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Conference report

Meeting report: WHO consultation on Respiratory Syncytial Virus (RSV) vaccine development, Geneva, 25–26 April 2016

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ABSTRACT

Respiratory syncytial virus (RSV) is a leading viral cause of respiratory morbidity and mortality in infants and young children worldwide. Low and middle income countries (LMICs) account for approximately 99% of the global mortality estimates in this population, with up to 200,000 RSV deaths per year. The vaccine product development pipeline is diverse with the most advanced clinical candidate currently in phase III efficacy testing in pregnant women. In addition, a long-acting RSV-neutralizing monoclonal antibody (mAb) to be administered at birth to prevent serious RSV-related respiratory disease is in late stage clinical development, as are additional conventional mAb for use in high-risk infants. Thus, there is a realistic possibility that an effective new intervention to prevent RSV disease will be available in the next 5–10 year horizon. In anticipation of this outcome, the Strategic Advisory Group of Experts for Immunization (SAGE), WHO's vaccine policy recommendation body, reviewed the status of RSV vaccine and monoclonal antibody development in April 2016. Although substantial progress towards licensure has broadened the research agenda to consider intervention impact and cost effectiveness, significant gaps remain in the data that will be needed to inform and support a policy recommendation for implementation. These aspects were the focus of WHO's second consultation on RSV vaccines and single dosage extended half-life mAb for prophylaxis.

1. Introduction

The RSV vaccine pipeline is amongst the most active of all pathogen areas, and consists of three classes of product: subunit vaccines mainly in development for maternal immunization (MI) and immunization of the elderly (≥60 years), live attenuated or recombinant viral vaccines for active paediatric vaccination, and prophylactic long-acting mAb targeted for seasonal or birth dosing. Although RSV vaccines are being developed for the elderly, this population is not a primary target for immunization in LMICs and those vaccine development efforts were therefore not a particular focus of this consultation.

WHO convened its first RSV consultation in 2015 to review the vaccine pipeline and provide guidance on development pathways to licensure, with consideration of low- and middle-income countries' perspectives [1]. The strategic focus of this first meeting was on the development of high quality, safe and efficacious RSV preventive interventions for populations at greatest risk of severe disease in LMICs, through:

(1) maternal/passive immunization to prevent RSV disease in infants less than 6 months;
(2) paediatric immunization to prevent RSV disease in infants and young children once protection afforded by maternal immunization wanes.

Consensus was reached on pilot case definitions for RSV clinical disease endpoints for efficacy evaluation. In addition, clinical development pathways in maternal and paediatric populations were discussed. Following this consultation, and with the advance of a vaccine candidate into phase III evaluations in pregnant women and the elderly, information on the status of RSV vaccine development was presented to SAGE in April 2016. SAGE commended the field on the progress to late stage clinical development, but cautioned that additional data would be needed to support a policy recommendation and implementation of effective RSV vaccines [2]. SAGE recommended that WHO and stakeholders identify the research and development activities that will be

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needed to both support licensure and to inform policy recommendations in order to minimise the lag between vaccine approval and widespread uptake in (LMICs). With this in mind, WHO convened its second consultation on RSV interventions in order to:

- convey the recommendations from SAGE to the RSV vaccine development community,
- identify key gaps in stratified disease burden data according to (a) age, geography and seasonality, (b) morbidity and mortality data in the community, and (c) baseline epidemiology that will enable vaccine effectiveness evaluation and eventual policy consideration,
- consider the activities needed to prepare for implementation of the first vaccine indicated for maternal immunization,
- agree upon priority activities to facilitate submissions for licensure, prequalification and policy-making assessments at the global level.

