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REVIEW

The Future of Respiratory Syncytial Virus Disease Prevention and Treatment

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ABSTRACT

Respiratory syncytial virus (RSV) is a major cause of respiratory tract infections in infants, young children, and older or immunocompromised adults. Although aerosolized ribavirin was licensed for RSV treatment on the basis of data demonstrating a reduced need for supplemental oxygen, ribavirin use is limited because of issues with efficacy, safety, and cost. Currently, the treatment of RSV is primarily supportive. New antiviral treatments for RSV are in the early stages of development, but it will be years until any of these may be licensed by the US Food and Drug Administration (FDA). Palivizumab, an RSV monoclonal antibody [immunoprophylaxis (IP)], has demonstrated effectiveness in disease prevention and is the only licensed IP for RSV disease in specific high-risk pediatric populations. Although its efficacy is well established, some challenges that may interfere with its clinical use include cost, need for monthly injections, and changing policy for use by the American Academy of Pediatrics (AAP). Preventing RSV disease would be possible through RSV vaccine development (e.g., live-attenuated, vector-based subunit, or particle-based). Alternatively, new long-acting monoclonal antibodies have demonstrated promising results in early clinical trials. Despite scientific advances, until new agents become available, palivizumab should continue to be used to reduce RSV disease burden in high-risk patients for whom it is indicated.

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Key Summary Points

Passive immunotherapy with palivizumab is the only licensed intervention currently available to prevent severe RSV disease in specific high-risk infants and children.

There is a significant unmet need for safe and effective antivirals, vaccines, and extended half-life monoclonal antibodies for optimal management of RSV.

Challenges associated with the development of an RSV vaccine include stringent safety standards in the target populations, including infants and pregnant women.

Currently, there are several antiviral agents, vaccines, and extended half-life monoclonal antibodies in clinical trials; however, it will likely be several years until market availability.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.13333481.

INTRODUCTION

Although respiratory syncytial virus (RSV) disease is self-limiting in otherwise healthy children and adults, serious lower respiratory tract infections (LRTI) such as bronchiolitis and pneumonia requiring hospitalization can occur in infants, high-risk children, adults with comorbidities, and elderly adults [1–3]. By 24 months of age, almost all children are infected by RSV, and reinfection occurs throughout one's lifetime [1].

Currently, treatment for RSV disease is mainly supportive and may include hydration, supplemental oxygen, suctioning of airways, and mechanical ventilation when needed [1]. Ribavirin is the only licensed antiviral therapy available for RSV disease. However, its use is currently limited to life-threatening RSV infections in immunocompromised patients because of concerns regarding patient toxicity and the safety of health care professionals, and an inconvenient route of administration (aerosol) [1, 4, 5]. Additionally, recent changes in the pricing structure have made this infeasible for many institutions [6]. Ribavirin has also not resulted in a meaningful impact upon clinically relevant outcomes, including reductions in mortality, duration of hospitalization, need for mechanical ventilation, and intensive care unit (ICU) admission [1, 4, 5]. Other agents may provide symptomatic relief but are not recommended by the American Academy of Pediatrics (AAP); these include beta-adrenergic agents, corticosteroids, and hypertonic saline. Antibiotics are considered when there is evidence of secondary bacterial infection [1, 7, 8].

Although the AAP recommends that RSV disease prevention efforts include education of caregivers regarding transmission control, good hand hygiene, avoidance of contagious settings (e.g., daycare) and exposure to tobacco smoke, and isolation of infected hospitalized patients (including those receiving ribavirin treatment), these strategies have a minimal proven impact upon the overall burden of RSV infection as nearly all children are infected at least once by the age of 2 years [1, 5, 9].

