Respiratory Syncytial Virus Bronchiolitis in Congenital Diaphragmatic Hernia: A systematic review of prevalence rates and Palivizumab prophylaxis

Leonie Lewis [1], Ian Sinha PhD [2], and Paul D Losty MD [1, 2,3]

[1] Women's And Children's Health, University of Liverpool, UK

[1,2] Alder Hey Children's Hospital NHS Foundation Trust

[3] Faculty Of Health And Life Sciences , University Of Liverpool, UK

Corresponding author:

Leonie Lewis,

Department of Women's and Children's Health,

University of Liverpool, UK

Email: hlllewis@liverpool.ac.uk

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Abstract

Background: The seasonality of Respiratory Syncytial Virus (RSV) epidemics have been disrupted during the Covid-19 pandemic, possibly because of lockdowns and social restrictions reducing viral transmission. Given uncertainties around the severity of upcoming RSV bronchiolitis epidemics, debate exists whether Palivizumab (RSV prophylaxis) should be administered to infants with Congenital Diaphragmatic Hernia (CDH), who may be vulnerable due to lung hypoplasia and pulmonary hypertension.

Aim: To evaluate (1) if CDH infants have higher risk of admission with RSV bronchiolitis than infants in the general population; (2) if Palivizumab prophylaxis may reduce this risk.

Methods: We included all eligible studies examining the risk(s) of RSV-positive bronchiolitis requiring hospital admission in (1) CDH infants without Palivizumab prophylaxis vs infants in the general population and (2) CDH infants with prophylaxis vs CDH infants without prophylaxis. The primary outcome evaluated was the risk of admission with RSV bronchiolitis. Data are reported descriptively and meta-analysed when appropriate.

Results: Three eligible retrospective cohort studies were identified: One study found CDH to be an independent risk factor for RSV hospitalisation (Odds ratio 3.30, 95% confidence interval 2.01-4.4); two studies compared RSV hospitalisation rates in CDH patients who had Palivizumab vs those that did not. The pooled Risk Ratio was 1.11 (95% CI 0.29-4.23, p=0.88). Overall, the quality of evidence was considered poor and one study was industry funded.

Conclusion: Whether CDH infants are at particular risk of severe bronchiolitis remains unclear. There is no evidence from this current systematic review that CDH infants should routinely receive Palivizumab vaccination prophylaxis.

Background

Respiratory Syncytial Virus (RSV) is a major cause of bronchiolitis, a common paediatric respiratory infection affecting almost 1/3 of children in their first year of life[1], most commonly between 3-6 months[2], and often during winter seasons [3]. Bronchiolitis is characterised by 'inflammation of the lining of the epithelial cells of the small airways in the lungs causing mucus production, inflammation and cellular necrosis of those cells' [4].

During 2020/21, the usual seasonal pandemic(s) of RSV bronchiolitis was disrupted[5-8]. Certain vulnerable infants can be considered 'at risk' of severe bronchiolitis, requiring hospitalisation. The most 'at-risk' infants may be given Palivizumab (RSV prophylaxis), a monoclonal antibody, via monthly intramuscular injection. In the UK and Canada Palivizumab is currently recommended in children who were born preterm and are < 9 months of age in the UK and <12 months in Canada with associated chronic lung disease, those <6 months old in the UK and <12 months in Canada with haemodynamically significant acyanotic congenital heart disease, those with severe combined immunodeficiency syndrome, or in infants and toddlers requiring long term ventilation up to the age of 2 years, as well as infants living in remote communities in Canada[9 10].

Recent systematic reviews and meta-analyses have further highlighted that infants with Down syndrome (Trisomy 21), a group not previously thought to be at risk of RSV bronchiolitis, may in fact be prone to hospitalisation[11-15]. Another potential and vulnerable group are those infants born with congenital diaphragmatic hernia (CDH). In these babies, failure of the diaphragm to close in utero allows herniation of abdominal viscera into the thoracic cavity. CDH babies have therefore co-associated lung hypoplasia and pulmonary

hypertension. It is estimated further that up to 50% of CDH infants experience chronic lung disease, often secondary to aggressive mechanical ventilation[16].

