Effectiveness of Palivizumab in Preventing RSV Hospitalization in High Risk Children: A Real-World Perspective

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Infection with respiratory syncytial virus (RSV) is one of the major causes globally of childhood respiratory morbidity and hospitalization. Palivizumab, a humanized monoclonal antibody, has been recommended for high risk infants to prevent severe RSV-associated respiratory illness. This recommendation is based on evidence of efficacy when used under clinical trial conditions. However the real-world effectiveness of palivizumab outside of clinical trials among different patient populations is not well established. We performed a systematic review focusing on postlicensure observational studies of the protective effect of palivizumab prophylaxis for reducing RSV-associated hospitalizations in infants and children at high risk of severe infection. We searched studies published in English between 1 January 1999 and August 2013 and identified 420 articles, of which 20 met the inclusion criteria. This review supports the recommended use of palivizumab for reducing RSV-associated hospitalization rates in premature infants born at gestational age < 33 weeks and in children with chronic lung and heart diseases. Data are limited to allow commenting on the protective effect of palivizumab among other high risk children, including those with Down syndrome, cystic fibrosis, and haematological malignancy, indicating further research is warranted in these groups.

1. Introduction

Globally, respiratory syncytial virus (RSV) is one of the major causes of childhood acute lower respiratory infection (ALRI) associated morbidity, hospitalization, and mortality. In 2005, there were an estimated 3.4 (95% CI 2.8–4.3) million episodes of severe RSV-associated childhood ALRIs necessitating hospital admission [1]. The risk of RSV infection is highest in children born prematurely or those with existing comorbidities including bronchopulmonary dysplasia/chronic lung disease (BDP/CLD), congenital heart disease (CHD), cystic fibrosis (CF), multiple congenital anomalies, and immunodeficiency [2–4].

The reported RSV hospitalization rate in premature infants ranges between 5.2% and 16.8% [5–8]. RSV hospitalization of high risk infants and children is associated with significant health care resource utilization and monetary costs [9, 10]. A high proportion of high risk infants and children hospitalized with RSV infection require admission to an intensive care unit and mechanical ventilation [11]. In the United States it has been estimated that the annual cost of hospitalization for RSV pneumonia in children aged < 4 years is approximately $US3 to 4 million [12]. There are additional costs associated with outpatient visits, follow-up, and lost productivity due to parents taking time off work to care for sick children [10].

These factors make prevention of RSV infection a global public health priority, although no active vaccination strategy is yet available. Palivizumab, a humanized monoclonal anti-RSV antibody, was shown to reduce hospitalizations and the clinical severity of RSV infection in high risk infants and children by 55% in a randomised controlled trial [3]. The updated
recommendation of the American Academy of Pediatrics (AAP) recommends prophylactic use of palivizumab for children with chronic lung disease of prematurity, congenital heart disease, or other chronic illnesses and for children born at gestational age (GA) less than 29 weeks [13]. The AAP recommends that eligible children should receive no more than five monthly doses of palivizumab [13]. Though guidelines for use of palivizumab for children born with chronic illness are similar across the developed countries, the cut-off gestational age for premature infants varies widely. New Zealand’s recommendation is for use in premature infants born at GA ≤ 28 weeks, infants discharged home on oxygen, or those born at GA 29–32 weeks with birth weight of 1000 g or less [14]. The cut-off for GA is <26 weeks in Sweden [15]. Recommendations from Australia and Canada include children born up to 32–35 weeks with two or more risk factors associated with RSV infection [16, 17]. Currently, palivizumab is not routinely recommended for use in children with immune deficiencies, Down syndrome, cystic fibrosis, upper airway obstruction, or other chronic lung diseases.

The cost of a single course of palivizumab is estimated to be as much as $US4458 per child [18]. Due to its high cost and limited evidence of cost-effectiveness [19], the use of palivizumab is restricted even in well-resourced settings. The cost-effectiveness of palivizumab is largely dependent on its effectiveness across specific subgroups of high risk children.