RSV immunoprophylaxis (IP) is highly effective in preventing severe RSV infections in high-risk infants and young children [5]. Palivizumab, a humanized monoclonal antibody (mAb), is the only Food and Drug Administration (FDA)-approved IP for severe RSV LRTI in specific high-risk pediatric populations, including infants born at $\leq$ 35 weeks' gestational age (wGA), children with hemodynamically significant congenital heart disease (CHD), and children with chronic lung disease of prematurity (CLDP) [5, 10]. Palivizumab is only recommended for prophylactic use; it is not indicated for the treatment of RSV infection. Data demonstrate that it does not impact outcomes once RSV infection has been established

[10, 11]. The efficacy and safety of palivizumab for prevention of RSV infection in high-risk pediatric populations are well established through randomized, placebo-controlled trials and post-licensure effectiveness studies [10, 12, 13]. However, some challenges limiting palivizumab use in accordance with its licensure include cost, short half-life resulting in the need for monthly injections, and a restrictive RSV IP policy from the AAP [1, 10, 14]. Currently, there is no vaccine available to prevent RSV infection [5].

There is an unmet need for clinically effective, safe, and cost-effective prevention and treatment options, including antiviral treatments, vaccines, and extended half-life mAbs. Here, we provide an overview of agents that are currently in the later stages of clinical development for both the prevention and treatment of RSV infection. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

THERAPEUTICS IN DEVELOPMENT FOR TREATMENT OF RSV INFECTION: ANTIVIRALS

In general, the goals of RSV disease treatment strategies are to (1) ameliorate symptoms, (2) promote more rapid resolution of disease, and (3) potentially reduce transmission by impacting viral load. After initial RSV exposure, the virus undergoes rapid replication in the upper respiratory tract before the onset of symptoms 2–3 days later. Once RSV reaches the lungs, administration of an antiviral may not be as effective and, in the case of ribavirin, it may trigger bronchospasms [7, 15, 16]. So far, the positive effects of antivirals have only been observed when they are instituted before symptoms occur. As the RSV fusion protein (F protein) is highly conserved with less antigenic variability than the G protein, the majority of new RSV disease treatments target the F protein [7].

Investigational RSV antiviral agents can be classified into fusion inhibitors, designed to prevent virus entry into the host cell, and replication inhibitors, which interfere with virus multiplication or assembly (Fig. 1) [5]. There are at least eight antiviral agents currently being tested in clinical trials. Most of these investigational agents are F protein inhibitors, each referenced by the alphanumeric designation assigned to it by the manufacturer (i.e., ALX-0171, RV521, AK0529, JNJ-53718678, MDT-637, GS-5806; Fig. 1) [5, 7, 17]. ALX-0171, an inhaled nanobody fusion inhibitor, exhibited an acceptable safety profile in phase 1 clinical trials performed in adults [7]. However, a phase 2 trial (NCT03418571) was terminated in 2019 because of insufficient efficacy of ALX-0171 in infants and young children hospitalized with RSV LRTI [18, 19]. An oral small-molecule RSV fusion inhibitor, RV521, was evaluated in a phase 2 trial (NCT03258502) that assessed the safety, pharmacokinetics, and antiviral activity of RV521 at two doses (200 mg and 350 mg) in healthy adults infected with RSV. The results demonstrated an acceptable safety profile and a significant decrease in total viral load (55% with 200 mg and 63% with 350 mg) compared with placebo [17, 20].

AK0529 (ziresovir) is an oral antiviral drug being developed for the treatment of RSV infection in children and adults. The drug has demonstrated good bioavailability and an acceptable safety profile in both target populations and is currently undergoing a multicenter phase 2 trial in adults with RSV infection (NCT03699202) [30, 31]. The safety and efficacy of the oral inhibitor JNJ-53718678 are currently being studied in a phase 2 trial (NCT03656510) in children aged $\geq$ 28 days to $\leq$ 3 years with RSV infection [5, 32]. In a phase 1b trial, JNJ-53718678 reduced viral load compared with placebo in hospitalized RSV-infected infants; another phase 2a single-center trial in RSV-infected adults showed that treatment with JNJ-53718678 was associated with a reduced mean viral load ($P \leq 0.05$), less severe disease, and a shorter duration of viral shedding compared with placebo [33, 34]. Although most antiviral candidates are F protein inhibitors, PC786 is an extended half-life potent L protein polymerase inhibitor. The inhalation route of administration leads to low systemic exposure, which may help minimize systemic adverse events in target

