WHO Preferred Product Characteristics for Next-Generation Influenza Vaccines
WHO Preferred Product Characteristics for Next-Generation Influenza Vaccines

Department of Immunization,
Vaccines and Biologicals
### Abbreviations & acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>GVAP</td>
<td>WHO Global Vaccine Action Plan</td>
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<tr>
<td>HA</td>
<td>Influenza hemagglutinin glycoprotein</td>
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<td>IVR</td>
<td>WHO Initiative for Vaccine Research</td>
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<tr>
<td>LMIC</td>
<td>Low and middle income country</td>
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<tr>
<td>PPC</td>
<td>Preferred product characteristic</td>
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<tr>
<td>TPP</td>
<td>Target product profile</td>
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<tr>
<td>VPPAG</td>
<td>WHO Vaccine Presentation and Packaging Advisory Group</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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Introduction

The World Health Organization (WHO) recommends that persons at high risk for severe influenza illness should be vaccinated annually against influenza. However, many low and middle income countries (LMICs) do not have national influenza vaccination programmes. The absence of such programmes can be partly explained by the challenges associated with current vaccines which need to be reformulated up to twice each year to match the anticipated circulating strains in the northern and southern hemisphere influenza seasons, are generally of moderate efficacy against ambulatory influenza illness, and provide protection of limited duration. There is therefore a public health need for improved influenza vaccines conferring broader and longer protection against severe illness, particularly in LMICs.

To encourage innovation in influenza vaccine development to address these needs, WHO has developed Preferred Product Characteristics for Next-Generation Influenza Vaccines. Preferred product characteristics (PPCs) describe WHO preferences for vaccine parameters, primarily the indications, target groups, immunization strategies, and clinical data for assessment of safety and efficacy. These preferences are shaped by the global unmet public health need in a WHO priority disease area.

This document is designed to provide early guidance for the improvement of current influenza vaccines and the development of new influenza vaccines. It addresses vaccine research and development within five and ten year time horizons. WHO encourages studies and data collection most relevant to LMIC policy-making but does not advocate for specific vaccine formulations for use in those settings. WHO encourages product development that results in a dual market for both high income country and LMIC settings to facilitate commercial development, affordable pricing, and global distribution. The PPCs indicate to product developers the influenza vaccine characteristics that are most useful to policy-makers in LMICs. PPCs do not provide clinical evaluation guidance, regulatory guidance, or data thresholds for policy-making, and do not quantify explicit performance thresholds which may introduce barriers to improvement and innovation.

WHO convened an advisory group of international experts on influenza vaccines and public health to develop the PPC document. This PPC Advisory Group prepared 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 throughout this document – the prevention of severe seasonal influenza illness through annual immunization of population groups at high risk in LMICs which have existing systems for vaccine delivery. The groups for which improved influenza vaccines are most needed are young children and elderly adults, as influenza vaccine effectiveness is suboptimal in both of these populations. Given the limitations in immunization systems for adults in low-resource settings, the priority target group of this document is young children, with immunization of other risk groups as a secondary target.

The PPC primary immunization strategy is the direct protection of immunized persons against influenza illness. Other important influenza immunization strategies, including vaccination of children to reduce transmission and influenza incidence at the household or community level, immunization of pregnant women to prevent influenza illness in infants, prevention of ambulatory influenza to ensure a healthy workforce, and responding to influenza pandemics, are discussed but are not considered to be part of the primary use case for the PPC document. However, technologies for production of improved influenza vaccines to address these different use case scenarios are likely to be similar.

Strategic goals for five and ten year time horizons and the preferred vaccine characteristics to address each strategic goal were defined by the PPC Advisory Group. The PPC 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. Many technical achievements may be required for a product to meet all of the WHO preferred characteristics; however, attaining even some of them would be of value for public health.

This document highlights influenza vaccine preferences for LMICs for consideration by vaccine developers and by manufacturers of licensed products. Substantial global resources and effort have been dedicated to the development of a next generation influenza vaccine that would decrease the need for annual reformulation and vaccination. If these efforts are successful, and if such products are affordable and programmatically suitable for LMIC use, they could make an important contribution towards meeting this public health need.

Although licensed broad-spectrum influenza vaccines which confer long-lasting immunity may not be available for many years, much could be done to ensure optimal use of existing vaccines and to adapt or modify current influenza vaccine technologies to address LMIC needs. While policy-makers in LMICs prioritize vaccines with demonstrated efficacy against severe illness, the impact of influenza vaccine programmes against important public health outcomes is uncertain.
A carefully-planned influenza vaccine study in LMICs with demonstration of vaccine efficacy against severe illness could change considerably how influenza vaccines are used globally. Further efforts to ensure that such vaccines are more programmatically suitable for LMIC contexts are necessary, such as integration into national routine immunization programmes, extending expiration dates to ensure year-round availability, improving thermostability, and achieving needle-free administration options.

The PPC Advisory Group stresses the need to continue efforts to develop next-generation influenza vaccines and to demonstrate the ability of current vaccines to address public health needs globally.
1. WHO preferred product characteristics

1.1. Background and purpose
Preferred product characteristics (PPCs) 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. These preferences are shaped by the global unmet public health need in a priority disease area for which WHO encourages vaccine development. WHO preferences reflect its mandate to promote the development of vaccines with high public health impact and suitability in low and middle income countries (LMICs).

PPCs are intended to drive innovation towards meeting public health needs by providing guidance on the development of new products or the improvement of existing products. PPCs address early stage vaccine research and development usually at least five to ten years prior to vaccine availability, and they are periodically reviewed and updated when necessary. PPCs are not static and do not set out product development exit criteria. Characteristics specific for particular products, including technologies to be used, vaccine content, and individual product development or manufacturing issues are beyond the scope of these documents.

