Chapter

Resolving the Debate on RSV Prophylaxis in Late Preterm Infants

Bosco Paes, Barry Rodgers-Gray and Xavier Carbonell-Estrany

Abstract

There is still active debate in the scientific literature about the importance of providing respiratory syncytial virus (RSV) prophylaxis to late preterm infants born at 33–35 weeks' gestational age (wGA). The American Academy of Pediatrics and the Canadian Paediatric Society position statements only advocate for RSV prophylaxis for infants <30 wGA. Several publications prove the contrary, reporting substantial morbidity and even mortality in older GA infants, following RSV infection. Consequently, other Societies, such as from Spain and Italy, have different criteria, and include as candidates 30–32 wGA infants and 33–35 wGA infants with risk factors for severe RSV disease. This chapter will systematically examine the current evidence for RSV prophylaxis in both early and late preterm infants 29–35 wGA and the cost-effectiveness of this strategy with the use of risk scoring tools. The authors will attempt to reconcile the misconception that late preterm infants do not merit RSV prophylaxis and hopefully resolve the long-standing debate that currently exists in many countries worldwide.

Keywords: respiratory syncytial virus, palivizumab, prematurity, cost effectiveness, prevention, risk scoring tools

1. Introduction

Respiratory syncytial virus (RSV) infection is a common cause of lower respiratory tract infection (LRTI) in young children and is associated with a high global burden of incurred illness. In 2015, 2.8 million new episodes of RSV-related infections were reported in children <5 years of age in high income countries [1]. Of these, at least 383,000 cases required hospital admissions with 3300 accompanying deaths [1]. These figures represent a major healthcare burden, with costs estimated to be $545 million in the United States alone in 2009 [2].

Preterm birth, those born <37 weeks' gestational age (wGA), has been associated with an increased risk for severe RSV-related disease requiring hospitalization (RSVH) [3]. Possible explanations for the increased RSV infection rates in preterm infants are incomplete airway development with reduced alveolar and bronchiolar diameter, increased air space wall thickness, immature immunologic responses, and reduced levels of maternally transmitted, RSV-specific antibodies compared to infants born at term [4]. Globally, about 15 million infants per year are estimated to be born premature, nearly 10% of all births, and thus are at potentially increased risk for RSV infection [5, 6]. Furthermore, the World Health Organization (WHO)

reported that the incidence of premature birth is rising [5]. This highlights the importance of preventing RSV-related LRTI and indeed, the WHO has declared the prevention of RSV to be a key healthcare priority [7]. Although several vaccines and antibodies are currently in preclinical or clinical development, it is likely to be several more years before any become commercially available [8, 9]. Therefore, current therapeutic prevention relies solely on palivizumab, a humanized monoclonal antibody, which is indicated for the prevention of RSVH in high-risk infants, such as preterm infants born at ≤35 wGA or those with bronchopulmonary dysplasia (BPD)/chronic lung disease (CLD) or congenital heart disease (CHD) [10, 11]. However, several current guidelines, most notably from the American Academy of Pediatrics (AAP) and the Canadian Pediatric Society, seek to rationalize its use by recommending palivizumab only for infants born at <29 wGA without CLD [12–15], leaving the majority of preterm infants without therapeutic protection.

Risk-scoring tools (RSTs), models to estimate the risk of RSVH based on predetermined risk factors, have been developed to help identify infants at highest risk for RSVH, which may allow for targeted and cost-effective prophylaxis of infants born late preterm [16–19]. Some guidelines, such as those from Spain [20], Italy [21] and Austria [22], advocate the use of such a risk factor-based approach to extend prophylaxis to those preterm infants ≥30 wGA at highest risk.

This chapter aims to provide a rationale for palivizumab prophylaxis in late preterm infants and show that this can be cost effective with the use of validated RSTs.

