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REVIEW

Past, Present and Future Approaches to the Prevention and Treatment of Respiratory Syncytial Virus Infection in Children

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ABSTRACT

Introduction: The REGAL (RSV Evidence – A Geographical Archive of the Literature) series has provided a comprehensive review of the published evidence in the field of respiratory syncytial virus (RSV) in Western countries over the last 20 years. This seventh and final publication covers the past, present and future approaches to the prevention and treatment of RSV infection among infants and children.

Methods: A systematic review was undertaken of publications between January 1, 1995 and December 31, 2017 across PubMed, Embase and The Cochrane Library. Studies reporting data on the effectiveness and tolerability of prophylactic and therapeutic agents for RSV infection were included. Study quality and strength of evidence (SOE) were graded using recognized criteria. A further nonsystematic search of the published literature and Clinicaltrials.gov on antiviral therapies and RSV vaccines currently in development was also undertaken.

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Results: The systematic review identified 1441 studies of which 161 were included. Management of RSV remains centered around prophylaxis with the monoclonal antibody palivizumab, which has proven effective in reducing RSV hospitalization (RSVH) in preterm infants < 36 weeks' gestational age (72% reduction), children with bronchopulmonary dysplasia (65% reduction), and infants with hemodynamically significant congenital heart disease (53% reduction) (high SOE). Palivizumab has also shown to be effective in reducing recurrent wheezing following RSVH (high SOE). Treatment of RSV with ribavirin has conflicting success (moderate SOE). Antibodies with increased potency and extended half-life are currently entering phase 3 trials. There are approximately 15 RSV vaccines in clinical development targeting the infant directly or indirectly via the mother.

Conclusion: Palivizumab remains the only product licensed for RSV prophylaxis, and only available for high-risk infants. For the general population, there are several promising vaccines and monoclonal antibodies in various stages of clinical development, with the aim to significantly reduce the global healthcare impact of this common viral infection.

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Keywords: Antibody; Antiviral; IGIV; Motavizumab; Respiratory syncytial virus; Ribavirin; Palivizumab; Prophylaxis; Special populations; Vaccine

INTRODUCTION

Respiratory syncytial virus (RSV)-associated lower respiratory tract infection (LRTI) imposes a substantial medical and financial burden on pediatric health services and families worldwide [1–3]. It is known to infect almost all children by 2 years of age [4], with the risk of severe illness increased in certain well-recognized high-risk groups, such as preterm infants with or without chronic lung disease (CLD)/bronchopulmonary disease (BPD) and those with congenital heart disease (CHD) [5–7]. Growing evidence suggests that a number of other underlying medical conditions are also associated with an increased risk of severe RSV infection [8], including Down syndrome [9–12], cystic fibrosis [8, 11, 13–15], congenital malformations [11, 16], cancer [17], and the immunocompromised [11, 18]. The risk of RSV hospitalization (RSVH) decreases with increasing age, peaking in the first few months of life [3, 19–21], though older children are still susceptible to severe disease [22]. Several studies have also demonstrated that exposure to RSV infection in the first 3 years of life is associated with long-term respiratory problems, including recurrent wheezing and asthma [23–25], and possibly allergic sensitization [26], which may persist into early adulthood [24, 27–29].

Treatment of RSV LRTI is currently limited by a lack of effective antiviral agents—with the possible exception of ribavirin in certain populations—and is primarily supportive, including the use of supplemental oxygen, mechanical ventilation, and fluid replacement therapy. Comprehensive hygiene measures are efficacious and cost-effective in preventing the spread of RSV, and should always be advocated as a prophylactic measure. Although vaccine candidates have been in clinical evaluation for nearly 50 years, none, to date, have reached licensing. Palivizumab, a humanized monoclonal antibody, is currently the only intervention licensed for the prevention of severe RSV disease. However, its use is limited to certain subsets of high-risk infants, including the preterm population and those with CLD/BPD and CHD. The World Health Organization (WHO) has recognized the importance of the unmet medical need of the management of respiratory viruses, and in 2012 launched the BRaVe (Battle against Respiratory Viruses) initiative [30]. This initiative provides a framework to help direct and facilitate research into respiratory viral infections [30]. A crucial component of undertaking any new research into RSV is to gain a full understanding of the current evidence base.

The REGAL (RSV Evidence – A Geographical Archive of the Literature) series defines our current understanding of RSV as well as, importantly, identifying gaps in our knowledge and future areas of research. This paper, which represents the final one of a series of seven

publications covering a range of topics on RSV, identifies and describes the main approaches to the prevention and treatment of RSV disease among infants and children which have been used over the last 20 years, and discusses promising drugs and RSV vaccines on the horizon.

METHODS

Study Objective

REGAL addressed seven specific research questions, covering: overall epidemiology [3], prematurity [5], CLD/BPD [6], CHD [7], long-term respiratory morbidity [29], other high risk groups (e.g., Down syndrome) [8, 9], and—the focus of the current paper—past, present and future approaches to the prevention and treatment of RSV. This paper has two specific aims. First, to systematically review the evidence for the following therapeutic interventions in the pediatric population over the last 20 years: RSV immunoglobulin (RSV-IGIV); palivizumab; motavizumab; and ribavirin. Secondly, to undertake a non-systematic review to identify and evaluate promising new therapies and vaccines for RSV which will be available in the near future.

Literature Searches

The systematic review of current and past therapies was undertaken using the same broad methodology as for the other REGAL publications, which has been described in detail elsewhere [3]. To identify relevant studies, we used the following general terms, combined with Medical Subject Headings (MeSH), in MEDLINE (PubMed), EMBASE and the Cochrane Library: ["RSV" OR "respiratory syncytial virus" OR "lower respiratory tract infection" OR "bronchiolitis" OR "acute respiratory tract infection" OR "LRTI" OR "ARTI"] AND ["palivizumab" OR "Synagis" OR "motavizumab" OR "immunoprophylax*" OR "prophylax*" OR "immunoglobulin" OR "immune globulin" OR "IVIG" OR "RespiGam" OR "ribavirin"] AND limits: "human, child (birth to 18 years)". No language limits were set on the database searches, with the caveat that an English translation of at least the abstract had to be available. All original studies and selected systematic reviews and meta-analyses were included in the review. As per the ambit of REGAL, studies conducted in Western countries were included, which were defined as the United States, Canada, and Europe (including Turkey and the Russian Federation). Selected studies of particular relevance or importance outside the Western countries were also included to supplement the evidence base. The systematic literature search included studies published between January 1, 1995 and December 31, 2017, with other relevant studies, published during the drafting of the manuscript, also included, as identified by the authors.

The non-systematic search to identify promising antivirals and RSV vaccines that are currently in development was undertaken in MEDLINE (PubMed), EMBASE, the Cochrane Library and ClinicalTrials.gov, supplemented by publications identified by the authors. No restrictions were placed on included publications.

Evaluation of Data

As part of the systematic review, studies were graded using a modified version of the Oxford Centre for Evidence-Based Medicine (CEBM) Levels of Evidence [31, 32]. Meta-analyses are graded as level 1 by the CEBM, but since such studies were excluded from our review, we considered level 1 to be randomized controlled trials (RCTs) and level 2 to be observational studies (with dramatic effect). Level 3 (non-randomized controlled cohort/follow-up study) and level 4 evidence (case-series, case–control studies, or historically controlled studies) were as per the CEBM definitions. For RCTs, a quality assessment of each citation was carried out using the five-point (1 = low quality; 5 = high quality) Jadad Scale [33]. Risk of bias was assessed using the Cochrane Collaboration's tool for RCTs [34] and the RTI Item Bank (score of

1 = very high risk of bias; score of 12 = very low risk of bias) for observational studies [35].

Compliance with Ethics Guidelines

The analysis in this article is based on previously published studies and does not involve any new studies of human or animal subjects performed by any of the authors.

RESULTS

Past and Present Preventative and Therapeutic Interventions

The systematic review identified 2032 publications. After excluding duplicates (– 605) and screening of titles (– 1240), abstracts (– 40) and full papers (– 0), 147 relevant studies remained (Fig. 1). Supplemented by 14 references identified from other sources, a grand total of 161 studies were included in the review. The vast majority of studies involved palivizumab (120 studies), with fewer studies available for RSV-IGIV (11), motavizumab (4), and ribavirin (19). Some studies included more than one intervention. Due to space restriction, only the key studies for palivizumab, RSV-IGIV and ribavirin have been cited and summarized in the text (defined as: RCTs, prospective studies, post-marketing studies, international registries, and large retrospective studies for disease areas with limited prospective data; all studies with a minimum of 100 subjects). Non-specific treatment and supportive measures, such as oxygen, bronchodilators, etc., are the subject of many Cochrane reviews [36–48] and Society Guidelines [49, 50] and are not discussed further. Hygienic measures are also not discussed in the text. Data extraction tables for all the studies identified in this systematic review, however, are available in the online supplementary material.

