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PERSPECTIVES

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Challenges in Maximizing Impacts of Preventive Strategies against Respiratory Syncytial Virus (RSV) Disease in Young Children

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Respiratory syncytial virus (RSV) is the most common cause of lower respiratory tract illness in infants and young children. It causes substantial morbidity and mortality in young children and older adults. As few therapeutic and prophylaxis options against RSV illness are currently available, there is a great need for effective RSV vaccines and immune-prophylaxis. Encouragingly, multiple vaccines and immuno-prophylaxis aiming to protect pediatric populations have shown promising progress in clinical trials. The three major preventive strategies include RSV F-protein-based vaccines for pregnant women, extended half-life monoclonal antibodies for neonates, and live-attenuated vaccines for infants. Each preventive strategy has its own merits and challenges yet to be overcome. Challenges also exist in maximizing vaccine impacts in the post-implementation era. This perspectives piece focuses on RSV preventive strategies in young children and highlights the remaining questions in current development of RSV immunization products and design of immunization programs.

OVERVIEW

Respiratory syncytial virus (RSV) is the leading cause of acute respiratory tract infections in young children. RSV epidemics typically start in the fall and peak in the winter in temperate regions but can circulate year-round in tropical areas [1]. RSV is estimated to cause 58,000 hospitalizations in the United States and more than 3.2 million hospitalizations worldwide in children under 5 years of age each year [2,3]. The deaths associated with RSV may range between 94,600 and 149,400 worldwide annually, with the majority occurring in low- and middle-income countries [3,4]. As few therapeutic and prophylaxis options against RSV illness are currently available, there is a great need for effective preventive strategies against RSV disease. Fortunately, several RSV vaccines and extended-life prophylaxis have recently shown promise in various stages of clinical trials [5-8].

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Abbreviations: RSV, respiratory syncytial virus; mAbs, monoclonal antibodies; Gavi, the Vaccine Alliance.

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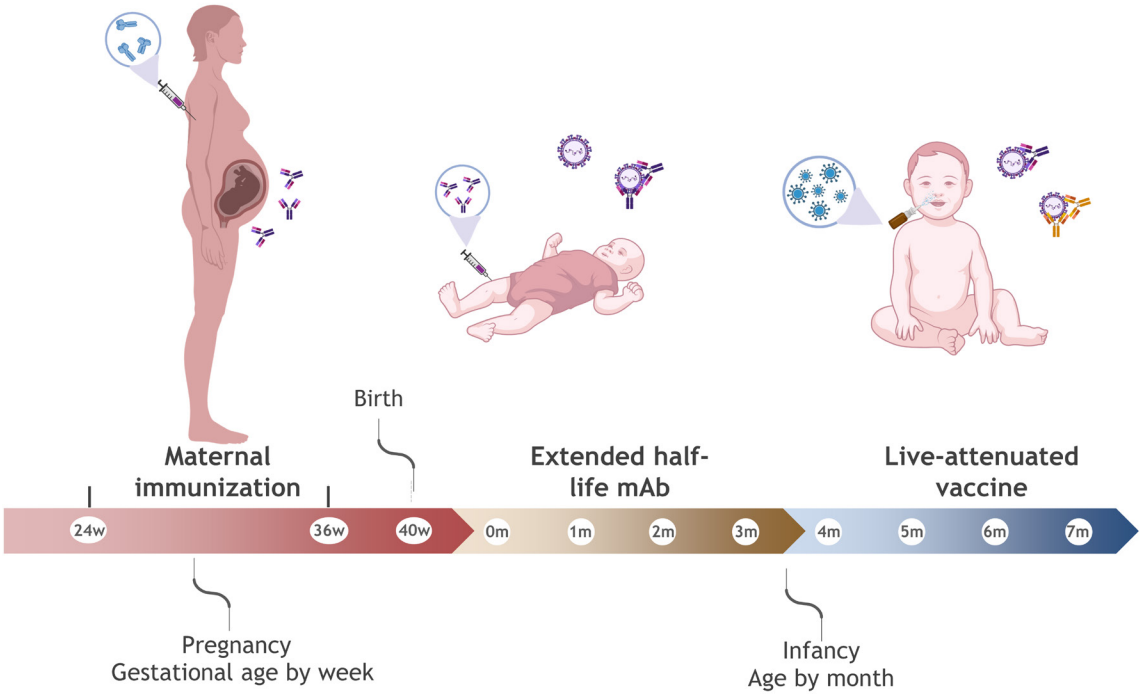

Figure 1. Potential preventive strategies against severe RSV diseases in young children. There are three major preventive strategies against severe RSV diseases in young children. Neonates can be protected by escalated antibody levels, either acquired transplacentally from their mother's high level of antibodies following F-protein-based maternal immunization or through direct passive immunization with extended half-life monoclonal antibodies. Intranasal administration of live-attenuated RSV vaccines can be used to protect older infants as it mimics natural infection. This figure is created with BioRender.com.

