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Commentary

WHO preferred product characteristics for monoclonal antibodies for passive immunization against respiratory syncytial virus (RSV) disease in infants – Key considerations for global use

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ABSTRACT

World Health Organization (WHO) preferred product characteristics describe preferences for product attributes that would help optimize value and use to address global public health needs, with a particular focus on low- and middle-income countries. Having previously published preferred product characteristics for both maternal and paediatric respiratory syncytial virus (RSV) vaccines, WHO recently published preferred product characteristics for monoclonal antibodies to prevent severe RSV disease in infants. This article summarizes the key attributes from the preferred product characteristics and discusses key considerations for future access and use of preventive RSV monoclonal antibodies.

1. Introduction

Respiratory syncytial virus (RSV) is a leading cause of respiratory disease in young children globally. In 2015, in children under five years of age, RSV was estimated to cause 33.1 million severe acute lower respiratory infections (ALRIs), with 3.2 million severe cases requiring hospitalization and 118,200 deaths [1]. Approximately 45% of RSV-ALRI related hospital admissions and in-hospital deaths occur in infants younger than 6 months of age [1]. Although RSV is a global disease, the greatest burden of RSV

Abbreviations: ALRI, acute lower respiratory infections; CHD, congenital heart disease; CLD, chronic lung disease; DTP, diphtheria, pertussis, and tetanus containing vaccine; EPI, Expanded Program on Immunization; LMICs, low- and middle-income countries; LRTI, Lower Respiratory Tract Infection; mAb, monoclonal antibody; PPC, preferred product characteristics; PQ, prequalification; RSV, respiratory syncytial virus; SAGE, Strategic Advisory Group of Experts on Immunization; WHO, World Health Organization.

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Table 1
Candidate long-acting mAbs in clinical development as of December 2021.

Product and Manufacturers	Phase of development	Clinical trial registration number	Estimated trial completion date
Nirsevimab (MEDI8897), Astra Zeneca and Sanofi Pasteur	Phase 2b	NCT02878330	Completed [7]
	Phase 3 in healthy late preterm and term infants	NCT03979313	Primary completion in March 2021. Study completion in March 2023.
	Phase 3 in preterm infants and children with chronic lung disease (CLD) and congenital heart disease (CHD) entering their first and second RSV seasons	NCT03959488	Primary completion in May 2021. Study completion in November 2022.
MK-1654, Merck	Phase 2b/3 in healthy preterm and full-term infants	NCT04767373	Primary completion in July 2024. Study completion in January 2025.
	Phase 3 in infants and children at increased risk for severe RSV disease	NCT04938830	Primary completion in August 2025. Study completion in April 2026.
RSM-01, Gates Medical Research Institute	Phase 1	NCT05118386	Primary completion in July 2022. Study completion in August 2022.

occurs in low-and middle-income countries (LMICs) where 99% of deaths and 88% of hospital admissions occur [1]. In addition, RSV has been associated with persistent wheezing and to an increased risk of the development of asthma in later life, however evidence to date has not established a causal link [2].

In 2016, WHO's Strategic Advisory Group on Immunization (SAGE) recommended that efforts be made to identify and fill gaps in evidence required for regulatory, prequalification and policy guidance for RSV preventive interventions, including maternal and paediatric immunization with RSV vaccines, and passive infant immunization with long-acting RSV monoclonal antibodies (mAbs) [3].

2. Long-acting RSV mAbs under development

In addition to a rich pipeline of vaccine candidates, there are several candidate long-acting mAbs currently in development [4]. Three products are in active clinical trials (Table 1). For the most advanced candidate, nirsevimab, initial regulatory filings are planned for 2022 [5]. Whether this product will be affordable to LMICs is not yet clear and will involve multiple factors, including cost, financing and supply. Similar information is also not available for the other two mAbs in clinical development. Sponsors of all three mAbs have acknowledged the global burden of RSV, and the preponderance of RSV mortality in LMICs [6].

3. Preferred product characteristics

WHO Preferred Product Characteristics (PPCs), published by WHO's department of Immunization, Vaccines and Biologicals, provide guidance to developers on WHO preferences for new immunization products, particularly from the perspective of LMICs. The documents are intended to promote the development of products for use in settings most relevant to global unmet public health needs. PPCs describe preferential product attributes pertaining to indications, target populations, use case(s) and immunization strategies, as well as preliminary consideration of data that should be collected for safety, efficacy, and policy evaluation. Programmatic considerations and affordability are also integral attributes. The primary target audience for WHO PPCs is any entity intending to seek WHO policy recommendations and prequalification for their products. It should be noted, however, that PPC documents specify WHO's preferences and do not specify minimally acceptable criteria for policy or prequalification.

WHO PPCs for maternal and paediatric RSV vaccines were published in 2017 [9]. Following a consultation process with global stakeholders, in 2021, WHO also published PPCs for mAbs aimed at providing passive immunization to infants against severe RSV disease [10]. This document focuses on long-acting mAbs that could be given once as a single intramuscular dose to protect for up to five months during the RSV season, thus delaying an infant's first RSV infection until they are older and less likely to develop severe clinical disease and poor outcomes. These preferences are described in Table 2.