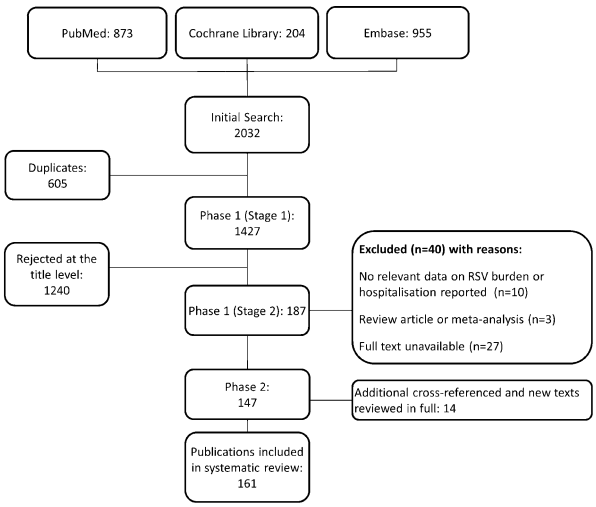

Fig. 1 PRISMA flow diagram. Treatment and prevention strategies for RSV over the last 20 years. *RSV* respiratory syncytial virus. References were screened for inclusion in two Phases. Phase I screening was split into two Stages, Stage 1—based on title and, for those meeting the inclusion criteria, Stage 2—based on abstract. Those references retained after Phase 1 were assessed based on the full paper in Phase 2

Prevention of RSVH

RSV-IGIV

RSV hyper immunoglobulin (RSV-IGIV), a polyclonal human intravenous (IV) antibody preparation, was the first successful prophylactic modality developed for preventing severe RSV in infants and children under the age of 2 years. In the seminal The National Institute of Allergy and Infectious Diseases (NIAID) trial [51, 52], in 249 infants and young children with BPD, CHD or prematurity (≤ 35 weeks' gestational age; wGA) alone, RSV-IGIV was shown to significantly reduce lower respiratory infection (LRI; 7 vs. 20 episodes in the control group), RSVHs (6 vs. 18), days in the hospital (43 vs. 128), and stays in the intensive care unit (ICU; 1 vs. 34 days, $P = 0.05$) in children administered at a high dose (750 mg/kg body weight) compared to controls. However, because five of six deaths occurred in children with heart disease, further trials were carried out in children with either prematurity (PREVENT trial) [53] or with CHD (CARDIAC trial) [54].

In 1996, RSV-IGIV became the first agent approved by the US Food and Drug Administration (FDA) for the prevention of RSV in preterm infants < 36 wGA and infants with BPD

Table 1 Incidence of RSVH and hospital resource use in children with BPD and/or history of prematurity (≤ 35 wGA) in the PREVENT trial [53]

	RSV-IGIV ($n = 250$)	Placebo ($n = 260$)	Reduction	*P* value
Incidence of RSVH (%)	8.0	13.5	41%	0.047
Total days of hospitalization per 100 children	60	129	53%	0.045
Total days of RSVH requiring increased supplemental oxygen per 100 children	34	85	60%	0.007
Number of hospital days with moderate or severe LRI (LRI score ≥ 3[a]) per 100 children	49	106	54%	0.049
Total days of ICU or mechanical ventilation for RSV per 100 children	28	50	–	–

ICU intensive care unit, *LRI* lower respiratory infection/illness, *RSV-IGIV* respiratory syncytial virus intravenous immunoglobulin, *RSVH* respiratory syncytial virus hospitalization

[a] LRI score: 0 = no respiratory illness/infection; 1 = upper respiratory tract illness (URI); 2 = mild LRI; 3 = moderate LRI; 4 = severe LRI; 5 = mechanical ventilation. The LRI score was calculated as the mode of the following three (A, B, C) component scores, or the mean if there was no mode: A. Oxygen saturation—0 = Baseline value (no URI), 1 = Baseline value (URI), 2 = Decrease < 5%, 3 = Decrease 5–10%, 4 = Decrease > 10%, 5 = Mechanical ventilation; B. Respiratory rate—0 = Baseline value (no URI), 1 = Baseline value (URI), 2 = Increase 1–14/min, 3 = Increase 15-30/min, 4 = Increase > 30/min, 5 = Mechanical ventilation; C. Retractions, Wheezing, Crackles—0 = No change (no URI), 1 = Minimal, 2 = Mild, 3 = Moderate, 4 = Severe, 5 = Mechanical ventilation [51]. Values for oxygen saturation, respiratory rate, and pulmonary findings were compared with baseline values on usual oxygen flow [51]

aged < 24 months. The pivotal study was the PREVENT trial [53], in which children received RSV-IGIV 750 mg/kg every 30 days for a maximum of 5 infusions. RSV-IGIV prophylaxis was associated with a 41% reduction in RSVH and a 53% reduction in total days of hospitalization per 100 children versus placebo (Table 1) [53]. Another study demonstrated that RSV-IGIV is effective in preventing severe RSV disease in preterm infants, with similar results to the PREVENT trial [55]. In a long-term follow-up study of children with CLD/BPD who had received RSV-IGIV 7–10 years previously in the seminal NIAID trial [51], these children were shown to have better lung function ($P = 0.02$) and less atopy (15 vs. 50%; $P < 0.04$) compared with matched children who had not received prophylaxis in that trial [26].

Despite the successful use of RSV-IGIV in preterm infants, there were safety concerns and an apparent lack of efficacy in some patient populations. The RCT undertaken in children with CHD (CARDIAC trial) failed to achieve its primary efficacy endpoint of reduced RSVH, being effective only in those infants aged < 6 months [54]. There was also a significantly higher frequency of cyanotic episodes and poor outcomes after surgery among children with cyanotic CHD in the RSV-IGIV group than in the control group (28 vs. 8.5%; $P = 0.009$). This was ascribed to hyperviscosity that occurred with the administration of 750 mg/kg of the RSV-IGIV [54]. Such data led to RSV-IGIV being indicated only for premature infants ≤ 32 wGA and those with CLD [56]. RSV-IGIV was eventually voluntarily withdrawn from the market in 2003 following the successful licensing of the first monoclonal antibody for RSV (palivizumab) in 1998. RSV-IGIV had demonstrated the potential of passive immunoprophylaxis in effectively and safely preventing RSVH, and the focus of research was directed towards the development of monoclonal antibodies.

Palivizumab

Following the demonstration that RSV-IGIV could successfully prevent RSV LRI and RSVH [51, 53], MedImmune and other vaccine manufacturers started developing monoclonal antibodies against RSV, with the hope of finding a simpler and safer route for prophylaxis. Of the three monoclonal antibodies developed [57–59], palivizumab was the only one that was licensed, in 1998. Palivizumab is a humanized monoclonal antibody administered via intramuscular (IM) injection at 15 mg/kg monthly during the RSV season, and is licensed for the prevention of severe RSV in high-risk children, including: children born at < 35 wGA and < 6 months at the onset of the RSV season; children < 2 years requiring treatment for BPD within the last 6 months; and children < 2 years of age with hemodynamically significant CHD (HS-CHD). The key study results for palivizumab, stratified by patient population, are summarized below.

Prematurity With or Without CLD/BPD Support for the efficacy of palivizumab in reducing RSVH rates in preterm infants with or without CLD/BPD comes from a number of RCTs and prospective studies conducted in the USA, Canada, and Europe [60–77]. In the registration study, IMpact-RSV [61], prophylaxis with palivizumab resulted in a 55% reduction in RSVH versus placebo in children with prematurity (≤ 35 wGA) or BPD (4.8 vs. 10.6%, respectively; $P < 0.001$). Significant reductions were observed in both children with BPD (39% reduction, $P = 0.038$) and preterm children without BPD (78% reduction, $P < 0.001$). For infants born at < 32 wGA, palivizumab reduced the RSVH rate by 47% ($P = 0.003$) and in infants born at 32–35 wGA by 80% ($P = 0.002$). Palivizumab also reduced the rate of admission to ICU (1.3 vs. 3.0%; $P = 0.026$), the incidence of all respiratory hospitalizations (16 vs. 22%; $P = 0.008$), and the total respiratory-related hospital days per 100 children (124 vs. 180 days; $P = 0.004$) versus placebo [61]. In a subgroup efficacy analysis of the cohort of preterm infants without BPD, palivizumab consistently reduced RSVH (64.5–100%) versus placebo across all 11 gestational age groups evaluated [78].

In the Spanish FLIP-2 study [66], the incidence of RSVH was significantly lower in infants born at 32–35 wGA who received prophylaxis with palivizumab than in untreated infants (1.3 vs. 4.1%; $P < 0.001$). The Palivizumab Outcomes Registry was established in 2000 to prospectively collect data on any child receiving palivizumab prophylaxis at any of the registry sites within the USA [77]. RSVH rates across the 4 seasons (2000–2004) for infants who received palivizumab prophylaxis ranged from 1.1 to 4.5% for infants born at < 32 wGA and 0.2–1.6% for infants born at 32–35 wGA [77]. In 2002, a meta-analysis of all studies to date, which compared studies with and without palivizumab prophylaxis, illustrated a weighted mean RSVH rate of 10.2% in infants 29–32 wGA without CLD who had not received prophylaxis compared to 2.0% in those who had received prophylaxis [79]. Corresponding rates in those born 32–35 wGA without CLD were 9.8 and 1.5%, respectively. In those with CLD/BPD, the weighted mean RSVH rate in children < 2 years old was 17.9% in those who had not received prophylaxis compared to 5.6% in those who had received it [79].

