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REVIEW

Defining the Epidemiology and Burden of Severe Respiratory Syncytial Virus Infection Among Infants and Children in Western Countries

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ABSTRACT

Introduction: The REGAL (RSV [respiratory syncytial virus] Evidence—a Geographical Archive of the Literature) series provides a comprehensive review of the published evidence in the field of RSV in Western countries over the last 20 years. This first of seven publications covers the epidemiology and burden of RSV infection.

Methods: A systematic review was undertaken for articles published between Jan 1, 1995 and Dec 31, 2015 across PubMed, Embase, The Cochrane Library, and Clinicaltrials.gov. Studies reporting data for hospital visits/admissions for RSV infection among children (≤18 years of age), as well as studies reporting RSV-associated morbidity, mortality, and risk factors were included. Study quality and strength of evidence (SOE) were graded using recognized criteria.

Result: 2315 studies were identified of which 98 were included. RSV was associated with

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12–63% of all acute respiratory infections (ARIs) and 19–81% of all viral ARIs causing hospitalizations in children (high SOE). Annual RSV hospitalization (RSVH) rates increased with decreasing age and varied by a factor of 2–3 across seasons (high SOE). Studies were conflicting on whether the incidence of RSVH has increased, decreased, or remained stable over the last 20 years (moderate SOE). Length of hospital stay ranged from 2 to 11 days, with 2–12% of cases requiring intensive care unit admission (moderate SOE). Case-fatality rates were <0.5% (moderate SOE). Risk factors associated with RSVH included: male sex; age <6 months; birth during the first half of the RSV season; crowding/siblings; and day-care exposure (high SOE).

Conclusion: RSV infection remains a major burden on Western healthcare systems and has been associated with significant morbidity. Further studies focusing on the epidemiology of RSV infection (particularly in the outpatient setting), the impact of co-infection, better estimates of case-fatality rates and associated risk factors (all currently moderate/low SOE) are needed to determine the true burden of disease.

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INTRODUCTION

Respiratory syncytial virus (RSV) is the most common cause of infection of the upper and lower respiratory tract in infants and young children worldwide and a major public health burden [1–10]. Globally, there are an estimated 33 million annual cases of RSV-associated lower respiratory tract infection in children under the age of 5 years, with at least 3.4 million episodes necessitating admission to hospital [1]. Although the risk of hospital admission is higher in known risk groups, such as those born prematurely, in particular, those with chronic lung disease (CLD)/bronchopulmonary dysplasia (BPD), and those with congenital heart disease (CHD) [11–15], the majority of severe cases of RSV infection occur among previously healthy term infants [14, 16]. Severe RSV infection remains a significant unmet medical need, and reducing the health burden of RSV has become a priority of the World Health Organization's (WHO) BRaVe (Battle against Respiratory Viruses) initiative [17, 18]. Part of the research agenda of this initiative is to define the burden of respiratory viral infections [18].

Over the last 20 years, there has been a considerable body of research published on RSV that has improved our understanding of the epidemiology in different risk groups, the acute and long-term burden to children and to healthcare systems, the underlying infection process and genetics, as well as preventive and management strategies. An understanding of the incidence and complications of RSV disease is essential for planning strategies to control RSV infection and to optimize the use of RSV prophylaxis and future RSV vaccines [19–21].

To provide a comprehensive understanding on severe RSV disease in infants and children in Western societies, an expert panel, comprising Neonatologists, Pediatricians, Pediatric Infectious Disease Specialists, Pediatric Cardiologists and Pediatric Pulmonologists from the United States, Canada and Europe, undertook an evidence-based search of the literature which has accumulated over the past two decades. The primary objective of REGAL (RSV Evidence—a Geographical Archive of the Literature) was to carry out a series of systematic

literature reviews and, then, to assess, quantify, summarize and grade the evidence base. By undertaking this review, the current state of the art in our understanding of RSV was defined as well as, importantly, gaps in our knowledge and future areas of research.

This paper represents the first of a series of seven publications encompassing different areas of the systematic review and covers in detail the overall methodology that was followed for each of the reviews, and summarizes the first topic: the epidemiology and burden of severe RSV infection requiring hospitalization among infants and children in Western societies.

METHODS

Objectives

The primary objective of REGAL was to address seven specific research questions (Table 1). The systematic literature reviews undertaken to answer each of these research questions all used the same broad methodology, which is described in detail below.

Search Strategy and Selection Criteria

Following a study protocol with pre-defined search terms, we conducted a systematic and comprehensive search of the medical literature electronically indexed in MEDLINE (PubMed), Embase and The Cochrane Library. Search strategies were devised for each systematic review and combined free-text search terms with medical subject headings (MeSH). An important part of the protocol was the countries to be included. The overall burden of RSV has been studied in many industrialized countries, and therefore, to ensure a manageable volume of publications, only studies conducted in Western countries were included, which we defined as the United States, Canada, and Europe (including Turkey and the Russian

Table 1 REGAL: study questions

1. What is the overall epidemiology and disease burden of severe RSV infection in Western countries, and what are the associated risk factors for RSVH?
2. What is the predisposition and associated morbidity, long-term sequelae and mortality of preterm infants (<37 wGA) without CLD/BPD or CHD, overall, and split by gestational age segments, to severe RSV infection, and what are the risk factors associated with RSVH?
3. What is the predisposition and associated morbidity, long-term sequelae and mortality of infants with underlying CLD/BPD to severe RSV infection in Western countries?
4. What is the predisposition and associated morbidity, long-term sequelae and mortality of infants with underlying CHD to severe RSV infection in Western countries?
5. What is the nature, incidence and impact of long-term respiratory morbidity associated with RSVH in infancy in Western countries, specifically early and late wheeze?
6. What other groups of infants with underlying medical conditions or chronic diseases are at high risk of RSVH and associated morbidity?
7. What are the optimal approaches and strategies for the prevention and treatment of severe RSV infection and what are the future perspectives in this regard?

BPD bronchopulmonary dysplasia, *CHD* congenital heart disease, *CLD* chronic lung disease, *RSV* respiratory syncytial virus, *RSVH* RSV hospitalization, *wGA* weeks' gestational age

Federation). The full protocol for the systematic reviews is available as part of the online supplement (Supplementary Material 1—REGAL Protocol). Our search included studies conducted in children (defined as ≤18 years) and published between January 1, 1995 and December 31, 2015. The target populations for REGAL included previously healthy term or preterm children [<37 week gestational age (wGA)], those with CLD/BPD, CHD, or other high-risk comorbid conditions (e.g., anatomic pulmonary abnormalities, neuromuscular disorders, Down syndrome, immunodeficiencies and cystic fibrosis) with 'proven' or 'probable' RSV. Children who had received immunoprophylaxis with palivizumab were included.

