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REVIEW

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Twenty-five years of palivizumab: a global historic review of its impact on the burden of respiratory syncytial virus disease in children

Xavier Carbonell-Estrany[a], Eric A.F. Simões[b,c], Louis Bont[d,e], Paolo Manzoni[f,g], Heather J. Zar[h,i], Anne Greenough[j], Octavio Ramilo[k], Renato Stein[l], Barbara Law[m], Asuncion Mejias[k], Manuel Sanchez Luna[n], Paul A. Checchia[o], Leonard Krilov[p], Marcello Lanari[q], Ron Dagan[r], Brigitte Fauroux[s], Bernhard Resch[t], Terho Heikkinen[u], Joseph B. Domachowske[v], Joanne G. Wildenbeest[w], Federico Martinon-Torres[x,y], Richard Thwaites[z], Merih Cetinkaya[aa], Adel S. Alharbi[bb], Carlos E. Rodriguez-Martinez[cc], Daniel E. Noyola[dd], Asiah Kassim[ee], Satoshi Kusuda[ff], Ji-Man Kang[gg,hh], Barry Rodgers-Gray[ii], Anna Platonova[jj], Fungwe Jah[kk] and Bosco Paes[ll]

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ABSTRACT

Introduction: Respiratory syncytial virus (RSV) causes significant morbidity and mortality in young children. For 25 years, palivizumab has been the only effective pharmaceutical RSV preventive.

Areas covered: We summarize the development and a quarter-century of real-world evidence with palivizumab. We highlight its positive impact on the burden of RSV in high-risk children. Based on lessons learnt from its implementation, we suggest strategies for effective and equitable deployment of newer RSV preventives.

Expert opinion: Following failure of the formalin-inactivated RSV vaccine in 1967, RSV intravenous immunoglobulin was approved in 1996 after three decades' research. Subsequently, palivizumab emerged as the most effective and safe RSV preventive, demonstrated by the IMpact trial, and was licensed in 1998 in the United States. Over the last 25 years, the benefits of palivizumab have been firmly established through a wealth of evidence, predominantly from high-income countries (HICs). To achieve a global impact with the newer RSV preventives, evidenced-based universal guidelines must be developed and endorsed by regulatory authorities and relevant scientific societies. Independent economic evaluations should incorporate all RSV-associated healthcare costs, reduction of long-term respiratory sequelae, and standardized outcomes. Most importantly, equity in product availability and implementation, particularly in low- and middle-income countries (LMICs) is essential.

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Article highlights

- Respiratory syncytial virus (RSV) is a major cause of morbidity and mortality in young children. Its global annual burden for children aged <5 years is 33 million lower respiratory tract infections (LRTI), 3.6 million hospital admissions (RSVH), and > 100,000 deaths.
- After 40 years of research since the discovery of RSV, palivizumab became the first RSV preventive to be safely and effectively implemented. Over the past 25 years, palivizumab has been the standard for RSV prevention for high-risk young children in high-income countries (HICs).
- Palivizumab still has a potential intermediary role to play in HICs and, possibly, upper middle-income countries as we transition to the new era of RSV prevention with the next generation of long-acting antibodies and maternal and infant vaccines.
- It is imperative that we build upon the success story of palivizumab in HICs and ensure that the deployment of the new RSV preventives is equitable and that low- and middle-income countries (LMICs), where the overwhelming burden of RSV resides (95% of RSV-LRTI episodes and 97% of RSV-attributable deaths), truly benefit from the approved interventions.

1. Introduction

Respiratory syncytial virus (RSV) is a leading cause of morbidity and mortality in young children. In children aged <5 years, annual global estimates indicate the virus is responsible for 33 million lower respiratory tract infections (LRTI), 3.6 million hospital admissions (RSVH), and over 100,000 deaths [1]. Whilst over 95% of RSV-LRTI episodes and 97% of RSV-attributable deaths occur in low- and middle-income countries (LMICs), there are particular population groups in all geographic locales at higher risk of severe RSV-LRTI [1,2]. Approximately 25% of all RSVHs are due to the increased susceptibility among preterm infants (<37 weeks' gestational age [wGA]). This increased susceptibility is likely owing to their smaller airways, immature immune system and reduced maternal antibody transfer at birth [3]. Compared to those without underlying medical conditions, children with congenital heart disease (CHD) and bronchopulmonary dysplasia/chronic lung disease (BPD/CLD), as well as other special populations, such as those with Down syndrome, are up to three times more likely to experience RSVH associated with longer hospital stay, supplemental oxygen administration, mechanical ventilation or intensive care unit (ICU) admission [3]. The substantial burden of RSV infection is compounded by the lack of effective treatment, resulting in disease management limited to supportive therapies. Therefore, RSV prevention remains the preeminent strategy to reduce the significant burden of illness and associated healthcare costs.

There have been several important advances in RSV prevention over the last 2–3 years [4–6]. In particular the approval of an efficacious, long-acting anti-RSV prefusion F (pre-F, site 0) monoclonal antibody (LAmAb; nirsevimab) in 2022 as well as a maternal bivalent RSV pre-F vaccine in 2023 [5,6]. Over 30 other RSV preventives are in clinical development using six different approaches: recombinant vector, subunit, particle-based, live attenuated, chimeric, and nucleic acid vaccines; and monoclonal antibodies [4,6]. Prior to these advances, for nearly 25 years there was only one safe and effective licensed option to prevent severe RSV-LRTI in high-risk groups – the anti-RSV pre- and post-F (site II) monoclonal antibody, palivizumab (Synagis®) [7]. Palivizumab provided an important proof-of-concept that a serum anti-RSV F monoclonal antibody could protect against severe RSV disease, and its usage in several high-risk groups of children has improved outcomes. The main challenges with palivizumab have been its restriction to high-risk children, when the majority of the burden resides in infants born at term without comorbidities, and the limited availability of the product in LMICs [1,2]. As the transition is made to newer RSV preventives, palivizumab can continue to provide interim benefits as progress is made toward finally overcoming the devastating clinical and economic burden of RSV disease for all children.

This article first provides a historical summary of the search for and development of an effective biological product to combat RSV infection. It then recounts the pivotal role palivizumab played in protecting high-risk infants and children over the last quarter century, particularly in high-income countries (HICs). In addition, we provide an expert view of its ongoing importance in the field of RSV prevention while awaiting the integration of new preventives in HICs. We also discuss the critical lessons learnt from our collective experience that will ensure a more effective and equitable deployment of the new interventions in LMICs.

2. The dark years prior to palivizumab – searching for the answer

RSV, first identified in 1956, is a single-stranded negative-sense RNA virus comprising 15,200 nucleotides encoding 11 proteins (9 structural, 2 non-structural) (Figures 1 and 2) [8,9]. Soon after discovery, RSV was widely recognized as a major cause of LRTI worldwide, particularly in young infants aged <6 months [10]. In temperate climates, RSV disseminated extensively every year following a temporal pattern with peaks during the winter months, which represented a serious and recurring threat to the pediatric population [10,11]. With almost a quarter of LRTI hospitalizations in young children between 1957 and 1961 associated with RSV, the development of an RSV vaccine became an immediate priority [10].

In 1966, predicated on the successful use of formalin-inactivation to produce vaccines for other virus such as polio and influenza, a formalin-inactivated RSV vaccine was evaluated [11]. After satisfactory safety results in animals and adult humans, clinical testing began in children and infants [11]. The RSV vaccine resulted in 43% of infants exhibiting a ≥ 4-fold rise in serum neutralizing antibody and 91% demonstrating a ≥ 4-fold rise in serum complement-fixing antibody [11,12]. However, the rate of RSV infection remained similar between RSV vaccinees and control infants receiving parainfluenza vaccines. Moreover, and of great concern, 80% of RSV vaccinees were hospitalized during an episode of RSV infection compared to only 5% of controls, and two deaths were reported [11]. Infants who received the formalin-inactivated RSV vaccine were not protected against natural infection, but in fact experienced an altered, enhanced clinical response to RSV infection. This phenomenon was characterized by a pathogenic Th2 memory response with eosinophil and immune complex deposition in the lungs after RSV infection [11,12].