Further real-world experience comes from a comparative study that examined the dosing regimens, compliance, and outcomes of preterm infants who received palivizumab within the Canadian Registry of Palivizumab (CARESS) [76]. Data for the 2006–2011 RSV seasons were compared for preterm infants born ≤ 32 wGA without underlying medical disorders to that of infants born 33–35 wGA. RSVH rates for infants of both ≤ 32 and 33–35 wGA following prophylaxis were found to be similar at 1.5 and 1.4%, respectively, and were lower than similar groups in the treated arm of the IMpact-RSV Study (5.8 and 1.8%, respectively) [61, 76]. Overall, the weighted mean for RSVH for palivizumab recipients versus untreated premature infants (≤ 35 wGA) in the prospective, comparative studies identified [61, 64, 65, 72] was 3 vs. 9.5%, respectively, (68% relative reduction; range: 64–100%) (Table 2). Stratified by wGA, palivizumab was associated with 62% (58–80%) reduction in RSVH in < 29 wGA infants [65, 78], 75% (75–79%) in 29-32 wGA infants [65, 78], and 71% (68–82%) in 32–35 wGA infants

Table 2 Prospective, comparative studies on the effectiveness of palivizumab prophylaxis in reducing RSVH

Author	RCT	Study design	Study population	RSVH (%)							
				Preterm < 29 wGA		Preterm 29-32 wGA		Preterm 32-35 wGA		Preterm ≤ 35 wGA	
				Untreated	Prophylax	Untreated	Prophylax	Untreated	Prophylax	Untreated	Prophylax
IMpact-RSV Study [61, 78] US, UK, Canada	+	Multicenter, randomized, double-blind, placebo-controlled	1502 children with prematurity (≤ 35 wGA) or BPD	10.0	2.0[a]	7.7	1.6[b]	10.1	1.8[b]	8.1	1.8[c]
Pedraz [65] Spain	−	Multicenter, comparing 2 untreated cohorts to 2 prophylaxed cohorts	3502 preterm infants ≤ 32 wGA (11.3% CLD [prophylaxed cohort]; 4.8% CLD [non-prophylaxed cohort])	13.0	5.4[d]	9.9	2.5[d]			10.4[f]	3.7[ef]
Blanken (MAKI) [25] Netherlands	+	Multicentre, randomized, double-blind, placebo-controlled	429 otherwise healthy infants 33-35 wGA					5.1	0.9[m]		
Figueras-Aloy [66] Spain	−	Multicenter, 2-cohort	5441 preterm infants 32–35 wGA (excluded CHD and other serious comorbidities)					4.1	1.3[c]		
Faldella [64] Italy	−	Single center follow-up of infants admitted to NICU soon after birth	225 preterm infants ≤ 32 wGA							9.9[h]	1.9[g]
Grimaldi [67, 72] France	−	Burgundy region, comparing untreated cohorts to prophylaxed cohorts over up to 5 RSV seasons	69 preterm infants ≤ 32 wGA with BPD (included 2 infants with CHD) 339 preterm infants ≤ 30 wGA without BPD (included 9 infants with CHD)							0.2–16.7[j]	0–2.0[ij]
Feltes [80] USA	+	Multicenter, randomized, double-blind, placebo-controlled	1287 children aged ≤ 24 months old with HS-CHD								
Medrano López [81] Spain	−	Multicenter, epidemiologic, covering 4 RSV seasons	2613 children ≤ 24 months old with HS-CHD[p]								
			Weighted mean rate [95% CI]	12.5 [11.5–13.5]	4.8 [4.1–5.4]	9.5 [8.7–10.4]	2.4 [1.9–2.8]	4.8 [4.2–5.2]	1.4 [1.1–1.6]	9.1–10.2 [8.1–9.6; 9.3–11.0]	2.9–3.0 [2.3–3.2; 2.5–3.4]

Table 2 continued

Author	RCT	Study design	Study population	RSVH (%)					
				CLD/BPD		CHD		Preterm and CHD/BPD/other comorbidities	
				Untreated	Prophylax	Untreated	Prophylax	Untreated	Prophylax
IMpact-RSV Study [61, 78] US, UK, Canada	+	Multicenter, randomized, double-blind, placebo-controlled	1502 children with prematurity (≤ 35 wGA) or BPD	12.8	7.9[b]				
Pedraz [65] Spain	−	Multicenter, comparing 2 untreated cohorts to 2 prophylaxed cohorts	3502 preterm infants ≤ 32 wGA (11.3% CLD [prophylaxed cohort]; 4.8% CLD [non-prophylaxed cohort])	19.7	5.5[g]			13.25	3.95[e]
Blanken (MAKI) [25] Netherlands	+	Multicentre, randomized, double-blind, placebo-controlled	429 otherwise healthy infants 33-35 wGA						
Figueras-Aloy [66] Spain	−	Multicenter, 2-cohort	5441 preterm infants 32–35 wGA (excluded CHD and other serious comorbidities)						
Faldella [64] Italy	−	Single center follow-up of infants admitted to NICU soon after birth	225 preterm infants ≤ 32 wGA						
Grimaldi [67, 72] France	−	Burgundy region, comparing untreated cohorts to prophylaxed cohorts over up to 5 RSV seasons	69 preterm infants ≤ 32 wGA with BPD (included 2 infants with CHD) 339 preterm infants ≤ 30 wGA without BPD (included 9 infants with CHD)					46.2	3.8–11.8[i]
Feltes [80] USA	+	Multicenter, randomized, double-blind, placebo-controlled	1287 children aged ≤ 24 months old with HS-CHD			9.7 (cyanotic: 7.9) (other [acyanotic]: 11.8)	5.3[b] (cyanotic: 7.9[n]) (other [acyanotic]: 11.8[o])		
Medrano López [81] Spain	−	Multicenter, epidemiologic, covering 4 RSV seasons	2613 children ≤ 24 months old with HS-CHD[p]			7.9	3.3[i]		

Table 2 continued

Author	RCT	Study design	Study population	RSVH (%)					
				CLD/BPD		CHD		Preterm and CHD/BPD/other comorbidities	
				Untreated	Prophylax	Untreated	Prophylax	Untreated	Prophylax
			Weighted mean rate [95% CI]	17.6 [16.5–18.6]	6.2 [5.5–6.9]	8.5 [7.6–9.4]	4.0 [3.3–4.6]	13.9 [12.7–14.9]	4.0-4.1 [3.3–4.6; 3.5–4.8]

BPD bronchopulmonary dysplasia, *CHD* congenital heart disease, *CI* confidence interval, *CLD* chronic lung disease, *HS-CHD* hemodynamically significant congenital heart disease, *RCT* randomized controlled trial *RSVH* respiratory syncytial virus hospitalization, *wGA* weeks' gestational age

[a] Non-significant vs. untreated

[b] $P < 0.05$ vs. untreated

[c] $P < 0.001$ vs. untreated

[d] $P < 0.0001$ vs. untreated

[e] Significance not reported

[f] ≤ 32 wGA

[g] $P < 0.007$ vs. untreated

[h] ≤ 32 wGA hospitalized for respiratory tract infection during the RSV season

[i] $P < 0.01$ vs. untreated

[j] ≤ 30 wGA

[k] $P = 0.003$ vs. untreated

[l] Evaluated adequate (full course) vs. inadequate (incomplete) prophylaxis

[m] $P = 0.01$ vs. placebo (infants 33–35 wGA)

[n] $P = 0.285$; cyanotic included: pulmonary atresia with ventricular septal defect, pulmonary atresia with intact septum, tetralogy of Fallot, single ventricle including hypoplastic left or right heart, tricuspid atresia, double-outlet right ventricle with transposed great arteries, Ebstein anomaly, or D-transposition of the great arteries with/without ventricular septal defect, with/without pulmonary stenosis

[o] $P = 0.003$; other (acyanotic) included remaining children not stratified as having cyanotic CHD

[p] HS-CHD defined as: heart failure clinic, malnutrition (weight percentile < 3 for age and sex), hypoxemia (desaturation, need for supplementary O_2) and/or requiring cardiac medication [82]

[25, 61, 66]. For infants with CLD/BPD, the mean weighted RSVH rate was 6.2% in palivizumab recipients versus 17.6% in untreated infants (65% relative reduction; range 38–72%) [61, 65]. A recently published study using propensity score weighted regression analysis has shown that, when adjusted for the fact that prophylaxis is most routinely offered to those with risk factors for RSVH, palivizumab was shown to have an efficacy of 58% for preventing RSVH in infants ≤ 1 year [60]. This is in line with the pivotal IMpact-RSV trial [61].