2. Literature search

A literature review was undertaken using PubMed, EMBASE, and the Cochrane Library of studies including <37 wGA infants without CLD or CHD but with confirmed or probable RSV infection, published between 01 January 1998 and 31 December 2018. To maximize comparability of data, only studies conducted in Western countries, defined as the US, Canada, and Europe (including Turkey and the Russian Federation) were included. The following search terms were used, combined with Medical Subject Headings (MeSH): ["RSV" OR "respiratory syncytial virus" OR "lower respiratory tract infection" OR "LRTI" OR "acute respiratory tract infection" OR "ARTI" OR "ARI" OR "lower respiratory infection (LRI)" OR "bronchiolitis"] AND ["preterm" OR "premature" OR "gestational age" OR "gestation"] AND ["hospitalization*] OR [predisposition" OR "risk factor"] OR ["palivizumab" OR "Synagis" OR "immunoprophylax*" OR "prophylax*"] OR ["cost effective*" OR "Cost"] AND limits: "human, child (birth to 18 years)". Additional publications and reference citations of potential relevance were included as identified by the authors. All original studies, systematic reviews, meta-analyses, and prophylaxis guidelines with at least an English abstract were reviewed.

As this chapter was based solely on published data, ethical approval was not required.

3. Results and discussion

3.1 Literature search

A total of 3532 publications were identified from the literature search, of which 136 were deemed relevant (**Figure 1**). Another 20 references were identified from other sources, resulting in a final number of 156 publications considered during the drafting of this chapter.

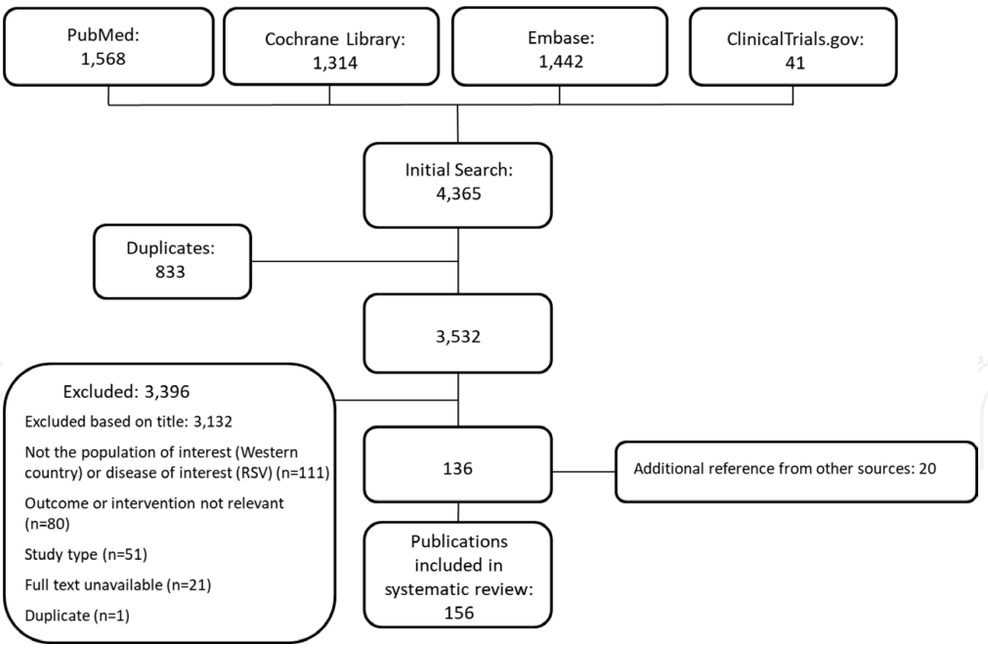

Figure 1.
PRISMA diagram: RSVH in preterm infants (<37 wGA) who received palivizumab.