A Spanish two-round Delphi study[17] of 48 expert panellists sought to reach a consensus for Palivizumab use in a number of chronic paediatric conditions, including patients who had undergone surgical correction of CDH. The group thought that infants with CDH, for their first two years of life, should receive palivizumab prophylaxis, but this was not based on a systematic review of evidence. Given the burden of care for infants and families of giving five injections in the first RSV season, and the cost implications of doing so, we sought to investigate if current clinical evidence reinforced this recommendation. In this study we aimed to systematically review and explore the contemporary literature to determine whether CDH is a ' risk factor' for severe RSV bronchiolitis and wanted to evaluate the beneficial use (or otherwise) of Palivizumab prophylaxis in infants with CDH.

Aims

(1) To evaluate if CDH infants have a higher risk of hospital admission with RSV bronchiolitis than infants in the general population

(2) if Palivizumab vaccination prophylaxis reduces the risk of hospital admission from RSV bronchiolitis in CDH infants.

Methods

This study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance[18]. A protocol was developed which defined - (I) study objectives, (II) selection criteria, (III) assessment of study quality, (IV) data extraction and (V) analysis. This review did not require IRB approval.

Search strategy

We searched PubMed and Scopus (a platform for searching multiple databases including EMBASE) from inception to March 2021 using the strategy [('CDH' OR 'Diaphragmatic Hernia') AND ('Bronchiolitis' or 'Respiratory Syncytial Virus' OR 'Respiratory Syncytial Virus Pneumonia')]. The database was last searched on 21/05/2021. Clinicaltrials.gov was searched for ongoing studies.

We included observational studies with an active or historical control that investigated the rates of hospital admission with RSV proven bronchiolitis in CDH infants under two years of age, with or without the use of Palivizumab. Randomised Controlled Trials (RCTs) of Palivizumab prophylaxis administration for infants with CDH were also eligible. We excluded studies where bronchiolitis was not caused by RSV as well as those where RSV caused a primary infection that was not bronchiolitis.

Two authors (LL and IS) screened potential studies based on title(s) and abstract.

Data extraction, quality assessment and data synthesis

Two authors (LL and IS) extracted data from all eligible studies, including study characteristics and results. Study characteristics comprised; (a) year of publication, (b) study type, (c) country of publication, (d) single or multi-centre, (e) number and years of RSV bronchiolitis seasons covered, (f) number of CDH index cases.

Study quality was assessed using the Cochrane Risk of Bias Tool for RCTs[19], and the Critical Appraisal Skills Programme (CASP) checklist for cohort studies[20].

Results were reported descriptively and included in meta-analysis where appropriate. The only outcome of relevance was the risk of hospitalisation with RSV proven bronchiolitis within 2 years of birth.

