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.

Keywords: American Academy of Pediatrics; High-risk preterm infants; Immunoprophylaxis; Monoclonal antibody; National Perinatal Association; Palivizumab; Respiratory syncytial virus; Treatment; Vaccine
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 ≤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.
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 ≥ 28 days to ≤ 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 ≤ 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...
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
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/Δ1313/1314L 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

![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](image-url)
adMV-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].

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 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].

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...
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 (≤ 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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REFERENCES

1. American Academy of Pediatrics. Respiratory syncytial virus. In: Kimberlin DW, Brady MT, Jackson MA, editors. Red Book: 2018–2021 Report of the Committee on Infectious Diseases. Elk Grove Village: American Academy of Pediatrics; 2018. p. 682–92.

2. Jain S, Williams DJ, Arnold SR, et al. Community-acquired pneumonia requiring hospitalization among U.S. children. N Engl J Med. 2015;372(9):835–45.

3. Leader S, Kohlhase K. Respiratory syncytial virus-coded pediatric hospitalizations, 1997 to 1999. Pediatr Infect Dis J. 2002;21(7):629–32.

4. Trang TP, Whalen M, Hils-Horeczko A, Doernberg SB, Liu C. Comparative effectiveness of aerosolized versus oral ribavirin for the treatment of respiratory syncytial virus infections: a single-center retrospective cohort study and review of the literature. Transpl Infect Dis. 2018. https://doi.org/10.1111/tid.12844.

5. Simões EAF, Bont L, Manzoni P, et al. Past, present and future approaches to the prevention and treatment of respiratory syncytial virus infection in children. Infect Dis Ther. 2018;7(1):87–120.

6. Chemaly RF, Aitken SL, Wolfe CR, Jain R, Boeckh MJ. Aerosolized ribavirin: the most expensive drug for pneumonia. Transpl Infect Dis. 2016;18(4):634–6.

7. Xing Y, Proesmans M. New therapies for acute RSV infections: where are we? Eur J Pediatr. 2019;178(2):131–8.

8. Ralston SL, Lieberthal AS, Meissner HC. Clinical practice guideline: the diagnosis, management, and prevention of bronchiolitis. Pediatrics. 2015;134(5):e1474–502.

9. Glezen WP, Taber LH, Frank AL, Kasel JA. Risk of primary infection and reinfection with respiratory syncytial virus. Am J Dis Child. 1986;140(6):S43–6.

10. SYNAGIS [package insert]. Gaithersburg, MD: MedImmune, LLC. 2017.

11. Geskey JM, Thomas NJ, Brummel GL. Palivizumab: a review of its use in the protection of high risk infants against respiratory syncytial virus (RSV). Biologics. 2007;1(1):33–43.

12. Anderson EJ, Carosone-Link P, Yoge R, Yi J, Simões EAF. Effectiveness of palivizumab in high-risk infants and children: a propensity score weighted regression analysis. Pediatr Infect Dis J. 2017;36(8):699–704.

13. Blanken MO, Rovers MM, Molenaar JM, et al. Respiratory syncytial virus and recurrent wheeze in healthy preterm infants. N Engl J Med. 2013;368(19):1791–9.

14. Resch B. Product review on the monoclonal antibody palivizumab for prevention of respiratory syncytial virus infection. Hum Vaccin Immunother. 2017;13(9):2138–49.

15. Piedimonte G. RSV infections: state of the art. Cleve Clin J Med. 2015;82(11 Suppl 1):S13–8.

16. DeVincenzo JP, Wilkinson T, Vaishnaw A, et al. Viral load drives disease in humans experimentally infected with respiratory syncytial virus. Am J Respir Crit Care Med. 2010;182(10):1305–14.

17. DeVincenzo J, Tait D, Oluwayi O, et al. Safety and efficacy of oral RV521 in a human respiratory syncytial virus (RSV) phase 2a challenge study. Am J Respir Crit Care Med. 2018;197:A7715.

18. Evaluation of ALX-0171 in Japanese children hospitalized for respiratory syncytial virus lower respiratory tract infection [NCT03418571]. 2019. https://clinicaltrials.gov/ct2/show/NCT03418571. Accessed 2 Aug 2019.

