TURUN
YLIOPISTO
UNIVERSITY
OF TURKU

Respiratory syncytial virus infections in children

Epidemiology and clinical presentation

Erika Uusitupa

TURUN YLIOPISTON JULKAISUJA – ANNALES UNIVERSITATIS TURKUENSIS
SARJA – SER. D OSA – TOM. 1936 | MEDICA – ODONTOLOGICA | TURKU 2025

TURUN
YLIOPISTO
UNIVERSITY
OF TURKU

RESPIRATORY SYNCYTIAL VIRUS INFECTIONS IN CHILDREN

Epidemiology and clinical presentation

Erika Uusitupa

TURUN YLIOPISTON JULKAISUJA – ANNALES UNIVERSITATIS TURKUENSIS
SARJA – SER. D OSA – TOM. 1936 | MEDICA – ODONTOLOGICA | TURKU 2025

University of Turku

Faculty of Medicine
Department of Clinical Medicine
Paediatrics
Doctoral Programme in Clinical Research

Supervised by

Professor Terho Heikkinen, MD, PhD
Department of Paediatrics
University of Turku
Turku, Finland

Docent Paula Tähtinen, MD, PhD
Department of Paediatrics
University of Turku
Turku, Finland

Reviewed by

Professor Matti Korppi, MD, PhD
Department of Paediatrics
University of Tampere
Tampere, Finland

Docent Katri Backman, MD, PhD
Department of Paediatrics and
Adolescent Medicine
Kuopio University Hospital
Kuopio, Finland

Opponent

Docent Niko Paalanne, MD, PhD
Department of Paediatrics and
Adolescent Medicine
University of Oulu
Oulu University Hospital
Oulu, Finland

The originality of this publication has been checked in accordance with the University of Turku quality assurance system using the Turnitin OriginalityCheck service.

Artificial intelligence tools (ChatGPT, Grammarly) were used for language editing.

ISBN 978-952-02-0476-1 (PRINT)
ISBN 978-952-02-0477-8 (PDF)
ISSN 0355-9483 (Print)
ISSN 2343-3213 (Online)
Painosalama, Turku, Finland 2025

To my family

UNIVERSITY OF TURKU
Faculty of Medicine
Department of Clinical Medicine
Paediatrics
ERIKA UUSITUPA: Respiratory syncytial virus infections in children – Epidemiology and clinical presentation
Doctoral Dissertation, 154 pp.
Doctoral Programme in Clinical Research
January 2026

ABSTRACT

Respiratory syncytial virus (RSV) is the leading cause of lower respiratory tract infections in children worldwide, with nearly all children infected by the age of three. Although the majority of cases are managed in outpatient care, RSV is responsible for over 3.5 million global hospitalizations annually among children less than five years old. However, knowledge regarding RSV infections in youngest infants and sex-related differences remains limited. The aim of this study was to determine the burden and clinical features of RSV in children.

In a prospective outpatient cohort study, children under 10 years of age were followed over two consecutive respiratory seasons. During each infection, they were clinically examined, and RSV viral load was measured from nasopharyngeal samples. Parents filled daily symptom diaries during the study. We found that higher RSV viral load was associated with a longer duration of symptoms from the age of two years onwards, although no clear link was observed with complications or antibiotic use.

Retrospective inpatient studies investigated laboratory-confirmed RSV hospitalizations at Turku University Hospital in 2006-2020. Cases were analyzed on a population basis, and data were obtained from patient medical records. We found that RSV hospitalization rates peaked at one month of age and declined with increasing age. Among infants under three months, hospitalization rates were up to twice as high as previously reported. Additionally, boys were hospitalized up to 50% more often than girls during early childhood, except in the first months of life. Boys also more frequently presented with respiratory distress, while no differences were found in other clinical features, complications, antibiotic use, or length of hospital stay.

Our findings indicate that the burden of RSV hospitalization in the first months of life is considerably greater than previously assumed, emphasizing the importance of preventive strategies during early infancy. The observed sex differences in disease burden and clinical presentation may offer insights into the pathogenesis of RSV. Furthermore, the association between viral load and symptom duration highlights the clinical relevance of antiviral therapy development.

KEYWORDS: RSV, children, outpatient care, hospitalization, viral load, clinical presentation

TURUN YLIOPISTO
Lääketieteellinen tiedekunta
Kliininen laitos
Lastentautioppi
ERIKA UUSITUPA: Lasten RS-virusinfektioiden epidemiologia ja kliininen kuva
Väitöskirja, 154 s.
Turun kliininen tohtoriohjelma
Tammikuu 2026

TIIVISTELMÄ

RS-virus on lasten yleisin alahengitystieinfektion aiheuttaja maailmassa, ja lähes kaikki ovat sairastaneet sen kolmeen ikävuoteen mennessä. Suurin osa tapauksista hoidetaan avohoidossa, mutta RSV aiheuttaa silti globaalisti yli 3,5 miljoonaa sairaalahoitoa vaativaa infektiota vuosittain alle viisivuotiailla. Vaikka RSV tunnetaan jo varsin hyvin, tietoa etenkin nuoremmista imeväisistä ja mahdollisista eroista sukupuolten välillä on kuitenkin edelleen vähän. Tämän tutkimuksen tavoitteena oli selvittää RSV:n tautitaakkaa ja kliinistä kuvaa lapsilla.

Prospektiivisessa avohoidon kohorttitutkimuksessa seurattiin kahden infektiokauden ajan alle 10-vuotiaita lapsia. Heidät tutkittiin jokaisen infektion yhteydessä, ja RSV:n virusmäärä määritettiin nenänielunäytteestä. Vanhemmat täyttivät oirepäiväkirjaa koko tutkimuksen ajan. Havaitsimme, että suurempi virusmäärä oli yhteydessä pidempään oirekestoon kahden vuoden iästä alkaen, mutta yhteyttä komplikaatioiden tai antibioottihoidon tarpeen suhteen emme havainneet.

Retrospektiivisissä sairaalatutkimuksissa tarkasteltiin virologisesti varmennettuja lasten RSV-sairaalahoitoja Turun yliopistollisessa keskussairaalassa vuosina 2006–2020. Tapaukset suhteutettiin alueen väestöön ja tiedot kerättiin potilasasiakirjoista. Havaitsimme, että RSV-sairaalahoidon tarve on huipussaan yhden kuukauden iässä ja vähenee iän myötä. Alle kolmen kuukauden ikäisillä sairaalahoidon tarve oli jopa kaksinkertainen aiemmin julkaistuihin tuloksiin verrattuna. Totesimme myös, että poikien riski joutua sairaalahoitoon oli jopa 50 % korkeampi kuin tytöillä lukuun ottamatta varhaislapsuuden ensimmäisiä elinkuukausia. Lisäksi pojilla esiintyi tyttöjä useammin hengitysvaikeutta RSV-sairaalahoidon yhteydessä, mutta muutoin oirekuvassa, komplikaatioissa, antibioottihoidon tarpeessa tai sairaalahoidon kestossa ei todettu eroa.

Tutkimuksemme osoitti, että imeväisten RSV-infektioista johtuva sairaalahoidon tarve on ensimmäisinä elinkuukausina selvästi aiemmin luultua suurempi, joten heihin kohdistuvien preventioiden merkitystä voidaan pitää entistäkin tärkeämpänä. Havaitsemamme sukupuolten välinen ero sairaalahoidon tarpeessa ja taudinkuvassa avaa mahdollisesti RSV-infektion patogeneettistä mekanismia. Viruslääkehoitojen kehittelyn kannalta osoittamamme yhteys RSV-virusmäärän ja oireiden keston välillä saattaa olla merkittävä.

AVAINSANAT: RSV, lapset, avohoito, sairaalahoito, virusmäärä, taudinkuva

Table of Contents

Abbreviations

ALRI	Acute lower respiratory infection
ARI	Acute respiratory infection
AOM	Acute otitis media
BPD	Bronchopulmonary dysplasia
CDC	Centers for Disease Control and Prevention
CHD	Congenital heart disease
CI	Confidence interval
CLD	Chronic lung disease
CNS	Central nervous system
CPAP/BiPAP	Continuous positive airway pressure / Bilevel positive airway pressure
Ct	Cycle threshold
ECDC	European Centre for Disease Prevention and Control
ED	Emergency department
EMA	European Medicines Agency
ERD	Enhanced RSV Disease
FDA	U.S. Food and Drug Administration
HFNC	High-flow nasal cannula
HIC	High-income country
HMPV	Human metapneumovirus
IQR	Interquartile range
ICD	International Classification of Diseases
IRR	Incidence rate ratio
IV	Intravenous
LFNC	Low-flow nasal cannula
LIC	Low-income country
LMIC	Low- and middle-income country
LOS	Length of stay
LRTI	Lower respiratory tract infection
mAb	Monoclonal antibody
MALRI	Medically attended lower respiratory infection

MIC	Middle-income country
NIs	Nucleoside/nucleotide inhibitors
NNIs	Non-nucleoside inhibitors
NNT	Number needed to treat
NPA	Nasopharyngeal aspiration
NPI	Non-pharmaceutical intervention
NS	Nasopharyngeal swab
PCR	Polymerase chain reaction
PICU	Pediatric intensive care unit
PIV	Parainfluenza virus
POCT	Point-of-care test
RCT	Randomized controlled trial
RNA	Ribonucleic acid
RSV	Respiratory syncytial virus
RSVH	Respiratory syncytial virus hospitalization
RR	Relative risk
RT-PCR	Reverse transcriptase polymerase chain reaction
wGA	weeks of gestational age

List of Original Publications

This thesis is based on the following publications, which are referred to in the text by the Roman numerals I–III.

I Uusitupa E, Waris M, Heikkinen T. Association of viral load with disease severity in outpatient children with respiratory syncytial virus infection. *J Infect Dis.* 2020;222:298–304. https://doi.org/10.1093/infdis/jiaa076.

II Uusitupa E, Waris M, Vuorinen T, Heikkinen T. Respiratory syncytial virus-associated hospitalizations in children: A 10-year population-based analysis in Finland, 2008-2018. *Influenza Other Respir Viruses.* 2024;18:e13268. https://doi.org/10.1111.irv.13268.

III Uusitupa E, Waris M, Vuorinen T, Heikkinen T. Comparison of hospitalization rates and clinical features between boys and girls with respiratory syncytial virus infection. *Manuscript*.

1 Introduction

Respiratory syncytial virus (RSV) is the leading cause of lower respiratory tract infections (LRTIs) in children globally (Wildenbeest et al., 2023), and nearly all children are infected by the age of three (Berbers et al., 2021). The clinical presentation of RSV infection ranges from mild upper respiratory symptoms to severe illness and death (Jiang et al., 2023). While most cases are mild and managed in outpatient settings, approximately 2% of otherwise healthy infants require hospitalization during their first year of life (Hak et al., 2024b). Globally, RSV leads to more than 3.5 million hospital admissions annually in children under five years, including nearly 1.5 million in infants aged 0–6 months (Li et al., 2022). RSV is also the second most common cause of death in infants worldwide, accounting for over 100,000 deaths annually in children under five, with the highest mortality occurring outside hospitals in low-income settings (Li et al., 2022).

Following the failure of the first RSV vaccine in the 1960s, significant progress has been made in preventing RSV infections. The first maternal RSV vaccine was approved in autumn 2023 to protect infants from severe RSV disease, with additional vaccines, including pediatric candidates, currently in development (Babawale et al., 2025). For over two decades, palivizumab was the only monoclonal antibody available for high-risk infants. However, the extended half-life monoclonal antibody nirsevimab was approved in 2022-2023 for the prevention of severe RSV disease in all infants. Finland became the first Nordic country to implement nirsevimab for the RSV season 2024–2025. The real-world data of the effectiveness of these preventions are promising (Drysdale et al., 2023; Phijffer et al., 2024a, 2024b).

Currently, there is no specific treatment for RSV. The only antiviral, ribavirin, is limited to select high-risk groups (Zhang et al., 2024). However, as with influenza, it is hypothesized that a potent antiviral could shorten the duration and reduce the severity of RSV illness (Malosh et al., 2018), making the development of effective RSV antivirals a high research priority (Zou et al., 2024).

Although risk factors for severe RSV disease are well known, most children requiring hospitalization are previously healthy full-term infants, particularly those under six months of age. With the recent introduction of RSV preventive interventions in clinical practice, there is a growing need for detailed epidemiological data to assess the cost-effectiveness of these interventions and to optimize their use. To date, however, population-based studies with virologically confirmed RSV data in this vulnerable age group of young infants have remained scarce.

2 Review of the Literature

2.1 Viral structure of RSV

2.1.1 Overview of RSV

RSV was first isolated in 1956 from respiratory-symptomatic chimpanzees and a year later from infants. It belongs to the Pneumoviridae family and the Orthopneumovirus genus (Figure 1) (Rima et al., 2017). RSV is an enveloped, single-stranded, negative-sense ribonucleic acid (RNA) virus, typically 150–300 nm in diameter. Due to its non-segmented genome, it cannot reassort genome segments and thus cannot cause large pandemics via antigenic shifts like influenza (Kaler et al., 2023). The RSV genome consists of 10 genes, encoding 11 proteins (G, F, SH, N, P, L, M, NS1, NS2, M2-1, and M2-2), each with specific roles in the virus lifecycle (Figure 2) (Battles and McLellan, 2019; Kaler et al., 2023). The most important of these are the G and F proteins, which are essential for viral entry and, as such, are primarily targeted in interventions such as monoclonal antibodies (mAbs) and vaccines.

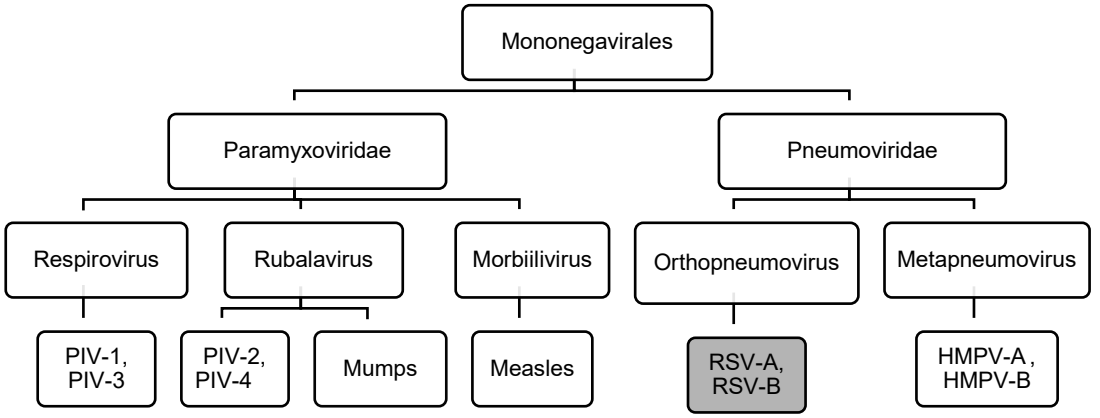

Figure 1. Lineage of RSV.
Modified from: Rima et al., 2017.
Abbreviations: HMPV, Human metapneumovirus; PIV, Parainfluenza virus

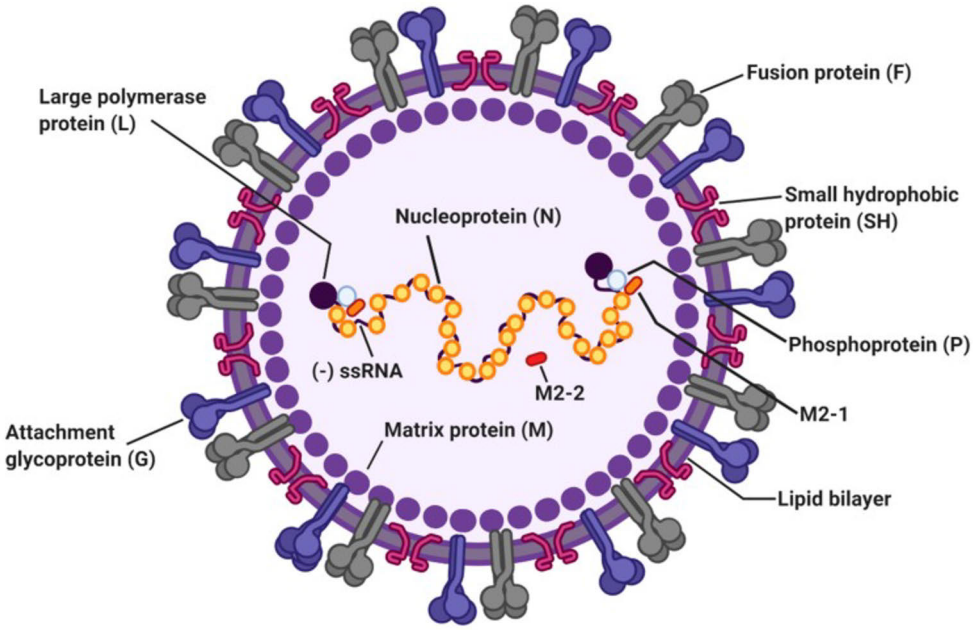

Figure 2. Structure of RSV.
Figure reproduced from Jung HE et al., 2020. Licensed under CC BY 4.0.

2.1.2 Proteins

2.1.2.1 Structural proteins

The outer lipid bilayer envelope of RSV contains three glycoproteins, the transmembrane proteins G and F, and the SH protein. The G protein (attachment glycoprotein) is responsible for the virus binding to the host cell surface, specifically the cilia of respiratory epithelial cells. The genome of the G protein varies greatly between different RSV strains, which has made it a challenging target for RSV interventions such as mAb and vaccines. The division of RSV into subtypes A and B is based on genetic variations in the G protein, primarily through duplications and antigenic drift (Bin Lu et al., 2019). The current predominant genotypes globally are RSV-A ON1 (Ontario, Canada, 2012) and RSV-B BA (Buenos Aires, Argentina, 1999).

The F protein (fusion protein) is responsible for the fusion of the viral envelope with the host cell membrane (i.e. formation of syncytia), allowing the virus to enter the host cell and release its genetic material. It also enables the virus to spread from one cell to another. Its genetic variation is significantly lower than that of the G protein, which is why it has been selected as a key antigen in vaccine development (Hause et al., 2017; Mejias et al., 2017; Schaerlaekens et al., 2024; Tan et al., 2013).

The discovery and stabilization of the prefusion (pre-F) conformation of the F protein in 2013 was a major breakthrough, after which two distinct conformations were identified: the metastable pre-F and stable post-F conformations, which contain six different epitopes, or antigenic sites (Figure 3). When an antibody binds to an epitope of the pre-F conformation, its structure locks in the pre-F form, preventing viral entry into the cell. The epitopes in the pre-F form and the antibodies targeting them have been found to be significantly more neutralizing compared to antibodies targeting the post-F form (McLellan et al., 2013a, 2013b). The antigenic sites I and II are present in both the pre- and post-F forms, with the latter being the target of palivizumab. The antigenic site Ø, located only in the pre-F form, has become a critical target for RSV interventions. Antibodies binding to site Ø have been found to have up to 50 times the neutralizing activity compared to palivizumab (McLellan et al., 2013b; Ngwuta et al., 2015; Zhu et al., 2017), and it is the target of potent neutralizing antibodies such as nirsevimab (Table 1).

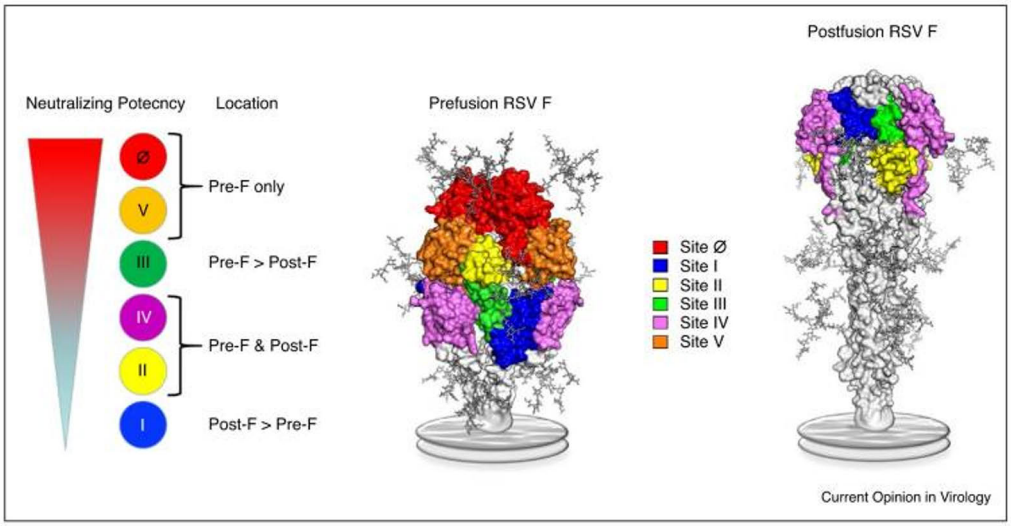

Figure 3. Conformations of RSV F protein and its antigenic sites.
Reprinted from Current Opinion in Virology, Vol. 23, Graham BS, Vaccine development for respiratory syncytial virus, pp.107-112, © 2017, with permission from Elsevier.

Table 1. Conformations of RSV F-protein, its antigenic sites, and targeting mAbs. The bolded text represents the conformation in which the antigenic site plays a more prominent role. Table modified from Schaerlaekens et al., 2024. Licensed under CC BY 4.0.

Neutralizing potency	Antigenic site	F-Conformation	Targeting mAbs
	Ø	Pre	nirsevimab, D25, AM22, 5C4
	V	Pre	suptavumab
	III	Pre > Post	MPE8
	IV	Pre and **Post**	clesrovimab, mAb19, 101F
	II	Pre and **Post**	palivizumab, motavizumab
	I	**Post** > Pre	2F, 44F, 45F, 131-2a

The third lipid envelope protein in addition to G and F proteins is the SH protein (Small Hydrophobic protein). It functions as an ion channel, regulating the permeability of the cell membrane and potentially facilitating the virus's entry into the host cell. The SH protein also participates in the regulation of host cell apoptosis and the avoidance of the immune response. (Schaerlaekens et al., 2024).

Beneath the envelope are ribonucleocapsid proteins, N, P, L, M, M2-1, and M2-2 proteins. The N protein binds to RSV RNA, protecting it from degradation. The P protein (phosphoprotein) acts as a cofactor and stabilizer for the L protein (large polymerase), while the L protein is responsible for the virus's replication and transcription, together with M2-1 and M2-2. The M protein (matrix) participates in the assembly of the virus and acts as a bridge between the envelope and nucleocapsid during the release process. (Schaerlaekens et al., 2024.)

2.1.2.2 Non-structural proteins

Non-structural proteins NS1 and NS2 inhibit the antiviral immune response by preventing the production and function of interferons, thus helping RSV evade the immune system (Schaerlaekens et al., 2024).

2.2 Pathophysiology

2.2.1 Transmission

RSV spreads primarily through direct contact between individuals or indirectly via contaminated objects, but transmission can also occur through airborne particles via droplets or aerosols (Kaler et al., 2023; Kutter et al., 2018). Infection typically occurs

when RSV enters the body through the nose or mouth mucus membranes. Additionally, RSV can be transmitted vertically from an infected mother to the fetus through the placenta (Manti et al., 2022).

When an infant becomes infected, the primary source in 50–70% of cases is an older sibling from the same household (Hall et al., 1976; Heikkinen et al., 2015). Once RSV enters a household, 35–50% of family members become infected within a week, and up to 90% of infants (Hall et al., 1976; Heikkinen et al., 2015; Munywoki et al., 2014). Similarly, in day-care groups, around 50% of children become infected within a week of the first detected case (Chu et al., 2013). RSV is highly contagious, with a reproduction number (R_0) of 3–5, depending on symptoms, population, and environmental factors (Kaler et al., 2023; Reis and Shaman, 2018). Viral shedding may begin a few days before symptoms and typically continues for 3 to 8 days (Kaler et al., 2023).

2.2.2 Replication

When RSV reaches the surface of the host's respiratory epithelial cells, its G protein binds to chemokine receptors on the host cell membrane (Bergeron and Tripp, 2022; Shang et al., 2021). Subsequently, the F protein leads to the fusion of the viral and host cell membranes, allowing the viral nucleocapsid to enter the host cell cytoplasm. From its negative-sense RNA genome, RSV polymerase synthesizes mRNA and produces structural and non-structural proteins, including surface glycoproteins. These synthesized proteins are modified and transported via the endoplasmic reticulum to the host cell membrane. The M protein plays a role in the assembly of new virions by packaging the nucleocapsid into viral particles. Finally, RSV is released from the host cell through budding, during which viral surface glycoproteins are incorporated into the viral envelope.

2.2.3 Pathogenesis

RSV can directly damage respiratory epithelium, yet the immune response plays a central role in disease progression (Bergeron and Tripp, 2021, 2022; Shang et al., 2021). The virus spreads from one cell to another through membrane fusion, forming cell clusters known as syncytia, from which the virus derives its name. This fusion allows the infection to extend from the upper to the lower respiratory tract. The host produces a strong interferon-gamma-driven immune response, often skewed toward type 2 cytokine production. This can lead to eosinophilia and increased mucus production, leading to obstruction in the small airways. Additionally, impaired ciliary function, reduced mucus clearance, airway swelling, and decreased lung compliance may occur. (Bergeron and Tripp, 2021.)

2.3 Epidemiology

2.3.1 Seasonality

2.3.1.1 Definition of RSV season and its importance

Recognizing and predicting the seasonality of RSV epidemics is crucial for optimizing the timing of monoclonal antibody therapies and vaccines to prevent severe disease. Additionally, it helps healthcare systems allocate resources more effectively. Some high-income countries (HICs) have national surveillance data, but data from low- and middle-income countries (LMICs) remain scarce (Suryadevara and Domachowske, 2021).

There are different ways to define an RSV season (Staadegaard et al., 2024). Traditionally, the Centers for Disease Control and Prevention (CDC) defines the onset of the RSV season as the first of two consecutive weeks with ≥10% positivity in RSV antigen tests, and the offset as the last of two consecutive weeks with <10% positivity (CDC, 2013). The epidemic between these two timepoints typically lasts less than five months, with a median duration of 8–24 weeks depending on geographical location (Li et al., 2019; Broberg et al., 2018). Alternatively, some studies define RSV season duration as the period in which at least 75% of annual positive samples are detected (Li et al., 2019). The seasonal peak is identified as the week with the highest percentage of antigen test positivity. With the increasing use of polymerase chain reaction (PCR) diagnostics and the declining use of antigen-based testing, new season definitions have emerged. Due to differences in sensitivity between testing methods, a 3% positivity threshold in PCR testing has been suggested as a potential indicator of RSV season onset (Midgley et al., 2017).

2.3.1.2 Global seasonality

Globally, RSV seasonality generally progresses from south to north and tends to be consistent within a country, with only a few weeks of regional variation (Obando-Pacheco et al., 2018; Staadegaard et al., 2021). In temperate regions, RSV seasons are relatively stable, occurring during winter months (Li et al., 2019; Staadegaard et al., 2021). In the Northern Hemisphere, it typically begins between September and January, peaking in winter and declining between February and May. In the Southern Hemisphere, epidemics start in spring, declining by October. (Obando-Pacheco et al., 2018; Staadegaard et al., 2021.) Across both hemispheres, seasonality follows a latitude-dependent pattern, with later onset at higher latitudes (Li et al., 2019). Tropical and subtropical regions exhibit more variability in RSV seasonality with

peaks occurring during rainy seasons and sometimes circulating year-round in warm humid climates (Shan et al., 2024; Staadegaard et al., 2021; Suryadevara and Domachowske, 2021). However, data from these regions remains limited (Suryadevara and Domachowske, 2021). RSV epidemics often precede influenza outbreaks by some weeks (Li et al., 2019; Obando-Pacheco et al., 2018).

In Europe, the season progresses from south to north and west to east (Li et al., 2019; Obando-Pacheco et al., 2018). RSV activity typically peaks in winter, though in northernmost regions, the peak can extend into early spring (Obando-Pacheco et al., 2018). In the US, the season runs December–March, beginning in the southeast and shifting northwest (Staadegaard et al., 2021). Some countries, like Finland, follow their distinct patterns (Obando-Pacheco et al., 2018).

Environmental and behavioral factors may influence RSV circulation. Cold, humid conditions and indoor crowding promote spread (Li et al., 2019). In tropical regions, factors like air pollution and socioeconomic conditions may also contribute to seasonality (Suryadevara and Domachowske, 2021).

RSV subtypes co-circulate, but dominance varies annually in two- or thee-years cycles (Waris, 1991; Hall et al., 1990; Zlateva et al., 2007). Subtype impact on seasonality remains unclear (Staadegaard et al., 2021; Vos et al., 2019; Yu et al., 2019).

2.3.1.3 Seasonality in Finland

Finland, like other Nordic countries (Eriksson et al., 2002; Havdal et al., 2022a; Jepsen et al., 2018; Renko and Tapiainen, 2020), as well as Croatia (Mlinaric-Galinovic et al., 2008), and Germany (Terletskaia-Ladwig et al., 2005), exhibits a biennial RSV seasonality, with alternating large and small epidemics. In Finland, a small epidemic occurs in the spring of odd-numbered years, followed by a large epidemic starting in November–December and continuing into the spring of the following even-numbered year. After this, RSV cases are rarely detected (Renko and Tapiainen, 2020; Waris, 1991). A Finnish study found slight geographical variation in RSV epidemics within the country (Gunell et al., 2016).

Since 2008, the RSV epidemic peak has shifted forward by a few months, from November to between February and May. This shift has been hypothesized to be linked to interactions between bacteria and viruses, particularly following the outbreak of the influenza pandemic and pneumococcal vaccination (Renko and Tapiainen, 2020). Since 2008, the biannual seasonality shifted to an annual pattern for a few years before returning to a biannual cycle (Vihikangas et al., 2022). In Finland, RSV subtype predominance alternates every two years (Waris, 1991; White et al., 2005).

2.3.1.4 Effect of COVID-19 pandemic

Due to the COVID-19 pandemic and the implementation of non-pharmaceutical interventions (NPIs), RSV nearly disappeared in many countries during the 2020–2021 season (Bender et al., 2024; Graziani et al., 2024, p.; Ippolito et al., 2021; Kuitunen et al., 2022; Principi et al., 2023; Stein and Zar, 2023). The same occurred for many other viruses (Alzaydi et al., 2024; Brañas et al., 2023; Graziani et al., 2024; Haapanen et al., 2021; Ippolito et al., 2021; Kuitunen et al., 2022). Following the relaxation of social restrictions, RSV cases increased, leading to unusually high case numbers and activity starting in the summer of 2021 (Alzaydi et al., 2024; Kuitunen et al., 2022, 2023; Stein and Zar, 2023). The first post-pandemic RSV season affected more older children compared to pre-pandemic levels in some countries (Harding et al., 2024; Pruccoli et al., 2023; Rao et al., 2023), and some studies suggested greater disease severity (Bähre et al., 2025; Rao et al., 2023), while others did not find significant differences (Pruccoli et al., 2023; Wang et al., 2025). After the delayed outbreak, the seasonality now appears to have returned to its pre-pandemic cycle (CDC, 2024).

Changes in RSV epidemiology during and after the COVID-19 pandemic may be explained by reduced RSV immunity, altered healthcare-seeking behavior and systems, SARS-CoV-2-induced immune dysregulation, and viral interactions (Abu-Raya et al., 2023). Similar changes in RSV seasonality were observed after the 2009 influenza pandemic (Li et al., 2021).

2.3.2 Risk factors

2.3.2.1 Overview of risk factors

Most children contract RSV disease by the age of 2 (Andeweg et al., 2021). Although the majority of hospitalized children are healthy full-term infants (Curns et al., 2024; Havdal et al., 2022a), there are several known biological and socio-demographic risk factors for severe RSV disease. The definition of severe disease is heterogeneous across studies, including the need for intensive care, prolonged hospitalization or treatment at pediatric intensive care unit (PICU), the requirement for mechanical ventilation, supplemental oxygen, or mortality. Due to the heterogeneity in disease definition, results may vary across studies. A Finnish-Swedish register-based study evaluated 1,500 potential risk factors of respiratory syncytial virus hospitalization (RSVH) in infants, taking into account both child- and family-related factors, and established a predictive model (Vartiainen et al., 2023). The risk factors for RSV infection, hospitalization, and severe disease are summarized in Table 2.

Table 2. Risk factors for RSV disease, hospitalization, severe illness, and death in children.

		Increases the risk of RSV			
RISK FACTOR	Meaning	Infection	Hospitalization	Severe disease	Death
PREMATURITY	Highest risk among the most preterm	x	x	x	Early preterm
SEX	Higher risk in males	x	x	x	
AGE	Highest risk in the youngest infants	x	x	x	
BIRTH TIMING	Infants born during or just before RSV season at the highest risk	x	x	x	
UNDERLYING MEDICAL CONDITION	Includes CLD, CHD, Immunosuppression, Trisomy 21	CLD CHD Immunosuppression Trisomy 21	CLD CHD Immunosuppression Neuromuscular disease Trisomy 21	CLD CHD Immunosuppression Neuromuscular disease Trisomy 21	CLD CHD Immunosuppression Neuromuscular disease Trisomy 21
PARENTAL SMOKING	Antenatal and postnatal exposure	x	x	x (no clear association with maternal smoking during pregnancy)	
NUMBER OF SIBLINGS	Risk increases with number of older siblings	x	x	x	
RESIDENTIAL CROWDING	Definitions vary between studies	x	x	x	
DAY-CARE ATTENDANCE		x	x	x	
LACK OF BREASTFEEDING	Longer duration provides better protection	x	x	x	

Abbreviations: CLD, chronic lung disease; CHD, congenital heart disease
(Andeweg et al., 2021; Carbonell et al., 2012; Carbonell-Estrany et al., 2013; Haerskjold et al., 2016; Jacoby et al., 2017; Kobiałka et al., 2023; Trusinska et al., 2024; Vartiainen et al., 2023; Wang et al., 2024; Wildenbeest et al., 2023)

2.3.2.2 Intrinsic factors

There are several intrinsic risk factors for RSV infection, including prematurity, sex, age during the RSV epidemic, and underlying medical conditions.

Approximately 5–10% of children are born prematurely at <37 weeks of gestational age (wGA) (Chawanpaiboon et al., 2019; European perinatal health report, 2015–2019) and they account for around 25% of all RSV hospitalizations during their first year (Wang et al., 2024). Prematurity is associated with an increased risk of RSV infection (Trusinska et al., 2024; Wang et al., 2024) and severe disease (Curns et al., 2024; Kobiałka et al., 2023; Shi et al., 2022; Trusinska et al., 2024) for many reasons. Preterm infants have smaller and immature airways and lungs, as well as reduced respiratory capacity and elevated susceptibility to bronchopulmonary dysplasia (BPD) compared to full-terms (Aujard and Fauroux, 2002; Chaw et al., 2020a; Sommer, 2011). Secondly, transfer of maternal RSV IgG antibodies occurs in the last trimester of pregnancy resulting in lower antibody levels among preterm infants (De Sierra et al., 1993; Dolatshahi et al., 2022; Sommer, 2011). Additionally, an immature immune system and weaker ability to clear virus-infected cells further increase the risk of severe RSV disease (Sommer, 2011). A recent meta-analysis of 64 studies revealed that the more premature the infant, the higher the RSV incidence, hospitalization rate, and risk of severe disease. Early preterm infants (<32 wGA) exhibit an almost fourfold increased risk of hospitalization compared to any gestational age (relative risk [RR] 3–3.9), with the risk persisting into the second year of life (RR 2.3) (Wang et al., 2024). A similar inverse relationship between prematurity and the risk of RSVH has been observed in other studies (Vartiainen et al., 2023).