3.2 What do current guidelines recommend?

There is considerable variation in the published recommendations from national guidelines on the use of palivizumab prophylaxis in preterm infants. The AAP 2014 policy [13, 14], which was unchanged following a review of new evidence in 2017 [15], recommends prophylaxis for healthy preterm infants only if born ≤29 weeks and 0 days (29o wGA) and aged <1 year at the start of the RSV season. The justification for this recommendation was partly based on a prospective, population-based surveillance program (n = 2149), undertaken from 2000 to 2005 in the US, which concluded that RSVH rates did not significantly differ between term (≥37 wGA) and preterm (<37 wGA) infants (5.3 vs. 4.6 per 1000 infants, respectively) [23]. Infants born at <30 wGA, on the other hand, experienced a significantly higher RSVH rate of 18.7 per 1000 infants [23]. Further evidence cited was from an analysis of the Tennessee Medicaid database (n = 248,652 infant-years), conducted in the 1990s, which reported higher rates of RSVH in infants <29 wGA compared to term infants with no underlying medical condition [24]. This difference remained consistently higher at up to 23 months of age: 0–5 months, 93.8 vs. 44.1 per 1000 infants; 6–11 months, 46.1 vs. 15.0 per 1000 infants; and, 12–23 months, 30.0 vs. 3.7 per 1000 infants [24]. Another study, which included 1029 ≤ 32 wGA preterm infants, found a decreasing RSVH incidence with increasing GA: ≤26 wGA, 139 per 1000 infants; 27–28 wGA, 99 per 1000 infants; 29–30 wGA, 75 per 1000 infants; and 30–32 wGA, 44 per 1000 infants [25]. Predicated on this evidence, the AAP concluded that the risk of RSVH is considerably higher in those born ≤29° wGA compared to those born between 29^{1} and 35^{6} wGA and, therefore, prophylaxis should be recommended only in the former [13, 14]. A similar recommendation and rationale is presented in the Canadian RSV position statement, published in 2015 [12]. The Canadian guideline concludes that it is "reasonable but not essential" to offer prophylaxis to infants born <30 wGA who are younger than 6 months at the start of the RSV season, but those born later do not merit prophylaxis, as the magnitude of difference in RSVH incidence between moderate to late preterm infants and infants born at term is not great enough to justify prophylaxis in this group [12]. The authors add that preterm infants are also less vulnerable to RSV infection nowadays

due to advances in technology and increased awareness of infection transmission. Preterm infants born >30 wGA are only eligible for prophylaxis if they live in remote regions and would require air transportation for hospitalization [12].

Other guidelines recommend more liberal use of prophylaxis for preterms, with Israeli guidelines, for example, recommending palivizumab for all preterm infants <33 wGA who are aged ≤1 year at the start of the RSV season and 33–35 wGA who are ≤6 months [26]. The Spanish and Italian guidelines recommend prophylaxis for those born between 29 and 31 wGA and aged ≤6 months at the start of the RSV season or if discharged during the season [20, 21]. For 32–35 wGA infants ≤6 months at the start of the RSV season, risk factors predisposing to severe infection and/or need for hospitalization guide the use of prophylaxis [20, 21]. Similar recommendations are reported in a recently published international, expert consensus guideline that guides cost-effective use of prophylaxis for high-risk 32–35 wGA infants with a validated RST [27]. Austrian guidelines have also adopted risk factors to guide prophylaxis for all 29–35 wGA infants, but with a chronological age cut-off of <6 months for 29–32 wGA and <3 months for 33–35 wGA [22].

3.3 Are late preterm infants at increased risk of RSVH compared to term infants?

Many studies in the literature report higher RSVH rates in late preterm infants and children (32–36 wGA) compared to those born at term (**Table 1**) [23, 28–31]. In a Dutch, community-based, cohort study that included 2099 children born between 2002 and 2003 (62 with RSVH), otherwise healthy 32–36 wGA children had a threefold higher RSVH rate compared with full term children (3.9 vs. 1.2%, respectively; relative rate 3.2) [28]. Further evidence comes from a US, retrospective, cohort study involving 599,535 children (7597 admitted for RSVH) that reported a higher RSVH incidence in 33–36 wGA children compared to full term children (12.1 vs. 7.8 per 1000 person-years) [29]. The adjusted hazard ratio for RSVH was 2.45 and 1.92 for children born at 33–34 wGA and 34–36 wGA, respectively [29]. Another US

Study	Number	Age (mo)	EP*	LP*	FT* (≥37 wGA)	Prophylaxed	EP/LP definition (wGA)
Hall 2013 [23]	2149	<24	18.7	6.9	5.3	20%	EP: <30 LP: 32–34
Boyce 2000 [24]	248,652 infant-years	<6	81.8	79.8	44.1	NR	EP: 29–32 LP: 33–35
Stevens 2000 [25]	1029	<12	230	119	NR	NR	EP: <29 MLP: 29–32
Gijtenbeek 2015 [28]	2099	<49	32	39	12	EP: 56.5% MP: 2.2%	EP: <32 LP: 32–36
Helfrich 2015 [29]	599,535	<24	NR	12.1+	7.8+	0%	LP: 33–36
Haerskjold 2015 [30]	421,943	<24	50.8+	28.0+	14.1+	NR	EP: 23–32 LP: 33–35
Cilla 2006 [31]	357	<12	44.2	78.1	1.91	0%	EP: <33 LP: 33–35

**Cases per 1000 infants; +cases per 1000 infant-years; RSVH, respiratory syncytial virus-related hospitalization; EP, early preterm; FT, full term; mo, months; LP, late preterm; MLP, moderate to late preterm; NR, not reported.*

Table 1.
Rates of RSVH.

