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Review

Expert Consensus on Palivizumab use for Respiratory Syncytial Virus in Developed Countries

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Expert Consensus on Palivizumab use for Respiratory Syncytial Virus in Developed Countries

Authors: Manuel Sánchez Luna, MD\textsuperscript{a}, Paolo Manzoni, MD\textsuperscript{b}, Bosco Paes, MD\textsuperscript{c}, Eugenio Baraldi, MD\textsuperscript{d}, Veerle Cossey, MD\textsuperscript{e}, Amir Kugelman, MD\textsuperscript{f}, Rupesh Chawla, MD\textsuperscript{g}, Andrea Dotta, MD\textsuperscript{h}, Rosa Rodríguez Fernández, MD\textsuperscript{i}, Bernhard Resch, MD\textsuperscript{j}, Xavier Carbonell-Estrany, MD\textsuperscript{k}

Affiliations:
\textsuperscript{a}Complutense University, Research Institute University Hospital Gregorio Maraño, Neonatology Division, Avda. de Séneca 2, 28040 Madrid, Spain
\textsuperscript{b}Neonatology and NICU, S.Anna Hospital. AOU Città della Salute e della Scienza, Corso Spezia 60, 10126 Torino, Italy and Respiratory Syncytial Virus Network (ReSViNET)
\textsuperscript{c}Department of Pediatrics (Neonatal Division), McMaster University, 1280 Main St W, Hamilton ON L8S 4L8, Canada
\textsuperscript{d}Women’s and Children’s Health Department, University of Padova, Via 8 Febbraio 1848, 35122 Padova, Italy and Respiratory Syncytial Virus Network (ReSViNET)
\textsuperscript{e}Neonatal Intensive Care Unit, University Hospitals Leuven, Department of Development and Regeneration, KU Leuven, Oude Markt 13, 3000 Leuven, Belgium
\textsuperscript{f}Neonatal Department, Rambam Health Care Campus, Rappaport Faculty of Medicine, Technion, Efron St 1, Haifa, Israel
\textsuperscript{g}Department of Pediatrics, Alberta Children’s Hospital, 2888 Shaganappi Trail NW, Calgary, Alberta T3B 6A8, Canada
\textsuperscript{h}Division of Newborn Medicine, Bambino Gesù Children’s Hospital and Research Institute, Piazza di Sant’Onofrio 4, 00165 Rome, Italy
\textsuperscript{i}Department of Paediatrics, Hospital General Universitario Gregorio Maraño, Calle del Dr. Esquerdo 46, 28007 Madrid, Spain
\textsuperscript{j}Division of Neonatology, Department of Paediatrics and Adolescent Medicine, Medical University of Graz, Auenbruggerpl. 2, 8036 Graz, Austria
\textsuperscript{k}Neonatology Service, Hospital Clinic, Institut d'Investigacions Biomediques August Pi Suñer (IDIBAPS), Carrer del Rosselló 149, 08036 Barcelona, Spain
Corresponding Author
Xavier Carbonell-Estrany, Hospital Clinic, Institut d'Investigacions Biomediques August Pi Suñer (IDIBAPS), Barcelona, Spain. Email: carbonell@comb.cat, Tel: +34 93 2041963

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Abstract
Respiratory syncytial virus (RSV) infection is a leading cause of hospitalisation in early childhood and palivizumab is the only licensed intervention for prevention. Palivizumab guidelines should reflect the latest evidence, in addition to costs-effectiveness and healthcare budgetary considerations. RSV experts from Europe, Canada and Israel undertook a systematic review of the evidence over the last 5 years and developed recommendations regarding prophylaxis in industrialised countries. Almost 400 publications were reviewed. This group recommended palivizumab for: preterm infants (<29 and ≤31 weeks gestational age [wGA] and ≤9 and ≤6 months of age, respectively; high-risk 32-35 wGA), former preterm children ≤24 months with chronic lung disease/bronchopulmonary dysplasia, children ≤24 months with significant congenital heart disease; and other high-risk populations, such as children ≤24 months with Down syndrome, pulmonary/neuromuscular disorders, immunocompromised, and cystic fibrosis. Up to 5 monthly doses should be administered over the RSV season. It is our impression that the adoption of these guidelines would help reduce the burden of RSV.

Educational aims
The reader will be able to:
1. Obtain up-to-date information on the epidemiology and burden of severe RSV infection in high-risk paediatric populations
2. Find evidence-based recommendations on the use of palivizumab and understand the differences between the recommendations suggested by this paper vs. the AAP guidelines
3. Understand the rationale and level of evidence for palivizumab for the prevention of severe RSV infection in high-risk infants and children

Directions for future research
1. Further quantification and understanding of the burden and economic impact of RSV infection in high-risk paediatric populations, in particular related to outpatient and emergency department visits and within the community
2. Further studies on the effectiveness of palivizumab in reducing severe RSV infection in children with underlying medical conditions (e.g. Down syndrome, cystic fibrosis,
anatomic pulmonary abnormalities, neuromuscular disorders, immunocompromised) and its ultimate impact on recurrent wheezing and asthma