4. Considerations for future global access

Single dose long acting monoclonal antibodies have the potential to be used within the routine immunization schedule. They are stable products that can be stored for at least 2 years in the standard cold chain of 2–8 °C. If long-acting RSV mAbs are to be used widely and indicated for use in all infants globally, then they must be priced similar to widely used vaccines, especially in LMICs. The current Gavi vaccine investment strategy, which runs until 2025, includes RSV immunization products, both maternal vaccines and long-acting mAbs. This is contingent on the availability of a licensed product, a SAGE recommendation, WHO prequalification, as well as meeting certain financial assumptions around pricing [17].

Currently, the only RSV mAb product to reach the market has been palivizumab, first licensed in the USA in 1998 [18]. The wholesale price for palivizumab in the United States is US$ 1468.91 for a 50-mg vial and US$ 2773.74 for a 100-mg vial, the dose per child is calculated as 15 mg/kg of body weight which is given once per month throughout the RSV season [19]. Because Palivizumab is expensive, recommendations for its use are limited to very high risk-children born at < 29 weeks gestation and it is used mainly in high income countries. In addition, without an extended half-life, monthly dosing over the duration of the RSV season is not programmatically suitable in most resource-constrained settings.

Monoclonal antibodies are, in general, more expensive to produce than vaccines; they are one of the most expensive classes of drugs, especially those used for oncology or to treat chronic diseases [20]. However, given the small dose of mAb required to

Table 2
Preferred product characteristics for long-acting RSV mAbs [10].

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.[1]
Target population	All infants in the first 6 months of life.	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. The primary target population aims to protect most infants during their first RSV season. Policy-makers may consider including: (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.
Schedule	A one-dose regimen is highly preferred. A single dose can be given as a birth dose or at any healthcare visit during the first 6 months of life.	Both seasonal and year-round dosing can be considered. 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. 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. 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. Policy-makers should select a delivery strategy based on local context and programmatic feasibility. 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.
Safety	Safety and reactogenicity comparable to WHO recommended vaccines given at the same age (e.g. HepB birth dose).	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. If more than one dose of mAb is to be given, then the impact of anti-drug antibodies (ADAs) should be evaluated.
Efficacy	At least 70% efficacy against RSV-confirmed severe disease for five months following administration (the median length of the RSV season).	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. Other efficacy endpoints of public health significance are: 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.

(*continued on next page*)

Table 2 (*continued*)

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. [11].	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	Must be licensed and approved by national regulatory authorities in countries of use. 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 [11,12].	Many principles and criteria of vaccine prequalification will apply to preventive mAbs [13]. Specific requirements for prequalification of biosimilar mAbs are outlined in the Pilot procedure for prequalification of biotherapeutic products and similar biotherapeutic products, though final guidance on prequalification of preventive mAbs has not yet been issued at this time (2021) [14]. Prequalification by WHO will facilitate approval and ability to purchase products in LMICs [13].
Access and affordability	RSV mAb should be accessible and affordable to LMICs in order to allow broad protection of the most vulnerable infants.	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. The mAb price should be similar to other new vaccines for feasibility of use in LMIC settings[2], and cost-effectiveness analyses should support use. The mAb price should be acceptable to Gavi investment case for use in Gavi-eligible countries [15]. Price considerations should also consider those LMICs that are not Gavi-eligible and their ability to pay.

[1] WHO proposed candidate case definitions for severe and very severed RSV associated LRTI were published previously [16].
[2] UNICEF prices for LMIC countries, including GAVI eligible countries and Middle Income Countries can be found here:www.unicef.org/supply/vaccines-pricing-data.

protect young infants against RSV and given new manufacturing technologies, the cost of preventive RSV mAbs could be relatively low, potentially enabling them to be marketed in a price range similar to the price points of newer vaccines in use in LMICs. Based on some projections, for a 50 mg dose of mAb, the cost of goods could be less than US$ 5 per dose [8].

Some recent modelling studies have found mAbs to be cost effective using certain assumptions/scenarios in LMICs, but such analyses would need to be re-done once information on efficacy and duration of protection as well as price are confirmed [21–23]. Moreover, post-introduction surveillance in early introducing countries to assess impact on mortality, hospitalization, antibiotic use and long-term sequelae, such as wheezing and asthma, will further clarify the use case for RSV mAbs.

Given the rapid development of both RSV mAbs and maternal immunization products, LMICs might be able to decide whether to introduce RSV immunization products within the next few years. Moreover, LMICs might eventually need to choose between RSV prevention products (i.e. maternal immunization versus monoclonal antibodies for infants), based on cost-effectiveness, programmatic feasibility, and supply. In the case of mAbs, countries will also need to define which schedule best suits their needs and local context. WHO plans to develop tools to support these decisions and assist early-introducing LMICs in preparing for and introducing these products.

WHO is also in the process of developing regulatory considerations on the preclinical and clinical evaluation of mAbs for infectious diseases, which will include a supplementary document specific to preventive RSV mAbs. These documents, which will be needed to enable WHO prequalification, are expected to be considered for adoption by the WHO Expert Committee on Biological Standardization in October 2022. Manufacturers will need to apply for WHO prequalification of licensed products in order to facilitate procurement by UN agencies and Gavi financing. Beyond WHO Prequalification, other support to assist national regulatory agencies in LMICs in approving these products may be required.

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Declaration of Competing Interest

Ruth Karron has been a consultant for MedImmune, Sanofi, and Merck. Heather Zar has participated in AstraZeneca and Merck studies of RSV-mAb. The other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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