19. Terry M. Sanofi cuts a whopping 38 R&D programs to refocus on cancer, immunology, and rare diseases. Biospace website. 2019. https://www.biospace.com/article/sanofi-q4-cleaning-house-trimming-r-and-d-cutting-costs/. Accessed 23 May 2019.

20. Safety, pharmacokinetics and antiviral activity of RV521 against RSV [NCT03258502]. ClinicalTrials.gov. 2017. https://clinicaltrials.gov/ct2/show/NCT03258502. Accessed 12 Aug 2019.

21. Coakley E, Ahmad A, Larson K, et al. LB6. EDP-938, a novel RSV N-Inhibitor, administered once or twice daily was safe and demonstrated robust antiviral and clinical efficacy in a healthy volunteer challenge study. Open Forum Infect Dis. 2019;6(suppl 2):S995.

22. Nam HH, Ison MG. Respiratory syncytial virus infection in adults. BMJ. 2019. https://doi.org/10.1136/bmj.i5021.
23. Novavax announces topline results from phase 3 PrepareTM trial of ResVax™ for prevention of RSV disease in infants via maternal immunization [press release]. Gaithersburg, MD: Novavax, Inc. 2019. http://ir.novavax.com/news-releases/news-release-details/novavax-announces-topline-results-phase-3-preparetm-trial. Accessed 23 May 2019.

24. Study of safety, reactogenicity and immunogenicity of GlaxoSmithKline’s (GSK) respiratory syncytial virus (RSV) maternal unadjuvanted vaccine in healthy pregnant women (aged 18 to 40 years) and their infants [NCT04126213]. ClinicalTrials.gov. 2020. https://clinicaltrials.gov/ct2/show/NCT04126213. Accessed 28 Aug 2020.

25. A phase 2B placebo-controlled, randomized study of a respiratory syncytial virus (RSV) vaccine in pregnant women [NCT04032093]. ClinicalTrials.gov. 2019. https://clinicaltrials.gov/ct2/show/NCT04032093. Accessed 12 Sep 2019.

26. Aliprantis A, Wolford D, Caro L, et al. A randomized, double-blind, placebo-controlled trial to assess the safety and tolerability of a respiratory syncytial virus (RSV) neutralizing monoclonal antibody (MK-1654) in healthy subjects. Poster presented at IDWeek 2018; October 6, 2018; San Francisco, CA. Poster 1971.

27. Blanco JCG, Boukhvalova MS, Morrison TG, Vogel SN. A multifaceted approach to RSV vaccination. Hum Vaccin Immunother. 2018;14(7):1734–45.

28. Fears R, Deval J. New antiviral approaches for respiratory syncytial virus and other mononegaviruses: inhibiting the RNA polymerase. Antiviral Res. 2016;134:63–76.

29. Nicholson EG, Munoz FM. A review of therapeutics in clinical development for respiratory syncytial virus and influenza in children. Clin Ther. 2018;40(8):1268–81.

30. Toovey S, Peng C, Yuan H, et al. Ziresovir (AK0529): update on clinical development for the treatment of respiratory syncytial virus (RSV) disease (O30). Oral presentation presented at 11th International Respiratory Syncytial Virus Symposium; November 2, 2018; Asheville, NC.

31. Anti-RSV study in Chinese patients (ASCENT) [NCT03699202]. ClinicalTrials.gov. 2019. https://clinicaltrials.gov/ct2/show/NCT03699202. Accessed 7 July 2020.

32. Study to evaluate safety and antiviral activity of doses of [NJJ-53718678 in children (>= 28 days to <= 3 years) with respiratory syncytial virus infection [NCT03656510]. ClinicalTrials.gov. 2019. https://clinicaltrials.gov/ct2/show/NCT03656510. Accessed 03 Aug 2019.

33. Martinon-Torres F, Rusch S, Huntjens D, et al. Antiviral effects, pharmacokinetics (PK) and safety of the respiratory syncytial virus (RSV) fusion protein inhibitor, [NJJ-53718678 (JNJ-8678), in RSV-infected infants with bronchiolitis, in the phase 1b study 53718678RSV1005. Poster presented at IDWeek 2018; October 3–7, 2018; San Francisco, CA. Poster 1958.