2. Overview of the RSV vaccination strategy for infants and children

There are three major populations at risk for RSV acute lower respiratory illness (ALRI) and its sequelae, namely, infants from 0 to 3 months of age who experience the greatest mortality, older infants (>3 months) and toddlers, and the elderly. The heterogeneous immune systems of these diverse at-risk populations require different immunization strategies. Maternal immunization strategies aim to protect neonates and very young infants via passive immunization, whereas vaccines for active immunization of RSV-naïve infants aim to induce neutralizing antibodies. For this reason, it is considered likely that both maternal and paediatric vaccines will be needed to optimise public health impact. Neonatal delivery of extended half-life monoclonal antibodies (mAb) is an alternative approach for immediate protection at birth, potentially extending protection over an entire RSV season. Non-replicating (subunit) RSV vaccines are targeted for maternal immunization as well as for other non-naïve populations (older children, elderly), whereas replicating RSV vaccines (live-attenuated or vectored) are under development for induction of the appropriate immune response for infant immunization. Considering the previously documented cases of enhanced respiratory disease following natural RSV infection in RSV-naïve recipients of formalin-inactivated RSV (FI-RSV) vaccine [3], use of replicating vaccines is considered the safest for active immunization of RSV-naïve populations. Live-attenuated RSV candidate vaccines have been administered to hundreds of RSV-naïve children and have never been associated with enhanced disease [4].

Since the first WHO RSV consultation in 2015, the number of candidates in development had increased from 54 to 62, with 19 of these now undergoing clinical testing [5]. In addition, the leading vaccine candidate, the RSV F nanoparticle vaccine manufactured by Novavax, entered Phase III efficacy testing in pregnant women and the elderly (discussed below) [6,7].

3. Update on RSV burden of disease estimates, vaccine impact modelling and surveillance studies

The available estimates of RSV burden of acute lower respiratory illness (ALRI, which includes pneumonia and bronchiolitis) are based on 2005 data [9]. Globally, 33.4 million cases of RSV-associated ALRI and 3.4 million cases of RSV-associated hospitalised (severe) ALRI were estimated, with 53,250–199,000 deaths due to RSV-associated ALRI. Revised estimates from 2015 data based on a systematic review and meta-analysis of 225 articles and unpublished data derived from 76 study sites in RSV Global Epi Network (RSV GEN), focusing on both community based case ascertainment and hospitalization rates, are expected in 2017.

This new analysis will include improved estimates with age stratification of RSV-associated ALRI and severe ALRI in LMICs, in children up to 2 years, and global hospitalization rates for RSV-ALRI in children less than 2 years. Preliminary data review indicates that though the highest incidence of RSV-ALRI and severe RSV-ALRI occur in the first 5 months of life (both in LMICs and globally), there is also a substantial disease burden in 6–11 months olds, as well as in older children. Significant gaps remain in obtaining accurate burden of disease estimates, particularly in LMICs, where healthcare systems are comparatively fragile. Access to diagnosis and hospitalization is limited in in a number of countries. Many healthcare providers do not test for RSV because even if RSV is confirmed, there is no treatment. Co-morbidities are frequent. Consequently, much undiagnosed RSV mortality and morbidity occurs in the community, and is likely to be vastly underestimated in these contexts [10]. To help address this, RSV is being assessed as part of the Child Health and Mortality Prevention Surveillance (CHAMPS) Initiative which aims to better determine the causes of childhood death globally through minimally invasive autopsies [11]. In addition, the relative contribution of social, biological, and clinical risk factors for RSV mortality in LMICs has been evaluated in a study involving 84,840 infants in low income populations in Buenos Aires [12]. Between 2011 and 2013, hospitalizations and deaths due to lower respiratory tract infection (LRTI) were recorded during the RSV season, all-cause hospital deaths and community deaths were monitored. 65.5% of infants with severe LRTI were infected with RSV and 157 infants experienced respiratory failure (RF) or died with RSV. In this setting, sepsis and pneumothorax were the main risk factors for poor outcomes. Shi et al. performed a systematic review of risk factors for RSV-associated ALRI in young children under 5, globally, and found 8 risk factors to be associated with ALRI, including prematurity, low birth weight, siblings and crowding [13].

The varying global seasonality of RSV means that the vaccine implementation strategy may need to be regional or country-specific and perhaps even subnational in countries that span several geographical zones, based on disease incidence [14]. Some areas have long, extended RSV seasons, whereas others have short seasons of high intensity and the extent of disease burden differs with seasonal variation. Further understanding of RSV seasonality in developing countries and various climatic regions is critical to informing the most cost-effective vaccine implementation strategy, particularly with respect to seasonal vs. year round vaccination.

3.1. Long term sequelae and association of RSV infection with wheezing and asthma

There is some evidence for an association between RSV infection and subsequent recurrent wheeze and asthma, although its association, pathology and causal mechanism is debated [15,16]. Asthma cannot be fully diagnosed before age 5 or 6 as lung function testing is a critical component of the diagnosis. Before this age, wheezing illness is often transient and allergic sensitization testing has imperfect sensitivity. Recently, a link with chronic obstructive pulmonary disease (COPD) has also been suggested [17].