No language limits were set on the database searches, with the caveat that English translations of at least the abstract had to be available. Since there is not a universal, standardized definition of severe RSV disease, for the purposes of this article, we have taken this to be 'RSV infection requiring hospitalization'. Randomized controlled trials, non-randomized controlled trials, crossover trials, single-arm studies, cohort studies (prospective and retrospective), case–control studies (prospective and retrospective), and case series were included, as well as published data from registries and medical databases. We also searched the database ClinicalTrials.gov, which provides information on current ongoing clinical research studies being conducted around the world. In addition, we hand-searched online journals and scanned the reference lists of identified citations and relevant abstracts presented at key meetings to find additional relevant publications for each of the reviews.

Two reviewers (J. Smith and J. Blake) undertook the search adopting a two-phase screening process. In Phase 1, the title (Stage 1) and, then, the abstract (Stage 2) of all identified studies were independently assessed for their relevance in answering the research question (details of the reviewers can be found in the Acknowledgments). The following short-term outcomes were assessed: incidence rates of severe RSV infection requiring medical treatment during the first or subsequent years of life, RSV hospitalization (RSVH) rates, length of stay (LOS) in hospital, RSVH-related outcomes [intensive care unit (ICU) admission, LOS in ICU, requirement for, and duration of, mechanical ventilation, non-invasive ventilation and oxygen], case-fatality rate, and risk factors for severe RSV infection requiring hospitalization. The following long-term outcomes were assessed: subsequent respiratory disease, including recurrent wheezing and asthma up to adulthood (≤18 years) following severe RSV infection in infancy. Other outcomes assessed were the effectiveness of palivizumab in reducing RSVH rates and associated morbidity, long-term sequelae and mortality in different subgroups of children with or without CLD/BPD, and future developments in RSV research including genetic phenotypes and polymorphisms.

All studies marked in Phase 1 as potentially relevant were then independently assessed at the full-text level by the same two reviewers for inclusion (Phase 2). Any disagreements were resolved after discussion with a third reviewer (B. Rodgers-Gray) and X. Carbonell-Estrany. The search results were compiled into a spreadsheet, including documentation of the reason(s) for excluding a study. Data were extracted for all identified articles by one reviewer and quality-checked by the second reviewer, and a written report was produced (Supplementary Material 2—Data Extraction Table). The authors reviewed the search results and report, made

any additions and amendments, and all approved the final list of studies for inclusion. For each systematic literature review, we fully documented the inclusion and exclusion processes using a PRISMA flowchart that detailed the number of included and excluded articles.

Data Synthesis

Included publications were graded according to the Oxford Centre for Evidence-Based Medicine Levels of Evidence [22, 23]: level 1 evidence (local and current random sample surveys [or censuses]); level 2 evidence (systematic review of surveys that allow matching to local circumstances); level 3 evidence (local non-random sample); level 4 evidence (case series). For randomized, controlled trials, a quality assessment for each citation was carried out using the five-point (1 = low quality; 5 = high quality) Jadad Scale [24]. For each study, we also conducted a risk of bias assessment using the RTI Item Bank (score of 1 = very high risk of bias; score of 12 = very low risk of bias) for observational studies [25] and the Cochrane Collaboration's tool for assessing risk of bias for randomized clinical trials [26].

METHODS USED FOR CURRENT STUDY: OVERALL EPIDEMIOLOGY AND BURDEN OF RSV

The target population for the first systematic literature review in our series was previously healthy term children or studies with mixed populations of term and preterm (<37 wGA) children and those with comorbidities. We excluded studies that focused exclusively on particular subgroups, such as preterm infants (<37 wGA), those with CLD/BPD or CHD, or other medical conditions (e.g. Down syndrome), since this systematic literature review considers the overall epidemiology and burden of RSV in infants and children. However, studies were included if a proportion of the study population had comorbidities.

In this first systematic literature review, we sought to answer the following question:

1. What is the overall epidemiology and disease burden of severe RSV infection in Western countries, and what are the associated risk factors for RSVH?

We performed a literature search using the following combination of search terms and limits: "RSV" OR "respiratory syncytial virus" AND "hospitalization" AND "epidemiology" OR "disease burden" OR "burden" OR "risk" OR "risk factor" AND "limits: human, infant aged up to 1 year; child (unspecified age)". "Bronchiolitis" and "pneumonia" were captured as part of the MeSH terms. It is recognized that while some relevant articles might have been missed by the searches, we are confident that the combined Boolean operators "AND" and "OR" of the key text words and index terms precisely captured the vast majority of relevant citations which were pertinent for this evidence-based review. The short-term outcomes of interest for this review included hospitalization rates due to severe RSV, hospital LOS, ICU admission and LOS, oxygen requirement, need for and duration of mechanical ventilation and/or non-invasive ventilation, case-fatality rates, and risk factors (including biological, environmental and social) for severe RSV infection requiring hospital admission.

Statement of Ethics Compliance

The analysis in this review article is based on previously published studies and does not

involve any new studies of human subjects performed by any of the authors.

RESULTS AND DISCUSSION

Articles Selected

A total of 98 publications were included in the final review: 90 identified from the database searches and a further 8 from reference lists/other sources (Fig. 1). Data extraction tables for all 98 studies, including evidence grades and risk of bias assessments, can be found in the online supplement (Supplementary Material 2—Data Extraction Table).

