Preferred Product Characteristics of Monoclonal Antibodies for Passive Immunization against Respiratory Syncytial Virus (RSV)

NOTE:

This draft has been prepared in consultation with the WHO Department of Immunization, Vaccines and Biologicals’ Technical Advisory Group for RSV.

This document is being posted for the purpose of inviting comments and suggestions on the proposals contained therein, which will then be considered by WHO’s Product Development for Vaccines Advisory Committee (PDVAC).

Written comments proposing modifications to this text must be received by 10 May 2020 and entered in the Comment Form (available separately), and should be addressed to the Responsible Officer: Ms Erin Sparrow at sparrowe@who.int.

Background and purpose of WHO preferred product characteristics (PPCs)

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 contemplating eventual WHO policy recommendation and prequalification. This document concerns only RSV mAbs intended to prevent RSV severe disease in young children. PPCs present preferred, rather than required, characteristics of products. Whether or not a product meets the PPC criteria, it can 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 (3,4). It is a prerequisite to procurement of a product by United Nations (UN) agencies and 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 considering 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 their first exposure to RSV.[5] [6] Much has been learned about the pathogenesis of ERD since then, and current RSV prevention strategies are designed to minimize the risk of ERD.[7] Several types of RSV vaccines and long-acting mAbs are currently in pre-clinical and clinical stages of development. To date, there is one licensed mAb, used in specified populations of high-risk infants in high-income and some middle-income countries, and there are no licensed RSV vaccines, though several mAbs and vaccines are in late-stage clinical development. The Preferred Product Characteristics for RSV vaccines for use in pregnant women and paediatric populations has been published previously (WHO/IVB/17.11).[8]

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 severe disease, peaking at 1–3 months of age.[9] RSV affects children in all countries of the world and by two years of age, virtually all children will have been infected. In 2015, RSV was estimated to cause 33.1 million acute lower respiratory tract infections (LRTIs) 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 27,100 occurred in LMICs.[10] Preliminary data from recent mortality surveillance studies 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, 12] [13, 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. Different seasonality patterns may have policy and programmatic implications as the protection afforded by monoclonal antibodies is short lived. Two subtypes of RSV, A and B, exist and both may co-circulate in a population in any given year.

Context of available interventions

The first formulation of passive protection against RSV disease was polyclonal, hyperimmune intravenous immunoglobulin (RSV-IGIV, RespiGam®) [15], manufactured by plasmapheresis from pooled plasma of healthy human donors selected for high titres of protective RSV antibodies as determined by microneutralization.[16] RSV-IGIV was used for RSV prevention in children under 24 months with a chronic lung disease, bronchopulmonary dysplasia, and in children less than 6 months old who were born prematurely.[17] RSV-IGIV was superseded by palivizumab, a more potent intramuscularly administered humanized RSV F mAb (Synagis®), which was approved by the US FDA in 1998. Palivizumab is approved for use at the start of the RSV season for prevention of severe RSV disease in specific high-risk children including those born prematurely or those with moderate to severe bronchopulmonary dysplasia or hemodynamically significant congenital heart disease.[18][19] Palivizumab is administered during the RSV season in five monthly doses, with a recommended dose of 15mg/kg of body weight. Although it has been registered in 65 countries,[20, 21] it is used in a restricted manner in wealthier countries due to its high cost. As of late 2019, palivizumab is registered in no low income countries, 3 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.[22] The efficacy of motavizumab, a second-generation RSV mAb, was compared to palivizumab in a phase 3 clinical trial. Motavizumab did not meet prespecified superiority criteria for the primary endpoint (protection against RSV hospitalization) when compared to palivizumab and cutaneous reactions were more frequently observed in motavizumab recipients than palivizumab recipients. This product was not brought to market.[23, 24]

Monoclonal antibodies with an extended half-life, which could protect infants during an entire RSV season with a single dose, are currently in development. 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 in all infants. Such products are the focus of this document.
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.

MAbs for RSV – preferred product characteristics.

The preferred approach to establish the clinical efficacy of an extended half-life RSV mAb would be in randomized controlled trials (RCTs), in which the product is compared to a placebo in the case of full-term healthy infants or compared to palivizumab in separate trials in high-risk infants where it is available as the standard of care. The primary endpoint of an RSV mAb trial in higher burden LMIC settings would likely be severe RSV disease (Table 1), which is sufficiently common in young infants to allow assessment in a trial of manageable size. A placebo-controlled trial would be justified in healthy term infants in LMICs (as palivizumab is not indicated for this population) and could also be justified in high-risk infants in LMICs if palivizumab is not the standard of care. Additional justification for such a trial is that, currently, there is no licensed RSV vaccine and no immune correlate of protection has been identified.[25] Situations where placebo-controlled trials can be justified have been described by WHO previously.[26] In such trials, sites in more than one LMIC would be desirable for demonstrating efficacy in populations with differing disease epidemiology, seasonality, and demographic characteristics.