The greater susceptibility of boys to respiratory tract infections among young children is well documented (Muenchhoff and Goulder, 2014; Peer et al., 2025). Among RSV, boys are more frequently infected and hospitalized (Curns et al., 2024; Haerskjold et al., 2016; Iwane et al., 2004; Rha et al., 2020; Wildenbeest et al., 2023), and tend to develop more severe disease than girls (Kobiałka et al., 2023; Simoes, 2003). However, data about sex differences in RSV infections from the youngest infants and prematurity is scarce and conflicting (Haerskjold et al., 2016; Wang et al., 2024). Suggested reasons for differences between sexes are genes, chromosomes, hormones, disparities in lung development during the fetal period, and anatomical structures (Ronen et al., 2007; Seaborn et al., 2010; Silveyra et al., 2021).

Young age during RSV epidemic is a major risk factor for RSV infection, hospitalization and (Andeweg et al., 2021; Cai et al., 2020) severe disease (Curns et al., 2024; Havdal et al., 2022b; Kobiałka et al., 2023; Trusinska et al., 2024), with infants under 6 months at the highest risk (Li et al., 2022; Thomas et al., 2021; Wildenbeest et al., 2023). However, monthly age group data on the youngest infants is scarce (Hall et al., 2013; Havdal et al., 2022a; Rha et al., 2020). Infants hospitalized with RSV bronchiolitis are generally younger than those with non-RSV bronchiolitis (García et al., 2010). Time of birth relative to local RSV season affects the risk of RSV infection and hospitalization in the first year of life (Andeweg et al.,

2021; Guo et al., 2025; Sommer, 2011; Vartiainen et al., 2023). Infants born during or just before the RSV season face a higher risk, likely due to prolonged early-life exposure and lower maternal antibody levels at the season onset (Kobiałka et al., 2023; Lloyd et al., 2014; Wang et al., 2024). In premature infants, the risk is especially pronounced (Carbonell et al., 2012).

Although the majority of RSV-infected and hospitalized children are otherwise healthy full-term young infants (Curns et al., 2024; Havdal et al., 2022a), certain underlying medical conditions are known to increase the risk of severe RSV disease (Curns et al., 2024; Haerskjold et al., 2016; Havdal et al., 2022b; Shi et al., 2022). The presence of an underlying condition is more pronounced in older children and fatal cases (Brenes-Chacon et al., 2024; Thorburn, 2009).

CLD, particularly BPD, is a well-recognized risk factor of RSV, extending the risk of hospitalization into the second year of life in premature children (Cai et al., 2020; Chaw et al., 2020a; Havdal et al., 2022b; Trusinska et al., 2024; Winterstein et al., 2018). While BPD is the most commonly studied form of CLD, full-term infants with pulmonary disease may also face increased risk (Aujard and Fauroux, 2002). CHD, particularly cyanotic types, increases the risk of RSV disease and its severe form (Chaw et al., 2020b; Chiu et al., 2016; Eriksson et al., 2002; Kristensen et al., 2009; Trusinska et al., 2024; Vartiainen et al., 2023). RSV immunoprophylaxis is recommended for children with hemodynamically significant CHD to prevent severe RSV disease during their first RSV season (Caserta et al., 2023). Also, immunocompromised conditions are associated with increased risk of severe RSV disease and mortality (Trusinska et al., 2024). However, the definition of immunosuppression varies across studies, making the comparison of results challenging. Children with neuromuscular diseases face a 6- to 12-fold increased risk of RSVH and greater mortality compared to the general pediatric population (Rose et al., 2021; Trusinska et al., 2024; Welliver et al., 2010). This is primarily due to reduced muscle tone, impaired respiratory function, and ineffective airway clearance, which limit the ability of these children to clear secretions and maintain adequate ventilation (Trusinska et al., 2024). Down syndrome is associated with nearly 7-fold increased risk of RSVH, as well as higher risk of severe disease and mortality (Löwensteyn et al., 2020; Trusinska et al., 2024). However, due to the syndrome's association with CHD, upper airway abnormalities, and immune dysfunction, variations in study methodologies complicate efforts to assess Down syndrome as an independent risk factor for RSV infection.

There are also other risk factors for severe RSV disease including low birth weight, small size relative to gestational age, and intrauterine growth restriction (Kobiałka et al., 2023; Trusinska et al., 2024). When adjusted for gestational age, low birth weight nearly doubles the risk of RSVH during the first year (Cilla et al., 2006), though inconsistent definitions across studies complicate direct comparisons

of the results. Possible explanations are differences in cytokine, lymphocyte, and antibody levels (Sheng et al., 2017).

2.3.2.3 Extrinsic factors

There are several extrinsic risk factors for RSV including the number of siblings, day-care attendance, lack of breastfeeding, smoking exposure, and mode of delivery.

The number of siblings, residential crowding, and day-care attendance increase the risk of RSV disease based on a greater probability of RSV exposure (Colosia et al., 2012; Haerskjold et al., 2016). The risk of RSV disease and hospitalization increases with the number of siblings (Haerskjold et al., 2016; Havdal et al., 2022b). According to a large long-term birth cohort study, RSV risk increased by 1.8 times with one sibling, 2.3 times with two siblings, and almost threefold with at least three siblings compared to firstborns (Jacoby et al., 2017). As RSV is often acquired from older siblings (Heikkinen et al., 2015), vaccinating other family members could also protect the infant.

Breastfeeding reduces both the incidence and severity of RSV-LRTI in infants <12 months of age (Manzoni et al., 2024; Mineva and Philip, 2023; Shi et al., 2022). Longer and exclusive breastfeeding offer stronger protection, but even brief partial breastfeeding during the first weeks of life provides some defence against RSVH (Kobiałka et al., 2023; Mineva and Philip, 2023; Jang et al., 2020). Breastmilk supports immunity through antibodies, cytokines, and growth factors, and promotes a healthy microbiome that enhances immune responses and reduces airway inflammation (Hanson, 1999; Lönnerdal, 2000).

Postnatal exposure to household smoking increases the risk of RSV infection and hospitalization by more than twofold compared to infants from non-smoking families (Carbonell et al., 2012; Carbonell-Estrany et al., 2013). Maternal smoking during pregnancy also raises the risk of RSVH (Manzoni et al., 2024) but does not affect disease severity (Havdal et al., 2022b). It's likely that impaired lung function caused by prenatal smoking predisposes children to RSV infection (Milner et al., 1999; Young et al., 2000).

Children born by caesarian section have been observed to have an increased risk of RSVH (Manzoni et al., 2024) up to the age of two years compared to vaginal delivery (Haerskjold et al., 2016). Possible reasons for this include differences in the production of various cytokines (Liao et al., 2017) and disparities in gut microbiota and its effect on immunity (Huurre et al., 2008).

A recent meta-analysis of 20 studies identified several maternal risk factors for RSV infection in infants, including young maternal age, low educational level, single parenthood, atopy, low vitamin D level, and ethnicity. However, findings on the impact of maternal age and race are conflicting and may be sensitive to sources of errors such as insurance systems and social factors. (Manzoni et al., 2024.)

2.3.3 Outpatient visits

2.3.3.1 Morbidity

While the burden of RSV in hospitalized children is well established, recent studies highlight its role in outpatient settings. Serological data suggest that 40–80% of children are infected with RSV by the age of 1, and nearly all by the age of 3 (Andeweg et al., 2021; Berbers et al., 2021; Kazakova et al., 2019; Kutsaya et al., 2016; Takashima et al., 2021). Among infants <1 year old, about one-third develop symptomatic RSV infection (Hak et al., 2025a; Thomas et al., 2021; Wildenbeest et al., 2023), though only about half of them seek medical care (Hak et al., 2025a). RSV causes 10% of acute respiratory infections (ARIs) in infants, slightly less in toddlers, about 1% in school-aged children, with a cumulative burden around 5% by adolescence (Heikkinen et al., 2017; Zhang et al., 2024).

RSV incidence varies by age, comorbidities, and geography (Table 3). In Finland, the seasonal incidence of RSV infection during the infants´ first RSV season is 330/1000 children, higher in boys (340/1000) than girls (315/1000) (Thomas et al., 2021). Among 0–24 month-old children, the average annual incidence is 370/1000, and it decreases to 117/1000 by age 3–6 years (Toivonen et al., 2020; Heikkinen et al., 2017). Preterm infants have higher rates, up to 520/1000 (incidence rate ratio [IRR] 1.6) (Thomas et al., 2021), and remain at risk in the second year of life (Wang et al., 2024). Around 20% of high-risk infants are affected during their first RSV season (Paramore et al., 2010).

80% of medically attended RSV cases during the first year of life occur in healthy full-term infants (Gantenberg et al., 2022; Simões et al., 2024). Annual outpatient incidence is around 100/1000 in children <5 years (Heemskerk et al., 2024), and up to 340/1000 in those ≤2 years (Toivonen et al., 2020). By age 2, up to one-third of children have received outpatient care for RSV (Hak et al., 2025a; Simões et al., 2024; Wildenbeest et al., 2023), sometimes with multiple visits during a single episode (Hak et al., 2025a; Sankatsing et al., 2025). RSV accounts for 15–20% of ARI primary care visits in children <5 years (Simpson et al., 2016) and for 60–70% of bronchiolitis-related emergency department (ED) visits in those <2 years (Nascimento et al., 2010; Toivonen et al., 2020). ED visits occur in about 10% of RSV cases in young children (Sankatsing et al., 2025; Thomas et al., 2021). ED and pediatric practice visits by age group in a prospective population-based U.S. study are presented in Table 4.

Globally, the outpatient RSV burden varies widely by healthcare accessibility and resources. In low-income countries (LICs) and middle-income countries (MICs), 50–60% of RSV acute lower respiratory infections (ALRIs) in infants <6 months are managed in an outpatient setting (Li et al., 2022).

Table 3. Annual RSV-LRTI incidence rates per 1000 children in different age groups and income levels. Modified from Li et al., 2022

Age, months	Low income	Lower-middle income	Upper-middle income	High income	Developing	Industrialised	Global
0–3	8	57.1	121.5	19.6	55	19.6	51.8
3–6	82.9	142.2	91.6	17.9	116.1	17.9	106.4
0–6	75.9	106	130.8	29	103.7	29	96.3
6–12	68.7	105.4	84.3	32.5	88.2	32.5	82.6
0–12	78.3	111.2	108.8	38.5	1010	38.5	94.6
12–60	35.9	25.4	-	-	27.7	-	-
0–60	49.3	51.4	55.2	24.3	51.6	24.3	48.8

Table 4. Annual population-based rates of outpatient treatment in children <5 years old with confirmed RSV infection. Modified from Hall et al., 2009.

Age groups, months	ED visits per 1000 children per year	Pediatric practices per 1000 children per year
0–5	40–70	110–160
6–11	45–70	160–190
12–23	25–40	50–80
24–59	10–15	30–80
0–59	20–30	60–100

2.3.3.2 Duration of RSV disease

RSV illness typically lasts 10–12 days (Hak et al., 2025a; Heikkinen et al., 2017; Thomas et al., 2021; Toivonen et al., 2020), with a usually longer duration in younger children (Heikkinen et al., 2017). Two weeks after illness onset, over half of children may still experience symptoms, while about one-third may have symptoms after a month (Hak et al., 2025a). Male sex and lower birth weight seem to be associated with prolonged symptoms (Utsunomiya et al., 2020). Duration is similar in medically and non-medically attended infections (Hak et al., 2024a). RSV-positive respiratory infections in young children last slightly longer than RSV-negative infections. The median duration of RSV-positive infections in children under two is 10 days, compared to 9 days for RSV-negative infections. (Toivonen et al., 2020.)

2.3.4 Hospitalizations

2.3.4.1 Hospitalization rates

In 2019, RSV caused 3.6 million hospitalizations in children under 5 years and 1.4 million in infants aged 0–6 months globally (Li et al., 2022). Hospitalization rates of children with RSV vary by age: 1.5% in <5 years old and 6.7% in <1 year old (Buchan et al., 2023; Thomas et al., 2021; Wong et al., 2021). About 2% of all healthy term infants are hospitalized for RSV during the first year of life (Hak et al., 2024b; Wildenbeest et al., 2023).

RSV accounts for nearly 20% of all infant hospitalizations during RSV season (Suh et al., 2022), and 25–50%, in some studies up to 90%, of respiratory-related hospitalizations depending on study design and age group (Bont et al., 2016; Curns et al., 2024; Hall et al., 2013; Reeves et al., 2020; Rha et al., 2020). Over 40% of RSV-related hospitalizations occur in infants <3 months, around 50% by 6 months, 75% by 1 year, and 90% by 2 years, among children <5 years of age (Del Riccio et al., 2023; Hall et al., 2013; Rha et al., 2020). RSVH rate is highest in infants <1 year (23-35/1000 children), peaking at 1 month (25/1000 children), then decreasing with age (Hall et al., 2013; Reeves et al., 2020; Rha et al., 2020; Thomas et al., 2021). Annual RSVH rates are higher in boys than in girls (4.7 vs 3.7/1000, <5 years old) (Buchan et al., 2023).

Although most RSV-hospitalized children are healthy term infants, preterm and children with certain comorbidities are at increased risk of hospitalization. Preterm infants have 2–3 times higher RSVH rates, especially the most immature, and the elevated risk can persist into the second year of life (Buchan et al., 2023; Curns et al., 2024; Wang et al., 2024). Immunoprophylaxis has reduced RSVH among preterms (Bennett et al., 2018). A Canadian birth cohort study reported in children <5 years with certain conditions higher annual RSVH rates: Down syndrome 26/1000, CLD/BPD 20/1000, CHD and cystic fibrosis 16/1000, compared to 4/1000 in healthy children (Buchan et al., 2023).

Hospitalization rates differ significantly based on healthcare system resources: Industrialized countries have better access to healthcare and higher hospitalization rates than developing countries (Figure 4) (Li et al., 2022). Within HICs, rates vary being lower in the Netherlands and Italy, and higher in France, Norway, Denmark, and Finland (Del Riccio et al., 2023; Reeves et al., 2020).

In addition to initial RSV hospitalization, around 7% of children <5 years old require rehospitalization. However, variation in the definition of rehospitalization makes comparison of studies challenging. The risk of rehospitalization is higher among preterm, CHD, CLD, and trisomy 21 patients, or if the child required intubation or had RSV pneumonia during the initial hospitalization. (Wong et al., 2021.)

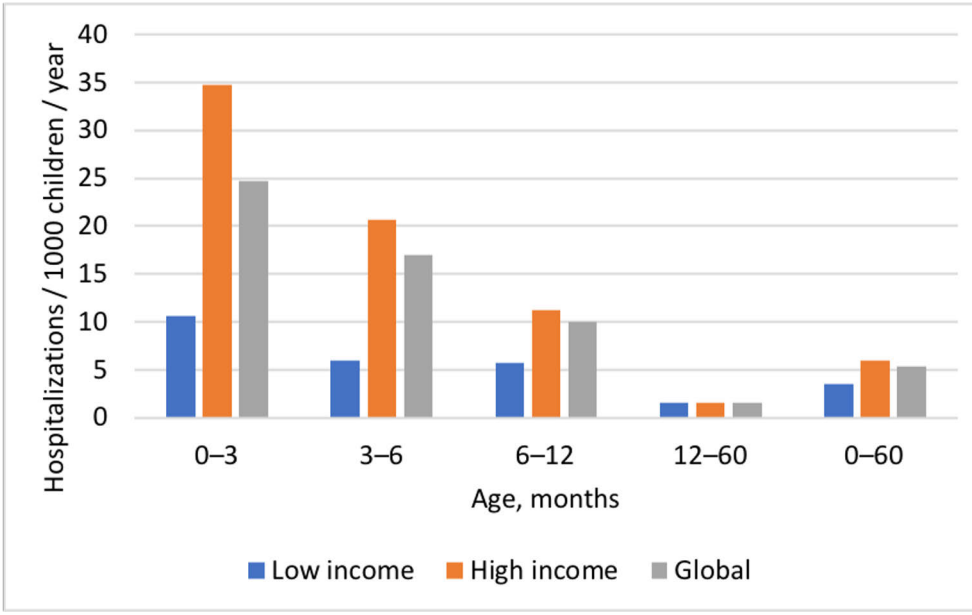

Figure 4. Annual RSV-associated acute LRTI hospitalizations per 1000 children in different ages and income levels. Modified from Li et al., 2022.

2.3.4.2 Length of hospital stay

The median length of stay (LOS) for RSV hospitalizations is typically 2 to 5 days, with some global variation (Bont et al., 2016; Hartmann et al., 2022; Wang et al., 2022b). In a study from seven European countries, the median LOS ranged from 2–4 days (interquartile range [IQR] 0.5–6 days), with the shortest being in Finland and longest in the Netherlands (Wang et al., 2022b).

2.3.4.3 Treatment at intensive care

Around 5-10% of children hospitalized with RSV require intensive care (Bont et al., 2016; Buchan et al., 2023; Fitzpatrick et al., 2024; Hartmann et al., 2022; Shanklin et al., 2024; Wildenbeest et al., 2023). Risk factors for PICU include age under 6 months, prematurity (aOR 1.3), and comorbidities (aOR 1.4) (Curns et al., 2024). PICU stays typically last 3–5 days (Hartmann et al., 2022; Shanklin et al., 2024).

2.3.5 Reinfections and immunity

Most children contract RSV by age two (Andeweg et al., 2021; Kazakova et al., 2019), but primary infection does not provide permanent immunity (Lambert et al., 2014; Parsons et al., 2024). Reinfection occurs in 30–50% of young children (Bont

et al., 2002; Kazakova et al., 2019; Kutsaya et al., 2016), especially if the primary infection occurs before 6 months of age (Foley et al., 2023). Although reinfections are common, a third infection by age three is rare (Kutsaya et al., 2016). Reinfection within the same RSV season is possible, more often between subtypes (Kombe et al., 2019), reflecting partial and subtype-specific immunity (Hall et al., 1991).

Maternal IgG antibodies begin to transfer across the placenta into the fetal bloodstream around the 26th gestational week, with transfer becoming more efficient during the third trimester (Chu et al., 2017; Coindy et al., 2024). As a result over 90% of newborns are seropositive at birth (Ochola et al., 2009; Pasittungkul et al., 2022). Consequently, preterm infants are at higher risk of RSV due to reduced IgG transfer (Chu et al., 2017; Coindy et al., 2024). High maternal antibody levels, measured during pregnancy, in cord blood, or from newborn serum, associate with reduced risk of RSVH (Coindy et al., 2024; Koivisto et al., 2022; Ochola et al., 2009), and may delay the infection (Walsh et al., 2018). Infants also receive antibodies via breast milk, though the extent of this transfer remains unclear (Coindy et al., 2024).

Maternal antibodies begin to wane around 2 months of age, with most infants becoming seronegative by 4–7 months (Coindy et al., 2024; Heinonen et al., 2019; Pasittungkul et al., 2022), though some retain antibodies up to 12 months (Berbers et al., 2021). The half-life of RSV antibodies is estimated at 1–2.5 months, with increasing susceptibility to infection as titers decline (Coindy et al., 2024; Heinonen et al., 2019).

Although the exact protective threshold is unknown (Coindy et al., 2024; Pasittungkul et al., 2022), higher titers correlate with lower risk of severe disease (Walsh et al., 2018). Following RSV infection, antibody levels decrease 25–30% annually (Kutsaya et al., 2016), increasing the risk of reinfection once levels fall below the protective threshold. Generally, reinfections are milder and rarely require hospitalization (Kawasaki et al., 2004).

Vaccinating infants after the waning of maternal antibodies at a few months of age has been considered as one possible way to reduce the RSV disease burden in infants. However, it remains unclear whether maternal antibodies might interfere with vaccine response and whether a booster dose would be needed later in infancy.

2.3.6 Mortality

Globally, RSV is the second leading cause of infant deaths (6.7%) after malaria (11.8%) (Lozano et al., 2012), causing one in thirty deaths among infants aged 1–6 months (Li et al., 2022). In children under five years, RSV accounts for 2% of all deaths and 13–22% of all ALRI deaths (Li et al., 2022), making it the second most common cause of ARI-related deaths after pneumococcal pneumonia (Roth et al.,

2018). In 2019, RSV caused an estimated 26,300 in-hospital deaths and 101,400 total deaths in children <5 years globally, about half of which occurred in infants aged 0-6 months (Table 5). Mortality is highest in LMICs and outside hospitals, and for every RSV in-hospital death, an estimated three additional deaths occur in the community. (Li et al., 2022.) Undoubtedly, not all outpatient deaths are registered worldwide.

RSV mortality shows significant regional variation, and 97–99% of RSV-ALRI deaths occur in developing countries (Li et al., 2022). In HICs, both overall (0.2/1000 children/year) and in-hospital RSV mortality (0.1–1/1000 children/year) are much lower than in LMICs (9/1000 and 18/1000 children/year, respectively) (Duan et al., 2023). In Western countries, the RSV case fatality is less than 0.5% (Bont et al., 2016). The RSV GOLD study series found that in LICs RSV deaths occur at a younger age (4–5 months vs. 7 months) and with fewer comorbidities (28–47% vs. 70%) compared to HICs (Scheltema et al., 2017). Considering the higher RSV hospitalization rate in HICs, alongside their lower RSV mortality, disparities in access to healthcare are highlighted (Li et al., 2022).

Risk factors for RSV mortality include CLD, CHD, Down syndrome, neuromuscular disease, immunodeficiency, low birth weight, being underweight, coinfections, and PICU need (Shi et al., 2022). Although preterm infants have higher individual risk, most RSV deaths occur in full-term infants (Reichert et al., 2022). Mortality has declined over time: in 2005 RSV accounted for 28% of ALRI deaths, decreasing to 13–22% by 2015 (Shi et al., 2017), a similar trend observed in other studies (Li et al., 2022; Wang et al., 2024). RSV mortality dropped by 66.7% globally during the COVID-19 pandemic (Bender et al., 2024).

Table 5. Number of RSV-attributable deaths and proportion (%) of all-cause deaths by age groups and income levels. Modified from Li et al., 2022.

Age, months	Low income	Lower-middle income	Upper-middle income	High income	Develop-ing	Industri-alized	Global
<1	2600 (0.8)	4700 (0.7)	1000 (0.6)	200 (0.6)	8300 (0.7)	200 (0.6)	8500 (0.7)
1–6	10000 (3.8)	22300 (3.6)	4100 (3.2)	500 (2.9)	36700 (3.6)	500 (2.8)	37200 (3.6)
0–6	12600 (2.1)	27000 (2.2)	5100 (1.8)	700 (1.3)	45000 (2.1)	700 (1.2)	45700 (2.1)
6–12	6300 (2.6)	12500 (2.4)	1600 (2.1)	100 (2)	20500 (2.5)	100 (1.9)	20600 (2.5)
0–12	18900 (2.2)	39600 (2.2)	6700 (1.8)	900 (1.4)	65500 (2.2)	800 (1.3)	66300 (2.2)
12–60	11200 (1.7)	21300 (1.6)	2400 (1.4)	200 (1.3)	35000 (1.6)	100 (1.2)	35100 (1.6)
0–60	30100 (2)	60900 (2)	9100 (1.7)	1000 (1.4)	100,500 (2)	900 (1.3)	101,400 (2)

2.4 Clinical presentation

2.4.1 Symptoms

2.4.1.1 Course of illness

According to a recent meta-analysis, the most common symptoms of RSV are cough (92%), nasal congestion (58%), rhinorrhea (53%), shortness of breath (50%), and dyspnea (47%) (Jiang et al., 2023). RSV can also cause extrapulmonary symptoms, including central nervous system (CNS) involvement, myocarditis, rashes, and hepatitis (Zhang et al., 2024). Although RSV symptoms resemble those of other respiratory viral infections and cannot be clinically distinguished based on symptoms alone, RSV tends to cause more nasal discharge and congestion, cough, respiratory distress, chest retractions, wheeze and apneas, and less fever compared to other viruses (Haddadin et al., 2021; Miron et al., 2023; Moe et al., 2017; Zhang et al., 2024). The incubation period is typically 4–6 days (Oppenlander et al., 2023), with symptoms peaking around 2–4 days after onset (Zhang et al., 2024), after which they begin to ease. The mean duration of symptoms is 11–12 days in young children, but this may be prolonged with coinfections (Karppinen et al., 2016). Symptoms following reinfections tend to be milder (Zhang et al., 2024).

2.4.1.2 Age groups

RSV symptoms and their severity vary significantly by age (Zhang et al., 2024). Feeding difficulties and respiratory distress are prominent among the youngest children, affecting 40% and 60% of infants less than 6 months of age respectively. These symptoms decrease with increasing age, as by the age of two, just over 20% of children experience respiratory distress. Upper respiratory symptoms, such as nasal discharge and congestion occur across all age groups, affecting about one-third of infants under 6 months (Saha et al., 2015). Older children more often present with fever and gastrointestinal symptoms, which are less typical in younger infants (Colosia et al., 2023; McGinley et al., 2022). Fever tends to last longer among older children (Utsunomiya et al., 2020).

2.4.1.3 Sex differences

There is limited data on sex differences in the clinical presentation of RSV infection. A Japanese study found that boys under 2 years of age had longer durations of cough and rhinorrhea than girls in outpatient settings (Utsunomiya et al., 2020). Generally,

in non-RSV-specific respiratory infections, boys are more often brought to the ED due to respiratory symptoms and are more likely to present with tachypnea, increased work of breathing, wheezing, and to receive inhaled medications than girls (Groeneveld et al., 2020).

2.4.1.4 Community and hospital care

A recent systematic review of 33 pediatric studies found that the most common RSV symptoms in both in- and outpatient settings were cough, fever, feeding difficulties, and abnormal breathing. In outpatient care, over 90% of children had cough, along with nasal congestion, fever, and feeding abnormalities, especially in the youngest infants. In addition to these symptoms, hospitalized children more often presented with respiratory symptoms such as dyspnea, wheezing, and tachypnea, especially in younger infants. Hospitalized children also exhibited more gastrointestinal symptoms, and cyanosis was reported in those requiring intensive care. (Colosia et al., 2023.)

2.4.2 Impact of viral load

2.4.2.1 Ct value

The cycle threshold (Ct) value is derived from reverse transcriptase polymerase chain reaction (RT-PCR) testing and used to estimate viral load in samples. It is defined by the number of cycles required for the viral RNA to be detected above a defined threshold. Ct value is inversely associated with viral load: the higher the Ct value, the lower the amount of viral RNA in the specimen, and vice versa. There are no specific Ct thresholds for RSV viral load, and they can vary between laboratories and be influenced by sample quality, time since symptom onset, and co-infections. In previous studies Ct values below 25 are considered to indicate high viral load and above it low viral load (Wishaupt et al., 2017).

2.4.2.2 Outpatients and inpatients

The relationship between viral load and disease severity in pediatric RSV infections remains inconclusive. Several studies have reported higher viral loads in hospitalized children, who generally present with more severe symptoms compared to outpatients with milder illness (Cruz et al., 2021). However, some studies have found the opposite results, where outpatient cases showed higher viral loads than inpatients (Brenes-Chacon et al., 2021; Garcia-Mauriño et al., 2019).

In many inpatient studies, higher RSV viral load has been associated with increased disease severity, including risk of PICU admission, need for respiratory support, and

longer duration of symptoms and hospitalization (Hasegawa et al., 2015; Piccirilli et al., 2023; Zhou et al., 2015). However, this correlation has not been consistently observed in all inpatient studies (Yan et al., 2017). In outpatients, higher viral load has been associated with more severe disease (Houben et al., 2010), and increased risk of hospitalization (Haddadin et al., 2021). Younger age has also been associated with higher viral loads in both in- and outpatient groups (Cruz et al., 2021; Yan et al., 2017).

Several factors may explain the inconsistent findings in viral load and disease severity, including variation in symptom duration before sample collection and variations in specimen collection methods (Golan-Tripto et al., 2024). Host immune response may also play a role: milder outpatient cases have shown higher viral loads, greater interferon expression, and reduced expression of inflammation-related genes compared to hospitalized children (Heinonen et al., 2020). In hospitalized children, symptoms may have persisted for longer before viral sampling, which may have resulted in the dominant features of the illness to shift from the initial phase of increasing viral replication to more immune-mediated pathology.

Viral load typically peaks around days 3–5 after symptom onset, followed by a gradual decline over time (McGinley et al., 2022; Zhou et al., 2015). Compared to influenza, the slower progression may provide a longer therapeutic window for starting antiviral treatment in the future.

2.4.3 Impact of RSV subtype

RSV A and B subtypes cause similar clinical characteristics and cannot be distinguished based on symptoms (Haddadin et al., 2021; McGinley et al., 2022; Thomas et al., 2021). However, RSV-A is more likely to cause fever (Hu et al., 2025; McGinley et al., 2022), and some studies suggest it may cause symptoms more frequently (Haddadin et al., 2021) and lead to more severe disease compared to RSV-B (Laham et al., 2017).

2.4.4 Complications

2.4.4.1 Overview and antibiotic treatment

RSV causes several complications such as acute otitis media (AOM), pneumonia, and extrapulmonary manifestations. RSV complications often lead to antibiotic treatment, and it has been estimated that 20–45% of inpatient infants and 10–70% of outpatient children receive antibiotics (Christakis et al., 2005; Farley et al., 2014; Hak et al., 2025b; Thomas et al., 2021). Among infants in the PICU, the treatment proportion may be up to 60% (Hak et al., 2025b). Variations reflect local differences in antibiotic

practices. On the other hand, it has been estimated that there is unnecessary use of antibiotics in RSV infections, highlighting the importance of identifying complications that truly require antibiotic treatment (Obolski et al., 2021).

2.4.4.2 Acute otitis media

AOM is the most common complication of RSV infection, affecting approximately half of all RSV-infected children (Heikkinen et al., 2017; Phillips et al., 2020) and up to 75% of those under 1 year of age (Thomas et al., 2021). AOM typically develops 3–5 days after the onset of respiratory symptoms (Heikkinen and Ruuskanen, 1994; Koivunen et al., 1999), often leading to antibiotic treatment (Tähtinen et al., 2011; Tapiainen et al., 2014). RSV is one of the most prevalent viruses identified in the middle ear effusion, being positive in about 10–20% of cases (Patel et al., 2007; Phillips et al., 2020), and in up to 75% when AOM occurs during RSV infection (Heikkinen et al., 1999).

2.4.4.3 Pneumonia

RSV is one of the most common causes of pneumonia, and it is associated with up to one quarter of all pediatric pneumonia hospitalizations (Jain et al., 2015; Juvén et al., 2000; Ruuskanen et al., 2011). RSV may also predispose children to secondary bacterial pneumonia, with co-infections occurring in approximately 20–50% of cases, most commonly with *Streptococcus pneumoniae* and *Haemophilus influenzae* (Juvén et al., 2000; Oliva and Terrier, 2021). Bacterial coinfections are identified by several methods from upper and lower respiratory tract secretions, including nasopharyngeal aspiration (NPA) combined with X-ray, pleural fluid, sputum, bronchoalveolar lavage, and in some studies through a rise in serum antibody titers or the detection of bacterial antigens in blood samples.

Secondary bacterial pneumonia involves both physiological and immunological mechanisms. Physiologically, RSV alters the permeability of epithelial tight junctions and structure of epithelial cells, impairs mucociliary clearance, and enhances bacterial adherence and virulence. Immunologically, changes have been observed in certain interleukins and reactive oxygen species production, as well as in neutrophil functionality, affecting bacterial clearance and growth in the respiratory tract. (Oliva and Terrier, 2021.)

2.4.4.4 Other complications

RSV can cause extrapulmonary complications affecting the CNS, cardiovascular, endocrine, hepatic, and renal systems (Eisenhut, 2006). Although the exact

mechanisms remain unclear, they likely involve systemic inflammation, cytokine overproduction, and direct viral invasion of organs via the bloodstream (Bohmwald et al., 2016). RSV has been detected in the CSF, brain, heart, liver, and blood (Eisenhut, 2006).

Neurological manifestations occur in 2–3% of all pediatric RSV cases and up to 40% of severe infections in children under two years (Bohmwald et al., 2016). Seizure is the most common neurological manifestation (85%), followed by lethargy, hypotonia, encephalitis, encephalopathy, and central apneas (Bohmwald et al., 2016; Eisenhut, 2006). Even though radiological and EEG changes have been observed, most children recover well (Saravanos et al., 2021).

Cardiovascular complications, including arrhythmias, hypotension, and myocarditis, occur in up to 40% of severe cases (Gkentzi et al., 2018). Other reported complications include hyponatremia, nephrotic syndrome, hepatitis, and myositis (Eisenhut, 2006; Gkentzi et al., 2018).

2.4.5 Co-infections

Multiplex PCR is currently widely used in ED settings, enabling the identification of coinfections with respiratory pathogens in clinical practice. Coinfections are common in children, reported in 20–70% of respiratory infections, depending on the study and the diagnostic panel used (Bermúdez-Barrezueta et al., 2023; Di Maio et al., 2024; Kouni et al., 2013). Coinfections are more frequently observed in children than adults (Nascimento-Carvalho and Ruuskanen, 2016), highest in children aged 1–2 years (Cebey-López et al., 2015), with some evidence of higher prevalence in girls (Bermúdez-Barrezueta et al., 2023).

Among RSV-positive children requiring hospitalization, coinfection occurs in 30–40% of cases (Moe et al., 2017), and up to 70% in outpatient cohorts (Chu et al., 2013). RSV frequently appears in coinfections due to its high prevalence (Kouni et al., 2013), but is often detected as a single pathogen. Common coinfecting viruses include influenza, bocavirus, and adenovirus (Bermúdez-Barrezueta et al., 2023; Cebey-López et al., 2015; Kouni et al., 2013). RSV and rhinovirus rarely coinfect (Di Maio et al., 2024; Karppinen et al., 2016), but when they do, the disease tends to be more severe (Li et al., 2020). RSV-A and RSV-B subtypes are co-detected in about 1% of samples (Bin Lu et al., 2019).

The impact of viral coinfection on disease severity is inconsistent across studies. Some studies report associations with hospitalization (Kouni et al., 2013) and a longer LOS (Bermúdez-Barrezueta et al., 2023), while others find no effect (Bermúdez-Barrezueta et al., 2023; Chu et al., 2013; Nascimento et al., 2010; Thomas et al., 2021). Some studies even suggest that coinfections may cause milder disease compared to single infections (Martin et al., 2012). In RSV-specific coinfections, the data remains

conflicting. Some studies report increased disease severity (Trusinska et al., 2024), while others do not (Li et al., 2020). Differences in definitions and viral combinations may explain this (Babawale and Guerrero-Plata, 2024).

RSV also coinfects with bacteria in 10–30% of hospitalized children, most commonly with *S. pneumoniae, H. influenzae, and S. aureus*. Children with RSV tend to be more often colonized with *S. pneumoniae* compared to healthy controls, and may experience more severe disease. (Lin et al., 2022.) The mechanism may involve nasal tissue damage and differences in IFN-gamma responses (Aberle et al., 2005).