CURRENT DEVELOPMENT STATUS OF THREE MAJOR RSV PREVENTIVE STRATEGIES

The development of RSV vaccines has experienced several failures. In 1966, a formalin-inactivated RSV vaccine was administered to infants and young children in field trials in the United States [9-12]. However, instead of being protected against RSV infection, vaccinated children who were seronegative for the virus before vaccination experienced vaccine-induced enhanced clinical reactions when naturally exposed to RSV [9,13]. Two toddlers died as a result of enhanced disease symptoms [9]. Due to this history, there has been concern about targeting seronegative infants with non-replicating RSV vaccines [13]. Thus, in the current pipeline, non-replicating RSV vaccines primarily target seropositive adult populations, such as pregnant women and the older adults [6].

As immune responses in neonates have not yet fully developed, the preferable preventive strategies for neonates have been to provide passive immunity [6,14]. One way to provide passive immunity is through direct administration of extended half-life monoclonal antibodies. The other way is through administration of RSV F-protein-based vaccines to pregnant women so that infants acquire an increased level of RSV neutralizing antibodies transplacentally.

For infants over 3 months old and young children who are seronegative for RSV, replicating live-attenuated and vectored RSV vaccines are considered the primary choice given the history of formalin-inactivated RSV vaccine enhanced disease [14] (Figure 1). Replicating RSV vaccines primarily target young infants because these vaccines are not immunogenic in seropositive children or adults [15-17]. As few results of the efficacy of pediatric vector-based RSV vaccines are published, the focus of this perspectives piece is on live-attenuated RSV vaccines.

Extended Half-life Monoclonal Antibodies for Neonates

Currently, the first-generation monoclonal antibody (mAb), palivizumab, is the only market-approved preventive strategy against RSV infections [6]. However, this immuno-prophylaxis is not a preferable preventive strategy for general infant populations because of the following reasons. 1) It has a very short duration of protection that lasts for only a month and therefore needs

repeated monthly dosing. 2) The administration pathway is through intramuscular injection. 3) The average price per dose is $1661 for infants younger than 6 months of age and the price is even higher for older infants as they require a higher dosage [18]. The total cost of palivizumab is so high that only high-income countries can afford the price and it is only given to high-risk infants when RSV is circulating [18-20].

Modifications on Fc region were made to extend the half-life of RSV neutralizing antibody [21-23]. After modification, the half-life was extended to 58 to 88 days [24,25], compared with 20 days in palivizumab [26]. Among them, one product, MK-1654, has entered a phase 3 clinical trial. Another product, MEDI8897 (nirsevimab), has completed a phase 3 clinical trial that showed protection against RSV in the general infant population for at least 150 days [24,27-30]. These extended half-life mAbs have a half-life that is three times longer than palivizumab [8,31]. Thus, the extended half-life mAbs have the potential to be administered as a single dose at birth or coadministered with routine pediatric vaccines to protect the general infant population for an entire RSV season [8]. However, several knowledge gaps and challenges remain in maximizing the impact of extended half-life mAbs.

The first challenge is to determine the optimal timing of administration. To maximize the window of protection, extended half-life mAbs should be administered as soon as possible after birth for infants born between fall and spring, the RSV season. For infants born outside the RSV season, the optimal timing of administration will depend on the duration of protection [20,32]. If the protection lasts for a year, the timing of administration will not matter. However, if the protection covers not much longer than an RSV season, the administration of available prophylaxis against RSV may need to be timed with the onset of RSV epidemics. Although a seasonal immuno-prophylaxis strategy sounds attractive in terms of cost-effectiveness [33], some complexities need to be taken into consideration. While RSV epidemics are highly seasonal, the onset of RSV epidemics varies markedly over space [34]. It remains in doubt whether it is more effective or efficient to use a country-level seasonal immuno-prophylaxis strategy considering the variations in RSV timing between nearby locations [20,34]. Second, if stakeholders consider administration schedules based on local epidemic onsets, it will require sophisticated surveillance systems to inform the local epidemic timing. It is not clear whether implementation of a complex seasonal immuno-prophylaxis strategy is feasible, especially in resource-limited settings [33].

