FROM EVIDENCE TO IMPLEMENTATION:

The Added Value of Health Economics for RSV Immunisation Implementation in Low- and Middle-Income Countries



NEELE RAVE

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From Evidence to Implementation:
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Van bewijs naar implementatie:
De waarde van gezondheidseconomie voor de implementatie van RSV-immunisatie in lage- en middeninkomenslanden

(met een samenvatting in het Nederlands)

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“By believing passionately in something that still not exist,
we create it”

Franz Kafka

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1

General Introduction and Thesis Outline

Does generating health economic evidence bring us closer to closing the gap in RSV immunisation access in low- and middle-income countries?

Respiratory Syncytial Virus (RSV) is a leading cause of lower respiratory tract infections (LRTIs) in children under five years of age, responsible for an estimated 33 million infections, 3.6 million hospitalisations and more than 101 000 deaths annually, with the vast majority occurring in low-and middl-income countries (LMICs).[1] The high burden of disease, combined with the absence of effective treatment or widely available immunisation strategies until recently, has placed sustained pressure on clinical services and health budgets, particularly in settings with constrained health-care infrastructure.

Recent advances in RSV immunisation strategies mark a turning point in the prevention of severe RSV-associated disease in early infancy. The licensure of a maternal prefusion F (PreF) vaccine and the introduction of long-acting monoclonal antibody (mAb) nirsevimab have introduced safe and highly effective options to prevent RSV-associated LRTI in early infancy.[2, 3] As a result, RSV is increasingly recognised as a vaccine-preventable disease. While implementation and uptake in high-income settings is progressing rapidly, LMICs, where RSV morbidity and mortality is greatest, continue to face substantial barriers related to financing, delivery infrastructure and equitable access.[4, 5] Global initiatives, including Gavi's commitment to support the introduction of the maternal RSV vaccine in eligible countries, represent an important step towards reducing these disparities and advancing equity in RSV prevention.[6]

With the availability of effective intervention strategies, the focus of RSV research and policy is shifting from product development to questions of delivery and implementation. Understanding where, when and how to implement these interventions most effectively and equitable has become a central challenge. In this context, health economic evidence can provide critical insights into the costs, benefits, affordability and feasibility of different immunisation strategies, helping to guide policy decisions in resource-limited settings.

A Brief History

RSV was first isolated in 1956 from chimpanzees with respiratory tract infections who were being used in polio research studies in Maryland. The virus was initially named Chimpanzee Coryza Agent (CCA).[7] Shortly thereafter, in 1957, the same virus was identified in infants presenting with bronchiolitis and pneumonia by researchers from the Johns Hopkins University, who named the virus Respiratory Syncytial Virus due to its characteristic formation of syncytia (multinucleated giant cells) formed by fusion of infected host cells.[8] Since the 1960s, RSV was recognised as one of the leading causes of LRTIs in young children. Early epidemiological investigations documented its clear seasonal outbreaks and significant burden on paediatric health services, particularly in terms of hospitalisation and mortality.[9]

Over the subsequent decades, research efforts have deepened our understanding of virology, pathogenesis and complex interaction with the host immune system. This knowledge has been critical in guiding vaccine and therapeutic development, although progress has been hampered by challenges such as the failure of a formalin-inactivated RSV vaccine in the 1960s, which caused enhanced respiratory disease upon subsequent natural infection.[10] Despite this setback, ongoing efforts in RSV vaccine development have continued to advance the field towards safe and effective immunisation strategies.

Virology

RSV is a highly contagious enveloped virus belonging to the Pneumoviridae family. It possesses a single-stranded, negative-sense RNA genome encoding eleven proteins essential for viral replication, host cell entry and immune evasion. Among these, the glycoprotein (G) and fusion protein (F) mediate viral binding to host cells and membrane fusion, respectively, while the small hydrophobic (SH) protein may modulate the host immune response. The matrix (M) protein provides structural stability and nucleoprotein (N) encapsulates the RNA genome. Replication and transcription are facilitated by the phosphoprotein (P), large polymerase (L) and transcription regulatory proteins M2-1 and M2-2. These proteins enable efficient viral propagation within the respiratory tract.[11]

Transmission occurs predominantly via respiratory droplets from sneezing and coughing, as well as through direct contact with contaminated surfaces followed by touching eyes, nose, or mouth. The virus can survive on hard surfaces for several hours, facilitating indirect transmission. Post-infection immunity is partial and wanes over time, making reinfection common throughout life.[12]

Burden

RSV is a common cause of a wide range of acute respiratory tract infections across all age groups. In children under five years of age, RSV is the most common viral cause of bronchiolitis and a major contributor to paediatric hospitalisations worldwide.[13] Furthermore, there is increasing evidence that RSV infection early in life is linked to recurrent wheezing during preschool years and asthma exacerbations later in childhood.[14, 15] In addition to paediatric populations, older adults and immuno-compromised individuals are also at an increased risk of severe RSV disease and related complications (Figure 1).[16]

Infants

RSV primarily infects the lower respiratory tract, with infants and young children being the most susceptible population. By the age of two, nearly all children have been infected with RSV at least once. While most infections present with mild upper respiratory symptoms, such as rhinorrhoea, nasal congestion, coughing and sneezing, a significant proportion of cases, particularly among infants under six months, progresses to severe LRTI, including bronchiolitis and pneumonia, often requiring hospitalisation.[17] Risk factors for severe disease include prematurity and underlying comorbidities such as congenital heart disease or chronic lung conditions.[18] However, approximately 80% of hospitalised infants are healthy and born at term.[19]

The global childhood burden of RSV is distributed unequally and disproportionately affects LMICs. In 2022, RSV was estimated to have caused approximately 33 million acute lower respiratory infections (ALRI) episodes in children under five years of age, resulting in 3.6 million hospital admissions and around 101 000 deaths worldwide.[1] Notably, over 97% of RSV-related deaths occurred in LMICs, where limited access to health care and supportive medical interventions significantly increases the risk of severe outcomes. Beyond acute morbidity and mortality, RSV contributes to long-term respiratory complications, including recurrent wheezing and asthma, which further increases its public health burden.[1] The economic burden is equally significant, with global costs estimated at approximately €4.82 billion (USD 5.4 billion) in 2017 in young children.[20] RSV-related hospitalisation expenses constitute more than half of these costs, predominantly borne by LMICs. In addition to direct medical costs, RSV imposes substantial indirect costs through caregiver's absenteeism and loss of productivity. Due to limited surveillance and diagnostic capacities, particularly in resource-limited settings, the true burden of RSV is likely underestimated, underscoring the need for improved epidemiological monitoring.

Elderly

Although most individuals experience their first RSV infection before the age of two, the infection does not induce lasting immunity, leaving individuals susceptible for reinfection throughout life.[21] For decades RSV has been considered a disease predominantly affecting early childhood. However, with increasing testing, it has been recognised as an important cause of morbidity and mortality in older adults. In 2015 it was estimated that around 336 000 hospitalisations and 14 000 in-hospital deaths were attributed to RSV-associated acute respiratory infection (ARI) in adults aged ≥65 years globally. In high-income countries (HICs), about 1.5 million episodes of RSV-ARI in this age group occurred annually, with substantial hospitalisation rates.[22] There are limited data available from LMICs,[23] reflecting gaps in surveillance and diagnostic testing. The primary sources of RSV infection in older adults are frequently their grandchildren in the community and staff in nursing care homes.[24]

Seasonality

RSV infections exhibit distinct seasonal patterns that vary by geographical region and climate.[25] In temperate climates, RSV epidemics typically occur annually during the colder months, lasting two to five months, with peak incidence commonly observed during late autumn through winter. In subtropical and tropical regions, RSV seasonality is generally less sharply defined and often corresponds with the rainy season, although the duration and intensity of outbreaks may vary significantly by location.[25]

Notably, the COVID-19 pandemic has profoundly disrupted established RSV seasonal patterns worldwide.[26] The implementation of non-pharmaceutical interventions (NPIs), such as lockdowns, social distancing, mask mandates and travel restrictions, resulted in a temporary substantial decline in RSV circulation, particularly in high-income countries. Additionally, reduced domestic and international travel during the early stages of the pandemic contributed to altered transmission dynamics, leading to atypical RSV activity with delayed or diminished seasonal peaks in several regions.[27]

Treatment

Although several antiviral agents have been investigated, progress in therapeutics has remained limited, with only a single candidate (ziresovir) from China showing efficacy in a Phase III trial.[28, 29] However, this drug is awaiting a confirmatory trial before approval in China. As a result, management of severe RSV disease remains primarily supportive and typically involves nasal suctioning, fluid administration to maintain hydration and most critically, supplemental oxygen therapy to alleviate respiratory distress and hypoxaemia. In cases of respiratory failure, mechanical ventilation may be required for survival.[30] Consequently, the therapeutic landscape for RSV remains underdeveloped, further underscoring the importance of effective preventive strategies.

Immunisation

Given the lack of effective treatment options for RSV, recent advancements in vaccine and monoclonal antibody development offer promising options to reduce RSV burden globally. Several products at different stages of development are currently underway (Figure 1).[31]

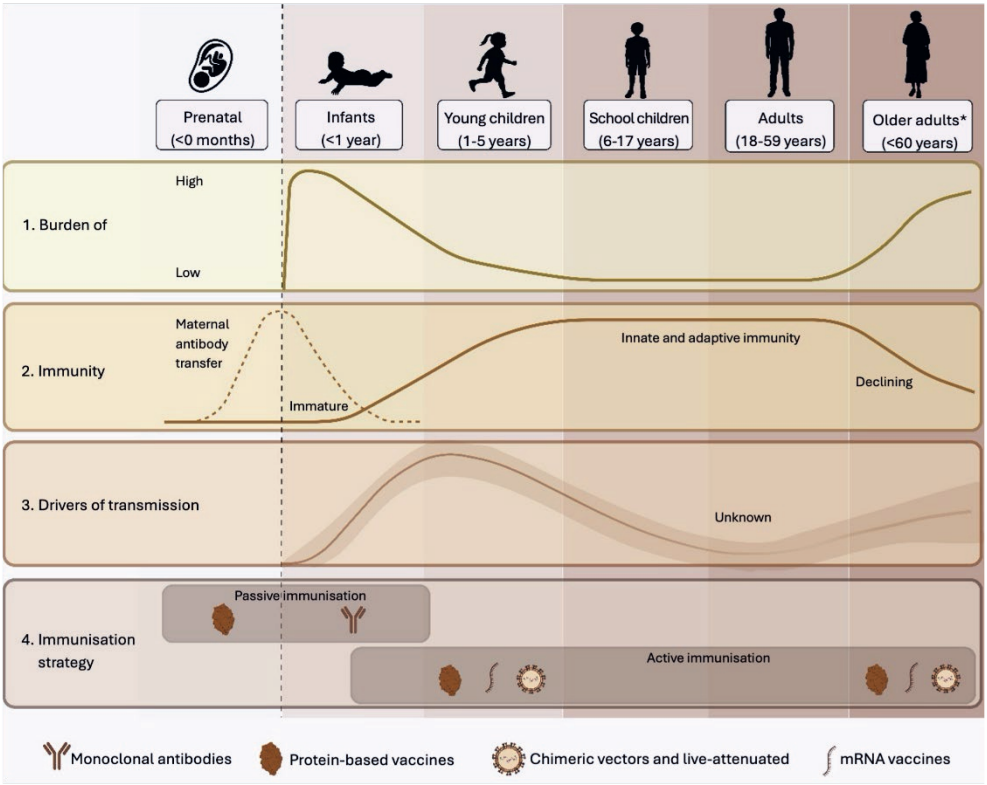

Figure 1. Conceptual overview of RSV prevention strategies per target population. Primary target populations for RSV immunisation include infants, young children and older or high-risk adults. Active immunisation is preferred for paediatric and adult populations, whereas passive immunisation is preferred for infants. *Including younger adults (18-60 years) with underlying comorbidity at high risk for severe RSV infection. **Despite young children being recognised as major contributors to RSV transmission, the precise role of specific age groups in transmission remains uncertain. Adapted from Terstappen et al., *Lancet Infect Dis* (2024).[32]

Infants

For many years and at the start of this PhD research in 2022, palivizumab was the only licensed option for the prevention of RSV infections in infants.[31] Palivizumab is a humanised monoclonal antibody that binds to the RSV F-protein and thereby inhibits viral entry into the host cells.[33] It requires monthly intramuscular administration during

the respiratory season and has been largely limited to high-risk infants in HICs due to its high cost.[34, 35]

Recent advances, however, have led to the development and licensure of new immunisation strategies that have the potential to substantially reduce the risk of severe RSV disease in early infancy.[36-39] The World Health Organization (WHO) recommends two primary products for global implementation: a PreF protein-based maternal vaccine (RSVpreF, Abrysvo®, Pfizer) and a long-acting monoclonal antibody (mAb) for infant prophylaxis (nirsevimab, Beyfortus®, AstraZeneca and Sanofi).[40] WHO recommends maternal vaccination during the third trimester of pregnancy to induce high levels of RSV-specific antibodies that are transferred across the placenta to the foetus, providing passive immunity after birth and protecting infants during the first six months of life, the period of greatest susceptibility for severe RSV-associated LRTI. In the Phase III MATISSE trial, maternal vaccination with RSVpreF was 70.0% effective (95% confidence interval [CI]: 50.6–82.5) in preventing severe medically attended RSV-associated ALRI within 180 days after birth.[3]

Nirsevimab, administered as a single intramuscular injection to infants before or at the start of their first RSV season or at birth if born during the RSV season, targets the RSV F-protein and provides direct passive protection.[41] Phase III data showed 76.8% efficacy (95% CI: 49.4–89.4) against hospitalisation for RSV-associated LRTI within 150 days of follow-up.[42] While maternal vaccination is given during pregnancy, long-acting mAb prophylaxis with nirsevimab is recommended for all infants entering their first RSV season, with some countries also extending its use to high-risk children entering their second season.[40]

In September 2025, the European Medicines Agency's Committee for Medical Products for Human Use (EMA) issued a positive opinion recommending approval of another long-acting mAb, clesrovimab (Enflonsia®, Merck),[43] for the prevention of RSV-associated disease in neonates and infants. Clinical data indicate 60.4% efficacy (95% CI: 44.1–71.9) against medically attended RSV infection within 150 days and 84.2% efficacy (95% CI: 66.6–92.6) against hospitalisation within the same period,[44] indicating another promising candidate for the prevention of RSV infection.

Toddlers & Pre-school children

For toddlers, several vaccine candidates are currently in early-phase development. While most are still in Phase I and Phase II, only one has reached Phase 3 evaluation. This live-attenuated intranasal vaccine administered in two doses eight weeks apart has demonstrated an acceptable safety profile, with adverse events comparable to those observed for other RSV immunisation strategies.[45]

However, the study was terminated in late 2025 after interim analyses indicated that the vaccine was unlikely to demonstrate adequate efficacy.[46]

Elderly

Although RSV poses a significant risk to infants and young children, its impact on older adults is also considerable. Several RSV vaccines for older adults have been approved by the EMA and are currently available. These vaccines demonstrate an efficacy ranging from 62–72% against acute respiratory infection and 82–94% against severe lower respiratory tract disease.[47-49]

Economic Evaluations of RSV Immunisation

With these recent advances, RSV is now considered a vaccine-preventable disease. At the start of this PhD research in 2022, immunisation strategies were still in clinical evaluation and little was known about their potential cost-effectiveness, particularly in LMICs, where the RSV burden is greatest. Evidence on the economic impact of RSV was fragmented and often based on HIC data. A recent systematic review identified only a small number of cost-of-illness and cost-effectiveness studies from LMICS, most focusing on palivizumab rather than newer and potentially more scalable interventions. These studies showed wide variations in both cost per RSV episodes (Figure 2) and cost-effectiveness estimates.[50] This underscores the urgent need for robust and context-specific economic evidence to inform national and global decision-making for RSV immunisation strategies.

Health economics is the study of the efficiency, effectiveness and value in the production, distribution and consumption of health, public health and health care services. Its scope extends beyond the assessment of individual interventions to include the financial burden of diseases, evaluation of health care delivery systems and guidance for policy decisions aimed at maximising health outcomes within constrained resources. A key aspect of health economics is economic evaluation, which compares alternative interventions to determine how limited resources can be allocated to achieve the greatest health benefit. Because resources devoted to one intervention cannot be used for another, understanding both costs and health effects is essential for informed decision-making.[51, 52]

Cost-of-Illness study

A first step in economic evaluations is often a cost-of-illness (COI) study, which quantifies the overall economic burden of a disease. The choice of perspective is fundamental as it determines which costs are included. A societal perspective includes all costs and the health effects, regardless of who incurs the costs and whom

the costs affect. In contrast, a health care perspective typically includes costs within the health system such as those covered by public parties and insurance schemes. Clearly defining the analytic perspective in advance is essential to ensure consistency and policy relevance.

COI studies generally measure direct medical costs (e.g., hospitalisations, medications), direct non-medical costs (e.g., transportation, caregiver time) and indirect costs such as productivity losses. In LMICs, these financial burdens can be particularly severe often stretching or exceeding the capacity of households and the health systems. Beyond quantifying the scale of the problem, COI studies also help to identify which populations are most affected, providing critical evidence to prioritise interventions and to design equitable and effective health policies.[51, 53]

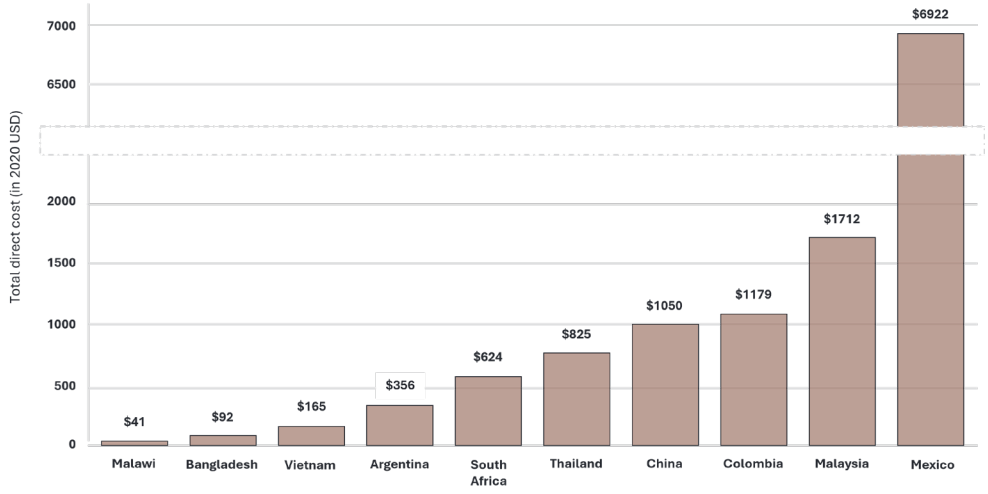

Figure 2. Estimated direct medical costs of inpatient RSV illness in LMICs, expressed in 2020 US dollars. Adapted and simplified from 'The RSV Roadshow'[54], based on Wittenauer et al., *BMC Medicine* (2023).[50]

Cost-effectiveness analysis

Building on COI studies, a cost-effectiveness analysis (CEA) assesses the value for money of interventions by comparing their costs and health benefits. An intervention is never cost-effective on its own, but always relative to an alternative intervention or standard care.[51] Results are typically expressed as incremental cost-effectiveness ratio (ICER):

$$\text{ICER} = \frac{\text{Cost}_1 - \text{Cost}_0}{\text{Effectiveness}_1 - \text{Effectiveness}_0}$$

where 1: new treatment and 0: comparator.

The interpretation of ICERs depends on the willingness-to-pay (WTP) threshold, representing the maximum amount a society or health system is willing to pay for an additional unit of health benefit, such as a quality-adjusted life years (QALY) gained or disability-adjusted life years (DALY) averted.[55-57] WTP threshold vary by context: HIC often use thresholds based on per-capita GDP or established policy benchmark, whereas LMICs may apply lower thresholds reflecting constrained budgets. The ICER may indicate whether an intervention is considered cost-effective. Interventions with an ICER below the threshold are generally regarded as good value for money, while those above the threshold may be deemed too costly relative to the health gains achieved.[52]

Health effects are commonly measured using QALYs or DALYs. A QALY combines quality and length of life, ranging from 0 (death) to 1 (perfect health). A DALY reflects the number of healthy life years lost due to illness, disability or premature death. Both metrics allow comparisons across different diseases and interventions, making them important tools for health policy and priority setting.[56, 57]

Decision modelling: the UNIVAC model

For evaluating immunisation strategies such as those against RSV, decision-analytic models are frequently used to project long-term costs and health outcomes. One such model is the UNIVAC model, a cohort-based universal vaccine impact and cost-effectiveness decision support model designed with a standardised Excel-based interface. The model incorporates age-specific disease burden, age- and dose-specific vaccine coverage and vaccine effectiveness to estimate the direct impact of vaccination on health outcomes. It simulates costs and effects over time, accounting for parameters such as waning immunity and local epidemiology. Typical outputs include avoided cases, hospitalisations, costs and health gains measured in QALYs or DALYs.[58, 59] UNIVAC provides a structured and transparent framework to support evidence-based policy decisions, particularly in settings with limited analytical capacity or resources.

OUTLINE OF THE THESIS

PART I of this thesis focuses on the burden of RSV in the Netherlands. During the COVID-19 pandemic and in the summer before the start of this PhD project, an unusual summer peak of RSV was observed in the Netherlands in 2021. Following this atypical epidemic, a distinct endemic pattern of RSV transmission was observed in 2022, after which RSV seasonality in the Netherlands gradually reverted to its typical winter pattern. **Chapter 2** examines in more detail the seasonality and clinical characteristics of children admitted with RSV infection before, during and after the COVID-19 pandemic. Following the introduction of nirsevimab in the Dutch National Immunisation Programme in September 2025, **Chapter 3** examines whether this strategy could be further optimised by taking into account the birth-month distribution of children hospitalised with RSV, as well as their age at admission.

Building on insights from the national RSV burden in the Netherlands, **PART II** shifts the focus to the impact of RSV infection in intensive care units (ICUs) in LMICs, where data on RSV disease is often limited. In collaboration with ten LMICs, children younger than 2 years admitted to ICUs with severe RSV infection were prospectively tested during two local RSV seasons. The findings of this study, The RSV GOLD III–ICU Network Study, are described in **Chapter 4**. This study not only marked the beginning of my PhD, as I was offered the opportunity to coordinate it over a period of one year, but it also served as a foundation for the selection of study sites for the RSV GOLD III–Health Economics Study, which formed the basis for later COI and CEA.