Although the WHO PPC parameters are commonly found in a similar tool developed by the pharmaceutical industry, known as target product profile (TPP), PPCs provide guidance tailored to the public health perspective. PPCs focus on the preferred characteristics, while industry TPPs often specify minimally acceptable criteria in addition to preferred criteria. PPCs do not quantify explicit performance thresholds which may serve as barriers to improvement and innovation.

PPCs do not provide new guidance on other characteristics often described in TPPs such as vaccine presentation, packaging, thermostability, or formulation and disposal; these topics are addressed by the WHO Vaccine Presentation and Packaging Advisory Group (VPPAG) and by the WHO prequalification process. The VPPAG interacts with manufacturers on issues related to presentation and packaging and has developed a preferred product profile on these subjects. The WHO prequalification process assesses vaccine quality, safety, efficacy, and suitability for use in LMICs. This process has identified programmatic suitability as one of the criteria which are used in reviewing vaccines submitted for prequalification for procurement by United Nations agencies.

Any next-generation influenza vaccine that becomes licensed and potentially available will undergo evidence-based assessment for policy recommendations by the
WHO Strategic Advisory Group of Experts (SAGE) on immunization.\textsuperscript{6} Additional information on influenza vaccine research and development is provided on the WHO website.\textsuperscript{7-12}

1.2 Target audience for WHO preferred product characteristics
The primary audience for this document includes all entities which seek to achieve widespread adoption of a specific influenza vaccine product in LMICs. The PPCs are intended to encourage innovation and development of vaccines that perform in settings most relevant to the global unmet public health need. It is important to note that whether or not a vaccine meets the PPC criteria, it would be assessed by WHO for possible policy recommendations according to the standard process. The PPCs are intended to highlight the influenza vaccine data most useful to policy-makers in LMICs; they are not intended to serve as clinical evaluation guidance, regulatory guidance, or data thresholds for policy-making.

1.3 Improved influenza vaccines: strategic priorities for WHO
Seasonal influenza is caused by influenza A and B viruses which circulate globally. In temperate and many tropical and subtropical regions, seasonal influenza viruses are typically transmitted during widespread outbreaks coinciding with winter or rainy periods. Other tropical or subtropical countries may experience prolonged seasonal influenza epidemics or year-round circulation. A hallmark of influenza viruses is their ability to undergo antigenic drift in response to population immunity. Because of antigenic drift, influenza vaccine antigen composition is reformulated regularly to match the vaccine strains as closely as possible to currently circulating influenza viruses.

Occasionally, influenza A viruses undergo antigenic shift. These changes may be caused by reassortment between different influenza A subtypes, such as between animal and human subtypes. Pandemic influenza can result if there is very limited or no immunity in the population, if sustained person-to-person transmission occurs, and if infection causes clinical illness. Given current vaccine technologies, an influenza pandemic will require the development of new, specific influenza vaccines in response to the emerging virus.

The influenza vaccine strain composition is recommended by WHO after review of the antigenic and genetic properties of circulating viruses worldwide.\textsuperscript{13} The vaccine strain selection is conducted twice annually to produce vaccine formulations tailored to the main periods of influenza activity in the northern and southern hemispheres. The composition of the northern hemisphere formulation is determined annually in February and the vaccine is generally available in August or September for use prior to the northern hemisphere winter. Similarly, the composition of the southern hemisphere formulation is determined annually in September and the vaccine is generally available in April for use prior to the southern hemisphere winter.

Most countries using influenza vaccines are in temperate regions. There are gaps in influenza vaccine availability between expiry of one influenza vaccine formulation and availability of the updated formulation for the same hemisphere. These gaps
are of little consequence in temperate countries with predictable winter influenza seasons, but many tropical countries have influenza seasonality that coincides with the vaccine availability gaps. While alternating use between northern and southern hemisphere formulations may allow a country to avoid availability gaps, it introduces additional challenges for vaccine procurement, distribution, stock management, and waste removal.

The WHO influenza vaccine policy recommendations aim to protect vulnerable risk groups against severe influenza-associated disease and death. WHO targets the following high-risk groups for influenza vaccination: children aged 6 through 59 months, pregnant women, elderly adults, individuals with specific chronic medical conditions, and health-care workers. Due to favourable performance of influenza vaccines in pregnant women and the availability of vaccination services for them in LMICs, WHO recommends that pregnant women be prioritized by countries initiating or expanding influenza vaccination programmes.

The WHO Global Vaccine Action Plan (GVAP) calls for the development of a universal influenza vaccine. The target is “at least one vaccine providing broad-spectrum protection against influenza A licensed by 2020”. There remains debate, however, about what constitutes a “universal” influenza vaccine. WHO working definitions of universal influenza vaccines typically include broader spectrum protection and longer lasting immunity than conferred by currently available influenza vaccines. A universal influenza vaccine could be either an entirely new type of vaccine or an improved version of the currently used vaccines. A new vaccine, where one course of vaccination with priming and boosting doses would provide life-long protection against influenza, without requiring any subsequent boosting doses or antigenic adaptation of the vaccine, is highly desirable but would take much longer to develop. Alternatively, a universal influenza vaccine may result from incremental improvements of non-replicating influenza vaccines in current use, whereby broader or longer lasting immunity would be induced, but they may still require regular boosting doses and are not expected to protect against all influenza A and B illnesses. Current influenza vaccines could be adapted with new technologies to produce improved vaccines or they could be evaluated using different vaccination strategies to demonstrate greater impact on illness or feasibility of use in LMIC settings. Such approaches may reduce the need for annual re-vaccination or increase vaccine effectiveness in years when there is a poor match between vaccine strains and circulating viruses.

