



WHO PREFERRED PRODUCT
CHARACTERISTICS OF

**monoclonal
antibodies
for passive
immunization
against
respiratory
syncytial virus
(RSV) disease**



World Health
Organization

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Abbreviations and glossary

ADA	anti-drug antibodies	LMIC	low- and middle-income countries
ALRI	acute lower respiratory infection	mAb	monoclonal antibody
CHD	chronic heart disease	MA	medically attended
CLD	chronic lung disease	PPC	preferred product characteristics
DALY	disability-adjusted life-year	PQ	WHO prequalification
DTP	diphtheria, tetanus and pertussis vaccine	QALY	quality-adjusted life-year
EPI	Expanded Programme on Immunization	RCT	randomized controlled trial
ERD	enhanced respiratory disease	RSV	respiratory syncytial virus
FDA	United States Food and Drug Administration	RSV-IGIV	RSV immunoglobulin intravenous
GAVI	Gavi, the Vaccine Alliance	SAGE	WHO Strategic Advisory Group of Experts (on immunization)
IVB	Department of Immunization, Vaccines and Biologicals	WHO	World Health Organization
LRTI	lower respiratory tract infection	UN	United Nations



Photograph courtesy of WHO / Erin Sparrow

1. Background and purpose of WHO preferred product characteristics

This document describes World Health Organization (WHO) preferences for characteristics of monoclonal antibody (mAb) products used for passive immunization against severe respiratory syncytial virus (RSV) disease in infants. These preferences are shaped by the global unmet public health need in priority disease areas for which WHO encourages the development of vaccines and other preventive interventions suitable for use in low- and middle-income countries (LMICs). While many characteristics are the same as those preferred in high-income countries, there are some characteristics that might be unique to LMIC settings (1).

The primary audience for this document includes all involved in the development of new RSV mAbs intended for global use, that is, those contemplating eventual WHO policy recommendation and prequalification. This document concerns only RSV mAbs intended to prevent severe RSV disease in infants, which is the outcome of greatest public health impact in LMICs. Preferred product characteristics (PPCs) present preferred, rather than required, characteristics of products. Whether or not a product meets the PPC criteria, a product can still be assessed for policy recommendations by the WHO Strategic Advisory Group of Experts (SAGE) on immunization and for WHO prequalification, which assesses product quality, safety, efficacy and suitability for use in LMICs (2). The prequalification process assesses products for programmatic suitability for use in LMICs, and has a number of mandatory, critical and

preferred characteristics that are evaluated (3). WHO prequalification facilitates the procurement of products by United Nations (UN) agencies and financing by Gavi (3). Low programmatic suitability of new products may delay or prevent their deployment in LMICs. PPCs are reviewed periodically and updated when necessary, with consideration given to any changes in scientific knowledge and technology.

Research and development on RSV preventive products has increased significantly in recent years (4). Vaccine development efforts stalled for several decades following clinical trials conducted in the 1960s, in which a formalin-inactivated whole virus vaccine led to enhanced respiratory disease (ERD) in RSV-naïve children upon subsequent exposure to RSV (5, 6). Much has been learned about the pathogenesis of ERD since then, and current RSV prevention strategies to protect infants, including mAbs, are designed to minimize the risk of ERD (7). Several types of RSV vaccines and long-acting mAbs are currently in preclinical and clinical stages of development. To date there is one licensed mAb, Synagis (palivizumab), for use in specified populations of high-risk infants and young children in high-income and some middle-income countries. While there are no licensed RSV vaccines, several mAbs and vaccines are in late-stage clinical development. The PPCs for RSV vaccines for use in pregnant women and paediatric populations have been published previously (WHO/IVB/17.11) (8).

2. The case for prevention of RSV disease in young infants

RSV is a leading cause of respiratory disease in young children globally. The virus causes infections at all ages, but young infants have the highest incidence of infection and severe disease, peaking in infants under 6 months of age, and by 2 years of age virtually all children will have been infected (9). In 2015, globally, RSV was estimated to cause 33.1 million severe acute lower respiratory infections (ALRIs) in young children under 5 years of age annually, with 3.2 million severe cases requiring hospitalization and up to 118 200 deaths (10). There were an estimated 1.4 million hospital admissions and 27 300 in-hospital deaths among infants younger than 6 months of age, of which >99% occurred in developing countries (10). Preliminary data from recent surveillance studies assessing mortality in several low resource settings in Africa, South Asia and South America suggest that 6–10% of all deaths in infants aged 7 days to 6 months may be associated with RSV (11–14). RSV transmission follows a marked seasonal pattern in temperate countries with winter epidemics; in tropical countries, RSV may have a single seasonal peak, multiple peaks or circulate year-round in countries near the equator (9). Different seasonality patterns may have policy and programmatic implications, as the protection afforded by mAbs, as well as by maternal immunization, will only last as long as effective serum concentrations can be maintained, which is likely to

be no more than six months. Two subtypes of RSV, A and B, exist and both may co-circulate in a population in any given year. Although some studies have shown an association between RSV ALRIs in infants and longer-term respiratory sequelae, the current evidence is inconclusive in establishing a causal association between RSV ALRI and recurrent wheezing of early childhood or asthma (15).