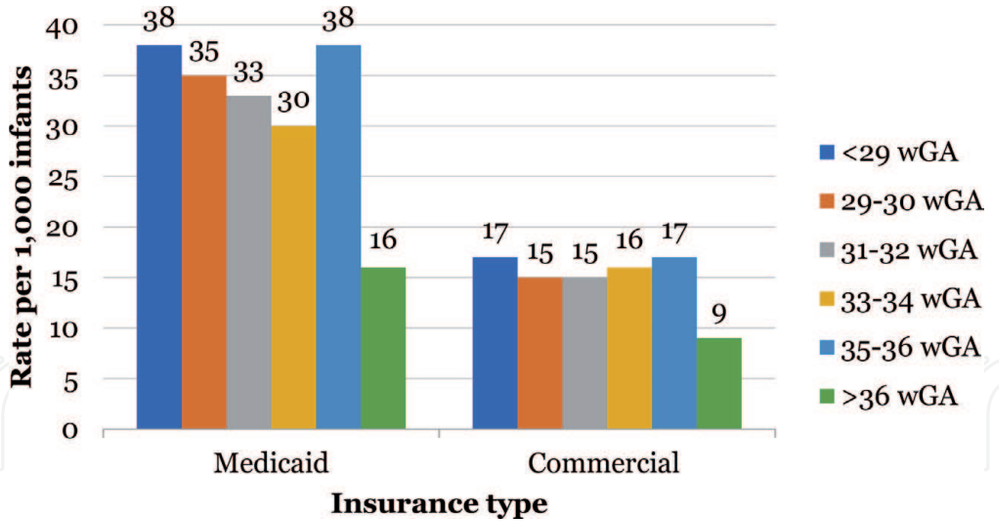

Figure 2.
Rates of RSVH by gestational age group [34]. Hospitalization rates of infants aged less than 1 year at the time of first RSVH in a large American database analysis involving 1,683,188 infants insured via Medicaid and 1,663,832 commercially insured infants [34]. RSVH, respiratory syncytial virus-related hospitalization; wGA, weeks' gestational age.

study, which included 247,566 infants (5322 RSVHs), found that 32–34 wGA infants were at double the risk of RSVH compared to term infants of the same age (odds ratio [OR] 1.94–2.41), and that the risk was highest in the youngest infants [32]. Young age was also associated with an increased risk of RSVH in 32–35 wGA infants in the REPORT study (n = 1642) [33]. Interestingly, older age was associated with higher rates of outpatient RSV visits, perhaps related to disease exposure [33]. A Danish database analysis found that, while RSVH incidence decreased with increasing GA, 33–35 wGA children still had a RSVH rate twice as high as full term children (28.0 vs. 14.1 per 1000 years at risk) [30]. Another retrospective study, from Spain, investigating infants born between 1996 and 2000 (n = 357), reported a RSVH rate of 44.2 per 1000 children for <33 wGA infants compared to 1.91 per 1000 for ≥38 wGA infants [31]. In this study, 33–35 wGA infants had the highest RSVH rate at 78.1 per 1000 [31].

Other studies have reported that there is not necessarily a simple linear relationship between lower GA and increased risk of RSVH. For example, in a large American database analysis involving 3,347,020 infants, RSVH rates were similar across all gestational age groups from <29 to 36 wGA (**Figure 2**) [34]. In 2016, a systematic review summarizing the evidence from 85 studies undertaken between 1995 and 2015 concluded that, due to considerable variability in methodologies and results, it could not be clearly determined that infants born at younger GAs had higher RSVH rates [3]. Overall, reported RSVH rates were approximately three times higher in premature than term infants, although there was considerable variability across studies (range 1.1–8.1 times higher) [3].