3. Continued research on future preventive therapies (antibodies and vaccines) and treatments for RSV infection, their degree of effectiveness and optimisation of use (e.g. pre- versus post-natal prophylaxis)

Key words: Respiratory syncytial virus, evidence-based medicine, Palivizumab, lower respiratory tract infection, neonatal lung disease

Abbreviations: RSV: Respiratory syncytial virus; wGA: weeks’ gestational age; WHO: World Health Organization; CLD: Chronic lung disease; CHD: Congenital heart disease; BPD: Bronchopulmonary dysplasia; MeSH: Medical Subject Headings; GRADE: Grading of Recommendations Assessment, Development and Evaluation; ICU: Intensive care unit; RSVH: RSV hospitalisation; HS: Haemodynamically significant; ER: Emergency room; RT-PCR: Reverse transcription polymerase chain reaction; AAP: American Academy of Pediatrics; GA: Gestational age; CPAP: Continuous positive airway pressure; QALY: Quality-adjusted life year; ICER: Incremental cost-effectiveness ratio; PICU: Paediatric ICU; SD: Standard deviation; CF: Cystic fibrosis
1. INTRODUCTION

In 2015, there were 2.8 million episodes of respiratory syncytial virus (RSV) infection in children aged <5 years in high income countries, resulting in around 383,000 hospital admissions and 3,300 deaths [1]. Prevention of RSV infection is a key priority of the World Health Organization (WHO) [2]; however, whilst there are approximately 45 RSV vaccines and antibodies in clinical or preclinical development, it may take several years before any of these become commercially available [3,4]. Palivizumab is the only intervention currently licensed for the prevention of severe RSV infection requiring hospitalisation in high-risk infants, namely preterm (≤35 weeks’ gestational age [wGA]) and those with bronchopulmonary dysplasia (BPD)/chronic lung disease (CLD) or congenital heart disease (CHD). In the absence of alternatives, it is important to cost-effectively maximise the use of palivizumab. The most recognised and widely followed guidelines for palivizumab are those published by the American Academy of Pediatrics (AAP) in 2014, which remained unchanged in 2017 [5,6]. Palivizumab guidelines must reflect the latest evidence and development in addition to the pharmacoeconomic impact. RSV experts from Europe, Canada and Israel, including representatives from European Neonatal, Perinatal and Paediatric Scientific Societies, undertook a systematic review of the evidence for RSV and palivizumab prevention over the last 5 years with the aim of developing up-to-date, evidence-based prophylaxis recommendations for developed countries.
2. METHODS

2.1 Remit of consensus

The consensus was limited to developed countries, defined as ‘Very High’ using the Human Development Index of the United Nations Development Programme (Supplementary: Protocol). Evidence on the following key areas was reviewed:

1. Epidemiology and burden of RSV – what is the current status and has this changed over the last 5 years?
2. Evidence for palivizumab in preterm infants ≤35 wGA, BPD/CLD and CHD – are current guideline recommendations still relevant?
3. Evidence in other populations at high, specific risk for severe RSV infection (e.g. Down syndrome) – Is the evidence strong enough for positive recommendations?
4. Evidence for respiratory morbidity (wheezing and/or asthma) following RSV infection – Is the evidence strong enough to support a causal link?
5. Cost-effectiveness of palivizumab – why are there conflicting results even when allowing for differing healthcare systems?

2.2 Evidence from AAP 2014

The complete list of references (158) included in the AAP 2014 guidelines Technical Report were reviewed and assessed by the authors [7].

2.3 Evidence 2013-2018

MEDLINE (PubMed), EMBASE, the Cochrane Library and ClinicalTrials.gov were searched for publications between 01-Jan-2013 to 31-Jan-2018 using the following terms, combined with Medical Subject Headings (MeSH): [“RSV” OR "respiratory syncytial virus" OR “lower respiratory tract infection” OR “bronchiolitis” OR "acute respiratory tract infection" OR “LRTI” OR “LRI” OR “ARTI” OR “ARI”] AND [“palivizumab” OR “Synagis” OR “immunoprophylax*” OR “prophylax*”] OR [“cost effective*” OR “Cost”] AND limits: “human, child (birth to 18 years)” (Supplementary: Protocol). All original studies and systematic reviews, with an English abstract, supplemented by those identified from other sources, were reviewed according to the PICO Framework [8].
2.4 Evaluation of evidence and recommendations

The consensus recommendations were developed as follows. First, the experts agreed on a framework. XCE drafted recommendations based on the framework, which were reviewed and edited first by EB, PM, BP and MSL and subsequently by RC, VC, AD, AK, BR and RRF. Finally, all authors reviewed and approved the final draft. Consensus was reached on all recommendations without recourse to voting. Publications by drug companies were carefully screened for inclusion. The strength of evidence for each recommendation was rated according to the Oxford Centre for Evidence-Based Medicine Levels of Evidence and Grading of Recommendations Assessment, Development and Evaluation (GRADE) [9,10].

2.5 Role of the funding source

The authors received no funding for the development of the recommendations.
3. EVIDENCE FOR RSV AND USE OF PALIVIZUMAB

3.1 Systematic review

A total of 378 publications were reviewed; 315 from the systematic review supplemented by 63 references from other sources (Figure 1 & Supplementary: Data Extraction Table).