“RSV is a leading cause of respiratory disease in young children globally. The virus causes infections at all ages, but young infants have the highest incidence of infection and severe disease.”

3. Context of available interventions

The first formulation of passive immunization against RSV disease was polyclonal, hyperimmune intravenous immunoglobulin (RSV-IGIV, RespiGam®) (16), manufactured by plasmapheresis from pooled plasma of healthy human donors selected for high titres of protective RSV antibodies as determined by microneutralization (17). RSV-IGIV was used for RSV prevention in children under 24 months -with bronchopulmonary dysplasia, a chronic lung disease, and in children under 6 months old who were born prematurely (18). RSV-IGIV was superseded by palivizumab, a more potent, intramuscularly administered RSV F mAb (Synagis®), which was approved by the United States Food and Drug Administration (FDA) in 1998. Palivizumab is recommended for monthly dosing during the RSV season for prevention of severe RSV disease in specific high-risk children, including those born very prematurely, or those with moderate to severe bronchopulmonary dysplasia or hemodynamically significant congenital heart disease (CHD) (19-21). Palivizumab is administered monthly during the RSV season, with a recommended dose of 15 mg/kg of body weight. Although it has been registered in 65 countries (22, 23), it is used in most countries in a restricted manner among very high-risk infants, in part due to its high cost. As of late 2019,

palivizumab is registered in no low-income countries, three lower-middle-income countries, 18 upper-middle-income countries and 44 high-income countries. A Cochrane review in 2013 concluded that palivizumab might not be cost-effective in LMICs (24). The efficacy of motavizumab, a second-generation RSV mAb, was compared to palivizumab in a phase 3 clinical trial. Motavizumab met the prespecified noninferiority criteria (protection against RSV hospitalization) when compared to palivizumab; however nominal cutaneous reactions were more frequently observed in motavizumab recipients than palivizumab recipients, and because there was no advantage shown for efficacy, cost or frequency of administration, the product did not receive approval from the FDA (25, 26).

Monoclonal antibodies with an extended half-life, which could protect infants during an entire RSV season with a single dose, are currently in development and clinical trials, one of which has shown promising levels of efficacy in a phase 2b trial (27). Such extended half-life mAbs promise to have simplified delivery requirements and to be less costly, making them potentially suitable for use in LMICs and for use for all infants, not just those at high-risk. Such products are the primary focus of this document.

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4. Clinical development of mAbs

Several extended half-life mAbs are currently in clinical trials. At this time, randomized controlled trials (RCTs), in which the product is compared to a placebo, are justified in populations of infants in which palivizumab is not currently recommended (28). Moreover, there are no licensed RSV vaccines at this time (29). In such trials, sites that include several LMIC populations would be desirable for demonstrating efficacy, due to potential differences in disease epidemiology, seasonality and demographic characteristics. While clinical trials often use RSV-associated medically attended-ALRI as a primary outcome, RSV-associated severe ALRI will likely be the most relevant outcome for policy decisions about use in LMIC settings, where RSV mortality is highest. Forthcoming guidelines from WHO on quality, safety and efficacy of preventive mAbs for RSV, similar to those produced for RSV vaccines (30), are expected within the next few years. Moreover, the ultimate criteria and approval for licensure of these products rests with national regulatory authorities.

Several protein-based RSV vaccines targeting pregnant women are also in clinical development; these vaccines could, if effective, result in transplacental antibody

transfer and protection of infants during the first few months of life (4). Comparative analyses of the relative advantages and disadvantages of mAbs and maternal immunization will be important for policy-making, including programmatic suitability and cost-effectiveness in LMICs, as well as the potential for complementary use.

“Monoclonal antibodies with an extended half-life, which could protect infants during an entire RSV season with a single dose, are currently in development and clinical trials.”

5. WHO strategic vision for RSV mAbs

To promote the development of high-quality, safe, affordable and effective mAbs that prevent severe RSV disease and RSV-related deaths in young children globally.

6. PPCs for RSV mAbs

Table 1. Preferred product characteristics

Parameter	Preferred Characteristic	Notes
Indication	Prevention of severe RSV disease during early infancy, the period of highest risk of severe RSV disease and mortality.	While manufacturers may choose to use medically attended disease as the primary endpoint for licensure, secondary endpoints measuring severe disease should be included, because severe RSV disease is most important from a public health impact perspective in LMICs. To allow for evaluation of severity in different settings and products, objective measures of severity such as elevated respiratory rate by age group and documented hypoxemia (by oxygen saturation) should be used. These should be measured on a continuous scale. Clinical signs of hypoxia or increased work of breathing (e.g. central cyanosis, nasal flaring, grunting, severe lower chest indrawing, inability to feed) can also be collected.
Target population	All infants in the first 6 months of life.	<p>Rates of RSV severe disease and mortality peak within the first 6 months of life, but continue to be elevated throughout infancy, after which they decline gradually throughout childhood.</p> <p>The primary target population aims to protect most infants during their first RSV season.</p> <p>Policy-makers may consider including:</p> <ul style="list-style-type: none">(i) all infants in the first 12 months of life, and/or(ii) children <2 years of age with risk factors (e.g. CLD, CHD and others) entering their second RSV season, based on local epidemiology and context.

