



WHO Preferred Product Characteristics for Respiratory Syncytial Virus (RSV) Vaccines

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CONTENTS

I. Introduction	5
II. Context of available interventions	6
III. WHO strategic vision for RSV vaccines.....	6
IV. RSV vaccines for maternal immunization, preferred product characteristics.....	7
V. RSV vaccines for paediatric immunization, preferred product characteristics.....	11
References.....	15

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I. INTRODUCTION

Respiratory Syncytial Virus (RSV) is a leading cause of respiratory disease globally. The virus causes infections at all ages, but young infants have the highest incidence of severe disease, peaking at 1–3 months of age. By 2 years of age, virtually all children will have been infected. RSV has been estimated to cause 34 million acute lower respiratory tract infections (LRTI) in young children annually, with over 3 million severe cases requiring hospitalization, and between 66,000 to 199,000 fatalities, 99% of which are in low- and middle-income countries (LMICs) (1). RSV transmission follows a marked seasonal pattern in temperate areas with mid-winter epidemics, but may occur during rainy seasons or year-round in the tropics.

RSV vaccine research and development activities have increased significantly in recent years (2). Vaccine development efforts had previously been slowed following reports from clinical trials conducted in the 1960s, in which a formalin-inactivated whole virus vaccine (FI-RSV) led to enhanced RSV disease (ERD) in children who subsequently were naturally infected for the first time with RSV (3). While the pathogenesis of ERD is not completely understood, strategies have been developed to reduce the risk and support further candidate vaccine development (4).

The World Health Organisation (WHO) Product Development for Vaccines Advisory Committee (PDVAC) considers it a priority to ensure that emerging RSV vaccines are suitable for licensure and meet policy decision-making needs to support optimal use in low- and middle-income countries in addition to high-income countries (5, 6). The WHO Preferred Product Characteristics (PPCs) described in this document were developed to provide guidance to scientists, regulators, funding agencies, and industry groups developing vaccine candidates intended for WHO prequalification (PQ) and policy recommendations. PPCs do not replace existing requirements related to WHO programmatic suitability for PQ (7), but are intended to complement them. In addition to meeting quality, safety, and efficacy requirements, it is also important that developers and manufacturers are aware of WHO's preferences for parameters that have a direct operational impact on immunization programs. Low programmatic suitability of new vaccines could result in delaying introduction and deployment.



II. CONTEXT OF AVAILABLE INTERVENTIONS

No vaccine is presently available to prevent RSV disease. In some high- and middle-income countries, the administration of the licensed monoclonal antibody, palivizumab (Synagis®) to very premature, immunosuppressed, or otherwise severely ill infants with significant underlying cardiac or pulmonary disease is recommended for prevention of severe RSV disease (8, 9). The development of monoclonal antibodies with extended half-life to meet needs for wider use in healthy infants is also an area of intense research. While some considerations presented here (such as WHO preferences regarding the demonstration of safety and clinical benefit, as well as access in resource-limited countries), are relevant to the field of monoclonal antibody development, specific detailed characteristics for monoclonal antibodies are beyond the scope of this document.



III. WHO STRATEGIC VISION FOR RSV VACCINES

To promote the development of high-quality, safe and effective RSV vaccines that prevent severe disease and death in infants less than 12 months of age and reduce morbidity in children less than 5 years of age, and to ensure they are available and affordable for global use including in LMICs.

Two priority approaches are identified:

- Development of vaccines for maternal immunization during pregnancy leading to trans-placental antibody transfer and prevention of severe RSV disease in neonates and young infants
- Development of vaccines for paediatric immunization to prevent RSV disease in infants and young children.