Several systematic reviews have demonstrated the effectiveness of palivizumab in reducing the subsequent hospitalization rates in high risk children. These reviews have concluded that palivizumab is effective in reducing RSV hospitalization rates by >40% in premature infants and high risk children. However most of these reviews have included efficacy trials conducted under strict controlled environment [20–22]. While randomised trials provide high level evidence of the efficacy of an intervention under idealised conditions, postlicensure observational studies assess the “real-world” value of an intervention under more realistic conditions, where eligibility criteria are less rigidly applied and doses may be delayed or omitted [23]. The objective of this narrative systematic review was to identify which high risk infants and children have been proven to benefit most from palivizumab prophylaxis under real-world practice settings, to identify gaps in existing knowledge, and to provide recommendations for future research.

2. Methods

2.1. Selection Criteria for the Studies

2.1.1. Study Type. Only full-length peer-reviewed observational studies (cohort, case-control, and cross-sectional studies including survey) published in English were included in the review. As the first randomised trial was published in September 1998 [3], we included studies that were published between January 1999 and August 2013. We excluded conference proceedings, review articles, or editorial reports. We also excluded clinical trial data as we were interested only in the “real-world” effectiveness of palivizumab.

2.1.2. Study Participants. Study participants were high risk infants and children aged < 2 years, including premature infants (GA < 37 weeks) and children with any chronic congenital conditions that may put them at risk of severe RSV disease.

2.1.3. Outcome Measure. As the primary interest for this review was the incidence/rate of RSV hospitalization as a measure of prevention of severe RSV disease by immunoprophylaxis with palivizumab, only studies that examined the effect of palivizumab on subsequent RSV hospitalization were included.

2.2. Identification of the Studies. We conducted a comprehensive MEDLINE search using the MESH terms “respiratory syncytial virus and primary prevention/immunization,” “respiratory syncytial virus and secondary prevention,” “respiratory syncytial virus and antibodies, monoclonal/or antibodies, monoclonal, humanized/,” “respiratory syncytial virus and hospitalization,” “respiratory syncytial virus and antioxidant,” “respiratory syncytial virus and passive immunization,” “respiratory syncytial virus and palivizumab,” and “respiratory syncytial virus and child.” Secondary searches were performed using EMBASE, CINHAL, and Global Health databases using the same keywords. Additional literature was identified by searching the citation list of the identified articles. We also looked for relevant literature using Google Scholar. All the searched results were merged into one single document and all duplicates were removed using Endnote. Once duplicates were removed, we examined the title and the abstract of the literature to exclude articles that did not meet our inclusion criteria. The full length of the relevant articles was retrieved and examined to further determine if they met inclusion criteria.

Each full-length article was reviewed by one researcher (NH) and the summary information extracted using a standardised form following the PRISMA guideline [24]. The data extracted for each article were author, year, and country of publication, time frame of the study, study population, sample size, intervention strategy, dosing regimen, study outcomes, and conclusion. The investigator then shared the abstracted summary form with all other investigators for their review and consensus.

3. Results

The initial search identified 420 articles (Figure 1). After removing studies that did not meet our inclusion criteria, 20 studies were included: 12 were cohort studies, 7 were record reviews, and one was a questionnaire-based survey. The included studies were conducted in the USA, Canada, Australia, Japan, Korea, and Europe (Figure 2).