2.5 Socioeconomic impact

2.5.1 Economic burden of RSV

RSV infections in children represent a significant economic burden. Globally in 2017, RSV-ALRIs in children <5 years of age were estimated to cost 4.8 billion €, with 55% of costs attributed to inpatient and 45% to outpatient care (Zhang et al., 2020). The average cost per RSV episode has been estimated to be approximately 3500€ for inpatient and 300–700€ for outpatient cases, varying widely due to differences in treatment practices, reporting methods, and access to healthcare (Díez-Gandía et al., 2021; Nyiro et al., 2024; Zhang et al., 2020). In a European multicenter study, the mean cost per outpatient RSV episode was around 400€ in direct and 500€ in indirect costs (Mao et al., 2023). When planning the implementation of RSV interventions, country-specific cost analyses are needed for accurate cost-effectiveness calculations.

2.5.2 Direct costs

Direct costs account for about one-quarter of the total costs including healthcare resource use and medications (Sankatsing et al., 2025). Hospitalization imposes a considerable burden, especially in high-risk and preterm infants, due to more severe disease and higher episode costs (Bowser et al., 2022; Haeberer et al., 2025; Han et al., 2024; Lade et al., 2025; Zhang et al., 2020). However, full-term infants account for over 80–90% of RSV hospitalizations and 70% of total RSVH costs (Bowser et al., 2022; Han et al., 2024). The cost burden of RSV exceeds that of other respiratory viruses (Bechini et al., 2024). A Danish registry study found that healthcare use is elevated before and for up to a year after RSV hospitalization (von Linstow et al., 2024).

RSV also causes frequent outpatient visits (Hak et al., 2024b), and more healthcare contacts and symptomatic days compared to RSV-negative ARI (Chu et al., 2013). AOM develops in 30–60% of RSV-infected children, often requiring antibiotics and pain medication, further increasing direct costs (Heikkinen et al.,

2017; Toivonen et al., 2020). In a Finnish birth cohort study, RSV-positive children used more antibiotics (35% vs. 16%) and analgesics (72% vs. 48%) than those with RSV-negative ARIs (Toivonen et al., 2020).

2.5.3 Indirect costs

RSV-related indirect costs, particularly parental work absenteeism, represent the largest part of the economic burden, up to three-quarters of total costs (Sankatsing et al., 2025). Parental work absence for at least one day occurs in over 50% of RSV cases (Heikkinen et al., 2017; Sankatsing et al., 2025), and is more common with RSV-positive than RSV-negative ARIs (Chu et al., 2013; Toivonen et al., 2020). The mean duration of parental work absence is 2–4 days (Sankatsing et al., 2025; Toivonen et al., 2020; Heikkinen et al., 2017; Hak et al., 2025a). In a European birth cohort study of nearly 1000 healthy full-term infants, 10% of non-medically attended RSV episodes led to parental absence and in over 40% of cases, at least one parent missed at least one workday (median 1 day, IQR 1–4.25) (Hak et al., 2024a). The most absences occur among the youngest children (Heikkinen et al., 2017).

RSV infections also cause day-care absences for children in approximately 50–65% of cases (Heikkinen et al., 2017; Sankatsing et al., 2025), and among children <24 months even >90% of cases (Toivonen et al., 2020). The average length of absence from day-care is around 3 days (Heikkinen et al., 2017). Compared to other respiratory viruses, RSV seems to cause more absences from day-care (Chu et al., 2013; Toivonen et al., 2020).

In addition to financial costs, RSV infections have a significant impact on the well-being of families. Even in non-medically attended cases, about 75% of parents report concern, and a third experience anxiety (Hak et al., 2024a). Health-related quality of life remains impaired even two weeks after symptom onset (Díez-Gandía et al., 2021).

2.6 Diagnosis

2.6.1 Diagnostics and its importance

The diagnosis of RSV is crucial for patient cohorting in hospitals to limit transmission. The likelihood of bacterial infection occurring concurrently with RSV is low. Rapid detection of RSV may reduce antibiotic use (Byington et al., 2002), potential further investigations, and hospitalizations compared to situations where the virus could not be detected (Levine et al., 2004). However, in some HICs with low antibiotic prescribing rates, specific viral diagnostics have not affected the initiation of antibiotic treatment (Mattila et al., 2022).

Viral samples can be obtained from various sources, such as saliva and oral mucosa (Buonsenso et al., 2023), but respiratory epithelial cells, particularly from the nasopharynx, are the most common and reliable site (Macfarlane et al., 2005; Zhang et al., 2024). Sampling methods like nasopharyngeal swab (NS) and NPA show similar sensitivity (Flynn et al., 2021), and therefore NS is preferred for its ease and comfort in clinical practice (Lambert et al., 2008). Diagnostic sensitivity is highest within the first four days of the RSV disease (Zhang et al., 2024).

Diagnostic practices vary between centers, and routine viral testing is generally not recommended, though used for cohorting and epidemiological studies in some guidelines. Most national protocols, including the Finnish national guideline, discourage the routine use of X-rays and blood or urine tests. (Backman et al., 2025; Kirolos et al., 2020.) Diagnostics of respiratory tract infections, including RSV, have evolved over time, with PCR currently considered the method of choice.

2.6.2 Viral culture

Virus culture was the first and previously long considered as the gold standard in the diagnostics of RSV infection (Henrickson and Hall, 2007). In this method, a sample taken from the patient is grown in optimized cell culture conditions, and even with current advanced techniques, detecting the virus still takes days (Leland and Ginocchio, 2007). In addition to being slow, the method is costly, which has limited its usability in clinical practice (Henrickson and Hall, 2007). Viral culture is very specific, as it is based on the detection of live virus, and it still has a place in RSV infections providing information about the virus's genetic characteristics and mutations (Henrickson and Hall, 2007).

2.6.3 Serology

Serological tests are not used to diagnose acute RSV infection in clinical practice, as the development of antibodies takes days (Welliver et al., 1980). However, measuring antibodies is beneficial in epidemiological studies (Kutsaya et al., 2016).

2.6.4 Antigen detection

Antigen tests detect virus-specific proteins, most commonly using immunofluorescence and immunochromatography. They are cheaper and faster, often providing results within a few minutes, but less sensitive than PCR tests, especially at low viral loads (Henrickson and Hall, 2007). Antigen detection is better in children than in adults (Chartrand et al., 2015), sensitive especially in the early stages of the disease (Shafik et al., 2011), and superior for RSV compared to many other respiratory viruses (Ivaska et al., 2013).

Rapid antigen detection tests, point-of-care tests (POCTs), can detect multiple viruses within 30 minutes, making them useful and cost-effective in ED settings (Gunell et al., 2016; Ivaska et al., 2013; Zhang et al., 2024; Mills et al., 2011). These tests are now also available for home use.

2.6.5 Reverse transcriptase polymerase chain reaction

PCR testing is currently the gold standard in RSV diagnostics due to its high sensitivity (86.4%–100%), specificity (97.7%–100%), and speed (Zhang et al., 2024). In the PCR method, RSV RNA detected in the sample is converted to DNA via reverse transcription, after which specific gene sequences characteristic of RSV are examined. Multiplex PCR assays are currently available to detect multiple viruses from the same sample. Some tests can identify around twenty different pathogens simultaneously, and some assays cover a wide range of viruses and also bacteria in a single sample. (Huang et al., 2018.)

2.7 Treatment

2.7.1 Supportive treatment

2.7.1.1 Overview of current stage

The treatment of RSV bronchiolitis is currently supportive, including fluid, nutritional, and respiratory support, and minimal handling (Mazur et al., 2024; Zhang et al., 2024). Despite extensive research, pharmacological treatments have not proven to be effective. Although there is substantial variation in management between centers in different countries, with over 30% of patients receiving non-evidence-based supportive therapy (Schuh et al., 2017), the Finnish national guideline is largely consistent with the majority of other treatment protocols (Backman et al., 2025). A review of 32 clinical guidelines by the RESCEU Investigators highlights the need for standardized treatment guidelines (Kirolos et al., 2020).

2.7.1.2 Fluid management

Approximately half of hospitalized bronchiolitis children require fluid therapy (Gill et al., 2021). While both enteral and intravenous (IV) hydration are used with mixed evidence, enteral hydration is generally recommended as the first-line approach (Kirolos et al., 2020; Zhang et al., 2024). Enteral management via nasogastric tube is effective, safe, and linked to fewer local complications, and reduced PICU

admissions and readmissions compared to IV fluids (Gill et al., 2021). While the method of fluid administration does not affect hospital LOS or time to full enteral feeding (Gill et al., 2021; Zhang et al., 2024), some evidence suggests that enteral feeding may shorten hospitalization and reduce oxygen supplementation needs compared to IV hydration (Sarkis et al., 2023). Overhydration should be avoided, and diuretics may benefit severe cases (Kulkarni et al., 2020).

2.7.1.3 Respiratory support

There are center-specific differences in respiratory support practices, but about 50% of hospitalized bronchiolitis patients require respiratory support (Aricò et al., 2023). Available options include low-flow nasal cannula (LFNC), high-flow nasal cannula (HFNC), continuous positive airway pressure/bilevel positive airway pressure (CPAP/BiPAP), and tracheal intubation. HFNC offers humidified high flow oxygen and has been an effective, well-tolerated, comfortable, and safe respiratory support method (Petkar et al., 2024), though optimal use and weaning strategies to prevent prolonged hospitalization remain unclear (Towriss et al., 2024). Compared to LFNC, HFNC may reduce the need for treatment escalation, length of hospital stay and requirement of supplemental oxygen while improving respiratory rates, without increasing adverse effects (Armarego et al., 2024; Franklin et al., 2018; Kepreotes et al., 2017). However, the evidence remains conflicting (Mazur et al., 2024). CPAP/BiPAP may have lower failure rates than HFNC (Habra et al., 2020).

Oxygen saturation thresholds for supplemental oxygen vary by centers, ranging from <90% to <95% (Kirolos et al., 2020; Zhang et al., 2024). Airway secretion suctioning is recommended as-needed in many protocols (Kirolos et al., 2020), despite limited evidence of effectiveness (Zhang et al., 2024), while chest physiotherapy is not advised (Mazur et al., 2024).

2.7.1.4 Pharmacological treatments

2.7.1.4.1 Inhalation therapy

Multiple inhaled medications for bronchiolitis, including epinephrine, saline, bronchodilators, magnesium sulfate, dexamethasone, and steam, show no clinical benefit and are not routinely recommended (Backman et al., 2025; Kirolos et al., 2020; Mazur et al., 2024; Zhang et al., 2024). Hypertonic saline may improve mucociliary clearance and reduce airway edema, and according to a Cochrane review may be beneficial in in- and outpatient bronchiolitis, though conflicting evidence exists and most clinical guidelines do not recommend its routine use (Backman et al., 2025; Kirolos et al., 2020; Mazur et al., 2024; Zhang et al., 2023; Zhang et al., 2024).

2.7.1.4.2 Other medical treatments

RSV immunoglobulin, erythropoietin, or caffeine have not reduced the disease severity of bronchiolitis (Sanders et al., 2023). Antibiotics are not recommended unless there is clear evidence of a bacterial coinfection, yet nearly one-third of RSV-LRTI cases receive them unnecessarily (Mazur et al., 2024; Zhang et al., 2024).

2.7.2 Antivirals

2.7.2.1 Potential of RSV antivirals

While new vaccines and monoclonal antibodies have been introduced to prevent severe RSV in infants, therapeutic antiviral development has been slower. However, the substantial burden of RSV is among outpatient older children, for whom an antiviral treatment would be ideal. Ribavirin remains the only approved antiviral for RSV treatment, with few others in clinical development (Zou et al., 2024) (Table 6).

Antivirals have shown benefits in other viral infections, such as influenza, raising expectations for RSV antivirals as well (Malosh et al., 2018). RSV´s longer incubation period and viral peak compared to influenza may offer a longer therapeutic window for initiating antiviral therapy (Bagga et al., 2013). Around half of infants hospitalized with RSV have had contact with healthcare 1–2 days before admission, but identifying these cases and enabling early initiation of antivirals is challenging, and symptoms have often already been present for some days by that point (DeVincenzo et al., 2004).

2.7.2.2 Ribavirin

Ribavirin interferes with viral RNA synthesis, replication and induces mutations in the RSV genome (Churiso et al., 2022). Small placebo-controlled studies from the last millennium demonstrated the efficacy of inhaled ribavirin, leading to its approval in 1985 and being the only antiviral for pediatric RSV (Hall et al., 1983). Later studies, however, show only modest benefits, with possible reduction in severity and mortality, but no long-term effects (Ventre and Randolph, 2007). A meta-analysis showed reduced mortality in hematological patients, but the study was highly heterogeneous regarding the age of the participants, administration route, dose, and duration. No difference was observed in other patient groups, which is why ribavirin is not administered to otherwise healthy pediatric patients. (Tejada et al., 2022.) Ribavirin's high cost, potential toxicity, and teratogenicity for healthcare staff limit its use to severe RSV infection in immunosuppressed patients (Zhang et al., 2024).

Table 6. Development stage of antivirals studied for RSV infection and their mechanism of action. The most promising candidates are bolded. Situation in 2024, although it remains highly dynamic. Modified from Bonneux et al., 2024.

Mechanism of action / Target	Antiviral	Development Stage in RSV infection
FUSION INHIBITORS	**Ziresovir** (AK-0529, RO-0529)	Pre-registration in China
	Sisunatovir (RV521, PF-07923568)	Discontinued
	Lonafarnib	Preclinical
	Rilematovir (JNJ-53718678), BMS-433771, MDT637 / VP-14637 ,BTA-C286, Enzaplatovir (BT-585, BTA-C585)	Discontinued, strategic decision
	Presatovir (GS-5806)	Discontinued, lack of efficacy
	TMC-353121 (R-391036, JNJ-27387581)	Discontinued, side effects at local site
	BTA-9881 (AZD-9639, MEDI-564), R-170591; R-53177; JNJ-2408068	Discontinued, safety concern
REPLICATION INHIBITORS, L NUCLEOS(T)IDE ANALOG INHIBITORS	**Molnupiravir** (EIDD-2801/MK-4482-017)	Phase 2a human challenge study
	S-337395	Phase 2
	D7487	Preclinical
	Lumicitabine (ALS-8176, JNJ-64041575), AT-889, AT-934, RBS-3149	Discontinued, safety concern, lack of efficacy
REPLICATION INHIBITORS, L CAP DOMAIN INHIBITORS	**EDP-323**	Phase 1
	BI compound D, MRK-1	Discontinued
REPLICATION INHIBITORS, L CONNECTOR DOMAIN INHIBITORS	AVG-233, AZ-27, PC786, YM-53403 , Triazole-1, Compound 1	Discontinued
REPLICATION INHIBITORS, M2-1 INHIBITORS	AT2 and analogs, Cyclopamine	Not reported
REPLICATION INHIBITORS, N INHIBITORS	**Zelicapavir**	Phase 2
	RSV-604 (A-60444), RV-299 (PF-07923567), ALN-RSV01	Discontinued
P INHIBITORS	Compound 3	Discontinued
HOST IMPDH INHIBITORS	**Ribavirin** (Rebetol)	Launched
	Merimepodib (VX-497), Compound 8	Not reported

2.7.2.3 Fusion inhibitors

2.7.2.3.1 Ziresovir

Fusion inhibitors block viral entry into host cells and prevent cell-to-cell spread (Rhodin et al., 2021). Ziresovir (AK-0529) is currently the most advanced antiviral after ribavirin. It is an RSV F protein inhibitor that primarily prevents viral entry into the host cell (Zhang et al., 2024). In a phase 3 AirFLO study in China involving about 300 children, 5-day oral treatment with ziresovir reduced symptoms (30% symptom score reduction on day 3) and viral load (77% reduction on day 5) compared to placebo in RSV-infected children up to 24 months of age. It was also safe and well tolerated. (Zhao et al., 2024.) Ziresovir is currently in the pre-registration stage in China.

2.7.2.3.2 Sisunatovir

Sisunatovir (RV521) reduced viral load by over 50–60% and symptom scores by 70–80% compared to placebo in adults in a phase 2 study (DeVincenzo et al., 2020). It was also found to be well tolerated and safe, leading to a Fast Track designation by the U.S. Food and Drug Administration (FDA) in 2020 for the treatment of severe RSV disease. In phase 2 clinical REVIVAL 1 study trial (trial identifier: NCT04225897), oral sisunatovir was investigated in infants aged 1–36 months with RSVH-LRTI. After promising results, it was decided to be discontinued due to strategic considerations rather than safety concerns.

2.7.2.4 Replication inhibitors

Replication inhibitors, including N- and L-protein inhibitors, target replication and RNA synthesis in cells that are already infected (Rhodin et al., 2021).

Currently, the most promising candidate is N-protein inhibitor zelicapavir (EDP-938) (Sevendal et al., 2024). In a phase 2 study in healthy adults, it reduced viral load by 70–80%, symptom scores by 60–80%, and mucus production compared to placebo, without differing adverse effects (Ahmad et al., 2022). In children up to 36 months of age, it was found to reduce viral load effectively compared to placebo, both in in- and outpatient settings (Enanta Pharmaceuticals, 2024).

L-protein inhibitors are divided into two categories: nucleoside/nucleotide analogs (NIs) and non-nucleoside inhibitors (NNIs). ALS-8176 demonstrated excellent efficacy in early clinical trials but was discontinued due to a lack of efficacy and reversible neutropenia after phase 2b. Several broad-spectrum antivirals approved for SARS-CoV-2, such as molnupiravir and VV116 (Tian et al., 2022; Yoon et al., 2018), are being evaluated for RSV. In a phase 2 study in healthy adults

(trial identifier: NCT05587478), S-337395 reduced RSV viral load by 90%, improved symptom scores, and was well tolerated with no serious adverse events. EDP-323 was also shown to be safe and well tolerated in healthy adults in a phase 1 randomized controlled trial (RCT) (trial identifier: NCT05587478). As a result, both have received Fast Track designation from the FDA.

2.7.2.5 Under clinical research

New RSV antivirals are being studied intensively and alternative administration routes like intranasal delivery are under investigation (Mitra et al., 2023). These may offer several advantages, including ease of use, reduced resource requirements, direct action at the site of infection, rapid onset of effect, the ability to achieve high concentrations locally, minimal systemic effects, and the potential to reduce aerosol transmission (Oti et al., 2024).

2.7.3 Monoclonal antibodies

Currently, no monoclonal antibodies are approved for the treatment of RSV. The most advanced candidates, gontivimab (ALX-0171) and motavizumab (MEDI-524), reached phase 2 trials but were discontinued due to a lack of clinical efficacy. Although inhaled gontivimab reduced viral load, it did not improve clinical outcomes in infants with RSVH-LRTI compared to placebo. Similarly, motavizumab showed no significant impact on viral load. (Cunningham et al., 2021; Ramilo et al., 2014.)

2.8 Prevention

2.8.1 Vaccines

2.8.1.1 History of RSV vaccines

In the 1960s, the first formalin-inactivated pediatric RSV vaccine induced a strong antibody response, but it targeted significantly non-protective epitopes. This resulted in poor efficacy and an increased risk of enhanced RSV disease (ERD) with more severe symptoms, leading to hospitalizations and, in some cases, death (Kim et al., 1969; Murphy and Walsh, 1988). The severe disease was linked to the presence of non-functional antibodies (Murphy and Walsh, 1988), Th2-skewed immune response, and eosinophilic infiltration in the lungs (Acosta et al., 2015).

Despite RSV´s known high burden and relatively low genetic variability (Kingwell, 2023), vaccine development has been slow until the discovery of the preF

conformation. As a result, the first maternal and elderly RSV vaccines were approved in 2023 (Pfizer Press Releases, 2023). Several new vaccine candidates are emerging, primarily targeting the preF conformation and its highly neutralizing epitopes (Walsh et al., 2023). Vaccine development aims to provide protection against both RSV subtypes, though RSV-B preF sites exhibit more variability (Hause et al., 2017).

2.8.1.2 Maternal vaccines

Maternal vaccines have previously shown effectiveness in protecting infants against infectious diseases like influenza, pertussis, and COVID-19 (Quincer et al., 2024), and promising candidates targeting other pathogens are in development (Madhi et al., 2023). Currently, there is one maternal RSVpreF vaccine (Abrysvo ®), licensed to protect infants from severe RSV during their first six months of life (Kingwell, 2023).

In a large RCT involving over 7,000 pregnant individuals at 24–36 weeks´ gestation, the RSVpreF bivalent vaccine showed 80–91% efficacy against severe RSV-LRTI within 90 days and 70–77% at 180 days. Higher efficacy was observed when the vaccine was administered later in pregnancy, which also reduced RSV-LRTI by 35% at 90 days and 57% at 180 days. (Kampmann et al., 2023.) Based on this study, the vaccine was approved by both the FDA and European Medicines Agency (EMA) in 2023 for preventing severe RSV in infants. Similar efficacy estimates of approximately 50–70% against RSV-LRTI, RSVH, and severe RSV-LRTI during the first six months of life have been reported in other studies (Dieussaert et al., 2024; Mapindra et al., 2024; Phijffer et al., 2024a). In contrast, protection against milder RSV infections has been more modest (Kampmann et al., 2023). Real-world data also demonstrate about 80% effectiveness against RSVH in the first three months of life and around 70% during the first six months, with protection against severe RSVH reaching up to 77% (Pérez et al., 2025; Simões et al., 2025).

The maternal vaccine is well tolerated in both mothers and infants, with mainly mild local injection side reactions and no increased risk of congenital anomalies, intrauterine growth restriction, or stillbirth (Kampmann et al., 2023; Mapindra et al., 2024; Pang et al., 2024; Phijffer et al., 2024a). In certain LICs and LMICs during the COVID-19 Delta variant, a slightly higher rate of preterm delivery was observed among vaccine recipients (5.7% vs. 4.7%), though this difference was not statistically significant and no causal link or mechanism for preterm labor has been established. Most experts consider this unlikely to be vaccine-related. (Kampmann et al., 2023; Phijffer et al., 2024a). As a precaution, however, the FDA has restricted

the use of the vaccine to 32+0 to 36+6 weeks' gestation, whereas the EMA has approved administration from 24 to 36 weeks (Willemsen et al., 2024).

Maternal RSV vaccination offers strong antibody responses with efficient transplacental transfer (ratio 1.4–2.1), correlating with infant antibody levels and lower infection risk (Bebia et al., 2023; Buchwald AG 2021; Simões et al., 2022; Yildiz et al., 2020). Nevertheless, some infants still develop severe RSV despite high antibody titers, highlighting remaining gaps in understanding RSV immunity (Jans et al., 2017).

The monovalent RSV-preF3-Mat vaccine (Arexvy ®) has been associated with a higher incidence of preterm delivery (6.8% vs. 4.9%, RR 1.37) when administered at 24–34 weeks' gestation in a phase 3 trial, leading to early trial termination (Dieussaert et al., 2024). Consequently, this vaccine did not receive FDA or EMA approval for maternal use, although it is licensed for use in older adults.

2.8.1.3 Pediatric vaccines

RSV poses the greatest risk to infants, but vaccinating them effectively is challenging due to their immature immune system and the presence of maternal antibodies, which can hinder the development of a strong and long-lasting vaccine response, especially during the first six months of life (Esposito et al., 2016). Additionally, live-attenuated vaccines require a delicate balance between immunogenicity and the risk of upper respiratory tract congestion. As a result, maternal vaccination or mAbs at birth may offer the best early protection, while pediatric vaccines could be introduced from 6 months onward. Furthermore, vaccinating older children may provide indirect protection to younger infants by reducing transmission.

Past concerns about vaccine-related challenges have slowed pediatric RSV vaccine development, but several promising candidates are in progress, especially live-attenuated ones (Table 7).

The most advanced candidate, RSV/ΔNS2/Δ1313/I1314L, demonstrated 67% efficacy against medically-attended RSV-ARI and 88% against medically-attended RSV-LRTI in a pooled analysis of seven phase 1 trials (Karron et al., 2021), and is currently in phase 3 testing in toddlers. Other promising candidates with strong immune responses include RSV/6120/ΔNS2/1030s and RSV/276. Like other live attenuated vaccines, these may cause mild upper respiratory symptoms, but unlike the 1960s vaccine, they do not induce ERD. (Cunningham et al., 2022; Karron et al., 2024.)

Table 7. Pediatric RSV vaccinations under development. Situation in 2025, although it remains highly dynamic. Modified from Babawale et al., 2025.

Vaccine Type	Mechanism of Action	Advantages and Disadvantages	Examples	Development Phase
LIVE ATTENUATED	To introduce mutations (e.g., temperature sensitivity, deletion of specific viral proteins) to limit viral replication.	(+) Strong and long-lasting immune response. (+) Administered directly into the respiratory tract intranasally, enhancing local immunity.	RSV/ΔNS2/Δ1313/I1314L * (RSVt) LIDΔM2-2 RSV/6120/ΔNS2/1030s MV-012-968	Phase 1, 2 *Phase 3
RECOMBINANT VECTOR-BASED	Uses a modified version of another virus (e.g., adenovirus or parainfluenza virus) to deliver RSV proteins to the immune system.	(+) Induces both humoral and cellular immune responses. (-) Potential effects of the vector virus?	Ad26.RSV.preF BLB-201	Tested in adults Phase 2
PROTEIN-BASED	Uses only RSV viral proteins to stimulate an immune response	(+) No live virus involved. (-) Weaker immune response, may require booster doses.	RSV pre-F	Approved for adults and pregnant women, under development for children.
NUCLEIC ACID-BASED	Delivers mRNA or DNA sequences that instruct the body to produce RSV proteins, triggering an immune response.	(+) Rapid development and adaptability. (+) Strong antibody response. (-) Unknown long-term effects and potential immune reactions.	mRNA-1345	Development halted at Phase 2 due to VAERD

Abbreviation: VAERD, vaccine-associated enhanced RSV disease

2.8.1.4 Older adults

Two RSV vaccines, RSVpreF (Abrysvo ®) and RSVPreF3 OA (Arexvy ®), received FDA and EMA approval in the summer of 2023 for use in adults aged 60 and older. Both have demonstrated high efficacy in preventing RSV infections, including severe RSV-LRTI, with effectiveness sustained across multiple RSV seasons and subtypes, and an acceptable safety profile (Falsey et al., 2024; Ison et al., 2024; Papi et al., 2023; Walsh et al., 2023). In 2024–2025, an mRNA-based RSV vaccine (mRESVIA®) was approved by the FDA and EMA for adults aged 60 and older, and for those 18-59 years old with an increased risk of severe RSV disease (FDA Vaccines mRESVIA, 2024; European Medicines Agency Medicines mResvia, 2024). In clinical trials, it demonstrated approximately 80% efficacy against RSV-LRTI and nearly 70% efficacy against RSV-ARI (Wilson et al., 2023). New mRNA, protein- and vector-based vaccines are under development, including combination vaccines targeting RSV and other respiratory viruses (Athan et al., 2024; PATH).

2.8.2 Monoclonal antibodies

2.8.2.1 Palivizumab

In newborns with the highest burden of RSVH, the immune system is still developing, and vaccines and antibody responses are less effective than in older children. Therefore, passive immunization through maternal vaccination or monoclonal antibodies is the primary strategy to prevent severe RSV (Heinonen et al., 2019).

Palivizumab (Synagis ®) was for a long time the only RSV prophylaxis for the prevention of severe RSV-LRTI in high-risk infants, particularly in HICs (Carbonell-Estrany et al., 2025). It is a humanized recombinant monoclonal IgG antibody that binds to the epitope site II of the RSV F-protein in both pre- and post-fusion conformations preventing viral fusion. It consists of 2 heavy and 2 light chains, of which 95% of human origin and 5% of murine origin.

Palivizumab was approved by the FDA in June 1998 and a year later by the EMA. The approval was based on a multicenter trial by the IMpact Study Group, where it reduced RSVH by 55% (10.6% vs 4.8%, number needed to treat [NNT] 17) in high-risk patients, particularly in preterm infants (78% reduction). It also reduced LOS and PICU admissions and was found to be safe and well-tolerated. (The IMpact-RSV Study Group, 1998.) Later studies have confirmed its effectiveness in the target populations. In children with CHD, it reduced RSVH by 45% (9.7% vs 5.3%) and hospital days by 56% compared to placebo (Feltes et al., 2003). It also reduced RSV infections, medically attended infections, hospitalizations, and wheezing days (Blanken et al., 2013; Garegnani et al., 2021), and in some cases PICU admissions (El-Atawi et al.,

2023). It may also reduce other respiratory-related hospitalizations (Bloomfield et al., 2020; Garegnani et al., 2021), and later asthma, although establishing causality remains challenging (Scheltema et al., 2018; Fang et al., 2023; Quinn et al., 2020).

The American Academy of Pediatrics issued its first palivizumab immunoprophylaxis recommendation in 1998 (American Academy of Pediatrics Committee on Infectious Diseases and Committee of Fetus and Newborn, 1998), which has since been regularly updated. The most recent update from 2023 recommends nirsevimab over palivizumab. However, if nirsevimab is unavailable, it recommends palivizumab for high-risk infants, including those under 12 months born before 29 wGA, or before 35 wGA with BPD or hemodynamically significant CHD. It is also recommended for preterm children up to 24 months with BPD or CHD who required treatment for their condition within 6 months before RSV season. (Caserta et al., 2023.) Regional variations exist regarding who receives palivizumab immunoprophylaxis (Luna et al., 2020).

Palivizumab is administered monthly, and a total of five intramuscular doses maintains protective antibody levels in most children during the season, with a mean half-life of 18–20 days (Robbie et al., 2012). While the exact protective threshold of serum palivizumab levels in humans is unclear, higher levels have been associated with reduced RSVH severity and rates of PICU admission (Forbes et al., 2014).

Palivizumab is considered safe and well-tolerated (Feltes et al., 2003; Garegnani et al., 2021). However, its use is limited by the need for monthly injections during the season, high costs, and inconsistent parental compliance with administration (Frogel, 2010). In addition to low RSV mortality in developed countries, short hospitalizations, and limited evidence of long-term benefits, its widespread use has not been justified.

2.8.2.2 Nirsevimab

Nirsevimab (Beyfortus ®) is a human monoclonal RSV IgG antibody that binds to the preF form at antigenic site Ø. Its advantages include extended half-life achieved with point mutations in the Fc-region, enabling a single intramuscular dose at the beginning of the season to protect throughout the entire season, up to 150 days (Griffin et al., 2020; Hammitt et al., 2022). Maximum serum concentration is reached within 5–9 days (Griffin et al., 2017). Nirsevimab generates a strong, long-lasting antibody response, with levels up to 10-fold higher than those of palivizumab (Wilkins et al., 2024).

Nirsevimab was approved for RSV prevention in infants by the EMA in October 2022 and the FDA in July 2023. Clinical trials leading to approval showed it to be safe, well-tolerated, and effective in healthy adults (Griffin et al., 2017), preterms, and full-terms, reducing RSV medically attended lower respiratory infections

(MALRIs) by 70–80% and RSVH by 77–78% (Griffin et al., 2020; Simões et al., 2023). Reductions were also observed in any-cause respiratory illness, MALRI, outpatient LRTI visits, and antibiotic prescriptions (Simões et al., 2023). In a phase 3 study with over 80% healthy term infants, it was safe and effective in late preterm and term infants, with 74.5% efficacy against MALRI and 62% efficacy against RSVH (0.6% vs 1.6%) compared to placebo (Hammitt et al., 2022). No differences in safety profile compared to palivizumab were observed (Domachowske et al., 2022). Based on these findings Advisory Committee on Immunization Practices recommended it for all infants <8 months during their first RSV season and for high-risk infants aged 8–19 months during their second season (Jones et al., 2023).

Since then, real-world data on nirsevimab's effectiveness in infants has been collected globally, with results even surpassing those seen in clinical trials. The effectiveness of nirsevimab against RSVH has been reported to be 74–89% in Europe (Ares-Gómez et al., 2024; Coma et al., 2024; Ezpeleta et al., 2024; Assad et al., 2024; Carbajal et al., 2024; Drysdale et al., 2023) and 80–93% in the US (Moline et al., 2025; Xu et al., 2025). Nirsevimab also reduces severe RSV disease by 70–90% (Carbajal et al., 2024; Coma et al., 2024) and all-cause LRTI hospitalizations by 60-80% (Drysdale et al., 2023; Xu et al., 2025). Protection against RSVH is higher in infants under 3 months (79% compared to 67% in 3–6 months) (Jimeno Ruiz et al., 2024) and declines over time, being 93% at 30 days and 88% at 150 days (Barbas Del Buey et al., 2024). NNT to prevent one RSV hospitalization is 15–25 (Ares-Gómez et al., 2024; Barbas Del Buey et al., 2024; Ezpeleta et al., 2024). Nirsevimab also appears to reduce outpatient burden reducing medically attended RSV-LRTI by 70–90% (Moline et al., 2025; Xu et al., 2025), outpatient visits by 60% (Xu et al., 2025), ED visits due to RSV bronchiolitis by 80% and all-cause bronchiolitis ED visits by almost 50% (Carbajal et al., 2024). Immunization coverage in these studies has been high, between 84–92% (Ernst et al., 2024; Ezpeleta et al., 2024).

Due to these great results, nirsevimab has been widely adopted in many European countries, in the USA, Canada, Australia, Japan, and Latin America. Finland was the first Nordic country to implement nirsevimab for the 2024–2025 RSV season. Based on the recommendation by Choices in health care, it was offered to all infants born between August 1, 2024, and April–May, 2025, who were <3 months old at the start of the RSV season, and to <12-month-old high-risk infants (Choices in health care, 2024). It was estimated that with this strategy and high immunization rates, Finland could prevent over 6000 outpatient and 1700 ED visits annually, nearly 6000 cases of AOM, almost 500 hospitalizations, and 65 PICU admissions.

Nirsevimab has proven to be safe and well tolerated regardless of gestational age or comorbidities (Ares-Gómez et al., 2024; Drysdale et al., 2023). Rare side effects include mild injection site reactions, fever, gastrointestinal symptoms, and rash, with a safety profile comparable to placebo and palivizumab (Mankad et al., 2024).

2.8.2.3 Clesrovimab

Clesrovimab (MK-1654) is a promising long-acting monoclonal antibody with a half-life of around 45 days. It binds to site IV of both the pre- and post-fusion forms of the RSV F protein, and its neutralizing capacity is superior to that of palivizumab. (Madhi et al., 2025.)

In a phase 2b/3 randomized, double-blind, placebo-controlled CLEVER trial involving full-term and healthy preterm infants under one year of age during their first RSV season, clesrovimab reduced RSV hospitalizations by 81–82%, LRTI hospitalizations by 91%, severe MALRI by 92%, MALRI by 60–88%, and ARI by 50% at 150- and 180-days post-administration. It was safe and well tolerated, with adverse effects similar to those of the placebo, mostly mild local injection site reactions in 10% of cases. (Zar et al., 2025.) In a phase 3 SMART trial, clesrovimab was found to be as safe and effective as palivizumab in high-risk infants for the prevention of RSV-MALRI and RSVH at day 150 (Zar et al., 2024a). Based on these studies, the FDA has approved clesrovimab (Enflonsia®) in June 2025 for the prevention of RSV infection in infants, with a single dose regardless of body weight, providing protection for the entire RSV season (MERCK News release, 2025). In September 2025, EMA´s human medicines committee also recommended its approval (European Medicines Agency News on Enflonsia, 2025).