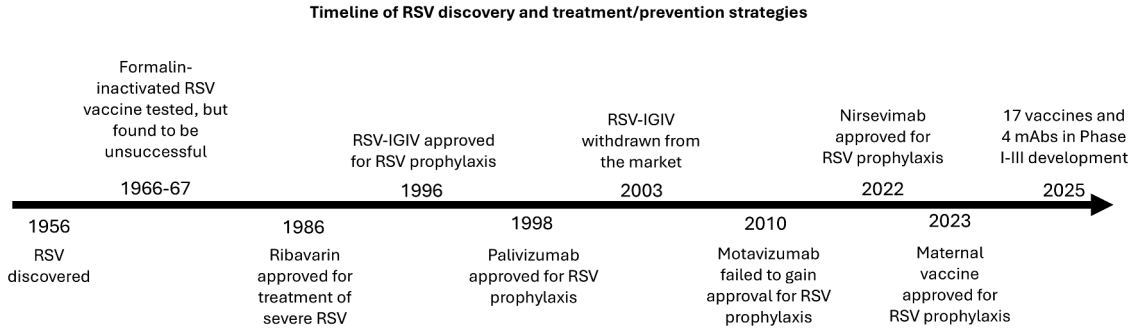

Figure 1. Timeline of RSV discovery and its treatment/prevention strategies.

BPD: bronchopulmonary dysplasia; IGIV: intravenous immunoglobulin; mAbs: monoclonal antibodies; RSV: respiratory syncytial virus; wGA: weeks' gestational age.

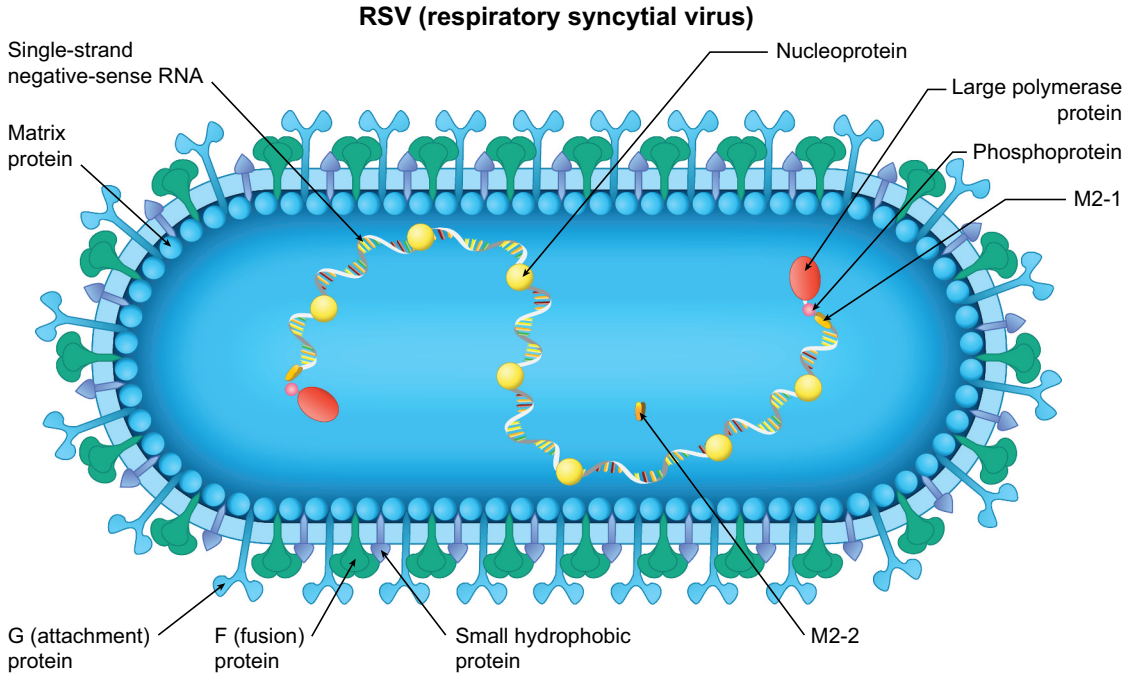

Figure 2. RSV virion structure.

RNA: Ribonucleic acid.

The failure of the inactivated vaccine precipitated the belief that only a live-attenuated vaccine would be safe for infants. Live-attenuated vaccines have several key advantages; a reduced likelihood of inducing enhanced disease with a subsequent RSV infection, replication in the presence of maternal antibodies, and stimulation of innate, humoral and cellular immunity, as well as intranasal administration [13]. However, over the succeeding years attempts to develop effective live vaccines containing attenuated RSV mutants proved unsuccessful. Mutants were under- or over-attenuated, genetically unstable, and did not prevent symptomatic infection [14]. Other approaches using purified RSV F glycoprotein and a chimeric FG molecule also failed due to low levels of neutralizing activity [14]. Moreover, standard polyclonal immunoglobulin preparations were not shown to prevent RSVH [15]. Development of a new vaccine, particularly for infants, poses several challenges [16,17]. First, the requirement for vaccination to occur in the presence of maternal antibodies which can produce an immunosuppressive effect and interfere with replication of live RSV vaccines. Second, the occurrence of repeated reinfections with different RSV subtypes following wild virus infection. Third, the paucity of suitable animal models reproducing human RSV infection to test vaccine efficacy in vivo [14–17]. Difficulties continue to persist with the United States Food and Drug Administration (FDA) pausing all pediatric RSV vaccine trials in December 2024 after a rise in severe RSV-related illnesses in the treatment arm of one study [18]. Conversely, maternal immunization avoids the difficulties of direct neonatal immunization at a time when the neonatal immune system displays impaired antibody affinity maturation and less efficient antigen presentation [19]. This approach has ultimately proved more successful with the first maternal bivalent RSV pre-F vaccine approved in 2023 [5].

In 1986, ribavirin, a broad-spectrum nucleoside analog that inhibits the replication of DNA and RNA viruses, was approved for aerosol treatment of severe RSV infection in infants and

children in the United States [20]. However, ribavirin was, and still is, infrequently prescribed due to toxicity concerns, administration difficulties particularly in ventilated patients, and high costs. It remains a therapeutic consideration in immunocompromised infants, where most benefits have been observed [21].

In 1991, an intravenous RSV enriched polyclonal hyperimmune globulin (RSV-IGIV), was developed using human plasma from healthy donors with high serum RSV-neutralizing antibody titers that brought the first real success to the decades of research [22,23]. Five monthly, parenteral doses of 750 mg/kg given throughout the RSV season proved safe and effective in high-risk (BPD, CHD and premature) infants and young children, demonstrated by significantly fewer LRTIs and RSVHs, along with a reduced length of hospital stay *versus* controls [22,23]. Later studies further supported RSV-IGIV use in prematurity and BPD with 41% reductions in RSVH [24]. However, they concluded RSV-IGIV should not be used in children with cyanotic CHD owing to a significant increase in unanticipated cyanotic episodes and poor outcomes post-surgery. This was deemed possibly due to infants with heart defects being particularly sensitive to volume load [25]. In 1996, RSV-IGIV prophylaxis was approved for use in children <24 months with BPD or birth at ≤ 35 wGA [26]. However, it required time-consuming monthly intravenous infusions. Moreover, being a blood product, it possessed variable neutralizing capacity due to batch-to-batch differences and posed a risk of transmission of blood-borne pathogens, albeit minimal due to modern viral inactivation production methods [15]. Mass production of RSV-IGIV also proved difficult and the therapy was expensive [27]. After 30 years of limited success in developing effective, safe, convenient and affordable RSV prevention strategies, a huge unmet need remained for all young children, especially those most vulnerable to severe RSV-LRTI.

3. Palivizumab – a new hope

In the 1990s, vaccine manufacturers began investigating monoclonal antibodies (mAb) against RSV in the hope of discovering an effective and safe method of prophylaxis that avoided the administration difficulties experienced with RSV-IVIG. Of the 9 structural proteins coded by the RSV RNA genome, the RSV G- and F-proteins, involved in viral recognition and entry into target cells, were recognized as major glycoprotein targets for neutralizing antibodies (Figure 2) [8,9,28]. In particular, antibody binding to the F-protein was found to prevent fusion of RSV with the cell membrane and to inhibit formation of syncytia in the epithelial cells of the respiratory tract, with a high degree of cross-reactivity among RSV subtypes A and B [28]. Several mAbs were developed and investigated [28–30]; however, palivizumab was the only one with a successful program and became the first mAb to be demonstrated effective against an infectious disease [5,31].