Figure 1: PRISMA diagram. Evidence for RSV and use of palivizumab 2013-2018

3.2 Epidemiology and burden of RSV in the Palivizumab era

There is inconclusive evidence that the overall hospital burden of RSV has changed during the Palivizumab era [11,12]. US studies from 1997-2012 indicate that the rate of RSV hospitalisation (RSVH) declined in certain high-risk populations following the introduction of palivizumab; in particular in children with haemodynamically significant CHD (HS-CHD), and CLD [12,13,14], but increased or remained stable in others, including Down syndrome and congenital airway anomalies [12,14]. In 2015, it was estimated that the RSVH rate in high income countries was 26.3, 11.3 and 1.4/1000 in children ≤5 months, 6-11 months, and 12-59 months of age, respectively [1]. Mortality rates were 0.2%, 0.9% and 0.7%, respectively [1].
Earlier studies focused almost exclusively on RSVHs, but there is growing evidence demonstrating the wider burden of RSV in emergency rooms (ER), outpatient offices and within the community [15,16,17,18,19,20]. During the RSV season, up to 62% of children presenting to the ER/outpatient visits with acute respiratory tract infection have RSV [15,16,19]. The incidence rates range from 144-352/1000 children [15,17,18]. This represents a 90-135% approximate increase in RSV cases when added to inpatient RSV numbers [17,20]. However, this may be underestimated due to lack of routine RSV testing. For example, a US study reported that 65% (441/678) of infants (<12 months) with a positive RSV reverse transcription polymerase chain reaction (RT-PCR) test at some point during the disease course, were not assigned a specific diagnosis of RSV in the ER when test results were not available at diagnosis [19]. All new RSV epidemiological studies should consider the outpatient population and its burden on healthcare resources.

Routine testing may more accurately define the start of the RSV season and facilitate resource planning and administration of palivizumab [21,22,23,24]. Conversely, the expense, availability, speed-of-access to results, suboptimal sensitivity/specificity, and the limited clinical value of testing for most children argue against routine use [25,26]. RT-PCR remains the most sensitive commercially available test, but is costly and infrequently available as point-of-care [25]. Rapid antigen detection tests are increasingly being used in the ER [25]. Based on evidence, routine testing cannot be recommended at present except, possibly, outside of the RSV season. However, this may change with the availability of newer, more sensitive and cost-effective, rapid tests [27,28].

3.3 Current guidelines for palivizumab and impact on RSV prevention

The 2014 AAP guidelines that remained unchanged in 2017 after review of new data [5], included several changes to the recommendations from the prior policy as shown in Table 1 [6,29,30]. Guidelines from Spain and Italy recommend wider use of palivizumab extending to former preterm infants 29-35 wGA and ≤6 months of age, and the use of risk factors to identify 32-35 wGA infants at highest risk [31,32]. Austrian guidelines have used risk factors to guide prophylaxis in all infants 29-35 wGA, with a chronological age of <6 months for
those born 29-32 wGA and <3 months for 33-35 wGA [33]. Israeli guidelines include all preterm infants <33 wGA at ≤1 year and 33-35 wGA at ≤6 months.

Applying the 2014 AAP guidelines resulted in a 35-47% reduction in palivizumab administration compared to previous years [34,35], primarily driven by a 62-95% use reduction in preterm infants [36,37]. Considering the overall RSVH rate in children <2 years, a retrospective US study reported no difference in the pre- versus post-2014 guidelines period (5.37/1000 vs. 5.78/1000 children, respectively; p=0.622) [35]. Other retrospective studies focusing specifically on preterm infants have shown increased RSVH rates in 29-35 wGA infants following the 2014 guidelines, particularly in infants ≤6 months [36,37,38,39]. Regarding RSVHs occurring in infants <12 months of age, the proportion in those 29-35 wGA increased by 26% (pre: 7.3% vs. post: 9.2%) in an Italian study [38], and by 103% (3.5% vs. 7.1%) in a US study [36]. The US study also showed increased morbidity in 29-35 wGA younger than 3-month infants compared to pre-2014 [36].
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Preterm infants without other comorbidities</td>
<td>- Infants born ≤31 weeks 6 days may benefit from a maximal number of 5 doses of RSV prophylaxis</td>
<td>- Palivizumab prophylaxis may be administered to infants born &lt;29 weeks’ gestation who are &lt;12 months at the start of the RSV season</td>
</tr>
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<td></td>
<td>- Infants from 32 -35 weeks’ gestation (32 weeks 0 days - 34 weeks 6 days) born &lt;3 months before onset or anytime during the RSV season may also be suitable if they have at least 1 of the following risk factors:</td>
<td>- For infants born during the RSV season, &lt;5 monthly doses will be needed</td>
</tr>
<tr>
<td></td>
<td>1. They attend childcare, defined as a home or facility in which care is provided for any number of toddlers in the childcare facility;</td>
<td>- Palivizumab prophylaxis is not recommended for preterm infants born ≥29 weeks gestation</td>
</tr>
<tr>
<td></td>
<td>2. Have ≥1 siblings or other children younger than 5 years who live permanently in the same household</td>
<td>- Some experts believe that even for infants born &lt;29 weeks, 0 days gestation, palivizumab prophylaxis is not justified</td>
</tr>
<tr>
<td></td>
<td>- Infants born from 32-35 weeks’ gestation who qualify for prophylaxis should receive prophylaxis only until they reach 90 days of age or a maximum of 3 doses (whichever comes first)</td>
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</tr>
<tr>
<td>CLD</td>
<td>- Palivizumab prophylaxis may be considered in infants and children who are &lt;24 months with CLD who receive medical therapy (supplemental oxygen, bronchodilator, diuretic or chronic corticosteroid therapy) for CLD within 6 months before the start of the RSV season</td>
<td>- Prophylaxis may be considered during the RSV season during the 1st year of life in infants with CLD of prematurity defined as gestational age &lt;32 weeks, 0 days and a requirement for &gt;21% oxygen for at least the first 28 days after birth</td>
</tr>
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</table>
- These infants and young children should receive a maximum of 5 doses
- Patients with the most severe CLD who continue to require medical therapy may benefit from prophylaxis during a 2nd RSV season
- 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