In 2015, the WHO Product Development for Vaccines Advisory Committee (PDVAC) considered the case for an improved seasonal influenza vaccine approach, optimizing the currently available vaccines to improve the magnitude, quality and duration of the protective response, and providing protection for more than one season. Development of improved seasonal influenza vaccines could be a relatively near-term feasible approach compared to the timelines for an entirely new universal
influenza vaccine. PDVAC therefore advised WHO to develop strategic public health goals and PPCs for improved seasonal influenza vaccines and to provide guidance on data that would be needed to demonstrate improved performance of such vaccines.\textsuperscript{17}

Given the GVAP mandate to develop broad-spectrum influenza vaccines that provide durable immunity and the PDVAC call for incremental vaccine improvements that could be realized in the near term,\textsuperscript{15,17} the PPC document focuses on two strategic goals. The first goal to be reached by 2022 promotes incremental vaccine improvements, and the second goal to be reached by 2027 promotes greater research and development advances towards vaccines providing broader protection against severe influenza illness.

1.4 Assumptions regarding vaccine research and immunization services
The PPC Advisory Group consulted experts in influenza research to develop common definitions for terms related to influenza virology and vaccine performance. Experts were also asked to advise on the likelihood that products with particular performance characteristics would be in advanced clinical development within five and ten year time horizons. Additional advice on immunization delivery systems was sought from experts on immunization in low resource settings. The expert responses informed the development of common definitions (Appendix 1) and evidence-based assumptions regarding vaccine research and immunization services (Appendix 2) used by the PPC Advisory Group.

Preferred characteristics of future influenza vaccines are compared to a standard product. WHO has chosen as a benchmark non-adjuvanted, non-replicating seasonal influenza vaccines that have been prequalified by WHO for procurement by United Nations agencies. These vaccines are extensively studied and widely available for use globally. No adjuvanted seasonal influenza vaccine has been prequalified by WHO for procurement by United Nations agencies, and no live attenuated influenza vaccine has been licensed for use in children younger than 2 years.

This document does not predict clinical trial demonstration of particular characteristics or licensure of novel products with such characteristics within the five or ten year time horizons. It is assumed that products which could feasibly have certain characteristics would be in advanced clinical development within those time periods. In some instances, particularly within the five-year PPC, products with particular characteristics may already be available; in this case they could be evaluated using different vaccination strategies to demonstrate greater impact on illness or feasibility of use in LMIC settings. While the assumptions are based on expert advice, it is impossible to predict with any certainty the availability of future technology. PPCs are therefore updated regularly to reflect the current state of knowledge regarding vaccine research and development.
Five-year assumptions regarding vaccine research and immunization system feasibility

**Vaccine cross-protection**
An improved influenza vaccine which can feasibly provide greater cross-protection against different influenza A and B viruses than currently prequalified non-replicating, non-adjuvanted seasonal influenza vaccines is likely to be in advanced clinical development within the next five years. Such vaccines are generally expected to have incremental improvements compared to current vaccines, have increased protection against drift variants of influenza A and B, and may include adjuvanted non-replicating vaccines or live attenuated influenza vaccines. Some currently licensed vaccines may already have greater cross-protection than currently prequalified non-replicating, non-adjuvanted seasonal influenza vaccines. In this case, the PPCs include demonstration of this characteristic.

**Vaccine duration of protection**
An improved influenza vaccine that has the potential to provide protection through one full year can feasibly be in advanced clinical development within the next five years. In certain years and particular populations, current seasonal non-adjuvanted influenza vaccines may have waning effectiveness through the course of the influenza season. Some currently licensed vaccines may already provide protection through one full year. In this case, the PPCs include demonstration of this characteristic.

**Immunization systems**
Existing immunization systems have the potential to vaccinate children aged 6 weeks through 59 months (with the strongest programmes for 6 weeks through 24 months), pregnant women, and health-care workers in low income countries. Immunization systems are unlikely to be widely available to immunize children aged 5 through 18 years or adults in low income countries within the next five years.
Ten-year assumptions regarding vaccine research and immunization system feasibility

**Vaccine cross-protection**

An influenza vaccine that can feasibly provide protection against particular influenza A phylogenetic HA groups (1 or 2) is likely to be in advanced clinical development within the next ten years, but not within the next five years. Such a vaccine is defined in this PPC document as a “universal-type influenza A vaccine” (Appendix 1). Such vaccines are generally expected to result from new approaches in vaccine design from currently available influenza vaccines (such as vaccines designed to stimulate antibodies targeting conserved virus epitopes or vaccines designed to stimulate cellular immune responses). A universal-type influenza vaccine which can feasibly provide protection against influenza B virus lineages is unlikely to be in advanced clinical development within the next ten years.

**Vaccine duration of protection**

An influenza vaccine which can feasibly provide universal-type protection against all influenza B virus lineages is unlikely to be in advanced clinical development within the next ten years.

**Immunization systems**

Existing immunization systems have the potential to immunize children aged 6 weeks through 59 months (with the strongest being 6 weeks through 24 months), pregnant women, and health-care workers in low income countries. Immunization systems are not assumed to be widely available to immunize children aged 5 through 18 years or adults in low income countries within the next ten years.

A full list of evidence-based assumptions used for this document is in Appendix 2.
1.5 Global unmet public health need and strategic goals for improved influenza vaccines

The PPC Advisory Group developed a consensus statement which served as the foundation for subsequent PPC development.

**Statement of global unmet public health need**
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 PPC Advisory Group developed two strategic goals, taking into account burden of disease, likelihood of product availability, and the practical realities of immunization systems in LMICs. The first goal specifies vaccine improvements by 2022 (five-year goal) and the second goal specifies vaccine improvements by 2027 (ten-year goal).

**Strategic Goal 1**
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.

Strategic Goal 1 is intended to promote 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. It is possible that demonstration of at least some preferred product characteristics for Strategic Goal 1 could be accomplished by 2022. Existing technologies may provide greater effectiveness against matched influenza A or B strains or better cross-reactive immunity to divergent influenza A or B viruses than benchmark vaccines. The primary vaccination series may require more than one vaccine dose.