Incidence of RSV Hospitalization

RSV has been associated with 12–63% of all acute respiratory infections (ARIs) [12, 16, 27–40] and 19–81% of viral ARIs causing hospitalization in infants and children [41–57] (Table 2). Importantly, while high-risk groups are particularly vulnerable to severe infection and are often the focus of study, the majority (typically >70%) of children

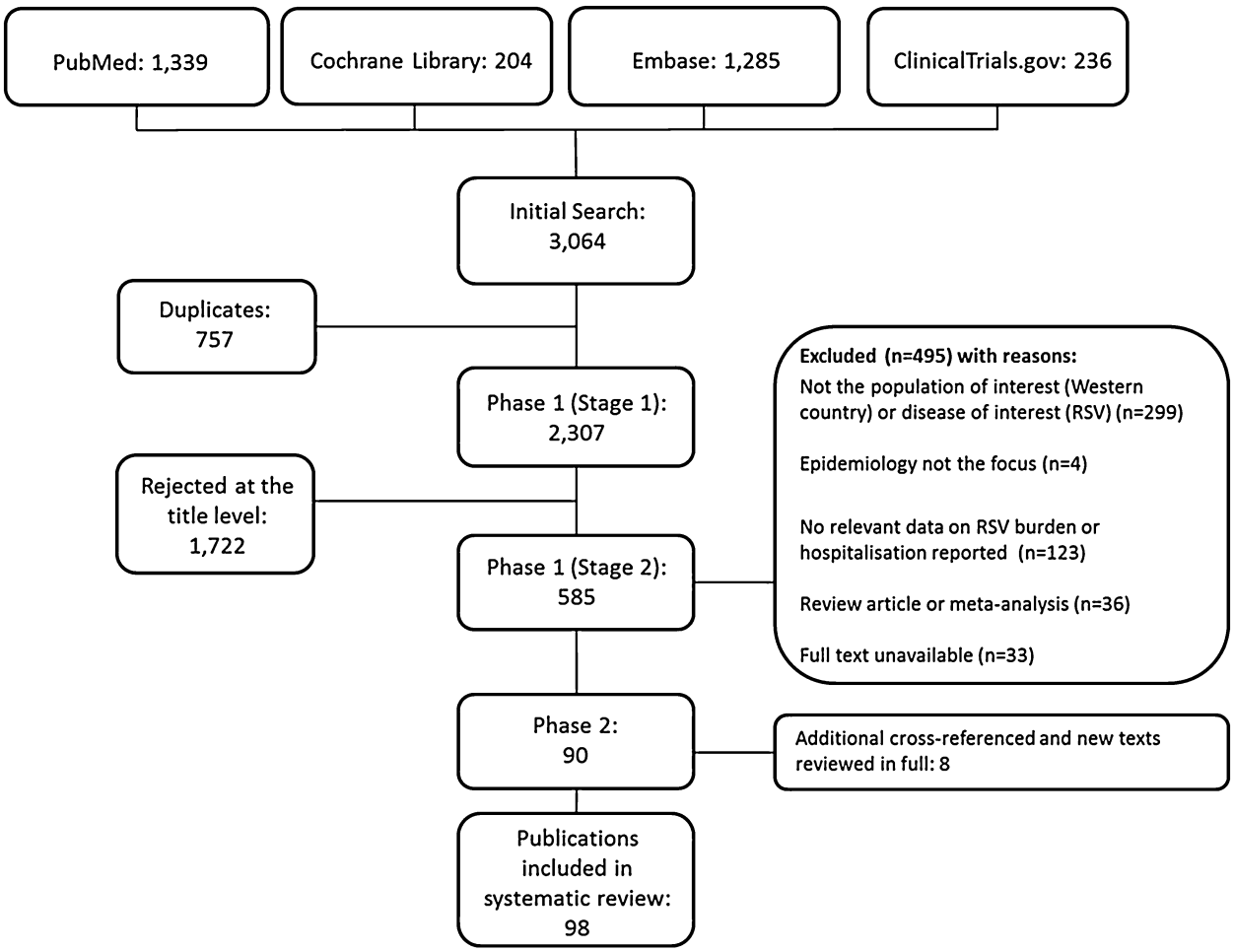

Fig. 1 PRISMA flow diagram: overall epidemiology and burden of severe respiratory syncytial virus (RSV) infection. The third reviewer (B. Rodgers-Gray) and X. Carbonell-Estrany were not required to resolve any disagreements during the review process

Table 2 Epidemiology of hospitalizations for RSV-associated bronchiolitis in infants and children

Study	Country	Design	% RSV/total ARIs	Hospitalization rate
Resch (2002) [57]	Austria	1-year prospective study (1999–2000); single center; all children <2 years hospitalized with viral U/LRTIs (included high-risk children [preterm, CHD])	21%[b]	Term: 7/1000/year
Resch (2000) [56]	Austria	4-year retrospective study (1994–1998); single center; all children hospitalized with viral U/LRTIs (included high-risk children [preterm, CHD, pulmonary disease, neurological disease])	26.7%[b]	Term: 6/1000/season
Santibanez (2012) [36]	Canada	2-year retrospective study (2008–2010); regional; all hospitalized children <19 years old with LRTI and RSV/LRTI (included high-risk children and infants [preterm, CHD, BPD/CLD])	29.5%	NR
Mlinaric-Galinovic (2009) [46]	Croatia	11-year retrospective study (1994–2005); national; all children <10 years old hospitalized with an ARI	32.2%	NR
Haerskjold (2015) [2]	Denmark	7-year population-based cohort study (1997–2003); 6 national registries; infants ≤24 months old (included high-risk infants [preterm, chronic disease (e.g. congenital malformations, intestinal lung disease, chromosomal abnormalities)])	Only RSV cases enrolled	<2 years: 14.9/1000 years at risk
Kristensen (1998) [83]	Denmark	6-month population-based, retrospective study (1995–1996); regional; infants <6 months old (included high-risk infants [preterm, CHD, BPD/CLD, neurologic disease, other])	NR	<6 months: 34/1000/season

Table 2 continued

Study	Country	Design	% RSV/total ARIs	Hospitalization rate
El-Hajje (2008) [48]	France	3-year prospective study (2002–2004); single center; children <16 years old admitted with an ARI, fever or asthma	80.8%[b]	NR
Weigl (2001) [29]	Germany	3-year retrospective study (1996–1999); city; children <16 years old admitted with an ARI	12.1%	<2 years: 7.25/1000
Tsolia (2003) [84]	Greece	4-year retrospective/prospective (1997–2000); regional; infants <12 months old admitted with bronchiolitis (included high-risk infants [preterm infants ≤36 wGA, CHD, and other underlying illnesses])	61.5%	NR
Constantopoulos (2002) [27]	Greece	2-year prospective, epidemiological study (1999–2000); 4 regions; children ≤2 years old admitted with ARI (included healthy full-term infants and high-risk infants [preterm, CHD, BPD/CLD])	33.1%	NR
Frassanito (2015) [31]	Italy	5-year retrospective study (2009–2014); single center; children <3 years old admitted with a viral ARI	54.2%	NR
Ferrara (2014) [32]	Italy	9-year retrospective study (2004–2013); single center; infants <12 months old admitted with bronchiolitis	31.3%	NR
Zuccotti (2011) [30]	Italy	12-month prospective, epidemiological study (2008–2009); 2-center; children <15 years old admitted with an ARI	34.1%	NR