Several protein-based RSV vaccines targeting pregnant women are in clinical development; these vaccines could, if effective, result in transplacental antibody transfer and protection of infants during the first few months of life, potentially up to 6 months of age.[4] Comparative analyses of the relative advantages and disadvantages, including programmatic suitability for LMICs, cost-effectiveness, and interchangeability of long-acting mAbs and maternal immunization will be important for policy making.

Table 1. Preferred product characteristics

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<tr>
<th>Parameter</th>
<th>Preferred Characteristic</th>
<th>Notes</th>
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<tr>
<td>Indication</td>
<td>Passive immunization for protection against severe RSV</td>
<td>Objective measures of severity should be used such as elevated respiratory rate by age group and documented hypoxemia. These should be measured on a</td>
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disease during the neonatal period and early infancy, the period of highest risk of severe RSV disease and mortality.  
Continuous scale. Clinical signs of hypoxia or increased work of breathing should also be collected (e.g. central cyanosis, nasal flaring, grunting, inability to feed). Ideally, an agreed definition of severe RSV disease could be used to compare outcomes across products and regions. Candidate case definitions were proposed by a WHO expert working group in 2015.[27]

| Target population | Preterm and full-term neonates and infants through 6 months of age.  
RSV mortality peaks at 4-6 months of age, but continues to be elevated throughout infancy.

| Schedule | A one dose regimen is highly preferred.  
A single dose can be given as a birth dose or at any healthcare visit through 6 months of age.  
Both seasonal and year-round dosing can be considered.  
1. In settings with clearly defined RSV seasonal circulation, dosing can occur at or just before the onset of the RSV season.  
2. Year-round dosing may be preferred in settings with continuous and/or inconsistent peaks of RSV circulation.  
mAb administration, either alone or in combination with other vaccines, can be done at the following time points:  
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. At any healthcare contact such as scheduled primary series EPI visits. (e.g. with DTP1, DTP2 or DTP3) through 6 months of age.  
Policy makers should select a delivery strategy based on local context and programmatic feasibility.

| Production platform | Produced using a well characterized cell line (e.g. CHO cells).

| Safety | Safety and reactogenicity at least as favourable as other WHO recommended vaccines  
No evidence of greater severity of RSV disease occurring after mAb wanes.
| Efficacy | Greater than 70% efficacy against RSV-confirmed severe disease for 5 months following administration (the median length of the RSV season). | A mAb with a lower efficacy and shorter duration of protection could be considered for use depending on the epidemiological setting and product-attributable disease reduction. Other efficacy endpoints of public health significance are:  
- Hospitalized RSV  
- Non-severe RSV LRTI (e.g. tachypnea or lower-chest wall indrawing without severe hypoxemia or danger signs)  
- All-cause severe LRTI, up to 1 year  
- Recurrent wheeze and asthma (would require follow-up for several years (2-6 years)  
- Antibiotic use |
<p>| 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. Surveillance for clinical breakthrough cases should be undertaken pre- and post-licensure; identification of breakthrough cases should prompt in-vitro neutralization studies of circulating RSV strains to identify potential escape mutant. |
| Co-administration | No significant negative impact on immune responses to co-delivered vaccines. Demonstrated safety of RSV mAb upon co-administration with other recommended pediatric vaccines. | Birth dose of mAb should show non-interference with birth dose of BCG, polio, Hepatitis B. mAb administration at EPI visits should show non-interference with co-administered EPI vaccines (e.g. DTP, HepB, Hib, PCV).[28] |</p>
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<th><strong>Route of administration</strong></th>
<th>Single intramuscular or subcutaneous dose using standard volumes for injection as specified in programmatic suitability for PQ.[2]</th>
<th>0.5 ml dose preferable for young infants.</th>
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<tr>
<td><strong>Registration, prequalification and programmatic suitability</strong></td>
<td>Must be licensed and approved by national regulatory authorities in countries of use. WHO defined criteria for programmatic suitability of vaccines and recommendations on presentation, packaging, thermostability, storage volume and disposal should be met, where applicable to mAbs.[2][25]</td>
<td>Many principles and criteria of vaccine prequalification will apply to preventive mAbs.[3] Specific requirements for prequalification of mAbs are outlined in <em>Pilot Procedure for Prequalification of Biotherapeutic Products and Similar Biotherapeutic Products</em>, though final guidance on prequalification of mAbs has not yet been issued at this time (2019).[29] Prequalification by WHO will facilitate approval and ability to purchase products in LMICs.[3]</td>
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<td><strong>Value proposition</strong></td>
<td>Dosage, regimen and cost of goods amenable to affordable supply. MAb should be cost-effective in LMICs.</td>
<td>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) should be evaluated pre- and/or post-licensure, as practicable. Cost-of-goods should allow the vaccine price to be similar to other new vaccines for feasibility of use in LMIC settings. mAb price should be acceptable to Gavi investment case for use in Gavi-eligible countries.[30]</td>
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**References**


[12] Blau D, RSV Burden from the CHAMPS Study, Presentation at 11th International RSV Symposium, 31 October to 4 November 2018, Asheville, USA.