3.1. Effectiveness of Palivizumab for Preventing RSV-Associated Hospitalization in Premature Infants (Table 1). Twelve papers [23, 25–35] reported the effectiveness of palivizumab in reducing RSV hospitalization in 89,469 premature infants with or without CLD. Five studies included premature infants...
372 papers identified from database search

372

Citations excluded:
duplicate citations: 274
irrelevant citations: 35

63 relevant citations remained

63

Citations excluded:
duplicate citations: 35
reviews: 11
studies not published in English: 12
cconference proceedings: 4
randomised clinical trials: 2

48 papers identified from additional sources

48

111 relevant citations remained

111

Detailed information evaluated (n = 47)

20 papers included in the final analyses

20

Citations excluded:
different outcome measures: 10
different study population: 6
nonprophylaxed high risk infants: 7
different intervention strategies: 2
study on ethical issues around clinical trial: 1
prophylactic regimen: 1

Figure 1: Flow diagram for selection of papers for the review.

Observational studies on effectiveness of palivizumab in preventing hospitalization in high risk infants and children (n = 20)

Types of study

Cohort studies: 12
Record reviews: 7
Survey: 1

Study sites

USA: 9
Canada: 3
Australia: 1
Sweden: 1
Austria: 1
France: 2
Spain: 1
Japan: 1
Korea: 1

Study population

Premature infants with/without CLD: 15
Children with congenital heart disease (HS-CHD): 2
Children with cystic fibrosis (CF): 2
Children with Down syndrome (DS): 1

Figure 2: Characteristics of the selected studies on effectiveness of palivizumab in reducing RSV-associated hospitalization in high risk infants and children.

born at GA < 36 weeks with or without CLD [23, 26, 28, 34, 35], three studies included only very preterm infants born at GA < 33 weeks [29–31], and four included only premature infants with CLD [23, 25, 30, 34, 36]. Two included studies compared differences in the rate of RSV hospitalization among prophylaxed and nonprophylaxed infants over one RSV season [25, 29], five studies compared rates in prophylaxed and nonprophylaxed groups over noncontemporaneous seasons [23, 26–28, 31], and in two studies rates in prophylaxed infants were compared with rates in nonprophylaxed infants from other published studies [33, 34].

Two of the five studies [26, 28] which included any premature infant born at GA < 36 weeks reported a statistically significant reduction (P < 0.05) in RSV hospitalization among prophylaxed compared to nonprophylaxed infants (19–29% rate reduction). Two of the remaining three studies [33, 34] did not have a contemporaneous comparison group or compared the rates to children from other published studies [3, 8]. The remaining study [23] which included late preterm infants (GA 33 to 35 weeks) reported a nonsignificant reduction of 0.6%. Some of the significant risk factors associated with increased risk of RSV hospitalization in premature infants born at GA ≤ 35 weeks included preterm births at GA < 31 weeks, intrauterine growth retardation, single mother family [29], and having siblings at home, more than 5 individuals in the household, and smokers at home [35].