Table 2 continued

Study	Country	Design	% RSV/total ARIs	Hospitalization rate
Corsello (2008) [38]	Italy	7-month prospective, surveillance study (2005–2006); regional; children <2 years old admitted with LRTI (included infants born <36 wGA)	40.9%	NR
Medici (2006) [50]	Italy	4 year prospective, observational study (2000–2004); national; children ≤4 years old admitted for an ARI (included previously healthy term and at-risk [≤35 wGA BPD/CLD] infants)	49%	NR
Lanari (2002) [33]	Italy	6-month prospective, epidemiological study (1999–2000); multicenter; children <2 years old admitted for LRTI (included preterm infants <36 wGA)	40.6%	NR
Zomer-Kooijker (2014) [51]	Netherlands	5-year prospective birth cohort study (2003–2005 and 2006–2007); single center; infants <12 months old (all previously healthy term infants)	Only RSV cases enrolled	<1 year: 8.4/1000/year
Gooskens (2014) [47]	Netherlands	2-year retrospective cohort study (2006–2007); single center; children <18 years old admitted with an ARI (included preterm infants and infants with bronchial hyper-responsiveness and cardiovascular disorders)	31%[b]	NR
Fjaerli (2004) [7]	Norway	8-year retrospective, population-based study (1993–2000); single center/region; children <2 years old admitted with bronchiolitis (included at-risk infants [preterm, Trisomy 21, CHD])	Only RSV cases enrolled	<12 months: 21.7/1000/year 1–2 years: 6.8/1000/year <2 years: 14.1/1000/year

Table 2 continued

Study	Country	Design	% RSV/total ARIs	Hospitalization rate
Flores (2004) [85]	Portugal	2-year prospective study (2000–2002); single center; children <3 years old admitted with acute bronchiolitis (included high-risk children [preterm <36 wGA, pulmonary disease])	60.9%	NR
Tatochenko (2010) [52]	Russian Federation	6-month prospective, observational study (2008–2009); multicenter; children ≤2 years old admitted with LRTI (included high-risk children [preterm, CLD/BPD, CHD])	37.9%	NR
Gil-Prieto (2015) [4]	Spain	15-year observational, retrospective survey (1997–2011); included >98% Spanish hospitals; children <5 years old admitted with bronchiolitis (included high-risk children [preterm, congenital cardiopathies/defects, BPD])	Only RSV cases enrolled	<2 years: 24.1/1000/year <5 years: 10.7/1000/year
Hervás (2012) [12]	Spain	12-year retrospective study (1995–2006); single center/region; children ≤2 years old admitted with acute bronchiolitis (included high-risk children [preterm, CHD, atelectasis/condensation, urinary tract infection])	62.7%	≤2 years: 55/1000[a]
García-García (2012) [42]	Spain	6-year prospective study (2004–2010); single center; children <14 years old admitted with community-acquired pneumonia	41.6%[b]	NR
Salvador García (2012) [28]	Spain	1-year prospective study (2008–2009); region; children <18 months old admitted with bronchiolitis	56.4%	NR
Calvo (2010) [39]	Spain	3-year prospective study (2005–2008); single center; children <2 years old admitted with acute viral bronchiolitis	61.3%	NR

Table 2 continued

Study	Country	Design	% RSV/total ARIs	Hospitalization rate
Artiles-Campelo (2006) [43]	Spain	3-year prospective study (2002–2005); single center; children <14 years old admitted with an ARI	74.5%[b]	NR
Díez Domingo (2006) [40]	Spain	2-year retrospective study (2001–2002); province; children <2 years old admitted with bronchiolitis	42.2%	<12 months: 40.2/1000/year[c]
Vicente (2003) [6]	Spain	4-year retrospective, population-based study (1996–2000); single center/province; children <5 years old admitted with an ARI	59.1%	<6 months: 37/1000/year <12 months: 25/1000/year
Svensson (2015) [61]	Sweden	7-year retrospective study (2004–2011); regional; children <5 years old with an RSV infection (included high-risk children [wheezy bronchitis, CHD, Down syndrome, small for gestational age])	Only RSV cases enrolled	<12 months: 17.4/1000/year 1–4 years: 0.6/1000/year <5 years: 4.2/1000/year
Erikksson (2002) [86]	Sweden	12-year retrospective study (1987–1998); single center; children admitted with confirmed RSV infection (included high-risk children [preterm, BPD/CLD, cardiac malformation, respiratory malformation, other chronic disease])	Only RSV cases enrolled	0.8–0.14/100/year
Bicer (2013) [52]	Turkey	1-year retrospective cohort study (2010–2011); single center; children <9 years old admitted with an ARI	32%[b]	NR
Hacımustafaoğlu (2013) [54]	Turkey	1-year study; multicenter; children ≤2 years old admitted with LRTI	37.9%	7.8/1000/year

Table 2 continued

Study	Country	Design	% RSV/total ARIs	Hospitalization rate
Turkish Neonatal Society (2012) [55]	Turkey	2-year prospective, epidemiological study (2008-2010); multicenter; children <2 years old with diagnosis of respiratory failure due to LRTI (excluded children with immunodeficiency, CF or congenital or acquired disorders affecting respiratory system)	16.9%	NR
Ajayi-Obe (2008) [37]	UK	2-year prospective, descriptive study (2002–2003 and 2003–2004); single center; children <6 years old presenting with influenza-like illness (included high-risk children [asthma, CHD, BPD, CF, sickle cell disease, chronic renal disease, thalassemia immunodeficiencies])	19.1% (2002–2003)[b] 27% (2003–2004)[b]	<6 months: 56.2/1000 person-years <12 months: 42.7/1000 person-years 2–3 years: 7.28/1000 person-years 4–5 years: 0.67/1000 person-years <6 years: 12.87/1000 person-years
Deshpande (2003) [63]	UK	3-year retrospective, population-based study (1996–1999); county; children <2 years old admitted with a respiratory illness (included high-risk children [preterm, BPD/CLD])	58.8%	<2 years: 16.3/1000[a]
Müller-Pebody (2002) [34]	UK	3-year retrospective study (1995–1998); national; children <5 years old admitted with LRTI (included high-risk children [preterm, BPD/CLD])	17.5%	<12 months: 28.3/1000/year 1–4 years: 1.3/1000/year
Hall (2013) [16]	US	5-year prospective, population-based study (2000–2005); 3 counties; children <2 years old admitted with an ARI (included preterm infants <37 wGA and infants with comorbid conditions)	26%	1 month: 25.9/1000[a] 3 months: 10.3/1000[a] 6 months: 4.1/1000[a] 12 months: 3.2/1000[a] 18 months: 2.6/1000[a] <2 years: 5.2/1000[a]