PART III presents the core of this PhD research, covering the entire research life cycle. This includes not only the initial stages of site selection and grant writing but also extends through the critical phases of data collection, data analysis and the writing process. Thanks to the great international collaboration, each phase contributed to the development of the findings and insights presented in the subsequent chapters. **Chapters 5–8** present the results of the COI studies and CEAs conducted in Mozambique and Nepal. These chapters provide valuable insights into the economic burden of RSV in both regions and examine the potential impact of newly available immunisation strategies in reducing this burden.

Finally, the thesis concludes with an overall discussion, in which findings from all parts of the work are summarised and placed within a broader scientific and policy context. Particular attention is given to how evidence on RSV burden and health economics can be translated into practical and context-specific immunisation strategies in LMICs, not only as a tool to inform policy decisions but also as a critical component in supporting equitable, evidence-based implementation of immunisation strategies.

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PART I

Clinical Characteristics and Seasonality of RSV in the Netherlands

2

Normalisation of Seasonality and Age Distribution of Paediatric RSV Infection Following the Pandemic Disruption in the Netherlands

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ABSTRACT

Background. The COVID-19 pandemic caused a global disruption in respiratory syncytial virus (RSV) epidemiology. However, data on RSV epidemiology in the post-pandemic period remain limited. We analysed shifts in RSV seasonality, age distribution, and disease severity among RSV-positive children in the Netherlands before, during, and after the pandemic.

Methods. Between May 2021 and April 2024, children under two years of age, admitted with RSV to 47 Dutch hospitals were included in a prospective surveillance study. We compared demographic and clinical characteristics of RSV-positive patients with data from the pre-COVID period (2018–2020), the COVID period and the post-COVID period (2022–2024).

Results. A total of 8,457 RSV-positive cases were included, with detailed data collected from 2,708 patients (13 hospitals). Following an unusual off-season shift and a period of endemic circulation, RSV seasonality has reverted to its typical pre-pandemic winter pattern. The median age at admission increased from 2.2 months (interquartile range [IQR]: 1.1–5.6) in the pre-pandemic period to 4.9 months (IQR 1.8–11.4, $P < .05$) during the summer outbreak (2021). This subsequently returned to pre-pandemic median age in the winter of 2023/2024 (2.7 months, IQR 1.3–8.0, not significant). We observed no differences in the prevalence of preterm birth or comorbidities among RSV-positive children before, during or after the COVID pandemic.

Conclusions. The COVID-19 pandemic profoundly disrupted RSV epidemiology. This prospective study demonstrates a rapid re-establishment of pre-pandemic patterns, including a return toward the typical age distribution during early childhood.

INTRODUCTION

Respiratory syncytial virus (RSV) is a major cause of lower respiratory tract infections in young children worldwide and one of the most common causes of hospitalisation in children under 5 years of age.[1] In the Netherlands, RSV epidemics normally occur during wintertime, peaking between November and January.[2] Each year, approximately 2% of all children under 5 years are hospitalised due to an RSV infection, with 0.1% requiring admission to a paediatric intensive care unit (PICU),[3] placing a significant burden on the Dutch health care system every winter.[4]

RSV, along with other respiratory viruses, was virtually absent during the winter of 2020/2021 most probably due to the implementation of nonpharmaceutical interventions (NPIs) to control the spread of COVID-19. Following the relaxation of NPIs, diverse patterns of resurgent RSV epidemics emerged across different countries[5]. Countries such as the Netherlands, Spain, and the United Kingdom, observed an interseasonal RSV resurgence during the summer of 2021.[6–8] In contrast, Finland reported no RSV cases until late 2021,[9] while France experienced even a second, distinct period of high RSV activity in the same year.[10] Subsequently, RSV patterns appeared to normalise in European countries, e.g., Bulgaria and England.[11, 12]

Several studies have evaluated the impact of COVID-19 on clinical characteristics and age distribution of RSV-related hospitalisations. While the incidence of RSV-related hospitalisations increased during and after the pandemic,[13,14] findings on age distribution and severity remain inconsistent. Some high-income countries reported a higher proportion of RSV-hospitalisations in children aged 12–24 months during the pandemic[15] with preliminary analysis from the Netherlands showing a similar trend.[6] In contrast, a German study observed an atypical age distribution in children under five, with a notably higher infection rate among 2- to 4-year-old during the 2021 season compared to pre-pandemic seasons.[14] However, studies from Finland,[9] Scotland and Spain found no significant age differences during the same period.[16] Regarding clinical characteristics, a Canadian study reported an increase in intensive care unit (ICU) admissions only among infants under 6 months, with no significant changes in length of stay (LOS) or the need for mechanical ventilation.[17] Conversely, Germany, the United States and Italy reported higher mechanical ventilation, prolonged LOS, and increased ICU admissions in children under 12 months during and post-COVID.[18, 19] A study from Turkey further reported increased mechanical ventilation, non-invasive ventilation, and bronchodilator therapy post-pandemic.[20]

Monitoring RSV circulation patterns as well as clinical characteristics of RSV-positive children is critical for hospital bed capacity planning during RSV peaks and optimising

intervention strategies. This prospective study aimed to reveal the impact of the pandemic on seasonality, as well as demographic and clinical characteristics, of RSV infection during early childhood in the Netherlands.

METHODS

Study Design

A brief report describing preliminary results from this surveillance initiative, including a concise overview of the methodology was published previously.[6] In the present study, we provide a comprehensive analysis of the complete dataset covering the entire study period (2018–2024), with a particular focus on the post-pandemic seasons. Furthermore, we present a more detailed methodology to support our analysis. From early May 2021 (week 18), during the unseasonal RSV peak in the Netherlands, through the end of the winter season 2023/2024 (week 18), passive surveillance was conducted at 47 Dutch hospitals, representing approximately 70% of health care provision in the Netherlands. These hospitals reported weekly data on the number of bronchiolitis-associated hospital admissions in children under 2 years of age. Cases were enrolled based on the clinical diagnosis of bronchiolitis made by the treating physician. Other acute respiratory infections (ARI) diagnoses, including pneumonia and recurrent wheezing were not included in the surveillance. Additionally, they provided the number of children tested for RSV and the corresponding RSV-positive cases. Data were shared either via Excel or through the Castor Electronic Data Capture (EDC) system.[21] Weekly data were shared with the National Institute for Public Health and the Environment (RIVM) and made publicly available on their website (https://www.rivm.nl/rs-virus/stand-van-zaken-rs-virus), providing real-time insight into RSV hospitalisation rates. The finalised surveillance data were subsequently published in the RIVM annual report: Annual reporting on surveillance of acute respiratory infections in the Netherlands, 2023/2024—RSV.[22] Additionally, as part of active surveillance, from the winter season 2018/2019 to 2023/2024, demographic and clinical data were collected from children under 2 years of age, hospitalised with RSV-positive acute respiratory infections in 13 hospitals. In these centres, RSV testing was routinely performed as part of standard care. Patients were either prospectively included by physicians or retrospectively identified using diagnosis treatment combination (DBC) codes and virology records, including only those with laboratory-confirmed RSV infection. Medical records were retrospectively reviewed, and available data were entered into the Castor.[21] Demographic data included age, sex, and household information. Clinical data comprised the date of admission, duration of stay on the regular ward or ICU, use of oxygen therapy, and mechanical ventilation, presence of co-infections and comorbidities, as well as palivizumab immunisation status.

The primary study outcome was the number of RSV-related hospital admissions in Dutch hospitals between May 2021 and April 2024. The secondary study outcomes were demographic and clinical characteristics of children being admitted to the hospital with RSV-positive acute respiratory infections.

Ethics

The Medical Research Ethics Committee of Utrecht University Medical Centre waived ethical approval for this study. Due to the nature of the study, no written informed consent was required for the primary outcome, as only admission numbers were collected. For the secondary outcome, informed consent was required and therefore obtained following local ethical guidelines. Eleven of the hospitals implemented an opt-out procedure. At two hospitals (University Medical Centre Groningen and Radboud University Medical Centre Nijmegen), informed consent was obtained through an opt-in procedure.

Statistical Analysis

Data of enrolled children were summarised using descriptive analysis. Categorical variables such as gender, prematurity, comorbidities and respiratory support were presented as absolute frequencies (n) and percentages (%) with respective P values, calculated using the test indicated below. Continuous variables such as age and LOS were presented as individual values, median with interquartile ranges (IQR) along with corresponding P values. Although we conceptually distinguished three periods (before, during and after the COVID-19 pandemic), we defined five groups according to the date of admission: (1) Pre-COVID (2018/2019 and 2019/2020 winter season (October–April); (2) COVID summer peak (May–August 2021); (3) Endemic Phase (September 2021–August 2022; (4) Post-COVID 1 (September 2022–August 2023): and (5) Post-COVID 2 (September 2023–April 2024). We compared various parameters among the five groups. First, we performed an overall statistical test: for categorical variables, we used a chi-square test. If the chi-square test indicated significant overall differences, we performed pairwise chi-square tests for each group combination. For continuous variables, we first assessed the distribution of each variable. As all continuous variables were non-normally distributed, we used the Kruskal–Wallis test to test for any differences across the five groups. When significant differences were found, we conducted pairwise comparisons with a Bonferroni correction. Statistical analyses were performed in IBM SPSS Statistics (Version 30.0.0, IBM Corp., Armonk, NY, USA).

RESULTS

The distribution of RSV-positive children varied markedly across the different groups (Figure 1). Between 3 May 2021, and 30 April 2024, a total of 8457 RSV-positive cases were reported at 47 participating hospitals (Figure 1A). In pre-pandemic seasons (2018/2019 and 2019/2020), RSV followed a typical winter pattern with peaks occurring between weeks 48 and 52 (Figure 1B). In contrast, an off-season RSV outbreak was observed during the summer of 2021, with a distinct peak between weeks 28 and 32. This was followed by year-round (endemic) circulation in 2022. RSV activity then resumed a winter epidemic pattern: In the 2023/2024 season, RSV activity peaked in November, approximately 4–6 weeks earlier than the peaks observed in late December/January during the 2022/2023 season and pre-pandemic seasons (Figure 1A and B).

Clinical characteristics were available from a total of 2708 RSV-positive paediatric patients (Table 1). The median age varied among the different study groups (Figure 2). We found a large increase in age at admission after the long pandemic-related interruption in RSV circulation, with the median age rising from 2.2 months in the pre-pandemic period to 4.9 months during the summer outbreak (2021). This subsequently normalised within 2 years, returning to 2.7 months in the winter of 2023/2024. In the post-pandemic seasons, we observed notable shifts in clinical severity indicators. The proportion of hospitalised RSV-positive children requiring non-invasive respiratory support decreased significantly during the summer peak (75% in the summer of 2021), which occurred alongside a shift toward older age groups (Figure 2). This was followed by an increase in the first post-COVID season to 80.3%, returning to pre-COVID levels (84.6%). ICU admissions, which had dropped to 14.4% during the 2021 summer outbreak, partially rebounded in the post-pandemic winters (23.6% in 2022/2023 and 21.6% in 2023/2024), although they remained below the pre-pandemic rate of 37.2%. Median hospital LOS decreased from 7 to 4 days during the summer outbreak (2021) and increased to 5 days in the subsequent seasons. In contrast, there were no significant differences in the proportion of preterm infants, palivizumab immunisation status, or prevalence of comorbidities across the five groups (all $P > 0.1$). When comparing ICU admissions only, a statistically significant difference was observed among children aged 12–23 months between the endemic and post-COVID seasons compared with the summer 2021, whereas no significant differences were found in other age groups. Also, no statistically significant differences found in comorbidities, need for mechanical ventilation or LOS in the ICU between the study groups (table 2). During the COVID-19 pandemic, routine testing was performed at all participating hospitals. However, in the post-COVID period, testing protocols were adjusted in some centres, where RSV testing was conducted only when clinically indicated. A similar

pattern was observed before the COVID-19 pandemic, when RSV testing was primarily performed in young and severely ill children.

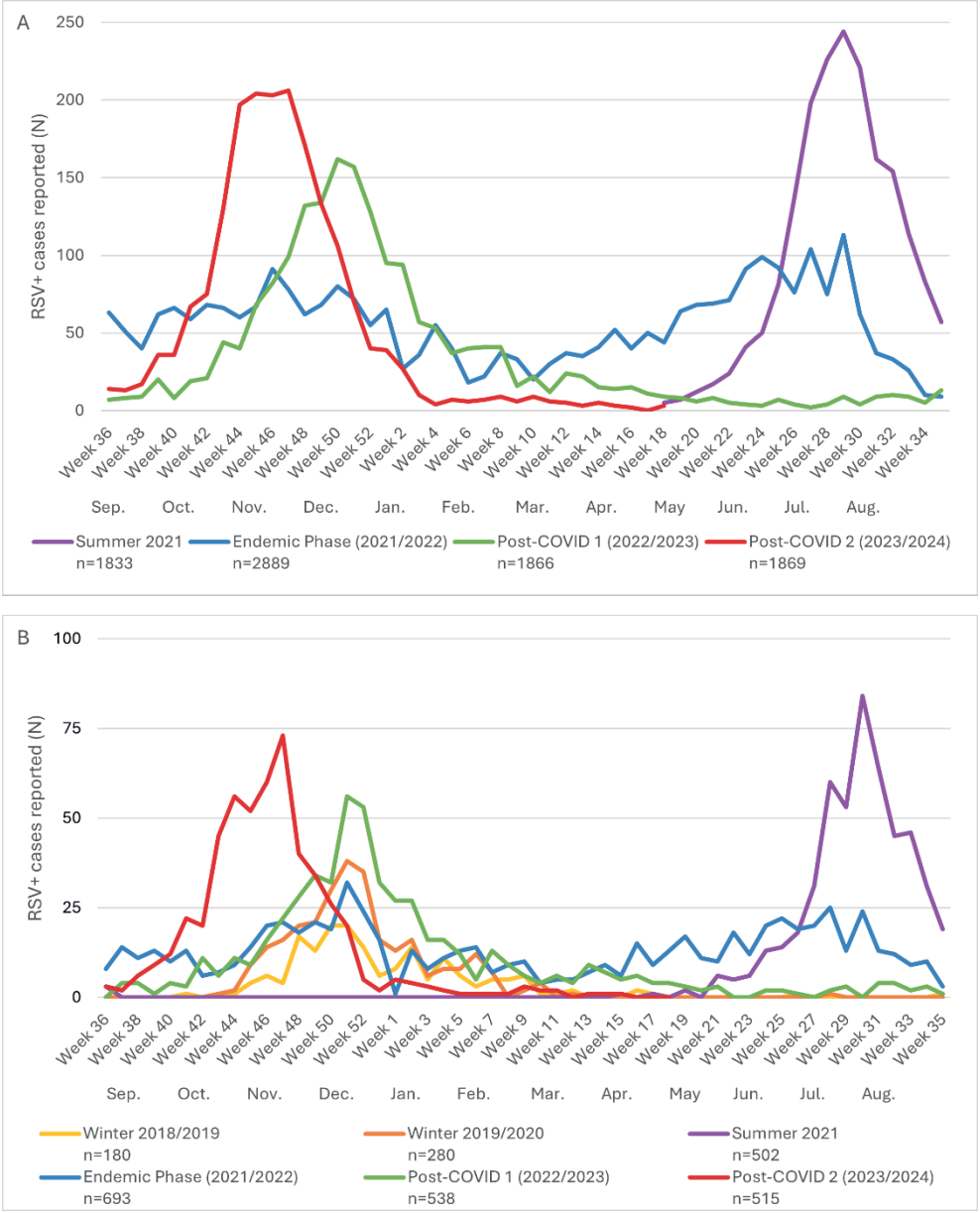

Figure 1. Weekly number of RSV-positive cases in children under 2 years of age across different epidemic seasons in the Netherlands from May 2021 to April 2024. (A) Comparison of RSV seasonality between pandemic and post-pandemic seasons, based on data from 47 hospitals (B) RSV seasonality patterns before, during, and after the COVID-19 pandemic, based on data from 13 hospitals.

Table 1. Characteristics of Children Admitted to 13 Hospitals With a Confirmed RSV Infection.

	Pre-COVID-19 (*n*=460)	Summer 2021 (*n* = 502)	Endemic Phase (*n*= 693)	Post-COVID-19 I (*n* = 538)	Post-COVID-19 II (*n* = 515)	Total (*n* = 2,708)	*P*-value[a]
Age, months (median, IQR)	2.17 (1.12–5.59)	4.92[h] (1.81–11.37)	4.14[h] (1.71-8.31)	3.61[h,] (1.48–7.36)[i]	2.69[i,j] (1.25–7.99)	3.42 (1.45–8.02)	<.001
Age categories, *n* (%)							
<3 m	271 (58.9)	189 (37.6)[h]	285 (41.1)[h]	242 (45.0)[h,i]	267 (51.8)[h,i,j,k]	1254 (46.3)	<.001
3–5 m	88 (19.1)	97 (19.3)	148 (21.4)	116 (21.6)	80 (15.5)	529 (19.5)	.085
6–11 m	59 (12.8)	99 (19.7)[h]	160 (23.1)[h]	127 (23.6)[h]	93 (18.1)[h,j,k]	538 (19.9)	<.001
12–23 m	42 (9.1)	117 (23.3)[h]	100 (14.4)[h,i]	53 (9.9)[i,j]	75 (14.6)[h,i,k]	387 (14.3)	<.001
Sex, *n* (%)							
Male	271 (55.9)	277 (55.2)	388 (56.0)	301 (55.9)	280 (54.4)	1517 (56.0)	.685
Preterm (GA < 37 wks), *n* (%)	71 (18.3)[c]	60 (15.3)[d]	83 (14.8)[e]	832 (20.0)[f]	77 (18.6)[g]	373 (17.2)	.179
Palivizumab immunisation status, n (%)	13 (2.9)	5 (1.0)	13 (1.9)	8 (1.5)	6 (1.2)	45 (1.7)	.238
Any comorbidity, *n* (%)[b]	51 (11.1)	38 (7.6)	75 (10.9)	67 (12.5)	54 (10.6)	285 (10.6)	.134
Cardiac	16 (3.5)	15 (3.0)	25 (3.6)	30 (5.6)	18 (3.5)	104 (3.8)	.214
Genetic/metabolic syndrome	27 (5.9)	21 (4.2)	30 (4.3)	31 (5.8)	22 (4.3)	131 (4.8)	.513
Neuromuscular	6 (1.3)	6 (1.2)	8 (1.2)	9 (1.7)	8 (1.6)	37 (1.4)	.930
Pulmonary	14 (3.0)	7 (1.4)	25 (3.6)	19 (3.5)	15 (2.9)	80 (3.0)	.204
Other	6 (1.3)	6 (1.2)	18 (2.6)	8 (1.5)	9 (1.7)	47 (1.7)	.334
Respiratory support, *n* (%)							
Noninvasive support	389 (84.6)	376 (74.9)[h]	527 (76.0)[h]	432 (80.3)[i]	411 (79.8)	2135 (78.8)	.001
Admission to IC, *n* (%)	171 (37.2)	72 (14.4)[h]	137 (19.8)[h,i]	127 (23.6)[h,i]	111 (21.6)[h,i]	618 (22.8)	<.001

Table 1. Continued.

	Pre-COVID-19 (*n*=460)	Summer 2021 (*n* = 502)	Endemic Phase (*n*= 693)	Post-COVID-19 I (*n* = 538)	Post-COVID-19 II (*n* = 515)	Total (*n* = 2,708)	*P*-value[a]
IC LOS, median (IQR)	7 (4–11)	5.5 (4–8)	6 (4–9)	6 (4–9)	7 (4–10)	6 (4–9)	.182
Hospital LOS, median (IQR)	7 (4–13)	4 (2–7)[h]	5 (3–8)[h]	5 (3–9)[h,i]	5 (3–8)[h,i]	5 (3–9)	<.001

Abbreviations: IQR, interquartile range; GA, gestational age; ICU, intensive care unit; LOS, length of stay.
[a] The overall P-value was calculated using the Chi-square test for categorical variables and Kruskal–Wallis for continuous, nonnormally distributed variables.
[b] The subcategories of comorbidities do not sum up, as individuals may have had multiple comorbidities simultaneously.
[c] 389/460.
[d] 393/502.
[e] 559/693.
[f] 410/583.
[g] 415/515. Fractions indicate cases with known prematurity status over total cases per group.
[h] Significantly different from pre-COVID phase.
[i] Significantly different from summer 2021.
[j] Significantly different from endemic phase.
[k] Significantly different from post-COVID I phase.

Table 2. Characteristics of Children Admitted to the ICU at 13 Hospitals With Confirmed RSV Infection.