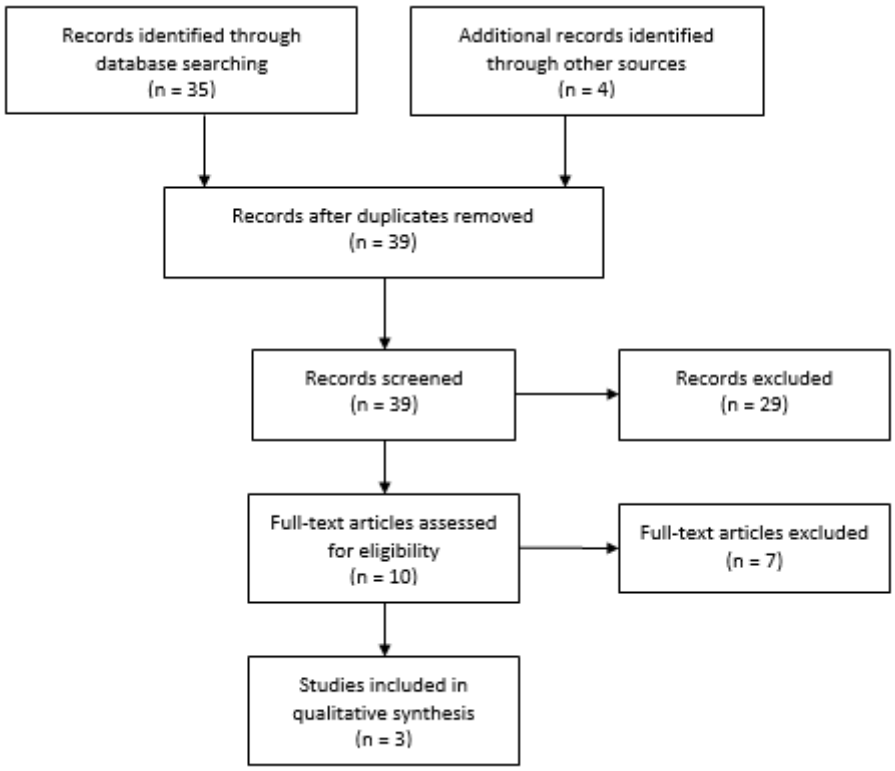
We aimed to report studies descriptively, and meta-analyses using Forest Plot studies that were comparable in methodology, inclusion criteria, and outcome. Plans for meta-analysis of RCT findings would be according to Cochrane methods[19].

Results

Study search and selection

The search of PubMed yielded 35 papers, and SCOPUS yielded 30 papers. A further 4 papers were found through cross-referencing. The search of clinicaltrials.gov found no ongoing trials. There were 30 duplicates, leaving a total of 39 potentially eligible papers. Titles and abstracts of selected papers were then assessed in full for eligibility, excluding 29 papers. Ten publications[21-30] remained, from which 7 more papers[21-27] were subsequently excluded (see **Table E1** for reasons for exclusion) We included 3 final studies[28-30], all of which were retrospective cohorts. **Figure 1** shows the PRISMA flowchart for the current study.

Figure 1: PRISMA flow diagram



Study characteristics and quality

Study characteristics are shown in **Table 1**. All three papers were retrospective cohort studies. Two[28 30] of the three papers reviewed were multi-centre studies. Studies were published from France and Austria. Papers covered eras of between four and eight complete viral bronchiolitis seasons. Due to their age(s) at the time of inclusion, some patients were included in multiple seasons.

Table 1: Study characteristics

	Fauroux[28]	**Resch[29]**	**Benoist[30]**
Year of publication	2020	2017	2016
Study type	Retrospective cohort	Retrospective cohort	Retrospective cohort
Country	France	Austria	France
Single or multi-centre	Multi	Single	Multi
Number of complete bronchiolitis seasons (October - March)	4	21	4
Years covered	2009-2013	1993-2014	2009-2013
Number of CDH patients	Mean of 267 per season	29	86

Assessments of study quality for each included paper are included in **Supplementary Table E2**. In short, studies were of poor quality. Definitions of control groups, including comorbidity status, were unclear[28]. The indications for administration of Palivizumab prophylaxis was indeterminant [29 30]. A single study was industry funded[28].

Study results

Rates of RSV bronchiolitis in infants with CDH compared with the general population

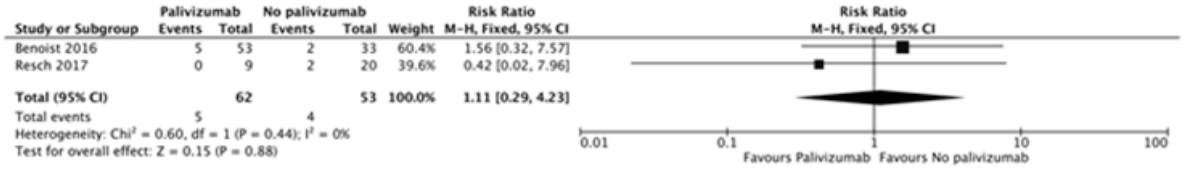
Only one analysis (Fauroux et al), which was a retrospective cohort study[28], compared the rates of RSV bronchiolitis in CDH with those in the general population. The authors found that CDH was an independent risk factor for hospitalisation with RSV proven bronchiolitis (Adjusted Odds Ratio [OR] 2.99, 95% Confidence Interval [CI] 2.01-4.44, p<0.0001 for CDH vs non-CDH for RSV hospitalisation).

