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Vaccine xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

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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ARTICLE INFO

Article history:
Received 14 November 2017
Accepted 17 November 2017
Available online xxxx

Keywords:
Influenza
Pandemic influenza vaccine
Seasonal influenza vaccine
Universal influenza vaccine
Vaccine development
Nextgeneration influenza vaccine

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.
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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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https://doi.org/10.1016/j.vaccine.2017.11.061
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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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groups are children aged 6–59 months, the elderly, people with chronic conditions and healthcare workers.

In HICs, burden of influenza disease is greatest in the elderly and in persons with chronic illness. The burden of influenza disease among risk groups, particularly adults, is not as well studied in LMICs, however recent data suggest similar patterns of severe influenza illness at extremes of age, but influenza mortality may be higher in younger persons than is seen in HIC settings [21,22]. For children, more is known. In 2016, influenza was estimated to be responsible for 1.4% of all <5 years mortality globally [23]. Others estimate that 99% of influenza mortality in this age group occurs in LMICs [24]. A 2016 study estimates the proportion of deaths caused by influenza is highest among those aged 1–12 months, with 2.8% of all deaths in this age group, worldwide [25].

All countries have immunization systems that can reach children <2 years [26], however influenza vaccine effectiveness is lower in this age group than in others pediatric age groups [1]. Further, influenza vaccines are not currently licensed for ages less than 6 months [10]. Improving vaccine performance in young children and aligning vaccine licensure with pediatric vaccine schedules in LMICs should be a global priority [3].

2. WHO preferences for next-generation influenza vaccines

2.1. Development of WHO preferred product characteristics (PPCs) for next-generation influenza vaccines

WHO's PPCs are intended to encourage innovation in vaccine development [2,3]. They describe WHO recommendations for attributes of vaccines, in particular their indications, target populations, 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 LMICs.

In 2016, WHO convened an advisory group of vaccine, public health, and research experts to recommend preferred product characteristics for next-generation influenza vaccines to be used in LMICs. The advisory group reviewed data on influenza disease burden, influenza vaccine performance, influenza vaccine research and development, immunization system logistics, and programmatic aspects of vaccine delivery. It declared 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,"* and set goals with five and ten-year time horizons to address the unmet need (Table 1).

The five-year (2022) goal was designed to promote 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. The ten-year (2027) goal was designed to promote research and development of new products that are aligned with the global unmet public health need.

The rationale, development process, and draft PPC was presented at this meeting for discussion and recommendations. Subsequently, two additional public consultations were held to solicit feedback on its contents. Afterwards, the document was revised, reviewed by the WHO PDVAC, and approved by WHO for publication. Details of the PPC document can be found on the WHO website [3].

Table 1
WHO Preferred Product Characteristics (PPCs) for next-generation influenza vaccines five and ten year strategic goals.

Five year goal	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
Ten year goal	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

2.2. Potential to meet the 5-year goal with existing vaccines

Some currently licensed live attenuated influenza vaccines (LAIVs) and adjuvanted inactivated influenza vaccines (IIVs) have the potential to induce broad and/or longer lasting protection and to meet the 2022 objective of the PPC.

LAIVs are the preferred vaccine in several countries for children older than two years [27].

The addition of adjuvants to IIV can increase the magnitude [28–30] and breadth of immune response [31]. Seasonal IIVs formulated with MF59 adjuvant are currently licensed in many countries for use in adults 65 years and over and in Canada for children aged 6 through 23 months [32]. However, both LAIVs and adjuvanted IIVs are restricted to age groups for which they are licensed, and as such do not address the global unmet needs defined in the PPC. Efforts to evaluate these products in expanded age groups represent a feasible opportunity to address LMIC needs with currently available products.