Palivizumab, a humanized murine mAb directed to an epitope in antigenic site II of the RSV F-protein (pre- and post-fusion), was created by researchers at MedImmune Inc. (Gaithersburg, MD) over a 10-year period [28]. The initial step in developing palivizumab involved immunization of a mouse with RSV to trigger antibody production [31,32]. Antibody producing B cells were then isolated from the mouse spleen and fused with a mouse myeloma cell line [31]. The mAb with the strongest binding affinity against the F-protein was selected (mouse mAb 1129) and humanized by cloning and sequencing the mAb DNA [31]. The complementarity-determining-region-sequences were identified and incorporated into human immunoglobulin (Ig) genes, resulting in a mAb that was 95% comparable to any other human antibody, with only 5% of its DNA relating to mice [31]. Essentially, a humanized IgG molecule with high-affinity binding for RSV F-protein and high efficacy in neutralizing RSV was created [31].

In vitro testing found the affinity of palivizumab was comparable to or marginally better than an isotype-matched chimeric derivative of the parent antibody [28]. It demonstrated broad and potent neutralization of RSV strains A and B (57 isolates consisting of 34 A and 23 B) in a dose-dependent manner. Notably, potency was enhanced 20- to 30-fold with palivizumab compared with RSV-IGIV [28]. *In vivo* testing using the cotton rat model, found palivizumab reduced RSV replication by >99% at a dose of 2.5 mg/kg (equivalent to a serum concentration of 25–30 mg/mL) and did not induce increased RSV primary or secondary infection [28].

In 1998, palivizumab became the first licensed mAb after approval by the FDA in the USA for RSV prophylaxis of high-risk children [33]. Approval within Europe by the European Agency for the Evaluation of Medicinal Products (EMEA; now known as the European Medicines Agency) quickly followed in 1999 and by 2003 over 45 countries worldwide had approved palivizumab [34,35]. Palivizumab is licensed for the prevention of severe RSV in high-risk infants, namely those born preterm (≤35 wGA) or with BPD/CLD or CHD [34]. Exact recommendations vary between countries and have been regularly updated, particularly in relation to use in special populations, such as Down syndrome and those with neurological conditions, and moderate-to-late preterm infants (Table 1) [36–44]. It should be noted that updates of the RSV preventive guidelines in international position and consensus statements were in part influenced by ongoing cost–benefit considerations as well as the scientific and clinical evidence. Independent risk factors for RSVH in young children and specifically in moderate-to-late preterm infants have been identified, and include proximity of birth to the RSV season, tobacco smoke exposure, siblings and/or daycare [45,46]. Risk scoring tools (RSTs) have subsequently been developed to predict RSVH risk and enable RSV prophylaxis to be recommended and utilized cost-effectively in the most vulnerable infants [46].

The recommended dose of palivizumab is 15 mg/kg of body weight, administered by intramuscular (IM) injection each month during the RSV season [34]. Ideally, the first dose should be given prior to the onset of the RSV season [34]. Globally, RSV epidemics typically travel from the south to the north, starting between March and June in most Southern Hemisphere countries and between September and December in Northern Hemisphere countries. In most countries across both hemispheres, the RSV season lasts approximately 5–6 months, although in countries with humid or rainy seasons, such as those near the equator, the RSV season tends to be

Table 1. A comparison of international guidelines on palivizumab from selected HIC and LMICs.

Patient group	2020 expert consensus for HICs [36]	USA [37,38]	Spain [40,41]	South africa [42]	Argentina [43]	South korea [44]
Preterm infants without other comorbidities	• ≤28^{6} wGA and ≤9 months at the start of the RSV season • 29° to 31^{6} wGA and ≤6 months at the start of the RSV season • 32° to 35^{6} wGA and high-risk (score: 50–56) using a country-specific or generalizable RST	• <29 wGA and <12 months at the start of the RSV season • Not recommended for infants born ≥ 29 wGA	• ≤28^{6} wGA and ≤9 months at the start of the RSV season • 29° to 31^{6} wGA and ≤6 months at the start of the RSV season • 32° to 34^{6} wGA if <10 weeks at the start of the season and with ≥ 1 sibling attending school or nursery school	• <36 wGA and <6 months of age at the start of the RSV season	• <29 wGA, <1000 g and ≤12 months at the start of the RSV season • <32 wGA, <1500 g and ≤6 months at the start of the RSV season • 32 to 34^{6} wGA if <10 weeks of age at the start of the RSV season with 2 additional risk factors: attendance at daycare, zero breast-feeding, siblings or school-age cohabitants	• <32 wGA and ≤6 months of age at the start of the RSV season • <36 wGA and born during the RSV season
Children with CLD/BPD	• Infants ≤12 months at the start of the RSV season • During the second year of life in children who remain at high-risk *(BPD/CLD and those at high-risk in the second year of life to be defined according to local experience and practice)*	• May be considered during the RSV season during the 1st year of life in infants with CLD of prematurity defined < 32° wGA and a requirement for > 21% oxygen for at least the first 28 days after birth • Prophylaxis during the 2nd year is only recommended in the above-mentioned infants if they continue to require medical support (chronic corticosteroid therapy, diuretic therapy, or supplemental oxygen) during the 6-month period before the start of the 2nd RSV season	• Infants ≤12 months at the start of the RSV season • During the second year of life in children with a persistent need of medical treatment or in whom it is considered appropriate due to the high risk of the patient based on clinical condition	• Children <24 months of age at the start of the RSV season	• Infants ≤12 months at the start of the RSV season • During the second year of life in children who have required treatment (oxygen supplementation, bronchodilators, diuretics) within 6 months of the start of RSV season or who are discharged during RSV	• Children <24 months of age who required treatment for BPD within the 6 months prior to the onset of RSV season
Children with CHD	• Infants ≤12 months with hemodynamically significant cyanotic or acyanotic disease • Children 12–24 months, cyanotic or acyanotic, who remain hemodynamically unstable	• Certain children who are <12 months with HS-CHD may benefit • Children most likely to benefit include infants with acyanotic heart disease who receive medications for congestive heart failure and will require cardiac surgical procedures, and infants with moderate-to-severe pulmonary hypertension	• Infants ≤12 months with HS-CHD • During the second year of life in children with persistent hemodynamic disturbance	• Children <24 months of age at the start of the RSV season with HS-CHD	• Infants <12 months with CCHS, cardiomyopathies, at start of the RSV season • Children <24 months with CHD on the heart transplant list or who have received a heart transplant during the RSV season	• Children <24 months of age with HS-CHD who meet one of the following criteria: • Currently receiving medication therapy to manage congestive heart failure • Having moderate to severe pulmonary hypertension • Having cyanotic heart disease
Down syndrome	• Children ≤24 months	• Not recommended in children with Down syndrome unless qualifying CHD, CLD, airway clearance issues, or prematurity	–	–	• Only consider in children with Down syndrome if they have comorbidities such as CHD or prematurity	–

(*Continued*)

Table 1. (Continued).

Patient group	2020 expert consensus for HICs [36]	USA [37,38]	Spain [40,41]	South africa [42]	Argentina [43]	South korea [44]
Cystic Fibrosis	• Infants ≤ 12 months • Children in the second year of life with manifestations of severe lung disease or weight < 10th percentile	• Infants with cystic fibrosis with clinical evidence of CLD and/or nutritional compromise in the 1st year of life may be considered for prophylaxis • Consider continued prophylaxis during the second year in infants with manifestations of severe lung disease or weight for length less than the 10th percentile	–	–	• Children <24 months with cystic fibrosis should be evaluated individually by a specialist	–
Anatomic pulmonary abnormalities or neuromuscular disorder	• Children ≤24 months with significant neuromuscular disease or congenital anomalies that compromises the respiratory tract (*e.g.* hypotonia, cerebral palsy, chronic interstitial pulmonary disease, airway and pulmonary malformations, tracheostomy)	• Infants with neuromuscular disease or congenital anomaly that impair the ability to clear secretions from the upper airway because of ineffective cough may be considered for prophylaxis during the 1st year of life	–	• May be considered in children with pulmonary neuromuscular disease	• Consider in children <24 months with severe neuromuscular diseases with high risk of respiratory failure or altered mechanism airway clearance; or in congenital diaphragmatic hernia with other associated risk factors (home oxygen, moderate-severe pulmonary hypertension) • Children with pulmonary malformations or interstitial lung disease should be evaluated by a specialist	–
Immunocompromised	• Children ≤24 months who are profoundly immunocompromised (*e.g.* primary immunodeficiency syndromes, immune suppression following hematopoietic stem cell transplantation, solid organ transplantation or cytotoxic chemotherapy)	• Consider for children <24 months who are profoundly immunocompromised during the RSV season	–	• Children ≤24 months with primary immunodeficiency • May be considered in other children with profound immunocompromise	• Consider for infants <12 months with severe combined immunodeficiencies	–
Dosing	• 15 mg/kg once a month to cover RSV season (maximum 5 doses) *(Children born during the season will require fewer doses)*	• 15 mg/kg once a month to cover RSV season (maximum 5 doses) *(Children born during the season will require fewer doses)*	• 15 mg/kg once a month to cover RSV season (maximum 5 doses) *(Children born during the season will require fewer doses)*	• 15 mg/kg once a month to cover RSV season (maximum 5 doses) *(Children born during the season will require fewer doses)*	• 15 mg/kg once a month to cover RSV season (maximum 5 doses) *(Children born during the season will require fewer doses)*	• 15 mg/kg once a month to cover RSV season (maximum 5 doses) *(Children born during the season will require fewer doses)*