Congenital Heart Disease In 2003, Feltes et al. [80] published the results of their large RCT involving 1287 children with HS-CHD (defined as patients with cyanotic CHD, single ventricle physiology, or those with acyanotic CHD who required medical therapy). Palivizumab prophylaxis resulted in a 45% reduction in RSVH versus placebo (5.3 vs. 9.7%, respectively; $P = 0.003$). In addition, children receiving palivizumab had significantly fewer total days of RSVH per 100 children (57.4 days palivizumab vs. 129 days placebo; $P = 0.03$) and RSV hospital days with increased oxygen requirement per 100 children (27.9 vs. 101.5 days, respectively; $P = 0.014$) [80]. Furthermore, unlike RSV-IGIV, it was safe in both infants and children with and without cyanotic heart disease [54], which led to its licensing in the US, Europe and many countries of the world for preventing severe RSV in infants and children with CHD.

Further evidence supporting the use of palivizumab in children with CHD comes from two non-comparative, prospective studies [67, 81], and from post-marketing observational studies from the United States [13, 83], Germany [84], and Canada [85, 86]. The Palivizumab Outcomes Registry observed a cumulative RSVH rate of 1.9% among 1500 infants and children with CHD who received prophylaxis between 2000 and 2004 [83]. Among infants and children with cyanotic (29%) and acyanotic (71%) CHD, hospitalization rates were 2.6 and 1.6%, respectively. More detailed follow-up information on diagnosis was available for the 2002–2003 and 2003–2004 seasons, which showed that 44.1% had HS-CHD (as diagnosed by a healthcare practitioner), with patent ductus arteriosus (21.5%), ventricle septal defect (16.7%), and atrial septal defect (11.4%) being the three most common diagnoses (Table 3) [83]. More recent data from CARESS suggest that children in their second year with HS-CHD, who remain unstable, are as equally at risk for RSVH (1.7%) as infants in their first year (2.3%) and merit prophylaxis [85]. This study used a more refined definition of HS-CHD, including those with uncorrected or palliated cyanotic CHD or acyanotic CHD associated with documented pulmonary hypertension (systolic pulmonary arterial pressure ≥ 40 mmHg) and/or a requirement for daily medication to manage congestive heart failure [85, 87]. These criteria intentionally exclude patients with uncomplicated or insignificant CHD and are consistent with those from the pivotal study by Feltes et al. in 2003 [80, 87]. The overall weighted mean for palivizumab recipients versus untreated infants with HS-CHD in the prospective, comparative studies identified [80, 81] was 4.0 vs. 8.5%, respectively, (53% relative reduction; range 45–58%) (Table 2).

Down Syndrome The medical needs for the prevention of RSVH in infants and children with Down syndrome are high [8–11], and there is growing clinical evidence to support the use of palivizumab in this population. In CARESS, RSVH rates in children with Down syndrome receiving palivizumab have been found to be low [88–91]. Yi et al. [89] compared hospitalization rates due to respiratory tract infection in 532 children with Down syndrome aged < 2 years who received palivizumab during the RSV season in the CARESS registry (2005–2012) with a similar, untreated cohort of 233 children with Down syndrome from the Netherlands (2003–2005) [9]. In total, 31 children were hospitalized for RSV (23 untreated and 8 treated), and palivizumab prophylaxis was associated with a 3.6-fold (72%) decrease in RSVH [89]. Four untreated children versus none of the treated group needed intensive care or respiratory support, and the mean number of days of oxygen treatment was significantly higher in the untreated group (19 vs. 2 days, respectively; $P < 0.001$). In a further post hoc analysis, 83 and 50% of RSVHs occurred within

Table 3 Diagnosis and care of subjects with CHD in the Palivizumab Outcomes Registry 2002–2004 ($n = 1101$) [83]

HS-CHD, *n* (%)[a]	485 (44.1%)
Primary diagnosis, *n* (%)	
Patent ductus arteriosus	237 (21.5)
Ventricular septal defect	184 (16.7)
Atrial septal defect	126 (11.4)
Single ventricle (including hypoplastic left or right ventricle)	67 (6.1)
Tetralogy of Fallot	63 (5.7)
Atrioventricular canal defect (endocardial cushion defect)	55 (5.0)
Pulmonary stenosis	45 (4.1)
Coarctation of the aorta	35 (3.2)
Heart murmur[b]	22 (3.2)
Transposition of the great arteries	28 (2.5)
Pulmonic atresia with ventricular septal defect	16 (1.5)
Aortic stenosis	14 (1.3)
Tricuspid atresia	14 (1.3)
Peripheral pulmonic stenosis[b]	8 (1.2)
Truncus arteriosus[b]	7 (1.0)
Double-outlet right ventricular with transposed great arteries	10 (0.9)
Pulmonary atresia with the intact septum	5 (0.5)
Ebstein's anomaly	5 (0.5)
Other	160 (14.5)
Current status of cardiac defect, *n* (%)	
Uncorrected, no surgery planned	260 (23.6)
Uncorrected, surgery planned for future	143 (13.0)
Partially corrected	207 (18.8)
Fully corrected with residual effect	84 (7.6)
Fully corrected with no residual effect	224 (20.3)
Resolved without surgery[b]	57 (8.3)
Unknown[b]	79 (11.5)
Other	47 (4.3)

HS-CHD hemodynamically significant congenital heart disease

[a] Diagnosis of HS-CHD was at the health care practitioner's discretion and independent from the primary diagnosis

[b] Data available only for 2003–2004 season ($n = 688$)

the first year of the child's life in untreated and treated groups, respectively [89].

Cystic Fibrosis Evidence for the use of palivizumab in children with cystic fibrosis is relatively limited and inconclusive as to its usefulness. A retrospective study by Giebels et al. [15] reported no RSVHs in 35 young children (80% < 1 year) with cystic fibrosis who received palivizumab, and 3 confirmed RSVHs in 40 children (73% < 1 year) with cystic fibrosis who were non-recipients (3 additional acute respiratory illnesses were also reported in the control group, but were not tested for RSV). Further information on the use of palivizumab for prevention of RSV in children with cystic fibrosis comes from international registries, including CARESS [90, 92] and the Palivizumab Outcomes Registry [93]. In the latter registry, there were no RSVHs in 91 children with cystic fibrosis who received palivizumab [93]. Other studies have also shown potentially positive effects of palivizumab, but overall inconclusive results, perhaps due to being underpowered [94, 95]. A recent systematic review of the safety and efficacy of palivizumab

in infants and children with cystic fibrosis, which included 10 studies (6 cohort studies, 2 before-and-after studies, 1 cross-sectional study, and 1 RCT) involving 3891 patients with cystic fibrosis, did not provide unequivocal support for palivizumab in this population [96]. This was because of study limitations (before–after study design, low RSVH rate, etc.) for the most part and non-comparability of studies [96].

Other Significant Underlying Medical Conditions Some information is available on palivizumab use in infants and children with other significant underlying medical conditions, including those with neuromuscular disease and congenital airway anomalies [90, 91, 97–100]. In a post hoc sub-analysis of CARESS, the RSVH rate in children receiving palivizumab varied from 0.78 to 11.8%, depending on the underlying medical condition (Table 4) [90]. Further data come from a recent prospective, multicenter, international cohort study that assessed the outcomes of 14,468 palivizumab recipients within CARESS and the Torino-Verona Italian Registry over the 2002–2014 RSV seasons [91]. Infants with neuromuscular disorders (7.88%), airway anomalies (5.95%), BPD (4.75%) and HS-CHD (4.10%) were found to have higher incidences of RSVH than preterm infants born ≤ 35 completed wGA (2.37%). There were, however, no significant differences in regard to hospital length of stay, rates of ICU admission, or need for mechanical ventilation among the different groups of palivizumab-treated patients. It is not known whether the higher RSVH rates in the infants with severe underlying comorbidities related to inadequate palivizumab dosing protocols or to a specific increased RSVH risk inherent in these infants. The study also included 56 immunocompromised infants, 3 of whom had human immunodeficiency virus (HIV), in which no RSVHs were reported [91].

Table 4 RSVH rates in children with significant underlying medical disorders who received palivizumab in CARESS (2006–2010) [90]

Underlying medical disorder	RSV hospitalization rate (%)
Cardiac ($n = 22$)	4.55
Pulmonary ($n = 127$)	1.73
Neuromuscular ($n = 78$)	6.90
Other ($n = 163$)	0.78
Multiple ($n = 57$)	2.01
Immunocompromised ($n = 17$[a])	11.8
Airway anomalies ($n = 178$)	2.70
Down syndrome ($n = 193$)	1.84
Cystic fibrosis ($n = 117$)	1.14

[a] Includes one child with HIV

Safety Palivizumab was shown to be well-tolerated in the RCTs, with adverse events (AEs) similar to those reported for placebo [61, 80]. Real-world experience has confirmed the good safety profile of palivizumab, with low rates of serious adverse events (SAEs) reported, including in children with complex medical disorders [101–103]. Chen et al. [101] reported that the overall number of SAEs found in infants [63.1% preterm infants ≤ 35 wGA and 36.9% children aged < 2 years with comorbidities (HS-CHD 11.1%, BPD 7.5%, complex underlying medical conditions 18.3%)] enrolled into CARESS was low. Six patients (0.05%) experienced a total of 14 possibly- or probably-related SAEs (mainly hypersensitivity reactions) for an incidence of 2.8 per 10,000 patient-months [101]. In a phase 4 post-marketing study, Bonnet et al. [102] reported that palivizumab was not associated with an increase in infection or arrhythmia, or overall primary SAEs (infection, arrhythmia, or death) in children with HS-CHD.