2.8.2.4 Other monoclonal antibodies

Motavizumab (MEDI-524) is a monoclonal antibody targeting RSV F protein site II, with higher binding affinity and up to 20-fold neutralizing activity than palivizumab (Wu et al., 2007). Phase 2 studies showed no significant benefits over placebo in LOS, disease severity, viral load, or wheezing episodes during the first 12 months (Ramilo et al., 2014). However, phase 3 trials demonstrated a 26% relative reduction in RSV hospitalizations and a 50% reduction in outpatient MALRI compared to palivizumab (Carbonell-Estrany et al., 2010), and an 87% reduction in RSVH compared to placebo (2% vs. 11%) (O'Brien et al., 2015). Despite its efficacy, hypersensitivity reactions and anti-drug antibody development led to the FDA withholding approval (Carbonell-Estrany et al., 2010; O'Brien et al., 2015).

Suptavumab (REGN2222) is a potent human monoclonal IgG1 antibody targeting site V of the RSV pre-F protein. In a phase 1 study, it was safe and well tolerated in healthy adults (Sivapalasingam et al., 2015). However, in a phase 3 study involving over 1000 preterm infants, it did not reduce RSVH or MALRIs, due to a mutation in the RSV-B subtype strain that led to a loss of efficacy (Simões et al., 2021). However, new monoclonal antibodies are under development, with the most advanced candidate in phase 2-3 (PATH).

2.8.3 Non-pharmaceutical

RSV is highly contagious (Kaler et al., 2023), and although pharmacological prevention methods currently exist, additional strategies remain essential. Monoclonal antibodies and vaccines are expensive, and not widely accessible in developing countries, highlighting the importance of NPIs.

During the COVID-19 pandemic, large-scale implementation of NPIs led to a dramatic decline in RSV cases, with a resurgence observed after restrictions were relaxed (Haapanen et al., 2021; Leija-Martínez et al., 2024). While interference between viruses is possible, the observed decrease in RSV infections among infants during periods of strict NPIs suggests these are effective in reducing RSV transmission (Lu et al., 2024).

European Centre for Disease Prevention and Control (ECDC) recommends NPIs such as hand and respiratory hygiene, avoiding face touching, and contact with sick people to prevent RSV infection (ECDC, 2025). However, recommendations vary across Europe. Hand and respiratory hygiene are most commonly recommended (in 95% of 30 countries), followed by avoiding crowded places (67%) and contact with sick humans (57%), staying home when ill (62%), and cleaning household items (57%) (Dallagiacoma et al., 2024).

2.9 Long-term effects of RSV

2.9.1 Asthma

In addition to immediate morbidity, RSV has long-term effects, particularly on respiratory health (Zhang et al., 2024). The association between RSV bronchiolitis and an increased risk of subsequent asthma was first described in 1959 (Wittig and Glaser, 1959). Since then, studies have consistently shown that early RSV-LRTI is associated with a higher risk of recurrent wheezing and asthma, ranging from 2 to 12 times higher, depending on the study (Jiang et al., 2023; Rosas-Salazar et al., 2023; Van Wijhe et al., 2022; Zar et al., 2024). However, there are still challenges including variations in the definitions of asthma across studies, differences in follow-up periods, and difficulties in establishing causality (Zar et al., 2024). A possible non-causal explanation is that RSV-LRTI may reflect an individual´s pre-existing vulnerability to respiratory illness (Brunwasser et al., 2020).

Severity of RSV correlates with higher risk of recurrent wheezing and asthma, with hospitalization linked to increased risk up to adolescence and adulthood (Bacharier et al., 2012; Backman et al., 2014; McGinley et al., 2022; Nguyen-Van-Tam et al., 2020; Sigurs et al., 2005; van Meel et al., 2022). Early RSV-LRTI, especially when hospitalized, results in impaired lung function (Sigurs et al., 2005;

Verwey et al., 2020), which may persist into adulthood (Backman et al., 2014; Coutts et al., 2020; Fauroux et al., 2017; Ruotsalainen et al., 2010) and may predispose to later development of chronic obstructive pulmonary disease (Martinez, 2009). However, the definition of disease severity varies across studies, and it remains unclear whether reduced lung function and increased asthma risk result from RSV infection itself or from an underlying susceptibility to severe disease.

The age at which RSV infection occurs also influences long-term respiratory outcomes. Infection before 6 months of age mainly raises asthma risk in the first 2 years of life, while infection at 6–23 months extends risk up to 6 years (Wang et al., 2022a). Other studies have similarly found a greater asthma risk when RSV is contracted later in infancy (Shiroshita et al., 2024). On the other hand, evidence suggests that delaying the timing of RSV infection might reduce subsequent respiratory morbidity (Zar et al., 2024b). A large U.S. cohort study (INSPIRE) estimated that avoiding RSV infection during the first year of life could prevent 15% of asthma diagnoses by age five (Rosas-Salazar et al., 2023).

The specificity of RSV, compared to other respiratory pathogens, in the development of asthma remains somewhat unclear (Van Wijhe et al., 2022). Higher risk of asthma has also been observed in non-RSV bronchiolitis, especially with rhinovirus (Makrinioti et al., 2022; Muñoz-Quiles et al., 2023; Orzołek et al., 2023; Ruotsalainen et al., 2013; Valkonen et al., 2009). However, the role of RSV is supported by prophylaxis studies. Palivizumab which reduces RSV-hospitalizations, also reduced wheezing and parent-reported asthma about 10% by age 6 in the MAKI trial, though no differences in lung function or physician-diagnosed asthma were observed (Fang et al., 2023; Blanken et al., 2013; Scheltema et al., 2018).

The mechanisms linking early RSV-LRTI to subsequent development of wheezing disorders include both direct and indirect effects (Baraldi et al., 2020; Zar et al., 2024b; Zhang et al., 2024). Direct effects include damage to the airway epithelium, such as cell injury, loss of ciliary cells, and changes in mucus production and viscosity (Zar et al., 2024b). Indirect mechanisms include alterations in systemic and mucosal immune responses, changes in airway microbiome, and disruptions in cellular metabolism (Rosas-Salazar et al., 2022; Zar et al., 2024b).

2.9.2 Other conditions

In addition to asthma and wheezing, early RSV infection has been linked to a higher risk of pneumonia (aOR 1.4), AOM (aOR 1.3), and antibiotic use (aOR 1.2) in infancy compared to those who did not experience RSV bronchiolitis (Abreo et al., 2020). However, the specific role of RSV in regulating the conditions remains debated.

3 Aims

The aims of the study were:

I To evaluate the impact of RSV viral load on disease severity in outpatient children.

II To determine population-based RSV hospitalization rates in monthly age groups for infants and young children.

III To compare rates and clinical presentations of RSV hospitalization between boys and girls.

4 Materials and Methods

A more detailed description of materials and methods are presented in the original publications.

4.1 Patients and study design

Study I, outpatient study

Data were derived from a prospective outpatient cohort study including children <10 years of age without any exclusion criteria. The study included two consecutive respiratory seasons from October 9, 2000, to May 20, 2001, and from October 1, 2001, to May 19, 2002. Children were recruited before the start of the season from the catchment area, including day-care centers, family day-care, and schools. At the start of the study, 1458 children were enrolled, of whom 1338 were active participants during the 2000–2001 season. In the second season of 2001–2002, 907 participants were enrolled and 893 completed the follow-up. Finally, the study comprised 2231 child-seasons of follow-up.

Parents were asked to bring their child to the study clinic whenever the child exhibited signs of respiratory infection or fever. The study clinic was open daily, including weekends and holidays, and visits were free of charge for families. Each visit included a clinical examination conducted by a study physician and detailed clinical data including symptoms and clinical findings were collected using a standardized questionnaire. If pneumonia or sinusitis were suspected, chest and sinus radiographs were performed. For AOM, diagnostic procedures included pneumatic otoscopy, tympanometry, and spectral-gradient acoustic reflectometry. In cases without complications at the initial visit, a follow-up visit was scheduled routinely 5-7 days later, or whenever parents considered it necessary.

Studies II and III, inpatient studies

Studies II and III were retrospective studies conducted at the Department of Pediatrics, Turku University Hospital. Study II covered 10 years from September 1,

2008, to August 31, 2018, while Study III spanned 14 years from July 1, 2006, to June 30, 2020.

In Study II, the study population included all children under the age of 16 years, and in Study III under 5 years old. Eligible patients were those with virologically confirmed RSV hospitalization at Turku University Hospital, which is the only pediatric tertiary-care hospital serving the Southwestern Finland region. To ensure population-based rates, only those children living within the hospital's defined catchment area were included in the studies. The average catchment population was 78,726 for children under 16 in Study II (10 years), and 23,725 for children under 5 in Study III (14 years).

4.2 Data collection

Study I

At each study visit, a standardized form was completed by the study physician. This included detailed information on the child's symptoms and their duration, clinical examination findings, the results of any laboratory or radiological investigations, as well as the final diagnosis and initiated treatment. Throughout the study seasons, parents were asked to complete a structured daily symptom diary, recording the child's symptoms and any resulting absences, either from day-care or school for the child, or from work for the parents, excluding any pre-planned days off like weekends. Parental compliance with diary completion was high: 85% of participants returned both symptom diaries, and 97% returned at least one diary. To determine the viral etiology of each respiratory episode, a nasal swab was obtained during the study clinic visit associated with that episode. Since our focus was on acute RSV infections, the analysis was restricted to children whose symptom duration before sample collection was no more than six days.

Studies II and III

During both Study II and Study III, viral diagnostics were routinely performed for all hospitalized children presenting with respiratory symptoms. To ensure identification of all virologically confirmed RSV infections, the data were retrieved from the database of the Department of Virology at the University of Turku and the patient database of Turku University Hospital. Duplicate records were removed using the patients' national identification numbers. Patient information, including patient characteristics, clinical presentation, treatment, and outcomes, was collected through a structured review of medical records. To calculate population-based incidence rates, annual data on the number of children in different age groups living within the hospital's catchment area were obtained from the official databases of Statistics Finland.

4.3 Laboratory methods

Study I

For each respiratory tract infection episode, a nasal swab was collected by inserting a sterile cotton swab 2–3 cm into the child's nostril. The swab was placed into a vial containing viral transport medium (Heikkinen et al., 2002). All virological testing was conducted at the Department of Virology, University of Turku. Detection of RSV was based on viral culture and RT-PCR using either the High Pure Viral Nucleic Acid Kit or the MagNA Pure LC extractor (Roche Diagnostics), following the manufacturers' instructions. The resulting extracts were stored at –70°C until further analysis. RSV RNA targeting the N gene was identified using RT-PCR. The viral load was estimated semi-quantitatively based on Ct value, the PCR cycle at which the amplification signal exceeds the detection threshold providing an indirect measure of RSV quantity in the sample. We divided the groups into high and low viral load based on a Ct value of 27, which was the mean Ct value in our study. This also resulted in similarly sized groups, maximizing statistical power.

Studies II and III

Nasopharyngeal samples were routinely collected from all hospitalized children presenting with respiratory symptoms during the study periods in order to determine the viral etiology. The diagnosis of RSV infection was based on RT-PCR, made at the Department of Virology, or antigen detection made at the emergency department.

4.4 Definitions

Study I

Complications were defined to be related to RSV if they were diagnosed within 14 days of the visit during which RSV infection was confirmed. AOM was diagnosed based on clinical signs of tympanic membrane inflammation, the presence of middle-ear effusion as verified by pneumatic otoscopy, and at least one symptom indicating acute infection. The diagnoses of pneumonia and sinusitis required both clinical symptoms and radiological confirmation of the condition. Children were defined as active participants if they visited the study clinic at least once during the surveillance season, or if they returned at least one of the two daily symptom diaries. The definition of total duration of illness included all consecutive days during which the child experienced fever, rhinitis, or cough.

Studies II and III

Length of hospital stay was defined as the number of nights the child spent in the hospital ward. In the uncommon cases where a child was admitted in the morning and discharged later that same day, the duration of hospitalization was recorded as one day. Rehospitalization was defined as an unplanned readmission to the hospital for the same illness, occurring without a complete resolution of symptoms between the admissions. Children were considered to have an underlying medical condition if they had a chronic lung disease, congenital heart disease, immunosuppressive condition, neuromuscular disorder, genetic disorder, or intellectual disability that impaired their ability to clear airway mucus. Respiratory distress was defined as any observable signs of breathing difficulty, such as intercostal or jugular retractions, tachypnea, wheezing, or nasal flaring, documented during the clinical examination and noted in the medical records.

4.5 Statistical analyses

In Studies II and III, the incidence rates of RSV hospitalizations in different age groups were calculated by dividing the number of RSV-hospitalized children by the corresponding age-specific population. The rates were expressed as average annual rates per 1000 children. Calculations of 95% confidence intervals (CIs) for hospitalization rates, their ratios, and rate differences between the groups were performed using Poisson distribution. In study I, the correlations between Ct values and symptom durations were evaluated using Spearman´s rank correlation.

Across all studies I–III, comparisons of continuous variables between two groups were performed using the t-test for normally distributed data, and the Mann-Whitney U test for non-normally distributed data. For comparisons involving more than two groups, one-way analysis of variance or the Kruskal-Wallis test was used, respectively, depending on the data distribution. Categorical variables were compared using the χ^2 test or Fisher's exact test when expected frequencies were less than 5. Two-sided p-values <0.05 were considered statistically significant. All statistical analyses were performed using SPSS Statistics (versions 25–27) and StatsDirect (versions 3.3.4 and 4.0.4).

4.6 Ethics

In study I, written informed consent was obtained from the parents or legal guardians of all participating children before study initiation. Studies II and III were approved by the Institutional Review Board at Turku University Hospital, and according to local research standards, no patient consent or Ethics committee approval was required.

5 Results

5.1 Association of RSV viral load with disease severity in outpatient children (Study I)

5.1.1 Study children and their Ct values

During the study period, a total of 201 children with newly diagnosed RSV infection were included. Of these, 106 (52.7%) had a higher viral load (Ct value <27) and 95 (47.3%) had a lower viral load (Ct ≥27). The mean Ct value across the cohort was 27.7.

The median age was 2.9 years in the higher viral load group and 3.2 years in the lower viral load group, with a difference of 4 months between the groups, which was statistically significant ($p = 0.020$). There was no significant difference in symptom duration before viral sampling between the groups.

5.1.2 Effect of viral load on symptom duration

In the primary analysis, children with higher viral load had significantly longer median durations of rhinitis (8 vs 6 days, $p < 0.001$), cough (8 vs 6 days, $p = 0.034$), fever (2 vs 1 day, $p = 0.018$) and any symptom (10 vs 8 days, $p = 0.024$) (Figure 5).

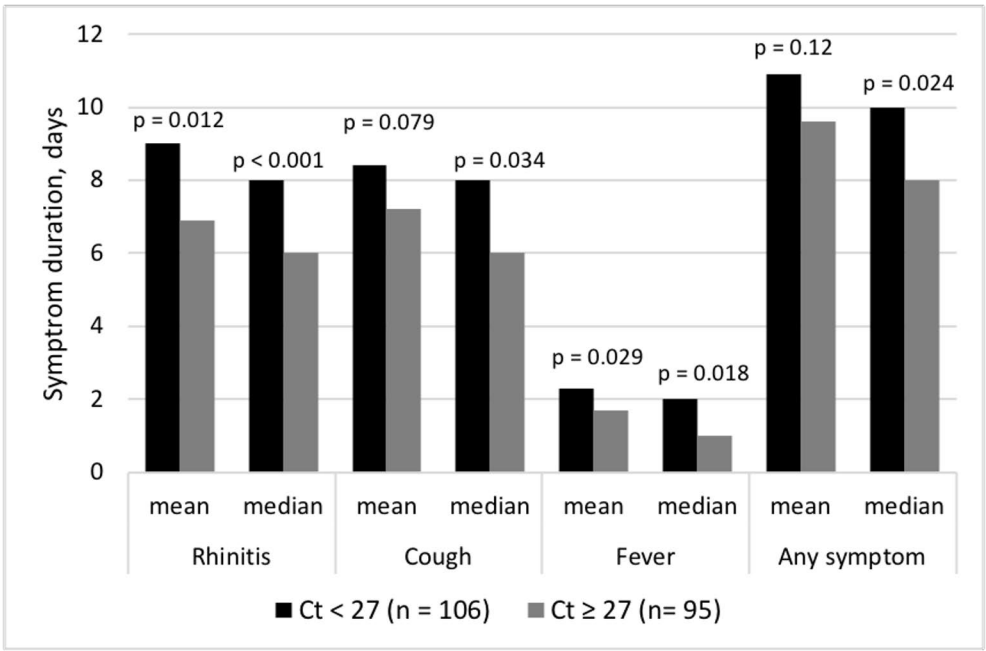

Figure 5. Symptom duration in children with higher (Ct <27) and lower (Ct ≥ 27) viral load groups.

In the secondary analysis, we compared three equal-sized groups based on their Ct value (high, intermediate, and low viral load), to confirm the observed association between viral load and symptom duration in the earlier two-group comparison. Those with the highest viral load consistently had longer durations of rhinitis, cough, fever, and any symptom. In contrast, children in the lowest viral load group had the shortest durations. A statistically significant difference in median duration of rhinitis was observed across the three groups ($p = 0.008$). While the differences in mean durations were not statistically significant between the groups, there was a consistent trend. An inverse correlation between Ct value and symptom duration is presented in Figure 6.

As children with higher viral loads were younger, a subgroup analysis by age was conducted. The association between higher viral load and longer symptom duration was observed in age groups 2–3 years and 4–9 years but not under 2 years. Among 2–3-year-olds, rhinitis lasted significantly longer in the high viral load group (median 9 vs. 5 days, $p < 0.001$), and the duration of any symptom was also significantly longer (10 vs. 8 days, $p = 0.012$).

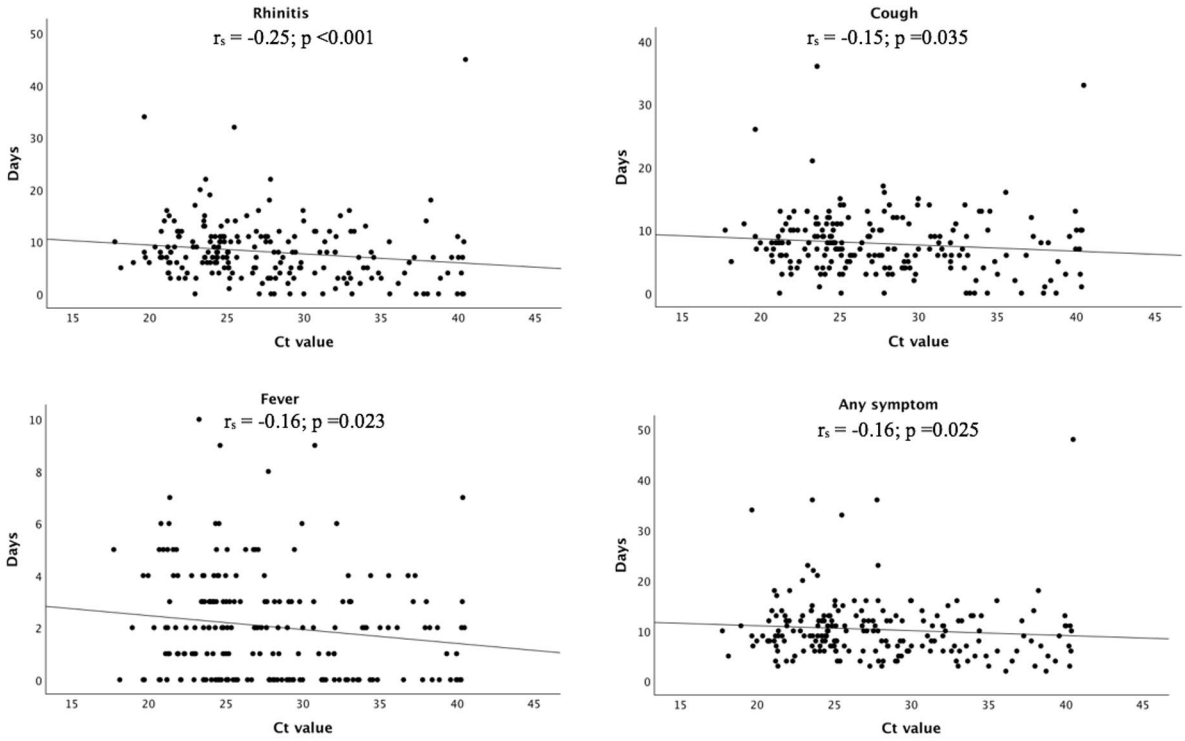

Figure 6. The correlation of Ct value and the duration of symptoms in RSV infection among 201 children. Modified from the original publication I from The Journal of Infectious Diseases.

5.1.3 Complications and antibiotic treatment based on viral load

In comparison between the two viral load groups, AOM was diagnosed in 56 children (52.8%) in the higher viral load group and 44 children (46.3%) in the lower viral load group (p = 0.36). There was no statistically significant difference in antibiotic treatment between the groups; 63 children (59.4%) were treated with antibiotics in higher viral load group and 47 (49.5%) in lower viral load group (p = 0.16).

5.2 RSV hospitalizations in young children and infants (Study II)

5.2.1 RSV hospitalizations and seasonality

A total of 1006 children were hospitalized for RSV infection during the 10-year study period. Of these, 469 (46.6%) were under 3 months old, 634 (63.0%) under 6 months, and 747 (74.3%) under 12 months. Preterm infants accounted for 96 (9.5%) cases, while 107 (10.6%) had an underlying condition. The prevalence of an underlying condition increased with age. Most hospitalizations (71.2%) occurred between October and March, and 90.4% occurred between October and April (Figure 7).

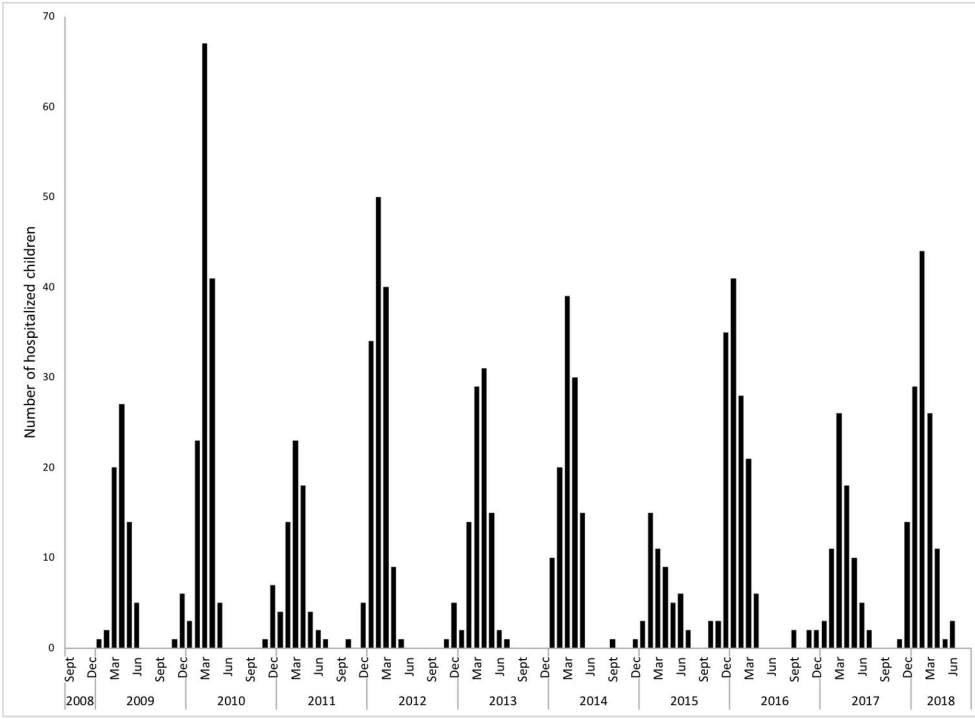

Figure 7. Monthly numbers of hospitalized children during the 10-year study period. Modified from original publication II from Influenza and Other Respiratory Viruses.

5.2.2 Incidence rates of RSV hospitalization

Among monthly age groups during the first year of life, the highest rate of RSV hospitalization was observed at 1 month of age (52.0/1000 children, 95% CI 45.2–

59.7), followed by <1 month (34.8/1000, 95% CI 29.2–41.1) and 2 months olds (32.2/1000, 95% CI 26.9–38.4). The rates in these groups were twice as high as reported in previous studies (Figure 8). In cumulative age groups, the RSV hospitalization rate was 39.7/1000 (95% CI 36.2–43.4) in children <3 months, 26.8/1000 (95% CI 24.8–29.0) in <6 months, 15.8/1000 (95% CI 14.7–17.0) in <12 months, 9.1/1000 in <2 years, 4.1/1000 in <5 years, and 1.3/1000 in <16 years old.

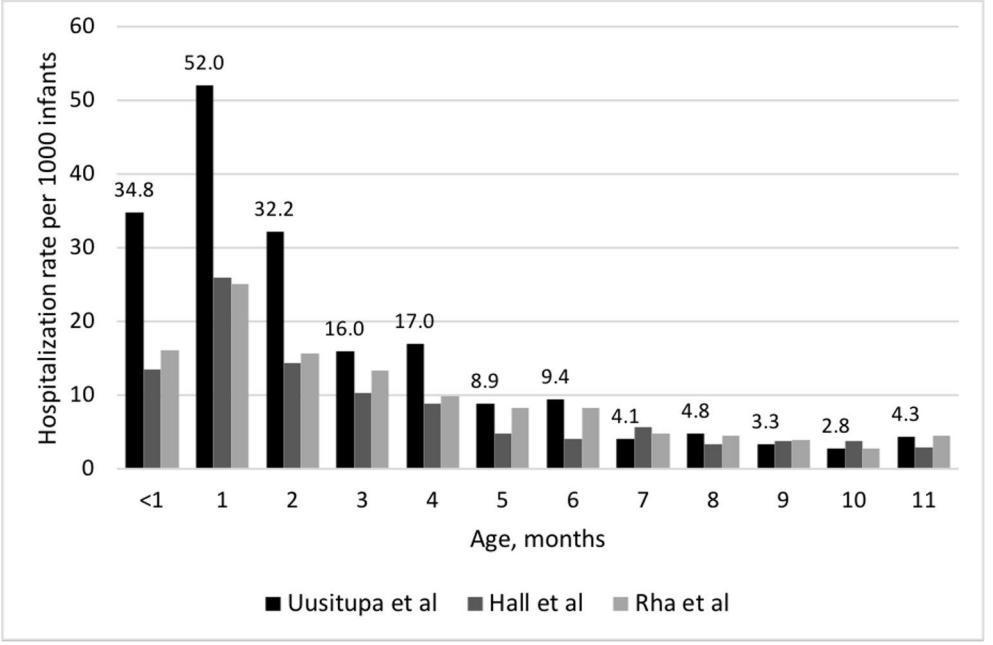

Figure 8. Average annual rates of RSV hospitalization per 1000 children in different ages among infants <12 months of age. The gray bars represent results from Hall et al., 2013, and Rha et al., 2020. Modified from original publication II from Influenza and Other Respiratory Viruses.

5.2.3 Clinical features and complications

Respiratory distress occurred in 808 (80.3%) children, most commonly at 2–5 months of age. AOM was also frequent in young infants, diagnosed in 47.0% of those under 1 year of age. Pneumonia was more common among older children, affecting 8.3% of those under 1 year of age and 40.9% of children aged 1 to 15 years ($p < 0.001$). Antibiotics were administered to 589 (58.5%) patients. Four deaths (0.4%) were recorded, all occurring in children aged ≥1 year with severe neuromuscular disease. Clinical features and complications in different ages are represented in Figure 9.

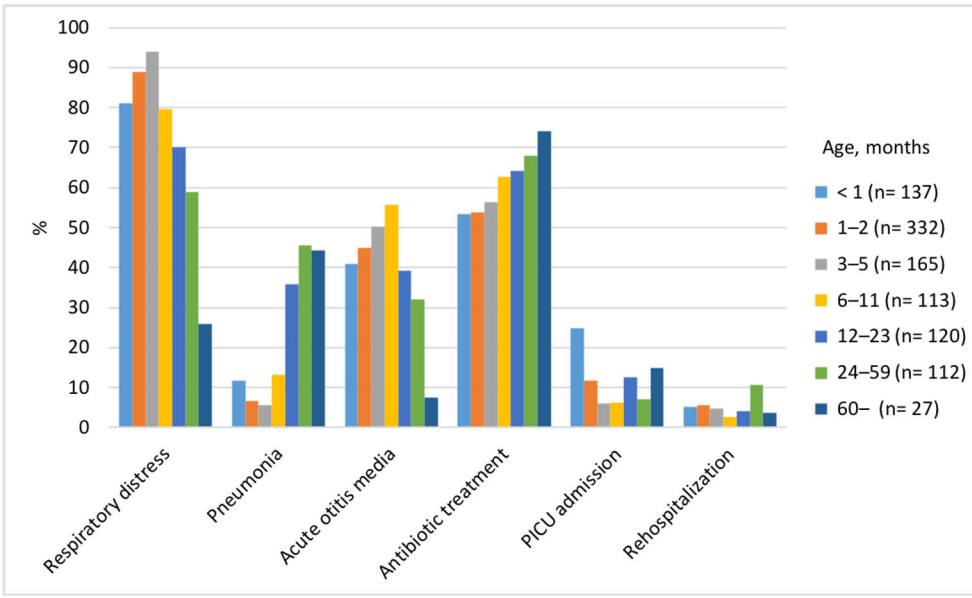

Figure 9. Clinical features and management of RSV-hospitalized children (n= 1006) at different ages.

5.2.4 Length of hospital stay

The median LOS for the whole study population was 2.0 days (IQR 1.0–4.0 days). Infants younger than 3 months had a longer LOS (median 3.0 days) compared to older age groups (1.0–2.0 days).

5.2.5 Treatment at PICU

In total, 117 (11.6%) children required admission to the PICU, with the highest rate of 24.8% observed among neonates <1 month old. In cumulative age groups, PICU admissions were 15.6% for <3 months, 13.1% for <6 months, and 12.0% for <12 months. PICU treatment was more common among preterm infants (25%) in comparison to full-term infants (10.2%) ($p < 0.001$). No significant difference in PICU admissions was observed between children with and without underlying conditions (13.1% vs 11.5%, $p = 0.62$).

5.3 Differences between boys and girls in RSV hospitalization rates and clinical symptoms (Study III)

5.3.1 Hospitalization rates

During the 14-year study period, a total of 1204 children <5 years old were hospitalized due to RSV infection. Of these, 671 (55.7%) were boys and 533 (44.3%) were girls. Among the hospitalized children, 46.1% were <3 months old and 63.3% were <6 months old. Most children were full-term (90.2%) and otherwise healthy (92.6%), with no significant differences observed between sexes.

Throughout the first two years of life, excluding the first month, boys consistently had higher hospitalization rates for RSV than girls (Figure 10). In the overall <5-year-old population, the hospitalization rate was 4.0 per 1000 for boys and 3.3 per 1000 for girls, IRR 1.21 (95% CI 1.07–1.35, p = 0.001). The sex difference was most pronounced between 3 and 23 months of age, when the hospitalization rate was 5.4 per 1000 for boys and 3.6 per 1000 for girls (IRR 1.50, 95% CI 1.25–1.80, p < 0.001).

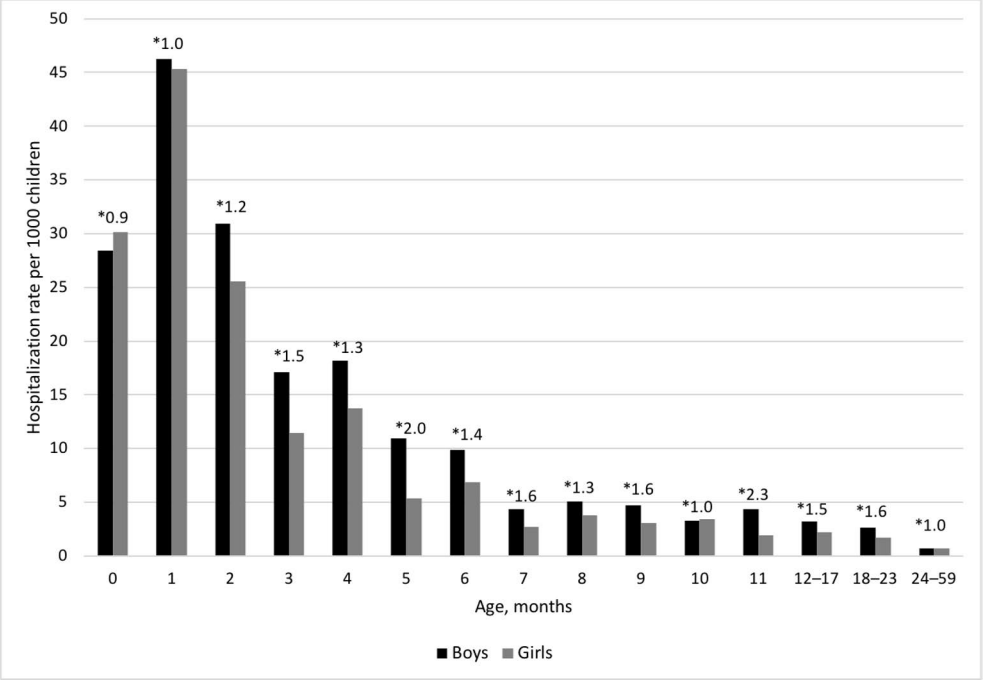

Figure 10. Average annual population-based rates of RSV hospitalizations per 1000 children in different age groups among boys and girls. * represents the ratio (boys to girls) in hospitalization rates in the age groups. Modified from original publication III.

5.3.2 Differences in clinical features and treatment

Across the whole <5-year-old study population, no significant sex differences were observed in clinical features of RSV infection (Figure 11). However, respiratory distress was more frequently observed among boys from 3 months of age and onwards: 324 of 381 boys compared to 207 of 268 girls (85.0% vs. 77.2%, p = 0.01). In a more detailed age-group analysis, the difference was most evident between 6 and 17 months of age, with respiratory distress observed in 128 of 141 boys and 70 of 92 girls (90.8% vs. 76.1%, p = 0.002) (Figure 12).

No sex differences were found in the LOS. Similarly, no differences in rehospitalization rates were observed: 41 of 671 boys and 24 of 533 girls (6.1% vs. 4.5%, p = 0.22). However, there was a signal of boys having more rehospitalizations among infants <3 months of age compared to girls in the same age (7.9% vs. 4.5%, p = 0.10).