A randomized clinical trial in otherwise healthy preterm infants born at a gestational age of 33–35 weeks demonstrated that prophylaxis with the RSV mAb palivizumab resulted in a 61% reduction in the total number of wheezing days during the first year of life [18]. Non-randomized studies showed similar effects with protection against wheeze up to age 6 [19]. Conversely, a phase III, placebo-controlled, safety and efficacy study of the RSV mAb mota-

vizumab in healthy full-term Native American infants resulted in an 87% relative reduction in the proportion of infants admitted to hospital with RSV and a 71% reduction in RSV-associated outpatient ALRI, but there was no effect on rates of medically attended wheezing in children aged 1–3 years [20]. This may be related to this specific population or a low incidence of wheeze in the motavizumab study [16]. The relationship between RSV and recurrent wheezing in Argentina is being further investigated in a prospective long term follow-up cohort study of 1200 infants in three groups: RSV LRTI, non-RSV LRTI, and healthy controls [15]. The objective of this study is to identify the socioeconomic and clinical predictors, as well as potential biomarkers for recurrent wheeze and asthma, and to further investigate disease phenotypes impacted by RSV. In line with the recommendations from SAGE, long term follow up subjects from randomized controlled vaccine trials is needed to evaluate the potential benefits of RSV interventions to reduce recurrent wheeze and asthma, which, if demonstrated, would substantially increase the cost-effectiveness of RSV preventive interventions.

3.2. Vaccine impact modelling and considerations for vaccination strategy

The use of modelling to analyze potential vaccine key characteristics (including efficacy) and assess their impact according to various vaccination strategies can contribute to predicting vaccine cost-effectiveness and inform decision making. Such efforts are ongoing to evaluate the merits of the various target groups in regards to potential herd immunity effects. A number of different approaches for assessment of RSV vaccine impact were reviewed, including whether vaccinating older infants (>6 months) in LMICs would have a significant public health impact. Using a compartmental age-structured model, Kinyanjui et al. have explored possible effects of immunization of infants [21], predicting that delayed delivery to 5–10 month olds would optimise impact on hospitalisations of RSV-associated disease, with a major contribution of herd immunity (indirect protection to those unvaccinated.) The importance of the indirect benefits of vaccination is further illustrated by a consensus modelling study by Pan-Ngum, which reported that vaccine characteristics leading to reduced duration of shedding and infectiousness in infected vaccinated individuals would have a disproportionally large impact on severe disease [22]. The model described by Poletti et al. is structured by social groupings, e.g. households and schools, and suggested that household transmission is responsible for a significant percentage of infant infections and that school-age children are the main source of infection within the household, suggesting that strategies targeting a wider age group including school children may significantly increase the public health impact [23]. This conclusion is supported by evidence from a study in rural Kenya, which showed that older children (siblings and cousins) were the source of exposure for 73% of the within-household infant RSV infections, and that majority of these children were attending school [24]. Evidence from one study suggests infectious exposure within households can originate from contact with children having asymptomatic infection [25].

3.3. Update on WHO RSV surveillance studies

Ongoing WHO initiatives may contribute to further characterization of RSV epidemiology. WHO coordinates the Global Influenza Surveillance and Response system (GISRS), which is a network of 143 national influenza centers (NICs) in 113 Member States, across all 6 WHO regions. Each year, more than one million clinical specimens from individuals with respiratory illnesses are tested for influenza. In many cases, influenza is not detected. RSV and influenza share common features like seasonality, a wide clinical disease severity spectrum and specific high risk groups. Importantly, unlike influenza, children with RSV ALRI are often afebrile, and surveillance case definitions need to take this difference into account.