| CHD | Infants and children who ≤24 months with haemodynamically significant cyanotic or acyanotic CHD may benefit from palivizumab prophylaxis
  o In particular infants who are receiving medication to control congestive heart failure, infants with moderate-to-severe pulmonary hypotension; and infants with cyanotic heart disease
| Certain children who are <12 months with haemodynamically significant CHD may benefit from palivizumab prophylaxis
| 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 |

| Anatomic pulmonary abnormalities or neuromuscular disorder | Immunoprophylaxis may be considered for infants who have either significant congenital abnormalities of the airway or a neuromuscular condition that compromises handling of respiratory tract secretions
| Infants and young children in this category should receive a maximum of 5 doses of palivizumab during the 1st year of life |
| 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 |

<p>| Immuno-compromised | Although specific recommendations for immunocompromised children cannot be made, infants and young children with CHD and severe |
| Prophylaxis may be considered for children &lt;24 months who are profoundly immunocompromised during the RSV season |</p>
<table>
<thead>
<tr>
<th>Condition</th>
<th>Recommendation</th>
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<tr>
<td>Children with Down Syndrome</td>
<td>- No recommendation given for infants with Down syndrome</td>
</tr>
<tr>
<td></td>
<td>• Prophylaxis is not recommended in children with Down syndrome unless qualifying CHD, CLD, airway clearance issues, or prematurity</td>
</tr>
<tr>
<td>Children with cystic fibrosis</td>
<td>- Routine prophylaxis is not recommended in children with cystic fibrosis</td>
</tr>
<tr>
<td></td>
<td>• Infants with cystic fibrosis with clinical evidence of CLD and/ or nutritional compromise in the 1st year of life may be considered for prophylaxis</td>
</tr>
<tr>
<td></td>
<td>• Continued prophylaxis during the 2nd year may be considered in infants with manifestations of severe lung disease (previous hospitalisation for pulmonary exacerbation in the 1st year of life or abnormalities on chest radiography or chest computed tomography that persist when stable) or weight for length less than the 10th percentile</td>
</tr>
<tr>
<td>Breakthrough RSV hospitalisation</td>
<td>- If an infant or child who is receiving palivizumab immunoprophylaxis experiences a breakthrough RSV infection, monthly prophylaxis should continue until a maximum number of 3 doses have been administered to infants in the 32-35 weeks’ gestational-age group or a maximum of 5 doses have been administered to infants with CHD, CLD, or preterm birth</td>
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<td></td>
<td>• If any infant or young child receiving monthly palivizumab prophylaxis experiences a breakthrough RSV hospitalisation, monthly prophylaxis should be discontinued</td>
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<table>
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<th>&lt;32 weeks' gestation</th>
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<tr>
<td>Use of palivizumab in the second year of life</td>
</tr>
<tr>
<td>• Individual patients may benefit from decisions made in consultation with neonatologists, paediatric intensivists, pulmonologists, or infectious disease specialists</td>
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</table>
3.4 Evidence for RSV prophylaxis in healthy infants born 29-35 wGA

The main rationale for the change in the AAP 2014 guidelines was the RSVH rate <5% in moderate preterm infants and evidence from one study [40] that two previously considered risk factors, day-care attendance and other children in the home, were not significantly associated with RSVH [6]. Importantly, RSVH rates have been reported to be more than double in infants 29-31 wGA compared to those 32-35 wGA [41,42]. It is well known that infants 29-35 wGA are at increased risk of RSVH compared to term infants [41,43,44,45], that palivizumab is effective at preventing RSVH in preterm infants ≤35 wGA (62-75% reduction in RSVH) [3,46,47], and that restricting prophylaxis increases RSVH rate in the preterm population [36,37,38,39]. There is also evidence that the risk of RSVH decreases with increasing gestational and chronological age [36,41,45]. It may not be realistic, feasible or even desirable to offer prophylaxis to all infants ≤35 wGA considering healthcare budgets restrictions; however, it is equally unacceptable not to offer prophylaxis to the most vulnerable subset of these infants.