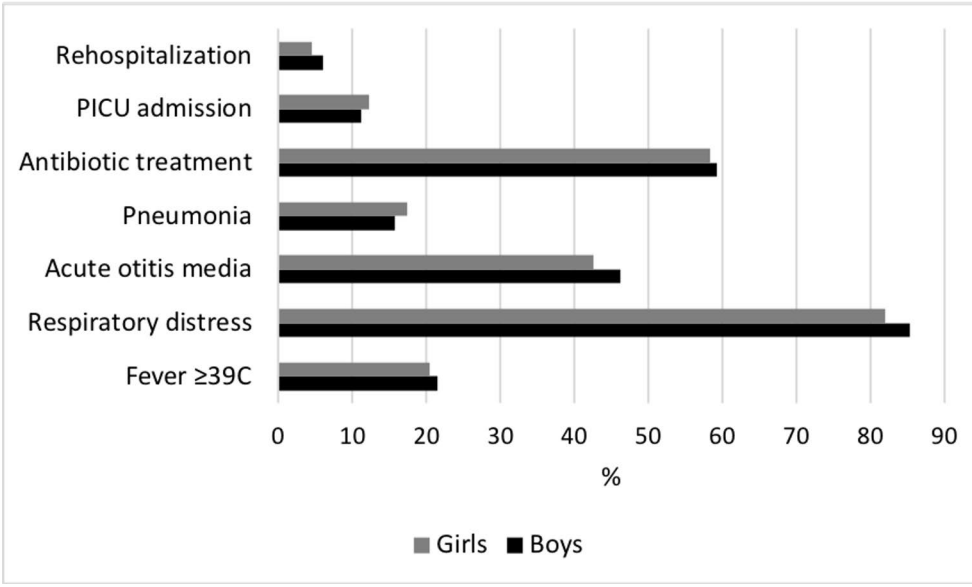

Figure 11. Clinical features and treatments in RSV-hospitalized boys and girls in the study population under 5 years of age.

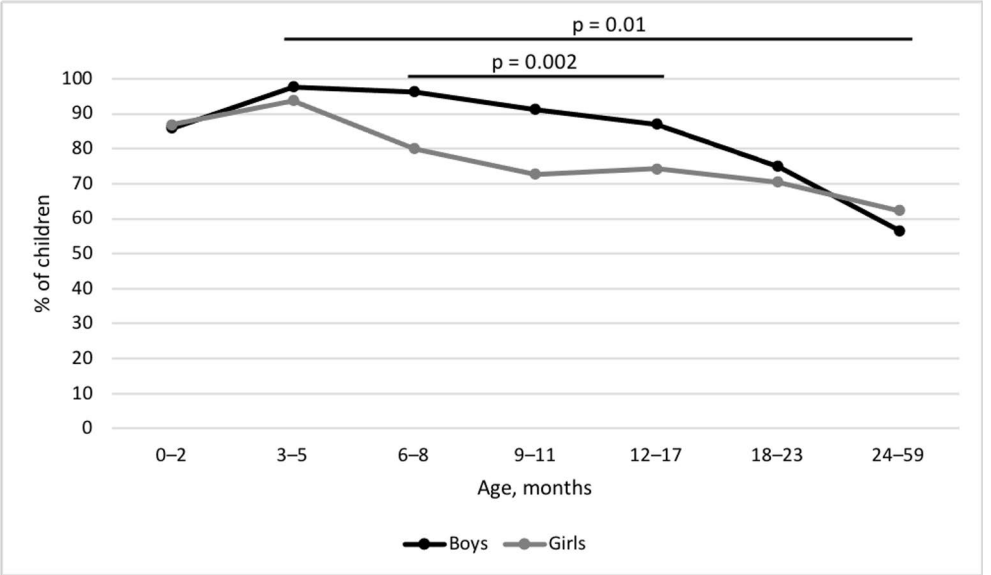

Figure 12. Proportions of boys and girls in different age groups with respiratory distress during their RSV hospitalization. Modified from original publication III.

5.3.3 Respiratory distress-associated hospitalizations

Hospitalizations due to respiratory distress with RSV infection were more frequent among boys than girls from early infancy up to nearly two years of age (Figure 13). In the total population of children <5 years old, the rates were 3.4 per 1000 for boys and 2.7 per 1000 for girls, IRR 1.26 (95% CI 1.11–1.42, $p < 0.001$). The difference was most pronounced between 3 and 23 months of age, with rates of 4.9 per 1000 and 2.9 per 1000 children respectively, IRR 1.66 (95% CI 1.37–2.03, $p < 0.001$).

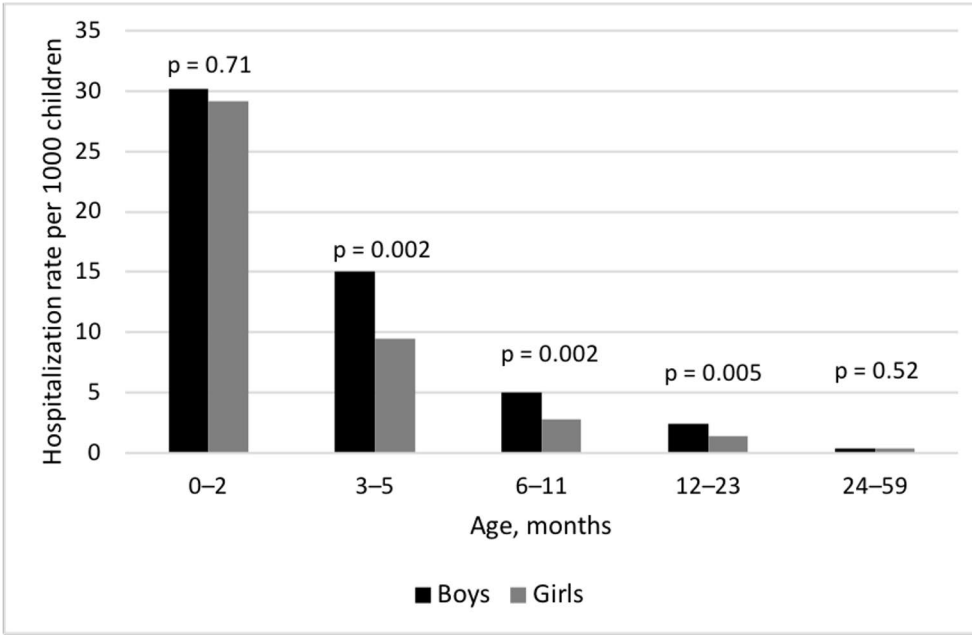

Figure 13. Respiratory distress-associated hospitalization rates in RSV infection in different age groups among boys and girls.

6 Discussion

6.1 Clinical characteristics of RSV infection (I, III)

6.1.1 Viral load (I)

We observed that a higher RSV viral load was associated with a longer duration of symptoms in outpatient children older than two years. In younger children, who generally had higher viral loads, as also reported in previous studies, no such association was found (Chen et al., 2024; Cruz et al., 2021; Heikkinen et al., 2015; Li et al., 2025). This may explain why earlier outpatient studies focusing on the youngest children have not identified an association between RSV viral load and symptom duration (Houben et al., 2010; Utsunomiya et al., 2020). Our findings underscore the importance of accounting for age in future studies examining RSV viral loads.

Several additional factors may explain the differences between studies. First, our study is to date the largest prospective pediatric outpatient study on RSV viral load, including daily symptom diaries filled out by parents. Second, in many previous studies, symptoms had already been present for up to 14 days before sample collection, which likely affected viral load levels due to the natural decline of RSV replication.

The average duration of any symptom was 9–10 days. The median duration of rhinorrhea and cough was 7 days, while fever lasted for 2 days. We also observed that symptom duration was longer in younger children compared to older ones. These findings are consistent with previous studies (Hak et al., 2025a; Heikkinen et al., 2017; Thomas et al., 2021; Toivonen et al., 2020).

We did not observe a statistically significant difference between RSV viral load and complications. AOM and the subsequent need for antibiotic treatment were more common in the higher viral load group compared to lower viral load group. However, our sample size was limited for detecting statistically significant differences between categorical variables like these. In some previous outpatient studies, higher viral load has been associated with more severe disease and increased risk of hospitalization (Haddadin et al., 2021; Houben et al., 2010), but the results are conflicting (Mattila et al., 2023). A small study by Houben et al., including only 30 infants, used a disease severity score including symptoms such as apnea, wheezing, retractions, and

tachypnea, features that can be difficult for parents to reliably evaluate (Houben et al., 2010). In inpatient settings, higher viral loads have often been linked to more severe disease (El Saleeby et al., 2011; Hasegawa et al., 2015; Piccirilli et al., 2023), although contradictory results exist (Thwaites et al., 2018; Wright et al., 2002; Yan et al., 2017). One hypothesis suggests that a higher viral load could trigger a stronger initial immune response, potentially preventing progression to severe disease.

Our findings demonstrate that RSV viral load is associated with the duration of symptoms in children treated in outpatient care where the disease burden is high. This suggests that an effective antiviral treatment, especially if initiated early in the course of illness, could potentially shorten disease duration and reduce complications, similar to influenza (Heinonen et al., 2010). However, early diagnosis remains a challenge due to the non-specific nature of RSV symptoms. On the other hand, the strong seasonality of RSV infections, and the slower rise in RSV viral load compared to influenza, may provide a longer therapeutic window for antiviral intervention. In the future, it may be possible for families to perform a rapid RSV test at home independently, which could help starting an effective antiviral treatment already in the early course of the illness.

We found no association between viral load and symptom duration during the first two years of life, which raises the question of whether other host factors might be more critical in determining disease course at this age. In contrast, the observed association between viral load and symptom duration after the age of two suggests that antiviral treatment might help shorten viral shedding in older children, which in turn could reduce RSV transmission to infants.

6.1.2 Sex differences (III)

The aim of our study was to describe population-based hospitalization rates and the clinical presentation of RSV infection in boys and girls across narrow age groups. We found that, especially during the first two years of life, excluding the first few months, the hospitalization rate of boys was higher than girls. The sex difference in hospitalization was most pronounced between 3 and 23 months of age, when boys had a 50% higher risk of hospitalization compared to girls. We also observed that boys exhibited respiratory distress more frequently than girls starting from the age of three months, with the most significant difference occurring between 6 and 17 months of age. When we specifically examined population-based RSV hospitalizations associated with respiratory distress, boys had a more than 60% higher rate than girls in the 3–23-month age group.

Higher RSV morbidity and risk of RSV hospitalization in boys have been reported in several previous studies. However, most population-based studies that consider the higher birth rate of boys have reported sex-specific hospitalization rates

only in broad age categories <5 years of age, and not in narrower ages (Buchan et al., 2023; Curns et al., 2024; Rha et al., 2020). Furthermore, the diagnoses of RSV infections were not laboratory confirmed in all studies, but were based on International Classification of Diseases (ICD) codes only (Buchan et al., 2023). In previous population-based studies with virological confirmation of RSV, the reported hospitalization rates for children under five have been higher for boys (3.3–4.7 per 1,000) than for girls (2.6–3.7 per 1,000), which are in line with the difference between sexes observed in our study (4.0 and 3.3 per 1,000, respectively).

In contrast with RSV hospitalization rates between boys and girls, there is very limited information on sex differences in the clinical presentation of RSV illness in children. A study from the RESCEU project did not find any differences in clinical features between boys and girls (McGinley et al., 2022). However, the study included just over 300 children under one year of age. They defined disease severity using the ReSViNET score, which includes seven parameters, some of which are respiratory-related, such as respiratory difficulty and frequency. However, the study did not report which specific parameters contributed to the score in boys and girls, leaving open the possibility that boys might have experienced more respiratory problems while girls might have shown more feeding intolerance or fever.

Overall, boys tend to present with more respiratory symptoms in studies unrelated to RSV. A large European multicenter study examining ED visits in children under 16 years of age found that respiratory presentations were more common in boys than girls, with boys receiving more inhalation medication (Zachariasse et al., 2020). Another European study involving nearly 20,000 febrile children under 18 years found that boys more frequently had tachypnea and increased work of breathing, and they were more often treated with inhalation therapy (Tan et al., 2022). However, no viral testing was performed in these studies, so the results cannot be directly attributed to RSV.

Several hypotheses have been proposed to explain sex differences in respiratory infection susceptibility and symptom presentation, which may also be relevant for RSV. In respiratory infections generally, it has been observed that males are more susceptible than females in early and late life, while during the reproductive years, the opposite trend occurs (Ursin and Klein, 2021). Possible explanations for sex differences in childhood include genetic, chromosomal, and hormonal differences, variation in lung development, and anatomical factors (Ronen et al., 2007; Seaborn et al., 2010; Silveyra et al., 2021).

Sex hormones may play a role in the observed differences. Testosterone, which is considered immunosuppressive, rises in male infants during the first months of life and then rapidly declines during the first year, remaining low until puberty (Ursin and Klein, 2021; Klein, 2000). Estrogen may enhance immune responses to viral infections and vaccines, although its levels remain low until puberty (Ursin and Klein, 2021).

Prenatal lung maturation is believed to be delayed in boys compared to girls, which may explain the higher frequency of respiratory complications such as respiratory distress syndrome and BPD in male newborns (Seaborn et al., 2010; Silveyra et al., 2021). These early respiratory challenges may influence susceptibility to severe RSV infection in infancy. Differences between sexes have also been observed in cytokine responses and innate immune activation (Schuurhof et al., 2010; Ursin and Klein, 2021). Anatomically, prepubertal boys have shorter and narrower airways, which have been associated with increased risk for viral infections, LRTI, and bronchial obstruction (Muenchhoff et al., 2014; Ronen et al., 2007; Ursin and Klein, 2021).

Interestingly, no sex differences in RSV-related hospitalizations or respiratory distress were seen during the first few months of life. One potential explanation is the presence of maternal IgG antibodies, which provide protection during early infancy. There is no reason to suspect differences in placental transfer or the effect of these antibodies between boys and girls. As maternal antibody levels wane after the first few months, the infant's own immune system plays a greater role, possibly revealing sex-based immunological differences. Around the same time, sex hormones begin to emerge, which may also explain why differences appear later in infancy. Finally, although all neonates have narrow airways, anatomical differences between sexes may become more pronounced with growth, potentially explaining why sex differences in respiratory symptoms and hospitalization only appear later in infancy.

6.2 RSV hospitalizations (II)

Our study aimed to provide a detailed description of monthly population-based RSV hospitalization rates in children, especially during the first year of life, over a long period and within a well-defined catchment area. We found that the highest risk of hospitalization occurred at 1 month of age, and in infants younger than 3 months the hospitalization rates were up to twice as high as previously reported. These results are significant for calculating cost-effectiveness related to RSV prevention and intervention strategies.

RSV hospitalizations in children have been studied extensively using different study designs. However, population-based virologically confirmed data on the youngest infants are still scarce. Previous population-based studies with laboratory-confirmed RSVH have reported rates of 16.9–18.5/1000 children in those under 6 months (Hall et al., 2009; Iwane et al., 2004), and 23.8–30/1000 in those under 3 months (McMorrow et al., 2024). In comparison, our rates were 26.8/1000 and 39.7/1000, respectively.

The age distribution of RSVH rates we observed aligns with other studies reporting monthly data. The peak occurred at 1 month of age, followed by <1-month-olds and 2-month-olds, with a decline with increasing age. In ICD-code-based studies, RSVH

rates at 1 month ranged from 25.1–29.6/1000, at <1 month from 16.1–17.8/1000, and at 2 months 15.6/1000 (Buchan et al., 2023; Suss et al., 2024). In contrast, laboratory confirmed studies report ranges of 25.1–31.2/1000, 6.1–25.0/1000, and 14.3–22.4/1000, respectively (Curns et al., 2024; Hall et al., 2013; Rha et al., 2020).

Several factors could explain the differences in RSVH rates. In our study, viral diagnostics were performed year-round, whereas many earlier studies only included the RSV season potentially missing cases (Hall et al., 2009; Hall et al., 2013; Rha et al., 2020). We conducted viral testing as a routine for all ARI hospitalizations, regardless of time or day, while some studies only performed testing at limited times during the week (Curns et al., 2024; Hall et al., 2013; Iwane et al., 2004; Rha et al., 2020) or based on physician decision (Li et al., 2022). Conversely, some samples may have been missed or given as false negatives in our setting, suggesting our values may still be slightly conservative. Our retrospective study included all RSVH cases, whereas some previous studies may have underreported due to the need for parental consent (Hall et al., 2009; Hall et al., 2013; Rha et al., 2020). On the other hand, multicenter studies provide better generalizability (Curns et al., 2024; Hall et al., 2013; Rha et al., 2020). In our cohort, 90% of children were otherwise healthy and born at term, which is slightly higher than in comparable studies (Hall et al., 2013; Rha et al., 2020). This further emphasizes the burden in this population.

In our study, approximately 10% required intensive care, with the highest rates among preterm infants and those <1 month old, of whom nearly 25% were admitted to the PICU. These values are consistent with previous studies (Bont et al., 2016; Hartmann et al., 2022). AOM developed in over 40% of cases, slightly less than reported elsewhere (Phillips et al., 2020; Thomas et al., 2021), while nearly 60% received antibiotics, exceeding earlier findings (Christakis et al., 2005; Farley et al., 2014). These differences may stem from the variety in age groups between studies, diagnostic practices for AOM, and local treatment practices.

For cost-effectiveness analyses of RSV preventive strategies, our age-specific long-term hospitalization rates and details on high-cost hospital stays are especially important.

6.3 Strengths and limitations (I-III)

6.3.1 Outpatient study (I)

The major strength of study I was its prospective design, in which all outpatient children were clinically examined using the same protocol, and a nasopharyngeal swab was collected during every episode of respiratory illness, regardless of symptom severity or day of the week. Sampling was limited to well-defined acute

infections, with more than 50% of participants in both groups having symptoms no longer than three days. Although the nasal swab procedure was not fully standardized, all samples were collected by a limited number of trained personnel and processed systematically, likely minimizing variability in sampling quality and viral load. Parents maintained daily symptom diaries, allowing for a reliable estimation of symptom duration. In addition, children were routinely re-examined to identify all complications.

6.3.2 Inpatient studies (II-III)

The main strengths of inpatient studies II and III include the long study period that helped to balance the annual variation in RSV incidence. Both studies were restricted to children living within the hospital's defined catchment area, and accurate population data were retrieved from Statistics Finland to allow precise denominators. In Study III, this also ensured that the higher birth rate among boys was accounted for. However, for infants in their first year of life, regional monthly age distributions were not available from the database. To estimate this, the annual birth cohort was divided by 12. In Finland, birth rates are highest in July–August and lowest in December, but the difference between these birth months is approximately one percentage point, which is unlikely to have an impact on the findings (StatFin Live births by sex, age of mother (5-year) and area, 1990–2024).

During the time of both inpatient studies II and III, routine viral diagnostics were performed for all hospitalized children with respiratory symptoms. Therefore, it is reasonable to assume that the majority of RSV cases were detected. Still, some hospitalizations may have gone untested for practical or human reasons or resulted in false negatives due to sample collection or test limitations. As a result, the reported hospitalization rates are likely conservative, and the true incidence may be slightly higher. Importantly, in study III analyzing sex differences, there is no reason to suspect any systematic difference in testing between boys and girls. Because antigen tests were commonly used and do not identify RSV subtypes, subtype data were available for only about 10% of cases, restricting analysis of sex-related differences in subtypes. Co-infections were not assessed either, although they may have been present in some cases. Furthermore, although data were extracted using structured reviews of medical records, some heterogeneity in clinical documentation exists.

6.3.3 Limitations of studies I-III

Although study I was the largest outpatient study to assess the relationship between viral load and clinical illness and each inpatient study included over 1000 children, the statistical power for categorical variables and subgroup analyses remained

occasionally limited. None of the studies specifically examined the impact of palivizumab, but the number of children receiving it was likely very small relative to the total cohort, minimizing its influence on the overall findings. Lastly, all three studies were conducted in a single tertiary care center, which may limit the generalizability of the results to other settings. However, this also ensured consistency in inclusion criteria, diagnostic procedures, and treatment protocols.

6.4 Future considerations

With the recent implementation of new RSV prevention strategies, including maternal vaccination and nirsevimab, more real-world evidence is still needed to assess their effectiveness, duration of protection, and potential differences in efficacy across RSV subtypes and between sexes. In addition, data on their impact on RSV seasonality, clinical characteristics, complications, and the overall burden of outpatient and inpatient care across age groups, particularly in large multicenter cohorts, are required. However, multicenter studies also have their own limitations due to data and quality heterogeneity. Additional data is important as many countries have not yet adopted these interventions, and sharing real-world results from early adopters will help others to evaluate the applicability of the strategies in similar settings and support wider implementation. Local cost-effectiveness analyses are essential to support the integration and long-term implementation of these preventive strategies in routine clinical practice.

Our findings indicated an association between viral load and symptom duration in outpatient children after the first years of life. As RSV antivirals are developed and studied, it is important to assess whether they reduce disease duration and severity in all ages, determine the optimal therapeutic window for initiation, and evaluate effects across patient subgroups and RSV subtypes. Moreover, potential indirect effects of antiviral use, such as reduced transmission to vulnerable infants when an older sibling receives treatment, should be further explored. Investigating sex-based differences and their underlying mechanisms in large multicenter studies may provide insights into the pathogenesis of RSV infections and their long-term consequences. Furthermore, examining viral interactions may yield novel information on RSV pathophysiology and immune modulation.

With significant advancements in preventive interventions for the youngest infants in recent years, there is a growing need for vaccines and antivirals for older infants and young children beyond infancy. This need extends also to outpatient settings, where the burden of RSV is substantial.

7 Summary and Conclusions

The purpose of this study was to (I) evaluate the effect of RSV viral load on disease course in the outpatient setting, (II) determine population-based RSV hospitalization rates, particularly across monthly age groups during infancy, and (III) compare RSV infections between boys and girls.

In the prospective follow-up Study I, we found that higher RSV viral load was associated with a longer duration of symptoms among outpatient children aged two years and older. We did not observe an association between viral load and RSV-related complications or antibiotic use, however, the sample size was limited for analyzing categorical outcomes. These findings support previous hospital-based studies suggesting an association between viral load and disease severity in RSV. As antiviral treatment for influenza has been shown to reduce disease burden, the development of effective RSV antivirals could have considerable clinical significance.

In Study II, we observed that population-based incidence rates of laboratory-confirmed RSV hospitalizations peaked at 1 month of age, and that infants under 3 months experienced hospitalization rates up to twice as high as previously reported. We also found that most hospitalized children were previously healthy full-term infants. The greater burden of RSV hospitalizations among young infants compared to previous reports have important implications for cost-effectiveness analyses of preventive interventions.

In the population-based Study III, we found that boys were hospitalized up to 50% more often than girls during the first years of life, excluding the very first months. Additionally, in the same age group, boys more frequently presented with respiratory distress. These findings highlight the need for further research into sex-based biological mechanisms that may underlie differences in RSV disease presentation and severity in children.

Acknowledgements

This doctoral thesis and the related studies were conducted at the Institute of Clinical Medicine, Faculty of Medicine, University of Turku, within the Doctoral Programme in Clinical Research, during the years 2018–2025. The work was financially supported by Turku University Foundation, State Research Funding to the Hospital District of Southwestern Finland, the Finnish Medical Foundation, the Foundation for Pediatric Research, the Finnish Cultural Foundation, Tampere Tuberculosis Foundation, the Research Foundation of the Pulmonary Diseases, Orion Research Foundation, Outpatient Care Research Foundation (Avohoidon Tutkimussäätiö), and Vaasa Medical Foundation.

First and foremost, I wish to express my deepest gratitude to my supervisors, Professor Terho Heikkinen and Docent Paula Tähtinen. Terho, you are not only a true global RSV expert but also an inspiring researcher. I am constantly impressed by your exceptional ability to write scientific texts with such clarity and accuracy. You challenge me to think independently while always being ready to offer concrete help when needed. Your calmness, precision, and great sense of humor are qualities I truly admire. Our meetings have always been warm, encouraging, and inspiring, leaving me motivated for the next steps. Paula, I am deeply grateful that you agreed to be my second supervisor during the final stages of my thesis. Without you, this work would not have found its way to a printer yet. Your encouragement and support have meant more than you can imagine. You are a wonderful supervisor, clinician, clinical lecturer, and person, a true role model in every way.

I would like to thank the members of my follow-up committee, Professor Ville Peltola and Docent Matti Waris. Ville, I admire not only your scientific accomplishments but also your clinical expertise and way of thinking. Matti, thank you for your virological expertise and for the valuable discussions in the challenging yet interesting field of virology. In addition to Matti, I also thank my other co-author, Docent Tytti Vuorinen, for her virological contribution to this work. I am grateful to all the researchers involved in data collection, as well as to the participating families.

My sincere thanks go to my reviewers, Professor Matti Korppi and Docent Katri Backman, for their time, effort, and valuable comments that helped improve this thesis. Heartfelt thanks to my dear friends, Emily and Aryan, for their careful

and effective language editing of the thesis. I also thank PhD Minna Lukkarinen for the opportunity to write my thesis at the TYKS Foundation research unit, where excellent coffee and the wisdom of experienced researchers are always available.

I am deeply grateful to Docents Heikki Lukkarinen and Minna Koskenvuo, former and current heads of the Department of Paediatrics and Adolescent Medicine at Turku University Hospital, for the opportunity to work in an inspiring, research-supportive community. I sincerely thank Tarja Holm, head of Pediatrics in Vaasa, for the opportunity to start my career in a workplace I still remember with warmth.

I am grateful to all my wonderful and talented paediatric colleagues at Turku University Hospital and Vaasa Central Hospital. It has been a privilege to work with such inspiring people. Special thanks to Anis for your encouragement and support throughout my career. Thanks for sharing laughs and listening to my frustrations. I am also truly grateful to Maria Backström, my mentor in Vaasa, for inspiring me both in research and in the fascinating world of pediatric rheumatology.

I feel lucky to have such wonderful friends around me, both at work and beyond, people who support me, make me laugh, and remind me of what truly matters. Thank you, Emma, for being one of my best friends since the very first day of med school. Thanks to my BB-group friends, Julia, Pauliina, Malin, and Josefine, for the great time in Turku (and the late-night panic consultations), and to Aino for the shared moments and talks along Kasitie. Despite the geographical distance, I hope we will keep our friendship strong. Thank you, Ruut, for your practical help during the final stages of this dissertation, and for being an awesome colleague. Thank you, Heidi R., Lotta, and Heta, for the moments shared at work and beyond, as well as all the other colleagues whose names, unfortunately, there isn't enough space to include in this already lengthy thesis. Thank you, Katri, for your long-lasting friendship. Even though our meetings are sometimes less frequent, it´s always easy to continue where we left off. Thanks to my dear group of med school friends, the Jones Club, may we always stay connected even as life takes us to different corners of Finland. Special thanks to the Menoryhmä girls, Emily, Henni, Ida, and Anni. I know I can share anything with you, and that you would support me no matter what. Once this project is completed, I intend to prioritize free time and friendships. Thank you, Elisa and Pasi, my "parents-in-law," for the relaxing dinners and cottage evenings together.

I want to express my heartfelt thanks to my dear family. My brother Antti, even though this dissertation has sometimes felt like a full-distance Ironman, you have shown what true long-term commitment really means. To my dear parents, words cannot express how grateful I am for everything you have done for me and Antti.

Thank you for your love, care, and encouragement in everything we do in life. You have always put us first, no matter how grown-up we have become.

Finally, I want to thank my beloved, Olli. Life between two cities has not always been easy, but every moment with you has been worth it. Thank you for your love, support, shared silliness, and for the wonderful people I've met through you. You've been the spirit of our homes during this project, literally filling them with warmth and light. I can´t wait for the next chapters in our life together. I love you.

Turku, October 2025
Erika Uusitupa

References

Aberle, J.H., Aberle, S.W., Pracher, E., Hutter, H.P., Kundi, M., Popow-Kraupp, T., 2005. Single versus dual respiratory virus infections in hospitalized infants: impact on clinical course of disease and interferon-gamma response. *The Pediatric infectious disease journal*, 24, 605–610.

Abreo, A., Wu, P., Donovan, B.M., Ding, T., Gebretsadik, T., Huang, X., et al., 2020. Infant Respiratory Syncytial Virus Bronchiolitis and Subsequent Risk of Pneumonia, Otitis Media, and Antibiotic Utilization. *Clinical infectious diseases*, 71, 211–214.

Abu-Raya, B., Viñeta Paramo, M., Reicherz, F., Lavoie, P.M., 2023. Why has the epidemiology of RSV changed during the COVID-19 pandemic? *eClinicalMedicine,* 61, 102089.

Acosta, P.L., Caballero, M.T., Polack, F.P., 2015. Brief History and Characterization of Enhanced Respiratory Syncytial Virus Disease. *Clinical and vaccine immunology*, 23, 189–195.

Ahmad, A., Eze, K., Noulin, N., Horvathova, V., Murray, B., Baillet, M., et al., 2022. EDP-938, a Respiratory Syncytial Virus Inhibitor, in a Human Virus Challenge. *The New England journal of medicine*, 386, 655–666.

Alzaydi, M., Alosaimi, A., Alghamdi, A.A., Bamogaddam, I.Y., Altassan, M.A., Almazrua, A., et al., 2024. Changes in seasonal respiratory viral infections among pediatric population around the COVID-19 pandemic; 2019–2023. *European journal of clinical microbiology & infectious diseases*, 43, 1589–1596.

American Academy of Pediatrics Committee on Infectious Diseases and Committee of Fetus and Newborn, 1998. Prevention of respiratory syncytial virus infections: indications for the use of palivizumab and update on the use of RSV-IGIV. *Pediatrics*, 102, 1211–1216.

Andeweg, S.P., Schepp, R.M., Van De Kassteele, J., Mollema, L., Berbers, G.A.M., Van Boven, M., 2021. Population-based serology reveals risk factors for RSV infection in children younger than 5 years. *Scientific reports*, 11, 8953.

Ares-Gómez, S., Mallah, N., Santiago-Pérez, M.I., Pardo-Seco, J., Pérez-Martínez, O., Otero-Barrós, M.T., et al., 2024. Effectiveness and impact of universal prophylaxis with nirsevimab in infants against hospitalisation for respiratory syncytial virus in Galicia, Spain: initial results of a population-based longitudinal study. *The Lancet. Infectious diseases*, 24, 817–828.

Aricò, M.O., Wrona, D., Lavezzo, G., Valletta, E., 2023. Nasal CPAP in the Pediatric Ward to Reduce PICU Admissions for Severe Bronchiolitis?. *Pediatric reports*, 15, 599–607.

Armarego, M., Forde, H., Wills, K., Beggs, S.A., 2024. High-flow nasal cannula therapy for infants with bronchiolitis. *The Cochrane database of systematic reviews*, 3, CD009609.

Assad, Z., Romain, A.S., Aupiais, C., Shum, M., Schrimpf, C., Lorrot, M., et al., 2024. Nirsevimab and Hospitalization for RSV Bronchiolitis. *The New England journal of medicine*, 391, 144–154.

Athan, E., Baber, J., Quan, K., Scott, R. J., Jaques, A., Jiang, Q., et al., 2024. Safety and Immunogenicity of Bivalent RSVpreF Vaccine Coadministered With Seasonal Inactivated Influenza Vaccine in Older Adults. *Clinical infectious diseases*, 78, 1360–1368.

Aujard, Y., Fauroux, B., 2002. Risk factors for severe respiratory syncytial virus infection in infants. *Respiratory medicine*, 96, S9-14.

Babawale, P.I., Guerrero-Plata, A., 2024. Respiratory Viral Coinfections: Insights into Epidemiology, Immune Response, Pathology, and Clinical Outcomes. *Pathogens*, 13, 316.

Babawale, P.I., Martínez-Espinoza, I., Mitchell, A.M., Guerrero-Plata, A., 2025. Preventing RSV Infection in Children: Current Passive Immunizations and Vaccine Development. *Pathogens*, 14, 104.

Bacharier, L.B., Cohen, R., Schweiger, T., Yin-Declue, H., Christie, C., Zheng, J., et al., 2012. Determinants of asthma after severe respiratory syncytial virus bronchiolitis. *The Journal of allergy and clinical immunology*, 130, 91–100.e3.

Backman, K., Piippo-Savolainen, E., Ollikainen, H., Koskela, H., Korppi, M., 2014. Adults face increased asthma risk after infant RSV bronchiolitis and reduced respiratory health-related quality of life after RSV pneumonia. *Acta paediatrica*, *103*, 850–855.

Backman, K., Helminen, M., Kekäläinen, E., Mikkola, I., Nieminen, T., Nuolivirta, K., et al., 2025. Working group summary of the 2023 full update of the Finnish national guidelines for paediatric lower respiratory tract infections. *Acta paediatrica*, *114*, 248–257.

Bagga, B., Woods, C.W., Veldman, T.H., Gilbert, A., Mann, A., Balaratnam, G., et al., 2013. Comparing influenza and RSV viral and disease dynamics in experimentally infected adults predicts clinical effectiveness of RSV antivirals. *Antiviral therapy*, 18, 785–791.

Baraldi, E., Bonadies, L., Manzoni, P., 2020. Evidence on the Link between Respiratory Syncytial Virus Infection in Early Life and Chronic Obstructive Lung Diseases. *American journal of perinatology*, 37, S26–S30.

Barbas Del Buey, J.F., Íñigo Martínez, J., Gutiérrez Rodríguez, M.Á., Alonso García, M., Sánchez-Gómez, A., Lasheras Carbajo, M.D., et al., 2024. The effectiveness of nirsevimab in reducing the burden of disease due to respiratory syncytial virus (RSV) infection over time in the Madrid region (Spain): a prospective population-based cohort study. *Frontiers in public health*, 12, 1441786.

Battles, M.B., McLellan, J.S., 2019. Respiratory syncytial virus entry and how to block it. *Nature reviews. Microbiology*, 17, 233–245.

Bebia, Z., Reyes, O., Jeanfreau, R., Kantele, A., De Leon, R.G., Sánchez, M.G., et al., 2023. Safety and Immunogenicity of an Investigational Respiratory Syncytial Virus Vaccine (RSVPreF3) in Mothers and Their Infants: A Phase 2 Randomized Trial. *The Journal of infectious diseases*, 228, 299–310.

Bechini, A., Salvati, C., Bonito, B., Del Riccio, M., Stancanelli, E., Bruschi, M., et al., 2024. Costs and healthcare utilisation due to respiratory syncytial virus disease in paediatric patients in Italy: a systematic review. *Public health*, 227, 103–111.

Bender, R.G., Sirota, S.B., Swetschinski, L.R., Dominguez, R.-M.V., Novotney, A., Wool, E.E., et al., 2024. Global, regional, and national incidence and mortality burden of non-COVID-19 lower respiratory infections and aetiologies, 1990–2021: a systematic analysis from the Global Burden of Disease Study 2021. *The Lancet. Infectious diseases*, 24, 974–1002.

Bennett, M.V., McLaurin, K., Ambrose, C., Lee, H.C., 2018. Population-based trends and underlying risk factors for infant respiratory syncytial virus and bronchiolitis hospitalizations. *PloS one,* 13, e0205399.

Berbers G., Mollema L., van der Klis F., den Hartog G., Schepp R., 2021. Antibody Responses to Respiratory Syncytial Virus: A Cross-Sectional Serosurveillance Study in the Dutch Population Focusing on Infants Younger Than 2 Years. *The Journal of infectious diseases,* 224, 269-278.

Bergeron, H.C., Tripp, R.A., 2021. Immunopathology of RSV: An Updated Review. *Viruses,* 13, 2478.

Bergeron, H.C., Tripp, R.A., 2022. RSV Replication, Transmission, and Disease Are Influenced by the RSV G Protein. *Viruses,* 14, 2396.

Bermúdez-Barrezueta L., López-Casillas P., Rojo-Rello S., Sáez-García L., Marugán-Miguelsanz J.M., Pino-Vázquez M.A., 2023. Outcomes of viral coinfections in infants hospitalized for acute bronchiolitis. *Virology journal*, 20, 235.