WHO is establishing a 3 year pilot study to assess the feasibility of RSV disease surveillance by NICs in 14 countries, across all WHO regions. The objective of this pilot study is to evaluate optimal case definitions and case ascertainment strategies for RSV, to assess RSV seasonality, and to identify age and risk groups for severe disease within the region of each site, as well as to identify potential RSV virus and antigen variability. This will include hospital-based surveillance for severe acute respiratory illness (SARI) with and without fever, community-based surveillance for ALRI with and without fever, and surveillance in 0- to 3-month-old illness that includes SARI, ALRI, and those diagnosed with apnea or sepsis. Three reference laboratories with established experience in RSV detection have been selected to support the study (Gastroenteritis and Respiratory Viruses Laboratory Branch, CDC, Atlanta; the Virus Reference Department, Public Health England, London; and the Centre for Respiratory Diseases and Meningitis, National Institute for Communicable Diseases, Johannesburg). One of the goals of this initiative is to better define the burden of RSV in pregnancy.

Long term, the goal is to expand RSV surveillance to other sites within the GISRS network to obtain additional information on RSV disease burden. In order to prepare for building laboratory capability in these sites, standardized reagents and protocols are being established that will support clinical trials of future RSV vaccine candidates. In June 2016, WHO convened the NICs and reference laboratories to finalize the GISRS-based RSV surveillance protocol, case definition, sampling criteria and reporting protocol.

4. The product development status of the most advanced RSV interventions, with potential for introduction in LMICs

It was recently reported that the phase III trial in the elderly of the unadjuvanted RSV F nanoparticle vaccine (Novavax) did not meet the pre-specified primary or secondary efficacy endpoints. In this trial, the attack rates for RSV acute respiratory disease (RSV-ARD) and moderate to severe RSV lower respiratory tract disease (RSV-msLRTD) were approximately 40% and 25%, respectively, of those observed in the previous Phase II study, in which statistically significant vaccine efficacy in prevention of RSV-ARD (44%) and RSV-msLRTD (46%) was observed [8]. The Phase III maternal immunization study is continuing with an alum adjuvanted formulation of the RSV F nanoparticle vaccine.

4.1. Candidate vaccines for maternal immunization

Novavax's RSV F nanoparticle vaccine is the most advanced candidate vaccine for the treatment of RSV illness via maternal immunization. A Phase III trial in multiple regions including LMICs began late 2015 following acceptable safety and encouraging immunogenicity in a Phase II study of 50 singleton pregnancies in which the induction of high and sustained titres of anti-RSV F IgG and palivizumab competing antibody was demonstrated. The study will enrol up to 8200 pregnant women in the 3rd trimester of pregnancy, and will evaluate prevention of RSV LRTI with hypoxemia in infants of vaccinated mothers. The study has a group sequential design, with DSMB oversight and iterative futility analyses planned. Enrolment is expected to be completed over 2–4 years, and will occur across both northern and southern hemispheres. Protective efficacy at 90, 120, 150, and 180 days will be assessed.

GSK is also developing a subunit based recombinant candidate based on RSV pre-fusion F antigen that is currently in phase II clinical studies in women of childbearing age. In addition, GSK has

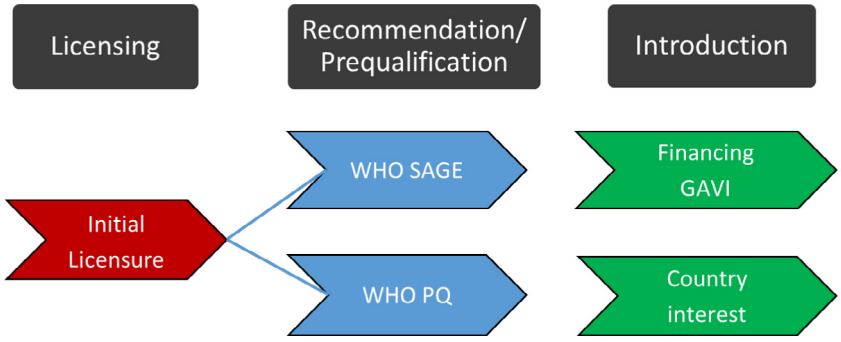

Fig. 1. Overview of the process beyond licensure to policy recommendation and in-country vaccine implementation.

invested in longitudinal RSV epidemiological studies to define incidence of disease using diagnostic and surveillance procedures applicable to vaccine efficacy studies in different settings.