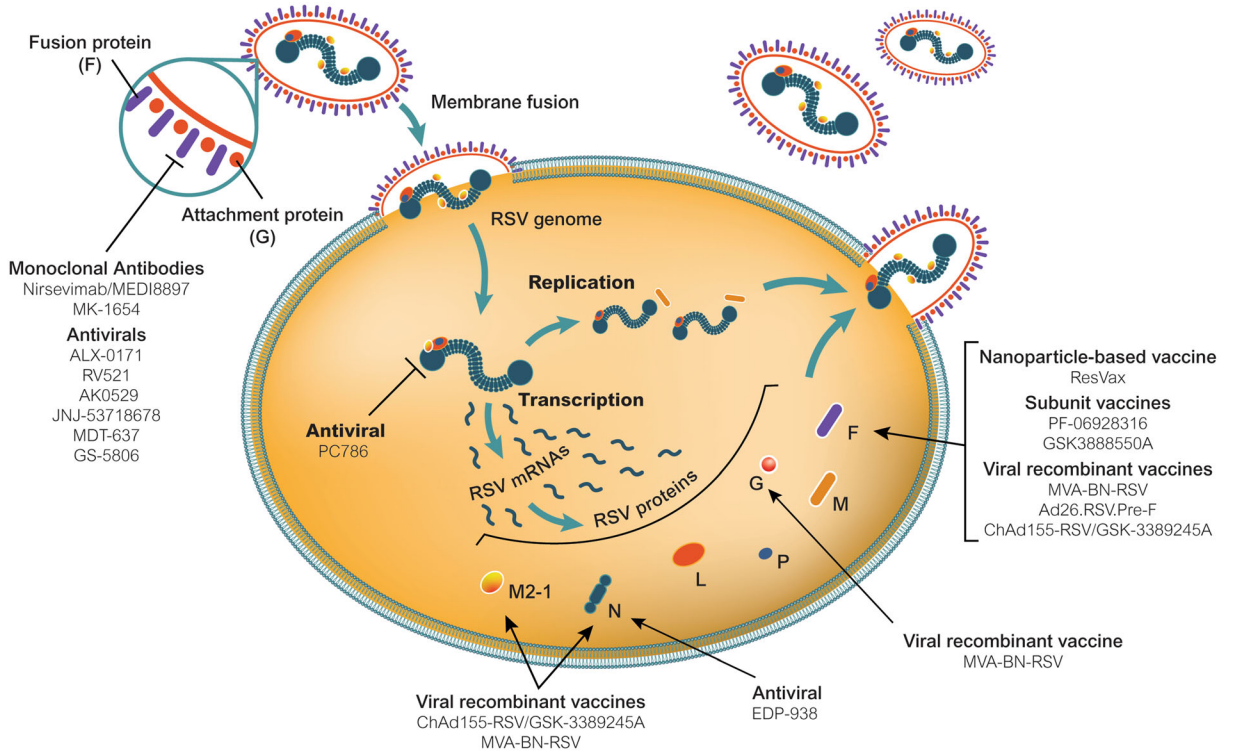

Fig. 1 Targets of antiviral agents in phase 2/3 clinical development [7, 21–29]. F fusion protein; G attachment glycoprotein; L large viral polymerase; M matrix protein; M2-1 protein, transcription factor; N nucleoprotein; P phosphoprotein

populations [35]. EDP-938 is an oral RSV N protein inhibitor currently in a phase 2 study of adults with RSV infection (NCT04196101) [21, 36].

Thus, despite some initial setbacks in attaining adequate efficacy and safety, some promising antiviral candidates remain in the early stages of development. None of the medications have yet reached phase 3 clinical trials. Consequently, we are still many years away from their approval for clinical use [5].

VACCINES IN DEVELOPMENT FOR PREVENTION OF RSV INFECTIONS

The unmet need for safe and effective preventive therapies combined with intense research over recent years has led to the development of several vaccine candidates, including products delivered directly and indirectly (maternal vaccines for the prevention of infection in newborns) (Fig. 2) [5, 37]. Initial attempts at vaccine development in the 1960s failed miserably. The formalin-inactivated investigational RSV vaccine did not prevent RSV infection; instead, those who developed primary RSV infection experienced enhanced RSV disease. Two infants died in this clinical trial; further findings suggested that formalin inactivation may have enhanced type 2 T helper cell immune responses [5, 14, 38, 39]. It is, therefore, essential to understand the immunologic mechanisms underlying the development of enhanced disease in order to produce safe and effective vaccines for the prevention of RSV. The failed trial halted human RSV vaccine trials for decades and has resulted in a very high level of scrutiny of candidate RSV vaccines since that time. Furthermore, a vaccine that produces an adequate response in the mother may not result in sufficient antibody transfer in the newborn, especially those who are born prematurely in