In all of the identified studies which included infants born at GA < 32 weeks, the rate of RSV hospitalization was lower in infants who received palivizumab [27, 29–31, 34];
| Author, year, and location | Study design | Timeline | Study population | Intervention strategy | Sample size | RSV hospitalization rates | Conclusion | Quality of study |
|---------------------------|-------------|----------|------------------|----------------------|-------------|--------------------------|-----------|-----------------|
| (1) Sorrentino and Powers, 2000, USA [33] | Retrospective chart review | 1998-1999 | Premature infants with GA ≤ 35 weeks and age < 2 years with CLD | Palivizumab only | 1839 | Infants without CLD = 2.1%, with CLD = 4.0%, and with CF = 0% | Hospitalization rates in prophylaxed children were similar to rates in prophylaxed children from IMPact-RSV trial [3] | Low |
| (2) Singleton et al., 2003, Alaska [26] | Cohort study | 1993–2001 | Premature infants GA < 36 weeks | Prepalivizumab era (1993–1996) versus postpalivizumab era (1998–2001) | Prepalivizumab era: 992 Postpalivizumab era: 1087 | Prepalivizumab era = 439/1000 births Palivizumab era = 150/1000 births (P < 0.01) | The rate decreased by 3-fold with palivizumab | Moderate |
| (3) Pedraz et al., 2003, Spain [27] | Cohort study | 1998–2000 and 2000–2002 | Premature infants with GA ≤ 32 weeks without CLD and children aged < 2 years with CLD | Prepalivizumab era (1998–2000) versus postpalivizumab era (2000–2002) | Nonprophylaxed group: 1583 Prophylaxed group: 1919 | Infants ≤ 28 week GA: nonprophylaxed = 13%, prophylaxed = 5.4% (P < 0.0001) Infants 29–32 week GA: nonprophylaxed = 9.9%, prophylaxed = 2.5% (P < 0.0000) Infants with CLD: nonprophylaxed = 19.7%, prophylaxed = 5.5% (P < 0.007) | Effective for children with GA ≤ 32 weeks and for children with CLD | Moderate |
| (4) Lacaze-Masmonteil et al., 2004, France [29] | Cohort study | 2000–2001 | Premature infants with <33 week GA | No palivizumab versus palivizumab | Nonprophylaxed group: 2370 Prophylaxed group: 376 | Nonprophylaxed = 20.1% Prophylaxed = 8.4% (P < 0.001) | Protective benefits for infants with GA < 33 weeks | Low |
| (5) Parnes et al., 2003, USA [34] | Record review | 2000-2001 | All children eligible for palivizumab according to AAP guidelines [40] | Received at least one dose of palivizumab | 2116 GA < 32 weeks: 986 (46.6%) GA 32–35 weeks: 957 (45.2%) GA > 35 weeks: 172 (8.1%) | All infants = 2.9% Infants with CLD = 5.8% Infants < 32 weeks of GA = 4.5% Infants > 35 weeks of GA = 0.6% | RSV hospitalization rates lower compared to rate of 13% in nonprophylaxed children from Spain [8] | Low |
| Author, year, and location | Study design | Timeline | Study population | Intervention strategy | Sample size | RSV hospitalization rates | Conclusion | Quality of study |
|----------------------------|--------------|----------|------------------|-----------------------|-------------|--------------------------|------------|-----------------|
| (6) Henckel et al., 2004, Sweden [30] | Cohort study | 1992–2002 | Preterm infants with CLD and age < 2 years and extremely preterm infants | No palivizumab versus Palivizumab | Nonprophylaxed group: 61,990, prophylaxed group: 23,351 | Infants with CLD: nonprophylaxed = 6.8%, prophylaxed = 7.3% (P = 0.91) | Use of palivizumab may be restricted to very preterm infants (GA < 26 weeks) suffering from severe CLD | Low |
| (7) Singleton et al., 2006, Alaska [28] | Cohort study | 1994–1997 and 2001–2004 | Premature infants GA < 36 weeks | Prepalivizumab era (1994–1997) versus postpalivizumab era (2001–2004) | 2555 children | Palivizumab era = 317/1000 births/year | Palivizumab reduced hospitalization rate in premature infants | Low |
| (8) Mitchell et al., 2006, Canada [23] | Cohort study | 1995–2002 | All premature infants | Prepalivizumab era (1995–1998) versus postpalivizumab era (1999–2002) (in Calgary palivizumab was introduced in 1999 whereas in Edmonton palivizumab was not administered) | Calgary: 2,876, postpalivizumab era = 842 | Edmonton = 71%, Calgary = 2.9% (P = 0.004) | Effective for infants with GA < 33 weeks with other comorbidities Could be upgraded to moderate | Moderate |
| Author, year, and location | Study design | Timeline | Study population | Intervention strategy | Sample size | RSV hospitalization rates | Conclusion                                                                 | Quality of study |
|---------------------------|-------------|----------|------------------|-----------------------|-------------|--------------------------|-------------------------------------------------------------------------------|-----------------|
| (9) Kusuda et al., 2006, Japan [25] | Nonrandomised questionnaire survey | 2002-2003 | All premature infants born at GA ≤ 35 weeks and infants with CLD | No palivizumab versus palivizumab | Nonprophylaxed group: 41 Prophylaxed group: 35 | Nonprophylaxed group = 1.3% Prophylaxed group = 1.4% | Small sample size to determine conclusive result | Very low |
| (10) Grimaldi et al., 2007, France [31] | Cohort study | 1999–2004 | Premature infants with GA ≤ 30 weeks without BPD | Prepalivizumab era (1999–2002) versus postpalivizumab era (2002–2004) | Prepalivizumab era: 118 Postpalivizumab era: 88 | Prepalivizumab era = 13.5% Postpalivizumab era = 1.1% (P < 0.0001) | Palivizumab reduced hospitalization rate | Low |
| (11) Chang et al., Hospital record 2010, Korea [36] | Hospital record review | 2004–2009 | Children were born at ≤ 35 weeks of GA, were < 2 years of age, and had received medical therapy for CLD | No palivizumab versus palivizumab | Nonprophylaxed group: 53 Prophylaxed group: 75 | Nonprophylaxed group = 22.6% Prophylaxed group = 4.0% (P < 0.001) | Palivizumab reduced RSV hospitalization in children with CLD | Low |
| (12) Paes et al., 2012, Canada [35] | Cohort study | 2006–2011 | Group 1: premature infants GA ≤ 32 weeks without preexisting medical disorders Group 2: premature infants GA 33–35 weeks completed weeks | Comparison between prophylaxed Group 1 and prophylaxed Group 2 | Group 1: 5,183 Group 2: 1,471 | Group 1 = 1.5% Group 2 = 1.4% (P = 0.3) | Palivizumab prophylaxis beneficial for infants with 33–35 week GA but should be country-specific | Low |
the reported reduction ranged between 1.2% and 12.4% and in 4 of 5 studies [23, 27, 29, 31] this reduction was statistically significant. Seven of eight studies [23, 25–27, 30, 33, 34, 36] that included premature infants with chronic lung disease reported a statistically significant reduction in children who received palivizumab compared to those who did not; the reduction varied between 0.5 and 29%. 