4.2. Candidate vaccines for paediatric use

Two vaccine candidates targeting children are now in Phase I clinical studies in healthy adults [5], based on viral vector platforms, and a number of live-attenuated RSV vaccines are being assessed in phase I clinical trials in children. GSK's Chimpanzee Adenovirus (ChAd155) encodes 3 antigens (F, N and M2.1) and is being developed as a two-dose regimen from 6 weeks of age onwards, with a minimum goal of 1 year duration of protection. Following the ongoing phase I study in adults, the candidate will be evaluated for safety and immunogenicity in RSV seropositive infants, followed by RSV seronegative infants, prior to age de-escalation to younger infants of target age range. Janssen are also developing an adenovirus vector based vaccine candidate, and evaluated homologous and heterologous prime boost regimens of Adenovirus 26 and Adenovirus35, both expressing the RSV F antigen. Since the meeting, Ad26.RSV.preF has been prioritized as the current lead candidate and is currently in Phase I clinical development (NCT02926430).

Several live-attenuated RSV strains developed by the Laboratory of Infectious Diseases (LID), NIAID, NIH are being evaluated as intranasal vaccines in phase 1 studies in RSV seronegative infants and children. These candidate vaccines contain deletions of the M2-2 or NS2 viral genes, and the intent is to identify the optimal candidate for advancement. Human parainfluenza (PIV) type 3 virus vectors expressing RSV pre-fusion F protein are also under development, with clinical studies expected to start in 2018. Development of lead vaccine candidates will occur in partnership between LID, NIAID and Sanofi Pasteur.

4.3. Monoclonal antibodies

mAbs offer the advantage over vaccines of having an instant biological effect and a well-defined mechanism of action. Historically, the cost of mAbs has been greater than the cost of vaccines and perceived as prohibitive for LMIC markets. However, significant advances in manufacturing technologies resulting in increased yields may reduce cost of goods. Medimmune's first generation mAb, palivizumab has been shown to protect against RSV-related hospitalizations in high risk infants [26]. In preparation for the patent expiration for palivizumab in 2015, WHO recently established a technology transfer centre at Utrecht University (Utrecht Center of Excellence for Affordable Biotherapeutics for Public Health), with the explicit aim to develop affordable medicines for low income countries [27]. A palivizumab biosimilar will be the first product that emerges from this venture, with an estimated price of $US 250 per child for full 5 courses. Its first market authorization is expected at the end of 2018.

In parallel, Medimmune has initiated work on a next-generation product with a longer half-life which may provide protection with a single administration. MEDI8897 is a fully humanised, high potency IgG1 mAb that targets a blocking epitope on the pre-fusion F antigen, with a YTE amino acid modification that extends half-life. MEDI8897 is under development as a single fixed dose, administered IM at birth or at onset of the RSV season, and expected to protect for a typical 5 month RSV season, after which a paediatric vaccination regimen could potentially be administered [28]. The first time in infants phase 1b/2a study in 32–35 week gestational age preterm infants (N = 89) has been completed, and a phase 2b clinical efficacy study in 29–35 week gestational age preterm infants was initiated November 2016 (N = 1500; NCT02878330). MEDI8897 has been granted FDA fast track designation, and study endpoints have been agreed with EMA PDCO and the FDA. If licensed, tiered pricing is envisaged in order to facilitate accessibility in low and middle income countries, and WHO pre-qualification will be sought.

5. Development of measurement and written standards to facilitate RSV vaccine development

Epidemiological studies suggest RSV neutralizing antibodies protect against serious RSV-associated ALRI [29,30], and for this reason, many RSV vaccines aim to induce high titers of RSV neutralizing antibodies. However, more than 10 different RSV neutralization assay (NA) formats are presently in use to assess neutralizing antibody responses, and therefore, it is not currently possible to compare data across studies.

PATH performed an inter-laboratory study to evaluate the extent of output variability across a broad variety of RSV neutralization assay formats. The study assessed feasibility for an International Standard (IS) to harmonize output across assay formats, and informed on sample types suitable for establishing an IS. Twelve diverse RSV neutralization assay formats were surveyed using a common blinded and randomized specimen panel. The participating laboratories included vaccine developers, contract laboratories, academia and regulatory agencies. Study results demonstrated consistently high precision, whereas the degree of agreement varied widely between assay formats. These results indicated that harmonization with an IS would likely improve agreement. This was further supported by the observation that samples used as pseudo standards for harmonization could significantly improve the degree of agreement across assay formats. Many RSV natural infection (NI) serum samples substantially improved agreement when used as pseudo standards, suggesting that NI sera may be suitable for developing an IS. Although some pooled clinical trial sera samples used as pseudo standards significantly improved agreement,

this observation was not generalizable. The use of complement in RSV neutralization assays was not evaluated, and may influence results. Study results indicated samples must be carefully screened as part of the IS development process.