Table 2 continued

Study	Country	Design	% RSV/total ARIs	Hospitalization rate
Hasegawa (2013) [70]	US	4-year serial, cross-sectional analysis of a nationally representative sample of children (2000, 2003, 2006, 2009); national; children <2 years old hospitalized with bronchiolitis (included high-risk children [preterm or ≥1 complex medical condition])	NR	<2 years: 17.9/1000 person-years[c] (2000); 14.8/1000 person-years[c] (2009)
Stockman (2012) [35]	US	10-year retrospective study (1997–2006); national; children <5 years old admitted for LRTI (included high-risk children [preterm, CHD, chronic respiratory distress])	~24%	0–2 months: 48.9/1000/year 3–5 months: 28.4/1000/year <12 months: 13.4/1000/year 1–2 years: 5.0/1000/year <5 years: 6/7/1000/year
Zhou (2012) [49]	US	16-year retrospective surveillance study (1993–2008); 13 states; all ages including adults admitted with influenza or RSV	19.5%[b]	<12 months: 23.5/1000 person-years 1–4 years: 1.78/1000 person-years
García (2010) [44]	US	6-year retrospective study (2002–2007); single center/region; children <2 years old admitted with bronchiolitis (included high-risk children [prematurity, CHD, BPD/CLD, Trisomy 21, congenital syndromes, immunodeficiencies, CF, neuromuscular disorders, respiratory tract disorders])	66%[b]	NR
Iwane (2004) [45]	US	12-month prospective, active, population-based, surveillance study (2000–2001); 2 counties; children <5 years old admitted with an ARI (included children with chronic conditions)	20%[b]	<5 years: 3.5/1000/year

Table 2 continued

Study	Country	Design	% RSV/total ARIs	Hospitalization rate
Leader (2003) [62]	US	3-year retrospective study (1997–2000); national; infants ≤12 months old admitted with RSV (included high-risk children [premature, CHD, BPD/CLD, chromosomal abnormalities])	Only RSV cases enrolled	≤12 months: 22.7/1000[a]

ARI acute respiratory infection, *BPD* bronchopulmonary dysplasia, *CF* cystic fibrosis, *CHD* congenital heart disease, *CLD* chronic lung disease, *GA* gestational age, *LRTI* lower respiratory tract infection, *NR* not reported, *RSV* respiratory syncytial virus, *U/LRTI* upper or lower respiratory tract infection, *wGA* weeks' gestational age

[a] Overall hospitalization rate during study period

[b] Virally confirmed ARIs tested

[c] Bronchiolitis-related hospitalizations

hospitalized with RSV-related ARI/bronchiolitis had no underlying medical conditions [14, 16, 44, 56–58]. To put the burden of RSV into context, in comparison to influenza, retrospective analyses show that RSV causes up to 16 times more hospitalizations and emergency department visits in children aged <5 years [49, 59, 60].

Hospitalization rates for RSV ARIs increase with decreasing age, peaking in the first few months of life [4, 6, 7, 16, 34, 35, 37, 56, 61]. Most retrospective studies have consistently shown RSVH to be the highest in the first year of life [7, 49, 56, 61]. In the prospective study by Hall et al. [16], 1-month-old infants, consistently, were the most likely to be hospitalized, almost twice as often as the next two most at-risk groups: infants <1 month old and infants 2 months old. Incidence rates for confirmed RSVH in the first year of life in healthy term infants may be relatively low at <1% [51], though around 2% of all infants including those with comorbidities are included [61, 62]. More studies in healthy term infants are required. Overall, studies have found that between 75% and 90% of infants hospitalized with RSV were aged ≤12 months, and between 44% and 83% were aged ≤6 months [6, 7, 12, 16, 44, 56, 63–65]. Only a minority (≤5%) of neonatally hospitalized children are rehospitalized for RSV infection [57, 66, 67].

Annual hospitalization rates for RSV-associated ARIs in the first year of life range from 3.2/1000/year [16] to 42.7/1000/year [37], and decreased with increasing age to 0.6/1000/year [61] to 1.78/1000/year [49] in children aged 1–4 years (Table 2). The reported rates of RSVH, however, vary considerably between studies and across seasons within the same study.

Incidence of RSV in Emergency Departments and Outpatient Settings

There are very limited data available on the incidence and burden of RSV infection managed on an outpatient basis or in the emergency department [14, 60]. Available studies suggest that the outpatient burden of RSV on healthcare resources has not been fully recognized by healthcare providers [14]. For example, a US study reported that only 3% of

outpatients with RSV infection received the diagnosis of RSV-associated illness, as compared with 45% of inpatients ($P < 0.001$) [14]. Based on study data, RSV infection was estimated to result in one of 334 hospitalizations, one of 38 visits to an emergency department, and one of 13 visits to a primary care office each year in the US [14]. Another US study estimated that, at a national level, more children required an emergency department visit for a RSV infection compared with an influenza infection (21.5 vs. 10.2 visits per 1000 children/year, respectively) [60]. The total estimated number of workdays missed annually by caregivers of children who required emergency department care was 716,404 days for RSV infections [60].

Trends in RSV Hospitalization Rates

A number of studies have examined the national trends in RSVH rates among infants and children over the past two decades. While some studies conducted in the United States [44, 68] and Canada [69] throughout the 1980s and 1990s and the early 2000s have shown a rise in RSVH rates, other studies, both in the United States [70] and in France [71], conducted between 1998 and 2009, report a decrease in the incidence rate of bronchiolitis and RSVH. Further studies in the United States and Europe report that RSVH rates have remained relatively stable over similar time periods [7, 35, 72]. A firm conclusion on long-term time trends is not possible.

Season-on-season RSVH rates have been shown to vary by up to a factor of two to three in the same geographic region [6, 7, 16]. The length and start date of the RSV season can also vary from year to year [50, 73–75]. In temperate, northern hemisphere countries the season typically starts in October or November, peaks in December or February, and finishes in March or April [4, 6, 7, 16, 44, 50, 63]. Changes in surveillance programs, testing rates, the RSV tests used, and admission criteria within and between countries, as well as variations in disease severity and levels of circulating virus, all contribute to the varying incidences reported over time and highlight the need for rigorous, uniform, and ongoing data collection.