The use of risk factors provides a pragmatic approach to targeting prophylaxis to the preterm infants at highest risk. The study quoted by the AAP that found no significant association of risk factors with RSVH, analysed a mixed population of preterm and term children <5 years old [40]. However, numerous studies in preterm infants 32-35 wGA (≤12 months) have found several highly significant risk factors for RSVH [48,49,50,51]. A risk scoring tool developed and validated with seven such studies has recently been published based on three risk factors: birth three months before and two months after the RSV season start date; smokers in household and/or smoking during pregnancy; and siblings (excluding multiples) and/or (planned) day-care (Figure 2) [52]. The tool has good predictive accuracy (area under the receiver operating characteristic curve: 0.773; sensitivity/specificity: 68.9%/73.0%) and provides cut-off scores for infants at low- (≤19; 1.0% RSVH rate), moderate- (20-45; 3.3%), and high-risk (50-56; 9.5%) [52]. Risk factors may also guide prophylaxis in infants 29-32 wGA [33]. However, prophylaxis could be justified in such infants solely based on high disease burden [41,42].
Several large studies have highlighted the importance of monthly dosing throughout the RSV season. Non-adherence to the 5-dose schedule or an extended dosing interval (>35 days) have been reported to increase RSVH rate by 21-61% [53,54,55,56]. At present, there are limited data supporting the use of a reduced dosing schedule (e.g. maximum of 3) in preterm infants 32-35 wGA [30,57]. Adherence to the recommended dosing schedule is improved by the implementation of management tools to identify patients and coordinate workflow, multidisciplinary collaboration, and early case management [58,59].

3.5 Evidence for RSV prophylaxis in infants and children with CLD/BPD
The effectiveness of prophylaxis in children with CLD/BPD is well established. A recent meta-analysis reported a 65% (38-72%) reduction in RSVH versus untreated infants [3]. Recent data from the Canadian CARESS registry for palivizumab showed that RSVH rates were similar in the first- and second-year of life in children with CLD (2.3% vs. 3.9%, respectively; hazard ratio [HR] 1.1, 95% confidence interval [CI] 0.4-2.9; p=0.920) [60]. Since the incidence of RSVH decreases in the second year of life, this suggests that the CARESS physicians could identify high-risk children whom they believed would benefit from an additional year of
prophylaxis due to continued oxygen dependency and/or medical therapy (e.g. bronchodilators) [60]. CLD/BPD children are also at risk for pulmonary hypertension [61], which contributes significantly to their morbidity and mortality. It seems wise to leave the identification of children with CLD/BPD who are at high-risk of RSVH to local experience and practice, rather than using definitions, such as oxygen use at 28 days and/or 36 wGA, or applying a GA cut-off <32 weeks.

3.6 Evidence for RSV prophylaxis in infants and children with CHD
Current guidelines recommend palivizumab in infants ≤1 year with HS-CHD. However, there is variability regarding prophylaxis in the second year of life [6,31,32]. The definition of HS-CHD in relation to RSV has also varied over time. The most recent studies use the following definition [62,63]:
- Uncorrected or palliated cyanotic or acyanotic CHD with pulmonary hypertension
- Systolic pulmonary arterial pressure ≥40 mmHg or mean pulmonary arterial pressure ≥25 mmHg, and/or
- Need for medication to manage congestive heart failure.

Importantly, this definition includes patients with cyanotic CHD, while the AAP 2014 guidelines question the benefit of prophylaxis in these patients based on the pivotal palivizumab trial that showed a significant reduction in RSVHs only in children with acyanotic (5.0% vs. 11.8% for placebo; p=0.003) not cyanotic (5.6% vs. 7.9%; p=0.285) CHD [6,64]. The authors clearly indicated that the study was underpowered for such subgroup analyses [64]. Furthermore, the more recent trial of motavizumab versus palivizumab reported a higher RSVH rate in acyanotic vs. cyanotic CHD in the palivizumab group (3.1% vs. 2.2%, respectively) [62]. Hence, there does not appear to be a strong rationale to exclude children with cyanotic HS-CHD from recommendations. Recent evidence also suggests that children with severe CHD diagnoses and/or who are unstable remain at high-risk of RSVH into the second year of life [65,66,67].

3.7 Evidence for RSV prophylaxis in other populations at specific high-risk
3.7.1 Down syndrome
In the absence of comorbidities, such as CHD, current guidelines do not routinely recommend palivizumab for children with Down syndrome [6,32]. Despite increasing
evidence that Down syndrome is a significant, independent risk factor for RSVH [68,69,70], clear recommendations have been limited by paucity of data on palivizumab effectiveness in this population. Several recent publications have sought to address this shortfall, and all provide further evidence that prophylaxis is effective in reducing the incidence of RSVH in children with Down syndrome [71,72,73,74]. In a combined Canadian-Dutch study (n=765), prophylaxis resulted in a 3.6-fold reduction RSVH incidence [72]. Palivizumab registry data from Canada, Italy and Germany indicate that RVSH incidence is similar in children with Down syndrome and those with standard indications for prophylaxis, such as CHD/CLD [71,73,74].