Bin Lu, Liu, H., Tabor, D.E., Tovchigrechko, A., Qi, Y., Ruzin, A., et al., 2019. Emergence of new antigenic epitopes in the glycoproteins of human respiratory syncytial virus collected from a US surveillance study, 2015–17. *Scientific reports*, 9, 3898.

Blanken, M.O., Rovers, M.M., Molenaar, J.M., Winkler-Seinstra, P.L., Meijer, A., Kimpen, J. L., et al., 2013. Respiratory syncytial virus and recurrent wheeze in healthy preterm infants. *The New England journal of medicine*, 368, 1791–1799.

Bloom-Feshbach, K., Alonso, W.J., Charu, V., Tamerius, J., Simonsen, L., Miller, M.A., et al., 2013. Latitudinal Variations in Seasonal Activity of Influenza and Respiratory Syncytial Virus (RSV): A Global Comparative Review. *PloS one,* 8, e54445.

Bloomfield, A., DeVincenzo, J.P., Ambrose, C.S., Krilov, L.R., 2020. RSV and non-RSV illness hospitalization in RSV immunoprophylaxis recipients: A systematic literature review. *Journal of clinical virology*, 129, 104339.

Bohmwald, K., Espinoza, J.A., Rey-Jurado, E., Gómez, R.S., González, P.A., Bueno, S.M., et al., 2016. Human Respiratory Syncytial Virus: Infection and Pathology. *Seminars in respiratory and critical care medicine*, 37, 522–537.

Bonneux, B., Jacoby, E., Ceconi, M., Stobbelaar, K., Delputte, P., Herschke, F., 2024. Direct-acting antivirals for RSV treatment, a review. *Antiviral research*, *229*, 105948.

Bont, L., Versteegh, J., Swelsen, W.T., Heijnen, C.J., Kavelaars, A., Brus, F., et al., 2002. Natural reinfection with respiratory syncytial virus does not boost virus-specific T-cell immunity. *Pediatric research*, 52, 363–367.

Bont, L., Checchia, P.A., Fauroux, B., Figueras-Aloy, J., Manzoni, P., Paes, B., et al., 2016. Defining the Epidemiology and Burden of Severe Respiratory Syncytial Virus Infection Among Infants and Children in Western Countries. *Infectious diseases and therapy*, 5, 271–298.

Bowser, D.M., Rowlands, K.R., Hariharan, D., Gervasio, R.M., Buckley, L., Halasa-Rappel, Y., et al., 2022. Cost of Respiratory Syncytial Virus Infections in US Infants: Systematic Literature Review and Analysis. *The Journal of infectious diseases*, 226, S225–S235.

Brañas, P., Muñoz-Gallego, I., Espartosa, E., Moral, N., Abellán, G., Folgueira, L., 2023. Dynamics of respiratory viruses other than SARS-CoV-2 during the COVID-19 pandemic in Madrid, Spain. *Influenza and other respiratory viruses*, 17, e13199.

Brenes-Chacon, H., Garcia-Mauriño, C., Moore-Clingenpeel, M., Mertz, S., Ye, F., Cohen, D.M., et al., 2021. Age-dependent Interactions Among Clinical Characteristics, Viral Loads and Disease Severity in Young Children With Respiratory Syncytial Virus Infection. *The Pediatric infectious disease journal*, 40, 116–122.

Brenes-Chacon, H., Eisner, M., Acero-Bedoya, S., Ramilo, O., Mejias, A., 2024. Age-specific predictors of disease severity in children with respiratory syncytial virus infection beyond infancy and through the first 5 years of age. *Pediatric allergy and immunology*, 35, e14083.

Broberg, E.K., Waris, M., Johansen, K., Snacken, R., Penttinen, P., European Influenza Surveillance Network, 2018. Seasonality and geographical spread of respiratory syncytial virus epidemics in 15 European countries, 2010 to 2016. *Euro surveillance,* 23.

Brunwasser, S.M., Snyder, B.M., Driscoll, A.J., Fell, D.B., Savitz, D.A., Feikin, D.R., et al., 2020. Assessing the strength of evidence for a causal effect of respiratory syncytial virus lower respiratory tract infections on subsequent wheezing illness: a systematic review and meta-analysis. *The Lancet. Respiratory medicine*, 8, 795–806.

Buchan, S.A., Chung, H., To, T., Daneman, N., Guttmann, A., Kwong, J.C., et al., 2023. Estimating the Incidence of First RSV Hospitalization in Children Born in Ontario, Canada. *Journal of the Pediatric Infectious Diseases Society*, 12, 421–430.

Buchwald, A.G., Graham, B.S., Traore, A., Haidara, F.C., Chen, M., Morabito, K., et al., 2021. Respiratory Syncytial Virus (RSV) Neutralizing Antibodies at Birth Predict Protection from RSV Illness in Infants in the First 3 Months of Life. *Clinical infectious diseases*, 73, e4421–e4427.

Buonsenso, D., Valentini, P., Mariani, F., Di Noi, S., Mazza, S., Palucci, I., et al., 2023. Comparison between Nasopharyngeal and Saliva Samples for the Detection of Respiratory Viruses in Children with Acute Lower Respiratory Tract Infections: A Pilot Study. *Children*, 10, 899.

Byington, C.L., Castillo, H., Gerber, K., Daly, J.A., Brimley, L.A., Adams, S., et al., 2002. The effect of rapid respiratory viral diagnostic testing on antibiotic use in a children's hospital. *Archives of pediatrics & adolescent medicine*, 156, 1230–1234.

Bähre, J., Lange, M., Salaschek, P., Twardella, D., Arens, S., Eberhard, F., et al., 2025. Distinct seasonality and increased respiratory failure in RSV patients < 2 years of age after emergence of SARS-CoV-2: data from the multicentric, prospective PAPI study. *European journal of pediatrics*, 184, 246.

Cai, W., Buda, S., Schuler, E., Hirve, S., Zhang, W., Haas, W., 2020. Risk factors for hospitalized respiratory syncytial virus disease and its severe outcomes. *Influenza and other respiratory viruses*, 14, 658–670.

Carbajal, R., Boelle, P.Y., Pham, A., Chazette, Y., Schellenberger, M., Weil, C., et al., 2024. Real-world effectiveness of nirsevimab immunisation against bronchiolitis in infants: a case-control study in Paris, France. *The Lancet. Child & adolescent health*, 8, 730–739.

Carbonell, X., Fullarton, J.R., Gooch, K.L., Figueras-Aloy, J., 2012. The evolution of risk factors for respiratory syncytial virus-related hospitalisation in infants born at 32-35 weeks' gestational age: time-based analysis using data from the FLIP-2 study. *Journal of perinatal medicine*, 40, 685–91.

Carbonell-Estrany, X., Simões, E.A., Dagan, R., Hall, C.B., Harris, B., Hultquist, M., et al., 2010. Motavizumab for prophylaxis of respiratory syncytial virus in high-risk children: a noninferiority trial. *Pediatrics*, 125, e35–e51.

Carbonell-Estrany, X., Fullarton, J.R., Gooch, K.L., Vo, P.G., Figueras-Aloy, J., Lanari, M., et al., 2013. Effects of parental and household smoking on the risk of respiratory syncytial virus (RSV) hospitalisation in late-preterm infants and the potential impact of RSV prophylaxis. *The journal of maternal-fetal & neonatal medicine*, 26, 926–931.

Carbonell-Estrany, X., Simões, E.A.F., Bont, L., Manzoni, P., Zar, H.J., Greenough, A., et al., 2025. Twenty-five years of palivizumab: a global historic review of its impact on the burden of respiratory syncytial virus disease in children. *Expert review of anti-infective therapy*, 23, 359–378.

Caserta, M. T., O'Leary, S. T., Munoz, F. M., Ralston, S. L., & COMMITTEE ON INFECTIOUS DISEASES, 2023. Palivizumab Prophylaxis in Infants and Young Children at Increased Risk of Hospitalization for Respiratory Syncytial Virus Infection. *Pediatrics*, 152 , e2023061803.

Cebey-López, M., Herberg, J., Pardo-Seco, J., Gómez-Carballa, A., Martinón-Torres, N., Salas, A., et al., 2015. Viral Co-Infections in Pediatric Patients Hospitalized with Lower Tract Acute Respiratory Infections. *PloS one*, 10, e0136526.

Centers for Disease Control and Prevention (CDC), 2013. Respiratory syncytial virus activity--United States, July 2011-January 2013. *MMWR. Morbidity and mortality weekly report*, *62*, 141–144.

Centers for Disease Control and Prevention, 2024. Respiratory Virus Hospitalization Surveillance Network (RESP-NET). Available at: https://www.cdc.gov/resp-net/dashboard/. [Accessed 9 June 2025]

Chartrand, C., Tremblay, N., Renaud, C., Papenburg, J., 2015. Diagnostic Accuracy of Rapid Antigen Detection Tests for Respiratory Syncytial Virus Infection: Systematic Review and Meta-analysis. *Journal of clinical microbiology*, 53, 3738–3749.

Chaw, P.S., Hua, L., Cunningham, S., Campbell, H., Mikolajczyk, R., Nair, H., RESCEU Investigators, 2020a. Respiratory Syncytial Virus-Associated Acute Lower Respiratory Infections in Children With Bronchopulmonary Dysplasia: Systematic Review and Meta-Analysis. *The Journal of infectious diseases*, 222, S620–S627.

Chaw, P.S., Wong, S.W.L., Cunningham, S., Campbell, H., Mikolajczyk, R., Nair, H., et al., 2020b. Acute Lower Respiratory Infections Associated With Respiratory Syncytial Virus in Children With Underlying Congenital Heart Disease: Systematic Review and Meta-analysis. *The Journal of infectious diseases ,* 222, S613-S619.

Chawanpaiboon, S., Vogel, J.P., Moller, A.-B., Lumbiganon, P., Petzold, M., Hogan, D., et al., 2019. Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. *The Lancet. Global health*, 7, e37–e46.

Chen, Y., Zhao, X., Ye, C., Zhou, J., Wang, J., Ye, X., 2024. Epidemiology and viral loads of respiratory syncytial virus in hospitalized children prior to and during COVID-19 pandemic in Hangzhou, China. *Journal of medical virology*, 96, e29855.

Chiu, S. N., Shao, P. L., Chen, H. C., Lin, M. T., Huang, L. M., Kao, F. Y., et al., 2016. Risk of Respiratory Syncytial Virus Infection in Cyanotic Congenital Heart Disease in a Subtropical Area. *The Journal of pediatrics*, 171, 25-30.

Choices in health care, 2024. Recommendation on Nirsevimab in the prevention of lower respiratory tract infection caused by respiratory syncytial virus (RSV). Available at: https://palveluvalikoima.fi/documents/1237350/210645968/Summary+Recommendation+on+Nirsevimab+in+the+Prevention+of+RSV.pdf/d3c8d252-cd82-a602-abea-53081398f263/Summary+Recommendation+on+Nirsevimab+in+the+Prevention+of+RSV.pdf?t=1715161760843. [Accessed 9 November 2024]

Christakis, D.A., Cowan, C.A., Garrison, M.M., Molteni, R., Marcuse, E., Zerr, D.M., 2005. Variation in inpatient diagnostic testing and management of bronchiolitis. *Pediatrics*, 115, 878–884.

Chu, H.Y., Kuypers, J., Renaud, C., Wald, A., Martin, E., Fairchok, M., et al., 2013. Molecular epidemiology of respiratory syncytial virus transmission in childcare. *Journal of clinical virology,* 57, 343–350.

Chu, H.Y., Tielsch, J., Katz, J., Magaret, A.S., Khatry, S., LeClerq, S.C., et al., 2017. Transplacental transfer of maternal respiratory syncytial virus (RSV) antibody and protection against RSV disease in infants in rural Nepal. *Journal of clinical virology,* 95, 90–95.

Churiso, G., Husen, G., Bulbula, D., Abebe, L., 2022. Immunity Cell Responses to RSV and the Role of Antiviral Inhibitors: A Systematic Review. *Infection and drug resistance*, 15, 7413–7430.

Cilla, G., Sarasua, A., Montes, M., Arostegui, N., Vicente, D., Pérez-Yarza, E., et al., 2006. Risk factors for hospitalization due to respiratory syncytial virus infection among infants in the Basque Country, Spain. *Epidemiology and infection*, 134, 506–513.

Coindy, E.L., Efstathiou, C., Talwar, S., Moureau, A., Vernhes, C., Openshaw, P.J.M., et al., 2024. Antibody-mediated protection against respiratory syncytial virus in children. *European respiratory review,* 33, 240106.

Colosia, A.D., Masaquel, A., Hall, C.B., Barrett, A.M., Mahadevia, P.J., Yogev, R., 2012. Residential crowding and severe respiratory syncytial virus disease among infants and young children: a systematic literature review. *BMC infectious diseases*, 12, 95.

Colosia, A., Costello, J., McQuarrie, K., Kato, K., Bertzos, K., 2023. Systematic literature review of the signs and symptoms of respiratory syncytial virus. *Influenza and other respiratory viruses*, 17, e13100.

Coma, E., Martinez-Marcos, M., Hermosilla, E., Mendioroz, J., Reñé, A., Fina, F., et al., 2024. Effectiveness of nirsevimab immunoprophylaxis against respiratory syncytial virus-related outcomes in hospital and primary care settings: a retrospective cohort study in infants in Catalonia (Spain). *Archives of disease in childhood*, 109, 736–741.

Coutts, J., Fullarton, J., Morris, C., Grubb, E., Buchan, S., Rodgers-Gray, B., et al., 2020. Association between respiratory syncytial virus hospitalization in infancy and childhood asthma. *Pediatric pulmonology*, 55, 1104–1110.

Cruz, J.S., de Souza Luna, L.K., Alves, V.R.G., Conte, D.D., Bellei, N.C.J., 2021. Viral load of respiratory syncytial virus among children from primary care and hospital settings admitted to a university hospital in Brazil (2009-2013). *Journal of medical virology*, 93, 3397–3400.

Cunningham, S., Piedra, P.A., Martinon-Torres, F., Szymanski, H., Brackeva, B., Dombrecht, E., et al., 2021. Nebulised ALX-0171 for respiratory syncytial virus lower respiratory tract infection in hospitalised children: a double-blind, randomised, placebo-controlled, phase 2b trial. *The Lancet. Respiratory medicine*, 9, 21–32.

Cunningham, C.K., Karron, R.A., Muresan, P., Kelly, M.S., McFarland, E.J., Perlowski, C., et al., 2022. Evaluation of Recombinant Live-Attenuated Respiratory Syncytial Virus (RSV) Vaccines RSV/ΔNS2/Δ1313/I1314L and RSV/276 in RSV-Seronegative Children. *The Journal of infectious diseases*, 226, 2069–2078.

Curns, A.T., Rha, B., Lively, J.Y., Sahni, L.C., Englund, J.A., Weinberg, G.A., et al., 2024. Respiratory Syncytial Virus-Associated Hospitalizations Among Children <5 Years Old: 2016 to 2020. *Pediatrics,* 153, e2023062574.

Dallagiacoma, G., Arthur Rhedin, S., Odone, A., Alfvén, T., 2024. A comparative analysis of non-pharmaceutical interventions for preventing the respiratory syncytial virus in 30 European countries. *Acta paediatrica*, 113, 1388–1395.

De Sierra, T.M., Kumar, M.L., Wasser, T.E., Murphy, B.R., Subbarao, E.K., 1993. Respiratory syncytial virus-specific immunoglobulins in preterm infants. *The Journal of pediatrics*, 122, 787–791.

Del Riccio, M., Spreeuwenberg, P., Osei-Yeboah, R., Johannesen, C.K., Fernandez, L.V., Teirlinck, A.C., et al., 2023. Burden of Respiratory Syncytial Virus in the European Union: estimation of RSV-associated hospitalizations in children under 5 years. *The Journal of infectious diseases*, 228, 1528–1538.

DeVincenzo, J.P., Aitken, J.B., Harrison, L.G., 2004. Opportunities for early therapy of respiratory syncytial virus (RSV) infection: what happens before hospitalization. *Antiviral research*, 62, 47–51.

DeVincenzo, J., Tait, D., Efthimiou, J., Mori, J., Kim, Y.I., Thomas, E., et al., 2020. A Randomized, Placebo-Controlled, Respiratory Syncytial Virus Human Challenge Study of the Antiviral Efficacy, Safety, and Pharmacokinetics of RV521, an Inhibitor of the RSV-F Protein. *Antimicrobial agents and chemotherapy*, 64, e01884-19.

Di Maio, V.C., Scutari, R., Forqué, L., Colagrossi, L., Coltella, L., Ranno, S., et al., 2024. Presence and Significance of Multiple Respiratory Viral Infections in Children Admitted to a Tertiary Pediatric Hospital in Italy. *Viruses*, 16, 750.

Dieussaert, I., Hyung Kim, J., Luik, S., Seidl, C., Pu, W., Stegmann, J.U., et al., 2024. RSV Prefusion F Protein-Based Maternal Vaccine - Preterm Birth and Other Outcomes. *The New England journal of medicine*, 390, 1009–1021.

Díez-Gandía, E., Gómez-Álvarez, C., López-Lacort, M., Muñoz-Quiles, C., Úbeda-Sansano, I., Díez-Domingo, J., et al., 2021. The impact of childhood RSV infection on children's and parents' quality of life: a prospective multicenter study in Spain. *BMC infectious diseases*, 21, 924.

Dolatshahi, S., Butler, A.L., Pou, C., Henckel, E., Bernhardsson, A.K., Gustafsson, A., et al., 2022. Selective transfer of maternal antibodies in preterm and fullterm children. *Scientific reports*, 12, 14937.

Domachowske, J., Madhi, S.A., Simões, E.A.F., Atanasova, V., Cabañas, F., Furuno, K., et al., 2022. Safety of Nirsevimab for RSV in Infants with Heart or Lung Disease or Prematurity. *The New England journal of medicine*, 386, 892–894.

Drysdale, S.B., Cathie, K., Flamein, F., Knuf, M., Collins, A.M., Hill, H.C., et al., 2023. Nirsevimab for Prevention of Hospitalizations Due to RSV in Infants. *The New England journal of medicine,* 389, 2425-2435.

Duan, Y., Jiang, M., Huang, Q., Jia, M., Yang, W., Feng, L., 2023. Incidence, hospitalization, and mortality in children aged 5 years and younger with respiratory syncytial virus-related diseases: A systematic review and meta-analysis. *Influenza and other respiratory viruses*, 17, e13145.

Eisenhut M., 2006. Extrapulmonary manifestations of severe respiratory syncytial virus infection--a systematic review. *Critical care*, 10, R107.

El Saleeby, C.M., Bush, A.J., Harrison, L.M., Aitken, J.A., Devincenzo, J.P., 2011. Respiratory syncytial virus load, viral dynamics, and disease severity in previously healthy naturally infected children. *The Journal of infectious diseases*, 204, 996–1002.

El-Atawi, K., De Luca, D., Ramanathan, R., Sanchez Luna, M., Alsaedi, S., Abdul Wahab, M.G., et al., 2023. Efficacy and Safety of Palivizumab as a Prophylaxis for Respiratory Syncytial Virus (RSV) Disease: An Updated Systemic Review and Meta-Analysis. *Cureus*, 15, e51375.

Enanta Pharmaceuticals, 2024. Enanta Pharmaceuticals Announces Positive Topline Results from First-in-Pediatrics Phase 2 Study Evaluating Zelicapavir for the Treatment of Respiratory Syncytial Virus (RSV). Available at: https://ir.enanta.com/node/12931/pdf. [Accessed 23 June 2025]

Eriksson, M., Bennet, R., Rotzén-Östlund, M., Von Sydow, M., Wirgart, B.Z., 2002. Population-based rates of severe respiratory syncytial virus infection in children with and without risk factors, and outcome in a tertiary care setting. *Acta paediatrica*, 91, 593–598.

Ernst, C., Bejko, D., Gaasch, L., Hannelas, E., Kahn, I., Pierron, C., et al., 2024. Impact of nirsevimab prophylaxis on paediatric respiratory syncytial virus (RSV)-related hospitalisations during the initial 2023/24 season in Luxembourg. *Euro surveillance*, 29, 2400033.

Esposito, S., Scarselli, E., Lelii, M., Scala, A., Vitelli, A., Capone, S., et al., 2016. Antibody response to respiratory syncytial virus infection in children <18 months old. *Human vaccines & immunotherapeutics*, 12, 1700–1706.

European Centre for Disease Prevention and Control, 2025. Available at: https://www.ecdc.europa.eu/en/respiratory-syncytial-virus-rsv. [Accessed 9 June 2025]

European Medicines Agency Medicines mResvia, 2024. Available at: https://s29.q4cdn.com/435878511/files/doc_news/Moderna-Receives-European-Commission-Approval-for-RSV-Vaccine-mRESVIAR-2024.pdf?utm. [Accessed 23 October 2025]

European Medicines Agency News on Enflonsia, 2025. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/enflonsia#news-on. [Accessed 20 October 2025]

European perinatal health report, 2015-2019. Available at: https://www.europeristat.com/wp-content/uploads/2022/11/Euro-Peristat_Fact_sheets_2022_for_upload.pdf. [Accessed 17 June 2025]

Ezpeleta, G., Navascués, A., Viguria, N., Herranz-Aguirre, M., Juan Belloc, S.E., Gimeno Ballester, J., et al., 2024. Effectiveness of Nirsevimab Immunoprophylaxis Administered at Birth to Prevent Infant Hospitalisation for Respiratory Syncytial Virus Infection: A Population-Based Cohort Study. *Vaccines*, 12, 383.

Falsey, A.R., Williams, K., Gymnopoulou, E., Bart, S., Ervin, J., Bastian, A.R., et al., 2023. Efficacy and Safety of an Ad26.RSV.preF-RSV preF Protein Vaccine in Older Adults. *The New England journal of medicine*, 388, 609–620.

Falsey, A.R., Hosman, T., Bastian, A.R., Vandenberghe, S., Chan, E.K.H., Douoguih, M., et al., 2024. Long-term efficacy and immunogenicity of Ad26.RSV.preF-RSV preF protein vaccine (CYPRESS): a randomised, double-blind, placebo-controlled, phase 2b study. *The Lancet. Infectious diseases*, 24, 1015–1024.

Fang, L.C., Wang, J.Y., Yu, H.H., Wang, L.C., Chiang, B.L., 2023. Respiratory-syncytial virus immunoprophylaxis on asthma symptoms development in prematurity with bronchopulmonary dysplasia. *The journal of allergy and clinical immunology. Global*, 2, 100161.

Farley, R., Spurling, G.K., Eriksson, L., Del Mar, C.B., 2014. Antibiotics for bronchiolitis in children under two years of age. *The Cochrane database of systematic reviews*, *2014*, CD005189.

Fauroux, B., Simões, E.A.F., Checchia, P.A., Paes, B., Figueras-Aloy, J., Manzoni, P., et al., 2017. The Burden and Long-term Respiratory Morbidity Associated with Respiratory Syncytial Virus Infection in Early Childhood. *Infectious diseases and therapy*, 6, 173–197.

FDA Vaccines mRESVIA, 2024. Available at: https://www.fda.gov/vaccines-blood-biologics/vaccines/mresvia?utm. [Accessed 23 October 2025]

Feltes, T.F., Cabalka, A.K., Meissner, H.C., Piazza, F.M., Carlin, D.A., et al., 2003. Palivizumab prophylaxis reduces hospitalization due to respiratory syncytial virus in young children with hemodynamically significant congenital heart disease. *The Journal of pediatrics*, 143, 532–540.

Fitzpatrick, T., Buchan, S.A., Mahant, S., Fu, L., Kwong, J.C., Stukel, T.A., et al., 2024. Pediatric Respiratory Syncytial Virus Hospitalizations, 2017-2023. *JAMA network open*, 7, e2416077.

Flynn, M.F., Kelly, M., Dooley, J.S.G., 2021. Nasopharyngeal Swabs vs. Nasal Aspirates for Respiratory Virus Detection: A Systematic Review. *Pathogens*, 10, 1515.

Foley, D.A., Minney-Smith, C.A., Lee, W.H., Oakes, D.B., Hazelton, B., Ford, T. J., et al., 2023. Respiratory Syncytial Virus Reinfections in Children in Western Australia. *Viruses*, 15, 2417.

Forbes, M.L., Kumar, V.R., Yogev, R., Wu, X., Robbie, G.J., Ambrose, C.S., 2014. Serum palivizumab level is associated with decreased severity of respiratory syncytial virus disease in high-risk infants. *Human vaccines & immunotherapeutics*, 10, 2789–2794.

Franklin, D., Babl, F.E., Schlapbach, L.J., Oakley, E., Craig, S., Neutze, J., et al., 2018. A Randomized Trial of High-Flow Oxygen Therapy in Infants with Bronchiolitis. *The New England journal of medicine*, *378*, 1121–1131.

Frogel, M.P., Stewart, D.L., Hoopes, M., Fernandes, A.W., Mahadevia, P.J., 2010. A systematic review of compliance with palivizumab administration for RSV immunoprophylaxis. *Journal of managed care pharmacy*, 16, 46–58.

Gantenberg, J.R., van Aalst, R., Zimmerman, N., Limone, B., Chaves, S.S., La Via, W.V., et al., 2022. Medically Attended Illness due to Respiratory Syncytial Virus Infection Among Infants Born in the United States Between 2016 and 2020. *The Journal of infectious diseases*, 226, S164–S174.

García, C.G., Bhore, R., Soriano-Fallas, A., Trost, M., Chason, R., Ramilo, O., et al., 2010. Risk Factors in Children Hospitalized With RSV Bronchiolitis Versus Non–RSV Bronchiolitis. *Pediatrics,* 126, e1453–e1460.

Garcia-Mauriño, C., Moore-Clingenpeel, M., Thomas, J., Mertz, S., Cohen, D. M., Ramilo, O., et al., 2019. Viral Load Dynamics and Clinical Disease Severity in Infants With Respiratory Syncytial Virus Infection. *The Journal of infectious diseases*, 219, 1207–1215.

Garegnani, L., Styrmisdóttir, L., Roson Rodriguez, P., Escobar Liquitay, C.M., Esteban, I., Franco, J.V., 2021. Palivizumab for preventing severe respiratory syncytial virus (RSV) infection in children. *The Cochrane database of systematic reviews*, 11, CD013757.

Gill, P.J., Anwar, M.R., Kornelsen, E., Parkin, P., Mahood, Q., Mahant, S., 2021. Parenteral versus enteral fluid therapy for children hospitalised with bronchiolitis. *The Cochrane database of systematic reviews*, 12, CD013552.

Gkentzi, D., Dimitriou, G., Karatza, A., 2018. Non-pulmonary manifestations of respiratory syncytial virus infection. *Journal of thoracic disease*, 10, S3815–S3818.

Golan-Tripto, I., Danino, D., De Waal, L., Akel, K., Dizitzer-Hillel, Y., Tal, A., et al., 2024. Viral load in hospitalized infants with respiratory syncytial virus bronchiolitis: a three-way comparative analysis. *European journal of pediatrics*, 183, 3471–3478.

Graham, B.S., 2017. Vaccine development for respiratory syncytial virus. *Current opinion in virology*, 23, 107-112.

Graziani, A., Bozza, S., Borghi, M., Mencacci, A., Camilloni, B., 2024. Circulation and Seasonality of Respiratory Viruses in Hospitalized Patients during Five Consecutive Years (2019–2023) in Perugia, Italy. *Viruses,* 16, 1394.

Griffin, M.P., Khan, A.A., Esser, M.T., Jensen, K., Takas, T., Kankam, M.K., et al., 2017. Safety, Tolerability, and Pharmacokinetics of MEDI8897, the Respiratory Syncytial Virus Prefusion F-Targeting Monoclonal Antibody with an Extended Half-Life, in Healthy Adults. *Antimicrobial agents and chemotherapy*, 61, e01714-16.

Griffin, M.P., Yuan, Y., Takas, T., Domachowske, J.B., Madhi, S.A., Manzoni, P., et al., 2020. Single-Dose Nirsevimab for Prevention of RSV in Preterm Infants. *The New England journal of medicine*, 383, 415–425.

Groeneveld, J.M., Ballering, A.V., van Boven, K., Akkermans, R.P., Olde Hartman, T.C., Uijen, A.A., 2020. Sex differences in incidence of respiratory symptoms and management by general practitioners. *Family practice*, 37, 631–636.

Gunell, M., Antikainen, P., Porjo, N., Irjala, K., Vakkila, J., Hotakainen, K., et al., 2016. Comprehensive real-time epidemiological data from respiratory infections in Finland between 2010 and 2014 obtained from an automated and multianalyte mariPOC® respiratory pathogen test. *European journal of clinical microbiology & infectious diseases*, 35, 405–413.

Guo L, Kenmoe S, Miyake F, Chung A, Zhang H, Bandeira T, et al., 2025. Respiratory syncytial virus hospitalisation by chronological month of age and by birth month in infants. *Nature communications*, 16, 6109.

Haapanen, M., Renko, M., Artama, M., Kuitunen, I., 2021. The impact of the lockdown and the re-opening of schools and day cares on the epidemiology of SARS-CoV-2 and other respiratory infections in children – A nationwide register study in Finland. *EClinicalMedicine,* 34, 100807.

Habra, B., Janahi, I.A., Dauleh, H., Chandra, P., Veten, A., 2020. A comparison between high-flow nasal cannula and noninvasive ventilation in the management of infants and young children with acute bronchiolitis in the PICU. *Pediatric pulmonology*, 55, 455–461.

Haddadin, Z., Beveridge, S., Fernandez, K., Rankin, D.A., Probst, V., Spieker, A.J., et al., 2021. Respiratory Syncytial Virus Disease Severity in Young Children. *Clinical infectious*, 73, e4384–e4391.

Haeberer, M., López-Ibáñez de Aldecoa, A., Seabroke, S., Ramirez Agudelo, J.L., Mora, L., Sarabia, L., et al., 2025. Economic burden of children hospitalized with respiratory syncytial virus infection in Spain, 2016-2019. *Vaccine*, 43, 126512.

Haerskjold, A., Kristensen, K., Kamper-Jørgensen, M., Nybo Andersen, A.-M., Ravn, H., Graff Stensballe, L., 2016. Risk Factors for Hospitalization for Respiratory Syncytial Virus Infection: A Population-based Cohort Study of Danish Children. *The Pediatric infectious disease journal*, 35, 61–65.

Hak, S.F., Venekamp, R.P., Billard, M.N., van Houten, M.A., Pollard, A.J., Heikkinen, T., et al., 2024a. Substantial Burden of Nonmedically Attended RSV Infection in Healthy-Term Infants: An International Prospective Birth Cohort Study. *The Journal of infectious diseases*, 229, S40–S50.

Hak, S.F., Venekamp, R.P., Wildenbeest, J.G., Bont, L.J., 2024b. Outpatient respiratory syncytial virus infections and novel preventive interventions. *Current opinion in pediatrics*, 36, 171-181.

Hak, S.F., Sankatsing, V.D.V., Wildenbeest, J.G., Venekamp, R.P., Casini, B., Rizzo, C., et al., 2025a. Burden of RSV infections among young children in primary care: a prospective cohort study in five European countries (2021-23). *The Lancet. Respiratory medicine,* 13, 153–165.

Hak, S.F., Venekamp, R.P., Billard, M.N., Cianci, D., Van Houten, M.A., Pollard, A.J., et al., 2025b. Antibiotic use attributable to RSV infections during infancy-an international prospective birth cohort study. *The Journal of antimicrobial chemotherapy*, 80, 1803–1812.

Hall, C.B., Geiman, J.M., Biggar, R., Kotok, D.I., Hogan, P.M., Douglas, R.G., 1976. Respiratory Syncytial Virus Infections within Families. *The New England journal of medicine,* 294, 414–419.

Hall, C.B., McBride, J.T., Walsh, E.E., Bell, D.M., Gala, C.L., Hildreth, S., et al., 1983. Aerosolized ribavirin treatment of infants with respiratory syncytial viral infection. A randomized double-blind study. *The New England journal of medicine,* 308, 1443–1447.

Hall, C.B., Walsh, E.E., Schnabel, K.C., Long, C.E., McConnochie, K.M., Hildreth, S.W., et al., 1990. Occurrence of Groups A and B of Respiratory Syncytial Virus over 15 Years: Associated Epidemiologic and Clinical Characteristics in Hospitalized and Ambulatory Children. *The Journal of infectious diseases,* 162, 1283–1290.

Hall, C.B., Walsh, E.E., Long, C.E., Schnabel, K.C., 1991. Immunity to and frequency of reinfection with respiratory syncytial virus. *The Journal of infectious diseases*, 163, 693–698.

Hall, C.B., Weinberg, G.A., Iwane, M.K., Blumkin, A.K., Edwards, K.M., Staat, M.A., et al., 2009. The burden of respiratory syncytial virus infection in young children. *The New England journal of medicine*, 360, 588–598.

Hall, C.B., Weinberg, G.A., Blumkin, A.K., Edwards, K.M., Staat, M.A., Schultz, A.F., et al., 2013. Respiratory Syncytial Virus–Associated Hospitalizations Among Children Less Than 24 Months of Age. *Pediatrics,* 132, e341–e348.

Hammitt, L.L., Dagan, R., Yuan, Y., Baca Cots, M., Bosheva, M., Madhi, S.A., et al., 2022. Nirsevimab for Prevention of RSV in Healthy Late-Preterm and Term Infants. *The New England journal of medicine*, 386, 837–846.

Han, H.J., Ryu, D., Kim, J.Y., Jang, S., Suh, H.S., 2024. Healthcare resource utilisation and costs in infants with confirmed respiratory syncytial virus infections: a national population cohort study. *BMC infectious diseases*, 24, 1152.

Hanson L.A., 1999. Human milk and host defence: immediate and long-term effects. *Acta paediatrica,* 88, 42–46.

Harding, E.R., Wildenbeest, J.G., Heikkinen, T., Dacosta-Urbieta, A., Martinón-Torres, F., Cunningham, S., et al., 2024. Inconsistent Increase in Age at Respiratory Syncytial Virus Hospitalization of Children Aged <2 Years During the Severe Acute Respiratory Syndrome Coronavirus 2 Pandemic: A Retrospective Multicenter Study in 4 European Countries. *The Journal of infectious diseases*, 230, e985–e995.

Hartmann, K., Liese, J.G., Kemmling, D., Prifert, C., Weißbrich, B., Thilakarathne, P., et al., 2022. Clinical Burden of Respiratory Syncytial Virus in Hospitalized Children Aged ≤5 Years (INSPIRE Study). *The Journal of infectious diseases*, 226, 386–395.

Hasegawa, K., Jartti, T., Mansbach, J.M., Laham, F.R., Jewell, A.M., Espinola, J.A., et al., 2015. Respiratory syncytial virus genomic load and disease severity among children hospitalized with bronchiolitis: multicenter cohort studies in the United States and Finland. *The Journal of infectious diseases*, 211, 1550–1559.

Hause, A.M., Henke, D.M., Avadhanula, V., Shaw, C.A., Tapia, L.I., Piedra, P.A., 2017. Sequence variability of the respiratory syncytial virus (RSV) fusion gene among contemporary and historical genotypes of RSV/A and RSV/B. *PloS one*, 12, e0175792.

Havdal, L.B., Bøås, H., Bekkevold, T., Kran, A.B., Rojahn, A.E., Størdal, K., et al., 2022a. The burden of respiratory syncytial virus in children under 5 years of age in Norway. *The Journal of infection*, 84, 205–215.