	Pre-COVID-19 (*n*=171)	Summer 2021 (*n* = 72)	Endemic Phase (*n*= 137)	Post-COVID-19 I (*n* = 127)	Post-COVID-19 II (*n* = 111)	Total (*n* = 618)	*P*-value[a]
Age, months (median, IQR)	1.48 (0.91–3.04)	1.87 (1.20–4.09)	1.81 (0.76–3.94)	1.87 (1.02–4.22)	1.45 (0.79–2.35)	1.58 (0.92–3.32)	.137
Age categories, *n* (%)							
<3 m	127 (74.3)	49 (68.1)	95 (69.3)	87 (68.5)	89 (80.2)	447 (72.3)	.204
3–5 m	19 (11.1)	10 (13.9)	20 (14.6)	18 (14.2)	9 (8.1)	76 (12.2)	.511
6–11 m	12 (7.0)	2 (2.8)	17 (12.4)	16 (12.6)	9 (8.1)	56 (9.1)	.084
12–23 m	13 (7.6)	11 (15.3)	5 (3.6)[i]	6 (4.7)[i]	4 (3.6)[i]	39 (6.3)	.008
Sex, *n* (%)							
Male	106 (62.0)	41 (56.9)	84 (61.3)	69 (54.3)	63 (56.8)	363 (56.8)	.660
Preterm (GA < 37 wks), *n* (%)	33 (22.0)[c]	20 (31.3)[d]	23 (18.9)[e]	27 (25.2)[f]	24 (25.5)[g]	127 (23.6)	.385
Palivizumab immunisation status, n (%)	7 (4.1)	3 (4.3)	2 (1.5)	1 (0.8)	1 (0.9)	14 (2.3)	.247
Any comorbidity, *n* (%)[b]	22 (12.9)	11 (15.5)	26 (19.4)	22 (17.5.9)	18 (16.5)	99 (16.2)	.628
Cardiac	8 (4.7)	5 (6.9)	10 (7.3)	12 (9.4)	10 (9.0)	45 (7.3)	.541
Genetic/metabolic syndrome	11 (6.4)	8 (11.1)	15 (10.9)	8 (6.3)	5 (4.5)	47 (7.6)	.231
Neuromuscular	3 (1.8)	2 (2.8)	2 (1.5)	3 (2.4)	4 (3.6)	14 (2.3)	.810
Pulmonary	8 (4.7)	4 (5.6)	7 (5.1)	5 (3.9)	6 (5.4)	30 (4.9)	.982
Other	3 (1.8)	1 (1.4)	3 (2.2)	5 (3.9)	3 (2.7)	15 (2.4)	.746
Respiratory support, *n* (%)							
Noninvasive support	169 (98.8)	72 (100.0)	136 (99.3)	123 (96.9)	111 (100.0)	611 (98.9)	.141
Mechanical ventilation	116 (67.8)	43 (59.7)	83 (60.6)	82 (64.6)	72 (64.9)	396 (64.1)	.660

Table 2. Continued.

	Pre-COVID-19 (*n*=171)	Summer 2021 (*n* = 72)	Endemic Phase (*n*= 137)	Post-COVID-19 I (*n* = 127)	Post-COVID-19 II (*n* = 111)	Total (*n* = 618)	*P*-value[a]
IC LOS, median (IQR)	7 (4–11)	5.5 (4–8)	6 (4–9)	6 (4–9)	7 (4–10)	6 (4–9)	.182
Hospital LOS, median (IQR)	15 (10.5–23.5)	12 (8–18)[h]	12 (9–18)[h]	14 (10–22)	14 (10–20)	14 (10–20)	.003

Abbreviations: ICU, intensive care unit; IQR, interquartile range; GA, gestational age; LOS, length of stay.
[a] The overall P-value was calculated using the Chi-square test for categorical variables and Kruskal–Wallis for continuous, non-normally distributed variables.
[b] The subcategories of comorbidities do not sum up, as individuals may have had multiple comorbidities simultaneously.
[c] 150/171.
[d] 64/72.
[e] 122/137.
[f] 107/127.
[g] 94/111. Fractions indicate cases with known prematurity status over total cases per group.
[h] Significantly different from pre-COVID phase.
[i] Significantly different from Summer 2021. However, after applying Bonferroni correction for multiple comparisons, these differences are no longer statistically significant.

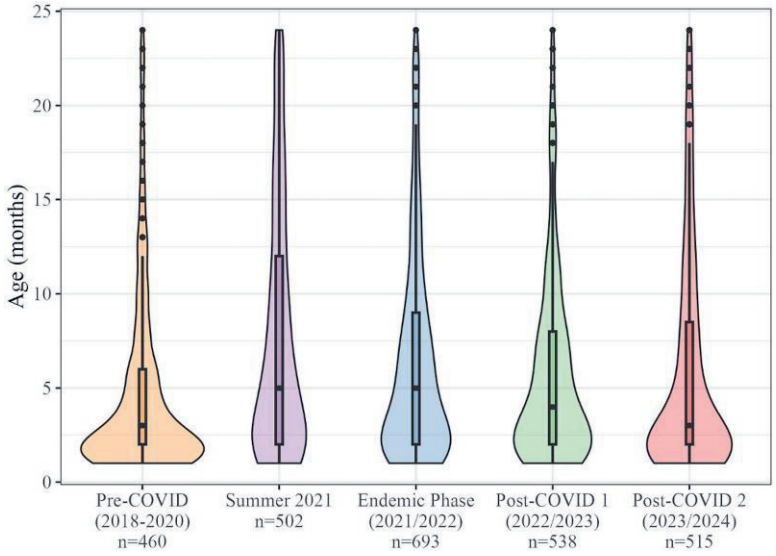

Figure 2. Age distribution of RSV-positive children under 2 years of age admitted t the hospital per group from October 2018 until April 2024. The x axis represents distinct time period before, during, and after the COVID-19 pandemic. The width of each violin shape at each age level (in months) reflects the relative frequency of RSV-positive cases at that age. The boxplots within each violin display the median age, the interquartile range, and outliers of RSV-positive cases for each time period.

DISCUSSION

The COVID-19 pandemic disrupted the seasonal pattern of RSV, initially leading to a decreased incidence of RSV-related hospital admissions in the Netherlands during the winter of 2020/2021, followed by a resurgence of cases in children under 2 years of age admitted during the summer of 2021. After the endemic phase in 2022, characterised by continuous transmission,[6] RSV seasonality in the Netherlands gradually returned to the typical pre-pandemic winter pattern. While both post-COVID seasons followed this general trend, the 2023/ 2024 season peaked earlier (November) compared with the 2022/2023 and pre-pandemic seasons, indicating a not yet complete return to pre-pandemic timing. This observation suggests that behavioural and social factors continued to influence RSV transmission dynamics beyond the initial post-pandemic year. Our study demonstrated that, although the seasonal timing of RSV activity during the first post-COVID season resembled pre-pandemic patterns, the clinical characteristics of hospitalised children appeared distinct. In contrast, during the second post-COVID season, clinical characteristics closely resembled pre-pandemic patterns. However, differences in testing practices, enrolment criteria and case definitions across study periods may have influenced these observations and

conclusions on disease severity comparisons should therefore be interpreted with caution. These evolving patterns likely reflect indirect effects of NPIs, shifts in fertility rate and month of delivery and reduced day-care attendance during and shortly after the pandemic. Similar findings have been described in other European countries, although the pace of normalisation varied across settings, possibly reflecting differences in immunity debt, timing of NPI relaxation and population behaviour.[23]

Post-COVID, we observed relatively more ICU admissions, longer hospital stays and more frequent need for non-invasive ventilation compared to those admitted during the COVID-19 pandemic (summer 2021 and endemic phase). Older median age at infection during COVID-19 may have influenced immune response, as older infants tend to experience less severe disease due to greater immune maturation, possibly explaining some of the observed variation in severity indicators.[24] These patterns are consistent with studies from Canada, the United States and Italy, although reported changes in severity vary by country and population.[17–19] SARS-CoV-2 was detected in only a small proportion of hospitalised RSV cases in our cohort, consistent with reports from other European studies showing that RSV/SARS-CoV-2 coinfections were rare and not associated with increased clinical severity.

When examining the higher ICU admission rates pre-COVID, it is important to note that RSV testing before 2020 was more often reserved for severe and younger cases, likely resulting in an overrepresentation of severe RSV infections in pre-pandemic data.

Beyond viral and clinical aspects, our findings highlight the influence of socialisation on RSV spread and seasonality. The unusual summer epidemic in 2021 coincided with the relaxation of NPIs and resumption of social interaction among infants, underscoring the importance of social contact patterns in shaping RSV transmission. This further supports the notion that RSV epidemiology is determined not only by viral characteristics but also by community-level behavioural and demographic changes.

The observed return of RSV seasonality and age distribution to near pre-pandemic patterns after 2 years suggests that RSV dynamics are resilient and tend to restabilise once NPIs are lifted. Similar trends were observed for other common paediatric respiratory viruses, such as influenza and human metapneumovirus (hMPV), whose seasonal circulation was initially disrupted during the COVID-19 pandemic but subsequently returned to pre-pandemic seasonality in the Netherlands.[23,25] In contrast, rhinovirus circulation persisted throughout the pandemic, reflecting its different transmission pathways. These observations indicate that pandemic-related disruptions in viral circulation are transient and underline the need for ongoing, adaptive surveillance to capture evolving risk patterns and to guide preventive

strategies such as the timing of immunisation strategies or daycare attendance recommendations for high-risk infants.

As shown in our study, severe RSV infection predominantly affected children under three months of age. At the time of conducting this study, RSV prevention in the Netherlands relied on the monoclonal antibody palivizumab, which is only administered to high-risk children under 2 years only.[26] Preterm infants in our study comprised approximately 17% of all children in the study cohort, but most (79%) did not meet the Dutch criteria for palivizumab administration. Recently, two intervention strategies have been approved for market use: the maternal vaccine Abrysvo and the long-acting monoclonal antibody nirsevimab, both offering longer protection against RSV with a single injection.[27, 28] These strategies have already been successfully introduced in several European countries.[29] The Dutch Health Council has recommended nirsevimab for all infants during their first winter season starting in 2025 to enhance RSV prevention. This recommendation has been adopted by the Ministry of Health and implemented from September 2025 onwards. Given that RSV causes severe disease in children under 2 years of age, as evidenced by its high representation among ICU admission in this current study, expanding RSV vaccination to include catch-up campaigns for older children entering their second RSV season should be considered.

A major strength of this study is the inclusion of data from multiple hospitals across the Netherlands, covering both the pre- and post-COVID-19 periods. However, several limitations should be acknowledged. Differences in testing and enrolment protocols among hospitals and across study periods likely introduced selection bias. In addition, the study's combined prospective and retrospective design may have resulted in missing or incomplete data capture, especially for brief admissions or inter-hospital transfers. Moreover, we lacked data on population-level denominators, such as total numbers of births or daycare attendance rates, which limits our ability to fully adjust for demographic and behavioural shifts following the pandemic. Despite these limitations, the consistency of trends across multiple indicators (e.g., age, ICU admissions, length of stay) support our main conclusion that RSV epidemiology in young children is gradually reestablishing pre-pandemic characteristics, even though under the continuing influence of changing social dynamics and public health practices.

CONCLUSION

Our study provides a comprehensive estimate of the impact of COVID-19 on the burden and characteristics of RSV-related bronchiolitis in children under 2 years of age in the Netherlands. Although RSV seasonality and clinical patterns are approaching pre-

pandemic conditions, ongoing variations in timing and transmission indicate that full normalisation is still influenced by social and demographic factors. These findings underline the importance of continued RSV surveillance and the integration of social and behavioural determinants into public health planning. Incorporating these contextual factors can help optimise the timing and targeting of national immunisation strategies.

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3

The Dutch National RSV Immunisation Programme: A Reflective Commentary

Neele Rave

Unpublished.

SUMMARY

The introduction of passive immunisation against respiratory syncytial virus (RSV) using nirsevimab within the Dutch National Immunisation Programme (NIP) represents an important public health milestone to reduce RSV-associated morbidity in early life. The current implementation adopts a dual-pathway strategy based on seasonal epidemiology, offering immunisation to infants born during the RSV season within 14 days after birth, while infants born outside the season receive protection prior to their first RSV season.

Based on available epidemiological evidence, I predict that there will be an unacceptably high number of infants with severe RSV infection among children who were not protected under the current strategy. If this prediction is confirmed during the first RSV season following the introduction of the national RSV immunisation programme, I recommend considering a reduction of the maximum age for RSV immunoprophylaxis to seven days after birth. The rationale for this recommendation, as well as a more detailed discussion of the underlying epidemiological evidence and programmatic implications, is provided in the subsequent sections of this report.

INTRODUCTION

Respiratory Syncytial Virus (RSV) is a leading cause of lower respiratory tract infections in infants, particularly during the first months of life.[1] In response to the substantial disease burden, a national passive immunisation strategy using the long-acting monoclonal antibody (mAb) nirsevimab (Beyfortus®) has been implemented in the Dutch National Immunisation Programme (NIP). This followed a 2024 recommendation by the Dutch Health Council to offer RSV protection to all infants during their first RSV season.[2]

In line with the seasonal epidemiology of RSV, the Netherlands has implemented a dual-pathway immunisation approach. Infants born during the RSV season, defined as October 1 to March 31 form the primary group and are offered nirsevimab within 14 days after birth. This timeframe is intended to provide early protection to the most vulnerable infants during peak viral circulation,[3] while also following operational guidance and taking logistical feasibility within the Dutch health care system into account.[4] Infants born outside the RSV seasons, between April 1 and September 30, form the catch-up group and receive nirsevimab shortly before or at the onset of their first RSV season.[3]

While the current strategy is based on clinical evidence and expert recommendations, combined with feasibility in the Dutch context, continued reflection and adaptive evaluation are important to ensure the programme remains aligned with emerging evidence, real-world effectiveness and broader public health objectives over time. This article reflects on the current implementation of RSV immunisation within the Dutch NIP and highlights areas for potential future improvements.

Observations From Previous RSV Surveillance Studies in Children <2 Years in the Netherlands

RSV seasonality

RSV epidemics in the Netherlands generally follow a seasonal pattern, with peak activity typically occurring in November and December. As demonstrated in the SPREAD study,[5] RSV-associated hospitalisations in children <2 years of age during the 2018/2019 and 2019/2020 seasons peaked between weeks 50 and 52 (December). However, during the COVID-19 pandemic, RSV transmission was substantially disrupted. In the winter of 2022/2023, RSV circulation returned to its typical winter seasonality, again peaking in week 52. A similar seasonal pattern was observed in 2023/2024, although the peak occurred approximately 4–6 weeks earlier than in previous years (Figure 1). Recent data from Dutch intensive care units, collected as

part of the Burden of RSV-Related Intensive Care Admissions of Kids (BRICK-II) study during the winter of 2024/2025, confirm the return to a regular winter peak between weeks 50 and 52 in RSV-related admissions among infants (Figure 2).[6] Across all study periods, RSV-related hospital admissions declined markedly from week 8 onwards, indicating consistently low levels of RSV circulation during late winter and early spring.

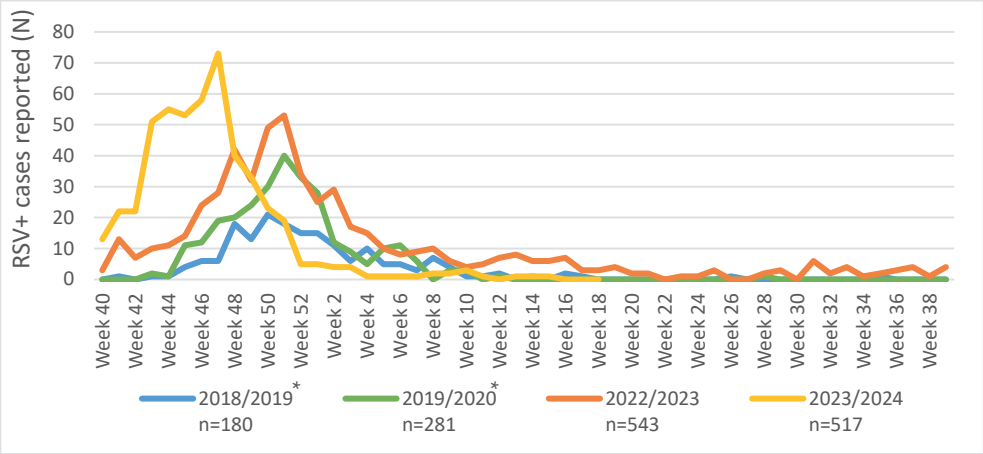

Figure 1: Weekly number of RSV-positive cases reported as part of the SPREAD Study in children under two years of age admitted to 13 Dutch hospitals across different RSV seasons in the Netherlands pre- and post-COVID.
*before the COVID-19 pandemic testing was primarily performed in young and severely ill children.

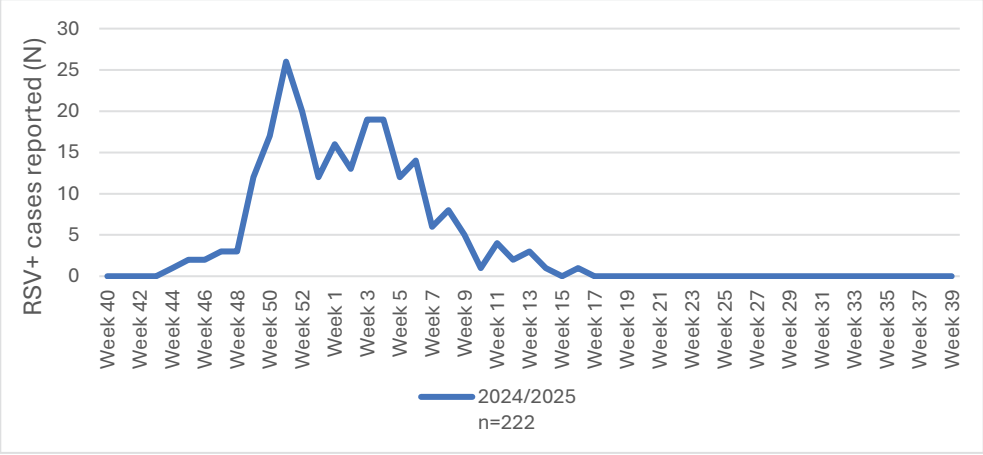

Figure 2: Weekly number of RSV-positive cases reported as part of the BRICK Study in children under one year of age admitted to the ICUs in 7 Dutch hospitals during the 2024/2025 RSV season.

RSV admission risk

Young age and particularly month of birth is a risk factor for RSV-associated hospitalisation in healthy, term-born infants, with the highest risk among infants born in autumn[1]. In line with this, data from the SPREAD study show that the highest risk of hospitalisation is seen in infants born between September and November, while those born between February and May having the lowest risk (Figure 3 and Table 1). Among RSV-hospitalised infants born in March, 9 of 58 (15.5%) were admitted during the same RSV season (8 of these admissions were during the 2022–2023 post-COVID season). Notably, only one infant required admission to the paediatric intensive care unit (PICU) at 17 days of age. In contrast, 49 of 58 (84.5%) infants born in March were admitted during the following RSV season, with 12 of 49 (24.5%) infants requiring PICU care during the following RSV season (Supplementary Table 1). Data from the BRICK-II study for the 2024-2025 season showed that no children born in March were admitted to the PICU during the same season, while 4 children were admitted during the following season (Supplementary Table 2).[6]

Table 1. Number of RSV related hospital admissions per birth months in children <1 year of age admitted to 13 Dutch hospitals across different RSV seasons in the Netherlands Pre-COVID (2018–2020) and post-COVID (2022–2024). Data from the SPREAD study.

Month of Admission	**Month of Birth**												**Total**
	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	
January	14	2	5	4	4	6	14	10	16	21	31	47	174
February	24	2	1	1	1	1	6	3	4	9	9	9	70
March	6	5	3*	2	4	2	2	3	2	3	3	4	39
April	3	4	6*	2	0	3	0	2	1	0	2	6	29
May	3	0	0	1	1	0	0	0	0	3	0	1	9
June	1	0	0	0	1	1	0	0	0	0	0	2	5
July	1	2	0	0	0	0	0	0	0	0	1	2	6
August	0	1	0	0	1	2	2	2	3	1	1	0	13
September	1	1	2	1	1	1	3	11	4	1	1	0	27
October	5	6	7	10	3	13	10	24	37	13	0	3	131
November	15	10	16	13	19	22	21	39	71	105	40	9	380
December	10	7	18	15	16	27	26	35	50	105	112	38	459
Total	83	40	58	49	51	78	84	129	188	261	200	121	1342

*8 of these 9 infants were admitted during the 2022–2023 season which was still affected by COVID-19.

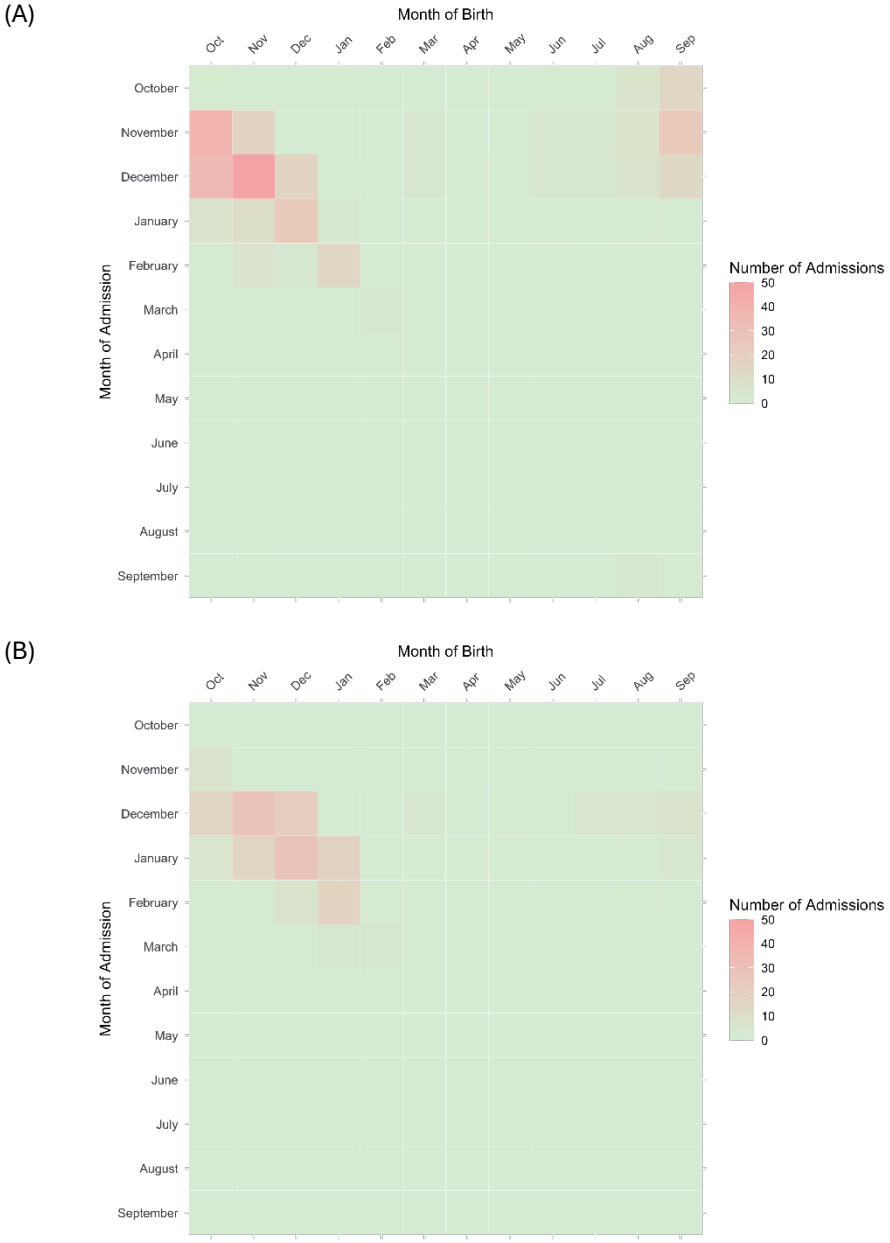

Figure 3. Heatmaps showing the number of RSV-related hospital admissions per birth month in children under 1 year of age admitted to paediatric intensive care units (PICUs) in Dutch hospitals. (**A**) Data from 5 PICUs across multiple RSV seasons in the Netherlands, pre-COVID (2018–2020) and post-COVID (2022–2024), from the SPREAD study. (**B**) Data from 7 PICUs during the 2024–2025 RSV season, from the BRICK-II study.