IV. RSV VACCINES FOR MATERNAL IMMUNIZATION, PREFERRED PRODUCT CHARACTERISTICS

Parameter	Preferred Characteristic	Notes
Indication	Active immunization of women during pregnancy, for prevention of severe RSV disease in offspring during the neonatal period and early infancy.	Preferred endpoint case definitions have been published (10).
Target population	Women in the second or third trimester of pregnancy.	Vaccination timing in pregnancy should maximize antibody transfer to the fetus and protection of the offspring, including for those born preterm, who are at increased risk of severe RSV disease. Vaccination during early pregnancy should be avoided, as the first months of pregnancy are associated with an increased risk of spontaneous abortion and could confound vaccine safety assessments. Given the difficulties related to access to obstetric care and the determination of precise gestational age in many LMICs, vaccines that can be delivered over a range of gestational ages are preferred. HIV infection should not be a contra-indication to vaccination.
Schedule	A one dose regimen is highly preferred.	A two-dose regimen, with a first priming dose possibly delivered prior to pregnancy, is not a preference, but may need to be considered. The role of additional doses in successive pregnancies should be evaluated, possibly post licensure.
Vaccine platform and adjuvant requirement	Well-characterized platforms with established favourable safety profiles, evaluated in pregnancy, and no known safety concerns for pregnant women. Live viral vaccines are not favoured, given the potential risk of adverse effects on the fetus. Preference for the absence of an adjuvant.	A formulation including an aluminium salt or another adjuvant with an extensively demonstrated favourable safety profile in pregnancy may be acceptable.

Parameter	Preferred Characteristic	Notes
Safety	<p>Safety and reactogenicity profile at least as favourable as current WHO-recommended routine vaccines for use during pregnancy (influenza, tetanus toxoid, acellular pertussis).</p> <p>No indication of ERD in the offspring.</p>	<p>Typical toxicology evaluation of investigational maternal vaccines, including reproductive toxicology, should be undertaken.</p> <p>Favourable safety in non-pregnant healthy women of child-bearing age should be shown before proceeding to evaluation in pregnant women.</p> <p>While transient, mild to moderate local symptoms would be acceptable, systemic reactions to vaccination in pregnancy are highly undesirable. Mild, transient reactogenicity with low grade, low rate fever may be acceptable. Serious adverse events related to vaccination including impact on the normal course of pregnancy, neonatal health, and development outcomes in infancy would not be acceptable.</p> <p>The GAIA (Global Alignment of Immunisation safety Assessment in pregnancy) project coordinated by the Brighton Collaboration in cooperation with WHO provides tools aimed to strengthen safety monitoring of vaccination during pregnancy, considering specificities in low-and-middle-income countries. The US FDA has also issued recommendations concerning vaccines intended for use in pregnancy (11, 12).</p>
Efficacy	<p>Greater than 70% vaccine efficacy against confirmed severe RSV disease in the offspring, from birth to age 4 months (and preferably more).</p>	<p>A vaccine with 50% vaccine efficacy against confirmed severe RSV disease in the offspring, from birth to age 3 months, may be considered as acceptable for use.</p> <p>Proposed priority study endpoint case definitions have been published (10).</p> <p>The dynamic of protection over time throughout infancy should be described, taking seasonality patterns into account.</p> <p>The vaccine efficacy against other endpoints of public health interest should also be evaluated, including:</p> <ul style="list-style-type: none"> • non-severe RSV respiratory disease • recurrent wheezing, hyper-reactive airway disease and asthma • RSV-related morbidity in vaccinated women • reduction of antibiotic use in infants
Strain specificity	<p>Vaccination protects against both RSV A and B subtypes.</p>	