WHO's Collaborating Center, the National Institute for Biological Standardization and Control (NIBSC) in the UK, initiated development of the first International Standard for Antiserum to Respiratory Syncytial Virus that will be included as a reference reagent in NAs to harmonize and enable comparison of data derived from clinical studies. This requires that an international collaborative study be carried out, and discussions are ongoing regarding the optimal design to ensure that the IS will be applicable to all assays currently in use, relevant for all geographic areas and participants. Considering the various activities that this will entail, submission of the IS to the ECBS for review and adoption is planned for 2017 or 2018.

With respect to the development of WHO written standard (i.e. Guidelines) for regulatory evaluation of quality, safety and efficacy, it was considered that it's premature to formulate guiding principles before reviewing scientific evidence of clinical data from phase III trials. Therefore, WHO's plan includes progress monitoring in 2017 and initiation of the guidelines development in 2018. Meanwhile, WHO is supporting the development of RSV vaccines through the recently revised Guidelines for Clinical Evaluation of Vaccines, that includes general guidance on vaccine evaluation and a specific statements on maternal immunization [31].

6. Regulatory perspectives

There has been discussion as to whether it will be possible to license an RSV vaccine based on an immunological correlate, such as a threshold of neutralizing antibody, rather than a clinical endpoint, in order to accelerate the time and reduce the cost of approval. No immunological threshold has been shown to predict protection from RSV disease, and mediators of protection (e.g., antibody, cell-mediated response, mucosal IgA) may vary by population and vaccine. For this reason, a clinical endpoint efficacy trial will most likely be required for some years ahead. With respect to clinical endpoints, RSV-associated hospitalization is not considered ideal from the global perspective as the criterion for admittance vary considerably within and between regions/countries, and the generalization of findings to areas with poor access to care may be problematic. There was consensus for RSV LTRI to be most relevant as the licensure endpoint, when considering the burden of disease, clinical relevance and feasibility. The 2015 WHO RSV vaccine R&D consultation led to the formulation of pilot case definitions [1], including pulse oximetry values, but there is as yet no adopted consensus on the optimal threshold SaO2 level, as well as concerns about the ability to standardize pulse oximetry measurements. Further work is needed towards building consensus on standard case definitions, however it was acknowledged that even if case definitions are not universally applied in all clinical studies, collection of appropriate source data (continuous SaO2, respiratory rates, etc.) would likely allow comparisons across studies. Identifying reliable methods of case ascertainment in vastly differing geographical and socioeconomic settings remains a significant challenge.

The safe advancement of paediatric vaccine candidates in face of the legacy of enhanced disease, and particularly the risk of vaccine-associated enhanced respiratory disease (ERD) in vaccinated seronegative infants, is critical. Subject matter experts, based on some level of experimental evidence, tend to classify the perceived risk for RSV-naïve infants according the specific vaccine platform under consideration [32]. Gene-based approaches, such as viral vector delivery or DNA vaccines are anticipated to mimic live virus vaccination in that antigen would be produced intracellularly, inducing CD8 T-cell responses. However, recombinant protein-based approaches would be theoretically more likely to induce a Th2 response similar to FI-RSV. In so far as is possible, preclinical testing should rule out signals associated with ERD (e.g., Th2-biased immune response, high magnitude antibody response with poor neutralizing activity, lung eosinophilia), followed by clinical studies in seropositive children, prior to progressing to clinical testing in seronegative infants. However, it is not possible to prove a negative, even with large clinical studies, and it is acknowledged that safety data in seropositive children will mitigate but not obviate the risk of post-vaccination ERD in RSV-naive infants. The current EU general expectation for a safety database of a novel vaccine is a minimum of 3000 exposed to the final dose regimen of the vaccine. Of particular relevance to paediatric vaccination will be evidence to support "negligible risk" of disease enhancement after vaccination of RSV-naive populations.