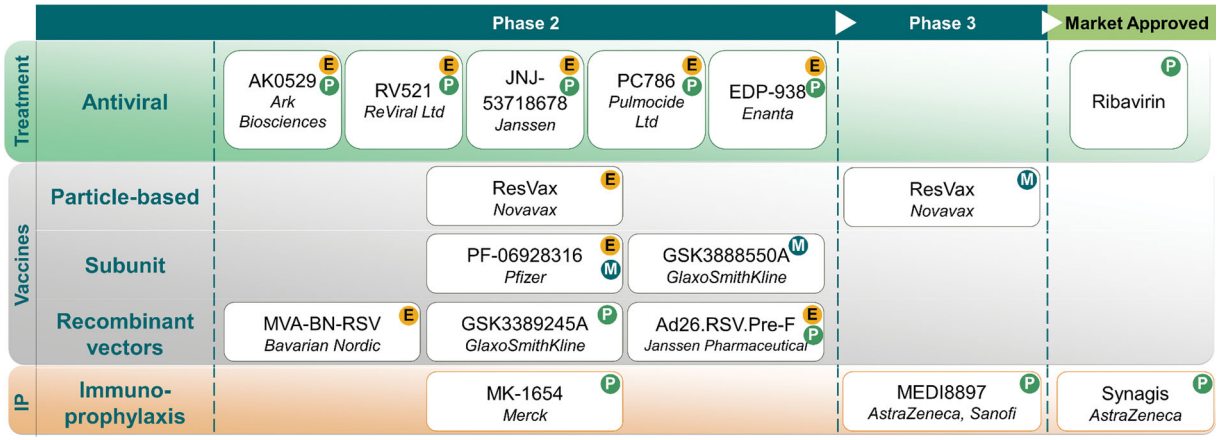

Fig. 2 RSV antivirals, vaccines, and mAbs under phase 2/3 clinical development [37, 41]. E elderly; IP immunoprophylaxis; M maternal; mAb monoclonal antibody; P pediatric; RSV respiratory syncytial virus

the late second and early third trimester before transplacental antibody transfer can occur [5, 14, 40].

Currently, there are at least 17 investigational RSV vaccines in clinical development, including live-attenuated, vector-based, particle-based, and subunit vaccines (Fig. 2) [37]. Live-attenuated vaccines are not associated with enhanced RSV in RSV-naïve populations following natural exposure and therefore are generally considered safe in pediatric patients and are being pursued for clinical development. In addition, live-attenuated vaccines have the advantage of an easy intranasal route of administration and can invoke a host mucosal immune response even in the presence of maternal antibodies [5, 42]. However, tolerability and safety have historically been an issue with live-attenuated vaccines as there may be insufficient attenuation of the virus, and these vaccines will likely be limited to pediatric populations because of natural immunity in older patients [5, 22, 43]. The National Institute of Allergy and Infectious Diseases (NIAID) is investigating several live-attenuated vaccines in children aged 6–59 months [5, 37]. These include RSV-ΔNS2/Δ1313/I1314L and RSV 276 (NCT03916185, NCT03227029, NCT03422237) and RSV 6120/ΔNS2/1030s (NCT03916185, NCT01893554) [44–47]. In addition, a recombinant bacille Calmette-Guérin (rBCG) live-attenuated vaccine expressing human RSV nucleoprotein (N), rBCG-N-hRSV, may offer combined protection against *Mycobacterium tuberculosis* and RSV. The target population for the vaccine includes infants, and it is currently being evaluated in a phase 1 trial (NCT03213405) in healthy adult males [42, 48, 49]. Overall, live-attenuated vaccines are being pursued owing to their relative safety profile in the RSV-naïve pediatric population, as compared with subunit and particle-based vaccines, which have the theoretic concern for heightened immune response and enhanced RSV disease [42, 43].