34. Stevens M, Rusch S, DeVincenzo J, et al. Antiviral activity of oral [NJJ-53718678 in healthy adult volunteers challenged with respiratory syncytial virus: a placebo-controlled study. J Infect Dis. 2018;218(5):748–56.

35. Cass L, Davis A, Murray A, et al. Safety and pharmacokinetic profile of PC786, a novel inhibitor of respiratory syncytial virus L-protein polymerase, in a single and multiple-ascending dose study in healthy volunteer and mild asthmatics. Poster presented at IDWeek 2018; October 3–7, 2018; San Francisco, CA. Poster 1335.

36. A study to assess EDP-938 for the treatment of acute upper respiratory tract infection with respiratory syncytial virus in adult subjects (RSVP) [NCT04196101]. ClinicalTrials.gov. 2020. https://clinicaltrials.gov/ct2/show/NCT04196101. Accessed 28 Aug 2020.

37. RSV vaccine and mAb snapshot. Vaccine Resource Library and PATH website. 2020. https://www.path.org/resources/rsv-vaccine-and-mab-snapshot/. Accessed 7 July 2020.

38. Kapikian AZ, Mitchell RH, Chanock RM, Shvedoff RA, Stewart CE. An epidemiologic study of altered clinical reactivity to respiratory syncytial (RS) virus infection in children previously vaccinated with an inactivated RS virus vaccine. Am J Epidemiol. 1969;89(4):405–21.

39. Kim HW, Canchola JG, Brandt CD, et al. Respiratory syncytial virus disease in infants despite prior administration of antigenic inactivated vaccine. Am J Epidemiol. 1969;89(4):422–34.

40. Wright M, Piedimonte G. Respiratory syncytial virus prevention and therapy: past, present, and future. Pediatr Pulmonol. 2011;46(4):324–47.

41. GlobalData. Respiratory syncytial virus (RSV): forecast in Asia-Pacific markets to 2028. https://pharma.globaldata.com/Analysis/TableOfContents/Respiratory-Syncytial-Virus—RSV—Forecast-in-Asia-Pacific-Markets-to-2028. 2019. Accessed 23 June 2020.

42. Mazur NI, Higgins D, Nunes MC, et al. The respiratory syncytial virus vaccine landscape: lessons from the graveyard and promising candidates. Lancet Infect Dis. 2018;18(10):e295–311.
43. Rossey I, Saelens X. Vaccines against human respiratory syncytial virus in clinical trials, where are we now? Expert Rev Vaccines. 2019. https://doi.org/10.1080/14760584.2019.1675520.

44. Safety and immunogenicity of a single dose of the recombinant live-attenuated respiratory syncytial virus (RSV) vaccines RSV ΔNS2/Δ1313/Δ1341L, RSV 6120/ΔNS2/1036s, RSV 276 or placebo, delivered as nose drops to RSV-seronegative children 6 to 24 months of age [NCT03916185]. ClinicalTrials.gov. 2019. https://clinicaltrials.gov/ct2/show/NCT03916185. Accessed 21 Oct 2019.

45. Evaluating the infectivity, safety, and immunogenicity of the recombinant live-attenuated respiratory syncytial virus vaccines RSV ΔNS2/Δ1313/Δ1341L or RSV 276 in RSV-seronegative infants 6 to 24 months of age [NCT03422237]. ClinicalTrials.gov. 2019. https://clinicaltrials.gov/ct2/show/NCT03422237. Accessed 11 Oct 2019.

46. Evaluating the safety and immune response to a single dose of a respiratory syncytial virus (RSV) vaccine in infants and children [NCT01893554]. ClinicalTrials.gov. 2019. https://clinicaltrials.gov/ct2/show/NCT01893554. Accessed 23 May 2019.

47. A study to evaluate the safety, reactogenicity, and immunogenicity of adenovirus serotype 26 based respiratory syncytial virus pre-fusion (Ad26.RSV. Pre-F) vaccine in RSV-seronegative toddlers 12 to 24 months of age [NCT03606512]. ClinicalTrials.gov. 2019. https://clinicaltrials.gov/ct2/show/NCT03606512. Accessed 2 Aug 2019.

53. A study of an Ad26.RSV.preF-based regimen in the prevention of reverse transcriptase polymerase chain reaction (RT-PCR)-confirmed respiratory syncytial virus (RSV)-mediated lower respiratory tract disease in adults aged 65 years and older [NCT03982199]. ClinicalTrials.gov. 2019. https://clinicaltrials.gov/ct2/show/NCT03982199. Accessed 2 Aug 2019.