Two further papers[26 27] investigated rates of bronchiolitis in CDH infants at their centres but neither included a comparison group, so are not included in this final analysis. Teo et al[26], a study from Singapore, notably, found the rates of bronchiolitis hospitalisation (not RSV proven) to be 33% (8/24). Masumoto et al[27], a study from Japan, found the rates of RSV bronchiolitis hospitalisation to be 14% (3/21).

Use of Palivizumab in infants with CDH

Two papers[29 30] examined the use of Palivizumab viral prophylaxis in CDH. In the two retrospective cohort studies, the rates of RSV bronchiolitis were compared between CDH infants with and without Palivizumab prophylaxis. Resch et al[29] found that 2/20 (10%) of infants with prophylaxis and 0/9 (0%) of infants without had proven RSV hospitalisation over two seasons. Benoist et al[30] found 2/33 (6%) of infants with prophylaxis and 5/53 (9%) of infants without were hospitalised with RSV. The pooled Risk Ratio was 1.11 (95% CI 0.29-4.23, p=0.88); Forest plot - Figure 2.

Figure 2: Forest plot from two cohort studies showing risk of RSV bronchiolitis in CDH infants with and without Palivizumab prophylaxis.



CDH: Congenital Diaphragmatic Hernia, CI: Confidence interval

The baseline incidence for RSV bronchiolitis hospitalisation was 9.64% (8/83) when combining observational studies and control arms of RCTs (Masumoto et al[27], Resch et al[29], and Benoist et al[30]).

The incidence of RSV bronchiolitis hospitalisation for those CDH infants who received palivizumab was 9.30% (4/43) (data from Resch et al[29] and Benoist et al[30]).

As there was no strong evidence that Palivizumab was beneficial in CDH we did not calculate 'Number Needed to Treat'.

Discussion

This current study shows that there is very limited quality evidence available with regard the acquired rate(s) of RSV bronchiolitis and use of Palivizumab viral prophylaxis in CDH. Only a single paper compared rates of RSV hospitalisation to that of the general population, for which comorbidity status was unclear[28]. The study authors (industry funded) nonetheless found here that CDH was an independent risk factor for RSV hospital admission.

Two papers compared the rates of RSV hospitalisation in CDH infants with and without viral prophylaxis[29 30]. On the basis of very low-quality evidence, there is no robust data to convincingly show that Palivizumab prophylaxis is beneficial for infants with CDH.

The publications included in this report were limited by their study design. The fact the studies were observational, rather than RCTs, left the studies open to bias[31]. Various RCTs have not confirmed the efficacy of treatment(s) when compared to corresponding observational studies [32 33]. In particular, the presence of confounding variables brought difficulty here. The infants were not treated at random, yet the studies gave no indication as to why individual infants were administered Palivizumab. The definitions of control groups were also vague. In particular study authors did not specify the comorbid status of controls, and again why they had received Palivizumab vaccination.

To the best of our knowledge this is the first systematic review seeking to address whether infants with CDH are at higher risk of acquiring severe RSV bronchiolitis, and whether Palivizumab vaccination mitigates this risk. The findings from this systematic review were limited in part by the poor quality of included eligible published studies. To this end we identified no RCTs - either completed or in progress - addressing this question.

As previously mentioned, a Spanish Delphi study[17] of some 48 expert panellists reached a consensus on the recommendation(s) for Palivizumab prophylaxis in CDH. They did however stress the need for further clinical trials. Such trials, as well as meta-analyses, have also found infants with Down syndrome (Trisomy 21), a group not previously considered, to be at an increased risk of RSV infection[11-15].