**Strategic Goal 2**
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.

Strategic Goal 2 is intended to promote vaccine research and development to produce products that are aligned with the global unmet public health need. A universal-type influenza A vaccine is likely to be in advanced clinical development within the next ten years; however the development of influenza B vaccines that can provide universal-type protection against all influenza B virus lineages is not expected to progress as far within the same time frame. As with Strategic Goal 1, the primary vaccination series may require more than one vaccine dose.
1.6 Target groups, immunization strategies, and use case
The WHO position on influenza vaccines and the global unmet public health need define a use case that is prioritized by the PPC – the prevention of severe seasonal influenza illness through routine immunization of high-risk groups in LMICs which have existing services for vaccine delivery. Among high-risk groups, influenza vaccine effectiveness is suboptimal in young children and elderly adults, indicating a need for research to improve vaccine efficacy in these groups. Systems exist in all LMICs that could potentially provide influenza vaccination for young children, pregnant women, and health-care workers. Among these groups, the frequency of severe influenza illness in LMICs is greatest in children <5 years of age. Balancing considerations of areas of research need with feasibility and disease burden, the primary use case for the PPC is children <5 years of age, prioritizing public health need while taking into account expected limitations of immunization systems (which in low-resource settings primarily serve children aged <2 years). Some countries may have mechanisms for provision of vaccines to other high-risk groups, such as pregnant women, adults with chronic disease, or elderly adults. These target groups received secondary prioritization by the PPC Advisory Group.

The PPC primary use case immunization strategy is the direct protection of immunized persons against severe influenza illness. Other important influenza immunization strategies received secondary prioritization by the PPC Advisory Group. The use of influenza vaccines to reduce transmission and influenza incidence at the household or community level is a strategy advocated by some public health agencies for both seasonal and pandemic influenza. Immunization of health-care workers can prevent transmission of influenza virus to vulnerable patient populations and ensure a healthy workforce during influenza epidemics and pandemics. Finally, influenza vaccines can modify the impact of influenza pandemics. Many of the technologies to produce improved influenza vaccines to address these different use case scenarios are likely to be similar to those for the PPC primary use case, however the data requirements to inform policies based on these different use case scenarios may differ.

A maternal influenza immunization strategy designed to prevent disease in young infants is a special use case that is not wholly considered by this document. Vaccination during pregnancy can prevent influenza illness in the mother and in her infant for several months after birth. At present, this is the only option for prevention of influenza in infants younger than 6 months. Vaccination of pregnant women involves unique safety considerations. In addition, a maternal vaccination strategy relies on maternal antibody transfer, and therefore vaccines which might work well in other scenarios (such as a live attenuated influenza vaccine) would not be appropriate for a maternal vaccination strategy designed to prevent disease in infants. The vaccine improvements advocated in the PPC are less relevant to the maternal influenza immunization use case, which is likely to rely on immunization during each pregnancy, and therefore durability of immune response is not a main priority.
While most temperate countries currently provide influenza vaccination in pre-seasonal campaigns, improved influenza vaccines with increased duration of protection will permit new immunization strategies. The PPC Advisory Group considered year-round immunization timed with existing immunization contacts, such as the routine childhood vaccination schedule or antenatal care. These immunization strategies were considered to be the most feasible for LMICs, while recognizing that some LMICs may have additional outreach strategies for providing vaccination, such as school-based programmes.

1.7 Clinical endpoints
Standardized clinical endpoints should be used in influenza vaccine efficacy studies which are conducted to inform immunization policies in LMICs. Severe influenza illness endpoints, such as acute lower respiratory illness, should be used in such studies. Severe illness clinical endpoints should be generalizable, feasibly applicable in studies conducted in LMIC settings, and reproducible. Ideally, severe illness endpoints should be validated against objective clinical outcomes. The PPC Advisory Group recommended that WHO develop guidance regarding standardized clinical endpoints for use in influenza vaccine studies; the guidance should also recommend standardization of clinical data collection, include a proposed minimum dataset to be collected in trial settings, and define a spectrum of severe illness. Influenza vaccine trials with severe illness endpoints will have to be larger than typical influenza vaccine clinical efficacy studies. However, evidence of demonstrated vaccine efficacy against severe influenza illness would be of high public health value and would be expected to have a greater impact on LMIC policy-making than trials designed to assess efficacy against ambulatory illness.
2. PPC for improved influenza vaccines

Strategic Goal 1: 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.

2.1 Indication

<table>
<thead>
<tr>
<th>Preferred characteristic</th>
<th>Rationale</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Prevention of severe influenza illness</td>
<td>Policy-makers from LMICs are expected to place higher value on vaccines indicated for prevention of severe illness than prevention of ambulatory illness.</td>
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2.2 Target population

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<th>Preferred characteristic</th>
<th>Rationale</th>
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<tbody>
<tr>
<td>Children aged 6 weeks through 59 months</td>
<td>Children were prioritized given their high influenza illness burden and existing immunization services in LMICs. The lower end of the age range was chosen to coincide with the first contact within routine childhood immunization schedules and is consistent with the duration of protection demonstrated from maternal influenza vaccination clinical trials. The upper end of the age range can feasibly be served within existing paediatric immunization services.</td>
<td>Vaccines with effectiveness in preventing severe, laboratory-confirmed influenza illness in other high-risk groups, including elderly adults, individuals with specific chronic medical conditions, health-care workers, and pregnant women, can be considered for use in these groups.</td>
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Vaccines with substantial demonstrated indirect effects can be considered for use in groups for which efficacy against only non-severe laboratory-confirmed influenza illness has been shown. For
example, these groups may include school-aged children (effects of herd immunity on other age groups within a community) or pregnant women (effects based on transplacental transfer of antibodies or prevention of direct mother-to-child transmission).

Vaccines with demonstrated effectiveness against non-severe laboratory-confirmed influenza illness can be considered for health-care workers and additional essential groups targeted for other public health purposes.