3.7.2 Cystic Fibrosis
The AAP guidelines recommend palivizumab in infants with cystic fibrosis (CF) with clinical evidence of CLD and/or nutritional compromise in the first year of life and in those with severe lung disease or weight <10th percentile in the second year of life [6]. Small, retrospective studies and registry data from the last 5 years show equivocal results on the effectiveness of palivizumab in children with CF [71,75,76,77,78,79]. Firmer evidence comes from a systematic review that found 7/10 CF studies reported a positive impact on RSVH rate [80], while a meta-analysis of six CF studies reported a RSVH rate of 1.8% (95% CI 0.8-4.8%) for palivizumab compared with 12.6% (95% CI 8.6-18.2%) for non-treated (p<0.001) [81].

3.7.3 Anatomic pulmonary abnormalities or neuromuscular disorders
The AAP recommends prophylaxis for infants’ ≤12 months with neuromuscular diseases or congenital anomalies that impair clearance of upper airway secretions [6]. Data from CARESS and Italian palivizumab registries reported a cumulative RSVH incidence of 7.88% in infants with neuromuscular disorders and 3.95% in those with pulmonary disorders [71]. In multivariate analysis, neuromuscular disorders were found to be an independent predictor of RSVH (odds ratio [OR] 4.29, 95% CI 2.30-8.00; p<0.01) [71].

3.7.4 Immunocompromised
The AAP guidelines state that palivizumab may be considered in children <24 months who are profoundly immunocompromised during the RSV season [6]. Evidence for palivizumab
remains limited in this population. A recent publication from the combined Canadian and Italian registries reported no RSVHs in the 56 immunocompromised infants that received palivizumab [71].

3.8 Evidence for long-term respiratory morbidity and RSV prophylaxis

There is an increasing body of evidence suggesting an association between RSV infection in infancy and recurrent wheezing and possibly asthma during childhood and COPD in adults [20,82,83,84,85]. Two recent studies of preterm infants 32-35 wGA (MAKI and SPRING) demonstrated a strong association between RSV infection in infancy and recurrent wheezing persisting to age 3, but normalised by age 6 [83,84]. Asthma rates of 8-76% following RSVH have been reported in follow-up studies up to 25 years [82]. It is reasonable to conclude that RSV infection in late preterm infants, born during a critical period of lung development and with decreased pulmonary function, can affect long-term respiratory outcome [86].

Several studies indicate that preventing RSV infection with palivizumab can reduce subsequent wheezing in premature children (≤35 wGA) [3,20,84,87,88]. In the MAKI trial, the proportion of children with wheezing was lower in the palivizumab group compared to the placebo group at the 6-year follow-up (11.6% vs. 19.9%; relative reduction 41.9%, 95% CI 6.5-63.9%) [84]. Similar results were seen in the Japanese CREW study, where physician-diagnosed recurrent wheezing was lower in palivizumab subjects than in untreated patients at 6 years (15.3% vs. 31.6%; p=0.003) [88]. However, in both studies there appeared to be no impact of palivizumab on asthma rates at 6 years [84,88].

A US retrospective study reported that the AAP policy change in 2009 for infants 32-35 wGA, which limited use of palivizumab to infants <3 months of age or to a maximum of 3 doses, resulted in a significant increase in recurrent wheezing (28.8% vs. 42.6%; OR 2.2, 95% CI 1.1-4.5; p=0.03) [89]. No information has been published to date regarding how implementation of the AAP 2014 guidelines has affected wheezing rates in this population.

3.9 Evidence for cost-effectiveness of RSV prophylaxis

Recent systematic reviews report incremental cost-effectiveness ratios (ICERs) ranging from USD$10000-170000/quality-adjusted life year (QALY) for children with CHD, $31000-
38000/QALY for those with CLD, and $800-800000/QALY for preterm infants (≤35 wGA) [90,91]. Factors such as availability and quality of epidemiological and clinical data, study characteristics, analytic models utilised, RSV seasonality, types and costs of resource use included, palivizumab acquisition costs and dosing schedule, inclusion of long-term consequences, and primary outcome measures all contribute to the variation in published ICERs [90,91]. Utilising risk factors to identify those at greatest risk of RSVH is widely applied to optimise cost-efficiency [49,50,51,52].

A salient example of contradictory results comes from two studies published within the last year assessing the cost-effectiveness of palivizumab in children 32-35 wGA [92,93]. A Dutch study found palivizumab not to be cost-effective, reporting an ICER of €214748/QALY [92], whilst a Spanish study found it to be cost-effective, at €17153/QALY [93]. Both analyses were based on robust studies undertaken in the native populations (Dutch: RISK/MAKI [20,84]; Spanish: FLIP-2/SPRING [83,94]). When the models were compared, however, a number of differences were apparent, most notably the cost of palivizumab (Dutch: €4717 based on 5.08 doses vs. Spain: €2111 based on 3.88 doses) and the time horizon (Dutch: 1 year vs. Spain: 6 years) (Table 2) [92,93]. Whilst the cost of palivizumab reflected local circumstances, the 6-year time horizon in the Spanish study allowed the longer-term effects of recurrent wheezing to be modelled [93]. Considering that there is evidence for recurrent wheezing extending to at least 3 years in the MAKI and SPRING studies (and longer in other studies) and that palivizumab is associated with reduced wheezing in this preterm population [3,20,83,84,87,88], using a 6-year time horizon seems a more appropriate approach [95].