Parameter	Preferred Characteristic	Notes
Immunogenicity	Established correlate/surrogate of protection based on a validated assay measuring antibody levels in the mother and/or the neonate.	<p>A detailed quantitative profiling of passively transferred antibodies, and relationship to timing of vaccination in pregnancy is desirable. Longevity of vaccine-induced maternal antibodies in infants should be characterized and the relationship to duration of protection should be investigated. The fine specificity of vaccine antigen neutralizing epitopes should be characterized, as they may have a significant influence on binding and functionality of the antibody induced. The generation of clinically relevant validated neutralization assay data, ideally using high-throughput formats, is an important goal. Quantitative assays measuring the ability of vaccine-induced antibodies to compete with monoclonal neutralizing antibodies (such as palivizumab or motavizumab) are interesting, but may not be reflective of all effector functions of vaccine-induced immunity, and should not replace the need to evaluate neutralization. The role of antibody transferred through breast-feeding should be investigated.</p> <p>The influence of maternal HIV infection and malaria in pregnancy should be evaluated.</p> <p>Collaborative efforts to establish relevant non-clinical assays, using open source reference reagents with international standards of quality, may greatly contribute to comparability assessments. The generation of a correlate of protection acceptable for regulatory purposes will support immune bridging steps, simplify clinical development plans, and accelerate the pathway to licensure.</p>
Non-interference	Demonstration of favourable safety and immunologic non-interference upon co-administration of other vaccines recommended for use in pregnancy.	<p>In LMICs, investigation of co-administration with tetanus vaccine should be investigated as a priority. Co-administration with Tdap, influenza and possibly GBS (if a vaccine for maternal use is available) should also be considered.</p> <p>The possible interference with specific paediatric EPI vaccines, particularly if a paediatric RSV vaccine is available, should be considered.</p>
Route of administration	Injectable (IM, ID, or SC) using standard volumes for injection as specified in programmatic suitability for PQ or needle-free delivery.	

Parameter	Preferred Characteristic	Notes
Registration, prequalification and programmatic suitability	The vaccine should be prequalified according to the process outlined in <i>Procedures for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies</i> (WHO/BS/10.2155). WHO defined criteria for programmatic suitability of vaccines should be met (13–15).	
Value proposition	Dosage, regimen and cost of goods amenable to affordable supply. The vaccine should be cost-effective and price should not be a barrier to access, including in low- and middle-income countries.	A RSV vaccine-associated reduction of antibiotic use in routine practice, and/or reduction in recurrent wheeze and subsequent asthma would be of high added value. The vaccine impact on health systems (such as reduction of RSV-related medical attendance and hospitalization) and other aspects of implementation science should be evaluated in large trials, pre or post-approval, as practicable.



V. RSV VACCINES FOR PAEDIATRIC IMMUNIZATION, PREFERRED PRODUCT CHARACTERISTICS

Parameter	Preferred Characteristic	Notes
Indication	Active immunization of infants, for prevention of RSV disease in infants and young children.	Preferred endpoint case definitions have been published (10).
Target population	Infants, for co-administration with existing vaccines from the Expanded Program on Immunization.	HIV infection and mild/moderate malnutrition should not be a contra-indication to vaccination.
Schedule	The vaccination regimen should provide the earliest protection and longest duration of protection possible.	<p>The optimal age schedule will depend on whether a maternal RSV immunization or infant RSV monoclonal antibody program is already introduced, in which case the infant vaccination schedule should aim to extend protection, as maternally-derived or monoclonal antibody levels wane. The development plan should assess interference between maternally acquired/monoclonal antibodies and infant vaccine immunogenicity and protection. The optimal age will depend on a balance between immunogenicity and whether or not interference is seen between paediatric vaccination and pre-existing circulating antibodies. Some vaccines may be less prone to interference from pre-existing antibodies than others, either because of the nature of the platform itself or based upon the route of delivery (e.g. mucosal rather than parenteral).</p> <p>In the absence of maternal immunization or monoclonal antibodies protecting very young infants, a schedule inducing very early protection would be desirable.</p> <p>Further research is needed to inform on the possibility of vaccination strategies targeting older children to reduce transmission and exposure in the most vulnerable younger children.</p> <p>The need for more than 3 doses for primary immunization is highly undesirable. Given the fact that the risk of severe outcomes is relatively concentrated in the very young, extended protection may not be a priority. The effect of booster doses may nevertheless be considered.</p>