Guidelines For certain groups of high-risk infants, including preterm infants with and without CLD/BPD and infants and children with HS-CHD, palivizumab has proven to be an effective and well-tolerated preventive strategy for RSVH. However, driven primarily by cost–benefit considerations, most national guidelines have restricted the use of palivizumab to sub-populations of the highest-risk children [104–111]. The American Academy of

Pediatrics (AAP) 2014 policy statement [104, 112] recommends that only preterm infants born < 29° wGA and < 1 year at the season start date, infants in the first year of life with CLD of prematurity (< 32° wGA and a requirement for > 21% oxygen for ≥ 28 days after birth) or those in the second year of life requiring medical support for CLD during the 6-month period before the start of the second RSV season, and infants with HS-CHD and < 1 year at the season start date, are eligible for palivizumab prophylaxis. The evidence behind these recommendations, however, is not always clear, and many countries use earlier guidelines that rely on identification of risk factors to guide prophylaxis [108, 109]. Other high-risk groups, such as Down syndrome, are very rarely addressed in the various guidelines [113], despite evidence to suggest a beneficial or protective role for palivizumab in these children.

Motavizumab

Motavizumab was a second generation humanized monoclonal antibody derived from palivizumab. The expectation was that motavizumab would provide increased efficacy after demonstrating 10-fold greater activity in preclinical studies [114], whilst maintaining the good safety profile of palivizumab. The safety and efficacy of motavizumab as a prophylactic treatment for RSV infection was evaluated in two pivotal RCTs [87, 115]. Carbonell–Estrany et al. [115] assessed safety and RSVH in 6635 preterm infants aged ≤ 6 months at enrolment or children aged ≤ 24 months with CLD who received either palivizumab or motavizumab at a dose of 15 mg/kg once a month for 5 months. Motavizumab recipients had a 26% relative reduction in RSVH compared with palivizumab recipients, achieving non-inferiority. Further analyses showed that motavizumab was superior to palivizumab for reduction of RSV-specific, outpatient medically-attended LRTIs (50% relative reduction). AEs were similar between treatments, although cutaneous events were more frequently reported in the motavizumab group (7.2 vs. 5.1%) [115]. In a subsequent study, Feltes et al. [87] compared the safety and tolerability of motavizumab and palivizumab in 1236 children with CHD aged ≤ 24 months. Again, despite the overall safety profiles being similar, skin rashes were observed more frequently in motavizumab recipients (19.3 vs. 16.2%). In terms of efficacy of motavizumab, results were similar to those reported by Carbonell-Estrany et al. [115], with an observed 25% relative reduction in the incidence of RSVH and 51% relative reduction in the RSV outpatient medically-attended LRTI rate compared with palivizumab [87]. Finally, a RCT of motavizumab in healthy aboriginal American infants, conducted between 2004 and 2007, in which 1417 received motavizumab and 710 placebo, demonstrated an 87% relative reduction in RSVH in the motavizumab group [116]. Hypersensitivity events were more common in the motavizumab arm (208/1417; 14.7%) than in the placebo arm (87/710; 12.3%; $P = 0.14$), about twice the rate as that in the pivotal trial (7.2 and 5.1%, respectively) [115]. Interestingly, antidrug antibodies were found in only 0.4% (3/717) of tested motavizumab recipients in this trial [116] compared to 1.8% (58/1227) in the pivotal trial [115].

In 2010, the FDA rejected the license application for motavizumab, primarily due to concerns over a lack of greater efficacy, increased hypersensitivity reactions relative to palivizumab, and the generalizability of the results, since non-inferiority was not reached in the sub-population of subjects from the northern hemisphere [114]. Recent findings have also indicated that motavizumab had no significant effect on RSV viral load or duration or severity of RSVH versus placebo when used in a treatment setting [117].

Prevention of Long-Term Outcomes with Antibodies Severe RSV LRTI has been associated with long-term respiratory problems, including recurrent wheezing and asthma, and possibly allergic sensitization later in life [25, 27–29]. The first long-term follow-up study of RSV prevention was in infants with BPD/CLD who had received RSV-IGIV 7–10 years earlier, which illustrated improved lung function among those who had received RSV-IGIV compared to controls [26]. It was hypothesized by the authors that RSV primarily causes direct

pulmonary epithelial damage and local immunologic alterations in the lungs, leading to long-term airway hyper-responsiveness and wheezing [26]. Subsequently, a study examined the role of preventing RSV LRI with palivizumab in Europe and Canada [118]. In this prospective, multicenter, double-cohort study, the incidences of recurrent wheezing and physician-diagnosed recurrent wheezing were significantly lower in 191 palivizumab-treated subjects (13 and 8%, respectively) compared with all 230 untreated subjects (26%, $P = 0.001$ and 16%, $P = 0.011$, respectively) and with 154 patients in the subgroup not hospitalized for RSV LRTI (23%, $P = 0.022$ and 16%, $P = 0.027$, respectively) [118]. In a subsequent analysis, this reduction in wheezing frequency was only seen in those children who did not have an atopic family history [119]. A third study, from Japan, was initiated soon after in which the outcomes of 349 infants born at 33–35 wGA without CLD who received palivizumab prophylaxis in the first 6 months of life were compared to 95 infants who did not receive prophylaxis [23]. At the 3-year follow-up, physician-diagnosed recurrent wheezing was observed in 6.4 and 18.9% of the infants in the two groups, respectively; this was significant after adjustment for differences in risk factors between the groups ($P < 0.001$) [23]. At the 6-year follow-up, there was no difference in atopic asthma between the two groups (15.3 and 18.2% in the treated and untreated groups, respectively; $P = 0.57$) [24]. On the other hand, there was a significant difference in physician-diagnosed recurrent wheezing (15.3 vs. 31.6%, respectively; $P = 0.003$) [24]. In this study, contrary to the European–Canadian study [119], significant differences were found only for recurrent wheezing in those with a family history of allergy within the Intention To Treat (all enrolled) analysis, the per protocol (those completing 6-year follow-up) analysis, and in those investigated for atopy (the atopic asthma population) [24].

A study (MAKI) investigating the pathogenesis of recurrent wheeze after RSV infection randomized otherwise healthy preterm infants born at 33–35 wGA to either monthly palivizumab injections (214 infants) or placebo (215 infants) during the RSV season [25]. Palivizumab treatment was shown to result in a relative reduction of 61% [95% confidence interval (CI) 56–65] in the total number of wheezing days during the first year of life [930 of 53,075 days in the RSV group (1.8%) vs. 2309 of 51,726 days (4.5%) in the placebo group] [25]. In contrast to the findings of the previous trials with palivizumab [24, 119], the MAKI study found that palivizumab reduced wheezing in the first year of life in children born at 33–35 wGA regardless of whether there was a family history of atopy [25].

Finally, in a recent RCT of the long-term effects of RSV prevention with motavizumab in aboriginal American infants, despite those that received motavizumab ($n = 1417$) showing an 87% relative reduction in RSVH versus placebo ($n = 710$), there was no effect on rates of medically attended wheezing in children aged 1–-3 years [116]. This study is at odds with the other RCTs from the US and Netherlands [25, 26], as well as the observational studies in Europe, Canada, and Japan [23, 24, 118, 119]. It is possible that differences in genetic makeup, or family history of asthma, or the low rates of recurrent wheezing in the aboriginal American populations studied may have accounted for the differences in outcome [120]. Another major difference is that the motavizumab trial involved both term and preterm infants [116], whereas the other studies involved only preterm infants [25, 26]. The 6-year follow-up study of the Dutch MAKI trial will shed light on the association in preterm infants.

Treatment of RSV LRTI

There are very limited treatment options available for RSV infection in children. Ribavirin was approved in 1986 for aerosol treatment of RSV infection in infants and children in the United States; however, it is infrequently prescribed and mainly limited to immunocompromised infants. Ribavirin has been shown in one study to reduce the incidence of airway reactivity in previously healthy children if given early [121, 122], though not in another study [123]. It has also been shown to reduce the risk of progression from URTI to LRTI and all-cause mortality in RSV-positive allo-hematopoietic stem

cell transplantation (HSCT) patients ranging from 3 to 70 years of age [124]. Ribavirin has been tested in combination with RSV-IGIV and palivizumab with generally positive results [17, 125, 126]. However, convincing data supporting its use as a treatment for children with RSV are lacking, and toxicity is a concern [123, 127–136]. Furthermore, multivariate analyses demonstrated that ribavirin treatment was associated with an increase in duration of hospital stay [128, 137]. Based on available data, ribavirin is not recommended in the current AAP guidelines on the diagnosis, management and prevention of bronchiolitis [104].