Havdal, L.B., Bøås, H., Bekkevold, T., Kran, A.B., Rojahn, A.E., Størdal, K., et al., 2022b. Risk factors associated with severe disease in respiratory syncytial virus infected children under 5 years of age. *Frontiers in pediatrics*, *10*, 1004739.

Heemskerk, S., van Heuvel, L., Asey, T., Bangert, M., Kramer, R., Paget, J., et al., 2024. Disease Burden of RSV Infections and Bronchiolitis in Young Children (< 5 Years) in Primary Care and Emergency Departments: A Systematic Literature Review. *Influenza and other respiratory viruses*, 18, e13344.

Heikkinen, T., Ruuskanen, O., 1994. Temporal development of acute otitis media during upper respiratory tract infection. *The Pediatric infectious disease journal*, 13, 659–661.

Heikkinen, T., Thint, M., Chonmaitree, T., 1999. Prevalence of various respiratory viruses in the middle ear during acute otitis media. *The New England journal of medicine*, 340, 260–264.

Heikkinen, T., Marttila, J., Salmi, A.A., Ruuskanen, O., 2002. Nasal swab versus nasopharyngeal aspirate for isolation of respiratory viruses. *Journal of clinical microbiology*, 40, 4337–4339.

Heikkinen, T., Valkonen, H., Waris, M., Ruuskanen, O., 2015. Transmission of Respiratory Syncytial Virus Infection Within Families. *Open forum infectious diseases*, 2, ofu118.

Heikkinen, T., Ojala, E., Waris, M., 2017. Clinical and Socioeconomic Burden of Respiratory Syncytial Virus Infection in Children. *The Journal of infectious diseases*, 215, 17–23.

Heinonen, S., Silvennoinen, H., Lehtinen, P., Vainionpää, R., Vahlberg, T., Ziegler, T., et al., 2010. Early oseltamivir treatment of influenza in children 1-3 years of age: a randomized controlled trial. *Clinical infectious diseases*, 51, 887–894.

Heinonen, S., Rodriguez-Fernandez, R., Diaz, A., Oliva Rodriguez-Pastor, S., Ramilo, O., Mejias, A., 2019. Infant Immune Response to Respiratory Viral Infections. *Immunology and allergy clinics of North America*, 39, 361–376.

Heinonen, S., Velazquez, V.M., Ye, F., Mertz, S., Acero-Bedoya, S., Smith, B., et al., 2020. Immune profiles provide insights into respiratory syncytial virus disease severity in young children. *Science translational medicine*, 12, eaaw0268.

Henrickson, K.J., Hall, C.B., 2007. Diagnostic assays for respiratory syncytial virus disease. *The Pediatric infectious disease journal*, 26, S36–S40.

Houben, M.L., Coenjaerts, F.E., Rossen, J.W., Belderbos, M.E., Hofland, R.W., Kimpen, J.L., et al., 2010. Disease severity and viral load are correlated in infants with primary respiratory syncytial virus infection in the community. *Journal of medical virology*, 82, 1266–1271.

Hu YL, Ho SY, Cheng AL, Huang YT, Fang CT, Chang LY., 2025. Comparison of Clinical Features and Severity of Subgroup A and B Respiratory Syncytial Virus Infection. *Journal of medical virology,* 97, e70453.

Huang, H.S., Tsai, C.L., Chang, J., Hsu, T.C., Lin, S., Lee, C.C., 2018. Multiplex PCR system for the rapid diagnosis of respiratory virus infection: systematic review and meta-analysis. *Clinical microbiology and infection*, 24, 1055–1063.

Huurre, A., Kalliomäki, M., Rautava, S., Rinne, M., Salminen, S., Isolauri, E., 2008. Mode of delivery - effects on gut microbiota and humoral immunity. *Neonatology*, 93, 236–240.

Ippolito, G., La Vecchia, A., Umbrello, G., Di Pietro, G., Bono, P., Scalia Catenacci, S., et al., 2021. Disappearance of Seasonal Respiratory Viruses in Children Under Two Years Old During COVID-19 Pandemic: A Monocentric Retrospective Study in Milan, Italy. *Frontiers in pediatrics*, 9, 721005.

Ison, M.G., Papi, A., Athan, E., Feldman, R. G., Langley, J.M., Lee, D.G., et al., 2024. Efficacy and Safety of Respiratory Syncytial Virus (RSV) Prefusion F Protein Vaccine (RSVPreF3 OA) in Older Adults Over 2 RSV Seasons. *Clinical infectious diseases*, 78, 1732–1744.

Ivaska, L., Niemelä, J., Heikkinen, T., Vuorinen, T., Peltola, V., 2013. Identification of respiratory viruses with a novel point-of-care multianalyte antigen detection test in children with acute respiratory tract infection. *Journal of clinical virology,* 57, 136–140.

Iwane, M.K., Edwards, K.M., Szilagyi, P.G., Walker, F.J., Griffin, M.R., Weinberg, G.A., et al., 2004. Population-Based Surveillance for Hospitalizations Associated With Respiratory Syncytial Virus, Influenza Virus, and Parainfluenza Viruses Among Young Children. *Pediatrics*, 113, 1758–1764.

Jacoby, P., Glass, K., Moore, H.C., 2017. Characterizing the risk of respiratory syncytial virus in infants with older siblings: a population-based birth cohort study. *Epidemiology and infection*, 145, 266–271.

Jain, S., Williams, D.J., Arnold, S.R., Ampofo, K., Bramley, A.M., Reed, C., et al., 2015. Community-acquired pneumonia requiring hospitalization among U.S. children. *The New England journal of medicine*, *372*, 835–845.

Jang, M.J., Kim, Y.J., Hong, S., Na, J., Hwang, J.H., Shin, S.M., et al., 2020. Positive association of breastfeeding on respiratory syncytial virus infection in hospitalized infants: a multicenter retrospective study. *Clinical and experimental pediatrics*, 63, 135–140.

Jans, J., Wicht, O., Widjaja, I., Ahout, I.M., de Groot, R., Guichelaar, T., et al., 2017. Characteristics of RSV-Specific Maternal Antibodies in Plasma of Hospitalized, Acute RSV Patients under Three Months of Age. *PloS one*, 12, e0170877.

Jepsen, M.T., Trebbien, R., Emborg, H.D., Krause, T.G., Schønning, K., Voldstedlund, M., et al., 2018. Incidence and seasonality of respiratory syncytial virus hospitalisations in young children in Denmark, 2010 to 2015. *Euro surveillance*, 23, 17-00163.

Jiang, M.Y., Duan, Y.P., Tong, X.L., Huang, Q.R., Jia, M.M., Yang, W.Z., et al., 2023. Clinical manifestations of respiratory syncytial virus infection and the risk of wheezing and recurrent wheezing illness: a systematic review and meta-analysis. *World journal of pediatrics*, 19, 1030–1040.

Jimeno Ruiz, S., Peláez, A., Labourt, A., Acuña, F.M., Linares, L., Llana Martín, I., et al., 2024. Evaluating the Effectiveness of Nirsevimab in Reducing Pediatric RSV Hospitalizations in Spain. *Vaccines*, 12, 1160.

Jones, J.M., Fleming-Dutra, K.E., Prill, M.M., Roper, L.E., Brooks, O., Sánchez, P.J., et al., 2023. Use of Nirsevimab for the Prevention of Respiratory Syncytial Virus Disease Among Infants and Young Children: Recommendations of the Advisory Committee on Immunization Practices - United States, 2023. *MMWR. Morbidity and mortality weekly report*, 72, 920–925.

Jung, H.E., Kim, T.H., Lee, H.K., 2020. Contribution of Dendritic Cells in Protective Immunity against Respiratory Syncytial Virus Infection. *Viruses*. 12, 102.

Juvén, T., Mertsola, J., Waris, M., Leinonen, M., Meurman, O., Roivainen, M., et al., 2000. Etiology of community-acquired pneumonia in 254 hospitalized children. *The Pediatric infectious disease journal*, 19, 293–298.

Kaler, J., Hussain, A., Patel, K., Hernandez, T., Ray, S., 2023. Respiratory Syncytial Virus: A Comprehensive Review of Transmission, Pathophysiology, and Manifestation. *Cureus*, 15, e36342.

Kampmann, B., Madhi, S.A., Munjal, I., Simões, E.A.F., Pahud, B.A., Llapur, C., et al., 2023. Bivalent Prefusion F Vaccine in Pregnancy to Prevent RSV Illness in Infants. *The New England journal of medicine*, 388, 1451–1464.

Karppinen, S., Toivonen, L., Schuez-Havupalo, L., Waris, M., Peltola, V., 2016. Interference between respiratory syncytial virus and rhinovirus in respiratory tract infections in children. *Clinical microbiology and infection,* 22, 208.e1–208.e6.

Karron, R.A., Atwell, J.E., McFarland, E.J., Cunningham, C.K., Muresan, P., Perlowski, C., et al., 2021. Live-attenuated Vaccines Prevent Respiratory Syncytial Virus-associated Illness in Young Children. *American journal of respiratory and critical care medicine*, 203, 594–603.

Karron, R.A., Luongo, C., Woods, S., Oliva, J., Collins, P.L., Buchholz, U.J., et al., 2024. Evaluation of the Live-Attenuated Intranasal Respiratory Syncytial Virus (RSV) Vaccine RSV/6120/ΔNS2/1030s in RSV-Seronegative Young Children. *The Journal of infectious diseases*, 229, 346–354.

Kawasaki, Y., Hosoya, M., Katayose, M., Suzuki, H., 2004. Role of serum neutralizing antibody in reinfection of respiratory syncytial virus. *Pediatrics international,* 46, 126–129.

Kazakova, A., Kakkola, L., Päkkilä, H., Teros-Jaakkola, T., Soukka, T., Peltola, V., et al., 2019. Serological Array-in-Well Multiplex Assay Reveals a High Rate of Respiratory Virus Infections and Reinfections in Young Children. *mSphere*, 4, e00447-19.

Kepreotes, E., Whitehead, B., Attia, J., Oldmeadow, C., Collison, A., Searles, A., et al., 2017. High-flow warm humidified oxygen versus standard low-flow nasal cannula oxygen for moderate bronchiolitis (HFWHO RCT): an open, phase 4, randomised controlled trial. *Lancet*, *389*, 930–939.

Kim, H.W., Canchola, J.G., Brandt, C.D., Pyles, G., Chanock, R.M., Jensen, K., et al., 1969. Respiratory syncytial virus disease in infants despite prior administration of antigenic inactivated vaccine. *American journal of epidemiology*, 89, 422–434.

Kingwell K., 2023. RSV vaccines score landmark FDA approvals. *Nature reviews. Drug discovery*, 22, 523–525.

Kirolos, A., Manti, S., Blacow, R., Tse, G., Wilson, T., Lister, M., et al., 2020. A Systematic Review of Clinical Practice Guidelines for the Diagnosis and Management of Bronchiolitis. *The Journal of infectious diseases*, 222, S672–S679.

Klein S. L., 2000. The effects of hormones on sex differences in infection: from genes to behavior. *Neuroscience and biobehavioral reviews*, 24, 627–638.

Kobiałka, M., Jackowska, T., Wrotek, A., 2023. Risk Factors for Severe Respiratory Syncytial Virus Infection in Hospitalized Children. *Viruses,* 15, 1713.

Koivisto, K., Nieminen, T., Mejias, A., Capella Gonzalez, C., Ye, F., Mertz, S., et al., 2022. Respiratory Syncytial Virus (RSV)-Specific Antibodies in Pregnant Women and Subsequent Risk of RSV Hospitalization in Young Infants. *The Journal of infectious diseases*, 225, 1189–1196.

Koivunen, P., Kontiokari, T., Niemelä, M., Pokka, T., Uhari, M., 1999. Time to development of acute otitis media during an upper respiratory tract infection in children. *The Pediatric infectious disease journal*, 18, 303–305.

Kombe, I.K., Munywoki, P.K., Baguelin, M., Nokes, D.J., Medley, G.F., 2019. Model-based estimates of transmission of respiratory syncytial virus within households. *Epidemics*, 27, 1–11.

Kouni, S., Karakitsos, P., Chranioti, A., Theodoridou, M., Chrousos, G., Michos, A., 2013. Evaluation of viral co-infections in hospitalized and non-hospitalized children with respiratory infections using microarrays. *Clinical microbiology and infection*, 19, 772–777.

Kristensen, K., Stensballe, L.G., Bjerre, J., Roth, D., Fisker, N., Kongstad, T., et al., 2009. Risk factors for respiratory syncytial virus hospitalisation in children with heart disease. *Archives of disease in childhood*, 94, 785–9.

Kuitunen, I., Artama, M., Haapanen, M., Renko, M., 2022. Respiratory virus circulation in children after relaxation of COVID-19 restrictions in fall 2021—A nationwide register study in Finland. *Journal of medical virology*, 94, 4528–4532.

Kuitunen, I., Renko, M., Tapiainen, T., 2023. The end of COVID -19 restrictions for children in autumn 2021 was followed by an unusually early, high-peak respiratory syncytial virus epidemic. *Acta paediatrica*, 112, 146–148.

Kulkarni, M., Slain, K.N., Rotta, A.T., Shein, S.L., 2020. The Effects of Furosemide on Oxygenation in Mechanically Ventilated Children with Bronchiolitis. *Journal of pediatric intensive care*, 9, 87–91.

Kutsaya, A., Teros-Jaakkola, T., Kakkola, L., Toivonen, L., Peltola, V., Waris, M., et al. 2016. Prospective clinical and serological follow-up in early childhood reveals a high rate of subclinical RSV infection and a relatively high reinfection rate within the first 3 years of life. *Epidemiology and infection*, 144, 1622–1633.

Kutter, J.S., Spronken, M.I., Fraaij, P.L., Fouchier, R.A., Herfst, S., 2018. Transmission routes of respiratory viruses among humans. *Current opinion in virology*, 28, 142–151.

Lade, C., Bayer, L., Huebbe, B., Riedel, J., Melnik, S., Brestrich, G., et al., 2025. Clinical and economic inpatient burden of respiratory syncytial virus (RSV) infections in children < 2 years of age in Germany, 2014-2019: a retrospective health claims analysis. *Infection*, 53, 393–404. ´

Laham, F.R., Mansbach, J.M., Piedra, P.A., Hasegawa, K., Sullivan, A.F., Espinola, J.A., et al., 2017. Clinical Profiles of Respiratory Syncytial Virus Subtypes A AND B Among Children Hospitalized with Bronchiolitis. *The Pediatric infectious disease journal*, 36, 808–810.

Lambert, L., Sagfors, A.M., Openshaw, P.J., Culley, F.J., 2014. Immunity to RSV in Early-Life. *Frontiers in immunology*, 5, 466.

Leija-Martínez, J.J., Esparza-Miranda, L.A., Rivera-Alfaro, G., Noyola, D.E., 2024. Impact of Nonpharmaceutical Interventions during the COVID-19 Pandemic on the Prevalence of Respiratory Syncytial Virus in Hospitalized Children with Lower Respiratory Tract Infections: A Systematic Review and Meta-Analysis. *Viruses*, 16, 429.

Leland, D. S., Ginocchio, C.C., 2007. Role of cell culture for virus detection in the age of technology. *Clinical microbiology reviews*, 20, 49–78.

Levine, D.A., Platt, S.L., Dayan, P.S., Macias, C.G., Zorc, J.J., Krief, W., et al., 2004. Risk of serious bacterial infection in young febrile infants with respiratory syncytial virus infections. *Pediatrics*, 113, 1728–1734.

Li, K., Bont, L.J., Weinberger, D.M., Pitzer, V.E., 2025. Relating in vivo RSV infection kinetics to host infectiousness in different age groups. *The Journal of infectious diseases*, jiaf138.

Li, Y., Reeves, R.M., Wang, X., Bassat, Q., Brooks, W.A., Cohen, C., et al., 2019. Global patterns in monthly activity of influenza virus, respiratory syncytial virus, parainfluenza virus, and metapneumovirus: a systematic analysis. *The Lancet. Global health*, 7, e1031–e1045.

Li, Y., Pillai, P., Miyake, F., Nair, H., 2020. The role of viral co-infections in the severity of acute respiratory infections among children infected with respiratory syncytial virus (RSV): A systematic review and meta-analysis. *Journal of global health*, 10, 010426.

Li, Y., Wang, X., Msosa, T., De Wit, F., Murdock, J., Nair, H., 2021. The impact of the 2009 influenza pandemic on the seasonality of human respiratory syncytial virus: A systematic analysis. *Influenza and other respiratory viruses* ,15, 804–812.

Li, Y., Wang, X., Blau, D.M., Caballero, M.T., Feikin, D.R., Gill, C.J., et al., 2022. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in children younger than 5 years in 2019: a systematic analysis. *The Lancet*, 399, 2047–2064.

Liao, S.L., Tsai, M.H., Yao, T.C., Hua, M.C., Yeh, K.W., Chiu, C.Y., et al., 2017. Caesarean Section is associated with reduced perinatal cytokine response, increased risk of bacterial colonization in the airway, and infantile wheezing. *Scientific reports*, 7, 9053.

Lin, H.C., Liu, Y.C., Hsing, T.Y., Chen, L.L., Liu, Y.C., Yen, T.Y., et al., 2022. RSV pneumonia with or without bacterial co-infection among healthy children. *Journal of the Formosan Medical Association*, 121, 687–693.

Lloyd, P.C., May, L., Hoffman, D., Riegelman, R., Simonsen, L., 2014. The effect of birth month on the risk of respiratory syncytial virus hospitalization in the first year of life in the United States. *The Pediatric infectious disease journal,* 33, e135-40.

Lozano, R., Naghavi, M., Foreman, K., Lim, S., Shibuya, K., Aboyans, V., et al., 2012. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *The Lancet,* 380, 2095–2128.

Lu, Y., Chen, Q., Ren, S., Zhang, Y., Yi, L., Qian, C., et al., 2024. Impact of COVID-19 Nonpharmaceutical Interventions on Respiratory Syncytial Virus Infections in Hospitalized Children. *Influenza and other respiratory viruses*, 18, e13291.

Luna, M.S., Manzoni, P., Paes, B., Baraldi, E., Cossey, V., Kugelman, A., et al., 2020. Expert consensus on palivizumab use for respiratory syncytial virus in developed countries. *Paediatric respiratory reviews*, 33, 35–44.

Lönnerdal B., 2000. Breast milk: a truly functional food. *Nutrition*, 16, 509–511.

Löwensteyn, Y.N., Phijffer, E.W.E.M., Simons, J.V.L., Scheltema, N.M., Mazur, N.I., Nair, H., et al., 2020. Respiratory Syncytial Virus-related Death in Children With Down Syndrome: The RSV GOLD Study. *The Pediatric infectious disease journal*, 39, 665–670.

Macfarlane, P., Denham, J., Assous, J., Hughes, C., 2005. RSV testing in bronchiolitis: which nasal sampling method is best?. *Archives of disease in childhood*, 90, 634–635.

Madhi, S.A., Anderson, A.S., Absalon, J., Radley, D., Simon, R., Jongihlati, B., et al., 2023. Potential for Maternally Administered Vaccine for Infant Group B Streptococcus. *The New England journal of medicine*, 389, 215–227.

Madhi, S.A., Simões, E.A.F., Acevedo, A., Novoa Pizarro, J.M., Shepard, J.S., Railkar, R.A., et al., 2025. A Phase 1b/2a Trial of a Half-life Extended Respiratory Syncytial Virus Neutralizing Antibody, Clesrovimab, in Healthy Preterm and Full-term Infants. *The Journal of infectious diseases*, 231, e478–e487.

Makrinioti, H., Hasegawa, K., Lakoumentas, J., Xepapadaki, P., Tsolia, M., Castro-Rodriguez, J.A., et al., 2022. The role of respiratory syncytial virus- and rhinovirus-induced bronchiolitis in recurrent wheeze and asthma-A systematic review and meta-analysis. *Pediatric allergy and immunology*, 33, e13741.

Malosh, R.E., Martin, E.T., Heikkinen, T., Brooks, W.A., Whitley, R.J., Monto, A.S., 2018. Efficacy and safety of oseltamivir in children: systematic review and individual patient data meta-analysis of randomized controlled trials. *Clinical infectious diseases*, 66, 1492–500.

Mankad, V.S., Leach, A., Chang, Y., Wählby Hamrén, U., Kiazand, A., Kubiak, R.J., et al., 2024. Comprehensive Summary of Safety Data on Nirsevimab in Infants and Children from All Pivotal Randomized Clinical Trials. *Pathogens*, 13, 503.

Manti, S., Leonardi, S., Rezaee, F., Harford, T.J., Perez, M.K., Piedimonte, G., 2022. Effects of Vertical Transmission of Respiratory Viruses to the Offspring. *Frontiers in immunology*, 13, 853009.

Manzoni, P., Viora, E., Lanari, M., Iantomasi, R., Montuori, E.A., Rodgers-Gray, B., et al., 2024. Maternal Risk Factors for Respiratory Syncytial Virus Lower Respiratory Tract Infection in Otherwise Healthy Preterm and Term Infants: A Systematic Review and Meta-analysis. *The Pediatric infectious disease journal*, 43, 763–771.

Mao, Z., Li, X., Dacosta-Urbieta, A., Billard, M.N., Wildenbeest, J., Korsten, K., et al., 2023. Economic burden and health-related quality-of-life among infants with respiratory syncytial virus infection: A multi-country prospective cohort study in Europe. *Vaccine*, 41, 2707–2715.

Mapindra, M.P., Mahindra, M.P., McNamara, P., Semple, M.G., Clark, H., Madsen, J., 2024. Respiratory Syncytial Virus Maternal Vaccination in Infants below 6 Months of Age: Meta-Analysis of Safety, Immunogenicity, and Efficacy. *Neonatology*, 121, 271–282.

Martin, E.T., Kuypers, J., Wald, A., Englund, J.A., 2012. Multiple versus single virus respiratory infections: viral load and clinical disease severity in hospitalized children. *Influenza and other respiratory viruses*, 6, 71–77.

Martinez F.D., 2009. The origins of asthma and chronic obstructive pulmonary disease in early life. *Proceedings of the American Thoracic Society*, *6*, 272–277.

Mattila, S., Paalanne, N., Honkila, M., Pokka, T., Tapiainen, T., 2022. Effect of Point-of-Care Testing for Respiratory Pathogens on Antibiotic Use in Children: A Randomized Clinical Trial. *JAMA network open*, *5*, e2216162.

Mattila, S., Honkila, M., Paalanne, N., Mäki-Koivisto, V., Halt, K., Jartti, T., et al., 2023. Clinical Outcomes of Acutely Ill Children According to Cycle Threshold Values of Respiratory Viruses Detected by Multiplex PCR Testing. *Journal of the Pediatric Infectious Diseases Society*, 12, 549–552.

Mazur, N.I., Caballero, M.T., Nunes, M.C., 2024. Severe respiratory syncytial virus infection in children: burden, management, and emerging therapies. *The Lancet*, 404, 1143–1156.

McGinley, J.P., Lin, G. L., Öner, D., Golubchik, T., O'Connor, D., Snape, M.D., et al., 2022. Clinical and Viral Factors Associated With Disease Severity and Subsequent Wheezing in Infants With Respiratory Syncytial Virus Infection. *The Journal of infectious diseases*, 226, S45–S54.

McLellan, J.S., Chen, M., Joyce, M.G., Sastry, M., Stewart-Jones, G.B.E., Yang, Y., et al., 2013a. Structure-Based Design of a Fusion Glycoprotein Vaccine for Respiratory Syncytial Virus. *Science,* 342, 592–598.

McLellan, J.S., Chen, M., Leung, S., Graepel, K.W., Du, X., Yang, Y., et al., 2013b. Structure of RSV Fusion Glycoprotein Trimer Bound to a Prefusion-Specific Neutralizing Antibody. *Science,* 340, 1113–1117.

McMorrow, M.L., Moline, H.L., Toepfer, A.P., Halasa, N.B., Schuster, J.E., Staat, M.A., et al., 2024. Respiratory Syncytial Virus-Associated Hospitalizations in Children <5 Years: 2016-2022. *Pediatrics*, 154, e2023065623.

Mejias, A., Garcia-Maurino, C., Rodriguez-Fernandez, R., Peeples, M.E., Ramilo, O., 2017. Development and clinical applications of novel antibodies for prevention and treatment of respiratory syncytial virus infection. *Vaccine,* 35, 496–502.

MERCK News release, 2025. Available at: https://www.merck.com/news/u-s-fda-approves-mercks-enflonsia-clesrovimab-cfor-for-prevention-of-respiratory-syncytial-virus-rsv-lower-respiratory-tract-disease-in-infants-born-during-or-entering-their-fir/. [Accessed 20 June 2025]

Midgley, C.M., Haynes, A.K., Baumgardner, J.L., Chommanard, C., Demas, S.W., Prill, M.M., et al., 2017. Determining the Seasonality of Respiratory Syncytial Virus in the United States: The Impact of Increased Molecular Testing. *The Journal of infectious diseases,* 216, 345–355.

Mills, J.M., Harper, J., Broomfield, D., Templeton, K.E., 2011. Rapid testing for respiratory syncytial virus in a paediatric emergency department: benefits for infection control and bed management. *The Journal of hospital infection*, 77, 248–251.

Milner, A.D., Marsh, M.J., Ingram, D.M., Fox, G.F., Susiva, C., 1999. Effects of smoking in pregnancy on neonatal lung function. Archives of disease in childhood. *Fetal and neonatal edition*, 80, 8–14.

Mineva, G., Philip, R., 2023. Impact of breastfeeding on the incidence and severity of respiratory syncytial virus bronchiolitis in infants: systematic review. *Rural and remote health*, 23, 8088.

Miron, V.D., Raianu, R.O., Filimon, C., Craiu, M., 2023. Clinical Differences between SARS-CoV-2 and RSV Infections in Infants: Findings from a Case-Control Study. *Viruses*, 16, 63.

Mitra, D., Afreen, S., Das Mohapatra, P.K., Abdalla, M., 2023. Threat of respiratory syncytial virus infection knocking the door: a proposed potential drug candidate through molecular dynamics simulations, a future alternative. *Journal of molecular modeling*, 29, 91.

Mlinaric-Galinovic, G., Welliver, R.C., Vilibic-Cavlek, T., Ljubin-Sternak, S., Drazenovic, V., Galinovic, I., et al., 2008. The biennial cycle of respiratory syncytial virus outbreaks in Croatia. *Virology journal*, 5, 18.

Moe, N., Krokstad, S., Stenseng, I.H., Christensen, A., Skanke, L.H., Risnes, K.R., et al., 2017. Comparing Human Metapneumovirus and Respiratory Syncytial Virus: Viral Co-Detections, Genotypes and Risk Factors for Severe Disease. *PloS one*, 12, e0170200.

Moline, H.L., Toepfer, A.P., Tannis, A., Weinberg, G.A., Staat, M.A., Halasa, N.B., et al., 2025. Respiratory Syncytial Virus Disease Burden and Nirsevimab Effectiveness in Young Children From 2023-2024. *JAMA pediatrics*, 179, 179–187.

Muenchhoff, M., Goulder, P.J.R., 2014. Sex Differences in Pediatric Infectious Diseases. *The Journal of infectious diseases,* 209, S120–S126.

Muñoz-Quiles, C., López-Lacort, M., Díez-Domingo, J., Orrico-Sánchez, A., 2023. Bronchiolitis, Regardless of Its Etiology and Severity, Is Associated With Increased Risk of Asthma: A Population-Based Study. *The Journal of infectious diseases*, 228, 840–850.

Munywoki, P.K., Koech, D.C., Agoti, C.N., Lewa, C., Cane, P.A., Medley, G.F., et al., 2014. The Source of Respiratory Syncytial Virus Infection In Infants: A Household Cohort Study In Rural Kenya. *The Journal of infectious diseases*, 209, 1685–1692.

Murphy, B.R., Walsh, E.E., 1988. Formalin-inactivated respiratory syncytial virus vaccine induces antibodies to the fusion glycoprotein that are deficient in fusion-inhibiting activity. *Journal of clinical microbiology*, 26, 1595–1597.

Nascimento, M.S., Souza, A.V., Ferreira, A.V., Rodrigues, J.C., Abramovici, S., Silva Filho, L.V., 2010. High rate of viral identification and coinfections in infants with acute bronchiolitis. *Clinics*, 65, 1133–1137.

Nascimento-Carvalho, C.M., Ruuskanen, O., 2016. Clinical Significance of Multiple Respiratory Virus Detection. *The Pediatric infectious disease journal*, 35, 338–339.

Nguyen-Van-Tam, J., Wyffels, V., Smulders, M., Mazumder, D., Tyagi, R., Gupta, N., et al., 2020. Cumulative incidence of post-infection asthma or wheezing among young children clinically diagnosed with respiratory syncytial virus infection in the United States: A retrospective database analysis. *Influenza and other respiratory viruses*, 14, 730–738.

Ngwuta, J.O., Chen, M., Modjarrad, K., Joyce, M.G., Kanekiyo, M., Kumar, A., et al., 2015. Prefusion F–specific antibodies determine the magnitude of RSV neutralizing activity in human sera. *Science translational medicine*, 7, 309ra162.

Nyiro, J.U., Nyawanda, B.O., Mutunga, M., Murunga, N., Nokes, D.J., Bigogo, G., et al., 2024. The cost of care for children hospitalized with respiratory syncytial virus (RSV) associated lower respiratory infection in Kenya. *BMC public health*, 24, 2410.

O'Brien, K.L., Chandran, A., Weatherholtz, R., Jafri, H.S., Griffin, M.P., Bellamy, T., et al., 2015. Efficacy of motavizumab for the prevention of respiratory syncytial virus disease in healthy Native American infants: a phase 3 randomised double-blind placebo-controlled trial. *The Lancet. Infectious diseases*, 15, 1398–1408.

Obando-Pacheco, P., Justicia-Grande, A.J., Rivero-Calle, I., Rodríguez-Tenreiro, C., Sly, P., Ramilo, O., et al., 2018. Respiratory Syncytial Virus Seasonality: A Global Overview. *The Journal of infectious diseases*, 217, 1356–1364.

Obolski, U., Kassem, E., Na'amnih, W., Tannous, S., Kagan, V., Muhsen, K., 2021. Unnecessary antibiotic treatment of children hospitalised with respiratory syncytial virus (RSV) bronchiolitis: risk factors and prescription patterns. *Journal of global antimicrobial resistance*, 27, 303–308.

Ochola, R., Sande, C., Fegan, G., Scott, P.D., Medley, G.F., Cane, P.A., et al., 2009. The level and duration of RSV-specific maternal IgG in infants in Kilifi Kenya. *PloS one*, 4, e8088.

Oliva, J., Terrier, O., 2021. Viral and Bacterial Co-Infections in the Lungs: Dangerous Liaisons. *Viruses*, 13, 1725.

Oppenlander, K.E., Chung, A.A., Clabaugh, D., 2023. Respiratory Syncytial Virus Bronchiolitis: Rapid Evidence Review. *American family physician*, 108, 52–57.

Orzołek, I., Ambrożej, D., Makrinioti, H., Zhu, Z., Jartti, T., Feleszko, W., 2023. Severe bronchiolitis profiling as the first step towards prevention of asthma. *Allergologia et immunopathologia*, 51, 99–107.

Oti, V.B., Idris, A., McMillan, N.A.J., 2024. Intranasal antivirals against respiratory syncytial virus: the current therapeutic development landscape. *Expert review of anti-infective therapy*, 22, 647–657.

Pang, Y., Lu, H., Cao, D., Zhu, X., Long, Q., Tian, F., et al., 2024. Efficacy, immunogenicity and safety of respiratory syncytial virus prefusion F vaccine: systematic review and meta-analysis. *BMC public health*, 24, 1244.

Papi, A., Ison, M.G., Langley, J.M., Lee, D.G., Leroux-Roels, I., Martinon-Torres, F., et al., 2023. Respiratory Syncytial Virus Prefusion F Protein Vaccine in Older Adults. *The New England journal of medicine*, 388, 595–608.

Paramore, L.C., Mahadevia, P.J., Piedra, P.A., 2010. Outpatient RSV lower respiratory infections among high-risk infants and other pediatric populations. *Pediatric pulmonology*, 45, 578–584.

Parsons, E.L., Kim, J.S., Malloy, A.M.W., 2024. Development of innate and adaptive immunity to RSV in young children. *Cellular immunology*, 399-400, 104824.

Pasittungkul, S., Thongpan, I., Vichaiwattana, P., Thongmee, T., Klinfueng, S., Suntronwong, N., et al., 2022. High seroprevalence of antibodies against human respiratory syncytial virus and evidence of respiratory syncytial virus reinfection in young children in Thailand. *International journal of infectious diseases,* 125, 177–183.

Patel, J.A., Nguyen, D.T., Revai, K., Chonmaitree, T., 2007. Role of respiratory syncytial virus in acute otitis media: implications for vaccine development. *Vaccine*, 25, 1683–1689.

PATH. Available at: https://www.path.org/our-impact/resources/rsv-vaccine-and-mab-snapshot/. [Accessed 23 October 2025]

Peer, V., Mandelboim, M., Jurkowicz, M., Green, M.S., 2025. Sex differences in acute respiratory tract infections—multi-year analysis based on data from a large tertiary care medical center in Israel. *Frontiers in public health*, 13, 1502036.

Pérez Marc, G., Vizzotti, C., Fell, D.B., Di Nunzio, L., Olszevicki, S., Mankiewicz, S.W., et al., 2025. Real-world effectiveness of RSVpreF vaccination during pregnancy against RSV-associated lower respiratory tract disease leading to hospitalisation in infants during the 2024 RSV season in Argentina (BERNI study): a multicentre, retrospective, test-negative, case-control study. *The Lancet. Infectious diseases*, 5., S1473-3099(25)00156-2.

Petkar, S., Wanjari, D., Priya, V., 2024. A Comprehensive Review on High-Flow Nasal Cannula Oxygen Therapy in Critical Care: Evidence-Based Insights and Future Directions. *Cureus*, 16, e66264.

Pfizer Press Releases, 2023. Available at: https://www.pfizer.com/news/press-release/press-release-detail/us-fda-approves-abrysvotm-pfizers-vaccine-prevention-0#:~:text=The%20approval%20was%20followed%20in%20June%20by,adults%2060%20years%20of%20age%20and%20older. [Accessed 9 June 2025]

Phijffer, E.W., de Bruin, O., Ahmadizar, F., Bont, L.J., Van der Maas, N.A., Sturkenboom, M.C., et al., 2024a. Respiratory syncytial virus vaccination during pregnancy for improving infant outcomes. *The Cochrane database of systematic reviews*, 5, CD015134.

Phijffer, E.W.E.M., Wildenbeest, J.G., Brouwer, C.N.M., de Hoog, M., Kneyber, M.C.J., Maebe, S., et al. 2024b. Healthcare costs related to respiratory syncytial virus in paediatric intensive care units in the Netherlands: a nationwide prospective observational study (the BRICK study). *The Lancet regional health. Europe*, 43, 100965.

Phillips, M., Finelli, L., Saiman, L., Wang, C., Choi, Y., Patel, J., 2020. Respiratory Syncytial Virus-associated Acute Otitis Media in Infants and Children. *Journal of the Pediatric Infectious Diseases Society*, 9, 544–550.