Vector-based vaccines currently under investigation have not been associated with enhanced disease. The immune response to vector-based vaccination has not been shown to have consistent interference by the presence of maternal antibodies. However, vaccine recipients do have the potential to develop antivector immunity, which could blunt the optimal immune response, particularly for booster vaccination doses [5]. A vaccine based on viral proteins encoded by the chimpanzee-derived type 155 adenovector, ChAd155-RSV/GSK-3389245A, is currently being investigated in a phase 2 trial (NCT02927873) of children aged 12–23 months and a phase 1 study of infants aged 6–7 months (NCT03636906) [37, 50, 51]. Other recombinant vector-based vaccines currently in phase 2 trials include adenovirus serotype 26-based RSV pre-fusion vaccine

(Ad26.RSV.Pre-F) in children aged 12–24 months (NCT03606512) and older adults (NCT03982199) and MVA-BN-RSV in older adults [37, 52–54]. MVA-BN-RSV produced a durable and sustainable immune response in the majority (> 60%) of tested subjects aged ≥ 55 years, according to a phase 2 extension study (NCT02873286) [37, 54, 55].

Unlike live-attenuated vaccines, particle-based vaccines may be immunogenic across a broader range of age cohorts, including pediatric and elderly populations [37, 42, 43]. ResVax, an RSV F protein recombinant, adjuvanted particle-based vaccine, is being studied in multiple populations, including pediatric (NCT02296463), older adults (NCT03026348, NCT02608502), and pregnant mothers (NCT02624947) [23, 37, 56].

Although vaccine development for RSV has been a global priority for the past several decades, the World Health Organization (WHO) estimates that it will be at least 5–10 years until a safe and effective vaccine is approved for clinical use [5, 37]. With increased prioritization of resources for COVID-19 pandemic vaccine development and the ramifications of effective social distancing (e.g., masking), the results of these randomized controlled trials may be blunted or not reach statistically meaningful endpoints. In the near term, these vaccines are not likely to be available for preterm infants and those with underlying CHD and CLDP without robust data demonstrating safety in these fragile children. Thus, continued use of IP in children eligible to receive IP according to the current AAP policy will likely continue for some time.

MATERNAL VACCINES IN DEVELOPMENT FOR PREVENTION OF RSV IN INFANTS

In general, the highest rate of RSV hospitalization occurs among infants aged < 6 months, with the majority occurring in those aged < 2 months [57]. Maternal vaccination is an appealing strategy to prevent severe RSV in vulnerable newborn infants as maternally transferred antibodies could confer protection against RSV [5]. However, titers of maternally transferred RSV antibodies decline rapidly after birth from 73% at 1 month to 2% at 6 months [5, 58]. Overall, adequate duration between the timing of maternal vaccination and birth is necessary for effective antibody development and subsequent transfer of optimal protection to newborn infants. Unfortunately for infants born before 32 wGA, this strategy is suboptimal since more than 50% of immunoglobulin transfer across the placenta occurs after 32 wGA [5, 59, 60]. Furthermore, if delivery occurs before the development of an adequate antibody response (approximately 2 weeks), maternal immunization may not be successful [61].

Currently, there are three maternal vaccines in clinical trials (ResVax in phase 3, PF-06928316 in phase 2, and GSK3888550A (RSVPreF3) in phase 2; Fig. 2) [23, 24, 62]. ResVax is the most advanced vaccine in clinical development. In a phase 3 global trial (NCT02624947) conducted in 4636 healthy pregnant women aged 18–40 years, ResVax was administered between 28 and 36 weeks of gestation before the RSV season. The vaccine was generally well tolerated but did not meet its primary endpoint of preventing RSV LRTI in infants. ResVax did, however, reduce hospitalizations due to RSV LRTI by 44% among infants born to vaccinated mothers [63]. PF-06928316 is an RSV subunit maternal vaccine currently being studied in a phase 2b trial (NCT04071158) conducted in healthy non-pregnant women aged 18–49 years [37, 64, 65]. Another phase 2b study will evaluate this RSV subunit vaccine in pregnant women between 24 and 36 weeks of gestation (NCT04032093) [25]. GSK3888550A is an unadjuvanted RSV pre-fusion maternal vaccine in phase 2 testing and is being evaluated in healthy pregnant women between 28 and 34 weeks of gestation (NCT04126213) and non-pregnant women (NCT04138056) [24, 66]. Although a promising strategy, maternal RSV vaccines providing passive protection for a transient postnatal period will likely not be effective in protecting infants who are born prematurely. A vaccine program that combines maternal immunization with

subsequent infant immunization is also being considered [5, 40].