Age distribution of admitted children

The SPREAD study showed that the majority of infants admitted to the hospital were under 3 months of age (57.9%), a trend that was even more pronounced in infants admitted to the PICU (78.0%). In addition, a substantial proportion of admissions occurred during the first 14 days of life, accounting for 6.0% of all included hospitalised cases and 10.4% of PICU cases in infants <1 year (Table 4), with 95% of these occurring between days 7 and 14.

Based on these findings, delaying RSV immunisation until days 7-14 after birth could result in an estimated one in 17 hospital admissions and one in 10 PICU admissions not being prevented, despite the intention to get immunisation. Data from the BRICK-II study during the 2024-2025 season show an even higher proportion, with 36 of 222 infants (16.2%) admitted to the PICU with RSV being 7–14 days of age.

Table 2. Age distribution of RSV-related hospitalised children <1 year of age admitted to 13 Dutch hospitals across different RSV seasons in the Netherlands Pre-COVID (2018–2020) and post-COVID (2022–2024). Data from the SPREAD study.

Age categories, n (%)	All cases N=1,342	PICU cases N=386
≤ 3 months	777 (57.9)	301 (78.0)
≤ 7 days	5 (0.4)	2 (0.5)
>7 days - ≤ 14 days	76 (5.7)	38 (9.8)
> 14 days - ≤ 28 days	162(12.1)	67 (17.4)
> 28 days - ≤ 3 months	534 (39.8)	194 (50.3)
> 3 - ≤ 6 months	282 (21.0)	47 (12.2)
> 6 - < 12 months	283 (21.1)	38 (9.8)

DISCUSSION

Surveillance data consistently demonstrate a pronounced peak of RSV activity in the Netherlands during November and December, with minimal detection by March. Despite this, current Dutch guidelines recommend the administration of nirsevimab to infants born throughout March, a period of low viral circulation. This raises questions about the timing of protection and potential optimisation of health care resource use. Observations in this manuscript show that most infants born in March were admitted during the following season, suggesting that including these infants in the catch-up group may be more aligned with seasonal risk and could enhance cost-effectiveness, assuming a duration of protection from nirsevimab of approximately 5–6 months as

demonstrated in clinical trials.[7, 8] Should future data indicate longer protection, these recommendations may need to be revised.

Furthermore, current guidelines recommend that nirsevimab is administered within 14 days after birth for infants born between October 1 and March 31, while other countries recommend administration within 7 days after birth.[9, 10] Our data indicate that around 6% of all infants admitted with an RSV infection are younger than 14 days, with 10.4% of all infants requiring PICU care being under 14 days of age. The RESCEU birth cohort study (2017–2020) showed similar numbers with 6.9% (10 of 145) RSV-associated hospitalisations in the first year of life occurring within 14 days after birth (unpublished data). This corresponds to a risk of roughly 1 in 1,000 healthy term infants being hospitalised within the first two weeks of life. Based on the 2023 birth rate in the Netherlands (164 000 births), an estimated 150–200 newborns might be admitted to the hospital before their scheduled immunisation, especially during the RSV peak. Furthermore, this could potentially affect parental acceptance of the immunisation programme, as parents might not understand why their infant was immunised too late. Immunising these infants earlier, within 7 days after birth, could help prevent hospitalisations that might otherwise occur. It is therefore necessary to evaluate the real impact of the current practice after the first season (winter 2025/2026).

In infants born in hospitals, following the current guidelines, nirsevimab is typically administered around 10 days after birth if they are still hospitalised. There appears to be no clear reason to routinely postpone this to 10 days after birth, as these infants could easily receive the immunisation earlier if no contraindications are present. Early immunisation could provide protection as soon as possible, especially for infants who are discharged within 2 weeks after birth. Additionally, previous trials have shown a low incidence of systemic and local reactogenicity.[7, 8, 11]

Considerations

Based on the observations outlined above, the following reflections highlight potential approaches to optimising the timing of nirsevimab administration:

(1) Primary vs. catch-up groups:
Consider redefining the primary group as infants born between October 1 and February 28/29, instead of March 31, with the secondary group or catch-up group including infants born between March 1 and September 30. For infants born in March, parents should be given the opportunity to discuss the timing of immunisation with their health care provider, allowing for a shared decision-making process to determine whether it is preferable to immunise immediately after birth or wait until the next RSV season based on individual risk factors (e.g.,

having older siblings) and parental preferences. If seasonality shifts or protection of nirsevimab extends beyond 6 months, these definitions may need to be adjusted accordingly.

(2) Immunisation timing:
Early immunisation in the primary group, ideally within 7 days after birth, may better align protection with the incubation period of RSV (typically 3–6 days). Delaying immunisation until >7–14 days after birth exposes a substantial proportion of infants (≈94–95%) to RSV before protective serum levels are achieved, which may reduce both effectiveness and cost-efficiency (Table 4).

These reflections are intended as personal observations on the implementation of RSV immunisation in the Dutch NIP, rather than as formal evaluations or directive guidance. They are based on surveillance and cohort data and are necessarily simplified, so they may not capture all nuances of programme implementation.

Furthermore, optimising RSV immunisation may benefit from a multidisciplinary approach, integrating clinical, epidemiological, behavioural and health system insights. Collaborative input from clinicians, public health experts, behavioural scientists, data analysts and other stakeholders may help to ensure that interventions are safe, effective and achieve high coverage.

In summary, the RSV immunoprophylaxis programme is different from other countries because we allow immunisation up to 14 days for practical reasons. Reflecting on the timing of nirsevimab administration in relation to RSV seasonality and early postnatal vulnerability highlights opportunities to enhance programme effectiveness. Multidisciplinary feedback and ongoing evaluation should guide adjustments as real-world data and societal factors evolve. Earlier administration of immunoprophylaxis may result in bigger impact of the national RSV immunisation programme.

Supplementary files can be downloaded from:

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PART II

Paediatric RSV Burden in Low- and Middle-Income Countries

4

Respiratory Syncytial Virus Infection among Children Younger than 2 Years Admitted to a Paediatric Intensive Care Unit with Extended Severe Acute Respiratory Infection in Ten Gavi-Eligible Countries: The RSV GOLD—ICU Network Study

RSV GOLD—ICU Network collaborators*

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ABSTRACT

Background. Patient-level data on life-threatening respiratory syncytial virus (RSV) infection in children in low-income and lower-middle-income countries (LMICs) are scarce, and this scarcity might limit demand for RSV interventions in LMICs who rely on support from Gavi, the Vaccine Alliance. We aimed to describe the characteristics of RSV-positive children younger than 2 years who were admitted to paediatric intensive care units (PICUs) with extended severe acute respiratory infection (eSARI) in Gavi-eligible countries.

Methods. The RSV GOLD—ICU Network study is a 2-year prospective, multicountry, observational study of children younger than 2 years admitted to a PICU with eSARI. The study was conducted at 12 referral hospitals in Bolivia, Cameroon, The Gambia, Ghana, Haiti, Mozambique, Nepal, Nigeria, Sudan, and Tanzania. For comparison with a high-income country, patients were also included from two referral hospitals in the Netherlands. Children were eligible for inclusion if they were aged between 4 days and 2 years, admitted to a PICU, and met the WHO eSARI definition. RSV infection was confirmed within 72 h of PICU admission via a molecular point-of-care test at LMIC study sites and via a PCR test at the Dutch study sites. Clinical data were extracted from admission charts of patients; underlying conditions that were identified at admission were classified as comorbidities. Socioeconomic and demographic data were collected via a written, structured, parental questionnaire.

Findings. Between April 28, 2021, and Sept 30, 2023, we included 2,118 children who were admitted to a PICU with eSARI in the ten participating countries. 614 (29.0%; range 23.0–38.2) of 2,118 children tested positive for RSV and 608 were included in descriptive analyses as six medical files were lost at one study site and data could not be retrieved. Among all 608 children infected with RSV, 379 (62%) were male and 229 (38%) were female. Median age at testing was 3.0 months (IQR 1.3–7.7). 30 (5%) of 608 children died from RSV infection. RSV fatality occurred at seven of ten participating LMIC study sites and was highest in Tanzania (seven [27%] of 26 children). Median age at testing of children who died with RSV infection was 1.8 months (IQR 1.1–4.2).

Interpretation. To our knowledge, this is the first prospective, multicountry study reporting data from children admitted to a PICU with life-threatening RSV infection in Gavi-eligible countries. As there is no access to intensive care for most children in LMICs, RSV prevention is urgently needed.

RESEARCH IN CONTEXT

Evidence Before This Study

In 2019, respiratory syncytial virus (RSV) was identified as the leading cause of childhood pneumonia in the Pneumonia Etiology Research in Child Health study. In 2019, RSV was associated with 3.6 million hospital admissions and 101,400 (uncertainty range 84,500–125,200) in-hospital and out-of-hospital deaths in children younger than 5 years globally. Burden of disease is highest in low-income and lower-middle-income countries (LMICs), where more than 97% of RSV-associated mortality occurs. As there is no access to intensive care for most children in LMICs, RSV prevention is urgently needed to decrease mortality in children younger than 5 years globally. To access RSV interventions, many LMICs depend on support from Gavi, the Vaccine Alliance. In 2018, Gavi committed to support future RSV-immunisation products in eligible countries for the 2021–25 strategic funding period. Gavi identified scarcity of country-level and age-stratified burden data from LMICs as key vaccine challenges in their RSV investment case. Individual, prospective, patient-level data are mainly available from high-income countries (HICs). We searched PubMed for studies published in English from Jan 1, 2000, to March 6, 2024, using the search terms "("RSV" OR "syncytial") AND ("mortality" OR "severe" OR "death" OR "fatal" OR "ICU" OR "intensive care") AND ("child" OR "children" OR "infant" OR "infants" OR "pediatric" OR "paediatric" OR "paediatrics")". There were no prospective, multicountry studies that reported granular data from RSV-positive children requiring admission to a paediatric intensive care unit (PICU). There were several HIC studies reporting RSV-positive PICU admissions; some LMIC studies reported RSV hospitalisations, sometimes including PICU admissions.

Added Value of This Study

To our knowledge, this is the first prospective, multicountry study reporting granular data from children admitted to a PICU with life-threatening RSV infection in Gavi-eligible countries. RSV was detected in 614 (29.0%; range 23.0–38.2) of 2,118 children admitted with extended severe acute respiratory infection (eSARI) according to the WHO eSARI definition. Median age at testing was 3 months (IQR 1.3–7.7), and RSV-related fatality occurred in 30 (4.9%) of 608 children. 99 (16.3%) of 608 children had one or more comorbidities and 80 (13.2%) were born prematurely. Parental awareness was low; only 19 (3.1%) of 604 parents had heard of RSV.

Implications of all the Available Evidence

Our study showed that RSV is a substantial contributor to life-threatening respiratory disease in children admitted to a PICU in Gavi-eligible countries. As there is no access

to PICUs for most children in these countries, preventive RSV interventions are urgently needed. Most children were born at term and did not have comorbidities, implying that RSV-preventive strategies should not be limited to groups at high risk of severe RSV infection. The median age of 3 months at time of life-threatening RSV infection indicates that both extended half-life monoclonal antibodies and maternal vaccination could be effective in preventing severe RSV infection in children in LMICs. Cost-effectiveness studies are required to further evaluate the health and economic effects of RSV interventions for children in LMICs. Increasing country-level awareness among parents, health-care staff, and policy makers is crucial to prioritise the implementation of RSV interventions.

INTRODUCTION

Respiratory syncytial virus (RSV) is the leading cause of lower respiratory tract infection (LRTI) and LRTI-related mortality in children younger than 5 years.[1] Global RSV disease burden predominantly affects children in low-income and lower-middle-income countries (LMICs), where more than 97% of RSV-associated mortality occurs.[1] Multiple RSV-intervention products are being developed; an RSV maternal vaccine and a long-acting, single-dose monoclonal antibody were market-approved by the US Food and Drug Administration for use in the USA in 2023.[2,3]

New RSV vaccines are available for high-income countries (HICs), but many LMICs depend on support from Gavi, the Vaccine Alliance. Every 5 years, Gavi prioritises new investments for its next strategic and funding cycle through its vaccine investment strategy.[4,5] Criteria to prioritise interventions are impact, cost, value, and programmatic feasibility[4,5] and Gavi support is contingent on recommendation by the WHO Strategic Advisory Group of Experts on Immunization (SAGE). Gavi's RSV investment, published in 2018, highlighted low in-country awareness of RSV disease burden as a key challenge for vaccine implementation.[5] Hence, country-specific and age-stratified burden data were deemed necessary to guide country-level policy on the introduction of RSV interventions in LMICs. Moreover, patient-specific data including gestational age help to improve vaccine-effect models[6] and cost-effectiveness analyses,[7] which are important for SAGE recommendation.

Although updated RSV disease-burden estimates are available for LRTI incidences, hospital admissions, and deaths in LMICs,[1] there are key gaps in our knowledge and understanding regarding severe RSV infections with poor clinical outcomes, particularly in children admitted to paediatric intensive care units (PICUs). Although PICUs are generally available and accessible in upper-middle-income countries

(UMICs) and HICs, they are less available and accessible in LMICs. Unavailability of timely PICU supportive care can contribute to RSV mortality.
We aimed to describe the characteristics of RSV-positive children younger than 2 years who were admitted to PICUs with extended severe acute respiratory infection (eSARI) in Gavi-eligible countries.

METHODS

Study Design

The study protocol and procedures have been described previously.[8] In short, the RSV GOLD—ICU Network study is a 2-year prospective, multicountry, observational study of children younger than 2 years admitted to a PICU with eSARI. As there is no standardised global definition for a PICU, patients were recruited from units where the most severely ill patients were typically admitted (ie, a PICU, a high-dependency unit, or both).

The study was conducted at 12 referral hospitals in ten LMICs: Bolivia (currently fully self-financing, but eligible for targeted Gavi support), Cameroon, The Gambia, Ghana, Haiti, Mozambique, Nepal, Nigeria, Sudan, and Tanzania (appendix 5 p 5). Two hospitals were included from Nepal and two from Sudan; when the study could not be conducted because of political challenges in the hospital in Sudan, another hospital was selected to continue the study. For comparison with a HIC, patients were also included from two referral hospitals in the Netherlands, using the same criteria. At four study sites (ie, The Gambia, Nepal, Nigeria, and Tanzania), patients were also included from neonatal intensive care units. However, for readability, we use the term PICU throughout the manuscript. The study was conducted between April 28, 2021, and Sept 30, 2023.

Ethical considerations of the RSV GOLD—ICU Network study have been published previously.[8] The institutional review board of the University Medical Centre Utrecht (Utrecht, Netherlands; protocol number 20–536) provided a waiver for this study as the Dutch Medical Research Involving Human Subjects Act was not applicable. Ethical approval was obtained from all participating study sites, including the Netherlands. Written informed consent was obtained from parents or guardians of patients. For parents or guardians who could not read or write, an oral translation of the informed consent form was provided by the study team.

Patients

Children were eligible for inclusion if they were aged between 4 days and 2 years, admitted to a PICU at one of the 12 referral hospitals, and met the WHO eSARI definition

(hereafter referred to as the eSARI group).[9] To establish whether this definition was sufficiently sensitive for detecting severe RSV infection, we also included children who were admitted to a PICU at three study sites (ie, Nepal, Ghana, and Mozambique) for reasons other than respiratory symptoms (hereafter referred to as the control group).

Procedures

RSV infection was confirmed within 72 h of PICU admission via a molecular point-of-care test (POCT; ID NOW RSV, Abbott, Scarborough, ME, USA) at LMIC study sites and via a PCR test at the Dutch study sites.[10] To assess POCT accuracy, we conducted RSV PCR analyses at accredited virology laboratories at two study sites, one in Ghana and one in Sudan. At three study sites (ie, Ghana, Mozambique, and Nepal), children with eSARI were also tested for influenza infection (ID NOW Influenza A & B 2, Abbott) as a comparator. Clinical data were extracted from admission charts of patients; underlying conditions that were identified at admission were classified as comorbidities. Socioeconomic and demographic data were collected via a written, structured, parental questionnaire. Sex data were collected by the physician; the options were male or female.

Patients were included during two predefined local respiratory seasons.[8] If RSV activity appeared to occur for a shorter or longer time than anticipated, patients were recruited until RSV positivity was less than 10% for 3 consecutive weeks. Peak-proportion RSV positivity was defined as the highest proportion of RSV-positive patients during a recruitment period of at least 4 consecutive weeks with at least four tested patients per week.

Statistical Analysis

For the eSARI group, we expected to recruit 2,800 children assuming 30% RSV positivity and 10% RSV-related fatality. This number yielded a two-sided 95% Clopper– Pearson CI with a width equal to 0.034, ranging from 28% to 32%. For the control group, we expected to recruit 1,200 children, assuming 5% RSV positivity. This number yielded a two-sided 95% Clopper–Pearson CI with a width equal to 0.026, ranging from 3.8% to 6.4%.8 We present descriptive statistics for all variables and report the denominator where data are missing, as children with missing data for a specific variable were not included in the analysis for that variable. For continuous variables, we report the median and IQR; for categorical variables, we report the frequency and proportion.

We used the χ^2 test or Fisher's exact test to measure statistical significance between groups for dichotomous parameters and the Mann–Whitney test for all continuous parameters. We computed the International Wealth Index[11] for each patient on the basis of parental questionnaires via a freely available SPSS syntax file.[12] The

International Wealth Index is an asset-based index of household economic status that can be compared across all LMICs and is based on data from 2.1 million households from 97 LMICs.[11]

To compare characteristics of children with fatal and non-fatal RSV infection, we used generalised linear mixed-effects models with a random intercept for study site. We restricted our analysis to the most important variables as the analysis method was not feasible for all variables due to convergence issues. We compared mean age, proportion of children younger than 6 months, comorbidity, and prematurity between children with fatal and non-fatal RSV infection.

As a post-hoc sensitivity analysis, we analysed the data excluding children from Nepal study sites as these were a majority of all included children. Furthermore, we analysed the data excluding children from the Bolivia study site as this site is no longer Gavi-eligible. Finally, we conducted a post-hoc logistic regression to test for confounding factors associated with fatality.

All statistical analyses were done in SPSS version 21.0 and R version 35.1.

Role of the Funding Source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit the paper for publication.

RESULTS

Between April 28, 2021, and Sept 30, 2023, we included 2,118 children who were admitted to a PICU with eSARI in the ten participating countries. 614 (29.0%; range 23.0–38.2) of 2,118 children tested positive for RSV and 608 were included in descriptive analyses as six medical files were lost at one study site and data could not be retrieved (Figure 1). Concordance between POCT and PCR was 86% in Ghana and 93% in Sudan (Figure 2). At three study sites (ie, Bolivia, The Gambia, and Nepal), data were sufficiently robust to measure peak proportions of RSV positivity. Peak RSV positivity ranged between 60% and 100% in Bolivia, 70% and 100% in the Gambia, and 60% and 70% in Nepal (appendix 5 p 7).

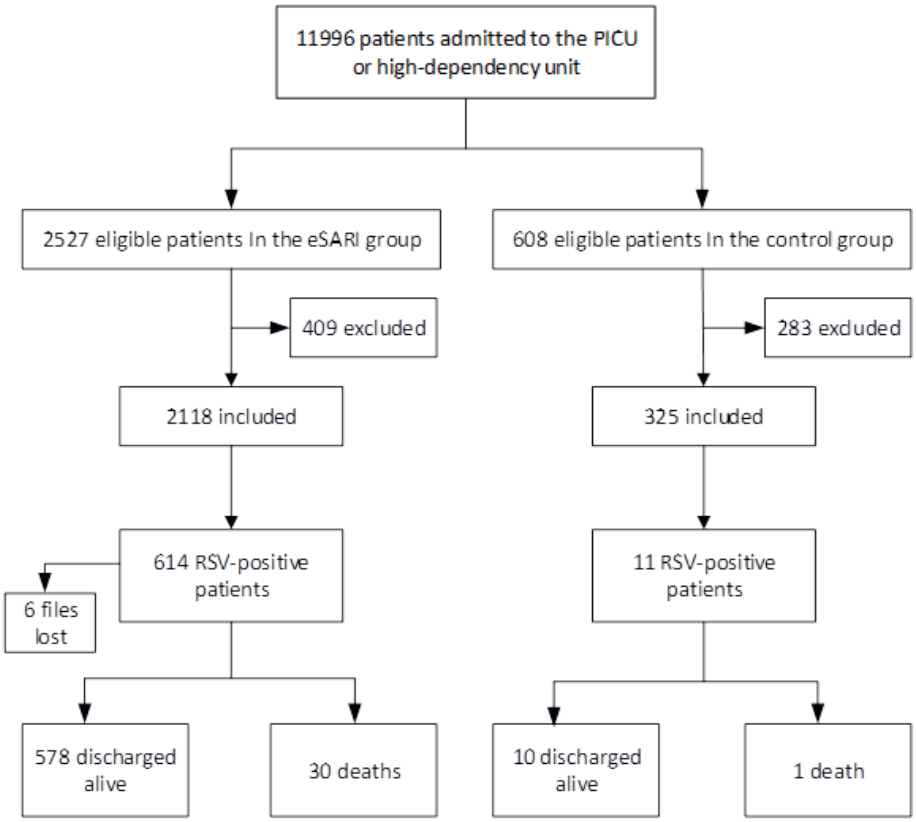

Figure 1. Study profile
Due to logistical challenges, not all study sites kept a list of reasons for exclusion or information on which eligible children were not screened and why. Reported reasons for exclusion were parental refusal to participate, child younger than 4 days, child not meeting inclusion criteria, child death before inclusion was possible, nasopharyngeal swab not done within 72 h of PICU admission, unavailability of study staff, quick transfer out of the PICU, and failed point-of-care test. eSARI=extended severe acute respiratory infection. PICU=paediatric intensive care unit. RSV=respiratory syncytial virus.