2.3. Potential to meet the 10-year goal with novel vaccines

Most currently licensed influenza vaccines aim primarily at the induction of strain-specific neutralizing serum antibodies to HA, which offer only limited protection against antigenically drifted or shifted viruses. Broadly protective vaccines that meet the 2027 goal will require immunization strategies that result in humoral and cellular immune responses directed to conserved epitopes shared by various influenza viruses, rather than immunodominant and variable epitopes that ARE affected by antigenic drift and shift [16]. This may entail innovative approaches such as rational antigen design, novel approaches to antigen delivery, adjuvants, and heterologous prime-boost regimens. As noted in recent reviews of the landscape of broadly protective or so-called "universal" influenza vaccines [16,33–36], there are several promising candidate vaccines in preclinical development. At the meeting it was noted that the success rate of any vaccine candidates in preclinical or early clinical development is very low, suggesting that the current pipeline of approximately 20 influenza vaccine candidates in the US and Europe is likely to yield few products that would ultimately achieve licensure.

3. Evaluation of next-generation influenza vaccines

Some of the vaccines to address the unmet global health need for influenza vaccines will be currently licensed vaccines used in new populations, such as children < 6 months; some will be novel as yet unlicensed vaccines. All will require testing for safety and efficacy in highly controlled settings and then effectiveness and safety studies performed in larger field trials and post-marketing surveillance.

3.1. Immunological and virological assessments

For next-generation influenza vaccines to meet the aspirations of public health, especially for LMICs, a better understand-

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ing is needed of the immune response to influenza infection and vaccination [37], the impact of repeat vaccination, and the nature of immune responses to vaccination in different target groups.

3.1.1. Assay development

There was much discussion about potential serological and cell-mediated immunity (CMI) assays, such as for T cells, memory B cells and antibody-dependent cellular cytotoxicity (ADCC) that could be used to understand more about immune responses to infection and vaccination.

New assays will be needed to detect antibodies to different viral target antigens (such as M2e or the HA-stalk region) and they must be applied to a broad range of virus strains [38]. Some assays will need live effector cells; the improvement and standardization of assays of ADCC was noted as a specific example [39]. These assays could be used to study antibody decay kinetics in longitudinal studies.

There is already a wide variety of CMI assays available but these are not yet standardized, and there are no established CMI-based correlates of protection (CoPs) [40]. The optimal timing of sample collection for CMI-based assays is likely to be 7–10 days after vaccination [41,42], which is very different to the day 21 or 28 sample collection typically used for serological assays.

3.1.2. Standardisation of assays

Further standardization of novel immunological assays will be needed so that immunogenicity results are reliable and can be compared among laboratories. This can be achieved by several approaches: harmonization of assays, use of international standards, assessment of laboratories (proficiency testing) and testing/re-testing by a centralized laboratory. In recent years, there has been progress in improving the comparability of laboratory assays through collaborative networks, such as the Consortium for the Standardisation of Influenza Seroepidemiology (CONSISE) [43]. Some EU-funded initiatives, such as UNISEC, FLUCOP and EDUFLUVAC, include standardisation [44,45].

3.1.3. Correlates of protection

Haemagglutination inhibition (HI) titre has been used as a relative CoP for IIVs: an HI titre of $\geq$40 being considered to be associated with greater than 50% reduction of the risk of influenza infection or influenza disease [46]. Next-generation vaccines will require new biomarkers, and in particular new CoPs [37,47,48], and will need to be assessed with new assays. The selection of assays and CoPs will depend on vaccine type, target antigen, and, possibly, the target human population; for example, the immune responses and protection induced by LAIVs and IIVs are different, but the differences cannot be explained using a range of currently available immunologic assays. Furthermore, LAIVs behave differently in adults compared with children [48]. Consequently, new regulatory guidelines will likely require efficacy studies for licensure of novel products.

3.2. Human challenge studies

The role and value of human challenge studies in influenza vaccine development was discussed at the meeting [47]. In addition to their potential value in down-selecting vaccine candidates, they allow detailed analysis of human immune responses and can provide initial information on new CoPs that can be further investigated in clinical trials [47]. However, they can be challenging to conduct and interpret for several reasons. Human challenge studies are usually conducted in small numbers of healthy adult volunteers who will have varying past exposure to influenza. A limited number of challenge viruses are available due to the time taken to develop and prepare them according to Good Manufacturing Practices. These viruses are not truly wild-type having been cultured repeatedly, with the potential for attenuation of disease-causing ability. Care must be taken to find susceptible volunteers for challenge trials and this may be compromised by population immunity to circulating influenza strains. Finally, since children will not be part of human challenge trials, results will have to take into consideration that there will undoubtedly be differences between adults and children in their response to the vaccine, as has been seen with LAIVs [48].