Administration of vaccines is often delayed or incomplete in preterm infants [5, 67]. It would be ideal to achieve direct protection of infants by providing them with long-term immunity through active immunization against RSV infection or at least against severe RSV disease. However, this may not be realistic, as natural RSV infections do not prevent subsequent RSV infections but may attenuate disease severity. Alternative approaches include providing infant protection by passive maternal antibody transfer. This can be done through the administration of a mAb (e.g., palivizumab) or a long-acting mAb (e.g., MEDI8897/nirsevimab) or through maternal vaccination during pregnancy to transfer antibody to the infant prior to delivery [5, 40]. On the basis of palivizumab studies, there is probably an "upper limit" of protection afforded against hospitalization with this strategy (approximately 60–80%) [5]. Of note, palivizumab administration provides additional efficacy in the prevention of ICU admissions [12]. However, the protection afforded by these strategies is dependent upon the half-life of the antibodies (a narrow window for palivizumab and maternal antibodies) [5]. Natural infection may still occur, but hopefully at a later age (1–2 years) when the airways are larger and less susceptible to the complications of RSV in neonates. True indirect protection is achieved through vaccination of other close infant contacts (e.g., household members, playmates) or maternal vaccination in which the mother is protected against RSV disease so that she (as a primary contact for the infant) does not transmit RSV to the infant [5, 40, 68].

Many practical considerations will have to be addressed prior to implementation of a maternal RSV vaccination program. These include whether a vaccine should be administered seasonally and where vaccination might occur (e.g., obstetrician's office). Guidance from groups such as the Advisory Committee on Immunization Practices (ACIP) and the American College of Obstetricians and Gynecologists (ACOG) will be required to address many of these practical issues.

EXTENDED HALF-LIFE MONOCLONAL ANTIBODIES FOR PREVENTION OF RSV

Infants born prematurely are at a higher risk of developing infections than term infants because of fewer maternal transplacental antibodies prior to birth, more immature immune systems, narrower airways, and immature lungs, which predispose the premature infants to a higher risk of severe RSV disease [5, 60, 67, 69, 70]. Overall, RSV IP is an appealing preventative strategy for RSV in high-risk infant populations, including infants born prematurely. This strategy could potentially protect through the first year of life until infants, including those born prematurely, develop better immune responses and larger airways that are structurally and functionally more mature [5].

Products in development for RSV IP are focused on providing long-term protection through the use of a modified mAb that has an extended half-life (nirsevimab and MK-1654; Fig. 2). Nirsevimab is a recombinant, human, extended half-life mAb with YTE substitution in the Fc (crystallizable fragment) region that targets the prefusion conformation of the RSV F protein. Owing to its extended half-life (85–117 days) and highly potent neutralizing activity against RSV, a single dose is expected to protect for at least 5 months, the length of a typical RSV season. A phase 1 trial (NCT02114268) in healthy adults demonstrated a comparable safety profile with placebo [5, 71, 72]. Nirsevimab was given a fast-track designation by the FDA in 2015 and is being evaluated in a phase 2/3 trial (NCT03959488) in preterm infants ($\leq$ 35 wGA) without CLDP/CHD and infants with CLDP/CHD aged < 1 year and a phase 3 trial (NCT03979313) that includes healthy late-preterm and term infants [5, 73–75]. A recently completed, single-dose, phase 2b study (NCT02878330) in preterm infants born at 29–35 wGA (nirsevimab, n = 969; placebo, n = 484) demonstrated significant reductions of medically attended RSV LRTI (70.1%) and LRTI RSVH (78.4%) compared with placebo. Adverse events and non-RSV LRTI were similar among the groups [76, 77].

Another mAb, MK-1654, is being studied in a phase 2 trial (NCT03524118) of 29–35 wGA infants and term infants [78, 79]. Like nirsevimab, the YTE modifications of the Fc portion of MK-1654 extend its half-life to approximately 70–85 days [79].