3.2. Effectiveness of Palivizumab in Preventing RSV-Associated Hospitalization in Children with Hemodynamically Significant Congenital Heart Disease (HS-CHD) (Table 2). One study based on hospital record review [37] investigated the effect of palivizumab among 266 children aged <2 years with CHD (Table 2). Rates of RSV hospitalization in prophylaxed children were 19% lower than for nonprophylaxed infants from a different RSV season. The authors concluded the reduction was modest compared to the effect demonstrated in the multinational trial that investigated palivizumab in children with CHD [38] and recommended further assessment of the real-world benefit of palivizumab in this group of children.

3.3. Effectiveness of Palivizumab in Preventing RSV-Associated Hospitalization in Children with Cystic Fibrosis (CF) (Table 2). Two studies included 2966 children with cystic fibrosis [39, 40]. One study compared RSV-associated hospitalization rates between prophylaxed and nonprophylaxed children during the same RSV season, reporting a nonsignificant reduction of 0.2% in the prophylaxed group. A retrospective record review of children with CF listed on a hospital based palivizumab registry reported significantly lower odds of RSV hospitalization in prophylaxed children compared to the reported risk from other published studies.

3.4. Effectiveness of Palivizumab in Preventing RSV-Associated Hospitalization in Children with Down Syndrome (Table 2). One study used data from the Canadian Registry of Palivizumab to compare the rate of RSV hospitalization among 600 children with Down syndrome who received prophylaxis with that of 12,710 children without Down syndrome who received palivizumab [41]. The hospitalization rate in children with Down syndrome (1.53%) was similar to that of other children receiving palivizumab (1.45%).