Table 2: Comparison of Spanish and Dutch health economic models assessing the cost-effectiveness of palivizumab in children born 32-35 wGA

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
<td>Preterm children born 32-35 wGA divided into 3 groups:</td>
<td>Preterm children born 32-35 wGA divided into 4 groups:</td>
</tr>
<tr>
<td></td>
<td>1. High-risk of RSVH (&gt; 10%) and with palivizumab prophylaxis</td>
<td>1. Total population</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Subpopulation with 2 major and 2 minor</td>
</tr>
<tr>
<td>Low risk of RSVH (placebo)</td>
<td>2.</td>
<td>3. Usual clinical practice (no prophylaxis)</td>
</tr>
<tr>
<td>---------------------------</td>
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</tr>
<tr>
<td></td>
<td>4.</td>
<td>Subpopulation with 2 major risk factors*</td>
</tr>
</tbody>
</table>

**Palivizumab dose**
- 5.08 doses (based on National Institute of Health of the Netherlands data)
- 3.88 doses (based on FLIP-II study data [94])

**Comparator**
- No prophylaxis

**Type of evaluation**
- Cost-utility analysis

**Outcome measure**
- Incremental cost per QALY

**Type of model**
- Decision tree based on MAKI [20] and RISK [84] studies
- Decision tree of hypothetical cohort of 1000 preterm infants with characteristics similar to the FLIP-II study [94]

**Perspective**
- Society
- Society and National Health System

**Horizon**
- 1 year
- 6 years

**Costs**

<table>
<thead>
<tr>
<th>Direct health costs:</th>
<th>Non-healthcare direct costs:</th>
<th>Indirect costs:</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Pharmacological costs (palivizumab and bronchodilators), hospitalisation costs, cost of admission to PICU</td>
<td>Transport by ambulance (transfer from a secondary hospital to a tertiary hospital), transport of parents to health centres</td>
<td>Loss of productivity of parents (2 days per RSVH)</td>
</tr>
<tr>
<td>b) Pharmacological and administration costs, hospitalisation costs, admission cost to the PICU and direct costs of the management of recurrent wheezing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>c) Indirect costs: management of recurrent wheezing</td>
<td></td>
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</tr>
</tbody>
</table>

**Palivizumab dose**
- 5.08 doses (based on National Institute of Health of the Netherlands data)
- 3.88 doses (based on FLIP-II study data [94])
Major risk factors included chronic age <10 weeks at the beginning of the RSV season or born during the first 10 weeks of the season, school-age siblings, or day care attendance; minor risk factors included maternal smoking during pregnancy and male gender.

All health economic studies should also include costs associated with ER visits, outpatients and primary care, to more accurately reflect the total burden of RSV infection. A Spanish study, using data from 2010-2011, estimated that a single ER visit for a RSV infection resulted in a total cost of €286.50 (standard deviation [SD] 151.5) [96]; equating to approximately €20 million per RSV season in Spain [96].

Further measures to support modelling should involve collaborative studies, using standardised terminology, to accurately assess the incidence of RSV infection both within the community and hospital and stratify outcomes, including healthcare resource use, mortality, and long-term respiratory morbidity, based on identified risk profiles. It is important that economic models consider the societal impact of RSV infection [97] and how certain risk factors, such as day-care attendance and smoking exposure, may vary between different socioeconomic groups and impact healthcare resource utilisation. Despite commonality in risk factors and certain similarities in healthcare resource use when managing a RSVH [44,52], differences between countries in terms of costs, where parents seek treatment, criteria for admission, protocols followed etc. render broad statements on cost-effectiveness challenging.

4. RECOMMENDATIONS FOR RSV PROPHYLAXIS

The use of palivizumab for the prevention of RSVH is recommended in a number of high-risk patient groups (Table 3).

Table 3: Summary of recommendations

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Level of evidence*</th>
<th>Strength of recommendation/</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palivizumab use</td>
<td>b) Probabilistic sensitivity analysis</td>
<td>b) Probabilistic sensitivity analysis</td>
</tr>
</tbody>
</table>
## Preterm infants without other comorbidities
Palivizumab is recommended for infants:

- ≤29 (≤28<sup>6</sup>) wGA and ≤9 months at the start of the RSV season
- 29-31 (29<sup>0</sup> to 31<sup>6</sup>) wGA and ≤6 months at the start of the RSV season
- 32-35 (32<sup>0</sup> to 35<sup>6</sup>) wGA and high-risk (score: 50-56) using a country-specific or generalisable risk factor scoring tool [52] (Figure 2)

