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

*DEPARTMENT OF IMMUNIZATION, VACCINES AND BIOLOGICALS*

Family, Womens's and Children's Health (FWC)

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World Health Organization
Department of Immunization, Vaccines and Biologicals
CH-1211 Geneva 27, Switzerland
• Fax: + 41 22 791 4227 • Email: vaccines@who.int •



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## WHO Secretariat

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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.<br><br>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.<br><br>Live viral vaccines are not favoured, given the potential risk of adverse effects on the fetus.<br><br>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** | Safety and reactogenicity profile at least as favourable as current WHO-recommended routine vaccines for use during pregnancy (influenza, tetanus toxoid, acellular pertussis).<br><br>No indication of ERD in the offspring. | Typical toxicology evaluation of investigational maternal vaccines, including reproductive toxicology, should be undertaken.<br><br>Favourable safety in non-pregnant healthy women of child-bearing age should be shown before proceeding to evaluation in pregnant women.<br><br>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.<br><br>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)*. |
| **Efficacy** | Greater than 70% vaccine efficacy against confirmed severe RSV disease in the offspring, from birth to age 4 months (and preferably more). | 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.<br><br>Proposed priority study endpoint case definitions have been published *(10)*.<br><br>The dynamic of protection over time throughout infancy should be described, taking seasonality patterns into account.<br><br>The vaccine efficacy against other endpoints of public health interest should also be evaluated, including:<br>• non-severe RSV respiratory disease<br>• recurrent wheezing, hyper-reactive airway disease and asthma<br>• RSV-related morbidity in vaccinated women |