3.5. Association between Dosing of Palivizumab and RSV-Associated Hospitalization (Table 3). The number of Palivizumab doses per child in each RSV season varied between the included studies. Three studies [34, 37, 42, 43] reported an association between the number of doses of palivizumab and the subsequent RSV-associated hospitalization rate in 4,372 children. Palivizumab registry review showed that missed or delayed dosing of palivizumab was associated with statistically significant increase in hospitalization rate in infants who missed or delayed a dose compared to those who were compliant with the scheduled dosing regimen of palivizumab (4.4% versus 2.4%; \( P = 0.02 \)) [34]. A cohort study [43] that included premature infants of GA 29 to 32 weeks also reported a lower RSV hospitalization rate in children prophylaxed according to the standard recommendation of 5 doses, compared with the rate in children who received inadequate prophylaxis, that is, children who did not receive the recommended five full doses (3.3% versus 8.1%, \( P = 0.07 \)). Another cohort study [37] among children with HS-CHD reported a reduction in RSV hospitalizations from 7–9 cases/year when children received palivizumab ad hoc to 2-3 cases/per year when prophylaxis was administered systematically and in accordance with recommendations (\( P = 0.03 \)). One study [44] reported a lower incidence of RSV hospitalization among 17,641 children who received palivizumab at home (0.4%) compared to 1226 children who received it in a clinic (1.2%) (\( P = 0.014 \)).

4. Methodological Quality of the Studies

We used the Cochrane GRADE approach to rate the quality of the included studies [45]. The GRADE approach is probably of most relevance for clinical trials as observational studies are inherently prone to bias. However observational studies can nonetheless be upgraded or downgraded based on design, consistency, and precision of results, directness of the evidence, risk of bias, and presence of confounders [45]. Two of the studies included in this review were downgraded to a “very low” quality due to small sample size [25] and lack of a contemporary comparison group [39] limiting the external validity of the study findings. Due to directness of evidence, precision, and comparability of the results, three of the included studies were upgraded to a moderate quality [23, 26, 27] while no other studies required downgrading.

5. Discussion

Palivizumab prophylaxis was first shown to reduce RSV-associated hospitalization by 39–78% in premature infants and in children with CLD/BPD in a multinational randomized controlled trial [3]. This landmark trial was subsequently followed by several postlicensure studies in various settings which were included in this review. Our review of these studies found that they also support protective effect of palivizumab against RSV hospitalization among premature infants and in children with CLD, although the size of benefit across the studies was more modest than reported in the clinical trial. Although we did identify studies that reported statistically significant reduction of RSV hospitalization rates among all premature infants with GA < 36 weeks [26, 28], these studies did not stratify the effectiveness in children born at GA 32–35 weeks with additional risk factors. This makes the results inconclusive for premature infants born at GA 32–35 weeks. The only study [23] that stratified by gestational age did not find a significant reduction in hospitalization rate in prophylaxed infants born at GA 33 to 35 weeks without CLD. The review of the studies suggests that groups of children who are likely to benefit most from palivizumab prophylaxis are premature infants born at GA ≤ 32 weeks and children with CLD. Though some international guidelines recommend use of palivizumab in premature infants born at GA < 29 weeks [13–15], highly resourced countries may also
| Author, year, and location | Study design | Timeline | Study population | Intervention strategy | Sample size | RSV hospitalization rate | Conclusion | Quality of study |
|---------------------------|--------------|----------|------------------|-----------------------|-------------|-------------------------|------------|-----------------|
| (13) Chang and Chen, 2010, USA [32] | Hospital record review | 2000–2006 | Children aged <2 years with HS-CHD | Prepalivizumab era (2000–2003) versus postpalivizumab era (2004–2006) | 266 children with HS-CHD | 19% reduction, HS-CHD patients comprised of 0.56% of all RSV hospitalization in prepalivizumab era and 0.46% in palivizumab era | Requires further investigation of cost-effectiveness of palivizumab in children with HS-CHD | Low |
| (14) Winterstein et al., 2013, USA [40] | Cohort study | 1999–2006 | Children < 2 years with CF | No palivizumab versus palivizumab | Nonprophylaxed group: 575 Prophylaxed group: 2300 | Nonprophylaxed group = 4.1 (2.8–6.0)/1000 season months Prophylaxed group = 2.4 (0.8–6.6)/1000 season months | Potential benefit inconclusive | Low |
| (15) Speer et al., 2008, USA [39] | Palivizumab registry review | 2000–2004 | Infants and young children with CF | No palivizumab in historical cohort versus palivizumab in study population | 91 | Significant reduction in hospitalization (compared to Abman et al. [50]: odds ratio = 33.07, 95% CI = 1.844–593.2, \( P < 0.0004 \); Armstrong et al. [51]: odds ratio = 18.67, 95% CI = 1.048–332.6, \( P < 0.0042 \)) | Further investigation for usefulness of RSV in children with CF | Very low |
| (16) Paes et al., 2013, Canada [41] | Record review of the palivizumab registry | 2006–2012 | High risk infants receiving at least one dose of palivizumab | Effect of palivizumab in children with DS compared to all other children | 13,310 children of which 600 were with DS | Hospitalization rate among prophylaxed DS children was 1.53% and similar to children with other standard indications (1.45%) | DS children aged <2 years should be considered candidates for palivizumab | Low |
Table 3: Studies on association between palivizumab dosing and RSV-associated hospitalization.