Of potential note, two of the key studies cited by the AAP as evidence to restrict prophylaxis to ≤29° wGA infants reported moderate to late preterm infants to be at high risk of RSVH when considering those aged <6 months [23, 24]. In the US population-based surveillance program [23], the RSVH rate for 32–34 wGA infants ≤5 months of age was 11.0 per 1000 children, compared to a rate of 2.6 per 1000 for those aged 6–23 months. Perhaps more revealing, the Tennessee Medicaid database analysis [24] reported a RSVH rate of 79.8 per 1000 children for 33–35 wGA infants <6 months old compared to 44.1 per 1000 for age-matched, low-risk infants (incidence rate ratio: 1.8, 95% confidence interval [CI]: 1.5–2.1).

3.4 What are the consequences of RSVH in late preterm infants?

The health burden associated with RSVH in late preterm infants has been shown to be substantial [28, 35–38]. A pooled analysis of 7 prospective studies from across the Northern Hemisphere, involving 7820 infants born 33–35 wGA [39–45], reported a median length of stay (LOS) in hospital for RSV of 5.7 days, with 22.2% of infants requiring intensive care unit (ICU) admission for a median of 8.3 days [35]. Supplemental oxygen support was required by 70.4% of cases for a median of 4.9 days and 12.7% required mechanical ventilation for a median of 4.8 days [35]. The US SENTINEL1 study (n = 709) reported a mean RSVH LOS of 5 days with 42% of 29–35 wGA infants being admitted to the ICU (mean ICU LOS: 6 days) [36]. Of those admitted to the ICU, 19% required mechanical ventilation [46]. In a Dutch cohort study [28], the RSV disease burden was found to be similar between <32, 32–36 and 38–42 wGA infants, with no significant differences in terms of hospital LOS (median of 8 vs. 7 vs. 7 days, respectively; $p > 0.3$), oxygen use (82.4 vs. 60.5 vs. 85.7%; $p > 0.1$), mechanical ventilation (5.9 vs. 15.8 vs. 42.9%; $p > 0.1$), or gavage feeding (29.4 vs. 39.5 vs. 42.9%; $p > 0.6$). Other studies, however, have indicated that the disease burden in late preterm infants is higher than in term infants [37, 38]. In a European survey of 3474 infants hospitalized with LRTI [37], while overall LOS in hospital was similar for 33–36 wGA and term infants (mean 11 vs. 9 days, respectively), 33.8% of the former were admitted to the ICU compared to only 14.1% of the latter. The highest disease burden was found in <29 wGA infants (mean LOS 29 days; 54.3% ICU) followed by 29–32 wGA infants (mean 24 days; 48.8% ICU) [37]. A retrospective US study [38], involving 215 term infants and 89 infants <37 wGA, reported that 33–35 wGA infants had the highest rate of intubation (38.7 vs. ≤32 wGA: 21.4% vs. 36 wGA: 20.0 vs. ≥37 wGA: 12.1%; $p = 0.002$) and longest hospital LOS (mean 8.4 vs. 6.8 vs. 4.9 vs. 4.1 days; $p < 0.0001$) and ICU LOS (mean 7.7 vs. 5.8 vs. 4.2 vs. 3.8 days; $p = 0.021$) compared with infants in other GA groups.

As a consequence of RSVH, preterm infants may develop longer-term morbidities, such as recurrent wheezing [47–51]. In the SPRING study, a multicenter, observational, nested, case–control study undertaken in Spain, 32–35 wGA infants with RSVH (n = 125) had a significantly higher incidence of recurrent wheezing through the first 6 years of life, independent of familial or childhood atopy, compared to infants born at the same GA without RSVH (n = 362) (66.7 vs. 49.2%, respectively; $p = 0.001$) [47]. While current wheezing rates remained higher in cases than controls each year, the difference remained significant only until 3 years old. Allied to this, respiratory-related quality of life was significantly lower in RSVH cases than controls (TAPQOL: 93.96 vs. 95.76, respectively; $p = 0.001$). Hospital resource use through 6 years of life was also higher in RSVH cases than controls (outpatient services: 84.0 vs. 66.3%, respectively, $p < 0.001$; emergency care: 62.4 vs. 33.7%, $p < 0.001$). Further analysis revealed that RSVH was the single most important factor for recurrent wheezing (OR: 4.40; $p < 0.001$) [47]. Similar results have been reported in the Dutch RISK study [51]. At the 6-year follow-up of this birth cohort of 2210 32–35 wGA infants, the current wheezing rate was 27.7% for RSVH cases and 17.6% for non-hospitalized infants (OR: 1.8; 95% CI: 1.11–2.85). RSVH was found to be an independent risk factor for current wheezing at 6 years in children without atopic predisposition (OR: 4.1; 95% CI: 1.22–12.52) [51]. Other studies have reported higher healthcare resource utilization (including emergency department visits, outpatient visits, and hospitalizations) in late preterm infants in the year following RSV LRTI compared to their counterparts without such an infection [52, 53].