Parameter	Preferred Characteristic	Notes
Vaccine platform and adjuvant requirement	A well characterized platform with existing favourable data on safety and immunogenicity in early life is preferred.	Adjuvant requirement should be investigated and justified if included.
Safety	<p>Safety and reactogenicity at least as favourable as other WHO-recommended routine vaccines for use in the Expanded Program on Immunization</p> <p>Safety profile demonstrates no or only mild, transient reactogenicity and no serious adverse events related to vaccination</p> <p>No indication of ERD in vaccinated children.</p>	<p>In addition to typical toxicology evaluation of investigational paediatric vaccines, preclinical investigations should include the evaluation of the risk of post vaccination ERD.</p> <p>Safety in children should first be investigated in RSV-experienced subjects, after favourable evaluation in older subjects. As ERD has historically been associated with vaccination of children without past RSV exposure, progression to younger infants and children with no past RSV infection who are seronegative at screening should be done under intense safety surveillance. Paediatric vaccination studies should include high quality medical oversight, with independent unblinded continuous safety data review, allowing detection of cases of RSV disease with features of enhanced severity, and early trial termination accordingly. A small number of seronegative infants only should be included initially, to allow for faster enrolment when enough evidence is accrued about the lack of post-vaccination ERD occurrence. This should be tailored to the available evidence about the level of risk, which may be lower for some vaccine platforms than others.</p>
Efficacy	<p>Greater than 70% vaccine efficacy against confirmed severe RSV disease over at least one-year post-vaccination.</p> <p>Reduction in frequency and severity of RSV illness.</p>	<p>A vaccine with 50% vaccine efficacy against confirmed severe RSV, over at least one-year post vaccination, may be considered as acceptable for use.</p> <p>Proposed priority study endpoint case definitions have been published (10).</p> <p>The dynamic of protection over time should be described, taking seasonality patterns into account. Protection over at least 2 years or successive RSV seasons, or more, would be preferred.</p> <p>The vaccine efficacy against other endpoints of public health interest should also be evaluated:</p> <ul style="list-style-type: none"> • non-severe RSV respiratory disease, • hyper-reactive airway disease and recurrent wheezing in children, • reduction of antibiotic use. <p>The demonstration of an effect of vaccination on RSV transmission, possibly requiring booster doses, would be of great public health interest, but may be left for evaluation in specifically designed post-approval trials.</p>

Parameter	Preferred Characteristic	Notes
Strain specificity	Vaccination should protect against both RSV A and B subtypes.	
Immunogenicity	Established correlate/surrogate of protection based on a validated immunoassay.	<p>An early, detailed characterization of immunogenicity may support the evaluation of the risk that primary vaccination of RSV-naïve infants may result in ERD upon natural exposure to RSV (4).</p> <p>The longevity of the immune response in infants should be characterized, and the relationship to duration of protection and need for booster doses should be investigated. The fine specificity of vaccine antigen neutralizing epitopes should be characterized, as they may have a significant influence on binding and functionality of the antibody induced. The generation of clinically relevant validated neutralization assay data, ideally using high-throughput formats is an important goal. Quantitative assays measuring the ability of vaccine-induced antibodies to compete with monoclonal neutralizing antibodies (such as palivizumab or motavizumab) are interesting, but may not be reflective of all effector functions of vaccine-induced immunity, and should not replace the need to evaluate neutralization.</p> <p>The influence of important comorbidities such as HIV infection, malnutrition, and malaria should be evaluated.</p> <p>Collaborative efforts to establish relevant non clinical assays, using open source reference reagents with international standards of quality, may greatly contribute to comparability assessments. The generation of a correlate of protection acceptable for regulatory purposes will support immune bridging steps, simplify clinical development plans, and accelerate the pathway to licensure.</p>
Co-administration with other vaccines	Demonstrated safety and non-inferior immunogenicity of RSV vaccine upon co-administration with other recommended pediatric vaccines. No significant negative impact on immune responses to co-delivered vaccines.	

Parameter	Preferred Characteristic	Notes
Registration, prequalification and programmatic suitability	The vaccine should be prequalified according to the process outlined in <i>Procedures for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies</i> . WHO defined criteria for programmatic suitability of vaccines should be met (13–15).	
Value proposition	Dosage, regimen and cost of goods amenable to affordable supply. The vaccine should be cost-effective and price should not be a barrier to access including in low- and middle-income countries.	The vaccine impact on health systems (such as reduction of RSV-related medical attendance and hospitalization) and other aspects of implementation science should be evaluated in large trials, pre or post-approval, as practicable.



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