Co-infections

RSV has a high rate of co-infection with other respiratory viruses with a similar seasonal pattern, such as influenza, rhinovirus (RV), human metapneumovirus (hMPV) and human bocavirus (HBoV) [28, 41, 76, 77], and also with bacterial pathogens [78, 79]. Co-infections, most commonly dual infections, have been reported to occur in up to 50% of RSV-hospitalized children, [76, 78, 79]. In a prospective study of 2525 children aged <14 years by Calvo et al. [76], 599 RSV single infections and 326 RSV multiple infections were detected. The most frequent dual infection was between RSV and RV (120 episodes) and the second between RSV and HBoV (60 episodes). Other dual RSV infections included 3 episodes of RSV and hMPV and 11 episodes of RSV and influenza [76].

Co-infections represent a major confounder in burden of disease analyses of RSV infection [78, 79]. At present, the clinical data available on co-infection, in terms of both the number of viruses involved and the severity of the condition, are variable and even, at times, contradictory [80]. Some studies have reported that multiple infections were associated with more severe disease and longer hospital stays than with single RSV infections [42, 76, 81]. Calvo et al. [76] found that hospitalization was longer for both RSV simple and RSV and HBoV

co-infection, lasting about 1 day (4.7 vs. 3.8 days; $P < 0.001$) longer than in simple HBoV infections. In contrast, Martinez-Roig et al. [80] found an inverse relationship between the number of viruses detected in nasopharyngeal aspirate, the need for oxygen therapy and hospitalization days. In this prospective study of 463 pediatric patients aged between 7 days and 15 years hospitalized with respiratory infections (none with risk factors for respiratory diseases), the most common co-infections were RV and RSV-B (10 cases) and RSV-A and RSV-B (5 cases). Hospitalization decreased with greater number of viruses ($P < 0.001$). Oxygen therapy was required by 26.75% (1 virus was detected in 55.34% of cases). A larger number of viruses resulted in less need for oxygen ($P < 0.001$). Ten cases required mechanical ventilation, 4 patients with bacterial co-infection and 5 with viral co-infection ($P = 0.69$). The most common co-infections were RV and RSV-B (10 cases) and RSV-A and RSV-B (5 cases) [80]. Findings from an earlier Canadian study of 742 children suspected to have a respiratory illness (33% with a comorbidity) support equivalent disease severity between single virus infection and virus co-infection [82]. In multivariable analysis, virus co-infection did not affect admission to hospital after adjustment for age and the presence of underlying conditions [82].

Morbidity and Mortality Associated with Severe RSV Infection

Morbidity

Severe RSV infection in infants and children is associated with substantial morbidity and constitutes a considerable burden on healthcare systems [83]. Kristensen et al. [83] showed that, compared with infants without predisposing conditions (aged <6 months), infants with predisposing conditions were hospitalized longer (median 5 vs. 9 days; $P < 0.001$) and were treated longer with continuous positive airway pressure (CPAP) (median 4 vs. 7 days; $P < 0.001$) and supplemental oxygen (median 3 vs. 5 days; $P = 0.05$). In term infants without predisposing conditions, age was a predictor of disease severity. Age correlated inversely with duration of oxygen therapy ($P < 0.02$), and infants treated with oxygen or CPAP were significantly younger than infants who did not receive respiratory support (oxygen: median age, 52 vs. 91 days; $P < 0.001$; CPAP: median age, 51 vs. 90 days; $P = 0.001$) [83]. Müller-Pebody et al. [34] observed that hospital LOS was significantly higher ($P < 0.001$) in high-risk children aged <1 year and in those aged 1–4 years. While Gijtenbeek et al. [88] observed higher hospitalization rates for confirmed RSV infection among preterm infants (32–36 wGA) than full-term infants, disease severity, length of hospitalization and the use of mechanical ventilation and oxygen were similar between gestational groups (Table 3).

Studies have shown that RSV ARI is associated with more severe disease than non-RSV ARI, resulting in a significant impact on healthcare resource utilization [12, 44, 57]. On average, infants spend 2–11 days in hospital for RSV ARIs, with around 2–12% being admitted to ICU (Table 3) [4, 6, 7, 12, 27, 29, 34, 39, 41, 44, 56, 57, 61–64, 70, 84, 87, 88]. Vicente et al. [6] reported that infants younger than 6 months had the longest duration of hospital stay. Perhaps unsurprisingly, different geographic regions have varying criteria for admission to hospital and subsequent management [89, 90], which can make comparisons of disease severity difficult.

Table 3 Length of stay in hospital, ICU admission, mechanical ventilation and mortality associated with severe RSV infection among hospitalized patients

Study	Country	Age	Study participants	LOS, median days (range)	ICU admission (%)	ICU LOS, median days (range)	Oxygen requirement (%)	Intubation and/or mechanical ventilation (%)	Non-invasive ventilation (%)	Case-fatality rate (%)
Resch (2002) [57]	Austria	<2 years	58 RSV+ (included preterms and children with comorbidities)	8.9 (mean)	3.4	NR	NR	NR	NR	0
Resch (2000) [56]	Austria	83% ≤6 months	245 RSV+ (included preterms and children with comorbidities)	11 (mean)	NR	NR	NR	6.1	1.2	0
Kristensen (1998) [83]	Denmark	<6 months	459 RSV+ (included children with comorbidities)	Overall: 6 (1–23) Without predisposing conditions: 5 (1–22)	NR	NR	NR	1.3	28.3	0
Soilly (2012) [91]	France	<2 years	467 (76% RSV; included children with comorbidities)	NR[a]	100[a]	8 (5–13)	36.9	26.5	22.7	1.28[e]
Grimaldi (2002) [63]	France		484 RSV+ (included preterms)	6	6.4	NR	NR	1.7	NR	0.2[b]
Weigl (2002) [79]	Germany	<16 years	150 RSV+ (included children with comorbidities)	9 (mean)	7.5%	NR	24.8	0.6	2.7	0
Tsolia (2003) [84]	Greece	<1 year	473 tested (61.5% RSV; included preterms)	6.3 (mean, SD 4.3)	Overall: 3.0 RSV+: 6.2	NR	NR	RSV+: 3.2	NR	0.7
Constantopoulos (2002) [27]	Greece	<2 years	1710 (33.1% RSV)	5.4 (mean)	NR	NR	67.6	NR	NR	NR
Zuccotti (2011) [30]	Italy	<15 years	575 (34.1% RSV; included children with comorbidities)	5.6 (mean)	0	NA	RSV+: 28.6	NR	NR	NR
Gijtenbeek (2015) [88]	Netherlands	43–49 months	2099 (3% confirmed RSVH; included preterms)	<32 wGA: 8 (mean 3–20) 32–36 wGA: 7 (mean 2–25) 38–42 wGA: 7 (mean 4–12)	NR	NR	<32 wGA: 82.4 32–36 wGA: 60.5 38–42 wGA: 85.7	<32 wGA: 5.9 32–36 wGA: 15.8 38–42 wGA: 42.9	NR	NR
Gooskens (2014) [47]	Netherlands	<18 years	274 (31% RSV; included children with comorbidities)	NR	NR	NR	73.0	2.0	NR	0
Fjaerli (2004) [7]	Norway	<2 years	764 RSV+ (included children with comorbidities)	4 (1–41)	NR	NR	NR	1.2	NR	0.3[b]