3.5 How effective is palivizumab prophylaxis in late preterm infants?

Palivizumab has proven effective in late preterm infants, reducing the incidence of RSVH by up to 82% in prospective, comparative studies (**Table 2**) [8, 10, 11, 39, 54]. A *post-hoc* analysis of the pivotal IMpact study, a randomized clinical trial including 724 preterm infants, showed the effectiveness of palivizumab to be similar in <29 wGA and 32–35 wGA infants (relative risk reduction: 80.4 vs. 82.1%, respectively) [11]. The Spanish FLIP-2 study, which reported a 68.3% reduction in RSVH with prophylaxis, found that not receiving palivizumab was an independent risk factor for RSVH (OR: 0.25; 95% CI: 0.13–0.49) in 32–35 wGA infants [39]. Registry data have confirmed the efficacy of palivizumab, with the Palivizumab Outcomes Registry from the US reporting RSVH rates of 0.2–1.6% in 32–35 wGA infants across four RSV seasons (2000–2004) [55], compared to 10.1% in the placebo arm of the IMpact trial [11]. Similar results were seen in the Canadian Registry of Palivizumab (CARESS) [56], with a RSVH incidence of 1.4% in 33–35 wGA infants during the 2006–2011 RSV seasons, compared to 8.2% (untreated subjects) in the IMpact study [11]. A propensity score weighted regression analysis based on a prospective, international trial (n = 849), showed that palivizumab prophylaxis significantly reduced RSVHs by 74.1% in 29–35 wGA infants, without comorbidities, aged ≤6 months [57].

Some studies have indicated that restricting palivizumab to ≤29 wGA infants does not increase the overall RSVH rate in children <2 years, while saving money on palivizumab prescriptions [58, 59]. A retrospective US study reported no difference in RSVH rates following introduction of the AAP 2014 policy (pre: 5.37/1000 vs. post: 5.78/1000; p = 0.622) [58]. Similar results were reported in Italy following introduction of the same policy in 2016, with the RSVH rate being 6.3/1000 before implementation and 5.5/1000 afterwards [59]. Other studies, however, have reported RSVH rates to have increased by up to 103% following implementation of a more restrictive policy [60–63].

Several studies have indicated that, by preventing RSV infection, palivizumab can reduce subsequent wheezing in premature children, including those born late preterm [48, 54, 64–66]. In the MAKI study, a randomized, placebo-controlled trial of palivizumab that included 429 infants born at 32–35 wGA, the proportion of children with wheezing was reduced by 41.9% in the palivizumab group at 6 years (11.6 vs. 19.9% for placebo) [48]. Similar results were seen in the Japanese CREW study (n = 444; 349 received palivizumab ≤1 year), where recurrent wheezing was significantly lower in palivizumab-treated, 33–35 wGA infants than chronologically age-matched untreated infants (15.3 vs. 31.6%, respectively; p = 0.003) [65].

Study	Number	Gestational age group	RSVH incidence		RRR (%)
			Palivizumab	Untreated	
Notario 2014 [11]	724	32–35 wGA	1.8%	10.1%	82.1%
		33–35 wGA	2.2%	8.2%	73.2%
MAKI study, Blanken 2013 [54]	429	33–35 wGA	0.9%	5.1%	82.4%
FLIP-2 study, Figueras-Aloy 2008 [39]	5441	32–35 wGA	1.3%	4.1%	68.3%

RRR: relative risk reduction; RSVH: Respiratory-syncytial-virus-related hospitalization; wGA: weeks' gestational age.

Table 2.
Prospective, comparative studies on the effectiveness of palivizumab prophylaxis in reducing RSVH in late preterm infants.