Clinical development plans for vaccines will most likely include randomized controlled trials with a non-RSV prevention arm, as for studies of new generation mAbs in populations that are not eligible for treatment with palivizumab according to local recommendations. The generation of long-term follow-up data, for at least 3 RSV seasons to assess impact on wheezing, and data stratification by region and gestational age at birth (pre-term vs term), is strongly encouraged.

It is acknowledged that efficacy trials are likely to be conducted in both high income and LMICs, and that regulators and policymakers will be looking for effectiveness data relevant to their own settings. The relevance and robustness of the primary endpoint standard case definition will be critical. From an US perspective, clinical data from non-IND studies in LMICs can support advancement to the next phase of clinical development and/or be used to support a marketing application, as long as they comply with specific requirements described in 21 CFR 312.120, including following ICH guidance on GCP. In a scenario where an efficacy trial is performed entirely outside the U.S., a clinical bridging study may be required to provide evidence that the vaccine will be effective when administered to a U.S. population. In the case of maternal immunization, data on the kinetics of a relevant antibody assay (e.g., maternal immune response, transplacental transfer, decay in infants) may contribute to bridge vaccine efficacy to populations not included in initial efficacy trial(s).

Both the FDA and EMA are developing and communicating guidance on development of RSV interventions and vaccines for administration to pregnant women. The FDA and NIH collaborated to co-sponsor a conference on Challenges and Opportunities in RSV Vaccine Development in June 2015 [32], and in November 2015, FDA's Vaccines and Related Biological Products Advisory Committee (VRBPAC) convened to discuss considerations for evaluation of the safety and effectiveness of vaccines (both existing and in development) that are administered to pregnant women to protect the infant [33]. While infant protection is the main expected benefit from the intervention, monitoring of infection/disease in the mother is encouraged. It is however acknowledged that studies will unlikely be powered to detect a clinical benefit for the mother.

7. WHO prequalification (PQ)

WHO vaccine prequalification is a service provided to UN purchasing agencies, such as UNICEF, as well as GAVI, that provides independent opinion/advice on the quality, safety and efficacy of vaccines for purchase. Its remit includes ensuring that candidate vaccines are suitable for the target population and meet the needs of the Expanded Programme on Immunization (EPI) through assessment of programmatic suitability [34]. WHO vaccine

Table 1
Considerations for vaccine licensure and vaccine policy recommendation.

Regulatory considerations		Policy considerations	
Quality	Manufacturing consistency Robust characterization Stability	Safety	Safety of the vaccine in broader populations and risk groups, with a focus on larger sample sizes, and both pre-licensure and post-licensure designs and surveillance systems
Safety	Initial licensure safety databases for new vaccines have varied from 6000 to 40,000 or so. Risk/Benefit profile	Efficacy & effectiveness	How the vaccine reduces disease in a population within a vaccination program Risk/Benefit profile
Efficacy	As measured by double-blind, randomized, clinical controlled trials, Sometimes inferred from immunogenicity	Vaccine Impact	Often modelled, predicts the reduction in infection or disease according to a certain vaccination strategy
		Feasibility of implementation	Fit within existing vaccine delivery infrastructure, such as the EPI or ANC visits
		Health economic evaluations	Cost effectiveness of vaccine in reducing disease and improving quality of life
		Role of the intervention in the context of existing or other emerging interventions	Drugs, diagnostics, other disease control strategies
		Broader perspectives including equity, community awareness and acceptability	Creating the awareness of the disease in affected population and creating a 'pull' mechanism

prequalification is contingent on regulatory approval by a national regulatory authority (NRA) that has been assessed as functional by WHO benchmarking. The NRA is normally that of the vaccine manufacturing country. The NRA provides ongoing cooperation with WHO in regulatory oversight of PQ'ed vaccines. WHO PQ is a prerequisite for UN agency procurement (Fig. 1). The target internal review time for evaluation for PQ is 270 days. Time taken for company responses is additional to this.

Prioritization of vaccines for WHO PQ is reviewed biennially, with the next review date in 2017. PQ prioritisation takes into account UN procuring agency requirements, WHO programmes and international health regulations. In the case of new vaccines, policy recommendations of WHO's Strategic Advisory Group of Experts (SAGE) for Immunization are taken into account. Vaccines that are available or expected to become available in the biennium years) are of primary consideration, however other vaccines of high interest may be considered for evaluation if they become available for supply before the next review date.

