenza vaccines are to be prioritized by LMICs for use. While it would be a major public health achievement if a vaccine product were demonstrated to meet all of the five-year or ten-year strategic goal parameters, demonstration of one or more of the recommended PPC characteristics for an influenza vaccine product would be of high value for public health. For all entities desiring to expand routine influenza vaccines use or to strengthen pandemic influenza vaccine preparedness in LMICs, we advise consideration of the WHO influenza vaccine product preferences.

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Author contributions

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Declaration of interests

Joseph S. Bresee has no conflict of interest to declare on this manuscript.

Fernando de la Hoz has no conflict of interest to declare on this manuscript.

Kari Johansen is a staff member of the European Centre for Disease Prevention and Control (ECDC) and has no interests to declare. The views expressed in the Article does not necessarily represent the views or advice of the ECDC.

Ruth A. Karron has no conflict of interest to declare on this manuscript.

Anand Krishnan has no conflict of interest to declare on this manuscript.

Shabir A. Madhi has no conflict of interest to declare on this manuscript.

Punam Mangtani has no conflict of interest to declare on this manuscript.

Kathleen M. Neuzil has no conflict of interest to declare on this manuscript.

David J. Spiro has no conflict of interest to declare on this manuscript.

Justin R. Ortiz has no conflict of interest to declare on this manuscript.

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