We elected *a priori* to measure only one outcome i.e. hospitalisation with RSV bronchiolitis, as this is the focus of much discussion around benefits and cost-effectiveness of Palivizumab vaccination. Future research should ideally be focussed on outcomes that are of relevance to children, families, clinicians and health policy-makers. Decisions around Palivizumab prophylaxis should be completed in an informed, shared process. Currently, we can only advise parents of CDH infants that there is an absence of 'meaningful evidence' around Palivizumab prophylaxis. CDH Infants who require home oxygen therapy, those who were born prematurely, and patients with significant pulmonary hypertension may in theory represent a cohort subgroup at particular risk of acquiring severe RSV bronchiolitis, but there is no currently no robust available evidence to counsel parents of such infants appropriately.

With a lack of good quality current evidence, concern(s) for RSV bronchiolitis infection in CDH infants still remain elusive. Larger cohort studies scrutinizing bronchiolitis risk in CDH

survivors are thus needed. Well-designed multicentre RCTs should seek to address the effectiveness and cost value of Palivizumab prophylaxis. Outcomes from future clinical trials if undertaken should be standardised and wholly relevant to parents / families and health care providers. Furthermore, a bronchiolitis ‘ core outcome set ‘ would be additionally helpful here.

To this end, it is large scale RCTs that have robustly demonstrated Palivizumab vaccination is effective and protective in premature babies [34]. CDH patients therefore need prospective RCTs to be rigorously designed to reach valid conclusions on the potential health benefits of RSV vaccination prophylaxis.

Conclusions

On the basis of currently available evidence, we cannot say with certainty whether CDH infants are at particular risk of acquiring severe viral RSV bronchiolitis. At the time of writing there is no compelling evidence CDH patients should routinely receive Palivizumab prophylaxis. Further cohort studies and RCTs are crucially required to address these unresolved questions.

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Table E1: List of excluded studies and reasons for exclusion

Reference	Reason for Exclusion
Manzoni et al[21]	Incorrect study design (literature review)
Muratore et al[22]	Incorrect population (bronchiolitis in those under 3 years) and unclear definition of bronchiolitis
Paes et al[23]	Incorrect population (looked at increased rates of RSV, but not in CDH infants)
Cortes et al[24]	Incorrect outcome (did not look at RSV bronchiolitis)
Kim et al[25]	No appropriate control group
Teo et al[26]	No control group and unclear definition of bronchiolitis
Masumoto et al [27]	No control group and unclear RSV prophylaxis status

Table E2: Quality assessment using CASP checklist for cohort studies[18]

	Fauroux et al[28]	Resch et al[29]	Benoist et al[30]
Did the study address a clearly focused issue?	Yes	Yes	Yes
Was the cohort recruited in an acceptable way?	Yes	Yes	Yes
Was the exposure accurately measured to minimise bias?	Can't tell (no definition for CDH)	No (indication for prophylaxis was indeterminant)	No (indication for prophylaxis was indeterminant)
Was the outcome accurately measured to minimise bias?	Yes	Yes	Yes
Have the authors identified all important confounding factors?	Can't tell (unclear comorbidity status of control group)	Can't tell	Can't tell
Have they taken account of the confounding factors in the design and/or analysis?	Yes	Can't tell	Can't tell
Was the follow up of subjects complete enough?	Yes	Yes	Yes
Was the follow up of subjects long enough?	Yes	Yes	Yes
How precise are the results?	Precise (95% CI's given)	Precise (95% CI's given)	Precise (95% CI's given)
Do you believe the results?	Can't tell (study population not clearly defined)	Can't tell	Can't tell
Can the results be applied to the local population?	Can't tell	Can't tell	Can't tell
Do the results of this study fit with other available evidence?	Can't tell	Yes	Yes
Does the study have implications for practice?	Yes	Yes	Yes