3.6 Can the use of risk factors target infants at highest risk for RSV infection and improve the cost-effectiveness of prophylaxis in the late preterm population?

A key argument for restricting the use of palivizumab to <29 wGA infants is cost-effectiveness. Late preterm infants represent approximately 85% of preterm births [6], and it is unrealistic that prophylaxis of all these infants would ever be cost-effective. For this reason, the use of risk factors, to identify infants at the highest risk of RSVH, appears a pragmatic approach. There have been several RSTs developed and validated, including those in Canada [17], Spain [18], and the Netherlands [41]. Recently, a RST, involving 32–35 wGA infants, was published using pooled, individual patient data (n = 13,475) from six prospective, observational studies across the Northern Hemisphere [16], which included Canada [40], Italy [42], the Netherlands [41], Spain [39], the US [44], and a multinational cohort comprising subjects from Europe, the Middle East, North America, and Asia [45]. The RST was externally validated against a further study from Ireland (n = 1078) [43]. The RST includes three risk factors: birth 3 months before and 2 months after the RSV season start date; smokers in the household and/or smoking during pregnancy; and siblings (excluding multiples) and/or (planned) day-care (**Figure 3**) [16]. Predictive accuracy was demonstrated to be good, with an area under the receiver operating characteristic curve (AUROC) of 0.773, and sensitivity/specificity of 68.9 and 73.0%, respectively. The RST 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%) for RSVH [16].

The cost-effectiveness of using the multinational RST has not been formally assessed; however, economic evaluations have been undertaken on the use of other RSTs or risk-factor based approaches to targeting prophylaxis in late preterm 33–35 wGA infants [19, 67, 68]. The Canadian RST, based on data from the PICNIC study [40], included seven variables: small for GA (<10th percentile); male sex; born early during the RSV season (November, December, January); family history without eczema; subject or siblings in daycare; >5 individuals in the home, including the subject; and, >1 smoker in the household [17]. The AUROC was 0.762 and sensitivity and specificity were 68.2 and 71.9%, respectively. The RST included cut-off scores of 0–48, 49–64, and 65–100 for low-, moderate-, and high-risk infants, respectively

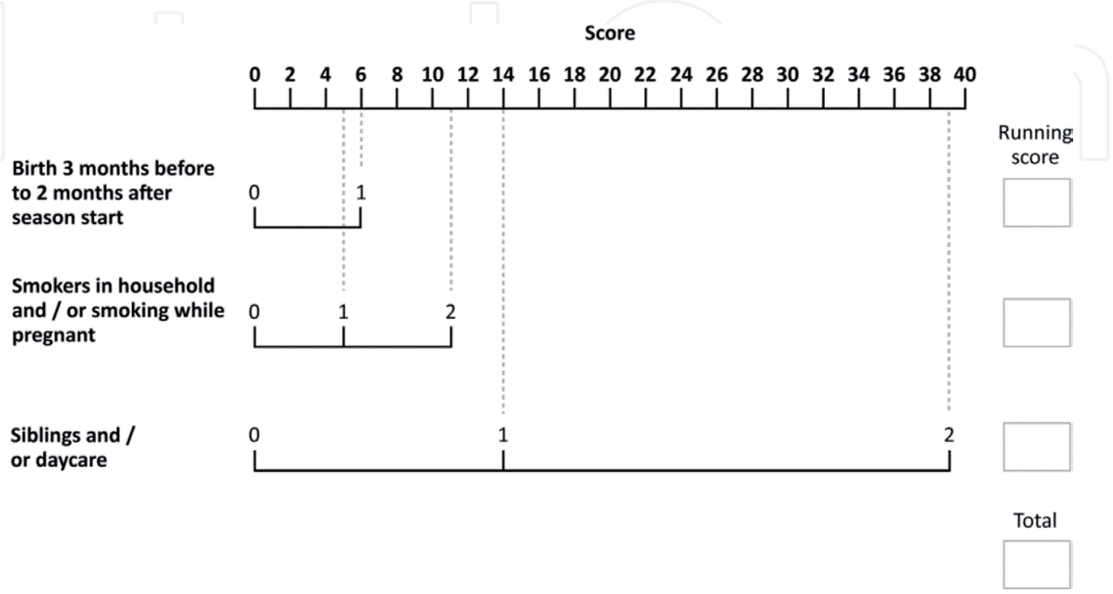

Figure 3.
Risk factor scoring tool for late preterm infants [16]. 0 = No/Not Present; 1 = Yes/Present for one risk factor; 2 = Yes/Present for both risk factors. Score—Low-risk: ≤19; Moderate-risk: 20–45; High-risk: 50–56.