The WHO PQ team encourages engagement throughout the development process, to introduce candidate products and their development program and identify any aspects that may impede WHO PQ and access to LMIC procurement mechanisms following licensure.

At the meeting, it was identified that there is not currently a pathway for PQ of monoclonal antibodies. This group's recommended that WHO should consider expanding the prequalification team's scope to include long-acting mAb. This was further endorsed by SAGE [2].

8. Considerations for RSV vaccine policy recommendation, financing and uptake

WHO's pivotal role in RSV vaccine development is to ensure that the public health needs are well established and communicated, and that candidates advancing towards licensure align with the programmatic needs. In order to avoid a delay between vaccine licensure and vaccine implementation, it is critical to understand the data requirements, or evidence, that will be required to support a policy recommendation for use. The policy recommendations are, in the case of vaccines for LMICs, provided by WHO's Strategic Advisory Group of Experts (SAGE) for Immunization, and are not the same as those for vaccine licensure issued by the Expert Committee on Biological Standardization (ECBS) (Table 1). Early understanding of these differences, and planning of pre-licensure studies that incorporate the elements for successful policy recommendation, will reduce the cost and timeframe to vaccine procurement and implementation, and ultimately optimise public health impact.

The programmatic suitability of a RSV vaccine or intervention, i.e. its compatibility with existing delivery systems such as the antenatal care (ANC) or EPI schedule will dramatically impact its cost effectiveness and determine its eventual coverage impact. Understanding the long-term public health benefits of vaccine introduction, over and above the primary end points of reduction of LTRI, such as reduction of recurrent wheeze and asthma will have a strong impact on cost effectiveness and create positive value proposition for policy makers and funders.

A commitment to vaccine financing is an important target of vaccine development for LMICs. Gavi's financing decisions are determined by their evidence based Vaccine Investment Strategy (VIS) that is reviewed every 5 years. VIS recommendations are based on evidence of vaccine impact, cost effectiveness, operational feasibility and others factors, while implementation of these recommendations ultimately depends on available resources, country demand, WHO normative guidance provided by the ECBS and PQ requirements. As such, WHO works closely with GAVI to scan the horizon for vaccines that will emerge ahead of the next VIS cycle, and facilitates development of evaluation criteria based on potential vaccine impact, cost and implementation feasibility in preparation for the next VIS (2018). GAVI may increasingly consider impact on morbidity as well as mortality as well as the fact that future vaccines may need to be used in a targeted fashion towards specific populations or sub-groups. For some vaccines, investment in post-licensure pilot studies may be needed in specific regions to evaluate and optimise the most effective implementation strategy.

9. WHO's SAGE recommendations on RSV vaccine and monoclonal antibody development: looking beyond licensure towards demonstrating impact on RSV disease

SAGE identified several key epidemiological gaps that need to be addressed in order to support a policy recommendation [2]. In particular, improved age-stratified disease burden data and the contribution of community mortality and morbidity to the overall disease burden in LMICs are needed to optimise the vaccination strategy and demonstrate vaccine impact. SAGE also underlined

the necessity for long term follow up of subjects from randomized controlled trials to evaluate the effects of RSV interventions in terms of recurrent wheeze. If a causal relationship between RSV infection and recurrent wheeze or asthma is demonstrated, it would substantially increase the cost-effectiveness of RSV preventive interventions.

In preparation for a global policy assessment and in country introduction for both maternal and passive immunization with long-acting mAb, SAGE emphasized the need to link the RSV maternal immunization platform with those of influenza, tetanus and pertussis vaccines. Consideration of appropriate co-administration studies will also be needed. This effort will require close coordination of activities within the vaccine implementation, respiratory infection, reproductive health, child health and vaccine safety communities. SAGE encouraged determination of prequalification pathways for long-acting mAb and initiation of early discussions with financing bodies to achieve potential major public health value of RSV vaccination that may become available in the next 5 years.

10. Conclusion

Whilst the clinical evaluation of RSV interventions progresses at an impressive rate, there are significant gaps in the data that will be needed to support a positive policy recommendation in a timely manner. As pointed out by SAGE, there is now a critical 4–5 year period that should be used to systematically fill gaps in evidence required from regulatory, prequalification and policy recommendation perspectives for RSV maternal immunization, passive immunization with long-acting monoclonal antibody and paediatric immunization.

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