3.3. Clinical trials

3.3.1. Clinical trial design

Clinical evaluations of next-generation influenza vaccines are likely to seek demonstration of efficacy that is not inferior to current vaccines and evidence of clinical benefit from increased breadth of protection and/or increased duration of immunity. Ultimately, fully-powered efficacy studies to demonstrate superior prevention of any-severity and severe influenza disease are desired. Efficacy studies will further need to establish the magnitude, quality and duration of immunity in unprimed children and in primed individuals of all ages, to understand the effect of previous exposures on protection and to discount the possibility of disease enhancement. Clinical trials spanning two to five years will be needed to establish the surrogates (and correlates) of durable immunity. It is unclear how long clinical trials will need to be open in order to prove efficacy of next-generation influenza vaccines in the face of antigenic drift that requires changing of vaccine components under the current influenza vaccine recommendation system. Evidence for protection against influenza B disease also should be addressed. Post-licensure studies will be necessary to collect evidence for protection in neonates, pregnant women, and other special populations. Finally, vaccine developers need to engage with regulatory authorities and the WHO early in the clinical trial design process.

Primary clinical endpoints could be the prevention of laboratory confirmed influenza disease, either mild or severe. Secondary endpoints could include efficacy against circulating viruses that are antigenically similar to, or drifted from the vaccine antigen. Care needs to be taken to assess possible age-shift or rebound effects, where vaccination delays infection but the disease is more severe if the individual is eventually infected [49].

Pivotal clinical studies with an inactive comparator could potentially be conducted in countries in which influenza vaccines are not yet recommended, provided that suitable clinical trial infrastructure is available to support the trials and baseline data are available for sample size calculations. Some developers will carry out clinical studies only in countries where they have an intention to market the product.

The number of subjects needed in a trial will depend on several factors, most notably the clinical endpoint selected. With prevention of mild-to-moderate disease as an endpoint, large trials will be required [50]. These numbers were considered in the meeting to be manageable in some settings, and are comparable with study sizes for other infant vaccines [51]. Care must be taken with study size calculations: one recent trial missed its pre-specified endpoint by assuming the attack rates in the study population would be similar for each influenza A subtype, which was not the case [52].

The use of test-negative design methodology for observational studies has increased our understanding of influenza vaccine effectiveness from one year to the next within a population [53–55]. It also allows comparison between countries and vaccine products, and should be useful for studies of vaccines after their introduction.

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3.3.2. Clinical endpoints and health outcomes

Standardized clinical endpoints are needed for influenza vaccine efficacy studies against severe disease. Severe illness clinical endpoints should be generalizable, reproducible, and feasible for studies conducted in LMICs. Ideally, severe illness endpoints should be validated against objective clinical outcomes. The PPC Advisory Group has recommended the development of standardized clinical endpoints for use in influenza vaccine studies, which should include guidance on standardization of clinical data collection, a minimum dataset to be collected in trial settings, and severity of illness scales. 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. Further, single year studies are vulnerable to failure due to year-to-year variability in influenza attack rates. Studies of at least two years duration are therefore preferable to mitigate against the risk of failure. Additional long-term studies will also be necessary to demonstrate the duration of clinical protection, however these studies need not be part of original efficacy trials and may be more amenable to study with observational methods.

3.3.3. Safety

Adverse events (AEs) following use of influenza vaccines can be influenced by host factors (age, gender, hypersensitivity, genetics, previous doses of vaccine), environmental factors (disease background, poverty), or vaccine-related factors (type, production method, adjuvants, other components, dose, route of administration, concomitant vaccines). It is not known which components are responsible for most AEs following influenza vaccination.