Future Approaches

Advances in RSV Vaccine Development

Considering that the vast majority (> 70%) of RSVHs are in children with no underlying medical conditions [3], there remains a significant unmet need for efficacious and cost-effective preventive interventions against RSV [138]. Over the last 60 years, intense research has focused on understanding the pathogenesis of RSV infections and immunity to this infectious virus [139]. The first attempt to produce an RSV vaccine was made in the 1960s, but the formalin-inactivated, alum-precipitated RSV vaccine failed to protect children when they were naturally infected with RSV, and resulted in severe consequences in the vaccinated children that has influenced subsequent investigations in this area to the present day [140]. Numerous vaccine candidates have been developed using a broad range of approaches in the attempt to induce a safe and efficacious immune response [141].

There are currently approximately 28 RSV vaccines and antibodies in preclinical development and another 17 in clinical development (Fig. 2) [142, 143]. RSV vaccine development is a high priority in global healthcare. Whilst no RSV vaccine has been licensed to date, the WHO estimates that RSV vaccination will be available in the next 5–10 years [30].

Target Populations for RSV Vaccines

There are three potential target populations for RSV vaccines when considering RSV LRTI in pediatric populations, namely young infants (< 6 months of age), young children (> 6 months of age), and pregnant women [144]. Due to the salient differences between these target populations, vaccine safety and efficacy concerns, as well as vaccine strategies, should be different. Therefore, there are opportunities for more than one type of vaccine, and choosing the target population best suited for a given vaccine is critical to the vaccine candidates' chances for success [141].

Among the candidates in advanced clinical trials, nanoparticle and subunit vaccines are the most promising for pregnant women, whereas live-attenuated, vector-based and subunit vaccines are those that appear optimal for the pediatric population [142, 145]. Subunit vaccines consist of purified proteins, ultimately aiming to induce high-affinity, neutralizing antibodies, and to facilitate cross-priming. Subunit and particle-based vaccines are currently in phase 2 and phase 3 clinical trials, respectively (Fig. 2) [143].

Infants and Young Children There is general consensus that focus should be placed on infants in their first 6 months of life, when the risk of severe RSV-associated respiratory disease is highest [146]. However, young infants have protective maternal neutralizing antibodies that are known to suppress the development of serum and antibody responses [145]. Additionally, researchers are cautious in conducting RSV vaccine studies in young infants due to the experiences with the formalin-inactivated-RSV vaccine in the 1960s [145]. The severe lung inflammation, worsened disease, and deaths that occurred with some early vaccines raised concerns that other non-replicating RSV vaccines might also predispose infants and RSV-naïve children to aberrant immune responses [146]. Children aged ≥ 6 months are RSV-naive in most cases and are therefore very similar to young infants; however, they have a more mature immune system, conditioning a reduced susceptibility to RSV complications, and lower levels of maternal antibodies [145].

A number of live-attenuated vaccines have been in phase 1 trials in both RSV seropositive and seronegative infants and children. The

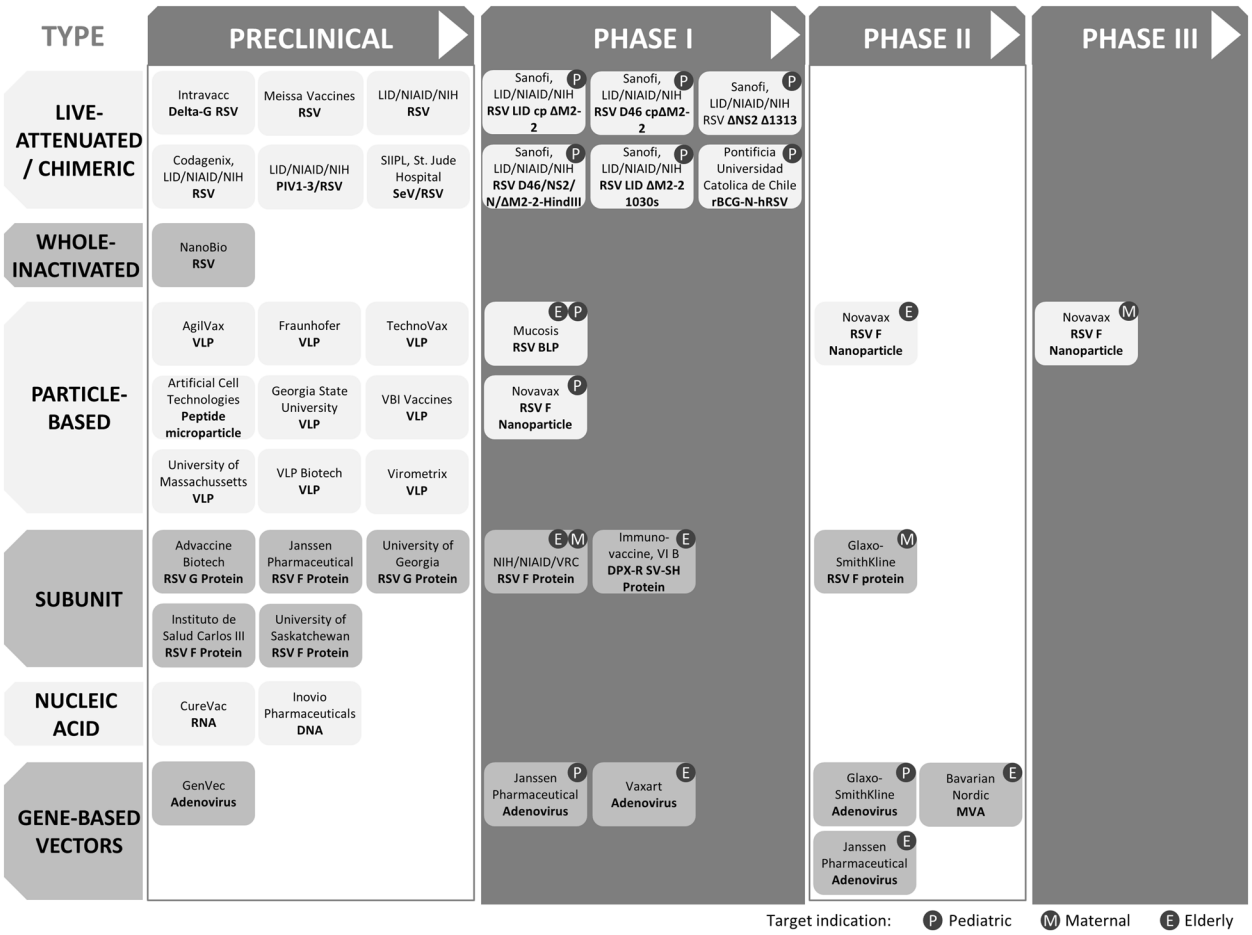

Fig. 2 A snapshot of vaccines to prevent RSVH in preclinical and clinical development worldwide. Adapted from the PATH (formerly the Program for Appropriate Technology in Health) [143]

NIAID are currently investigating the following vaccines in infants and children 6–59 months of age: RSV LID ΔM2-2 1030 s (NCT02952339, NCT02794870) [147, 148]; RSV LID cp ΔM2-2 (NCT02948127, NCT02890381) [149, 150]; RSV D46/NS2/N/ΔM2-2-HindIII (NCT03099291, NCT03102034) [151, 152]; RSV ΔNS2/Δ1313/I1314L (NCT03227029, NCT01893554) [153, 154]; RSV D46cpΔM2-2 (NCT02601612) [155]; and RSV 276 (NCT03227029) [153]. Several studies have been completed [148, 150, 156–160], though few results have been formally published [161]. Advantages of a live-attenuated vaccine approach include that there is little risk of inducing enhanced disease with a subsequent RSV infection, they can be delivered intranasally, they can replicate in the presence of maternal antibodies, and they can broadly stimulate innate, humoral and cellular immunity [142]. Conversely, finding the right balance between safety and immunogenicity, the risk of reversion to wild-type, and producing a stable vaccine virus for mass production are key challenges with this approach [142]. The most promising candidate appears to be RSV LID ΔM2-2 [161].

Vector-based approaches have the advantages of avoiding concerns about the level of attenuation of a live-attenuated virus vaccine and the risk of enhanced disease with the subunit approach, while also reducing the likelihood that maternal antibodies would inhibit an immune response in young infants [142]. A chimpanzee-derived adenovirus vector, GSK3389245A (also known as ChAd155-RSV), is currently being investigated in a phase 2 study

in RSV seropositive infants aged 12–23 months (NCT02927873) [162]. The study is currently recruiting participants [162]. A key challenge to overcome with the vector-based approach is the potential for the development of anti-vector immunity that might limit immune responses to subsequent immunizations [142].