BPD: bronchopulmonary dysplasia; CHD: congenital heart disease; CLD: chronic lung disease; HIC: high-income countries; HS-CHD: hemodynamically significant congenital heart disease; LMIC: low- and middle-income countries; RSV: respiratory syncytial virus; RSVH: respiratory syncytial virus hospitalization; wGA: weeks' gestational age.

prolonged (up to 10 months) or endemic [47]. Most evidence including the pivotal phase III clinical trials for palivizumab relates to five, monthly injections during one RSV season [34]. Although several abbreviated dosing regimens have been recommended to reduce cost [48], including by extending dosing intervals [49], full-season monthly dosing provides the only proven protection from RSVH [50,51]. In certain circumstances, for example, when infants are born late during the RSV season, they may receive less than five doses. Although more limited, data are available on greater than five doses and palivizumab is indicated for as long as the risk of RSV infection is prevalent [34]. The successful licensing and subsequent use of palivizumab resulted in RSV-IGIV being voluntarily withdrawn from the market in 2003 [52]. A second generation humanized monoclonal antibody, motavizumab, was subsequently derived from affinity maturation of palivizumab. However, in 2010, despite its enhanced RSV neutralizing activity over palivizumab, due to concerns over a lack of superior efficacy and increased hypersensitivity reactions relative to palivizumab, motavizumab was not approved by the FDA [52].

4. Palivizumab – a game changer

4.1. Efficacy in randomized controlled trials (RCTs)

The efficacy of palivizumab was first established in the pivotal registration trial, IMpact-RSV (Supplementary Appendix Table A1) [53]. During the 1996–97 RSV season, 1,502 children born prematurely (≤35 wGA) or with BPD in 139 centers across the USA, UK and Canada were randomized 2:1 to receive 5 IM doses of palivizumab (15 mg/kg) or placebo every 30 days [53]. Palivizumab prophylaxis resulted in a 55% reduction in RSVH (4.8% palivizumab *vs* 10.6% placebo, $p < 0.001$) in all children, 78% in premature children without BPD (1.8% *vs* 8.1%, $p < 0.001$), and 39% in those with BPD (7.9% *vs* 12.8%, $p = 0.038$) [53]. Sub-analysis of premature infants without BPD demonstrated that palivizumab reduced RSVH (64.5%–100%) in all 11 gestational age groups assessed, including substantial relative risk reductions for the moderate-to-late preterm infants (82% for both the 32–34 and 32–35 wGA groups) [54]. The latter results were supported by the Dutch multicenter MAKI trial [55]. In otherwise healthy 33–35 wGA infants treated with palivizumab compared with placebo, there was a lower incidence of RSVH and medically attended RSV-LRTI (0.9% *vs* 5.1%, $p = 0.01$ and 0.9% *vs* 4.7%, $p = 0.02$, respectively). In the IMpact-RSV trial, palivizumab prophylaxis also led to a significantly shorter duration of RSVH (36.4 days/100 children *vs* 62.6 placebo days/100 children, $p < 0.001$), fewer days with increased oxygen (30.3 days *vs* 50.6 days, $p < 0.001$) and a lower incidence of ICU admission (1.3% *vs* 3%, $p = 0.026$) [53]. *Post-hoc* analysis of the IMpact trial found that a higher serum palivizumab level was associated with decreased disease severity [56]. Specifically, palivizumab levels correlated with duration of RSVH and ICU stay, supplemental oxygen use and duration, as well as mechanical ventilation use and duration ($p < 0.05$) and was the only independent predictor of ICU admission ($p = 0.009$) [56]. Efficacy in CHD was demonstrated by a multicenter RCT conducted in North America and Europe enrolling 1,287 young children with hemodynamically significant CHD (HS-CHD) [57]. Compared with placebo, palivizumab led to a 45% reduction in RSVH (5.3% palivizumab *vs* 9.7% placebo, $p = 0.003$), a 56% reduction in total days of RSVH (57.4 *vs* 129.0 days/100 children, $p = 0.003$), and a 73% reduction in days with increased supplemental oxygen (27.9 *vs* 101.5 days/100 children, $p = 0.014$) [57].

Systematic reviews [7,58] of these pivotal RCTs [53,55,57] alongside further RCTs [59,60] that have been conducted on otherwise healthy premature infants have shown that, compared to placebo, palivizumab reduced RSVH by 55–56%, RSV-LRTI rate by 67–68%, supplemental oxygen use by 82%, and ICU admission by 50%. In the registrational trials for motavizumab, which was not licensed for use primarily due to safety concerns surrounding increased rates of non-fatal skin reactions, palivizumab prophylaxis resulted in a 1.9% RSVH rate in preterm infants (≤35 wGA) and those with BPD/CLD [61] and 2.6% in those with HS-CHD [62]. Most recently, a phase 1/2b randomized placebo-controlled trial found that daily intranasal palivizumab showed no efficacy in preventing RSV infection in healthy preterm infants (38.3% palivizumab *vs* 23.4% placebo, adjusted odds ratio [aOR] 2.2, 95% CI 0.7–6.5) [63], reinforcing the need for IM dosing.

4.2. Effectiveness in real-world studies

A wealth of real-world evidence demonstrating the effectiveness of palivizumab has been published over the last 25 years, primarily from HICs. The first came from 1,839 of the 56,000 infants who received palivizumab during the 1998–1999 RSV season following its approval in the USA [35,64]. Comparing favorably to the IMpact trial, the overall RSVH rate was 2.3% for all prophylaxed patients, 4.0% for those with BPD/CLD and 2.1% for premature patients without BPD/CLD [64]. Similarly, encouraging results were seen in future seasons of prophylaxis with overall RSVH rates declining from 2.9% in 2000 to 0.7% in 2004 (Table 3) [65–70]. Rates also decreased for all high-risk groups: <32 wGA (4.5% to 1.1%), 32–35 wGA (1.6% to 0.2%), BPD/CLD (5.6% to 1.8%), and CHD (4.3% to 1.5%) [68,69].

Further real-world data stems from other international registries [71–77], most notably the Canadian Registry of Synagis (CARESS) [78–83] and numerous observational studies [84–88]. The overall RSVH rate in the most recent published CARESS analysis spanning 12 seasons (2005–2017) and including over 25,000 children was 1.6% [83]; broadly similar to the majority of international registries (Table 2). Within CARESS, preterm infants had similarly low RSVH rates regardless of wGA and lower overall RSVH rates *versus* infants with BPD/CLD or CHD [78]. Moreover, for children with BPD/CLD and HS-CHD, RSVH rates were similar in the first and second year of life, suggesting palivizumab is both effective and necessary for the protection of infants up to 2 years of age [81,82].

In addition to data provided by registries, various observational studies have been conducted, particularly across Europe. In the Spanish FLIP-2 study, a prospective 2-cohort study enrolling premature infants born 32–35 wGA, palivizumab lowered the RSVH rate by 68.3% (1.3% *vs* 4.1% for no prophylaxis, $p <$

Table 2. A comparison of RSVH rates from major international registries for healthy term/preterm infants and those with CHD or BPD/CLD who received palivizumab.