### 2.3 Safety

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<th>Preferred characteristic</th>
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<tr>
<td>Vaccine risk-benefit assessment should favour vaccine use to prevent severe influenza illness. An increase in mild reactogenicity may be acceptable if the vaccine prevents severe disease. Severe reactogenicity should occur at a rate similar to or less than that associated with currently prequalified non-replicating, non-adjuvanted seasonal influenza vaccines.</td>
<td>The preferred vaccine safety profile depends on the burden and severity of the disease being prevented.</td>
<td>The minimal desired reactogenicity profile will differ by target population. For example, some reactogenicity events are less acceptable in certain age groups, such as fever in infants aged &lt;3 months which can mimic early childhood sepsis and lead to hospitalization and unnecessary invasive tests. Sufficient safety data should be collected from pregnant women according to global and national regulatory standards to allow for permissive use.</td>
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### 2.4 Co-administration

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<tr>
<td>For influenza vaccines intended to be given within routine immunization schedules, absence of clinically important interference with concomitantly administered vaccines should be documented.</td>
<td>Vaccines used as part of routine immunization schedules should not adversely affect the performance of concurrently administered vaccines.</td>
<td>For vaccination of children &lt;6 months of age, the effect of maternal antibodies on infant response should be documented.</td>
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### 2.5 Duration of protection

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<th>Preferred characteristic</th>
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<tr>
<td>The duration of efficacy should be determined for a minimum of one full year (or through an entire influenza season in temperate regions) and should be similar to, or better than, that of currently prequalified non-replicating non-adjuvanted seasonal influenza vaccines.</td>
<td>The preferred duration of protection of at least one year represents an advancement in influenza vaccine performance which is feasible within the next five years.</td>
<td>Following maternal immunization, protection of newborn infants for a period longer than six months is unlikely to be feasible and could be only three to four months.</td>
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Vaccines with demonstrated effectiveness in prevention of severe laboratory-confirmed influenza illness for a minimum of one full year would be adequate for other WHO-defined high-risk groups after efficacy has been documented in children aged 6 weeks through 59 months.
## 2.6 Outcome measure and efficacy

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<th>Preferred characteristic</th>
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<tr>
<td>Severe laboratory-confirmed influenza illness is the preferred outcome measure for efficacy studies. One or both of the following advancements in influenza vaccine performance are preferred for demonstration of vaccine efficacy:</td>
<td>The availability of influenza vaccines that have greater efficacy either against matched circulating strains or against unmatched drifted strains compared to currently available products would represent a significant advancement in public health.</td>
<td>Post licensure randomized clinical trials and some quasi-experimental trial designs are suitable for demonstration of vaccine performance. The evaluation of vaccine efficacy against vaccine-matched strains should have a sufficient number of cases for comparisons. Absence of demonstrated efficacy in settings with too few cases of strain-specific disease for comparison should not be interpreted as absence of efficacy. Improvement compared to existing vaccines may not necessarily be demonstrated through non-inferiority clinical trials. Non-severe laboratory-confirmed influenza illness can be considered an appropriate endpoint for groups with high indirect effects of vaccination or for groups in which prevention of ambulatory influenza illness is recommended, such as health-care workers and other essential groups targeted for other public health purposes. Demonstrated rate reductions against severe illness without laboratory confirmation of influenza virus infection, e.g. as in a vaccine probe study, would also be an adequate demonstration of vaccine performance.</td>
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<tr>
<td><strong>1) The vaccine efficacy should be better than that of currently prequalified non-replicating non-adjuvanted seasonal influenza vaccines for the specific age group for vaccine-matched strains against the recommended outcome measure.</strong></td>
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<td><strong>OR</strong></td>
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<td><strong>2) The vaccine efficacy should be better than that of currently prequalified non-replicating non-adjuvanted seasonal influenza vaccines for the specific age group for circulating antigenically drifted strains against the recommended outcome measure.</strong></td>
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### 2.7 Immunogenicity

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<td>Correlates of protection of influenza vaccines against severe influenza illness are needed to minimize costs of trials and to promote innovation.</td>
<td>There is a relative correlate of protection for HA-based vaccines against laboratory-confirmed influenza illness, but no established correlate of protection for severe influenza outcomes. There is no correlate of protection against severe laboratory-confirmed influenza illness for either HA or non-HA based influenza vaccines. There is no correlate of protection for non-HA based influenza vaccines or live attenuated influenza vaccines against laboratory-confirmed influenza illness of any type.</td>
<td>Immunogenicity studies may be indicated as bridging studies to extrapolate vaccine performance for new age groups, or as part of clinical evaluation in groups for which prevention of non-severe laboratory-confirmed influenza is an adequate outcome (school-aged children, pregnant women, health-care workers and other essential groups targeted for public health purposes).</td>
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### 2.8 Registration and prequalification

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<tr>
<td>The product should be prequalified according to standard procedures for assessing the acceptability of vaccines for purchase by United Nations agencies.</td>
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### 2.9 Programmatic suitability

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<td>The WHO defined criteria for programmatic suitability of vaccines should be met.</td>
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### 2.10 Value proposition

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<tr>
<td>Dosage, regimen, and cost of goods should be compatible with affordable supply. The vaccine should be cost-effective and price should not be a barrier to access, including in LMICs.</td>
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3. PPC for universal-type influenza A vaccines

**Strategic Goal 2:** 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.

### 3.1 Indication

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<thead>
<tr>
<th>Preferred characteristic</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevention of severe laboratory-confirmed influenza illness caused by human influenza A virus infection.</td>
<td>Policy-makers from LMICs are likely to place highest value on vaccines indicated for prevention of severe illness. The focus is on influenza A given its greater severity of disease and the feasibility of a product becoming available within the next ten years.</td>
</tr>
</tbody>
</table>

### 3.2 Target population

<table>
<thead>
<tr>
<th>Preferred characteristic</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persons aged 6 weeks and older belonging to a group at high risk for severe influenza illness (children aged 6 weeks through 59 months, elderly adults, persons with chronic medical conditions, and pregnant women).</td>
<td>All population groups that are considered to be at high risk for severe influenza illness, as specified in the WHO position on influenza vaccines, should be targeted by influenza immunization programmes.</td>
</tr>
</tbody>
</table>

**Comments**

- Vaccines with substantial demonstrated indirect effects can be considered for use in groups for which efficacy against only non-severe laboratory-confirmed influenza illness has been shown. These groups may include school-age children (indirect effects on other age groups within a community) or pregnant women (effects of transplacental transfer of antibodies to protect newborn infants).