Pregnant Women Maternal immunization could be the best strategy to protect infants during their period of greatest vulnerability to RSV infection and severe disease [145]. Maternal immunization avoids the challenges of direct neonatal immunization at a time when the neonatal immune system shows impaired antibody affinity maturation and less efficient antigen presentation [163]. The aim of vaccinating in pregnancy (in the second or third trimester) is to boost the maternal RSV antibody level available for transplacental transfer above the risk threshold of severe disease and to maintain this putatively protective level for longer—ideally more than at least the first 3 months of life [163]. Indeed, one of the challenges to maternal vaccination is the timing: depending on the time of year in which a third trimester vaccination occurs there is a risk that any conferred immunity may not last throughout the infant's first RSV season [142]. It is expected that passive immunization continues during the breastfeeding period, protecting the infant from early and recurrent infections [164]. However, any vaccine administered to pregnant women will need to meet high tolerability and safety standards [165].

The safety and immunogenicity of a recombinant RSV fusion (F) protein nanoparticle vaccine has been evaluated in healthy adults aged 18–48 years and women of childbearing age. The vaccine, designed for use in the third trimester, appears safe, immunogenic, and reduced RSV infections [166, 167]. A phase 2 study showed that the vaccine reduced RSV infections by 52% over a 90-day period in healthy non-pregnant women aged between 18 and 35 years [168]. Phase 3 testing in healthy pregnant women in the third trimester is currently ongoing, with their infants evaluated for RSV LRTI with hypoxemia through the first 90 days of life [169]. Recruitment began in December 2015, and the study is estimated to be completed in June 2020 (NCT02624947) [169].

A RSV prefusion (F) protein vaccine, GSK3003891A, has recently completed phase 2 testing in healthy women (NCT02753413) [170], although plans for a phase 2 study in pregnant women and infants born to vaccinated mothers have been withdrawn (NCT03191383) [171]. The reason cited for cancelling the study was due to instability of the prefusion (F) antigen during manufacturing. No safety concerns were identified in past or ongoing studies [171]. The NIAID Vaccine Research Center, which first uncovered the crystal structure of the RSV prefusion F protein, has designed a stabilized RSV prefusion F protein vaccine (DS-Cav1) that is stabilized as a trimeric subunit vaccine. DS-Cav1 is currently being evaluated in healthy adults (NCT03049488) [172]. DS-Cav1 is a very promising candidate vaccine for maternal immunization.

Other Vaccine Candidates

Other promising vaccine candidates, which have been assessed in phase 1 studies in older adults, include: Ad26.RSV.FA2, a stabilized prefusion F protein expressed in a replication incompetent serotype 26 adenovirus vector (NCT02561871, NCT02440035) [173–175]; and a universal RSV vaccine designed to induce protective immune responses against both subtypes A and B, MVA-BN-RSV, a recombinant modified Vaccinia Ankara vector encoding for the F, GA/GB, N and M2 proteins (NCT02419391, NCT02873286) [176, 177]. Whether these vaccine candidates move successfully through the licensing pathway into pregnant women or children remains to be seen.

Finally, it remains to be established if a combined strategy of maternal and infant immunization will need to be deployed to reduce morbidity and mortality from RSV disease globally [163].

Advances in Prophylaxis

Antibodies Prophylaxis remains a key strategy to prevent RSV LRTI, and there have been

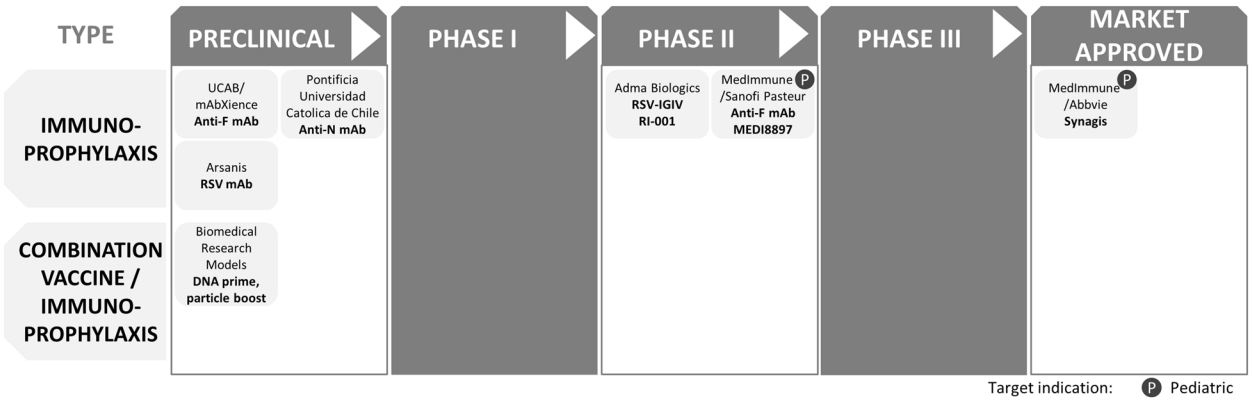

Fig. 3 A snapshot of monoclonal antibodies to prevent RSVH in preclinical and clinical development worldwide. Adapted from the PATH (formerly the Program for Appropriate Technology in Health) [143]

continuous efforts at identifying compounds that could effectively decrease hospitalization rates and disease severity [145, 178]. The previous success of monoclonal antibodies, such as palivizumab, has promoted research into new monoclonal RSV therapies with improved capacity to block the fusion (F) protein (Fig. 3) [142, 143, 178]. Two of the most promising candidates are described below.

MEDI8897 This investigational, recombinant, human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that targets the prefusion conformation of the RSV F protein is under clinical development for the prevention of RSV LRTI in infants [179]. MEDI8897 provides a potential opportunity to protect all infants from RSV disease, irrespective of comorbidities, based on an increased potency and extended half-life that supports once-per-RSV season dosing [179, 180]. It has received fast-track designation for continuing assessment by the FDA.

A phase 1, first-in-human, placebo-controlled study evaluated the pharmacokinetics and safety profile of MEDI8897 in 136 healthy adults as a prelude to a clinical study in infants [179]. Patients were randomized to receive a single dose of MEDI8897 ($n = 102$) or placebo ($n = 34$) in 1 of 5 cohorts (300, 1000, or 3000 mg IV or 100 or 300 mg IM) and were followed for 360 days. The mean half-life of MEDI8897 was 85–117 days across dose groups, and bioavailability after 300-mg IM dose administration was 77%. Time to maximum concentration following IM dosing was 5–-9 days. Antidrug antibody responses were detected in a similar proportion of placebo (15.2%) and MEDI8897 (13.7%) recipients. The safety profile of MEDI8897 was similar to placebo. These preliminary results support clinical studies of the IM administration of a single dose of MEDI8897 in the target population of infants to provide protection for the duration of the RSV season [179]. Based upon analysis of interim data from the phase 1 study, a separate phase 2b clinical study is currently assessing MEDI8897 in healthy preterm infants who are between 29 and 35 wGA and entering their first RSV season (NCT02878330) [181]. It is expected that results of the trial will be available in 2018.

RI-001 A phase 2 study is evaluating the safety and efficacy of RI-001, an RSV-IGIV, for the prevention of LRTIs in pediatric immunocompromised patients identified as being infected with RSV in the upper respiratory tract (NCT00632463) [182]. Administration of RI-001 on a compassionate use basis to 15 immunocompromised patients (aged 2 months to 71 years; four ≤ 2 years) with RSV LRTI, who had either failed conventional therapy or had significant risk of progression, was shown to be well tolerated and to result in significant increases in serum-neutralizing antibody titers to RSV [183]. Eleven of the 15 patients (73.3%) improved following treatment and were discharged from hospital [183].

REGN2222 Another monoclonal antibody directed against the RSV F protein, which was in phase 3 development, suptavumab (REGN2222), recently failed to meet its primary endpoint of preventing medically-attended RSV infections in preterm (< 36 wGA) infants ≤ 6 months and has been discontinued from clinical development [184]. The double-blind, placebo-controlled global Phase 3 NURSERY study randomized 1149 healthy pre-term infants to one of three study groups in a 1:1:1 ratio: suptavumab 30 mg/kg as a single dose; suptavumab 30 mg/kg administered as two doses 8 weeks apart; or placebo [184, 185]. The primary endpoint was defined as requiring hospitalization and/or sought medical care for a centrally-adjudicated RSV infection assessed at Day 150. To date, no data from the study have been presented.

TRL3D3 Prior to this anti-G protein antibody, all previous monoclonal antibodies were directed against the F protein. In animal models, TLR3D3 demonstrated a hundredfold greater efficacy than palivizumab in ameliorating airway inflammation, despite being a non-neutralizing antibody [186]. It is possible that this anti-G antibody could be used as a potential treatment of RSV.