Country	Registry	Years	Population	RSVH rate (%)
USA	Palivizumab outcomes registry -prospective, observational	1998–1999 [67]	All infants	2.3
			($n = 1,839$)	2.1
			Premature without BPD/CLD	4.0
			CLD	
		1999–2000 [67]	All infants	2.4
			($n = 2,830$)	1.3
			Healthy preterms	3.9
			CLD	
		2001–2002 [67]	All infants	1.5
			($n = 5,091$)	
		2000–2001 [66]	All infants	2.9
			($n = 2,116$)	
			(986 < 32 wGA; 957 32–35 wGA; 172 > 35 wGA)	
			Premature without CLD ($n = 1,616$)	2.1
			CLD ($n = 500$)	5.8
			CHD ($n = 102$)	4.3
		2000–2004 [68,69]	All infants ($n = 19,548$)	1.3
			<32 wGA ($n = 7,826$)	1.84
			32–35 wGA ($n = 9,317$)	0.83
			>35 wGA ($n = 2,400$)	1.13
			All CHD	1.9
			($n = 1,495$)	
			Acyanotic CHD ($n = 1,067$)	1.6
			Cyanotic CHD ($n = 428$)	2.6
Canada	Canadian Therapeutic Products Program -prospective, observational	1999–2000 [74]	All infants ($n = 480$)	2.4
			Premature ($n = 345$)	1.6
			CLD ($n = 40$)	6.0
	CARESS registry-prospective, observational	2005–2009 [78]	All infants ($n = 5,286$)	1.38
			Premature infants ($n = 3,741$)	1.12
			<28 wGA	1.34*
			29–32 wGA	1.25*
			33–35 wGA	0.2*
			CLD ($n = 449$)	1.31
			HS-CHD ($n = 508$)	1.99
		2006–2010 [79]	≤35 wGA ($n = 4,880$)	1.3
		2006–2011 [80]	≤32 wGA ($n = 5,183$)	1.5
			33–35 wGA ($n = 1,471$)	1.4
		2005–2015 [81,82]	CLD 1st year ($n = 847$)	2.3
			CLD 2nd year	3.9
			($n = 450$)	
			HS-CHD 1st year ($n = 1,380$)	2.3
			HS-CHD 2nd year	1.7
			($n = 529$)	
		2005–2017 [83]	All infants ($n = 25,003$)	1.6
			(15,821 premature;	
			2,103 BPD/CLD;	
			2,628 hS-CHD)	
Spain	Spanish registry (IRIS) – case-control	1998–2002 [73]	1583 untreated infants *vs* 1919 PVZ treated	Control 13.25 *vs* PVZ 3.95
France	French Drug agency -prospective, observational study	1999–2000 [75]	All infants ($n = 516$)	8.1
			(258 < 28 wGA;	
			182 29–32 wGA;	
			31 33–35 wGA;	
			28 > 35 wGA;	
			400 CLD)	
Germany	German registry – prospective, observational	2002–2007 [72]	All infants ($n = 10,686$)	2.5
			(6,967 < 33 wGA; 1,500 33–35 wGA; 481 > 35 wGA)	(worst-case scenario)
		2009–2016 [76]	All infants ($n = 13,802$)	1.2
			(9,981 < 35 wGA)	(worst-case scenario)

*$p = 0.395$.

BPD: bronchopulmonary dysplasia; CHD: congenital heart disease; CLD: chronic lung disease; HS-CHD: hemodynamically significant congenital heart disease; PVZ: palivizumab; RSVH: respiratory syncytial virus hospitalization; wGA: weeks' gestational age.

0.001) [84]. Palivizumab was shown to be an independent risk factor for preventing hospitalization (OR 0.25; 95% confidence interval [CI] 0.13–0.49) [84]. A 58.2% reduction in RSVH has also been reported in Spanish infants with CHD who received prophylaxis with palivizumab (3.3% *vs* 7.9% with no prophylaxis; $p < 0.01$) [85]. In Italian preterm infants (≤32 wGA), sixfold lower RSVH rates have been reported in the palivizumab recipients *versus* untreated infants ($p = 0.007$) [86].

Real-world evidence from LMICs is limited due to the systemic barriers these countries have faced in accessing the

Table 3. Cost-effectiveness for palivizumab *versus* no palivizumab.

Country	Population	Cost *per* QALY	WTP threshold
Canada [129] (HIC)	32–35wGA (moderate-high risk using IRST)	CAD 28,496 [EUR 19,016]	CAD 50,000 [EUR 33,367]
Colombia [129] (LMIC)	32–35wGA (moderate-high risk using IRST)	COP 44,791,775 [EUR 9,751]	COP 84,659,313 [EUR 18,431]
Italy [129] (HIC)	32–35wGA (moderate-high risk using IRST)	EUR 14,567	EUR 40,000
South Korea [129] (HIC)	32–35wGA (moderate-high risk using IRST)	KRW 28,437,702 [EUR 19,184]	KRW 41,655,203 [EUR 28,100]
Singapore [130] (HIC)	29–35 wGA (32–25 wGA moderate-high risk using IRST)	SGD 37,579 [EUR 26,018]	SGD 75,000 [EUR 51,926]
Malaysia [131] (LMIC)	29–31 wGA	MYR 43,523 [EUR 9,016]	MYR 44,143 [EUR 9,145]
Dominican Republic [132] (LMIC)	29–35 wGA (32–35 wGA moderate-high risk using IRST)	USD 21,487 [EUR 19,432]	USD 30,333 [EUR 27,432]
Mexico [133] (LMIC)	32–35 wGA using IRST	MEX 205,688 [EUR 9,379]	MEX 231,395 [EUR 10,551]

HIC: high-income country; IRST: International Risk Scoring Tool; LMIC: low- and middle-income country; QALY: quality-adjusted life year; wGA: weeks' gestational age; WTP: willingness-to-pay.

product, and costs related to the implementation of palivizumab. Low RSVH rates, similar to those observed in HICs, have been reported in small cohorts of children who have received palivizumab in LMICs. A multicenter observational study of 458 high-risk infants <35 wGA, and those with BPD and HS-CHD who received palivizumab across seven Latin American countries between 2011 and 2012 reported an RSVH rate of 2.9 *per* 100 patient-years [89]. A later study, focusing on Colombian infants <32 wGA, BPD and HS-CHD, supported the regional use of palivizumab, with an RSVH rate of 1.8% and a 1% reduction in mortality (palivizumab arm 0.2% *versus* overall mortality 1.2%) [90].

A 2024 global systematic review identified 55 observational studies/registries providing real-world evidence on the effectiveness of palivizumab in preventing severe RSV-LRTI in high-risk infants [87]. RSVH rates ranged from 0.7–4.0% in premature infants (16 studies), 0.0–5.5% for children with BPD/CLD (10 studies), and 2.1–12.2% for those with HS-CHD (four studies) [87]. Another review of real-world studies in moderate-to-late late preterm infants reported a fourfold reduction in RSVH rates with palivizumab (six studies) [88]. Overall, the real-world evidence is substantial, comparable to RCTs, and undeniably supports palivizumab as a highly effective RSV immunoprophylaxis in high-risk infants and young children both under stringent controlled conditions and in everyday practice.

4.3. Evidence in high-risk populations beyond CHD and BPD/CLD

Clinical evidence to support palivizumab use in high-risk populations with underlying conditions beyond CHD and BPD/CLD has continually grown as the use of prophylaxis in this group has expanded in HICs. For example, CARESS data from Canada reported an increase in palivizumab use from 4.4% in 2005–2006 to 22.5% in 2016–2017 in children with Down syndrome, airway anomalies, pulmonary disorders, cystic fibrosis, neurological impairments, immunocompromise, cardiac disease aged >2 years and other conditions [83]. Recently, a small multicenter phase II, open-label, clinical trial also demonstrated that in 23 children with pulmonary hypoplasia, airway stenosis, congenital esophageal atresia, inherited metabolic and neuromuscular disease, palivizumab was well tolerated and potentially effective in the prevention of serious respiratory symptoms and RSVH [91].

4.3.1. Down syndrome

Down syndrome is a significant, independent risk factor for RSVH increasing the risk by between three- and sevenfold [45,92]. Three meta-analyses confirmed that following RSVH, children with Down syndrome aged <3 years, both with and without CHD, experience significant morbidity in terms of length of hospital stay, oxygen need, mechanical ventilation, admission to intensive care and mortality [88,93,94]. A Canadian-Dutch cohort study found in children with Down syndrome palivizumab reduced RSVH 3.6-fold (72%) [95]. No children receiving palivizumab were admitted to ICU compared to four untreated children, and oxygen use was significantly less (2 *vs* 19 mean days, $p < 0.001$) [95]. A Japanese study enrolling 632 children ≤2 years with Down syndrome between 2007 and 2015 reported a 59% reduction in RSVH compared with untreated children (OR 0.41 95% CI 0.18–0.92, $p = 0.03$) [96]. Although a subsequent study conducted by the same authors concluded palivizumab was not associated with a reduction in RSVH from 2010 to 2019 in children with Down syndrome in Japan [97]. The effectiveness of palivizumab in Down syndrome is further supported by registry data from Canada, Germany and Italy, which all demonstrated low RSVH rates (1.20–4.14%) similar to premature infants and those with CHD/CLD [98–100].