It is important to remember that failures can occur at any stage of clinical development. In June 2010, the FDA Antiviral Drugs Advisory Committee declined approval of MedImmune's motavizumab (MEDI-524) in a 14 to 3 decision. The decision was predicated on the perception of increased risk of anaphylactic reaction (although only an increased incidence of rash could be demonstrated in the trial) and lack of evidence of superior efficacy compared with palivizumab [80]. MEDI-524 was not developed as a product despite what many would have defined as successful phase 3 trials [81, 82]. Another investigational RSV F protein mAb, REGN2222, was discontinued in 2017 after it failed to meet its primary endpoint of reducing medically attended RSV infections in < 36 wGA infants aged ≤ 6 months in a phase 3 trial [5, 83].

It would be ideal to have maternal vaccines, pediatric vaccines, and mAbs all available for prevention of RSV disease in pediatric populations. Maternal immunization could boost the level of maternal RSV antibodies and if efficiently transferred across the placenta could circumvent the need for direct immunization during the neonatal period. However, major challenges with maternal vaccines include diminished antibody transfer in preterm infants and that the period of conferred protection from transplacentally acquired maternal antibodies may not last throughout the RSV season because of declines in maternal antibody after birth. The timing of maternal vaccine administration with respect to birth is also relevant. Important roles for extended half-life mAbs may include providing protection to infants born prematurely whose mothers were not vaccinated or from whom transplacental antibodies are expected to be low during the RSV season [5]. Both a maternal vaccine (ResVax) and a long half-life mAb (MEDI8897) are the two leading candidates in clinical trials [37]. Either of these strategies is expected to delay severe RSV infection but may need to be complemented by other approaches, including a pediatric vaccine, when one becomes available.

There is a substantial unmet need for RSV prevention in low, middle-income countries (LMIC) [84, 85]. It remains unlikely that new vaccines and long-acting monoclonals will be able to address this unmet need owing to substantial development-related costs. RSV-associated infant morbidity and mortality disproportionately affect families residing in resource-poor areas of the world [86, 87]. The recent inclusion of clinical trial sites in low-income and lower middle-income nations begins to address the unmet need for RSV prevention in two important ways [77, 88]. First, it raises awareness among stakeholders about the impact of RSV disease across these regions. Second, study results include important safety and efficacy data derived from diverse populations, including infants born and residing in these countries. In order for the most promising novel interventions for RSV prevention among infants to realize their maximum potential, they will need to be available to infants worldwide and not restricted by cost to higher-resource countries.

CURRENT POLICY AND GUIDELINES GOVERNING RSV IP USE

Palivizumab is the only IP available for the prevention of severe RSV infection until new prevention strategies become available [5]. Although the FDA established its indication for RSV IP use based on well-controlled, randomized trials, the AAP's 2014 policy restricted its use to infants born at < 29 wGA, children with CHD, and children with CLDP. After reviewing recent evidence showing an increased burden of RSV disease associated with restricted IP use as recommended by the AAP for high-risk infants and children, the National Perinatal Association (NPA) published separate guidelines for RSV IP use in 2018 that more closely align with the FDA indication and include all ≤ 32 wGA infants and 32–35 wGA with identified risk factors [10, 89, 90]. Reaffirmation of the AAP 2014 policy in 2019 is unfortunate, especially in

light of mounting evidence for an increased risk of hospitalization, severity, and costs associated with RSV in infants born between 29 and 34 wGA [89, 91–95]. Because the 2014 changes in the AAP policy reduced the accessibility of RSV IP across vulnerable pediatric populations, the AAP should consider revising its current policy, at least until new modalities for RSV disease prevention become available [90].

CONCLUSION

The unmet need for safe and effective RSV therapies and modes of prevention has led to the development of many promising candidates, including antivirals, vaccines, and mAbs. There are several seemingly promising antiviral agents in early clinical trials. Challenges to be encountered while generating safe and effective RSV vaccines or monoclonals include stringent safety measures in targeted pediatric and maternal populations. Generation of novel RSV vaccines will hopefully help reduce the global burden caused by RSV [5]. Until new interventions become available, it is important to optimize the use of palivizumab in high-risk infants and children [90].

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