Among all 608 children infected with RSV, 379 (62%) were male and 229 (38%) were female. Median age at testing was 3.0 months (IQR 1.3–7.7). Median age ranged between 1.2 months and 8.5 months across individual sites (Table 1; appendix 5 p 8). 99 (16%) of 607 had at least one comorbidity; congenital heart disease was the most common, affecting 57 (58%) of 99 children. 80 (13%) of 598 children had been born prematurely, mainly between 32 weeks and less than 37 weeks gestational age (Table 1). 552 (91%) of 608 mothers had been vaccinated against tetanus during pregnancy and 521 (89%) had at least four antenatal-care visits (appendix 5 p 8). However, parental awareness was low; only 19 (3%) of 605 parents had heard of RSV. By comparison, in

the Netherlands, 99 (92%) of 108 parents had heard of RSV. 200 (33%) of 608 patients had been referred from another hospital (Table 2; appendix 5 p 12). Children were hospitalised for a median duration of 7.0 days (IQR 5.0–11.0) and 57 (9%) received mechanical ventilation. Antibiotics had been administered to 406 (67%) patients (Table 2; appendix 5 pp 12, 14, 15, 23). In Nigeria, a decline in admission rates was observed in the second recruitment season compared with the first season. In Nepal, the second respiratory season was delayed by several weeks compared with the first season. However, in Ghana, there were no differences between both seasons.

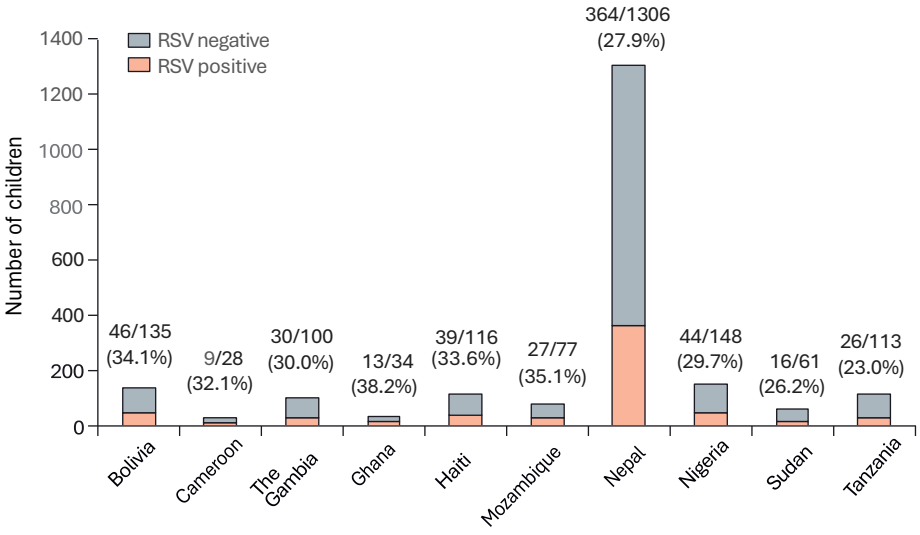

Figure 2. RSV positivity among children younger than 2 years admitted to the paediatric intensive care unit with extended severe acute respiratory infection. RSV=respiratory syncytial virus.

In total, 30 (5%) of 608 children died from RSV infection. RSV fatality occurred at seven of ten participating LMIC study sites and was highest in Tanzania (seven [27%] of 26 children; Table 3; appendix 5 pp 18, 21). Median age at testing of children who died with RSV infection was 1.8 months (IQR 1.1–4.2; Figure 3). Although few children died, we compared characteristics between children with and without fatal RSV infection. Mean age (p=0.084), proportion of children younger than 6 months (p=0.058), and proportion of children born prematurely (p=0.96) did not differ between the two groups. The proportion of children with comorbidity was higher among those with fatal RSV infection than those with non-fatal RSV infection, which remained significant after adjustment for referral from another health facility and age at testing (p=0.0010 and p<0.0001; Table 3).

Table 1. Baseline characteristics of RSV-positive children younger than 2 years admitted to the paediatric intensive care unit with extended severe acute respiratory infection.

	Bolivia (n=46)	Cameroon (n=9)	The Gambia (n-30)	Ghana (n=13)	Haiti (n=33)*	Mozambique (n=27)	Nepal (n=364)	Nigeria (n=44)	Sudan (n=16)	Tanzania (n=26)	Total (n=608)
Sex											
Male	29 (63%)	4 (44%)	18 (60%)	6 (46%)	18 (55%)	11 (41%)	241 (66%)	30 (68%)	9 (56%)	13 (50%)	379 (62%)
Female	17 (37%)	5 (56%)	12 (40%)	7 (54%)	15 (45%)	16 (59%)	123 (34%)	14 (32%)	7 (44%)	13 (50%)	229 (38%)
Age at testing, months	2.9 (1.1–6.9)	4.0 (1.9–5.9)	8.5 (2.0–12.0)	2.9 (2.7–11.7)	2.4 (1.3–5.2)	4.1 (2.0–4.9)	3.2 (1.3–8.4)	1.9 (1.0–5.6)	4.0 (3.0–4.9)	1.2 (0.8–2.1)	3.0 (1.3–7.7)
Aged <6 months	32 (70%)	7 (78%)	12 (40%)	9 (69%)	27 (82%)	22 (81%)	236 (65%)	35 (80%)	13 (81%)	22 (85%)	415 (68%)
Siblings aged <12 years	27 (59%)	6/8 (75%)	27 (90%)	11 (85%)	22 (67%)	17 (63%)	167 (46%)	32/43 (74%)	11 (69%)	16 (62%)	336/606 (55%)
Child-care or shared-care attendance	1 (2%)	1/8 (13%)	1 (3%)	1 (8%)	9 (27%)	21 (78%)	25/356 (7%)	2/43 (5%)	0	4 (15%)	65/598 (11%)
Exclusive breastfeeding until age 4 months	14 (30%)	3 (33%)	28 (93%)	6 (46%)	10 (30%)	13 (48%)	193 (53%)	31/43 (72%)	12 (75%)	18 (69%)	328/607 (54%)
Prematurity	15 (33%)	3 (33%)	1 (3%)	3 (23%)	5/30 (17%)	4/25 (16%)	34/361 (9%)	6/43 (14%)	1 (6%)	8/24 (33%)	80/598 (13%)
WGA <28 weeks	2 (4%)	0	0	0	NA	1/25 (4%)	0	0	0	1/24 (4%)	4/556 (1%)

Table 1. Continued.

	Bolivia (n=46)	Cameroon (n=9)	The Gambia (n-30)	Ghana (n=13)	Haiti (n=33)*	Mozambique (n=27)	Nepal (n=364)	Nigeria (n=44)	Sudan (n=16)	Tanzania (n=26)	Total (n=608)
WGA 28 weeks to <32 weeks	7 (15%)	0	0	1 (8%)	1/20 (5%)	3/25 (12%)	8/361 (2%)	0	0	4/24 (17%)	21/556 (4%)
WGA 32 weeks to <36 weeks	6 (13%)	3 (33%)	1 (3%)	2 (15%)	NA	0	26/361 (7%)	5/43 (12%)	1 (6%)	3/24 (13%)	50/556 (9%)
Comorbidity	11 (24%)	0	2 (7%)	6 (46%)	10 (30%)	2 (7%)	42 (12%)	12/43 (28%)	3 (19%)	11 (42%)	99/607 (16%)
Vaccinated according to local immunisation schedule and age	37/44 (84%)	9 (100%)	29 (97%)	9 (69%)	18 (55%)	24/26 (92%)	232/363 (64%)	34/42 (81%)	11 (69%)	20 (77%)	423/602 (70%)
Maternal immunisation†	33/45 (73%)	9 (100%)	30 (100%)	11 (85%)	23/32 (72%)	19/23 (83%)	356/362 (98%)	40/42 (95%)	13 (81%)	25/25 (100%)	559/597 (94%)

Data are n (%), n/N (%), or median (IQR). NA=not available. RSV=respiratory syncytial virus. WGA=weeks gestational age. *Six RSV-positive children were not included as medical files were lost before data collection started.

† Any vaccine administered during pregnancy, including tetanus, diphtheria, pertussis, influenza, and COVID-19.

Table 2. Clinical characteristics of RSV-positive children younger than 2 years admitted to the paediatric intensive care unit with extended severe acute respiratory infection.

	Bolivia (n=46)	Cameroon (n=9)	The Gambia (n-30)	Ghana (n=13)	Haiti (n=33)*	Mozambique (n=27)	Nepal (n=364)	Nigeria (n=44)	Sudan (n=16)	Tanzania (n=26)	Total (n=608)
Presentation at admission											
Referral from other health facility	33 (72%)	1 (11%)	21 (70%)	13 (100%)	7 (21%)	11 (41%)	79 (22%)	12/43 (28%)	5 (31%)	18 (69%)	200 (33%)
Time between onset of symptoms and hospital admission, days	4.0 (3.0–6.0)	4.0 (2.0–5.5)	2.0 (1.8–3.0)	2.0 (1.0–3.0)	4.0 (3.0–5.0)	3.0 (2.0–5.0)	3.0 (2.0–4.8)	3.0 (2.0–5.0)†	3.0 (2.0–5.0)	3.0 (1.8–4.0)	3.0 (2.0–5.0)
Fever (ie, temperature >38°C)	22 (48%)	9 (100%)	8 (27%)	9 (69%)	13 (39%)	2 (7%)	242 (66%)	27/43 (63%)	12 (75%)	7 (27%)	351/607 (58%)
Oxygen saturation on room air	90.0% (86.5–91.5)§	91.0% (81.5–95.5)¶	90.0% (85.5–95.3)	95.5% (89.0–98.0)	92.0% (90.0–96.0)‖	92.0% (83.8–97.0)	88.0% (85.0–92.0)**	90.0% (84.5–94.0)††	87.0% (82.3–88.5)‡‡	87.0% (80.0–90.0)§§	88.0% (85.0–93.0)¶¶
Concomitant non-respiratory diagnosis	5 (11%)	0	4 (13%)	1 (8%)	5 (15%)	19/26 (73%)	79 (22%)	18/43 (42%)	3 (19%)	13 (50%)	147/606 (24%)
Meningitis	0	NA	1 (3%)	1 (8%)	0	2 (7%)	3 (1%)	2 (5%)	0	1 (4%)	10 (2%)
Encephalopathy	0	NA	1 (3%)	0	0	2 (7%)	1 (<1%)	1 (2%)	0	1 (4%)	6 (1%)
Sepsis	1 (2%)	NA	1 (3%)	1 (8%)	1 (3%)	6 (22%)	67 (18%)	15 (34%)	2 (13%)	13 (50%)	107 (18%)
Other	5 (11%)	NA	2 (7%)	0	4 (12%)	17 (63%)	15 (4%)	5 (11%)	2 (13%)	1 (4%)	51 (8%)
Hospital acquired RSV infection	0	0	0	0	0	0	3/354 (1%)	0/43	0/15	1/12 (8%)	4/579 (1%)

Table 2. Continued.

	Bolivia (n=46)	Cameroon (n=9)	The Gambia (n-30)	Ghana (n=13)	Haiti (n=33)*	Mozambique (n=27)	Nepal (n=364)	Nigeria (n=44)	Sudan (n=16)	Tanzania (n=26)	Total (n=608)
Disease management											
Oxygen support	41 (89%)	9 (100%)	28 (93%)	4 (31%)	12 (36%)	20 (74%)	279 (77%)	33 (75%)	16 (100%)	16 (62%)	458 (75%)
Non-invasive ventilatory support (ie, CPAP or HFNC)	15 (33%)	1 (11%)	0	10 (77%)	15 (45%)	0	50 (14%)	0	0	13 (50%)	104 (17%)
Mechanical ventilation	14 (30%)	NA	0	0	0	6 (22%)	24 (7%)	0	0	13 (50%)	57 (9%)
Systemic corticosteroids administered	30 (65%)	5 (56%)	25 (83%)	1 (8%)	0	5 (19%)	68 (19%)	3 (7%)	0	20 (77%)	157 (26%)
Antibiotics administered	36 (78%)	6 (67%)	6 (20%)	11 (85%)	8 (24%)	25 (93%)	262 (72%)	37 (84%)	0	15 (58%)	406 (67%)
Disease course											
Oxygen support, days	5.0 (3.0–9.0)	2.0 (2.0–3.5)	2.0 (1.0–3.0)	2.5 (2.0–23.3)	3.5 (2.0–4.0)	3.0 (2.3–4.8)	3.0 (2.0–5.0)	3.0 (2.0–4.5)	2.5 (2.0–5.8)	10.0 (5.5–14.0)	3.0 (2.0–5.0)
Duration of non-invasive ventilatory support, days	4.0 (3.0–8.0)	3.0	NA	4.0 (2.3–8.3)	3.0 (2.0–4.0)	NA	3.0 (2.0- 5.0)	NA	NA	5.0 (3.0–11.5)	3.0 (2.0–5.0)
Duration of mechanical ventilation, days	8.0 (6.3–29.0)	NA	NA	NA	NA	3.0 (1.0–11.5)	5.0 (3.0–13.8)	NA	NA	5.0 (4.0–11.5)	5.0 (4.0–13.5)

Table 2. Continued.

	Bolivia (n=46)	Cameroon (n=9)	The Gambia (n-30)	Ghana (n=13)	Haiti (n=33)*	Mozambique (n=27)	Nepal (n=364)	Nigeria (n=44)	Sudan (n=16)	Tanzania (n=26)	Total (n=608)
Duration of hospital stay, days||||	9.0 (4.0–19.5)	4.0 (3.5–9.0)	2.5 (1.8–5.0)	9.0 (7.5–14.0)	8.0 (6.0–9.0)	5.0 (4.0–7.0)	7.0 (5.0–11.0)	6.0 (4.0–7.0)	3.5 (3.0–7.0)	21.5 (10.8–35.0)	7.0 (5.0–11.0)
Referral to other health facility	6 (13%)	0	2 (7%)	0	1 (3%)	0	3 (1%)	0	0	1 (4%)	13 (2%)
Mortality	1 (2%)	0	1 (3%)	1 (8%)	0	5 (19%)	11 (3%)	4 (9%)	0	7 (27%)	30 (5%)

Data are n (%), n/N (%), or median (IQR). CPAP=continuous positive airway pressure. HFNC=high-flow nasal cannula. NA=not applicable. RSV=respiratory syncytial virus. *Six RSV-positive children were not included as medical files were lost before data collection started.

† n=43.

‡ n=607.

§ n=45.

¶ n=8.

|| n=27.

** n=310.

†† n=40.

‡‡ n=14.

§§ n=23.

¶¶ n=535.

|||| Including admission to the general ward, if applicable.

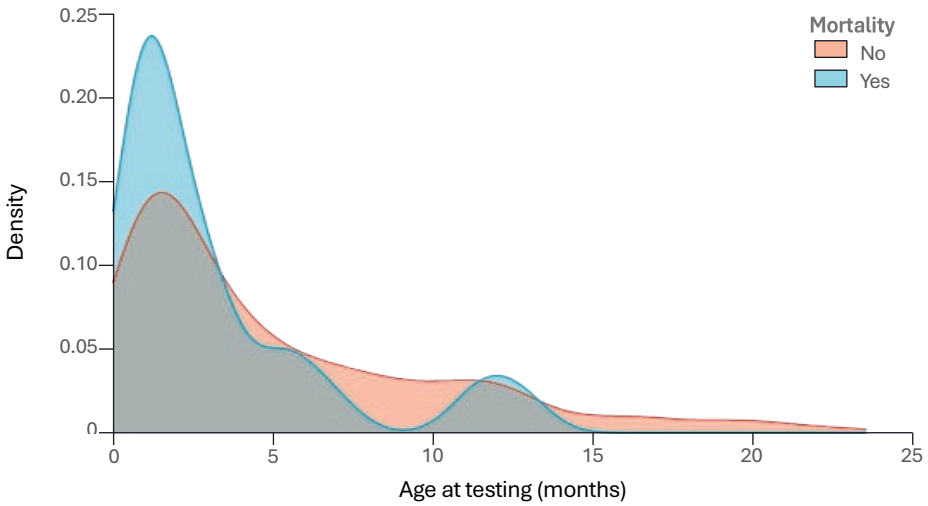

Figure 3: Age distribution of RSV-positive children younger than 2 years admitted to the paediatric intensive care unit with extended severe acute respiratory infection. RSV=respiratory syncytial virus.

In Ghana, Mozambique, and Nepal, we included 11 (3%) of 325 RSV-positive children admitted to a PICU who did not meet the WHO eSARI definition. In four (36%) of 11 patients, reason for admission was sepsis. One child (9%) died with RSV infection; median age was higher than in the eSARI group (10.6 months, IQR 0.9–12.8; appendix 5 p 25).

We included 108 children with severe RSV infection from the Netherlands (appendix 5 p 26) as an example of a HIC. Children infected with RSV were significantly younger than in LMICs (median age 1.7 months, IQR 0.7–3.5 vs 3.0 months, 1.3–7.7; p<0.0001) and were more often born prematurely (23 [21%] of 108 vs 80 [13%] of 598; p=0.038) than in LMICs. Presence of comorbidity was similar in both groups (appendix 5 p 26). Children from the Netherlands more often had older siblings (99 [92%] of 108 vs 336 [55%] of 606; p<0.0001), were more often completely vaccinated according to local immunisation schedule and age (103 [96%] of 107 vs 423 [70%] of 602; p<0.0001), went to child care or shared care more often (27 [26%] of 106 vs 65 [11%] of 598; p<0.0001), and were less often exclusively breastfed until age 4 months (41 [38%] of 108 vs 328 [54%] of 607; p=0.0024). Fatality among RSV-positive children was lower in the Netherlands than in LMICs (1 [1%] of 108 vs 30 [5%] of 608; p<0.0001).

In Ghana, Mozambique, and Nepal, we tested children with eSARI for influenza as a comparator disease (appendix 5 p 25). Altogether, influenza infection was considerably less frequent than RSV infection. 38 (3%) of 1,417 children were positive for influenza

and two (5%) of 38 died with influenza infection. Median age was 5.6 months (IQR 1.8–8.7) and 29 (76%) of 38 children presented with fever. Influenza co-infection occurred in seven (2%) of 403 RSV-positive children. Median age was higher (5.6 months, IQR 1.8–8.7 vs 3.2 months, 1.5–8.2) and duration of hospitalisation was longer (12 days, 6–15 vs 7 days, 5–10) compared with RSV-positive children without influenza co-infection. Respiratory samples for 440 (74%) of 598 RSV-positive patients were tested for other pathogens; 12 (3%) of 439 patients had respiratory co-infection (appendix 5 p 12).

364 (60%) of 608 patients were recruited in Nepal. However, most conclusions did not change after excluding data from Nepal. Children born prematurely increased from 80 (13%) of 598 to 46 (19%) of 237 and those with comorbidity increased from 99 (16%) of 607 to 57 (24%) of 243, whereas median age decreased from 3.0 months (IQR 1.3–7.7) to 2.8 months (1.3–6.7). At the Nepal site, we followed up children who went home against medical advice; among four who died after leaving the hospital, three had been tested for RSV and one was RSV positive. After excluding data from Bolivia, the main conclusions did not change.

Table 3. Baseline and clinical characteristics of RSV-related deaths compared to non-fatal RSV infections in children younger than 2 years admitted to the PICU with eSARI in LMICs.

	Fatal RSV infection (n=30*)	**Non-fatal RSV infection (n=578)**
Sex		
Male	14 (47%)	365 (63%)
Female	16 (53%)	213 (37%)
Age at testing, months	1.8 (1.1-4.2)	3.1 (1.3-7.9)
Aged <6 months	26 (87%)	389 (67%)
Siblings aged <12 years	15/29 (52%)	321/577 (56%)
Child-care or shared-care attendance	7/29 (24%)	58/569 (10%)
Exclusive breastfeeding until age 4 months	18/29 (62%)	310 (54%)
Prematurity	5/29 (17%)	75/569 (13%)
WGA <28 weeks	2/27 (7%)	2/529 (<1%)
WGA 28 weeks to <32 weeks	0/27	21/529 (4%)
WGA 32 weeks to <37 weeks	3/27 (11%)	47/529 (9%)
Comorbidity	13/29 (45%)	86 (15%)
Vaccinated according to local immunisation schedule and age	18/27 (67%)	405/575 (70%)
Maternal immunisation†	23/26 (89%)	536/571 (94%)
Presentation upon admission		
Referral from other health facility	18/29 (62%)	182/577 (32%)

Table 3. Continued.

	Fatal RSV infection (n=30*)	Non-fatal RSV infection (n=578)
Time between onset of symptoms and hospital admission, days	3.0 (2.0-4.0)‡	3.0 (2.0-5.0)
Fever (i.e., temperature >38°C)	15/29 (52%)	336 (58%)
Oxygen saturation on room air	85.0% (80.0-94.0)§	88.0% (86.0-93.0)¶
Concomitant non-respiratory diagnosis	16/29 (55%)	131/577 (23%)
Meningitis	4 (13%)	6 (1%)
Encephalopathy	3 (10%)	3 (1%)
Sepsis	12 (40%)	95 (16%)
Other	5 (17%)	46 (8%)
Hospital-acquired RSV infection	0/23	4/556 (1%)
Disease management		
Oxygen support	14 (47%)	444 (77%)
Non-invasive ventilatory support (i.e., CPAP or HFNC)	7 (23%)	97 (17%)
Mechanical ventilation	16 (53%)	41 (7%)
Systemic corticosteroids administered	10 (33%)	147 (25%)
Antibiotics administered	26 (87%)	380 (66%)
Disease course		
Duration of oxygen support, days	4.0 (2.8-7.8)‖	3.0 (2.0-5.0)**
Duration of non-invasive ventilatory support, days	3.0 (1.0-9.0)††	3.0 (2.0-5.0)‡‡
Duration of mechanical ventilation, days	4.5 (4.0-11.5)§§	7.0 (3.5-14.0)¶¶
Duration of hospital stay, days‖‖	8.0 (4.0-16.5)***	7.0 (5.0-10.0)†††
Referral to other health facility	NA	13 (2%)

Data are n (%), n/N (%), or median (IQR). NA=not available. RSV=respiratory syncytial virus. WGA=weeks gestational age.
* Six RSV-positive children were not included as medical files were lost before data collection started.
† Any vaccine administered during pregnancy, including tetanus, diphtheria, pertussis, influenza, and COVID-19.