4.3.2. Cystic fibrosis

Cystic fibrosis is also a significant risk factor, which has been found to double a child's risk of RSVH [45]. Individual studies have demonstrated inconclusive results regarding palivizumab effectiveness in children with cystic fibrosis; however, stronger evidence is provided by systematic reviews and a meta-analysis of such studies [101,102]. A meta-analysis, published in 2015, identified six studies and reported a significantly lower RSVH rate in palivizumab treated children (1.8% *vs* 12.6% for untreated, $p < 0.001$) [101]. Two years later another review reported that in seven of 10 identified studies

palivizumab had a positive impact on RSVH rate, including five studies that showed statistically significant differences compared with no prophylaxis [102].

4.3.3. Anatomic pulmonary abnormalities and neuromuscular disorders

Data from CARESS (2005–2017) showed children with either neuromuscular disorders or congenital airway anomalies receiving palivizumab had a greater RSVH risk *versus* those prophylaxed for standard indications (hazard ratio [HR] 2.26, 95% CI 1.38–3.72, $p = 0.001$ and HR 2.1, 95% CI 1.0–4.4, $p = 0.037$, respectively) [103,104]. Moreover, combined CARESS and Italian Registry data from the 2002–2014 RSV seasons reported palivizumab-exposed infants with neuromuscular disorders (7.88%) and airway anomalies (5.95%) had the highest incidence of RSVH, with both acting as significant predictors of RSVH after multivariable logistic regression (OR 4.29, 95% CI 2.30–8.00, $p < 0.01$ and OR 3.23, 95% CI 1.92–5.43, $p < 0.01$, respectively) [98]. Even with palivizumab, infants with neuromuscular disorders or congenital airway anomalies remain at risk of RSVH through the first 2 years of life and require careful surveillance.

4.3.4. Immunocompromised

In CARESS, RSVH in prophylaxed, immunocompromised children was similar to standard indications (preterms, BPD/CLD and HSCHD; HR < 0.005, $p = 0.953$), although immunocompromised children did have a significantly higher risk of hospitalization for any respiratory illness (HR 2.4, 95% CI 1.3–4.7, $p = 0.009$) [105]. No RSVHs were recorded in 56 immunocompromised infants who received palivizumab prophylaxis within the combined CARESS and the Italian Registry data [98]. A recent systematic review identified six studies investigating palivizumab use in 625 immunocompromised children. Rates of RSVH were low (0–3.1%), and similar to those reported for infants receiving palivizumab for other indications [106].

4.4. Reduction of long-term respiratory morbidity

A review of 74 studies examining the long-term respiratory morbidity associated with RSV, including the well-known Sigurs et al. [107–110] and SPRING [111] data, concluded RSV-LRTI was a significant risk factor for ongoing respiratory sequelae. This was characterized by recurrent wheezing (rates 4–-47%), asthma (rates 8–76%) and impaired lung function within the first decade of life and potentially beyond [112]. In an international cohort (Spain, Germany, The Netherlands, Canada, Poland, and Sweden) of otherwise healthy preterm infants followed for 2 years, palivizumab was found to significantly reduce both recurrent wheezing and physician-diagnosed recurrent wheezing rates compared with untreated subjects (13% *vs* 26%, $p < 0.001$ and 8% *vs* 16%, $p = 0.011$, respectively) [113]. *Post-hoc* analysis found palivizumab reduced the relative risk of recurrent wheezing by 80%, but only in children without a family history of atopy [114]. The MAKI RCT reported palivizumab-associated relative reductions of 41.9% (95% CI 6.5–63.9; 11.6% *vs 19*.9% for placebo) and 41.3% (95% CI 10.3–61.6%; 14.1% *vs* 24.0%) in the proportion of moderate-to-late preterm infants with wheeze and parent-reported asthma after 6 years of life, respectively [115]. However, no differences in physician-diagnosed asthma or lung function at 6 years were reported [115]. In a Japanese case–control study, physician-diagnosed recurrent wheezing was significantly reduced in infants receiving palivizumab at three (6.4% *vs* 18.9%, $p < .001$) and 6 years (15.3% *vs* 31.6%, $p = 0.003$), but not after 10 years [116–118]. The asthma risk in these Japanese palivizumab recipients was only significantly reduced after adjusting for gestational age, smoking, and family history of allergy ($p = 0.031$) at 3 years, whilst there was no impact at six and 10 years [116–118]. Overall, these data suggest that, by preventing severe RSV disease, palivizumab might reduce long-term respiratory morbidity in these children for at least up to 6 years.

5. Palivizumab – a trusted option

Over the last 25 years, nearly 5.8 million infants and children across the world have received palivizumab for RSV prophylaxis [119]. As well as being highly effective, palivizumab has been consistently demonstrated to be safe and well-tolerated with low rates of treatment-related adverse events (AEs) in both RCTs (0–12%) and observational real-world data (0–7%) [87]. Meta-analysis of three RCTs (IMpact-RSV Study Group 1998, Subramanian 1998, Feltes 2003) reporting on AEs found no difference at 150 days' follow-up between palivizumab and placebo or no intervention (RR 1.09, 95% CI 0.85–1.39) [7]. Moreover, in clinical trials, AE rates were similar between palivizumab and placebo regardless of indication (≤35wGA and/or BPD/CLD: 11% *vs* 10%; CHD 7.2% *vs* 6.9%). There were also no palivizumab-related serious AEs (SAEs – typically defined as any AE that resulted in death, life-threatening situation, inpatient hospitalization, persistent or significant disability or incapacity, congenital anomaly or birth defect, or other medically important events) [87].

To reaffirm the safety of palivizumab demonstrated by the IMpact trial, an Expanded Access trial collecting additional safety data on palivizumab-treated preterm infants (≤35 wGA) with or without BPD/CLD was commenced in 15 countries in the Northern Hemisphere where palivizumab was not readily available [120]. Palivizumab-related AE rates were low (6.9%) and SAEs were primarily hospitalizations (RSVH rate 2.1%) and one case of RSV bronchiolitis not requiring hospitalization [120]. Subsequent European safety data from the PROTECT study [121] and a phase IV post-marketing study [122] reported low palivizumab-related AE rates (2.1%) in preterm infants 29–32 wGA without BPD/CLD. Similarly, there were no palivizumab-associated significant increases in overall SAEs (infection, arrhythmia, or death) in children with HS-CHD. Perhaps the most comprehensive real-world safety data come from CARESS. Over 13,000 infants (63.1% ≤35 wGA, 11.1%, HS-CHD, 7.5% BPD/CLD and 18.3% complex underlying medical conditions) who received 57,392 injections demonstrated low rates of SAEs with only 0.05% experiencing an event judged as possibly or probably related to palivizumab (incidence: 2.8 *per* 10000 patient-months) [123]. Additionally, data from Europe and Canada confirmed palivizumab use during a second RSV season was not associated with adverse immune responses (significant anti-palivizumab

antibody response) or an increase in SAEs (12.7% in both the first and second season, of which none were palivizumab-related) [124]. Limited safety data available from LMICs aligns with that from HICs, as evidenced by real-world evidence from the Latin America region which reported no palivizumab-related SAEs [89]. Low discontinuation rates due to treatment-related AEs across both RCTs [53,57,59] (0–0.3%) and the real-world setting (0–0.5%) [121,120,123,124] further emphasize palivizumab is a well-tolerated form of RSV prophylaxis in high-risk infants.

The safety and tolerability profile of palivizumab likely contribute to the high levels of adherence that have been reported. Adherence rates (expected number of doses *versus* actual number received) within the pivotal Impact [53] and Feltes 2003 [57] RCTs were 92% and 93%, respectively. Whilst adherence rates in real-world studies have been more variable (25–100%) [125], due in part to variations in definitions of adherence [126], reassuringly the rates reported by the larger international registries, such as CARESS [80] (92.6%) and USA Palivizumab Outcomes Registry [64,65,68] (79.9–86%), remained high; overall inter-dose interval adherence rates were reasonable (CARESS: 83.8–92.7% [127] and 71.9–75.7% [80]; USA: 65.2–69.5% [66]). Crucially, higher rates of adherence have been associated with significant reductions in RSV disease and RSVH [64,125,127], and the incidence of intubation, duration of hospitalization, intensive care stay and respiratory support [127]. This highlights the importance of palivizumab being a well-tolerated and highly acceptable means of immunoprophylaxis that concomitantly reduces morbidity in adherent infants.