### Children with CLD/BPD
Palivizumab is recommended:

- For 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*

### Children with CHD
Palivizumab is recommended for:

- Infants ≤12 months with haemodynamically significant cyanotic or acyanotic disease
- Children 12-24 months, cyanotic or acyanotic, who remain haemodynamically unstable

### Down syndrome (without other comorbidities)
Palivizumab is recommended for:

- Children with Down syndrome ≤24 months

### Cystic Fibrosis (without other comorbidities)
Palivizumab is recommended for:

- Infants ≤12 months
- Children in the second year of life with manifestations of severe lung disease or weigh <10<sup>th</sup> percentile

### Anatomic pulmonary abnormalities or neuromuscular disorder
Palivizumab is recommended for:

- 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)

### Immunocompromised
Palivizumab is recommended for:

- Children ≤24 months who are profoundly immunocompromised (e.g. primary immunodeficiency syndromes, immune suppression following...
haematopoietic stem cell transplantation, solid organ transplantation
or cytotoxic chemotherapy)

Dosing

- 15 mg/kg once a month to cover RSV season (maximum 5 doses) for all
  children

Children born during the season will require fewer doses

*1a: systematic review of randomised controlled trials (RCTs); 1b: individual RCT; 2a: systematic review of cohort studies; 2b: individual cohort study; 2c: outcomes research registries; 3a: systematic review of case-control studies; 3b: individual case-control study; 4: case series; 5: expert opinion

†GRADE – A: consistent with level 1 studies (high quality); B: consistent with level 2 or 3 studies or extrapolations from level 1 studies (moderate quality); C: level 4 studies or extrapolations from level 2 or 3 studies (low quality); D: level 5 evidence (very low quality)

4.1 Discussion and Conclusions

The expert panel developed these up-to-date consensus recommendations based on a systematic evaluation of the current evidence, a careful assessment of existing national practices, and their own experiences in managing infants and children with severe RSV infection. The recommendations are broadly in line with the AAP 2014 policy, but with several notable differences. Specifically, the group recommends prophylaxis in infants ≥29 wGA (with risk factors used for 32-35 wGA), as there is clear evidence that this is a high-risk population and that RSVH rates have significantly increased since the implementation of the 2014 policy. A key concern in this large population is cost. Therefore, the panel recommends the use of a validated risk factor scoring tool in moderate-late preterm infants to ensure that prophylaxis is targeted to those at highest risk of complications. Other cost-effectiveness measures include restricting prophylaxis in infants <29 wGA to those ≤9 months of age to minimise potentially unnecessary treatment over two RSV seasons. Another key difference from the AAP policy is to recommend prophylaxis for children with CHD who remain haemodynamically unstable in the second year of life irrespective of cyanosis, as studies have shown that these children remain at a significantly increased risk of RSVH. Finally, the group recommends that the definition of CLD/BPD and the designation of high-risk in the second year of life be under the remit of the treating physician or local practice, due to the number of definitions available and the impact of contemporary practice on the relevance of those definitions. The panel believes that these recommendations are evidence-based and provide a flexible framework for adoption and
strongly endorse their implementation to help better manage the consequences of RSV infection in vulnerable infants and children.

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This consensus did not receive funding. Most authors (all except Barry Rodgers-Gray) attended a prior advisory board organized by AbbVie on a different topic, and working together realized that there was a growing consensus among them on specific issues related to RSV prophylaxis. Following the meeting, the authors decided to independently establish an expert working group with the aim of developing an RSV prophylaxis consensus paper. They invited BR-G to join the group. Barry Rodgers-Gray, who has worked with many of the group and published widely on RSV, provided project management and editorial support. All of the steps towards the writing of this manuscript following the advisory board were an independent activity of the authors.

Declaration of interest
MSL has acted as an expert advisor and speaker for AbbVie and has received honoraria in this regard. PM has acted as an expert advisor and speaker for AbbVie, TEVA, Janssen, SANOFI-Pasteur, Medimmune and GSK and has received honoraria in this regard. BP has acted as an expert advisor and speaker for AbbVie and has received honoraria in this regard. EB has acted as an expert advisor and speaker for AbbVie, Janssen, Sanofi-Pasteur and has received honoraria in this regard. VC has acted as an expert advisor and speaker for AbbVie and has received honoraria in this regard. AK has acted as an expert advisor and speaker for AbbVie and has received honoraria in this regard. RC has acted as an expert advisor and speaker for AbbVie and has received honoraria in this regard. AD has acted as an expert advisor and speaker for AbbVie and has received honoraria in this regard. RRF has acted as an expert advisor and speaker for AbbVie and has received honoraria in this regard. XCE has acted as an expert advisor and speaker for MedImmune, GSK, Novavax, Regeneron, Janssen, and has received honoraria in this regard.
REFERENCES


[67] Friedman D, Wong PC. Risk of Respiratory Syncytial Virus Hospitalization in the First and Second Years of Life in Pediatric Patients with Congenital Heart Disease. Pediatr Cardiol 2017;38:1311-1312.


Interaction between healthcare professionals and parents is a key determinant of parental distress during childhood hospitalisation for respiratory syncytial virus infection (European RSV Outcomes Study [EROS]). Acta Paediatr 2018;107:854-860.