Therapeutic Drugs to Treat RSV Infection

Several drugs have been identified for treating RSV infection, either by preventing the entry of the virus into target cells or by preventing replication or assembly of viral particles. A number of these molecules are currently in (advanced) preclinical or clinical development (Table 5) [187]. Recent efforts to develop RSV antiviral drugs have focused primarily on fusion inhibitors or virus gene silencing [144]. So far, several small-molecule RSV entry inhibitors targeting the F protein have been identified [187]. Encouraging results from a number of clinical studies undertaken in the last 5 years [188–191] have increased optimism that a clinically effective antiviral therapy targeted at high-risk groups may be on the horizon and could become available for clinical use within a few years [192, 193].

Table 5 Drug candidates for treating RSV disease [187, 215]

Fusion inhibitors	**GS-5806, MDT-637 (VP-14637); JNJ-2408068 (R-170591); TMC353121; BMS-433771; BTA-C585; P13 and C15; JNJ-53718678; AK-0529; RFI-641**
Single domain, trivalent antibody fragment derived from *Camelidae* (Nanobody)	ALX-0171
L ("large")-protein inhibitors	JNJ-64041575[a]; BI-D; AZ-27
N-protein targeting RSV inhibitor	RSV604
Other potential targets include: N-P protein–protein interaction; SH-protein; M2-1 protein	

[a] Alternative names: ALS-008176; ALS-8176; AL 8176; JNJ-1575

One of the most promising candidates is ALX-0171, an inhaled trimeric Nanobody that binds to the RSV F protein, which has shown positive results in a phase 1/2a study in children hospitalized with RSV infection (NCT02309320) [194, 195]. In this study, 53 children, aged 1–-24 months, were administered ALX-0171 or placebo once per day for 3 consecutive days [196]. No treatment-related serious adverse events were reported (primary endpoint), and ALX-0171 was show to have a rapid effect on viral replication (decrease vs. placebo seen after first dose) [196]. This has led to the on-going phase 2b RESPIRE dose-ranging, efficacy study of ALX-0171 (NCT02979431) [197, 198]. In this randomized, double-blind, placebo-controlled, multicenter study, three different doses of inhaled ALX-0171, administered once daily for 3 consecutive days, will be assessed in approximately 180 infants (aged 1–24 months) hospitalized with RSV LRTI. The primary endpoint is to evaluate the anti-viral effect of treatment (time for viral load to drop below assay

quantification limit in nasal swabs specimens), with topline results expected in the second half of 2018 [197, 198].

GS-5806 (Presatovir), an inhibitor that blocks viral-envelope fusion with the host-cell membrane, was the first of the orally available drug candidates to complete a phase 2 clinical trial [188]. Among the 54 healthy adults infected with RSV, treatment with GS-5806 was shown to reduce the viral load ($P < 0.001$) and severity of symptom scores ($P = 0.005$) versus placebo [188]. Further phase 2 studies in hospitalized adult patients naturally infected with RSV (NCT02135614) [199], in lung transplant recipients with RSV infection (NCT02534350) [200], and in HSCT recipients with RSV infection (NCT02254408, NCT02254421) [201, 202] have all been completed with full publication of the results awaited. No studies in infants and children are currently ongoing.

Other fusion inhibitors in clinical trials include AK-0529, JNJ-53718678, and BTA-C585. AK-0529, which have been studied in healthy adults [203] and are currently recruiting for a phase 2 study in infants hospitalized with RSV infection (NCT02654171) [204]. A phase 2 study of JNJ-53718678 has been completed in healthy adult participants infected with RSV and showed a reduced viral load and disease severity and duration versus placebo [205]. A phase 1 study in RSVH infants, however, was suspended due to health authority feedback regarding drug formulation (NCT02593851) [206]. BTA-C585 has been investigated in phase 1 (NCT02558413, NCT02668367) [207, 208] and 2 (NCT02718937) [209] studies in healthy adult volunteers, though no data have yet been reported.

Another promising therapeutic candidate is the oral RSV replication inhibitor JNJ64041575 (lumicitabine). Results from a phase 2 RSV challenge study in adults ($n = 62$) have been reported, with the time to non-detectability on polymerase-chain-reaction assay ($P < 0.001$), the peak viral load ($P \leq 0.001$), the area under the curve (AUC) for symptom score ($P < 0.05$), and the AUC for mucus weight lower in all groups receiving JNJ64041575 than in the placebo group [210]. Ongoing studies include a phase 2 study in infants and children (28 days–36 months) hospitalized with RSV infection (NCT03333317) [211], a phase 2 study in adults hospitalized with RSV infection (NCT02935673) [212], and a phase 1 study in infants hospitalized with RSV infection (NCT02202356) [213]. A long-term follow-up of the phase 2 study in infants and children (NCT03333317) is planned to evaluate the subsequent impact of JNJ64041575 on the incidence of asthma and wheezing in these children (NCT03332459) [214].

Limitations

The most significant limitation is the lack of available therapies and interventions for RSV despite decades of research. While there is a strong body of evidence for palivizumab in the key indicated groups (preterm, CLD/BPD, CHD), more data in other high risk populations, such as those with Down syndrome or neurological disorders, would be welcome.

Key statements/findings	Level of evidence[a]
Palivizumab	
Currently, the only product licensed for prophylaxis against RSV	Level 1 studies: 5
Preterm infants < 35 wGA: 68% (range 64–100%) reduction in RSVH (absolute risk reduction: 0.2–14.7%)	Risk of bias[b]: low
	Quality[c]: high
Children with CLD/BPD: 65% (range 38–72%) reduction in RSVH (absolute risk reduction: 4.9–14.2%)	
Children with CHD: 53% (range 45–58%) reduction in RSVH (absolute risk reduction: 4.4–4.6%)	
Limited data in other comorbidities	
Significantly reduced subsequent wheezing episodes	Level 1 studies: 1
	Risk of bias[b]: low
	Quality[c]: high
Ribavirin	
Licensed for treatment of severe RSV infection	Level 1 studies: 4
Lack of evidence supporting its efficacy and concerns over toxicity	Risk of bias[b]: unclear
	Quality[c]: low
Strongest evidence in immunocompromised infants	
Future therapies	
There are currently around 28 RSV vaccines in preclinical development and WHO estimates the availability of an RSV vaccine within 5–10 years	N/A
Nanoparticle and subunit vaccines are the most promising for pregnant women, whereas live-attenuated, vector-based and subunit vaccines are optimal for the pediatric population	N/A
Several new antibodies targeting the RSV fusion (F) protein are showing promise (e.g. MEI8897) and entering phase 3 trials	N/A
Recent efforts to develop RSV antiviral drugs have focused primarily on fusion inhibitors or virus gene silencing; a number are in development and could become available for clinical use within a few years	N/A

Key statements/findings	Level of evidence[a]
Key areas for research	
1. Currently approved therapies	
More up-to-date research and published, prospective RCTs are needed to determine:	
The effectiveness of palivizumab in reducing RSVH and improving outcomes in children with underlying medical conditions, such as Down syndrome, cystic fibrosis, congenital airway anomalies, immunocompromising or neuromuscular disease	
The ultimate impact of palivizumab on longer-term sequelae, such as recurrent wheezing	
2. Future therapies for prevention and treatment	
Continued research is needed on:	
Receptive strategies, such as pre- versus post-natal prophylaxis	
Establishing whether there is a causal link between RSV infection and asthma, possibly via a follow-on to a phase 3 vaccine or prophylaxis trial	
The optimal timing of therapy with antiviral drugs	
Whether the combination of antiviral drugs and immunomodulatory therapies might improve outcomes, as suggested by Prince et al. [216]	

N/A not applicable, *RSVH* respiratory syncytial virus hospitalization, *RCT* randomized controlled trial

[a] CEBM) Levels of Evidence [31, 32] where Level 1 = RCTs

[b] Cochrane risk of bias assessment [34], where low = average of 5/7 domains assessed as low risk of bias, high = average of 5/7 domains assessed as high risk of bias, and unclear for scores inbetween (see online supplementary material for full breakdown)

[c] Average Jadad score [33], where ≥ 3 = high quality (see online supplementary material for full breakdown)

CONCLUSION

Since the failure of early vaccines and the risk of adverse events associated with IGIV immunotherapy, passive immunity with palivizumab has been the mainstay of RSV prophylaxis. The available evidence supports the effectiveness and safety of palivizumab, particularly in high-risk groups, such as preterm infants and those with BPD/CLD and CHD. More evidence is required for palivizumab in certain high-risk populations, such as those with cystic fibrosis, and there remains an unmet need when considering that the majority of RSVHs occur in children born at term without comorbidities.

Prenatal maternal immunization is a potential avenue for infant prophylaxis against RSV, but progress on this will be slowed by the stringent safety standards necessary for any drug aimed toward pregnant women. Likewise, development of new preventive therapies aimed at infants will require rigorous evaluation. That said, there are several promising vaccines and monoclonal antibody compounds in early-stage testing and it is anticipated that new, effective therapies will become available in the next 5 years or so. It is hoped that these new therapies and ongoing research will result in a reduced burden of disease for what currently remains one of the leading causes of childhood hospitalization worldwide.

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