Table 3 continued

Study	Country	Age	Study participants	LOS, median days (range)	ICU admission (%)	ICU LOS, median days (range)	Oxygen requirement (%)	Intubation and/or mechanical ventilation (%)	Non-invasive ventilation (%)	Case-fatality rate (%)
Gil-Prieto (2015) [4]	Spain	<5 years	326 175 RSV+ (included children with comorbidities)	≤5 years: 5.7 (SD 8.2) ≤2 years: 5.9 (SD 8.7)	NR	NR	NR	NR	NR	0.14
Hervás (2012) [12]	Spain	≤2 years	2384 (62.7% RSV; included children with comorbidities)	6 (SD 6–7)	RSV+: 10.7	NR	RSV+: 67	RSV+: 2.7	RSV+: 1.1	0.13
Calvo (2010) [39]	Spain	<2 years	370 (69.3% single RSV)	5 (mean)	2.3	NR	78.6	NR	NR	NR
Vicente (2003) [6]	Spain	<5 years	635 bronchiolitis hospitalizations (59.1% RSV)	5.9 (mean) <6 months: 6.9 (mean) >6 months: 5.2 (mean)	7	NR	NR	NR	NR	NR
García-García (2001) [41]	Spain	<2 years	617 (viral agent in 55.6% of episodes [83.6% due to RSV])	6.6 (mean, SD 3.5)	NR	NR	NR	NR	NR	NR
Svensson (2015) [61]	Sweden	<5 years	1764 RSV + children (included children with comorbidities)	3 (1–150)	3.7	3 (1–130)	NR	1.5	1.1	0
Deshpande (2003) [63]	UK	<2 years	497 RSVH (included children with comorbidities)	2 (IQR 0–19)	2.7	NR	NR	1.5	NR	0.2[d]
Thorburn (2009) [11]	UK	All children admitted to PICU	406 RSV+ (included children with comorbidities)	PICU admissions only reported	NR	5 (IQR 4–9)	NR	96.5	3.5	4.4
Müller-Pebody (2002) [34]	UK	<5 years	12,298 admissions (17.5% RSV; included children with comorbidities)	<1 year: 8 (0–243)[e] 1–4 years: 7 (0–560)[e] <1 year: 3 (0–305)[f] 1–4 years: 3 (0–478)[f]	NR	NR	NR	NR	NR	<1 year: 0.2–3.3[b,e] 1–4 years: 0.6–2.7[b,f]
Hasegawa (2013) [70]	US	<2 years	544 828[g]	2.4–2.5[h]	NR	NR	NR	NR	NR	NR for RSV
García (2010) [44]	US	<2 years	4800 (66% RSV+; included children with comorbidities)	3 (IQR 2–5)	11.6	4 (IQR 2–7)	56.3	6	NR	0.1

Table 3 continued

Study	Country	Age	Study participants	LOS, median days (range)	ICU admission (%)	ICU LOS, median days (range)	Oxygen requirement (%)	Intubation and/or mechanical ventilation (%)	Non-invasive ventilation (%)	Case-fatality rate (%)
Leader (2003) [62]	US	≤1 year	718,008 ED visits (311,077 RSV)	3.9 (mean, 95% CI: 3.2–4.6)	NR	NR	NR	NR	NR	4.1[c]
Brooks (1999) [87]	US	≤1 year	542 RSV+	12 (3–96)[h]	1.8	NR	NR	25	NR	NR

CI confidence interval, *ED* emergency department, *ICU* intensive care unit, *IQR* interquartile range, *LOS* length of stay, *NA* not applicable, *NR* not reported, *RSV+* respiratory syncytial virus positive, *RSVH* respiratory syncytial virus hospitalizations, *SD* standard deviation, *wGA* weeks' gestational age

[a] Study of children admitted to PICU with bronchiolitis

[b] Deaths during study period

[c] % of RSV- and LRTI-related deaths out of all deaths recorded in the United States during the post-neonatal period (28–365 days) in 1999

[d] Due to RSV-related illness

[e] High-risk infants (prematurity and comorbidities)

[f] Low-risk infants (full-term and no chronic respiratory disease

[g] Weighted estimate of bronchiolitis discharges derived from four data sets

[h] Results for years 2000 and 2009, respectively

Nosocomial RSV Infection

There are limited published data on the epidemiology of nosocomial RSV infection, but in infants with comorbidities, it often follows a severe course of disease, sometimes resulting in mortality [11]. Typically, nosocomial RSV infection occurs at a low rate (0.4–6%) [83, 92, 93]. A recent study conducted in 44 neonatal ICUs in Turkey reported a higher rate of nosocomial infection in newborns (9.6%) [94]. Nosocomial RSV infection was shown to be more severe than community-acquired RSV in a prospective, multicenter, surveillance study undertaken in Germany over 6 consecutive seasons (1999–2005) [93]. The median LOS was 72 days [interquartile range (IQR) 31–131] for nosocomial RSV infection compared with 7 days (IQR 4–10) for community-acquired RSV ($P < 0.001$). Significantly more children were admitted to ICU (52% vs. 9%, respectively; $P < 0.001$) and required mechanical ventilation (56.7% vs. 12.6%; $P < 0.001$) [93].