DISCUSSION

To our knowledge, this is the first prospective, multicountry study reporting data from children admitted to a PICU with life-threatening RSV infection in Gavi-eligible countries. RSV was detected in 23.0–38.2% of children with eSARI who required PICU

admission during respiratory seasons. This finding was consistent among study sites and indicates that RSV is a global health problem.

In our study, most life-threatening RSV admissions occurred during the first 6 months of life and almost half of children were younger than 3 months. This finding is in line with findings from another study conducted at a PICU[13] and supports both maternal vaccination and timing monoclonal-antibody administration immediately after birth or at the start of the RSV season to provide protection during the first weeks of life. Median age at death was younger than in our previous publication on RSV in-hospital deaths from UMICs and LMICs (4.0 months).[14] However, the proportion of children with comorbidities was similar to our previous report (46%).[14]

Most children admitted to a PICU with severe RSV infection were born at term. The proportion of preterm-born children in the participating LMIC study sites was lower than at the Dutch study sites and then in a systematic review on RSV and bronchiolitis-related PICU admissions in HICs (31%).[15] Possibly, in LMICs, children born preterm are likely to die earlier in life due to preterm birth complications before they acquire RSV infection. Moreover, RSV-related hospitalisation is inversely related to gestational age at birth and the survival rate of extremely premature babies in low-resource settings is low.[16]

RSV fatality was lower than our anticipated 10%.[8] There are several potential explanations for this difference. First, some deaths were missed in this study, possibly due to reduced readiness to participate in the study in bereaved parents compared with parents of children who had not died. Second, we believe there was not always sufficient time to enrol patients whose health deteriorated quickly. Third, we presume that most RSV-related mortality in LMICs occurs in children without access to intensive care, in resource-limited hospitals with few respiratory-support options, and in rural settings. In a mortality surveillance study conducted in India, RSV-associated mortality was 7-fold to 10-fold higher in the community than in the hospital.[17]

RSV fatality varied between sites, although the number of deaths per site was too low for a statistical comparison. Variation between sites might be related to available care. For example, access to mechanical ventilation was not available in four of the 12 participating hospitals. RSV-related mortality at the PICU in Mozambique was high in this study but lower than their all-cause respiratory-related PICU mortality that has been previously reported.[18] Differences in mortality rates could also be explained by differences in patient populations between study sites. In Tanzania, children were recruited at the PICU, whereas children were recruited at a combined PICU and high-dependency unit in Nigeria.

We found that RSV awareness among parents in LMICs was low; only 3% of parents had heard of RSV before compared with 92% in the Netherlands. Raising country-level awareness among parents, health-care staff, and policy makers will be crucial to prioritise the implementation of RSV interventions.

Strengths of this study include the prospective, multicountry design; granularity of data; and large sample size. We ensured that RSV testing was started before the start of the RSV season and ended at least 3 weeks after the end of the RSV season. To understand the contribution of RSV infection in children without eSARI, we included a control population and found that RSV was rare in these children. This finding implies high sensitivity of the WHO eSARI definition to identify young children hospitalised with RSV infection.

This study had several limitations. First, due to unavailability of a standardised PICU definition, we might have missed children with life-threatening RSV infection admitted to the general ward in case of insufficient PICU capacity.[8] Second, RSV fatality was likely underestimated as not all deceased children could be enrolled in the study due to practical and ethical challenges around mortality. Third, we did not have a follow-up after hospital discharge and could therefore not record post-discharge mortality. However, a 2020 case series suggested that there might be an increased mortality risk in the first month after RSV illness.[19] Fourth, at some study sites, RSV testing was not done immediately after PICU admission, which could have resulted in missed deaths as the majority of paediatric deaths occur within the first 24 h after admission in LMICs.[20] In our study, one child died within 24 h, indicating possible missed deaths. Fifth, recruitment rates might have been lower than expected due to the COVID-19 pandemic. The decline we observed could be partly explained by economic hardship after the pandemic. However, as no data are available on local RSV seasonality before the start of this study, we were unable to compare with previous RSV seasons in the participating study sites.[21] Sixth, the study design did not include testing for pathogens other than RSV (and influenza at three sites), although some study sites conducted testing for other pathogens as part of clinical care. Respiratory samples of 440 RSV-positive patients were tested for other pathogens and 12 patients had respiratory co-infection. Thus, not all respiratory-related PICU admissions or mortality can be directly attributed to RSV, although the Pneumonia Etiology Research for Child Health study showed that RSV is usually symptomatic.[22] Seventh, due to logistical challenges, not all study sites kept a list of reasons for exclusion or information on which eligible children were not screened and why. We were therefore unable to clarify the study profile any further. Finally, conducting research in politically unstable settings is often challenging. We initially selected a study site in Afghanistan; however, the study was terminated in August 2021, before enrolment had started due to the political situation. In Sudan and

Nigeria, enrolment was temporarily halted due to political conflict or health-worker strikes (13 weeks in Sudan and 2 weeks in Nigeria).

In conclusion, RSV positivity was 29.0% (95% CI 27.1–31.0) across all ten sites in children younger than 2 years in Gavi-eligible countries during respiratory season. This proportion was consistent among study sites. Our study substantiates the decision for Gavi's vaccine investment strategy recommendation to support RSV-immunisation products in LMICs. As there is no access to intensive care for many children in LMICs, access to RSV interventions is urgently needed and will contribute to a decrease in global morbidity and mortality in children younger than 5 years. As most children were born at term and did not have comorbidities, future RSV-preventive strategies should not only target groups at high risk of severe RSV infection. Our data could inform vaccine-effect models and advocate for urgent access to new RSV-preventive interventions for young children in LMICs. Furthermore, cost-effectiveness studies are required to evaluate the health and economic effects of RSV interventions for children in LMICs.

Supplementary files can be downloaded from:



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PART III

Economic Burden and Cost-Effectiveness of RSV Immunisation Strategies in Low- and Middle-Income Countries

5

Estimating the Economic Burden of Respiratory Syncytial Virus Infection among Children <2 Years Old Receiving Carein Maputo, Mozambique

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ABSTRACT

Background. Data on costs of respiratory syncytial virus (RSV) in low- and lower-middle-income countries are urgently needed to inform the introduction of recently developed vaccines. We estimated the costs of lower respiratory tract infections associated with RSV infection in Mozambique.

Methods. We conducted a prospective cohort study to assess household and societal costs of RSV infection in children <2 years old who sought care in a referral hospital or a primary health centre in Mozambique during one local RSV season (February to August 2023). We used molecular point-of-care testing to confirm RSV status. We collected direct medical and non-medical costs and indirect cost data from hospital records and patient-level questionnaires at the initial visit and 2–4 weeks post-discharge.

Results. We recruited 544 children; 52.6% were girls and the median age was 9.3 months. From the sample, 286 children from the outpatient department, 233 from the paediatric wards, and 25 from the intensive care unit (ICU). RSV was confirmed in 42 (14.7%) out- patients, 111 (47.6%) inpatients, and 6 (24.0%) ICU cases. The mean total costs associated with RSV were USD 43 (95% confidence interval (CI) = 11–76) for outpatients, USD 612 (95% CI = 544–680) for inpatients, and USD 1161 (95% CI = 837–1485) for ICU cases. The government covered 16.9%, 89.9%, and 80.0% of overall societal costs for outpatients, inpatients, and ICU patients, respectively. The average household out-of-pocket costs for life-threatened RSV cases were more than 1.5 times the monthly minimum wage of USD 91, causing a high financial burden on families in Mozambique.

Conclusion. RSV infection represents a significant health care and economic burden in children <2 years old. Our results provide input for cost-effectiveness analyses and in- formed decision-making when considering RSV immunisation in Mozambique.

INTRODUCTION

Respiratory syncytial virus (RSV) causes a substantial burden of acute lower respiratory tract infections (LRTIs) in children under five years old, with approximately 33 million RSV-associated respiratory tract infections and 118 000 deaths estimated to occur annually in this group.[1] Most infections (95%), as well as more than 97%of deaths related to RSV, occur in low- and middle-income countries (LMICs).[2]

Targeted intervention strategies could significantly influence RSV-associated respiratory disease outcomes. While several preventive interventions are still under development,[3] two have recently been approved. One of them, nirsevimab – a long-acting monoclonal antibody (mAb) given as a single injection to infants for coverage throughout the whole RSV season – demonstrated significant benefits in a multinational randomised controlled trial.[4] The second intervention involved a phase III maternal immunisation trial, which showed promising results for a bivalent prefusion F vaccine administered to pregnant women during the third trimester, which effectively protects infants against RSV for up to six months postpartum.[5]

RSV-related health burden and cost data in LMICs, specifically in Mozambique, are scarce. In Mozambique, approximately 24.8% of all childhood deaths are attributed to LRTIs.[6] with RSV playing a substantial role.[7] A hospital-based study conducted in Maputo, Mozambique, between 2017 and 2018, showed an RSV infection incidence rate of 23.1% among children <2 years old.[8] Another study estimated RSV infection incidence rates of 58.3 (95% confidence interval (CI) = 43.0–79.0) per 1000 children.[2] A more recent study on the intensive care and high-dependency unit in Maputo reported that 35.1% of patients admitted with severe acute respiratory infection symptoms tested positive for RSV.[9]

As prevention strategies emerge, determining the burden of RSV and the associated costs of care in LMICs is critical and will improve our understanding of the economic and health care burden that may be averted by the introduction of those strategies. This information will assist stakeholders in prioritising and guiding evidence-based selection among available preventive interventions, particularly in contexts where resources are scarce. Therefore, we aimed to determine the direct medical and non-medical costs as well as indirect costs of LRTIs associated with RSV infection among children seeking care in urban health care facilities in Maputo, Mozambique, from the perspectives of the health system, households, and society.

METHODS

Study Setting

We conducted this prospective study as part of the multi-country RSV Global Online Mortality Database (GOLD) III–Health Economics Study, which took place in Ghana, Mozambique, Nepal, and Nigeria. All four countries were receiving financial and programmatic support from Gavi, the Vaccine Alliance. The study took place during one local RSV season and built upon the RSV GOLD III–Intensive Care Unit (ICU) Network Study, which was previously conducted in these countries to investigate the burden of life-threatening RSV.[9] In Mozambique, the study was conducted at Maputo Central Hospital referral hospital and Maputo's 1st of May Health Centre primary health care centre.

A national policy emphasising primary health care, equity, and quality services guides the health system in Mozambique. International aid is a significant source of financing; it prioritises initiatives targeting major health issues such as HIV/AIDS, malaria, tuberculosis, and maternal as well as child health. Urban areas have seen diversification in health financing, although this remains a small portion of overall funding. In the two health facilities covered in our study, donations from international aid also play a large role in financing medications, medical supplies, and facility equipment. We considered costs for patient care requiring such resources a health system cost.

Study Population

All children <2 years old who visited either of the health care facilities with (severe) acute respiratory infection during the local RSV season, ie between February and August 2023, were eligible for inclusion. We excluded children aged below 28 days and those with an onset of symptoms occurring more than ten days before the facility visit.

We categorised cases by severity: non-severe (outpatient only), severe (inpatient, no ICU admission), and life-threatened (ICU admission or fatality). Study staff were available during weekdays. Children admitted during the weekend were screened via admission books and clinical files on Mondays and, if eligible, were included in the study. At the 1st of May Health Centre, no children were recruited during the weekend. A nasopharyngeal swab was obtained within 72 hours and tested for RSV using the molecular point-of-care ID Now RSV test;[10,11] we included both RSV-positive and RSV-negative patients in our analysis, allowing for a comparison of costs for RSV and non-RSV cases.

The National Committee for Bioethics in Health (Ref: 806/CNBS/22) and the Medical Research Ethics Committee NedMec (#20-536) of the University Medical Centre in Utrecht, the Netherlands, approved the study protocol.

Sample Size Calculations

To determine the sample size needed for estimating the costs of LRTIs associated with RSV infection, we used the following formula[12]:

$$n = ceiling\left[\left(\frac{precision^2}{CV^2 \times Z^2_{1-a/2}} + \frac{1}{N_o}\right)\right]^{-1}$$

We used a Z-score of 1.96 and its 95% confidence interval (CI), a coefficient of variation of 0.5, and precision at ±10% of the mean cost. We used the caseload (N0) and RSV-positivity rate of 35.1% from a previous RSV study conducted at the ICU at Maputo Central Hospital[9] to calculate the target sample size. We estimated that, to achieve the optimal sample size of 91 RSV-positive inpatients and 94 RSV-positive outpatients, we had to enrol 260 inpatients and 309 outpatients with LRTI. Enrolment numbers may range from 122 to 910 LRTI inpatients and 128 to 900 LRTI outpatients, depending on the observed prevalence during the RSV season.

Data Collection

We collected the data during one local respiratory season, from February until August 2023. Trained study staff administered questionnaires designed for the RSV GOLD III – Health Economics Study, which were translated into Portuguese. Caregiver questions covered demographics and socioeconomic status, pre-facility visit illness history, and related costs. In addition, all costs from the day of the visit were reported. Patient medical records were reviewed upon discharge for detailed information on laboratory tests, imaging, procedures, and medication. For both inpatients and outpatients, follow-up phone calls occurred two to four weeks after facility visit/discharge to obtain information on subsequent illness-related costs, whether any additional facility visits took place for illness-related symptoms, and, if so, which costs were incurred. We assessed cost data from the health system and household perspectives, which were then combined to calculate the total costs from the societal perspective. A detailed overview of the study setup, the cost analysis (including the various cost components and the bottom-up approach used for data collection and analysis), can be found in the Online Supplementary Document). The local study team entered all data into the Castor electronic data capture system.[13]

Data Analysis

We summarised the demographic and clinical characteristics of all patients. We used a bottom-up costing approach to estimate the treatment costs associated with respiratory illness. In general, we calculated direct medical and non-medical costs by multiplying the quantity used by unit cost for all items across all cost categories. For indirect costs, we considered the income loss reported by the household, as well as productivity loss. We determined total costs as the sum of direct medical costs, direct non-medical costs, and indirect costs. Furthermore, we analysed the costs concerning the severity of cases based on the location of admission.

Statistical Analysis

Since almost all cost data were non-normally distributed, we used both means and medians to summarise cost data. We checked for skewness and used bootstrapping with 1000 replications to obtain the 95% CI for the mean cost since the data were not normally distributed. The lower limits of the 95% CI were censored to zero to reflect the fact that cost data were nonnegative. We used the Mann-Whitney U test to compare the non-normally distributed continuous variables between RSV-positive and RSV-negative cases and compared costs for non-severe, severe, and life-threatened groups using the Kruskal-Wallis test, considering a P-value ≥0.05 to indicate no significant difference between the groups. We conducted all statistical analyses separately for RSV- positive and RSV-negative patients. The analyses were done using Stata, version 18.0 (StataCorp LLC, College Station, TX, USA).

RESULTS

Patient Characteristics

We included 544 patients in the study (Figure 1), of whom 286 (52.6%) attended the 1st of May Health Centre, 233 (42.8%) were admitted to the general wards, and 25 (4.6%) were admitted to the ICU. An overview of weekly counts of recruited children during the study period is provided in the supplementary materials (Figure S2 in the Online Supplementary Document). Almost a third (n= 159, 29.2%) of included children tested positive for RSV (Table 1). The mean age of RSV-positive inpatient cases was 6.9 months (standard deviation (SD) = 6.3) at the time of enrolment, and the majority were female (n= 89, 56.0%). The median length of stay among RSV-positive inpatients was 4.3 days (interquartile range (IQR) = 3–5) for severe cases and six days (IQR = 5–8) for life-threatened cases. Of all patients, 193 (35.5%) sought care before the index visit, more often (P = 0.0034) among those testing positive for RSV (n = 67, 44.4%) compared to non-RSV cases (n = 126, 32.1%).

Cost per Episode – Societal Perspective

The mean total cost from the societal perspective per RSV episode was USD 43 (95% CI = 11–76) for non-severe cases and USD 612 (95% CI = 544–680) for severe cases (Table 2). Mean costs for the few children with a life-threatening RSV infection were almost twice the total costs for severe cases at USD 1161 (95% CI= 837–1485). Direct medical costs accounted for the highest proportion of the total costs for both severe (91.9%) and life-threatened cases (86.3%) with RSV infection. Total mean costs of non-RSV-associated LRTIs were much lower for non-severe cases (USD 19 vs. USD 43), comparable for severe cases (USD 586 vs. USD 612), and 1.5 times higher for life-threatened cases (USD 1755 vs. USD 1161). Total costs differed significantly by RSV status ($P < 0.001$) and were higher for RSV-positive (USD 482; 95% CI = 415–549) compared to RSV-negative cases (USD 285; 95% CI = 221–348). Costs were predominantly influenced by overhead expenses and the length of stay. When cases with a length of stay exceeding ten days are excluded, costs for life-threatened cases for RSV-positive as well as non-RSV cases become more comparable (Table S1 in the Online Supplementary Document).

Health System Costs

Mean direct medical costs for the health system (Table 3) were comparable for outpatient cases who tested positive for RSV and those who tested negative (USD 7.25 vs. USD 7.27; $P = 0.0968$), but lower for severe RSV-negative cases (USD 449 vs. USD 550; $P = 0.0068$) and higher for non-RSV life-threatened cases (USD 1508 vs. USD 928; $P = 0.5043$). As expected, costs increased with longer hospital stays and severity of illness, regardless of RSV status. Additionally, medical expenses for more severe cases included higher costs for medication, as well as laboratory and imaging services.

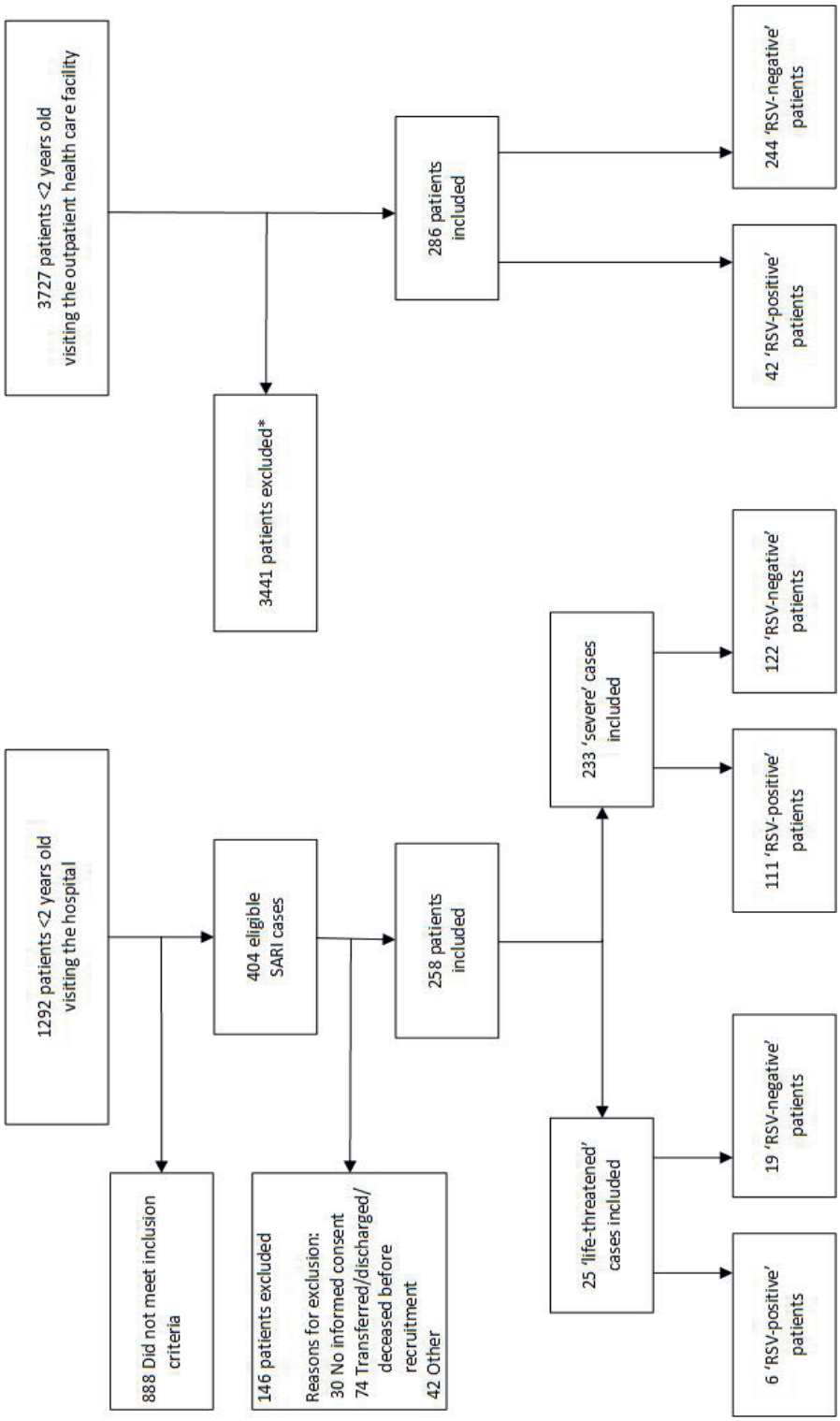

Figure 1. Flow diagram illustrating the total number of outpatients and inpatients included and excluded from the study. RSV – respiratory syncytial virus, SARI – severe acute respiratory infection. *Reasons for exclusion unknown, not included.