The second challenge is that mutations in neutralizing epitopes of RSV may threaten the efficacy of mAbs because they affect the affinity between mAbs and the virus [14,35]. Compared with vaccines, mAb products are more sensitive to viral mutation because each mAb targets a single conserved epitope. Nirsevimab binds to the site 0 epitope on the RSV pre-fusion F protein and MK-1654 binds to the site 4 epitope on both the RSV pre- and post-fusion F protein [21,36]. In contrast, RSV vaccines have the potential to generate diverse antibody responses that target multiple epitopes.

F-protein-based RSV Vaccines for Pregnant Women

Another passive immunization strategy to protect infants from severe RSV diseases is to immunize pregnant women with a non-replicating F-protein-based vaccine because replicating vaccines are not immunogenic in adults [15,17]. Phase 3 and phase 2b clinical trials of RSV vaccination in pregnant women suggested an overall reduced incidence of medically significant RSV lower respiratory tract illness and RSV hospitalization in infants born to vaccinated mothers compared with the placebo group [37,38]. However, the phase 3 trial failed to demonstrate significant efficacy against the primary endpoint. Nevertheless, other maternal vaccines may provide greater protection than mAbs for young infants because of the additional indirect effect in disrupting RSV transmission from mother to child [39].

There are several challenges with maternal RSV vaccines that have yet to be overcome. First, maternal immunization products have not yet been shown to have a long duration of protection in large birth cohorts. Though the overall efficacy against RSV hospitalization was 50.4% in lower-middle-income countries at day 180 after birth, it was only 2.1% in high-income countries in the completed phase 3 clinical trial [37]. It remains unclear what caused the efficacy discrepancy between lower-middle-income and high-income countries. It could be the differences in RSV incidence, age distribution of exposure, RSV disease severity, the level of pre-existing antibodies in pregnant women, or other unrecognized factors.

Another important consideration is the time from vaccination to delivery in pregnant women. Maternal vaccines offer higher placental antibody transfer when given at least 4 weeks before delivery [40]. While preterm infants are among the most vulnerable population to severe RSV disease, maternal vaccines may provide little protection to infants born prematurely.

Furthermore, compared with neonates who are directly immunized with mAbs, the protection of passive immunity will be affected by the transplacental antibody transfer in the maternal immunization strategy. Previous studies suggested that maternal HIV infection, placental malaria, maternal malnutrition, prematurity, and lower birth weight are associated with reduced transplacental antibody transfer [41-44]. As these conditions are preva-

lent in low- and middle-income countries, further studies about the efficacy of maternal immunization strategy in these subpopulations are needed to ensure effectiveness.

Replicating RSV Vaccines for Seronegative Infants and Young Children

Replicating vaccines aim to protect infants over 3 months of age from severe RSV diseases [16,45]. Although this active immunization strategy is still in the early stage of clinical trials, several live-attenuated vaccine products have shown promising results [46-49]. Live-attenuated vaccines are highly immunogenic in seronegative children, with >4-fold increases of RSV-neutralizing antibodies in 95% of vaccinees that received RSV vaccine D46/NS2/N/ΔM2-2-HindIII and in 80% of vaccinees that received RSV vaccine ΔNS2/Δ1313/I1314L [46,47].

Live-attenuated RSV vaccines have several advantages. First, most live-attenuated RSV vaccines are expected to be administered intranasally [50,51]. The needle-free vaccination has the potential to increase vaccine acceptance among parents and young children. Also, the vaccine virus will first replicate in the airway because of the intranasal administration, which can induce mucosal, humoral, and cellular immune responses [16]. These broad immune responses are anticipated to be comparable to the immune responses triggered by natural infection [46,47]. Together, they can provide enhanced protection against severe RSV diseases caused by wild-type RSV infection. Moreover, live-attenuated RSV vaccines may offer indirect benefits to those who are not vaccinated by preventing transmission. With more infants and young children gaining immunity against wild-type RSV infection, the transmission of wild-type RSV will be disrupted [50].

Nonetheless, there are still several challenges for live-attenuated RSV vaccines to move forward. First, the degree of attenuation and dosage selection for live-attenuated RSV vaccines need to balance immunogenicity and reactogenicity. Several vaccine candidates had low seroconversion rates because of over-attenuation while the development of some other candidates was suspended due to the concern that these vaccines may be insufficiently attenuated and may cause severe adverse events for infants under 6 months of age [52-56].