An Institute for Vaccine Safety white paper was published following a systematic review of the safety of influenza vaccines in children, assessing many thousands of reports [56]. It concluded, *"All vaccines intended for use in children require safety testing in the target age group, especially in young children. Safety of one influenza vaccine in children should not be extrapolated to assumed safety of all influenza vaccines in children.*"

Inclusion of pregnant women in vaccine clinical trials may be challenging in many countries yet the benefits of protection against influenza are well documented for pregnant women and infants [11]. Data from pregnancy registers, (i.e. women who become pregnant during participation in vaccine trials), or from post-marketing reports may be accepted by regulatory authorities as support for the use of the vaccine in this group.

If the vaccine contains a novel adjuvant, additional collection of safety data is likely to be required as well as follow-up longer than 12 months after the last dose, which is currently required. Vaccine developers already collect data on induction or aggravation of potentially immune-mediated diseases (for the US Food and Drug Administration) and AEs of special interest (for the EMA) [57], however surveillance for these conditions is lacking in many less developed countries.

4. Regulation of novel vaccines

Evaluation of applications for regulatory approval of novel influenza vaccines will follow standard practices with a complete data package, and evidence to support the claims made. Regulators may permit some extension of claims based on adequate data. For example, a vaccine claiming longer-lasting protection might demonstrate three years' protection at first licensure and then extend this to five years or more through a supplementary filing. Manufacturers might also want to seek a license in adults and children and then further indications for the elderly, infants aged less than six months and pregnant women. Demonstration of broad protection in pre-clinical models will be needed to support these claims in humans where not all strains can be tested during clinical evaluation.

In addition, post-vaccination sera from clinical studies can be tested against a panel of virus strains in serologic studies. In general, as for all novel products, regulators encourage vaccine developers to speak to them early to help plan product-specific development.

New guidelines for marketing authorization applications for seasonal and what used to be referred to as pre-pandemic and pandemic vaccines have recently been published by the European Medicines Agency (EMA) and came into effect in February 2017 [58,59]. They set a requirement to conduct randomized clinical trials in young children (aged 6 months to 3 years) and place emphasis on the use of a post-marketing risk management plan to monitor the benefits and risks of influenza vaccines. The guidelines cover IIVs, LAIVs and vaccines with adjuvants, and its principles are applicable to several approaches towards novel vaccines.

5. Post-licensure studies

5.1. Safety and efficacy

As noted, post-licensure studies will be necessary to collect evidence for protection in neonates, pregnant women, and other special populations. In addition, post-introduction surveillance will be required to detect serious AEs, which may occur at a very low rate and not be detectable until vaccines are used widely.

5.2. Vaccine-probe studies

There was much interest in funding influenza vaccine-probe studies in LMICs. These studies would be designed to look at the impact of vaccine use on both influenza-specific endpoints as well as relevant public health outcomes such as all-cause severe lower respiratory tract infections, deaths and healthcare usage. Such studies have been useful for demonstrating the public health value of *Haemophilus influenzae* (Hib), *Streptococcus pneumoniae* and rotavirus vaccines. For influenza [60] such studies could provide data to establish the preventable burden of influenza disease and inform vaccine introduction decisions in low-resource settings [50,61].

For a probe study to be successful, the availability of a safe and effective vaccine in the targeted age group is necessary. Some participants considered that suitable vaccine(s) might already be available for a probe study, such as IIVs with MF59 adjuvant in young children. Some participants expressed concern that sufficiently effective vaccines are not yet available, and that conducting a probe study under this scenario would likely harm the value proposition for routine use of influenza vaccines, as impact on broader disease outcomes may not be demonstrated. To mitigate this risk, it would be important to have a properly-powered, multi-year study in which a subset of children were followed for laboratory-confirmed influenza outcome to establish if a null result was due to low attack rates, poor vaccine efficacy, and/or insufficient influenza-associated severe disease outcomes.

6. Encouraging, funding and supporting next-generation vaccines

The Global Vaccine Action Plan sets a goal of, "A*t least one vaccine providing broad spectrum protection against influenza A virus*

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licensed," by 2020 [62]. Although it was judged unlikely that this goal will be met, it was noted that the global health community has an opportunity to "begin with the end in mind" and plan for implementation of next-generation influenza vaccines, especially in LMICs.