Table 1. Demographics and clinical characteristics of RSV-positive and RSV-negative children <2 years old by severity level.*

	RSV-positive				RSV-negative				All patients
	Total	Non-severe	Severe	Life-threatened	Total	Non-severe	Severe	Life-threatened	Total
Total number of participants	159	42	111	6	385	244	122	19	544
Age in months, x̄ (SD)	6.9 (6.3)	10.0 (7.1)	5.9 (5.8)	3.3 (2.1)	10.2 (6.4)	10.2 (6.4)	10.5 (6.4)	9.4 (7.0)	9.3 (6.6)
Female	89 (56.0)	26 (61.9)	58 (52.3)	5 (83.3)	197 (51.2)	126 (51.6)	61 (50.0)	10 (52.6)	286 (52.6)
Household size, MD (IQR)	5 (4–6)	6 (4–7)	5 (4–6)	4 (3–5)	5 (4–7)	5 (4–7)	5 (4–6)	5 (3–6)	5 (4–7)
Level of education of primary caregiver secondary school or higher	140 (88.1)	32 (76.2)	103 (92.8)	5 (83.3)	330 (85.7)	202 (82.8)	114 (93.4)	14 (73.7)	470 (86.4)
Distance to health care facility in km, x̄ (SD)	11.4 (9.9)	3.1 (2.3)	14.2 (9.0)	18.2 (21.5)	9.8 (23.1)	3.0 (3.8)	18.8 (31.6)	39.6 (48.4)	10.3 (20.1)
Diagnosis at admission									
Bronchiolitis	78 (50.7)	0 (0.0)	75 (70.1)	3 (60.0)†	41 (10.9)	0 (0.0)	39 (33.1)	2 (11.8)	119 (22.4)
Pneumonia	32 (20.8)	0 (0.0)	30 (28.0)	2 (40.0)†	77 (20.4)	0 (0.0)	72 (61.0)	5 (29.4)	109 (20.5)
URTI	39 (25.3)	39 (92.9)	0 (0.0)	0 (0.0)	223 (59.0)	221 (91.0)	2 (1.7)	0 (0.0)	262 (49.3)
Other	5 (3.3)	3 (7.1)	2 (1.9)	0 (0.0)	37 (9.8)	22 (9.1)	5 (4.2)	10 (58.8)	42 (7.9)
Prematurity	27 (17.0)	7 (16.7)	19 (17.1)	1 (16.7)	32 (8.4)	16 (6.6)	13 (10.8)	3 (16.7)	59 (11.0)
Comorbidity	18 (11.3)	2 (4.8)	15 (13.5)	1 (16.7)	45 (11.7)	20 (8.2)	21 (17.2)	4 (21.1)	63 (11.6)
Length of stay in days, MD (IQR)	4 (3–5)	NA	4 (3–5)	6 (5–8)†	3 (2–5)	N/A	3 (2–4)	12 (6–21)‡	3 (2–5)
Previous medical consultation	71 (44.9)	12 (29.3)	53 (47.8)	6 (100)	122 (31.7)	52 (21.3)	53 (43.4)	17 (89.5)	193 (35.5)
Follow-up care	102 (68.9)	9 (24.3)§	89 (84.0)	4 (80.0)†	152 (47.1)	32 (16.7)¶	108 (91.5)	12 (92.3)‖	254 (53.9)
Mortality	1 (0.7)	0 (0.0)	0 (0.0)	1 (16.7)	4 (1.1)	0 (0.0)	0 (0.0)	4 (23.5)††	5 (1.0)

IQR – interquartile range, MD – median, RSV – respiratory syncytial virus, SD – standard deviation, URTI – upper respiratory tract infection, x̄ – mean. *Values presented as n (%) unless specified otherwise. †Missing data due to incomplete or missing clinical records (n = 5/6). ‡Missing data due to incomplete or missing clinical records (n = 15/19). §Missing data due to incomplete or missing clinical records (n = 37/42). ¶Missing data due to incomplete or missing clinical records (n = 192/244). ‖Missing data due to incomplete or missing clinical records (n = 13/19). ††Missing data due to incomplete or missing clinical records (n = 17/19).

Table 2. Societal cost (in 2023 USD) per LRTI episode for RSV-positive and RSV-negative children <2 years old, by severity level.

	RSV-positive (n = 159)			RSV-negative (n = 385)		
	Non-severe (n = 42)	**Severe (n = 111)**	**Life-threatened (n = 6)**	**Non-severe (n = 244)**	**Severe (n = 122)**	**Life-threatened (n = 19)**
Total costs						
x̄ (95% CI)	43.42 (11.34–75.50)	611.78 (543.91–679.64)	1160.70 (836.70–1484.70)	19.17 (15.82–22.51)	586.12 (484.92–687.31)	1755.47 (1,110.42–2400.51)
MD (IQR)	18.13 (10.63–37.69)	550.03 (417.56–724.99)	1216.59 (1,008.67–1319.18)	13.35 (10.31–19.84)	461.75 (306.18–711.95)	1321.51 (875.95–3086.02)
Direct medical costs						
x̄ (95% CI)	13.45 (11.47–15.42)	561.95 (497.51–626.39)	1001.62 (590.03–1413.22)	13.05 (11.22–14.87)	484.49 (402.77–566.22)	1530.94 (960.82–2101.05)
MD (IQR)	10.80 (8.96–16.79)	442.37 (332.01–679.77)	1,029.70 (876.94–1255.93)	10.92 (9.04–13.74)	416.29 (286.03–575.41)	1,084.76 (269.33–3030.67)
Hospitality/facility-based fees						
x̄ (95% CI)	7.47 (7.27–7.68)	524.95 (462.26–587.64)	772.86 (432.84–1112.87)	7.61 (7.11–8.12)	444.39 (365.36–523.42)	1,339.49 (820.43–1858.55)
MD (IQR)	7.32 (7.32–7.32)	396.78 (264.00–652.16)	750.25 (652.16–1046.59)	7.32 (7.32–7.32)	391.30 (260.87–521.75)	782.67 (260.87–2608.66)
Medication costs						
x̄ (95% CI)	5.03 (3.65–6.41)	7.70 (5.85–9.56)	65.32 (4.92–125.72)	4.69 (4.08–5.30)	10.43 (7.54–13.32)	20.89 (8.29–33.48)
MD (IQR)	3.48 (1.64–7.43)	4.70 (1.05–10.74)	37.36 (13.16–75.76)	3.56 (1.72–6.34)	5.28 (1.58–13.83)	9.43 (6.98–27.17)

Table 2. Continued.

	RSV-positive (n = 159)			RSV-negative (n = 385)		
	Non-severe (n = 42)	**Severe (n = 111)**	**Life-threatened (n = 6)**	**Non-severe (n = 244)**	**Severe (n = 122)**	**Life-threatened (n = 19)**
Laboratory costs						
x̄ (95% CI)	0.00 (0.00–0.00)	12.65 (10.37–14.93)	118.75 (28.04–209.45)	1.93 (0.00–5.19)	11.99 (9.83–14.15)	107.12 (62.09–152.15)
MD (IQR)	0.00 (0.00–0.00)	6.26 (6.26–12.52)	71.56 (30.69–237.30)	0.00 (0.00–0.00)	6.26 (6.26–10.17)	88.82 (0.00–189.03)
Imaging costs						
x̄ (95% CI)	2.09 (0.00–6.06)	14.13 (13.04–15.22)	26.09 (12.29–39.89)	0.00 (0.00–0.00)	14.42 (13.10–15.74)	46.09 (23.63–68.55)
MD (IQR)	0.00 (0.00–0.00)	15.65 (15.65–15.65)	23.48 (15.65–46.96)	0.00 (0.00–0.00)	15.65 (15.65–15.65)	39.13 (0.00–78.26)
Procedure costs						
x̄ (95% CI)	1.78 (0.00–4.45)	0.83 (0.24–1.41)	11.82 (0.00–25.14)	0.00 (0.00–0.00)	0.15 (0.03–0.27)	11.60 (0.69–22.52)
MD (IQR)	0.00 (0.00–0.00)	0.00 (0.00–0.27)	1.07 (0.00–30.60)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.53 (0.00–1.34)
Miscellaneous costs						
x̄ (95% CI)	1.78 (0.00–3.99)	2.51 (1.22–3.79)	6.78 (0.00–16.30)	1.25 (0.03–2.48)	2.06 (0.87–3.24)	5.01 (0.43–9.59)
MD (IQR)	0.00 (0.00–0.16)	0.00 (0.00–2.23)	0.00 (0.00–7.83)	0.00 (0.00–0.00)	0.00 (0.00–0.31)	0.00 (0.00–4.77)

Table 2. Continued.

	RSV-positive (n = 159)			RSV-negative (n = 385)		
	Non-severe (n = 42)	**Severe (n = 111)**	**Life-threatened (n = 6)**	**Non-severe (n = 244)**	**Severe (n = 122)**	**Life-threatened (n = 19)**
Direct non-medical costs*						
x̄ (95% CI)	5.56 (2.90–8.22)	15.68 (11.78–19.57)	25.05 (0.00–62.09)	3.37 (2.29–4.44)	26.05 (18.12–33.98)	10.93 (0.23–21.64)
MD (IQR)	0.71 (0.00–6.42)	5.37 (1.97–22.85)	4.63 (1.57–12.31)	0.47 (0.00–2.82)	12.32 (3.20–28.17)	1.22 (0.47–13.46)
Transport costs						
x̄ (95% CI)	0.91 (0.03–1.78)	5.95 (4.20–7.70)	23.98 (0.00–61.44)	0.72 (0.37–1.07)	8.23 (5.09–11.38)	5.04 (1.16–8.92)
MD (IQR)	0.47 (0.00–0.94)	2.27 (1.03–4.72)	1.97 (0.47–12.31)	0.00 (0.00–0.47)	3.29 (1.13–8.13)	0.56 (0.00–4.48)
Meal costs						
x̄ (95% CI)	0.16 (0.00–0.37)	5.37 (2.74–8.01)	0.00 (0.00–0.00)	0.12 (0.07–0.17)	8.45 (3.33–13.57)	0.05 (0.00–0.14)
MD (IQR)	0.00 (0.00–0.00)	0.00 (0.00–2.90)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)
Caretaker costs						
x̄ (95% CI)	0.00 (0.00–0.00)	0.57 (0.00–1.38)	0.00 (0.00–0.00)	0.71 (0.00–1.59)	1.18 (0.00–3.46)	0.00 (0.00–0.00)
MD (IQR)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)

Table 2. Continued.

	RSV-positive (n = 159)			RSV-negative (n = 385)		
	Non-severe (n = 42)	**Severe (n = 111)**	**Life-threatened (n = 6)**	**Non-severe (n = 244)**	**Severe (n = 122)**	**Life-threatened (n = 19)**
Indirect costs						
x̄ (95% CI)	24.41 (0.00–56.12)	34.15 (21.84–46.47)	134.03 (18.09–249.98)	2.75 (1.31–4.19)	75.57 (39.54–111.61)	213.60 (26.05–401.14)
MD (IQR)	0.00 (0.00–3.69)	8.44 (0.00–30.08)	80.43 (0.00–264.35)	0.00 (0.00–1.06)	12.67 (0.00–46.96)	14.01 (0.00–227.86)
Lost income						
x̄ (95% CI)	3.99 (0.74–7.23)	4.29 (1.16–7.41)	18.26 (0.00–48.54)	0.76 (0.04–1.47)	6.39 (0.00–12.82)	13.02 (0.00–30.38)
MD (IQR)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–7.83)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)
Lost productivity						
x̄ (95% CI)	20.15 (0.00–50.87)	23.26 (12.88–33.64)	120.67 (0.00–255.48)	1.60 (0.53–2.67)	61.77 (30.38–93.15)	194.78 (4.35–385.20)
MD (IQR)	0.00 (0.00–0.49)	0.00 (0.00–20.81)	0.00 (0.00–253.89)	0.00 (0.00–0.00)	0.00 (0.00–30.58)	0.00 (0.00–175.50)
Lost leisure						
x̄ (95% CI)	0.28 (0.00–0.60)	6.60 (5.05–8.16)	15.22 (2.52–27.92)	0.40 (0.20–0.59)	7.92 (5.68–10.16)	16.06 (6.29–25.83)
MD (IQR)	0.00 (0.00–0.00)	4.22 (0.00–8.44)	9.76 (0.00–29.56)	0.00 (0.00–0.00)	4.22 (0.00–12.67)	7.39 (0.00–25.33)

CI – confidence interval, IQR – interquartile range, MD – median, RSV – respiratory syncytial virus, LRTI – lower respiratory tract infection, x̄ – mean. *Besides transport, meal, and caretaker costs, lodging costs are also included in this category; however, only a few cases have costs here and are not shown in the table.

Table 3. Direct medical cost (in 2023 USD) covered by the health system per LRTI episode for RSV-positive and RSV-negative children <2 years old by severity level.

	RSV-positive (n = 159)			RSV-negative (n = 385)		
	Non-severe (n = 42)	**Severe (n = 111)**	**Life-threatened (n = 6)**	**Non-severe (n = 244)**	**Severe (n = 122)**	**Life-threatened (n = 19)**
Direct medical costs*						
x̄ (95% CI)	7.25 (7.24–7.26)	549.91 (485.76–614.06)	928.46 (505.52–1,351.39)	7.27 (7.25–7.30)	448.92 (383.19–514.64)	1508.01 (945.27–2,070.74)
MD (IQR)	7.24 (7.24–7.24)	435.39 (312.04–674.18)	931.00 (706.52–1,212.33)	7.24 (7.24–7.24)	410.72 (280.55–550.13)	1076.47 (264.55–2,981.56)
Hospitality/facility-based fees						
x̄ (95% CI)	7.25 (7.24–7.25)	521.29 (458.54–584.04)	760.86 (418.08–1,103.64)	7.24 (7.24–7.25)	420.98 (356.41–485.55)	1337.99 (818.56–1,857.43)
MD (IQR)	7.24 (7.24–7.24)	388.17 (260.87–649.03)	717.38 (652.16–1,043.46)	7.24 (7.24–7.24)	388.17 (257.74–518.60)	782.60 (257.74–2,605.53)
Medication costs						
x̄ (95% CI)	0.01 (0.00–0.02)	1.77 (1.32–2.21)	15.77 (4.47–27.07)	0.00 (0.00–0.00)	1.74 (1.38–2.11)	13.63 (1.67–25.59)
MD (IQR)	0.00 (0.00–0.00)	0.89 (0.43–2.08)	7.73 (6.81–33.48)	0.00 (0.00–0.00)	0.89 (0.66–2.08)	6.81 (6.22–11.74)
Laboratory costs						
x̄ (95% CI)	0.00 (0.00–0.00)	12.56 (10.28–14.85)	113.92 (20.46–207.38)	0.11 (0.00–0.22)	11.95 (9.80–14.11)	107.12 (62.09–152.15)
MD (IQR)	0.00 (0.00–0.00)	6.26 (6.26–10.17)	57.08 (30.69–237.30)	0.00 (0.00–0.00)	6.26 (6.26–10.17)	88.82 (0.00–189.03)
Imaging costs						
x̄ (95% CI)	2.09 (0.00–6.06)	14.13 (13.04–15.22)	26.09 (12.29–39.89)	0.00 (0.00–0.00)	13.98 (12.79–15.17)	46.09 (23.63–68.55)
MD (IQR)	0.00 (0.00–0.00)	15.65 (15.65–15.65)	23.48 (15.65–46.96)	0.00 (0.00–0.00)	15.65 (15.65–15.65)	39.13 (0.00–78.26)
Procedure costs						
x̄ (95% CI)	1.41 (0.00–4.10)	0.83 (0.24–1.41)	11.82 (0.00–25.14)	0.00 (0.00–0.00)	0.15 (0.03–0.27)	11.60 (0.69–22.52)
MD (IQR)	0.00 (0.00–0.00)	0.00 (0.00–0.27)	1.07 (0.00–30.60)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.53 (0.00–1.34)

CI – confidence interval, IQR – interquartile range, MD – median, RSV – respiratory syncytial virus, LRTI – lower respiratory tract infection, x̄ – mean.
*Miscellaneous costs are part of direct medical costs; however, those costs that are >95% covered by the households and are not shown.

Table 4. Household out-of-pocket costs (in 2023 USD) per LRTI episode for RSV-positive and RSV-negative children <2 years old by severity level.

	RSV-positive (n = 159)			RSV-negative (n = 385)		
	Non-severe (n = 42)	**Severe (n = 111)**	**Life-threatened (n = 6)**	**Non-severe (n = 244)**	**Severe (n = 122)**	**Life-threatened (n = 19)**
Total cost						
x̄ (95% CI)	16.02 (11.33–20.71)	38.61 (31.70–45.52)	131.69 (14.84–248.53)	10.30 (7.48–13.11)	75.94 (30.26–121.61)	62.94 (17.40–108.48)
MD (IQR)	8.10 (2.90–26.76)	28.58 (14.41–44.99)	60.62 (15.42–294.66)	5.46 (2.78–11.00)	33.03 (15.65–66.33)	25.64 (6.42–65.66)
Direct medical cost						
x̄ (95% CI)	6.19 (4.21–8.17)	12.04 (9.88–14.20)	73.16 (0.00–169.99)	5.78 (3.95–7.60)	35.58 (0.00–78.56)	22.93 (0.00–45.91)
MD (IQR)	3.56 (1.72–9.55)	8.22 (4.71–14.09)	20.43 (10.25–43.60)	3.68 (1.80–6.50)	9.18 (4.56–18.79)	6.35 (3.14–18.87)
Hospitality/facility-based costs						
x̄ (95% CI)	0.23 (0.02–0.44)	3.66 (3.36–3.96)	12.00 (0.00–31.04)	0.37 (0.00–0.88)	23.41 (0.00–64.21)	1.49 (0.73–2.26)
MD (IQR)	0.08 (0.08–0.08)	3.13 (3.13–3.21)	1.57 (0.00–3.13)	0.08 (0.08–0.08)	3.13 (3.13–5.48)	0.08 (0.00–3.13)
Medication costs						
x̄ (95% CI)	5.02 (3.64–6.41)	5.94 (4.20–7.67)	49.55 (0.00–110.68)	4.69 (4.08–5.30)	8.69 (5.85–11.53)	7.26 (2.65–11.86)
MD (IQR)	3.48 (1.64–7.43)	3.14 (0.08–7.83)	16.90 (6.35–38.12)	3.56 (1.72–6.34)	3.47 (0.08–10.25)	1.77 (0.17–12.76)
Laboratory						
x̄ (95% CI)	0.00 (0.00–0.00)	0.08 (0.00–0.17)	4.83 (0.00–12.56)	0.42 (0.00–1.17)	0.04 (0.00–0.09)	0.00 (0.00–0.00)
MD (IQR)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–2.35)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)
Miscellaneous costs						
x̄ (95% CI)	1.87 (0.00–4.16)	2.43 (1.14–3.71)	6.78 (0.00–16.30)	1.17 (0.03–2.32)	1.95 (0.76–3.13)	4.75 (0.52–8.98)
MD (IQR)	0.00 (0.00–0.16)	0.00 (0.00–1.80)	0.00 (0.00–7.83)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–4.77)

Table 4. Continued.

	RSV-positive (n = 159)			RSV-negative (n = 385)		
	Non-severe (n = 42)	**Severe (n = 111)**	**Life-threatened (n = 6)**	**Non-severe (n = 244)**	**Severe (n = 122)**	**Life-threatened (n = 19)**
Direct non-medical costs†						
x̄ (95% CI)	5.56 (2.90–8.22)	15.68 (11.78–19.57)	25.05 (0.00–62.09)	3.37 (2.29–4.44)	26.05 (18.12–33.98)	10.93 (0.23–21.64)
MD (IQR)	0.71 (0.00–6.42)	5.37 (1.97–22.85)	4.63 (1.57–12.31)	0.47 (0.00–2.82)	12.32 (3.20–28.17)	1.22 (0.47–13.46)
Transport costs						
x̄ (95% CI)	0.91 (0.03–1.78)	5.95 (4.20–7.70)	23.98 (0.00–61.44)	0.72 (0.37–1.07)	8.23 (5.09–11.38)	5.04 (1.16–8.92)
MD (IQR)	0.47 (0.00–0.94)	2.27 (1.03–4.72)	1.97 (0.47–12.31)	0.00 (0.00–0.47)	3.29 (1.13–8.13)	0.56 (0.00–4.48)
Meal costs						
x̄ (95% CI)	0.16 (0.00–0.37)	5.37 (2.74–8.01)	0.00 (0.00–0.00)	0.12 (0.07–0.17)	8.45 (3.33–13.57)	0.05 (0.00–0.14)
MD (IQR)	0.00 (0.00–0.00)	0.00 (0.00–2.90)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)
Indirect costs						
x̄ (95% CI)	4.26 (0.85–7.68)	10.89 (7.16–14.62)	33.48 (0.00–74.07)	1.15 (0.42–1.88)	14.31 (7.38–21.24)	29.07 (4.52–53.63)
MD (IQR)	0.00 (0.00–0.00)	4.22 (0.00–14.09)	13.68 (0.00–29.56)	0.00 (0.00–0.00)	4.22 (0.00–12.67)	12.67 (0.00–27.45)
Lost income						
x̄ (95% CI)	3.99 (0.74–7.23)	4.29 (1.16–7.41)	18.26 (0.00–48.54)	0.76 (0.04–1.47)	6.39 (0.00–12.82)	13.02 (0.00–30.38)
MD (IQR)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–7.83)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)
Lost leisure						
x̄ (95% CI)	0.28 (0.00–0.60)	6.60 (5.05–8.16)	15.22 (2.52–27.92)	0.40 (0.20–0.59)	7.92 (5.68–10.16)	16.06 (6.29–25.83)
MD (IQR)	0.00 (0.00–0.00)	4.22 (0.00–8.44)	9.76 (0.00–29.56)	0.00 (0.00–0.00)	4.22 (0.00–12.67)	7.39 (0.00–25.33)

CI – confidence interval, IQR – interquartile range, MD – median, RSV – respiratory syncytial virus, LRTI – lower respiratory tract infection, x̄ – mean. *Direct medical out-of-pocket costs for imaging and other services are negligible and are not shown here. †Besides transport and meal costs, caretaker and lodging costs are included in this category; however, only a few cases have costs here and are not shown in the table

Household Costs

Of 544 caregivers, 516 reported out-of-pocket costs (Table 4). Overall, direct medical out-of-pocket costs accounted for between 28.2% and 36.6% of the total out-of-pocket cost related to one RSV illness episode. The mean direct medical out-of-pocket costs for RSV-positive patients were USD 6 (95% CI = 4–8) for non-severe cases, USD 12 (95% CI = 10–14) for severe cases, and USD 73 (95% CI = 0–170) for life-threatened cases. The overall mean out-of-pocket costs for RSV-positive patients receiving inpatient care (Table S2 in the Online Supplementary Document) were almost three times higher compared to outpatient cases (USD 43 vs. USD 16). Direct non-medical out-of- pocket costs, such as transportation, food, and caretaker costs, accounted for between 19.0% and 40.6% of the total household costs related to one RSV illness episode. Indirect out-of-pocket costs accounted for approximately 25% of the overall out-of-pocket expenses for RSV-positive cases, irrespective of the severity. Among non-RSV cases, the overall out-of-pocket costs for outpatients were significantly lower than those for RSV cases (USD 10 vs. USD 16; P = 0.0321). Similarly, we found cost differences for severe and life-threatened cases; however, these were not statistically significant (P = 0.1496 and P = 0.4004, respectively). Most families of patients with non-severe (48.6%), severe (87.0%), and life-threatening (100.0%) illnesses reported having used savings to cover disease-related treatment costs.