Parameter	Preferred Characteristic	Notes
Schedule	<p>A one-dose regimen is highly preferred.</p> <p>A single dose can be given as a birth dose or at any healthcare visit during the first 6 months of life.</p>	<p>Both seasonal and year-round dosing can be considered.</p> <ol style="list-style-type: none"> 1. In settings with clearly defined RSV seasonal circulation, dosing can occur in the few months before the onset of, and during, the RSV season. 2. Year-round dosing might be preferred in settings with continuous and/or inconsistent peaks of RSV circulation. <p>MAb administration, either alone or in combination with other vaccines, can be done at the following time points.</p> <ol style="list-style-type: none"> 1. Birth dose (or soon after) is preferred for newborns likely to have their first RSV exposure in the first 5 months of life. 2. It can be done during any healthcare contact, such as the scheduled primary series EPI visits (e.g. with DTP1, DTP2 or DTP3) during the first 6 months of life. <p>Policy-makers should select a delivery strategy based on local context and programmatic feasibility.</p> <p>A mAb requiring more than one dose to protect throughout the RSV season may be considered, based on local cost-effectiveness analyses and programmatic suitability.</p>
Safety	<p>Safety and reactogenicity comparable to other WHO recommended vaccines given at the same age (e.g. HepB birth dose).</p>	<p>While the age of first infection is expected to shift to older ages with the use of mAbs, evidence should be provided indicating an overall reduced risk of severe RSV disease compared to no intervention.</p> <p>If more than one dose of mAb is to be given, then the impact of anti-drug antibodies (ADAs) should be evaluated.</p>
Efficacy	<p>At least 70% efficacy against RSV-confirmed severe disease for five months following administration (the median length of the RSV season).</p>	<p>A mAb with a lower efficacy and shorter duration of protection could still have a significant public health impact, depending on the epidemiological setting and product-attributable disease reduction, and on cost-effectiveness.</p> <p>Other efficacy endpoints of public health significance are:</p> <ul style="list-style-type: none"> • hospitalized RSV • medically attended RSV LRTI • all-cause severe LRTI, up to 1 year • recurrent wheeze and asthma (would require follow-up for several years (2–6 years)) • all-cause mortality • antibiotic use.

Parameter	Preferred Characteristic	Notes
Strain specificity	Protects against both RSV A and B subtypes.	Prior to efficacy trials, mAbs should demonstrate neutralization capacity in vitro against circulating contemporary A and B subtypes. Potential escape mutants should be mapped, based on known epitope structures, and mAb-binding characteristics from in vitro studies and sequences of circulating strains should be tracked. RSV F protein structure determination, from clinical case surveillance, should be undertaken pre- and post-licensure; identification of emerging F sequence variations should prompt in vitro neutralization studies to determine whether F sequence variations alter susceptibility to anti-RSV monoclonal antibodies.
Co-administration	RSV mAbs are not expected to interfere with any current co-administered childhood vaccines.	Potential interference with any RSV vaccines licensed in the future will need to be evaluated.
Route of administration	Single intramuscular or subcutaneous dose using standard volumes for injection, as specified in programmatic suitability for prequalification (2).	0.5 ml dose preferable for young infants, but up to and including 1.0 ml is considered suitable for WHO prequalification.
Registration, prequalification and programmatic suitability	<p>Must be licensed and approved by national regulatory authorities in countries of use.</p> <p>WHO-defined criteria for prequalification and programmatic suitability of vaccines, and recommendations on presentation, packaging, thermostability, storage volume and disposal should be met, where applicable to mAbs (2, 29).</p>	<p>Many principles and criteria of vaccine prequalification will apply to preventive mAbs (3). Specific requirements for prequalification of mAbs are outlined in the <i>Pilot procedure for prequalification of biotherapeutic products and similar biotherapeutic products</i>, though final guidance on prequalification of preventive mAbs has not yet been issued at this time (2020) (31).</p> <p>Prequalification by WHO will facilitate approval and ability to purchase products in LMICs (3).</p>

Parameter	Preferred Characteristic	Notes
Access and affordability	RSV mAb should be accessible and affordable to LMICs in order to allow broad protection of the most vulnerable infants.	<p>The impact of RSV mAbs on health systems (such as reduction of hospitalization burden and decrease in antibiotic use) and the immunization programme (such as cold storage capacity), and on quality-adjusted life-years (QALYs) and/or disability-adjusted life-years (DALYs) should be evaluated pre- and/or post-licensure, as practicable.</p> <p>The mAb price should be similar to other new vaccines for feasibility of use in LMIC settings, and cost-effectiveness analyses should support use.</p> <p>The mAb price should be acceptable to Gavi investment case for use in Gavi-eligible countries (32). Price considerations should also consider those LMICs that are not Gavi-eligible and their ability to pay.</p>

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