Piccirilli, G., Rocca, A., Borgatti, E.C., Gabrielli, L., Zama, D., Pierantoni, L., et al., 2023. Respiratory Syncytial Virus-Load Kinetics and Clinical Course of Acute Bronchiolitis in Hospitalized Infants: Interim Results and Review of the Literature. *Pathogens*, 12, 645.

Principi, N., Autore, G., Ramundo, G., Esposito, S., 2023. Epidemiology of Respiratory Infections during the COVID-19 Pandemic. *Viruses,* 15, 1160.

Pruccoli, G., Castagno, E., Raffaldi, I., Denina, M., Barisone, E., Baroero, L., et al., 2023. The Importance of RSV Epidemiological Surveillance: A Multicenter Observational Study of RSV Infection during the COVID-19 Pandemic. *Viruses,* 15, 280.

Quincer, E.M., Cranmer, L.M., Kamidani, S., 2024. Prenatal Maternal Immunization for Infant Protection: A Review of the Vaccines Recommended, Infant Immunity and Future Research Directions. *Pathogens*, 13, 200.

Quinn, L.A., Shields, M.D., Sinha, I., Groves, H.E., 2020. Respiratory syncytial virus prophylaxis for prevention of recurrent childhood wheeze and asthma: a systematic review. *Systematic reviews*, 9, 269.

Ramilo, O., Lagos, R., Sáez-Llorens, X., Suzich, J., Wang, C.K., Jensen, K.M., et al., 2014. Motavizumab treatment of infants hospitalized with respiratory syncytial virus infection does not decrease viral load or severity of illness. *The Pediatric infectious disease journal*, 33, 703–709.

Rao, S., Armistead, I., Messacar, K., Alden, N.B., Schmoll, E., Austin, E., et al., 2023. Shifting Epidemiology and Severity of Respiratory Syncytial Virus in Children During the COVID-19 Pandemic. *JAMA Pediatrics*, 177, 730.

Reeves, R.M., van Wijhe, M., Tong, S., Lehtonen, T., Stona, L., Teirlinck, A.C., et al., 2020. Respiratory Syncytial Virus-Associated Hospital Admissions in Children Younger Than 5 Years in 7 European Countries Using Routinely Collected Datasets. *The Journal of infectious diseases*, 222, S599–S605.

Reichert, H., Suh, M., Jiang, X., Movva, N., Bylsma, L.C., Fryzek, J.P., et al., 2022. Mortality Associated With Respiratory Syncytial Virus, Bronchiolitis, and Influenza Among Infants in the United States: A Birth Cohort Study From 1999 to 2018. *The Journal of infectious diseases*, 226, S246–S254.

Reis, J., Shaman, J., 2018. Simulation of four respiratory viruses and inference of epidemiological parameters. *Infectious Disease Modelling*, 3, 23–34.

Renko, M., Tapiainen, T., 2020. Change in respiratory syncytial virus seasonality in Finland. *Acta paediatrica*, 109, 202–203.

Rha, B., Curns, A.T., Lively, J.Y., Campbell, A.P., Englund, J.A., Boom, J.A., et al., 2020. Respiratory Syncytial Virus–Associated Hospitalizations Among Young Children: 2015–2016. *Pediatrics,* 146, e20193611.

Rhodin, M.H.J., McAllister, N.V., Castillo, J., Noton, S.L., Fearns, R., Kim, I.J., et al., 2021. EDP-938, a novel nucleoprotein inhibitor of respiratory syncytial virus, demonstrates potent antiviral activities in vitro and in a non-human primate model. *PLoS pathogens*, 1, e1009428.

Rima, B., Collins, P., Easton, A., Fouchier, R., Kurath, G., Lamb, R.A., et al., 2017. ICTV Virus Taxonomy Profile: Pneumoviridae. *The Journal of general virology*, 98, 2912–2913.

Robbie, G.J., Zhao, L., Mondick, J., Losonsky, G., Roskos, L.K., 2012. Population pharmacokinetics of palivizumab, a humanized anti-respiratory syncytial virus monoclonal antibody, in adults and children. *Antimicrobial agents and chemotherapy*, 56, 4927–4936.

Ronen, O., Malhotra, A., Pillar, G., 2007. Influence of Gender and Age on Upper-Airway Length During Development. *Pediatrics,* 120, e1028–e1034.

Rosas-Salazar, C., Tang, Z.Z., Shilts, M.H., Turi, K.N., Hong, Q., Wiggins, D.A., et al., 2022. Upper respiratory tract bacterial-immune interactions during respiratory syncytial virus infection in infancy. *The Journal of allergy and clinical immunology*, 149, 966–976.

Rosas-Salazar, C., Chirkova, T., Gebretsadik, T., Chappell, J.D., Peebles, R.S., Jr, Dupont, W.D., et al., 2023. Respiratory syncytial virus infection during infancy and asthma during childhood in the USA (INSPIRE): a population-based, prospective birth cohort study. *The Lancet*, 401, 1669–1680.

Rose, E.B., Dahl, R.M., Havers, F.P., Peacock, G., Langley, G.E., 2021. Respiratory Syncytial Virus-Associated Hospitalizations in Children With Neurological Disorders, 2006-2015. *Journal of the Pediatric Infectious Diseases Society*, 10, 951–957.

Roth, G.A., Abate, D., Abate, K.H., Abay, S.M., Abbafati, S., Abbasi, N., et al., 2018. Global, regional, and nationalage-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet*, 392, 1736-1788.

Ruotsalainen, M., Piippo-Savolainen, E., Hyvärinen, M.K., Korppi, M., 2010. Respiratory morbidity in adulthood after respiratory syncytial virus hospitalization in infancy. *The Pediatric infectious disease journal*, 29, 872–874.

Ruotsalainen, M., Hyvärinen, M.K., Piippo-Savolainen, E., Korppi, M., 2013. Adolescent asthma after rhinovirus and respiratory syncytial virus bronchiolitis. *Pediatric pulmonology*, 48, 633–639.

Ruuskanen, O., Lahti, E., Jennings, L.C., Murdoch, D.R., 2011. Viral pneumonia. *The Lancet*, 377, 1264–1275.

Saha, S., Pandey, B.G., Choudekar, A., Krishnan, A., Gerber, S.I., Rai, S.K., et al., 2015. Evaluation of case definitions for estimation of respiratory syncytial virus associated hospitalizations among children in a rural community of northern India. *Journal of global health*, 5, 010419.

Sanders, S.L., Agwan, S., Hassan, M., Bont, L.J., Venekamp, R.P., 2023. Immunoglobulin treatment for hospitalised infants and young children with respiratory syncytial virus infection. *The Cochrane database of systematic reviews*, 10, CD009417.

Sankatsing, V.D.V., van Summeren, J., Abreha, F.M., Pandolfi, E., Chironna, M., Loconsole, D., et al., 2025. Economic Impact of Respiratory Syncytial Virus Infections in Children Under 5 Years of Age Attending Primary Care in Italy: A Prospective Cohort Study in Two Regions. *Influenza and other respiratory viruses*, 19, e70074.

Saravanos, G.L., King, C.L., Deng, L., Dinsmore, N., Ramos, I., Takashima, M., et al., 2021. Respiratory Syncytial Virus-Associated Neurologic Complications in Children: A Systematic Review and Aggregated Case Series. *The Journal of pediatrics*, 239, 39–49.e9.

Sarkis, R., Liu, W., DeTallo, C., Baloglu, O., Latifi, S.Q., Agarwal, H.S., 2023. Association of enteral feeds in critically ill bronchiolitis patients supported by high-flow nasal cannula with adverse events and outcomes. *European journal of pediatrics*, 182, 4015–4025.

Schaerlaekens, S., Jacobs, L., Stobbelaar, K., Cos, P., Delputte, P., 2024. All Eyes on the Prefusion-Stabilized F Construct, but Are We Missing the Potential of Alternative Targets for Respiratory Syncytial Virus Vaccine Design? *Vaccines,* 12, 97.

Scheltema, N.M., Gentile, A., Lucion, F., Nokes, D.J., Munywoki, P.K., Madhi, S.A., et al., 2017. Global respiratory syncytial virus-associated mortality in young children (RSV GOLD): a retrospective case series. *The Lancet. Global health*, 5, e984–e991.

Scheltema, N.M., Nibbelke, E.E., Pouw, J., Blanken, M.O., Rovers, M.M., Naaktgeboren, C.A., et al., 2018. Respiratory syncytial virus prevention and asthma in healthy preterm infants: a randomised controlled trial. *The Lancet. Respiratory medicine*, 6, 257–264.

Schuh, S., Babl, F.E., Dalziel, S.R., Freedman, S.B., Macias, C.G., Stephens, D., et al., 2017. Practice Variation in Acute Bronchiolitis: A Pediatric Emergency Research Networks Study. *Pediatrics*, 140, e20170842.

Schuurhof, A., Bont, L., Siezen, C. L., Hodemaekers, H., van Houwelingen, H.C., Kimman, T.G., et al., 2010. Interleukin-9 polymorphism in infants with respiratory syncytial virus infection: an opposite effect in boys and girls. *Pediatric pulmonology*, 45, 608–613.

Seaborn, T., Simard, M., Provost, P.R., Piedboeuf, B., Tremblay, Y., 2010. Sex hormone metabolism in lung development and maturation. *Trends in endocrinology and metabolism*, 21, 729–738.

Sevendal, A.T.K., Hurley, S., Bartlett, A.W., Rawlinson, W., Walker, G.J., 2024. Systematic Review of the Efficacy and Safety of RSV-Specific Monoclonal Antibodies and Antivirals in Development. *Reviews in medical virology*, 34, e2576.

Shafik, C.F., Mohareb, E.W., Youssef, F.G., 2011. Comparison of direct fluorescence assay and real-time rt-PCR as diagnostics for respiratory syncytial virus in young children. *Journal of tropical medicine*, 2011, 781919.

Shan, S., Zhang, W., Gao, H., Huang, P.-Y., Du, Z., Bai, Y., et al., 2024. Global Seasonal Activities of Respiratory Syncytial Virus Before the Coronavirus Disease 2019 Pandemic: A Systematic Review. *Open forum infectious diseases*, 11, ofae238.

Shang, Z., Tan, S., Ma, D., 2021. Respiratory syncytial virus: from pathogenesis to potential therapeutic strategies. *International journal of biological sciences,* 17, 4073–4091.

Shanklin, A., Olson, T., Patel, A.K., Trujillo Rivera, E.A., Pollack, M.M., 2024. Respiratory Syncytial Virus and US Pediatric Intensive Care Utilization. *JAMA network open*, 7, e2440997.

Sheng, Y.J., Xu, S.S., Li, X.J., Liu, J.L., Wu, X.L., Xu, X.F., 2017. Low birth weight contributed to increased serum IL-6 levels in infantile respiratory syncytial virus infection. *BMC pediatrics*, 17, 205.

Shi, T., McAllister, D.A., O'Brien, K.L., Simoes, E.A.F., Madhi, S.A., Gessner, B.D., et al., 2017. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in young children in 2015: a systematic review and modelling study. *The Lancet,* 390, 946–958.

Shi, T., Vennard, S., Mahdy, S., Nair, H., RESCEU investigators, 2022. Risk Factors for Poor Outcome or Death in Young Children With Respiratory Syncytial Virus–Associated Acute Lower Respiratory Tract Infection: A Systematic Review and Meta-Analysis. *The Journal of infectious diseases,* 226, S10–S16.

Shiroshita, A., Gebretsadik, T., Wu, P., Kubilay, N.Z., Hartert, T.V., 2024. Association between age of respiratory syncytial virus infection hospitalization and childhood asthma: A systematic review. *PloS one*, 19, e0296685.

Sigurs, N., Gustafsson, P.M., Bjarnason, R., Lundberg, F., Schmidt, S., Sigurbergsson, F., et al., 2005. Severe respiratory syncytial virus bronchiolitis in infancy and asthma and allergy at age 13. *American journal of respiratory and critical care medicine*, 171, 137–141.

Silveyra, P., Fuentes, N., Rodriguez Bauza, D.E., 2021. Sex and Gender Differences in Lung Disease. *Advances in experimental medicine and biology*, 1304, 227–258.

Simpson, M.D., Kieke, B.A., Jr, Sundaram, M.E., McClure, D.L., Meece, J.K., Sifakis, F., et al., 2016. Incidence of Medically Attended Respiratory Syncytial Virus and Influenza Illnesses in Children 6-59 Months Old During Four Seasons. *Open forum infectious diseases*, *3*, ofw081.

Simões, E.A.F., 2003. Environmental and demographic risk factors for respiratory syncytial virus lower respiratory tract disease. *The Journal of pediatrics*, 143, 118–126.

Simões, E.A.F., Forleo-Neto, E., Geba, G.P., Kamal, M., Yang, F., Cicirello, H., et al., 2021. Suptavumab for the Prevention of Medically Attended Respiratory Syncytial Virus Infection in Preterm Infants. *Clinical infectious diseases*, 73, e4400–e4408.

Simões, E.A.F., Center, K.J., Tita, A.T.N., Swanson, K.A., Radley, D., Houghton, J., et al., 2022. Prefusion F Protein-Based Respiratory Syncytial Virus Immunization in Pregnancy. *The New England journal of medicine*, 386, 1615–1626.

Simões, E.A.F., Madhi, S.A., Muller, W.J., Atanasova, V., Bosheva, M., Cabañas, F., et al., 2023. Efficacy of nirsevimab against respiratory syncytial virus lower respiratory tract infections in preterm and term infants, and pharmacokinetic extrapolation to infants with congenital heart

disease and chronic lung disease: a pooled analysis of randomised controlled trials. *The Lancet. Child & adolescent health*, 7, 180–189.

Simões, E.A.F., Botteman, M., Chirikov, V., 2024. Epidemiology of Medically Attended Respiratory Syncytial Virus Lower Respiratory Tract Infection in Japanese Children, 2011-2017. *The Journal of infectious diseases*, 229, 1112–1122.

Simões, E.A.F., Pahud, B.A., Madhi, S.A., Kampmann, B., Shittu, E., Radley, D., et al., 2025. Efficacy, Safety, and Immunogenicity of the MATISSE (Maternal Immunization Study for Safety and Efficacy) Maternal Respiratory Syncytial Virus Prefusion F Protein Vaccine Trial. *Obstetrics and gynecology*, 145, 157–167.

Sivapalasingam, S., Caballero-Perez, D., Houghton, M., Yang, F., Davis, J., Gao, B., et al., 2015. Phase 1 Study Evaluating Safety, Tolerability, Pharmacokinetics and Immunogenicity of REGN2222 in Healthy Adults: A New Human Monoclonal RSV-F Antibody for RSV Prevention. *Open Forum Infectious Diseases*, 2, 912.

Sommer, C., 2011. Risk Factors for Severe Respiratory Syncytial Virus Lower Respiratory Tract Infection. *The open microbiology journal*, 5, 144–154.

Staadegaard, L., Caini, S., Wangchuk, S., Thapa, B., De Almeida, W.A.F., De Carvalho, F.C., et al., 2021. Defining the seasonality of respiratory syncytial virus around the world: National and subnational surveillance data from 12 countries. *Influenza and other respiratory viruses,* 15, 732–741.

Staadegaard, L., Dückers, M., Van Summeren, J., Van Gameren, R., Demont, C., Bangert, M., et al., 2024. Determining the timing of respiratory syncytial virus (RSV) epidemics: a systematic review, 2016 to 2021; method categorisation and identification of influencing factors. *Euro surveillance*, 29, 230024.

StatFin. Live births by sex, age of mother (5-year) and area, 1990-2024. Available at: https://pxdata.stat.fi/PXWeb/pxweb/fi/StatFin/StatFin__synt/statfin_synt_pxt_12dq.px. [Accessed 9 May 2025]

Stein, R.T., Zar, H.J., 2023. RSV through the COVID-19 pandemic: Burden, shifting epidemiology, and implications for the future. *Pediatric pulmonology*, 58, 1631–1639.

Stensballe, L.G., Devasundaram, J.K., Simoes, E.A.F., 2003. Respiratory syncytial virus epidemics: the ups and downs of a seasonal virus. *The Journal of infectious diseases*, 22, S21–S32.

Suh, M., Movva, N., Jiang, X., Bylsma, L.C., Reichert, H., Fryzek, J.P., et al., 2022. Respiratory Syncytial Virus Is the Leading Cause of United States Infant Hospitalizations, 2009-2019: A Study of the National (Nationwide) Inpatient Sample. *The Journal of infectious diseases*, 226, S154–S163.

Suryadevara, M., Domachowske, J.B., 2021. Epidemiology and Seasonality of Childhood Respiratory Syncytial Virus Infections in the Tropics. *Viruses,* 13, 696.

Suss, R.J., Simões, E.A.F., 2024. Respiratory Syncytial Virus Hospital-Based Burden of Disease in Children Younger Than 5 Years, 2015-2022. *JAMA network open*, 7, e247125.

Takashima, M.D., Grimwood, K., Sly, P.D., Lambert, S.B., Chappell, K.J., Watterson, D., et al., 2021. Epidemiology of respiratory syncytial virus in a community birth cohort of infants in the first 2 years of life. *European journal of pediatrics,* 180, 2125–2135.

Tan, C.D., El Ouasghiri, S., von Both, U., Carrol, E.D., Emonts, M., van der Flier, M., et al., 2022. Sex differences in febrile children with respiratory symptoms attending European emergency departments: An observational multicenter study. *PloS one*, 17, e0271934.

Tan, L., Coenjaerts, F.E.J., Houspie, L., Viveen, M.C., Van Bleek, G.M., Wiertz, E.J.H.J., et al., 2013. The Comparative Genomics of Human Respiratory Syncytial Virus Subgroups A and B: Genetic Variability and Molecular Evolutionary Dynamics. *Journal of virology*, 87, 8213–8226.

Tapiainen, T., Kujala, T., Renko, M., Koivunen, P., Kontiokari, T., Kristo, A., et al., 2014. Effect of antimicrobial treatment of acute otitis media on the daily disappearance of middle ear effusion: a placebo-controlled trial. *JAMA pediatrics*, 168, 635–641.

Tejada, S., Martinez-Reviejo, R., Karakoc, H.N., Peña-López, Y., Manuel, O., Rello, J., 2022. Ribavirin for Treatment of Subjects with Respiratory Syncytial Virus-Related Infection: A Systematic Review and Meta-Analysis. *Advances in therapy*, 39, 4037–4051.

Terletskaia-Ladwig, E., Enders, G., Schalasta, G., Enders, M., 2005. Defining the timing of respiratory syncytial virus (RSV) outbreaks: an epidemiological study. *BMC infectious diseases*, 5, 20.

The IMpact-RSV Study Group., 1998.Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. *Pediatrics*, *102*, 531–537.

Thomas, E., Mattila, J.-M., Lehtinen, P., Vuorinen, T., Waris, M., Heikkinen, T., 2021. Burden of Respiratory Syncytial Virus Infection During the First Year of Life. *The Journal of infectious diseases*, 223, 811–817.

Thorburn, K., 2009. Pre-existing disease is associated with a significantly higher risk of death in severe respiratory syncytial virus infection. *Archives of disease in childhood*, 94, 99–103.

Thwaites, R.S., Coates, M., Ito, K., Ghazaly, M., Feather, C., Abdulla, F., et al., 2018. Reduced Nasal Viral Load and IFN Responses in Infants with Respiratory Syncytial Virus Bronchiolitis and Respiratory Failure. *American journal of respiratory and critical care medicine*, 198, 1074–1084.

Tian, L., Pang, Z., Li, M., Lou, F., An, X., Zhu, S., et al., 2022. Molnupiravir and Its Antiviral Activity Against COVID-19. *Frontiers in immunology*, 13, 855496.

Toepfer, A.P., Amarin, J.Z., Spieker, A.J., Stewart, L.S., Staat, M.A., Schlaudecker, E.P., et al., 2024. Seasonality, Clinical Characteristics, and Outcomes of Respiratory Syncytial Virus Disease by Subtype Among Children Aged < 5 Years: New Vaccine Surveillance Network, United States, 2016–2020. *Clinical infectious diseases*, 78, 1352–1359.

Toivonen, L., Karppinen, S., Schuez-Havupalo, L., Teros-Jaakkola, T., Mertsola, J., Waris, M., et al., 2020. Respiratory syncytial virus infections in children 0-24 months of age in the community. *The Journal of infection*, 80, 69–75.

Towriss, C., Dafydd, C., Edwards, M., 2024. High-flow weaning strategies for infants with bronchiolitis: protocol for a pilot randomised controlled trial in the UK. *BMJ open*, 14, e087672.

Trusinska, D., Zin, S.T., Sandoval, E., Homaira, N., Shi, T., 2024. Risk Factors for Poor Outcomes in Children Hospitalized With Virus-associated Acute Lower Respiratory Infections: A Systematic Review and Meta-analysis. *The Pediatric infectious disease journal*, 43, 467-476.

Tähtinen, P.A., Laine, M.K., Huovinen, P., Jalava, J., Ruuskanen, O., Ruohola, A., 2011. A placebo-controlled trial of antimicrobial treatment for acute otitis media. *The New England journal of medicine*, 364, 116–126.

Ursin, R.L., Klein, S.L., 2021. Sex Differences in Respiratory Viral Pathogenesis and Treatments. *Annual review of virology*, 8, 393–414.

Utsunomiya, T., Hibino, A., Taniguchi, K., Nagai, T., Saito, N., Tanabe, I., et al., 2020. Factors Contributing to Symptom Duration and Viral Reduction in Outpatient Children With Respiratory Syncytial Virus Infection. *The Pediatric infectious disease journal*, 39, 678–683.

Valkonen, H., Waris, M., Ruohola, A., Ruuskanen, O., Heikkinen, T., 2009. Recurrent wheezing after respiratory syncytial virus or non-respiratory syncytial virus bronchiolitis in infancy: a 3-year follow-up. *Allergy*, 64, 1359–1365.

van Meel, E.R., Mensink-Bout, S.M., den Dekker, H.T., Ahluwalia, T.S., Annesi-Maesano, I., Arshad, S.H., et al., 2022. Early-life respiratory tract infections and the risk of school-age lower lung function and asthma: a meta-analysis of 150 000 European children. *The European respiratory journal*, 60, 2102395.

van Wijhe, M., Johannesen, C.K., Simonsen, L., Jørgensen, I.M., RESCEU Investigators, Fischer, T.K., 2022. A Retrospective Cohort Study on Infant Respiratory Tract Infection Hospitalizations and Recurrent Wheeze and Asthma Risk: Impact of Respiratory Syncytial Virus. *The Journal of infectious diseases*, 226, S55–S62.

Vartiainen, P., Jukarainen, S., Rhedin, S.A., Prinz, A., Hartonen, T., Vabalas, A., et al., 2023. Risk factors for severe respiratory syncytial virus infection during the first year of life: development and validation of a clinical prediction model. *The Lancet. Digital health*, 5, e821–e830.

Ventre, K., Randolph, A.G., 2007. Ribavirin for respiratory syncytial virus infection of the lower respiratory tract in infants and young children. *The Cochrane database of systematic reviews*, CD000181.

Verwey, C., Nunes, M.C., Dangor, Z., Madhi, S.A., 2020. Pulmonary function sequelae after respiratory syncytial virus lower respiratory tract infection in children: A systematic review. *Pediatric pulmonology*, 55, 1567–1583.

Vihikangas, T., Palmu, S., Koivisto, A.-M., Heikkilä, P., 2022. Changes in Bronchiolitis Incidence During the Last Two Decades in Tampere, Finland: A Retrospective Study. *The Pediatric infectious disease journal,* 41, 867–871.

von Linstow, M.L., Rudolfsen, J.H., Olsen, J., Skovdal, M., Staerke, N.B., 2024. Burden of disease and cost of illness of infants less than 6 months of age hospitalised with respiratory syncytial virus in Denmark - a 10-year national register-based study. *BMC infectious diseases*, *24*, 1098.

Vos, L.M., Teirlinck, A.C., Lozano, J.E., Vega, T., Donker, G.A., Hoepelman, A.I., et al., 2019. Use of the moving epidemic method (MEM) to assess national surveillance data for respiratory syncytial virus (RSV) in the Netherlands, 2005 to 2017. *Euro surveillance,* 24, 1800469.

Walsh, E.E., Wang, L., Falsey, A.R., Qiu, X., Corbett, A., Holden-Wiltse, J., et al., 2018. Virus-Specific Antibody, Viral Load, and Disease Severity in Respiratory Syncytial Virus Infection. *The Journal of infectious diseases*, 218, 208–217.

Walsh, E.E., Pérez Marc, G., Zareba, A.M., Falsey, A.R., Jiang, Q., Patton, M., et al., 2023. Efficacy and Safety of a Bivalent RSV Prefusion F Vaccine in Older Adults. *The New England journal of medicine*, 388, 1465–1477.

Wang, W., Luo, X., Ren, Z., Fu, X., Chen, Y., Wang, W., et al., 2025. Impact of COVID-19 pandemic measures on hospitalizations and epidemiological patterns of twelve respiratory pathogens in children with acute respiratory infections in southern China. *BMC infectious diseases*, 25, 103.

Wang, X., Li, Y., Nair, H., Campbell, H., RESCEU Investigators, 2022. Time-Varying Association Between Severe Respiratory Syncytial Virus Infections and Subsequent Severe Asthma and Wheeze and Influences of Age at the Infection. *The Journal of infectious diseases*, 226, S38–S44.

Wang, X., Li, Y., Vazquez Fernandez, L., Teirlinck, A.C., Lehtonen, T., van Wijhe, M., et al., 2022b. Respiratory Syncytial Virus-Associated Hospital Admissions and Bed Days in Children <5 Years of Age in 7 European Countries. *The Journal of infectious diseases*, 226, S22–S28.

Wang, X., Li, Y., Shi, T., Bont, L.J., Chu, H.Y., Zar, H.J., et al., 2024. Global disease burden of and risk factors for acute lower respiratory infections caused by respiratory syncytial virus in preterm infants and young children in 2019: a systematic review and meta-analysis of aggregated and individual participant data. *The Lancet*, 403, 1241–1253.

Waris, M., 1991. Pattern of Respiratory Syncytial Virus Epidemics in Finland: Two-Year Cycles with Alternating Prevalence of Groups A and B. *The Journal of infectious diseases*, 163, 464–469.

Welliver, R.C., Kaul, T.N., Putnam, T.I., Sun, M., Riddlesberger, K., Ogra, P.L., 1980. The antibody response to primary and secondary infection with respiratory syncytial virus: kinetics of class-specific responses. *The Journal of pediatrics*, 96, 808–813.

Welliver, R.C., Sr, Checchia, P.A., Bauman, J.H., Fernandes, A.W., Mahadevia, P.J., Hall, C.B., 2010. Fatality rates in published reports of RSV hospitalizations among high-risk and otherwise healthy children. *Current medical research and opinion*, 26, 2175–2181.

White, L.J., Waris, M., Cane, P.A., Nokes, D.J., Medley, G.F., 2005. The transmission dynamics of groups A and B human respiratory syncytial virus (hRSV) in England & Wales and Finland: seasonality and cross-protection. *Epidemiology and infection*, 133, 279–289.

Wildenbeest, J.G., Billard, M.-N., Zuurbier, R.P., Korsten, K., Langedijk, A.C., Van De Ven, P.M., et al., 2023. The burden of respiratory syncytial virus in healthy term-born infants in Europe: a prospective birth cohort study. *The Lancet. Respiratory medicine,* 11, 341–353.

Wilkins, D., Wählby Hamrén, U., Chang, Y., Clegg, L.E., Domachowske, J., Englund, J.A., et al., 2024. RSV Neutralizing Antibodies Following Nirsevimab and Palivizumab Dosing. *Pediatrics*, 154, e2024067174.

Willemsen, J.E., Borghans, J.A.M., Bont, L.J., Drylewicz, J., 2024. Disagreement FDA and EMA on RSV Maternal Vaccination: Possible Consequence for Global Mortality. *The Pediatric infectious disease journal*, 43, e1–e2.

Wilson, E., Goswami, J., Baqui, A.H., Doreski, P.A., Perez-Marc, G., Zaman, K., et al., 2023. Efficacy and Safety of an mRNA-Based RSV PreF Vaccine in Older Adults. *The New England journal of medicine*, *389*, 2233–2244.

Winterstein, A.G., Choi, Y., Meissner, HC., 2018. Association of Age With Risk of Hospitalization for Respiratory Syncytial Virus in Preterm Infants With Chronic Lung Disease. *JAMA pediatrics*, 172, 154–160.

Wishaupt, J.O., Ploeg, T.V., Smeets, L.C., Groot, R., Versteegh, F.G., Hartwig, N.G., 2017. Pitfalls in interpretation of CT-values of RT-PCR in children with acute respiratory tract infections. *Journal of clinical virology,* 90, 1–6.

Wittig, H.J., Glaser, J., 1959. The relationship between bronchiolitis and childhood asthma; a follow-up study of 100 cases of bronchiolitis. *The Journal of allergy*, 30, 19–23.

Wong, K., Robinson, J.L., Hawkes, M.T., 2021. Risk of Repeated Admissions for Respiratory Syncytial Virus in a Cohort of >10 000 Hospitalized Children. *Journal of the Pediatric Infectious Diseases Society*, 10, 352–358.

Wright, P.F., Gruber, W.C., Peters, M., Reed, G., Zhu, Y., Robinson, F., et al., 2002. Illness severity, viral shedding, and antibody responses in infants hospitalized with bronchiolitis caused by respiratory syncytial virus. *The Journal of infectious diseases*, 185, 1011–1018.

Wu, H., Pfarr, D.S., Johnson, S., Brewah, Y.A., Woods, R.M., Patel, N.K., et al., 2007. Development of motavizumab, an ultra-potent antibody for the prevention of respiratory syncytial virus infection in the upper and lower respiratory tract. *Journal of molecular biology*, 368, 652–665.

Xu, H., Aparicio, C., Wats, A., Araujo, B.L., Pitzer, V.E., Warren, J.L., et al., 2025. Estimated Effectiveness of Nirsevimab Against Respiratory Syncytial Virus. *JAMA network open*, 8, e250380.

Yan, X.L., Li, Y.N., Tang, Y.J., Xie, Z.P., Gao, H.C., Yang, X.M., et al., 2017. Clinical characteristics and viral load of respiratory syncytial virus and human metapneumovirus in children hospitaled for acute lower respiratory tract infection. *Journal of medical virology*, 89, 589–597.

Yildiz, M., Kara, M., Sutcu, M., Mese, S., Demircili, M.E., Sivrikoz, T.S., et al., 2020. Evaluation of respiratory syncytial virus IgG antibody dynamics in mother-infant pairs cohort. *European journal of clinical microbiology & infectious diseases,* 39, 1279–1286.

Yoon, J.J., Toots, M., Lee, S., Lee, M.E., Ludeke, B., Luczo, J.M., et al., 2018. Orally Efficacious Broad-Spectrum Ribonucleoside Analog Inhibitor of Influenza and Respiratory Syncytial Viruses. *Antimicrobial agents and chemotherapy*, 62, e00766-18.

Young, S., Arnott, J., O'Keeffe, P.T., Le Souef, P.N., Landau, L.I., 2000. The association between early life lung function and wheezing during the first 2 yrs of life. *The European respiratory journal*, 15, 151–157.

Yu, J., Liu, C., Xiao, Y., Xiang, Z., Zhou, H., Chen, L., et al., 2019. Respiratory Syncytial Virus Seasonality, Beijing, China, 2007-2015. *Emerging infectious diseases*, 25, 1127–1135.

Zachariasse, J.M., Borensztajn, D.M., Nieboer, D., Alves, C.F., Greber-Platzer, S., Keyzer-Dekker, C.M.G., et al., 2020. Sex-specific differences in children attending the emergency department: prospective observational study. *BMJ open*, 10, e035918.

Zar, H.J., Bont, L.J., Manzoni, P., Muñoz, F.M., Ramilo, O., Chen, P.Y., 2024a. Phase 3, Randomized, Controlled Trial Evaluating Safety, Efficacy, and Pharmacokinetics of Clesrovimab in Infants and Children at Increased Risk for Severe Respiratory Syncytial Virus Disease. Available at: https://bsac.org.uk/wp-content/uploads/2025/05/3.pdf. [Accessed 20 June 2025]

Zar, H.J., Cacho, F., Kootbodien, T., Mejias, A., Ortiz, J.R., Stein, R.T., et al., 2024b. Early-life respiratory syncytial virus disease and long-term respiratory health. *The Lancet. Respiratory medicine*, 12, 810–821.

Zar, H.J., Simoes, E., Madhi, S., Ramilo, O., Senders, S., Shepard, J.S., et al., 2025. 166. A Phase 2b/3 Study to Evaluate the Efficacy and Safety of an Investigational Respiratory Syncytial Virus (RSV) Antibody, Clesrovimab, in Healthy Preterm and Full-Term Infants. *Open Forum Infectious Diseases*, 12, ofae631.003.

Zhang, L., Mendoza-Sassi, R.A., Wainwright, C.E., Aregbesola, A., Klassen, T.P., 2023. Nebulised hypertonic saline solution for acute bronchiolitis in infants. *The Cochrane database of systematic reviews*, 4, CD006458.

Zhang, S., Akmar, L.Z., Bailey, F., Rath, B.A., Alchikh, M., Schweiger, B., et al., 2020. Cost of Respiratory Syncytial Virus-Associated Acute Lower Respiratory Infection Management in Young Children at the Regional and Global Level: A Systematic Review and Meta-Analysis. *The Journal of infectious diseases*, 222, S680–S687.

Zhang, XL., Zhang, X., Hua, W., Xie, ZD., Liu, HM., Zhang, HL., et al., 2024. Expert consensus on the diagnosis, treatment, and prevention of respiratory syncytial virus infections in children. *World journal of pediatrics*, 20, 11-25.

Zhao, S., Shang, Y., Yin, Y., Zou, Y., Xu, Y., Zhong, L., et al., 2024. Ziresovir in Hospitalized Infants with Respiratory Syncytial Virus Infection. *The New England journal of medicine*, 391, 1096–1107.

Zhou, L., Xiao, Q., Zhao, Y., Huang, A., Ren, L., Liu, E., 2015. The impact of viral dynamics on the clinical severity of infants with respiratory syncytial virus bronchiolitis. *Journal of medical virology*, 87, 1276–1284.

Zhu, Q., McLellan, J.S., Kallewaard, N.L., Ulbrandt, N.D., Palaszynski, S., Zhang, J., et al., 2017. A highly potent extended half-life antibody as a potential RSV vaccine surrogate for all infants. *Science translational medicine*, 9, eaaj1928.

Zlateva, K.T., Vijgen, L., Dekeersmaeker, N., Naranjo, C., Van Ranst, M., 2007. Subgroup Prevalence and Genotype Circulation Patterns of Human Respiratory Syncytial Virus in Belgium during Ten Successive Epidemic Seasons. *Journal of clinical microbiology*, 45, 3022–3030.

Zou, G., Cao, S., Gao, Z., Yie, J., Wu, J.Z., 2024. Current state and challenges in respiratory syncytial virus drug discovery and development. *Antiviral research*, 221, 105791.

List of Figures and Tables

Figures

Tables

TURUN
YLIOPISTO
UNIVERSITY
OF TURKU

Painosalama, Turku, Finland 2025

ISBN 978-952-02-0476-1 (PRINT)
ISBN 978-952-02-0477-8 (PDF)
ISSN 0355-9483 (Print)
ISSN 2343-3213 (Online)