| Author, year, and location | Study design | Timeline | Study population | Intervention strategy | Sample size | Dose of palivizumab | RSV hospitalization rate | Conclusion | Quality of study |
|----------------------------|--------------|----------|------------------|----------------------|-------------|---------------------|------------------------|------------|------------------|
| (17) Forgel et al., 2008, USA [44] | Palivizumab outcome registry review | 2000–2004 | High risk infants and young children eligible for palivizumab | Association between rates of RSV hospitalization and site of palivizumab administration | 17,641 in clinic setting and 1226 in home setting | 88% in home setting and 81% in clinic setting received the appropriate number of dosing | Received palivizumab at home: 0.4% (5/1226) | Home administration of palivizumab may be preferred for high risk infants at risk of RSV hospitalization | Low |
| (18) Palivizumab Outcomes Registry Study Group, 2003, USA [34] | Record review | 2000–2001 | All children eligible for palivizumab according to AAP guidelines [40] | Received at least one dose of palivizumab | 2,049 | 1,638 of 2,049 (80%) children were compliant with the scheduled dosing of palivizumab | RSV hospitalization slightly higher in noncompliant infants (3.4% versus 2.8%, \( P = 0.48 \)) | Missed or delayed palivizumab injections may increase the incidence of hospitalization | Low |
| (19) Resch et al., 2006, Austria [43] | Cohort study | 2001–2003 | Premature infants of GA 29–32 weeks with and without BPD | Comparison between infants receiving adequate dosing of palivizumab and those receiving at least 1 dose of palivizumab | 238 children received palivizumab | Mean number of injections/child 2.5 ± 1.6 | Adequate prophylaxis: 3.3% Inadequate prophylaxis: 8.1% (\( P = 0.07 \)) | Missed or delayed palivizumab injections may increase the incidence of hospitalization | Low |
| (20) Chadha et al., 2012, USA [42] | Cohort study | 2005–2009 | Premature infants < 32 week GA | Relation between different dosing rate of palivizumab and hospital admission | 965 infants | 0 doses: <29 week GA = 42%, 29–31 week GA = 39.8% At least 1 dose: <29 week GA = 58%, 29–31 week GA = 60.2% Full dose: <29 week GA = 14.8%, 29–31 week GA = 17.6% | Weak positive correlation between palivizumab dosing and hospital admissions \( P = 0.057 \) Spearman rho = 0.012 | Overall reduced dosing of palivizumab and seasonal variation in severity of RSV disease may have affected the results | Low |
| Author, year, and location | Study design | Timeline  | Study population | Intervention strategy | Sample size | Dose of palivizumab | RSV hospitalization rate | Conclusion | Quality of study |
|---------------------------|-------------|-----------|------------------|-----------------------|-------------|---------------------|--------------------------|------------|-----------------|
| (21) Alexander et al., 2012, Australia [37] | Cohort study | 2005–2009 | Infants with HS-CHD | Patients who received palivizumab on ad hoc basis (2005–2007) versus patients who received it systematically (2008–2009) | 120 (3 in 2005–2007 and 117 between 2008 and 2009) | 2005–2007: mean 1-2/child 2008-2009: mean 4/child | 2005–2007: 7–9 patients/year 2008–2009: 2-3 patients/year (P = 0.03) | Systematic administration of palivizumab reduced hospitalization rates | Low |
consider palivizumab for premature infants born at GA 29–32 weeks as per Canadian and Australian recommendations [16, 17].