54. Bavarian Nordic announces positive data from phase 2 extension study of its universal RSV vaccine [press release]. Copenhagen, Denmark: Bavarian Nordic A/S. 2018. https://www.globenewswire.com/news-release/2018/08/08/1548876/0/en/Bavarian-Nordic-Announces-Positive-Data-from-Phase-2-Extension-Study-of-its-Universal-RSV-Vaccine.html. Accessed 2 Aug 2019.

55. RSV-MVA-BN vaccine phase II trial in ≥ 55 year old adults [NCT02873286]. ClinicalTrials.gov. 2019. https://clinicaltrials.gov/ct2/show/NCT02873286. Accessed 12 Aug 2019.

56. Clinical trials. Novavax website. 2019. https://novavax.com/page/12/clinical-trials. Accessed 14 Aug 2019.

57. Anderson EJ, DeVincenzo JP, Simões EAF, et al. SENTINEL1: Two-season study of respiratory syncytial virus hospitalizations among US infants born at 29 to 35 weeks' gestational age not receiving immunoprophylaxis. Am J Perinatol. 2020;37(4):421–29.

58. Hacimustafaoglu M, Celebi S, Aynaci E, et al. The progression of maternal RSV antibodies in the offspring. Arch Dis Child. 2004;89(1):52–3.

60. Yeung CY, Hobbs JR. Serum-gamma-G-globulin levels in normal premature, post-mature, and "small-for-dates" newborn babies. Lancet. 1968;1(7553):1167–70.

61. Chu HY, Englund JA. Maternal immunization. Clin Infect Dis. 2014;59(4):560–8.

62. A study to describe the safety and immunogenicity of a RSV vaccine in healthy adults [NCT03529773]. ClinicalTrials.gov. 2019. https://clinicaltrials.gov/ct2/show/NCT03529773. Accessed 23 May 2019.
63. Madhi SA, Polack FP, Piedra PA, et al. Respiratory syncytial virus vaccination during pregnancy and effects in infants. N Engl J Med. 2020;383(5):426–39.

64. A study of a RSV vaccine when given together with Tdap in healthy nonpregnant women aged between 18 to 49 years [NCT04071158]. ClinicalTrials.gov. 2019. https://clinicaltrials.gov/ct2/show/NCT04071158. Accessed 12 Sep 2019.

65. Pfizer Inc. The free library website. 2019. https://www.thefreelibrary.com/Pfizer%20Inc-(NYSE%3APFE).-a0595026500. Accessed 25 Sep 2019.

66. A study of a vaccine against respiratory syncytial virus (RSV) when given alone and together with a vaccine against diphtheria, pertussis and tetanus (Tdap) viruses to healthy non-pregnant women [NCT04138056]. ClinicalTrials.gov. 2020. https://clinicaltrials.gov/ct2/show/NCT04138056. Accessed 28 Aug 2020.

67. Gagneur A, Pinquier D, Quach C. Immunization of preterm infants. Hum Vaccin Immunother. 2015;11(11):2556–63.

68. Heikkinen T, Valkonen H, Waris M, Ruuskanen O. Transmission of respiratory syncytial virus infection within families. Open Forum Infect Dis. 2015. https://doi.org/10.1093/ofid/ofu118.

69. Boyce TG, Mellen BG, Mitchel EF Jr, et al. Rates of hospitalization for respiratory syncytial virus infection among children in medicaid. J Pediatr. 2000;137(6):865–70.

70. Langston C, Kida K, Reed M, Thurlbeck WM. Human lung growth in late gestation and in the neonate. Am Rev Respir Dis. 1984;139(4):607–13.

71. Griffin MP, Yuan Y, Takas T, et al. Single-dose nirsevimab for prevention of RSV in preterm infants. N Engl J Med. 2020;383(5):415–25.

72. Safety, tolerability, and pharmacokinetics of MK-1654 in infants (MK-1654-002) [NCT03524118]. ClinicalTrials.gov. 2019. https://clinicaltrials.gov/ct2/show/NCT03524118. Accessed 2 Aug 2019.