[17]. A cost-effective analysis from 2008, using a decision analytic model, reported incremental cost-effectiveness ratios (ICERs) of CDN$179,699, CDN$34,215, and CDN$5765 per quality-adjusted life year (QALY) for low-, moderate-, and high-risk infants, respectively; the ICERs for moderate- and high-risk infants were considered cost-effective under the Canadian healthcare system (medications commonly adopted with ICERs per QALY of CDN$50–75,000 at that time) [19]. The Dutch RST was based on data from the RISK study and included four variables: family atopy; birth Aug-14 to Dec-01; breastfeeding; and siblings or daycare attendance [41]. The AUROC was 0.703 and the cut-off score for low-risk was defined as <16 (3.5% RSVH rate) and for high-risk as ≥16 (10.0% RSVH rate) [41]. Assuming all high-risk infants would receive prophylaxis, a decision model analysis produced an ICER of €214,748 per QALY, for moderately preterm infants 32–35 wGA, which was considered not cost-effective at a threshold of €80,000 per QALY [67]. Another analysis on 33–35 wGA infants, using data from the Spanish FLIP-2 study [39], assessed cost-effectiveness based on infants having either 2 major risk factors and 2 minor risk factors (group A), 2 major and 1 minor risk factors (B), or 2 major risk factors (C) [68]. Major risk factors included chronological age < 10 weeks at the start of the RSV season or being born during the first 10 weeks of the season, school-age siblings or daycare attendance; whereas minor risk factors included maternal smoking during pregnancy and male sex [69]. Again using a decision analytic model, the incremental cost-utility ratio of €11,550.37, €14,177.18 and €13,937.61 per QALY gained for groups A, B and C, respectively, were derived and were deemed all highly cost-effective based on a threshold of €30,000 per QALY from both a National Health System and societal perspective [68]. An Austrian analysis reported palivizumab prophylaxis to be cost-effective in 33–35 wGA infants at €21,862 per QALY from the healthcare system perspective, when administered to those <3 months of age with risk factors [70]. It is important to note that the Canadian, Spanish and Austrian analyses modeled the effects of long-term respiratory morbidity, using life-time (Canadian and Austrian) and 6-year time horizons (Spanish), while the Dutch study included follow-up to only 1 year of age [19, 67, 68, 70]. This could, in part, account for the differences in cost-effectiveness reported. It would be interesting to see the impact on the ICERs if the increased rates of wheezing in children with a history of RSVH at 6 years in the RISK study (27.7 vs. 17.6% for non-hospitalized) were incorporated into the Dutch cost-effectiveness analysis. The ICERs reported from all three studies reflect costs from the healthcare system or payer perspective; including the societal impact of RSVH could potentially reduce the ICERs by 15–40% [19, 68]. The models also do not include the impact of RSV in the community setting, which could reduce the ICERs still further.

4. Conclusion

There is a sizable body of evidence demonstrating that late preterm infants are at increased risk of RSVH, resulting in substantial morbidity, both in terms of acute hospitalization and longer-term respiratory sequelae. While we await the availability of a safe and effective vaccine or a newer monoclonal antibody with an extended half-life, palivizumab remains the only proven therapy for reducing the incidence of RSVH in late preterm infants, and may also reduce subsequent wheezing. The use of RSTs and risk factors provides a mechanism to cost-effectively target the most vulnerable of these infants to receive palivizumab. It is recommended that countries adopt the multinational RST (**Figure 3**) and adapt this with local data and cut-offs, as available, to meet country-specific requirements and available funding.

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Conflict of interest

Xavier Carbonell-Estrany has acted as expert advisor and speaker for AbbVie and has received honoraria for this. Bosco Paes has received research funding and compensation as advisor and lecturer from AbbVie Corporation. Barry Rodgers-Gray is an employee of Strategen; Strategen has received fees for work on various projects for AbbVie. The authors have no other conflict of interest to declare.

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