Second, so far, live-attenuated RSV vaccines are not immunogenic in infants and children who are seropositive for RSV [46-49]. In practice, pediatric vaccines are given to children of certain ages without a serology test. Since RSV infection is so common that most children have had an infection by the time they are 2 years of age [57], the effectiveness of live-attenuated RSV vaccines in the general pediatric population may be much lower than the estimates of vaccine efficacy in seronegative infants.

Third, further work is required to identify the optimal immunization window. To date, live-attenuated RSV vaccines have been tested in infants greater than 6 months of age, children, and adults. The future plan is to de-escalate age to also target infants under 6 months because half of the RSV-associated hospitalizations occur in this population [58]. However, the efficacy of live-attenuated RSV vaccines could be blunted by the presence of maternal antibodies and the immature immune system in infants under 6 months of age [59,60].

Fourth, despite the promising immunogenicity data, questions remain about the duration of vaccine-induced immunity. Previous research on wild-type RSV infection suggested that immune responses to RSV are short-lived, and reinfection can occur within the same season [61-63]. Recent findings of early-stage clinical trials showed that titers of vaccine-induced RSV-neutralizing antibodies slightly decreased over time but still remained at a relatively high level after an RSV season [46,47]. More importantly, vaccine recipients demonstrated notable anamnestic responses upon exposure to wild-type RSV [7,46,47]. These findings suggest that a single dose of live-attenuated RSV vaccine may provide sufficient protection for young children throughout an RSV season. Nonetheless, further studies with a larger sample size and younger infant population are needed to confirm the long-lasting vaccine-induced immunity and to determine whether introducing a booster dose is necessary.

A Shared Unanswered Question

One remaining knowledge gap shared by all three RSV preventive strategies is the potential benefit of these preventive strategies against subsequent RSV infections, asthma, and recurrent wheezing. It is still not clear whether passive preventive strategies may allow mucosal RSV infections but prevent severe RSV diseases. If proved to be true, the development of adaptive immunity at mucosal surfaces would be an additional benefit as it lowers the probability of subsequent RSV infections. By reducing the probability of getting severe RSV diseases, these RSV immunization strategies, either passive or active, may also reduce the probability of asthma development. Although several studies suggested a causal relationship between RSV infection and asthma [64-66], randomized clinical trials using RSV prophylaxis have not yet been able to reach an agreement on the benefit of reducing RSV infection during infancy on the subsequent development of asthma and recurrent wheezing [67-69].

CHALLENGES FOR ACHIEVING MAXIMUM VACCINE IMPACTS IN THE POST-IMPLEMENTATION ERA

Unknowns in Combined Usage

While needle-free live-attenuated vaccines may be favorable and provide effective protection for young infants against RSV infections, they would not offer direct protection to the most vulnerable population, those who are under 2 months of age and have immature immune systems [45]. Therefore, it is likely that we need to rely on the combination of live-attenuated vaccine and either a maternal immunization strategy or extended half-life monoclonal antibodies to provide full protection to young children at high risk of severe RSV disease. However, little research has investigated how antibodies gained from passive immunization may interfere with the live-attenuated vaccine virus. A combined immunization strategy may require a different vaccination schedule of live-attenuated vaccines to avoid a reduced efficacy. If interference exists, optimal vaccination windows could potentially be identified by measuring the waning rate of existing antibodies [70].

Vaccine Allocation in Resource-limited Settings

With the support from Gavi, the Vaccine Alliance, low- and middle-income countries may benefit from low-cost RSV vaccines and monoclonal antibodies when these preventive strategies are available [71]. The introduction of RSV preventive strategies could substantially reduce infant morbidity and mortality in low- and middle-income countries [33,72,73]. Nonetheless, several challenges remain in maximizing RSV vaccine impact in resource-limited settings. The first challenge is to determine the eligibility criteria for RSV preventive interventions. Depending on many factors including price, Gavi support, and country-level approval processes, different countries may set different eligibility criteria to prioritize the vaccines to those most in need and therefore maximize the cost-effectiveness of preventative strategies. Second, although the purchasing price of RSV preventive interventions may be low or even free for the low- and middle-income countries, the financial cost and human resources related to the storage, distribution, and administration of these preventive interventions may be substantial [74]. This challenge is especially prominent for the remote areas where most of the RSV-associated mortality occurrs. Combining with existing immunization schedule and delivery programs may help maximize the cost-effectiveness of upcoming RSV preventive strategies.

CONCLUSION

The promising results from late-stage clinical trials of RSV preventive interventions provide hope for reducing RSV-associated morbidity and mortality worldwide. To maximize the impact, researchers, policy-makers, and other stakeholders should work together to address unanswered research questions and optimize post-market approval implementation.

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