73. Walker EP. MedPage Today website. FDA advisers turn down new RSV drug. https://www.medpagetoday.com/publichealthpolicy/fdageneral/20456. 2010. Accessed 19 Sep 2019.

74. US FDA grants breakthrough therapy designation for potential next-generation RSV medicine MEDI8897 [press release]. AstraZeneca PLC 2019. https://www.astrazeneca.com/media-centre/press-releases/2019/us-fda-grants-breakthrough-therapy-designation-for-potential-next-generation-rsv-medicine-medi8897.html. Accessed 23 May 2019.

75. A study to evaluate the safety and efficacy of MEDI8897 for the prevention of medically attended RSV LRTI in healthy late preterm and term infants (MELODY) [NCT03979313]. ClinicalTrials.gov. 2019. https://clinicaltrials.gov/ct2/show/NCT03979313. Accessed 12 Sep 2019.

76. A study to evaluate the safety and efficacy of MEDI8897 for the prevention of medically attended RSV LRTI in healthy preterm infants. (MEDI8897 Ph2b) [NCT02878330]. ClinicalTrials.gov. 2019. https://clinicaltrials.gov/ct2/show/NCT02878330. Accessed 12 Sep 2019.

77. Motavizumab. ClinicalTrials.gov. 2019. https://www.clinicaltrials.gov/ct2/results?term=motavizumab. Accessed 12 Sep 2019.

78. Regeneron to discontinue development of supratumab for respiratory syncytial virus [press release]. Tarrytown, NY: Regeneron Pharmaceutical, Inc. 2017. https://newsroom.regeneron.com/news-releases/news-release-details/regeneron-discontinue-development-supratumab-respiratory. Accessed 23 May 2019.
85. Stein RT, Bont LJ, Zar H, et al. Respiratory syncytial virus hospitalization and mortality: systematic review and meta-analysis. Pediatr Pulmonol. 2017;52(4):556–69.

86. Shi T, McAllister DA, O’Brien KL, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in young children in 2015: a systematic review and modelling study. Lancet. 2017;390(10098):946–58.

87. Aranda SS, Polack FP. Prevention of pediatric respiratory syncytial virus lower respiratory tract illness: perspectives for the next decade. Front Immunol. 2019;10:1006.

88. Griffin MP, Yuan Y, Takas T, et al. Single-dose nirsevimab for prevention of RSV in preterm infants [supplementary appendix]. N Engl J Med. 2020;383(5):415–25.

89. American Academy of Pediatrics Committee on Infectious Diseases; American Academy of Pediatrics Bronchiolitis Guidelines Committee. Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. Pediatrics. 2014;134(2):415–20.

90. Goldstein M, Phillips R, DeVincenzo JP, et al. National Perinatal Association 2018 respiratory syncytial virus (RSV) prevention clinical practice guideline: an evidence-based interdisciplinary collaboration. Neonatol Today. 2017;12(10):1–14.

91. Goldstein M, Krilov LR, Fergie J, et al. Respiratory syncytial virus hospitalizations among US preterm infants compared with term infants before and after the 2014 American Academy of Pediatrics guidance on immunoprophylaxis: 2012–2016. Am J Perinatol. 2018;35(14):1433–42.

92. Rajah B, Sánchez PJ, Garcia-Maurino C, Leber A, Ramilo O, Mejias A. Impact of the updated guidance for palivizumab prophylaxis against respiratory syncytial virus infection: a single center experience. J Pediatr. 2017;181:183–188.e1.

93. Krilov LR, Fergie J, Goldstein M, Brannman L. Impact of the 2014 American Academy of Pediatrics immunoprophylaxis policy on the rate, severity, and cost of respiratory syncytial virus hospitalizations among preterm infants. Am J Perinatol. 2020;37(2):174–83.

94. Kong AM, Krilov LR, Fergie J, et al. The 2014–2015 national impact of the 2014 American Academy of Pediatrics guidance for respiratory syncytial virus immunoprophylaxis on preterm infants born in the United States. Am J Perinatol. 2018;35(2):192–200.

95. American Academy of Pediatrics Committee on Infectious Diseases: American Academy of Pediatrics Bronchiolitis Guidelines Committee. Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. Pediatrics. 2014;134(2):415–20. Reaffirmed February 2019.