- Vaccines with demonstrated effectiveness against non-severe laboratory-confirmed influenza illness can be considered for health-care workers and other essential groups targeted for other public health purposes.
Clinical development of new classes of vaccines would likely require a step-wise, iterative approach beginning in adults before progression to children, pregnant women, and other vulnerable groups.

### 3.3 Safety

<table>
<thead>
<tr>
<th>Preferred characteristic</th>
<th>Rationale</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine risk-benefit assessment should favour vaccine use to prevent severe influenza illness. An increase in mild reactogenicity may be acceptable if the vaccine prevents severe influenza illness. Severe reactogenicity should occur at a rate similar to or less than that of currently prequalified non-replicating non-adjuvanted seasonal influenza vaccines.</td>
<td>Preferred vaccine safety profile depends, in part, on the burden and severity of the disease being prevented.</td>
<td>The minimal desired reactogenicity profile will differ by target population. For example, some reactogenicity events are more medically important in certain age groups such as fever in children &lt;3 months of age which can mimic early childhood sepsis and lead to hospitalization and unnecessary invasive tests. Sufficient safety data should be collected from pregnant women to allow for permissive use.</td>
</tr>
</tbody>
</table>

### 3.4 Co-administration

<table>
<thead>
<tr>
<th>Preferred characteristic</th>
<th>Rationale</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>For influenza vaccines intended to be given within routine immunization schedules, absence of clinically important interference with concomitantly administered vaccines should be documented.</td>
<td>Vaccines used as part of routine immunization schedules should not adversely affect the performance of concurrently administered vaccines.</td>
<td>For vaccination of children &lt;6 months of age, effect on maternal antibodies should be documented.</td>
</tr>
</tbody>
</table>
3.5 Duration of protection

<table>
<thead>
<tr>
<th>Preferred characteristic</th>
<th>The duration of efficacy should be a minimum of five years.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rationale</td>
<td>The preferred duration of protection of at least five years represents an advancement in influenza vaccine performance which is feasible within the next ten years.</td>
</tr>
<tr>
<td>Comments</td>
<td>Following maternal immunization, protection of newborn infants for a period longer than six months is unlikely to be feasible and could be only three to four months.</td>
</tr>
<tr>
<td></td>
<td>Demonstration of efficacy against mismatched strains, with a laboratory-confirmed influenza endpoint, could be studied separately from duration of protection.</td>
</tr>
<tr>
<td></td>
<td>Duration of protection may be determined through post-licensure studies.</td>
</tr>
</tbody>
</table>

3.6 Outcome measure and efficacy

<table>
<thead>
<tr>
<th>Preferred characteristic</th>
<th>Severe laboratory-confirmed influenza illness is the preferred outcome measure for efficacy studies.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Both of the following advancements in influenza vaccine performance are preferred for demonstration of vaccine efficacy:</td>
</tr>
<tr>
<td></td>
<td>1) The vaccine efficacy should be better than that of currently prequalified non-replicating, non-adjuvanted seasonal influenza vaccines for the specific age group for vaccine-matched strains over the preferred duration of protection.</td>
</tr>
<tr>
<td></td>
<td>AND</td>
</tr>
<tr>
<td></td>
<td>2) The vaccine efficacy should be better than that of the currently prequalified non-replicating non-adjuvanted seasonal influenza vaccines for the specific age group for antigenically drifted strains in circulation for the preferred duration of protection (five years).</td>
</tr>
</tbody>
</table>
Rationale
Policy-makers from LMICs are likely to place highest value on vaccines indicated for prevention of severe illness. The availability of influenza vaccines that have greater efficacy against matched circulating strains and also against unmatched drifted strains compared to currently available products would represent a major achievement for public health.

Comments
Post licensure randomized clinical trials and some quasi-experimental trial designs are suitable for demonstration of vaccine performance.

The evaluation of vaccine efficacy against vaccine-matched strains should have a sufficient number of cases for comparisons. Absence of demonstrated efficacy in settings with too few cases of strain-specific disease for comparison should not be interpreted as absence of efficacy.

Improvement compared to existing vaccines may not necessarily be demonstrated through non-inferiority clinical trials.

Non-severe laboratory-confirmed influenza illness can be considered an appropriate endpoint for groups with high indirect effects of vaccination or for groups in which prevention of ambulatory influenza illness is recommended, such as healthcare workers and other essential groups targeted for other public health purposes.

Non-severe laboratory-confirmed influenza illness can be considered an appropriate endpoint for groups with high indirect effects of vaccination or for groups in which prevention of ambulatory influenza illness is recommended for other public health purposes.

While the preferred indication includes prevention of human influenza A virus infection, it is expected that an influenza vaccine with broad activity against influenza A phylogenetic HA groups (1 or 2) may protect against novel influenza A viruses from the same groups.