One study found a lower rate of RSV hospitalization among children with HS-CHD who received palivizumab [32], a group widely recommended for prophylactic use of palivizumab in international guidelines [13–17]. This reduction, however, was not statistically significant and was much less than the clinical trial that demonstrated a reduction of 45% in children with HS-CHD [38]. The low observed reduction may be attributed to the fact that the study groups were not contemporaneous and RSV transmission may vary across seasons. It may also be that organised and systematic administration of palivizumab is required to achieve a benefit in children with CHD [46]. We identified only one observational study of children with HS-CHD which limits our ability to draw firm conclusion for this group. However as all the guidelines have prioritised children with HS-CHD it may be beneficial to consider these children for five monthly doses of palivizumab during the first RSV season [13].

Three studies [39–41] examined the effect of palivizumab immunoprophylaxis for preventing RSV-associated hospitalization in other groups of high risk children who are not covered by specific recommendations in the AAP guidelines [47], such as children with CF and Down syndrome. These studies did not report a statistically significant reduction of RSV hospitalization rate in these groups of children. In the absence of data from well conducted observational studies demonstrating real-world benefit of palivizumab, international guidelines [13–17] which do not recommend routine use of palivizumab in these groups of children seem appropriate.

We endeavoured to identify all potentially relevant observational studies by using a comprehensive search strategy. As with all systematic search strategies it is possible that we have inadvertently overlooked some relevant studies, for example, unpublished work or studies published in languages other than English. Our review was based on observational studies and inability to completely control for confounding factors is a major limitation of the included studies. In particular “confounding by indication,” in which infants at highest risk of disease are targeted for prophylaxis, has the potential to result in underestimation of the protective effect. In addition many of the included studies compared rates of hospitalization in children receiving prophylaxis with children not receiving prophylaxis from different cohorts and in different RSV seasons and some were conducted over one RSV season. RSV transmission varies over time and geographical location [48, 49] confounding direct interpretation of the results.

We did not include a meta-analysis in our review as the studies included in this review were generally of varying quality, assessed heterogeneous populations, and employed different methodologies limiting quantitative synthesis. The review of the included studies prevents us from drawing firm conclusions except for among preterm infants (GA < 33 weeks) and those with CLD and HS-CHD. Further studies of palivizumab in children with Down syndrome, CF, or hematologic malignancies and other high risk groups may inform the current guidelines for immunoprophylaxis. Also studies documenting the association between number of palivizumab injections and RSV infection may better define the optimal dosing of the immunoprophylaxis with respect to burden and cost.

6. Authors’ Conclusion

RSV continues to be one of the major causes of childhood hospitalization worldwide. This review supports use of palivizumab for premature infants born at gestational age < 33 weeks and in selected subgroups of children at high risk of developing severe RSV disease, in particular children with CLD or HS-CHD. Recommendations for targeted immunoprophylaxis for specific groups at high risk for severe RSV disease need to be based on better effectiveness data, along with country-specific data on burden of RSV disease, prevalence of risk factors, and the availability of funds for preventive interventions.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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