There was optimism that better influenza vaccines would be in advanced clinical development within the next 10 years and enable more equitable access and higher impact. Large, experienced vaccine producers as well as smaller companies have identified and are developing next-generation influenza vaccine candidates. In part because it is not possible to predict which vaccine antigens, formulation or vaccination schedule will be successful, non-clinical and clinical development of the candidates will require significant funding.

There is continuing interest and support from public sector and non-governmental funders. Funding agencies can help at a number of different stages of vaccine development by establishing Public-Private Partnerships (PPPs) to accelerate development and lower risks for pharmaceutical companies; facilitating collaborations; developing and providing access to reagents, assays, and animal models; supporting advanced manufacturing; and financing human challenge studies and clinical trials [47].

To sustain interest and inform investments, WHO and others will need to continue to work closely with stakeholders on modeling vaccine demand, costs and prices, especially when several vaccine products with different claims are available. Vaccine purchasers will want estimates of cost-saving in their populations [63] as much as estimates of disease and deaths averted.

7. Conclusions

The development of next-generation influenza vaccines involves addressing issues that are specific to influenza vaccines, most notably the antigenic shift and drift of the influenza virus, as well as obstacles that are common to the development of many vaccines and that have been successfully surmounted in the past.

Much can be learned from other PPPs to support vaccine development and introduction for better access in low-resource settings. Some of these vaccines have faced similar challenges to influenza: malaria, Japanese encephalitis, meningitis A and dengue each have restricted geographical risk in mainly LMIC targets; pneumococcal vaccines require multiple, geographically specific serotypes; and Hib-vaccine developers faced challenges in the communication of burden of disease and required very large sample sizes for clinical trials. WHO can play a role in supporting research and development; communicating public-sector preferences; independently evaluating vaccine candidates for probability of success, and comparing vaccines at late stages of development. At this meeting it was agreed that it will be important to have strong, optimistic and trusted voices to continue to advocate for public and private funding throughout this process.

Acknowledgements

We acknowledge Marc Perut and Chiara Gerardi of the World Health Organization for their contributions to planning and organization of the WHO meeting. We also thank Angela Hwang for editorial advice.

Financial Support

The authors acknowledge the contributions of the Centers for Disease Control and Prevention (CK14-1402), which provides financial support to the World Health Organization Initiative for Vaccine Research. The authors also acknowledge contributions of the US National Institutes of Health (U01AI108543-01), which provided grant funding for partial support of this meeting.

Disclaimer

Justin R. Ortiz and Joachim Hombach are employees of the World Health Organization. Jacqueline Katz is an employee of the US Centers for Disease Control and Prevention. David J. Spiro is an employee of the US National Institutes of Health. The authors alone are responsible for the views expressed in this publication and they do not necessarily represent the decisions or policies of the World Health Organization, the Centers for Disease Control and Prevention, or the National Institutes of Health.

Conflicts of interest

Armen Donabedian: None.

Othmar G. Engelhardt: Institution has received grants from the European Union Seventh Framework Programme for work on universal influenza vaccines and funding for other influenza virus work from BARDA, the Department of Health (UK), the Innovative Medicines Initiative and IFPMA.

Julian Hickling: Working in Tandem receives consultancy fees from Vaxxas Pty Ltd.

Joachim Hombach: None.

Rebecca Jones: Working in Tandem receives consultancy fees from Vaxxas Pty Ltd.

Jacqueline M. Katz: Institution has received funds for work on influenza vaccine viruses from IFPMA and Seqirus.

Shabir A. Madhi: Institution has received grant funding on influenza from BMGF and CDC.

Kathleen M. Neuzil: None.

Justin R. Ortiz: None.

Guus F. Rimmelzwaan: Institution has received grant funding on influenza from European Commission.

James Southern: None.

David J. Spiro: None.

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Please cite this article in press as: Ortiz JR et al. 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. Vaccine (2017), https://doi.org/10.1016/j.vaccine.2017.11.061

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Please cite this article in press as: Ortiz JR et al. 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. Vaccine (2017), https://doi.org/10.1016/j.vaccine.2017.11.061