Demonstrated rate reductions against severe illness without laboratory confirmation of influenza virus infection, e.g. as in a vaccine probe study, would also be an adequate demonstration of vaccine performance.
### 3.7 Immunogenicity

<table>
<thead>
<tr>
<th>Preferred characteristic</th>
<th>Rationale</th>
<th>Comments</th>
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<tbody>
<tr>
<td>If a correlate of protection against severe laboratory-confirmed influenza illness is identified for a specific class of influenza vaccine, immunogenicity studies will be adequate to demonstrate vaccine efficacy.</td>
<td>Correlates of protection of influenza vaccines against severe influenza illness are needed to minimize costs of trials and to promote innovation.</td>
<td>Immunogenicity studies may be indicated as bridging studies to extrapolate vaccine performance to new age groups or as part of clinical evaluation in groups for which prevention of non-severe laboratory-confirmed influenza is an adequate outcome (school-aged children, pregnant women, health-care workers and other essential groups targeted for public health purposes).</td>
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</tbody>
</table>

### 3.8 Registration and prequalification

<table>
<thead>
<tr>
<th>Preferred characteristic</th>
<th>Rationale</th>
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<tbody>
<tr>
<td>The product should be prequalified according to standard procedures for assessing the acceptability of vaccines for purchase by United Nations agencies.</td>
<td></td>
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</tbody>
</table>

### 3.9 Programmatic suitability

<table>
<thead>
<tr>
<th>Preferred characteristic</th>
<th>Rationale</th>
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</thead>
<tbody>
<tr>
<td>WHO defined criteria for programmatic suitability of vaccines should be met.</td>
<td></td>
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</table>

### 3.10 Value proposition

<table>
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<tr>
<th>Preferred characteristic</th>
<th>Rationale</th>
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<tbody>
<tr>
<td>Dosage, regimen, and cost of goods should be compatible with affordable supply. The vaccine should be cost-effective and price should not be a barrier to access, including in LMICs.</td>
<td></td>
</tr>
</tbody>
</table>
4. Considerations on programmatic suitability

In addition to meeting quality, safety, and efficacy requirements, it is also important that developers and manufacturers consider the WHO preferences for parameters that have a direct operational benefit for immunization programmes. Low programmatic suitability of new vaccines could result in delaying introduction and deployment. Introductions of new vaccines that have higher dose volume, entailing a need for increased cold chain capacity or additional disposal requirements, have had a negative impact on operations of immunization programmes. Therefore early stage consideration of the capacity of immunization systems to reach target groups, delivery mechanisms, product presentation, and packaging parameters is encouraged. Deferring these considerations may lead to additional costs and delays required for reformulation later in the development pathway.

Recognizing the need to encourage early consideration of these issues, WHO has published several documents that describe WHO preferences for vaccine presentations, packaging, and programmatic suitability. The WHO prequalification process assesses vaccine quality, safety, efficacy, and suitability for use in LMICs. This process has resulted in prequalification criteria for programmatic suitability, which are used to review vaccines submitted for prequalification for procurement by United Nations agencies. Additional guidance on the prequalification process can be found on the WHO website.20–22

Influenza vaccine developers and manufacturers should refer to the current version of these documents to obtain further information with respect to the parameters and the relevant recommendations to ensure that their target product and development programme meet WHO preferences. Taking account of these preferences will help to ensure not only the development of highly efficacious and safe products that have characteristics desirable for LMIC settings, but also facilitate a successful outcome for vaccine developers following the WHO programmatic suitability for prequalification process.

Beyond the minimum requirements for WHO prequalification, vaccine developers should be aware of the call from immunization programmes 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 foreseen in the next decade include greater availability of needle-free administration for vaccine delivery in low income countries and improved thermostability to allow
vaccines to be stored at ambient temperatures and obviate the need for a refrigerated cold chain. For immunization programmes in countries with prolonged or atypical influenza seasons, addressing the gaps in vaccine availability, caused by fixed expiration dates appropriate for temperate countries, is also an important issue. Research and collaboration between academics, vaccine developers, and delivery device developers, as well as dialogue and engagement with regulators and WHO to facilitate such advances, could be transformative for immunization programmes within the next decade.
References


Appendix 1.
Definitions of terms

The PPC Advisory Group consulted experts in influenza virology and vaccinology to define the following key terms for the purpose of the PPC document.

Influenza virus

- **Influenza type**: Refers to genus, i.e. type A, B, or C, all of which affect humans. In general, influenza A viruses cause more severe influenza illness, and only influenza A viruses can cause pandemics. For a universal influenza vaccine, protection against types A and B would be sufficient as C viruses do not cause significant disease.

- **Influenza A group**: Influenza A viruses can be divided into two groups based on the phylogenetic relationship of haemagglutinin surface proteins. Group 1 viruses include H1, H2, H5, and H9 viruses. Group 2 viruses include H3 and H7 viruses.

- **Influenza subtype**: Influenza A viruses are classified according to subtypes based on two surface proteins, the haemagglutinin (HA) and neuraminidase (NA), e.g. H1N1, H7N9, H5N1, H3N2 etc. Currently there are 18 known HA subtypes and 11 known NA subtypes.

- **Heterosubtypic protection**: Cross-protection to infection with an influenza A virus subtype different from the subtype which elicited immunity. For example, a vaccine based on H1N1 subtype antigen that provided protection against an H3N2 virus would provide heterosubtypic protection.

- **Antigenic drift**: Influenza A and B viruses are constantly accumulating mutations in the HA and NA proteins which allows them to escape immune recognition, a process called “antigenic drift”, resulting in repetitive ongoing seasonal influenza outbreaks.

- **Antigenic shift**: Major changes in the influenza type A HA antigen, often with changes also in the NA antigen, caused by reassortment between different influenza A subtypes, such as between animal and human subtypes. The resulting viruses can potentially cause regional outbreaks or a global pandemic.
• **Seasonal influenza:** Caused by influenza A and B viruses that circulate globally. In temperate and many tropical and subtropical climates, seasonal influenza viruses are typically widely transmitted during seasonal outbreaks coinciding with winter or rainy periods. Other tropical or subtropical countries may experience more prolonged seasonal influenza epidemics or year-round circulation.

• **Pandemic influenza virus:** A novel influenza A virus to which there is very limited or no immunity in the population, which has sustained spread from person to person, and causes clinical illness.

**Vaccine breadth of protection**

• **Definitive universal influenza vaccine:** A vaccine that protects against any influenza strain of both influenza A and B viruses, independent of subtype, shift, or drift.

• **Universal-type influenza A vaccine:** A vaccine that protects against particular influenza A phylogenetic HA groups (1 or 2) is likely to be in advanced clinical development within the next ten years.