6. Palivizumab – a cost-effective investment?

Cost-effectiveness of palivizumab prophylaxis depends on multiple factors, most of which can vary across different countries and over time. These include the population prophylaxed, availability, and quality of country-specific epidemiological and clinical data (including medically attended RSV-LRTI rates), RSV seasonality, access to care, types and costs of resource use involved, palivizumab dosing schedule, and costs (vary greatly depending on agreements with health providers), consideration of long-term consequences, primary outcome measures, and the type of analytical model utilized [36]. Consequently, a broad range of results have been reported by economic analyses with incremental cost-effectiveness ratios (ICERs) ranging from USD$800–800,000/quality-adjusted life year (QALY) for infants ≤35 wGA, $10,-000–170,000/QALY for children with CHD, and $31,000–-38,000/QALY for children with CLD/BPD [36]. A systematic review of 28 economic analyses highlighted the significant impact the population chosen for prophylaxis can have on palivizumab cost-effectiveness [128]. From a healthcare payer perspective, ICERs ranged from $5,188–791,265/QALY for preterm infants (29–35 wGA), $177–169,103 for preterm infants with risk factors, $9,837–139,051/QALY for infants with CHD, and $3,984–40,036/QALY for infants with BPD/CLD. At a willingness-to-pay threshold of $100,000/QALY, 86% of evaluations for preterm infants, 86% of evaluations for preterm infants with risk factors, 90% of evaluations for infants with CHD, and 100% of evaluations for infants with BPD/CLD were cost-effective [128].

The aforementioned RSTs used to predict RSVH risk and identify the otherwise healthy moderate-to-late premature infants at highest risk are therefore vital in helping target RSV prophylaxis cost-effectively in this group [46]. An evidence-based cost-utility model (CUA), developed in 2023, incorporating the International Risk Scoring Tool (IRST) found risk factor-guided palivizumab prophylaxis of 32–35wGA infants to be cost-effective in four different continents: North America (Canada), South America (Colombia), Europe (Italy) and Asia (South Korea) (Table 3) [129]. Standardizing results to CAD demonstrated palivizumab to be consistently cost-effective *versus* the Canadian willingness-to-pay (WTP) threshold (CAD 50,000/QALY gained) with the cost *per* QALY in CAD being similar to, or lower than the native Canadian cost *per* QALY [129]. Subsequent analyses have also shown risk-factor guided palivizumab to be cost-effective in moderate-to-late preterm infants from Singapore [130], Malaysia [131], the Dominican Republic [132] and Mexico [133] (Table 3). Key drivers of cost-effectiveness across these models were utility scores, rates of long-term respiratory morbidity, and palivizumab efficacy, and cost [129–133]. This recent evidence demonstrates the utility of palivizumab across different RSV epidemic patterns, geographies and climates, and healthcare systems.

Despite the predominant burden of preterm RSV disease being in LMICs, palivizumab use in these countries has been limited due to its significant cost, and the need for monthly injections which require timely access to a healthcare facility. In addition to epidemiological and clinical evidence, there is a geographic disparity in available economic evidence in LMICs compared to HICs, highlighted by a global systematic review which found only 3 out of 44 costing studies were conducted in LMICs [134]. However, a subsequent systematic review that included six studies on palivizumab, provided some evidence on cost-effectiveness from a LMIC perspective [135]. The ICERs were estimated from USD$4671/DALY in Mali, to $22,863/QALY in Mexico. The ICERs *per* hospitalization averted ranged from $4140 in Malaysia to $71,226 in Argentina [135]. Considering a WTP threshold of times one GDP *per capita per* DALY averted, none of the reports deemed palivizumab cost-effective [135]. Regardless of cost-effectiveness, the purchase costs of palivizumab must also be balanced against other major healthcare priorities when resources are limited, for example, pneumococcal vaccine immunization.

7. Palivizumab – a success story

Since its licensure over 25 years ago, palivizumab has achieved the primary aim of significantly reducing RSVH rates in high-risk infants, predominantly in HIC settings [136–142]. In the USA, between 1997 and 2012, RSVH rates declined among high-risk infants (by 17% in all infants <2 years, 47% in BPD/CLD, 36–49.7% in CHD), coincident with widespread palivizumab use in these population [136–138]. Similarly, in France, RSVH rates fell significantly from 14.3%, 16.7%, and 10.2% in three seasons without prophylaxis (1999–2002), to 0% and 2%

in two seasons with prophylaxis (2002–2004) in premature infants (≤30 wGA) [139]. This decrease was mirrored in infants ≤32 wGA with BPD/CLD (RSVH pre-palivizumab 46.2% *vs* post 11.8% and 3.8%) [140]. Moreover, changes to palivizumab guidelines have further highlighted the successful impact of palivizumab. In 2014, the American Academy of Pediatrics stopped recommending RSV prophylaxis in otherwise healthy 29–35 wGA infants [141]. Since then, several national database studies have consistently demonstrated a significant correlation between a decrease (45–95%) in palivizumab use in this population and an increase in the RSVH rate (1.41–2.56 times higher) [141]. Likewise, in 2016, the Italian Drug Agency restricted palivizumab eligibility criteria and excluded administration for infants born at >29 wGA [142]. These policy changes led to a significant increase in RSVH (pre-policy change 1.9% *vs* post-policy change 5.1%; OR 2.77, 95% CI 0.98–7.8, $p = 0.045$), highlighting the significant benefit palivizumab had in this population [142]. Subsequent guidelines from the Italian Society of Neonatology (SIN) reversed this decision to include those infants born 29–35 WGA and age <6 months in the presence of risk factors [143].

8. Conclusion

Over the past 25 years, palivizumab has changed the face of RSV prevention for high-risk young children in HICs. As the first successfully implemented RSV preventive, a wealth of evidence demonstrates its effectiveness and safety in preventing severe RSV disease in high-risk children. Importantly, spanning a quarter century of use, palivizumab has been shown to be effective in populations around the world, with no evidence of induced resistance or reduced effectiveness due to escape mutants. After decades searching for an effective and safe RSV preventive, palivizumab can justifiably be recognized as setting the stage for the current era of RSV prevention. New prolonged half-life monoclonal antibodies, maternal RSV vaccination, and potentially infant RSV vaccination will hopefully further reduce severe RSV disease in all children over the upcoming years. The surge in RSV cases post-coronavirus disease in 2019 served as a reminder of both the critical importance of non-pharmacological interventions for the control of RSV infection and the need for continued development of the therapeutic armamentarium against RSV [144].

9. Expert opinion: palivizumab – a still relevant option?

Palivizumab has paved the way for future RSV preventives and is currently being replaced globally by the next generation of antibodies, and maternal and infant vaccines. However, palivizumab still has an intermediary role to play during this evolving era of RSV prevention as the newer preventives are integrated into healthcare systems around the world [145], albeit initially, this will be predominantly in upper middle and HICs (Figure 3). The newer RSV preventives, including long-acting mAbs (*e.g.* nirsevimab, clesrovimab), maternal vaccines, and infant vaccines, differ from palivizumab in terms of mechanisms and target sites of action (palivizumab = site II of pre- and post- F; nirsevimab = site 0 of pre-F; clesrovimab = site IV of pre- and post-F), administration, and coverage over the duration of the RSV season. It is likely that complementary strategies may be employed to ensure maximum protection for children, dependent on product cost-effectiveness and availability across countries [4,6]. The key strengths of palivizumab are its extensive legacy, with over 25 years of evidence demonstrating its efficacy, effectiveness, and long-term safety profile, its well-established placebo-controlled trial data in extremely premature infants (<29 wGA) and those with BPD/CHD, and real-world experience in many special populations, that closely simulate efficacy gleaned from the RCTs [53,55,57,95,98–102]. Extrapolated pharmacokinetic data in the nirsevimab trials was utilized to show efficacy in these populations (<29 wGA and BPD/CHD) [146], as this was required for licensing, but evidence is accumulating from real-world studies on its effectiveness and safety in high-risk children [147].