Case-Fatality Rates

The Global Burden of Disease study estimated that RSV accounted for 1.6% of deaths worldwide in 2010 [95]. Available data from the published literature suggest that the mortality rate for RSV is low in the West (typically <0.5%) [4, 7, 12, 44, 56, 57, 63–65, 96], whereas higher rates have been reported in low- and middle-income countries [97, 98]. Despite advances in neonatal care, rates of mortality have been shown to remain relatively stable over time. A study in the United States reported a case-fatality rate for bronchiolitis-associated deaths of infants aged <1 year of 2.2/100,000 live births in 1979 vs. 2.4/100,000 in 1997 [99]. In a recent 15-year study in Spain, the case-fatality rate was 0.14%, ranging from 0.11% in infants

Table 4 Reported risk factors for severe RSV disease requiring hospitalization in otherwise healthy term and mixed populations of children

Independent risk factors for severe RSV infection requiring hospitalization	
Presence of older sibling [2, 108]	
Birth in proximity to RSV season [16, 109, 110]	
Low birth weight [108, 110]	
Birth order [33, 109]	
Male sex [108]	
Young age (<6 months) [14, 16, 27, 100]	
Exposure to smoking [86, 101, 108]	
Maternal age [110]	
Suburban residence [110]	
Other risk factors associated with RSV hospitalization	
Vitamin D deficiency [111]	
Family history of atopy/atopic diagnosis [101, 112, 113]	
Climatic factors and air pollution [114–116]	
High altitude above 2500 m [104]	
Socioeconomic status/parental education [117]	
Delivery by cesarean section [105]	
	Level of evidence[a]
Key statements/findings	
In western countries, RSV has been associated with 12–63% of all ARIs and 19–81% of viral ARIs causing hospitalization in children	1
Annual hospitalization rates for RSV-associated ARIs ranged from 3.2/1000 children to 42.7/1000 in the first year of life, and decreased with decreasing age to 0.6/1000–1.78/1000 in children 1–4 years	1
Longitudinal studies have reported varying annual incidences of RSVH over time: some have reported an increase, some a decrease, and others relative stability	2
RSV co-infections are frequent (bacterial and viral co-infections have been reported in up to 50% of patients hospitalized with severe RSV ARI). However, the relationship with severity of disease is not clear	1
Infants spend an average of 2–11 days in hospital for RSV ARIs, around 2–12% are admitted to the ICU, and the mortality rate is <0.5% and limited to children with severe comorbidity	1/2
A number of risk factors have been independently associated with an increased risk for severe RSV disease in children, including: male sex; age <6 months; birth during the first half of the RSV season; crowding/siblings; and day-care exposure	1
Key areas for research	
The current evidence base likely underestimates the true epidemiology and burden of severe RSV infection, particularly, the burden related to outpatient and emergency department visits requires further study	
The impact of co-infections on the severity of RSV infections requires further definition and study	
Mortality rates are mainly based on excess mortality estimates during the RSV season in a few studies. Refining global mortality estimates and defining associated risk factors require further study	
Geographical differences in RSV epidemiology need to be defined	

ARI acute respiratory infection, *ICU* intensive care unit, *RSVH* respiratory syncytial virus hospitalization

[a] Level 1: local and current random sample surveys (or censuses); Level 2: systematic review of surveys that allow matching to local circumstances; Level 3: local non-random sample; Level 4: case series [22]

aged 1 year to 0.18% in children aged 4 years [4]. In several studies, the case-fatality rate was higher among high-risk children, including those with BPD/CLD, CHD and immunodeficiency [4, 7, 11, 34].

Risk Factors for RSV Hospitalization

Several important independent risk factors for RSV hospitalization have been identified, including male gender, birth in proximity to RSV season, history of prematurity and tobacco smoke exposure (Table 4). Age, in particular, has been found to be a significant predictor in the severity of infection and RSV hospitalization, with the youngest age groups (<6 months) more frequently hospitalized for a RSV infection [14, 16, 27, 100, 101]. In contrast, some risk factors, such as breastfeeding, have been found to be protective [33, 102]. While the predominance of severe RSV bronchiolitis in boys compared to girls is well known, its mechanism is not yet understood [103]. A study found that the interleukin-9 genetic polymorphism (rs2069885) has an opposite effect on the risk of severe RSV bronchiolitis in boys and girls [103]. Some lesser known risk factors reported in the literature include high altitude above 2500 m [104], maternal atopy [101] and delivery by cesarean section [105]. Black and aboriginal race has also been shown in some studies to be a risk factor for severe disease [14, 65, 90, 101, 106], but not in others [16, 35, 107]. The reasons for these racial disparities, however, remain unclear, but may relate to social factors. Risk factors for RSV-related mortality have not been well described. Insights into risk factors that predispose infants to severe RSV infection and subsequent hospitalization are important to identify strategies to prevent infection, as well as to inform guidelines for palivizumab prophylaxis.

Limitations

There are a few key limitations when considering this review. With a remit to cover 20 years of study and research into the epidemiology and burden of RSV, it is recognized that improvements and changes in medical practice over time would influence the findings and conclusions drawn. The availability, type, and level of diagnostic testing for RSV undertaken over the review period is particularly relevant. Older studies—if any—predominantly used rapid antigen testing, shell vial culture, and viral culture, which are generally less sensitive than current PCR (polymerase chain reaction)-based assays. As described above, some studies, particularly the older ones, tended to describe the epidemiology and burden of bronchiolitis or ARIs without a totally accurate measure of how much of that burden or any additional burden related to RSV. We consider that there is a really important economical impact of RSV infection on emergency departments and outpatients, on co-infections, and on RSV-specific mortality rates. Unfortunately, there are also limited economical data of outpatient RSV economical burden For this reason, this review may underestimate the true burden of RSV.

CONCLUSIONS

Despite the availability of current preventative measures, the findings of this review confirm that RSVH still represents a large burden of disease in Western countries since it is associated with significant morbidity. Further studies focused on the epidemiology and the incidences of RSV ARIs to determine the true

burden of disease, particularly in the outpatient setting, are needed. Well-coordinated surveillance programs within and across Western countries involving centers and hospitals with robust electronic medical records systems for patient identification and that test a high proportion of hospitalized children or visiting outpatients with respiratory illness for RSV, would be the ideal. Also, the development of more effective preventive strategies in high-risk children, as well as in healthy populations, is essential to reduce the overall burden of RSV ARI, which will be the focus of a subsequent paper in the REGAL series.

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