• **Next-generation influenza vaccine:** A vaccine that provides more cross-protection against different influenza A or B subtypes than the currently prequalified non-replicating, non-adjuvanted seasonal influenza vaccines, and that does not need to be administered or updated annually.

• **Improved influenza vaccine:** A vaccine that performs better than currently prequalified non-replicating, non-adjuvanted seasonal influenza vaccines.

**Vaccine performance**

• **Vaccine efficacy:** Reduced risk of influenza illness among vaccinated persons resulting from vaccination under ideal circumstances; estimated from randomized controlled trials.

• **Vaccine effectiveness:** Reduced risk of influenza illness among vaccinated persons attributed to vaccination in real-world conditions; estimated from observational studies.

• **Vaccine impact:** Reduction in incidence of disease in a population where some members are vaccinated; describes the total (direct and indirect) benefit of a vaccine programme in a population.

• **Vaccine protection:** Reduced risk of influenza illness among vaccinated individuals; this is a non-specific term.
Vaccine properties

- **Advanced clinical development (or late-stage clinical development):** A vaccine candidate that has reached phase IIb or phase III human trials is said to be in advanced clinical development.

- **Vaccine match:** The antigenic similarity and correspondence between the virus in the vaccine and the viruses circulating among people during a given influenza season. Antigenic relatedness of the HA as assessed in laboratory assays is used to determine how well the virus or virus component present in the vaccine corresponds in its antigenic properties to circulating viruses.

- **Vaccine mismatch:** The antigenic dissimilarity and lack of correspondence between the virus in the vaccine and viruses circulating among people during a given influenza season. A vaccine mismatch occurs when viruses circulating among people during a given influenza season have acquired genetic and antigenic differences relative to the viruses used to make the vaccine for that season. The degree of mismatch can vary. Vaccine effectiveness would be expected to be lower when the match is poor. Nevertheless, during the time of a vaccine mismatch, vaccines may still provide some level of protection to vaccine recipients.

- **Vaccine cross-protection:** The ability of a vaccine subtype to induce cross-reactive immunity to divergent viruses. For example, current vaccines to H7 viruses provide some cross-protection to all H7 viruses (irrespective of the NA subtype).

- **Broadly reactive:** The ability of a vaccine to induce greater cross-protection than typical non-replicating influenza vaccines in current use. Broadly reactive vaccines are expected to protect, at a minimum, against a wide range of influenza A drifted strains of the same subtype.
Appendix 2.
Assumptions regarding vaccine research and immunization systems

The PPC Advisory Group consulted experts in influenza vaccine research to advise on the feasibility that products with particular performance characteristics may be in advanced clinical development within five and ten year time horizons. The PPC Advisory Group sought additional advice on immunization systems from experts on immunization in low-resource settings. The evidence-based assumptions below reflect the advice of these experts and serve as the basis for influenza vaccine technology availability and immunization system options in the PPC document.

Vaccine cross-protection

• A definitive universal influenza vaccine which can feasibly protect against any influenza strain of both influenza A and B viruses is unlikely to be in advanced clinical development within the next ten years.

• An influenza vaccine which can feasibly protect against all influenza A subtypes is unlikely to be in advanced clinical development within the next ten years.

• An influenza vaccine which can feasibly protect against all influenza B viruses is unlikely to be in advanced clinical development within the next ten years.

• An influenza vaccine that can feasibly provide protection against particular influenza A phylogenetic HA groups (1 or 2) is likely to be in advanced clinical development within the next ten years, but not within the next five years. Such a vaccine is defined in this PPC document as a “universal-type influenza A vaccine” (Appendix 1). Such vaccines are generally expected to result from new approaches in vaccine design from currently available influenza vaccines (such as vaccines designed to stimulate antibodies targeting conserved virus epitopes or vaccines designed to stimulate cellular immune responses).

• An influenza vaccine which can feasibly provide protection against influenza B virus lineages is unlikely to be in advanced clinical development within the next ten years.

• An improved influenza vaccine which can feasibly provide greater cross-protection against different influenza A and B viruses than currently prequalified non-replicating, non-adjuvanted seasonal influenza vaccines...
is likely to be in advanced clinical development within the next five years. Such vaccines are generally expected to have incremental improvements compared to current vaccines, have increased protection against drift variants of influenza A and B, and may include adjuvanted non-replicating vaccines or live attenuated influenza vaccines.

**Vaccine duration of protection**

- An improved influenza vaccine that can feasibly provide protection for up to five years is likely to be in advanced clinical development within the next ten years, but not in the next five years.

- An improved influenza vaccine that has the potential to provide protection through one full year can feasibly be in advanced clinical development within the next five years.

- A vaccine to be delivered to women before or during pregnancy that can feasibly protect newborn infants through subsequent pregnancies is unlikely to be in advanced clinical development within the next ten years.

- A vaccine that can be delivered to women before or during pregnancy that can feasibly protect newborn infants for a period greater than six months is unlikely to be in advanced clinical development within the next ten years.

**Influenza illness burden**

- Groups defined by WHO to be at risk for severe influenza illness include children younger than five years, elderly persons, individuals with specific chronic medical conditions, and pregnant women. While health-care workers are not documented as having increased risk for severe influenza illness, they can expose vulnerable populations to influenza virus, and they are critical for the functioning of health systems which may be disrupted during severe influenza seasons or pandemics.

- The incidence rates of severe influenza illness in pregnant women, infants in the first three months of life, and healthy adults are expected to be so low that randomized clinical trials designed to prevent severe influenza outcomes in those groups may not be feasible.

**Immunization systems**

- Existing immunization systems have the potential to vaccinate children aged 6 weeks through 59 months (with the strongest programmes for 6 weeks through 24 months), pregnant women, and health-care workers in low income countries.

- Immunization systems are unlikely to be widely available to immunize children aged 5 through 18 years or adults in low income countries within the next ten years.
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