Palivizumab might have a more general supportive role in combination with the newer preventives. The pivotal trial for the RSVpreF maternal vaccine demonstrated efficacy (prevention of severe medically attended RSV-LRTI) of 81.8% (99.5% CI 40.6–96.3) within 90 days after birth and 69.4% (97.58% CI 44.3–84.1) within 180 days after birth [148]. If a LAmAb is unavailable in a country, palivizumab could be utilized to 'top up' protection in infants born prematurely to mothers who received the RSVpreF vaccine as there may have been insufficient placental transfer of maternal antibodies to the fetus [149]. Guidelines suggest a minimum of 14 days are required post-maternal vaccination to achieve adequate protection in the infant [150]. For example, in the USA as the earliest recommended time for vaccination is 32 wGA, the earliest an infant could be born and be considered fully protected by the maternal RSVpreF vaccine is 34 wGA; therefore, infants born at 32–34 wGA could be candidates for additional protection *via* palivizumab, in the interim where a LAmAb is not available [150]. In countries where maternal vaccination is recommended earlier during pregnancy, such as after 28 wGA in the UK, infants are more likely to be born after 14 days post-maternal vaccination [151]. However, it will be crucial to monitor uptake of maternal vaccination as uptake of other vaccines in pregnancy, namely pertussis and influenza, has been falling in the UK over recent years [151]. In LMICs, high uptake of maternal tetanus vaccination has been demonstrated [152,153]. This suggests that the implementation of a maternal RSV vaccine may be more feasible in Gavi-eligible countries, especially if a more affordable, multidose, vial format of the vaccine which is currently under development, becomes available [154].

For nirsevimab, studies showed infants were protected from medically attended RSV-LRTI through 150 days after the injection with no evidence of waning (efficacy in preterm infants: 78.4%, 95% CI 51.9–90.3; in late-preterm/term infants [full cohort]: 76.4%, 95% CI 62.3–85.2) [155–157]. However, the RSV season and thus the period of risk can extend beyond 6 months in endemic RSV environments (*e.g.* Taiwan, Colombia) as well as in certain seasonal RSV environments during some years (*e.g.* Japan) [158–160]. Therefore, consideration might be given as to whether these infants and children are still protected in these circumstances, particularly if they are

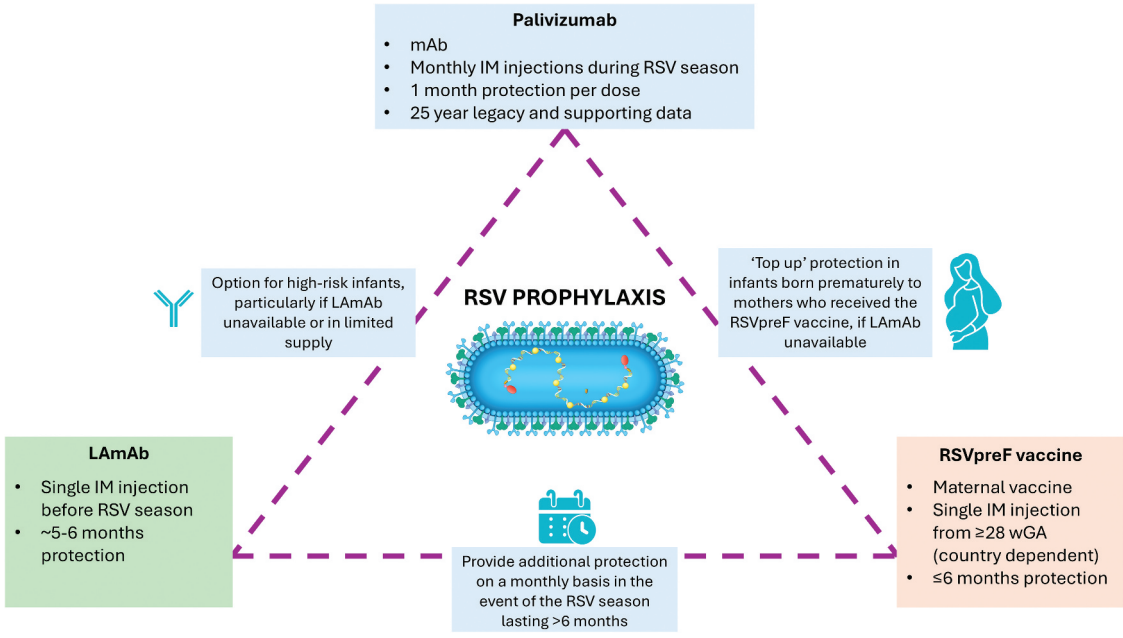

Figure 3. Visual summary depicting the potential uses of palivizumab in this new era of RSV prophylaxis.

IM: intramuscular; LAmAb: long-acting monoclonal antibody; mAb: monoclonal antibody; RSV: respiratory syncytial virus; wGA: weeks' gestational age.

considered at high risk for RSV infection. There is minimal data for nirsevimab showing protection to 361 days (12 cases occurred up to day 361: 6/308 infants [1.9%] in the nirsevimab group and 6/154 [3.9%] in the placebo group) [156]. To date, there is limited evidence showing protection against RSV infection beyond 6 months. US guidelines for Hawaii and Alaska, where RSV seasonality is less predictable, do recommend a second dose of nirsevimab for Native children [161,162]. If a LAmAb is unavailable, palivizumab may have a small niche to provide additional monthly protection for countries with a prolonged RSV season. Availability and costs incurred to healthcare systems will need to be carefully considered based on the selected options.

More generally, limited supply and inequity in global market access, particularly for nirsevimab [163], means that presently palivizumab continues to remain an important preventive option for high-risk infants and children, especially those with complex medical disorders, in many HICs. Guidelines from the American Academy of Pediatrics (AAP), Centers for Disease Control and Prevention (CDC), and Canadian National Advisory Committee on Immunization (NACI) all recommend that if nirsevimab is not available or not feasible to administer, high-risk palivizumab-eligible infants and children should receive palivizumab as previously recommended [164–166]. Whilst access to the newer preventives should be prioritized, palivizumab could provide a bridge to universal immunization in high-risk infants and children in upper middle and HICs, while awaiting the newer preventives [145]. In 2025, palivizumab licensure is still being actively sought in some new countries, including India and the Philippines. In most LMICs, where the greatest burden of RSV resides, palivizumab is less affordable, and so this strategy is not an economic reality. Therefore, the disparity in availability and implementation of newer RSV preventives in LMICs must be addressed urgently to reduce the global burden of RSV disease [167,168].

Moving forward, the use of pioneering technologies and a deeper understanding of the immunological complexities, including host–pathogen interactions, will be vital for developing and enhancing new and future RSV preventive strategies, particularly accelerating progress toward an effective vaccine for young children. Moreover, just as lessons were learnt from the failure of the formalin inactivated RSV vaccine, lessons should be heeded from three decades of palivizumab success to optimize RSV immunization both now and in the years ahead. The development and use of palivizumab has increased scientific knowledge surrounding mAbs and provided vast real-world health and economic data that was lacking prior to its implementation. Numerous HICs across the world have successfully employed palivizumab immunization programs and LMICs have administered a birth BCG vaccine or other vaccines in early infancy using immunization programs. The existing infrastructure and foundation of such national programs should be utilized, alongside the following key learnings from palivizumab implementation, to ensure accessibility, affordability, and the smooth roll-out of future RSV preventives in both HICs and LMICs:

(1) There was difficulty in creating universal guidelines for the use of palivizumab with countries and even states/provinces within the same country implementing differing prophylaxis policies. Although there will always be local variation in factors such as RSV seasonality and available budgets, RSV preventive guidelines should be consistent globally to ensure fair and equitable access for all infants and young children.
(2) There is an urgent need for evidence-based guidelines to be prepared and endorsed by regulatory authorities, all relevant scientific societies (*e.g.* RSV Foundation

(ResViNET) and the International Respiratory Syncytial Virus Society), and healthcare professionals from specialties involved in the use of RSV prevention.

(3) It is imperative to consider the impact of RSV preventives not only during the acute phase of the infection, but also on the reduction of subsequent long-term sequelae; thus, conducting long-term follow-up studies of new preventives is crucial.

(4) The multitude of pharmacoeconomic studies that have been performed with palivizumab should be avoided. They must be carried out by independent professionals to avoid biases and should ideally include the economic impact of:

RSV within the community and children attending emergency rooms, not just RSVHs

Long-term respiratory morbidity following severe RSV infection in infancy

Effect of prevention of RSV disease on all-cause pneumonia, and on subsequent non-RSV pneumonia and respiratory infections

(4) Entwined with the above, there is a need to standardize definitions of acute respiratory infection, LRTI, severe LRTI, outpatient visits, emergency visits, medically attended RSV-LRTI and RSVH

(5) Equity in availability and implementation of newer RSV preventives in LMICs will be crucial to reducing the global burden of RSV disease and will require strong collaboration between public health organizations and originator pharmaceutical companies

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