DISCUSSION

This is the first prospective study to evaluate costs related to LRTI throughout an entire RSV season in Mozambique, reporting direct medical, direct non-medical, and indirect costs from health system and household perspectives. It provides a further understanding of RSV's impact by estimating the economic burden of RSV-related facility visits in a low-income country. This information is crucial for informing policy decision-makers and evaluating new intervention strategies to prevent RSV infections. It provides insight into the direct medical, non-medical, and indirect costs incurred due to RSV in Maputo, Mozambique. RSV-related hospitalisations in children <2 years old caused a substantial economic burden on the Mozambican health system and households. Inpatient care costs for children treated at the ICU were approximately twice as high as those for patients treated in the paediatric wards.

In our introduction, we highlighted the lack of data on RSV-related health burden and costs in Mozambique. We referenced a hospital-based study conducted in Maputo, which reported an incidence rate of RSV infections of 23.1% among children <2 years old.[8] Moreover, a recent investigation on intensive care in Maputo found that 35.1% of patients <2 years old admitted with extended severe acute respiratory infection

symptoms tested positive for RSV.[9] Our study shows once again the high burden of RSV on the health system in Mozambique, with 29.2% of the included patients testing positive for RSV.

Globally, RSV-related cost data from LMICs are sparse. Malawi is the only low-income country in Africa with available cost-of-illness data for RSV. Mean costs per RSV episode reported in Malawi in 2018 were USD 62 for inpatient cases and USD 13 for outpatients.[14] Taking inflation into account, RSV-related costs in Malawi corresponded to 11.2% and 2.3% of the GDP per capita for inpatients and outpatients, respectively, in 2023. The costs from our study in Mozambique are much higher, contributing to 105.2% for inpatient cases and 7.1% of GDP per capita for outpatient cases. Another cost-of-illness study from neighbouring upper-middle-income South Africa demonstrated comparable costs for hospitalised children, with the cost per severe RSV illness episode totalling USD 681 in 2016 (USD 865 when adjusted for inflation to 2023).[15] This suggests that, despite the economic differences between Mozambique and South Africa, health care infrastructure, treatment practices, and cost drivers may be more aligned than expected.

Several factors could explain the observed differences across countries, including variations in the availability and accessibility of health care. While Mozambique and Malawi are both classified as low-income countries, the quality of care may differ. In some cases, the quality of care in these countries may be closer to that observed in South African facilities, despite the differences in economic status. Additionally, differences in treatment protocols and clinical guidelines can significantly impact illness-related costs and contribute to cost discrepancies. Moreover, the completeness of the costs included in our study might also contribute to the differences observed when compared to other studies. These inter-country differences highlight the need of country-specific cost estimates to inform decision-making at the national level.

A similar study conducted in Mopeia, a more rural area of Mozambique, estimated the costs of malaria in children.[16] Although most costs were incurred by younger children, it is important to note that this study focussed on costs incurred by children under five years old. The mean costs for the society per severe episode of malaria were reported as USD 108 (USD 131 when adjusted for inflation to 2023). While the treatment and management of malaria and respiratory illness may not be directly comparable, the costs estimated for severe RSV-positive cases from our study contribute to the findings by highlighting the substantial economic impact of infectious diseases within the Mozambican health system. Costs for malaria care in Mopeia may be lower due to the rural setting and the nature of district hospitals, where overhead costs are likely lower

and the level of care provided may be less comprehensive, resulting in lower overall costs.

Several studies have identified catastrophic health expenditures related to severe RSV illness from 24% up to 100% of the monthly income.[14] In Malawi, out-of-pocket costs accounted for 24% of the monthly household income. In South Africa, severe RSV illness was associated with overwhelming out-of-pocket personal expenses averaging more than 100% of the mean monthly income. A similar observation was made in Kenya, another LMIC where over 90% of the households reported adverse financial impacts due to the costs of RSV illness. While the Government of Mozambique strives to provide coverage for direct medical costs for patients, families still face substantial out-of-pocket expenses. For severe and life-threatened RSV cases, these costs remain high, ranging from approximately 43% to 145% of the monthly minimum wage per person (USD 91 in 2023). In our study, all families with children admitted to the ICU reported having to use their savings to cover expenses. Addressing this economic burden is crucial to reducing financial strain on families, lowering childhood mortality, and advancing poverty reduction efforts.

Given the median age of 3.3 months of children with life-threatening RSV infection in our study, both mAbs and maternal vaccination would likely have a high impact on preventing paediatric life-threatening RSV infection in Mozambique. Our detailed quantification of RSV-related costs is key for decision-making, prioritising future preventive strategies, and achieving effective allocation of health resources. Moreover, data could be used for estimating the full impact of introducing a mAb or maternal vaccine in Mozambique. The data derived here provide a basis for subsequent cost-effectiveness analyses, allowing for the economic impact of mAbs and maternal vaccines on RSV to be better evaluated and inform decisions regarding the most cost-effective intervention strategy to be introduced in Mozambique.

This study had several limitations. First, a major weakness is the lack of accessible cost data from the health system. Unit expenses for each category were obtained from the administrative office due to a lack of individual documentation in the public domain and are sometimes based on charges rather than actual costs to the health system. Additionally, by relying on administrative cost data, it is possible that not all relevant costs were captured, which could lead to inaccuracies in the cost estimates. Second, we only captured incurred costs without considering the quality of care received. Third, the study population consisted of patients from a single referral hospital and one health care centre in the capital of Mozambique, limiting the generalisability of the findings to the whole country. Fourth, a high participant/caregiver burden (due to lengthy interviews) potentially affected the quality of data and reduced participation rates.

Furthermore, follow-up interviews conducted via phone calls may have contributed to lower response rates when compared to regular in-person follow-up visits. We note, however, that study adherence was high. Sixth, the validity of the household cost findings may be compromised by reliance on self-reported cost data from parents/caregivers, since discussing costs and income can be sensitive in Mozambique. Lastly, using the average wage as a proxy may not fully capture individual income differences, potentially introducing bias into the estimates of indirect costs and therefore the overall household costs.

CONCLUSION

Our study highlights the substantial financial burden that (severe) RSV imposes not only on the government but also on the households. This economic strain further underscores the urgent need for preventive strategies to mitigate long-term health care costs and reduce the economic impact on families. The findings reinforce the importance of ensuring that effective and affordable interventions are accessible, particularly in LMICs, as Mozambique where the burden of RSV is disproportionally high. It is crucial for stakeholders to fully understand the economic impact of RSV to evaluate the potential implementation of immunisation strategies. Prioritising prevention strategies and ensuring access to effective interventions for all children in Mozambique should be a key focus. We call on stakeholders to act by assessing the cost-effectiveness of available interventions and working towards making RSV prevention in Mozambique a reality.

Supplementary files can be downloaded from:



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6

Assessing the Cost of Illness of RSV and Non-RSV Acute Respiratory Infections in Nepali Children

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ABSTRACT

Background. Low- and middle-income countries (LMICs) bear the greatest burden of the global respiratory syncytial virus (RSV) morbidity and mortality, but lack cost data to evaluate the health-economic impact of RSV burden on families, the healthcare system, and society. This prospective observational study was performed by the RSV GOLD III–Health Economic Research Group and estimated the costs associated with RSV illness in Nepal.

Methods. We collected healthcare resource utilisation data from children <2 years old fulfilling the World Health Organization (severe) acute respiratory infections ((S)ARI) case definition over one local respiratory season (July to November 2023) at two public hospitals in Nepal. We used hospital records and caregiver interviews to collect direct medical, direct non-medical, and indirect cost data to generate total per-patient costs.

Results. We included 730 patients with a mean age of 6.8 (standard deviation = 5.8) months. RSV infection was confirmed in 72.6% of the inpatients (n/N = 469/646) with SARI. The mean total cost per RSV episode was USD 43 (95% confidence interval (CI) = 25–62) for non-severe, USD 312 (95% CI = 293–332) for severe, and USD 664 (95% CI = 381–947) for life-threatened patients. Of the total costs, the healthcare system incurred USD 16 (36.3%), USD 58 (18.6%), and USD 57 (8.6%) in each category of illness. Household-level costs were 1.4% (USD 19) of the country's gross domestic product per capita for non-severe, 15.1% (USD 200) for severe, and 35.7% (USD 472) for life-threatened patients, with costs for inpatients often reaching catastrophic levels.

Conclusion. Our findings show a significant healthcare and economic burden of RSV illness in Nepal, highlighting the need to prioritise RSV prevention strategies. Our cost burden data can inform the modelling of costs and benefits of future RSV interventions in Nepal.

INTRODUCTION

Respiratory syncytial virus (RSV) is an important cause of hospitalisation and mortality due to lower respiratory tract infections (LRTIs) in children under five years old worldwide. An estimated 33 million respiratory tract infections and 118 000 deaths are associated with RSV annually, with most infections and deaths occurring in low- and middle-income countries (LMICs).[1] RSV tends to be most severe in young infants aged less than six months, with most infections occurring within the first year of life.[1] Global estimates suggest that RSV contributes approximately 1.2 million disability-adjusted life years, imposing an economic burden of approximately USD 5.4 billion annually.[2] A significant proportion of this burden is borne by LMICs, with nearly 55% of global costs attributed to acute lower respiratory tract infections requiring hospitalisation.[2]

Acute respiratory infections (ARIs) persist as a considerable public health problem in Nepal, with a prevalence rate of 2.1% observed among children under five years old.[3] Data on the RSV disease burden and associated costs, however, remain sparse. The virus has been identified as a major primary respiratory viral pathogen in young Nepali children hospitalised with severe pneumonia, as well as in rural community settings.[4] Furthermore, recent evidence has shown its significant impact on the intensive care unit admissions in urban Nepal during the 2021 and 2022 seasons, where it was found to account for 27.9% of the children with severe ARI.[5] For this reason, RSV prevention strategies are needed to protect young infants who are at the highest risk of severe RSV-associated LRTIs in Nepal.

Several intervention strategies against RSV are now available that can potentially change this scenario, two of which have recently been market approved. A maternal prefusion RSV vaccine (RSVpreF) demonstrated promising results in a phase III maternal RSV immunisation trial, showing vaccine efficacy of 81.8% (99.5% confidence interval (CI) = 40.6-96.3) against severe medically attended lower respiratory tract infection (LRTI) due to RSV in infants from birth through the first 90 days of life.[6] Similarly, a long-acting monoclonal antibody (mAb), nirsevimab, administered as a single injection at birth, has demonstrated high efficacy (76-80%) in clinical trials against severe RSV-LRTI and medically attended RSV-LRTI up to 150 days in preterm and full-term infants.[7-9] Optimal implementation of these interventions in LMICs will require accurate studies of disease costs to inform cost-effectiveness analyses and guide decision-making.

Despite the substantial impact of RSV on public health and economics, data on its financial burden on families and the healthcare system remain limited in LMICs. Some studies, however, have provided insight into the economic impact in these settings. For

instance, recent research in Kenya reported the mean costs of severe RSV illness among infants, expressed in 2021 USD, to be USD 329 (95% CI = 251-408) and USD 527 (95% CI = 405-649), respectively, in two semi-rural regions of Kenya.[10] Estimates from 2020 in Malawi reported mean costs per RSV episode at USD 62 (95% CI = 51-74).[11] To our knowledge, the only recent study from an Asian LMIC comes from Vietnam; it estimated the median costs of RSV-associated LRTI at USD 165 (IQR = 95-249).[12] Thus, cost estimates are needed to further understand the economic burden of RSV in LMICs, particularly in regions like Nepal.

We aimed to estimate the cost of RSV illness in Nepali children from the perspectives of the health system, households, and society. Our findings could provide valuable insights for informing decision-making regarding the cost-effectiveness of introducing RSV intervention strategies for improved health outcomes.

METHODS

This prospective research project is part of a larger study, the RSV Global Online Mortality Database (GOLD) III–Health Economics Study, conducted in four LMICs: Ghana, Mozambique, Nepal, and Nigeria. The study took place during one local respiratory season to assess the cost of illness of RSV in children <2 years old. Its foundational approach has been described in detail elsewhere.[13] Here we provide an overview of the most critical elements and highlight any country-specific deviations.

Study Setting

This study took place at the outpatient and inpatient departments of the Kanti Children's Hospital (KCH) and Tribhuvan University Teaching Hospital (TUTH) in Kathmandu, Nepal. The KCH is a referral paediatric hospital, while the TUTH is a tertiary referral general hospital. Each of the hospitals provides outpatient care six days a week, along with a general paediatric ward and high-dependency care that includes intensive care. The KCH has 108 beds in the general wards, 12 in the high-dependency unit (HDU), and 28 in the neonatal/paediatric intensive care unit (ICU). The TUTH has 54 general ward beds, 6 HDU beds, and 12 neonatal/paediatric ICU beds.

Study Population

All patients between four days to <2 years old admitted or visiting the outpatient department of either hospital between July and November 2023 that met the World Health Organization (WHO) (S)ARI case definition were eligible for enrolment, if parent/guardian consent was provided. The severity of RSV was classified on the location of admission: non-severe for outpatient visits only; severe for admission to the

general, respiratory, and intermediate wards or HDU; and life-threatened for ICU admission or death.

Due to the high volumes of patients at the outpatient clinic and an inability to evaluate every patient with respiratory symptoms, only a subset of patients seen at the outpatient clinic were randomly included in the study whenever data collectors were available to screen patients in the clinic for acute respiratory symptoms.

The Nepal Health Research Council, ethical review committees of both hospitals, and the Medical Research Ethics Committee NedMec (#20–536) of the University Medical Centre in Utrecht approved the study protocol. All study procedures followed relevant local regulations and the principles of the Declaration of Helsinki.

Sample Size Calculations

To estimate the number needed to achieve the desired sample sizes, we used the following formula:[14]

$$n = ceiling\left[\left(\frac{precision^2}{CV^2 \times Z^2_{1-a/2}} + \frac{1}{N_o}\right)\right]^{-1}$$

We utilised a Z-score of 1.96 (95% CI), a coefficient of variation of 0.5, and a precision level of ±10% of the mean costs, along with a case load (N0) and an RSV-positivity rate of 27.9% based on a previous RSV study at the KCH and TUTH.[5] This analysis determined that we had to enrol 465 ARI outpatients and 327 ARI inpatients to obtain the optimal sample size of 93 RSV-positive outpatients and 91 RSV-positive inpatients. The enrolment numbers varied from 128 to 900 ARI outpatients and 122 to 910 ARI inpatients, depending on the observed prevalence during the RSV season.

Study Timeline

The study took place during one local respiratory season, from July 2023 until November 2023. RSV testing was, however, continued in children <2 years old admitted with (S)ARI diagnosis until the end of the RSV season in the second week of February 2024 to determine if the characteristics of children enrolled in the cost of illness evaluation differed from children with RSV disease towards the end of the RSV season.

Data Collection

Trained study staff administered questionnaires designed for the RSV GOLD III–Health Economics Study. In contrast to other study sites such as Mozambique,[13] where data was collected on paper, data in Nepal were directly recorded electronically using the Electronic Data Capture System Castor[22] and the Kobo Toolbox.[23] Follow-up occurred

four to six weeks after discharge. Child and family demographic and clinical data gathering took place via direct interviews and hospital records for outpatient and inpatient cases (Figure S1 in the Online Supplementary Document).

We used billing data, including out-of-pocket and health system expenditures, to identify resource utilisation, as well as direct medical and overhead costs associated with care received within the facility. We estimated costs from the health system and household perspectives to calculate costs from the societal perspective. The health system perspective covered direct medical costs, with costs calculated using unit prices per service at the KCH and TUTH. We also included patients receiving support for treatment costs from health insurance or social funding sources (not the healthcare provider). Household costs included out-of-pocket medical expenses, non-medical costs, as well as indirect costs from caregivers' lost income and leisure time (self-reported), with all costs related to acute respiratory infection. We excluded unrelated medication and services from household costs, but included them in societal costs.

Sample Collection

RSV testing occurred as part of the study protocol and was not routine practice at the participating hospitals. Samples were collected as previously described in the ICU Network Study, published elsewhere.[5] While the standard method for RSV testing is typically polymerase chain reaction (PCR), we used the ID Now molecular test device, which has been validated in previous studies, and has shown reliable results when compared to the gold standard for RSV testing (i.e. the PCR method), particularly in the Nepali setting.[15]

Due to the unexpectedly high RSV positivity rate among the included patients during the study period, all patients <2 years old admitted to the participating hospitals were tested for RSV at two intervals during the study period. Testing all children in this age range made verifying whether the high positivity rates were consistent across the broader population or confined to those with (S)ARI possible.

Data Analysis

We used a bottom-up costing approach to estimate treatment costs for respiratory illness by identifying the resources consumed at the individual patient level, multiplying the quantity of each resource by its respective unit costs, and stratifying the costs by severity of RSV illness, including both medical and non-medical expenses. We estimated caregiver transportation costs based on travel distance and fuel consumption, and calculated indirect costs (including lost income and leisure) by multiplying the hourly income by working hours lost due to caregiving. We imputed

missing caregiver wages using the mean average wage of other respondents. We monetised the value of lost leisure time by using the minimum wage in Nepal.[16]

Overhead costs were allocated to individual patients based on their length of stay, deducting any registration fee and bed charges already paid. If the calculated administration fee (which included overhead costs, facility expenses, and staff costs) was greater than or equal to the registration fee and bed charges already included, the administration fee was not changed. If the administration fee was lower than the registration fee and bed charges paid, we added the difference to the total administration fee.

Total costs were the sum of direct medical costs, direct non-medical costs, and indirect costs for RSV-positive and non-RSV (S)ARI patients. Since cost data were predominantly non-parametric, we summarised cost data using both median and mean values. Cost data in our study are strongly right-skewed due to a few statistical outliers. We verified the values of these outliers for accuracy and included them in the final analysis, as they accurately reflected the true nature of the distribution of cost data. Costs were collected in NPR and converted to 2023 USD using the annual average exchange rate for 2023 (NPR 132.12 per USD 1). We conducted all statistical analyses separately for RSV-positive and non-RSV (S)ARI patients using Stata BE, version 18.0 (StatCorp LLC, College Station, Texas, USA).

RESULTS

Patient Characteristics

Between 1 July 2023 and 30 November 2023, 730 patients were enrolled in the study (Figure 1), of whom 532 (72.8%) tested positive for RSV: 63 (11.8%) at the outpatient clinic, 441 (82.9%) at the wards (n = 278) and HDU (n = 163), and 28 (5.3%) at the ICU. The mean age of RSV-positive children was 9.1 months for non-severe, 6.7 months for severe, and 4.0 months for life-threatened patients at the time of enrolment (Table 1). Most RSV-positive children in the study were male (n = 320, 60.2%). Inpatients accounted for 88.5% of all patients, primarily due to the high burden at the outpatient clinics and the consequent limitation on the number of patients that could be included there. We observed an RSV positivity rate of 72.6% for inpatients with SARI (Figure S2 in the Online Supplementary Document). Verification by testing all children <2 years old admitted to the hospitals confirmed the high observed RSV positivity rate (Table S1 in the Online Supplementary Document). The median duration of hospitalisation for RSV-positive severe patients was 4 days (interquartile range (IQR) = 3–5), compared to 7 days (IQR = 4.5–10) for life-threatened patients. Twelve children died during the study period,

with eight deaths occurring in the hospital. Of these, one-eighth tested positive for RSV. Four more deaths were identified during follow-up, with one testing positive for RSV (Tables S2 and S3 in the Online Supplementary Document).

Cost per Episode

Societal costs

The mean total societal costs per RSV episode were USD 43 (95% CI= 25-62) for non-severe patients, USD 312 (95% CI = 293-332) for severe patients, and USD 664 (95% CI = 381-947) for life-threatened patients. About half of the total costs were direct medical costs. Overall, costs for non-RSV (S)ARI patients were higher, with life-threatened patients showing the largest difference (USD 810 vs USD 664; P = 0.01) (Table 2). When comparing outpatients and inpatients, the treatment costs for RSV patients were slightly lower than those for non-RSV (S)ARI (Table S4 in the Online Supplementary Document). In particular, medical costs for non-RSV life-threatening cases were higher (Table S5 in the Online Supplementary Document).

Health system costs

Health system costs (Table 3) were comparable for severe and life-threatened RSV patients, with USD 58 (95% CI = 54–62) and USD 57 (95% CI = 32–83) per illness episode. Main cost drivers were administrative fees, including registration fees, bed charges, and staff costs. Similar results were found for non-RSV (S)ARI patients, with an additional average of USD 10.

Household costs

Overall, the National Health Insurance System covered 28 patients (3.8%) included in the study. Of the 532 RSV-positive patients, all caregivers reported out-of-pocket household costs (Table 4). The mean total out-of-pocket household costs were USD 19 (95% CI=10–28), USD 200 (95% CI=187– 214), and USD 472 (95% CI=324–620) for non-severe, severe, and life-threatened patients, respectively. Direct medical expenses were the largest component of household costs for all caregivers, contributing 30.8%–52.6% to the overall costs paid by households. Direct non-medical costs such as transport and food were reported by 525 (98.1%) of the caregivers, differing between USD 8 and USD 119. For severe and life-threatened RSV-positive inpatients, indirect costs were between 58.9% and 175.4% of the mean monthly household income in Nepal.

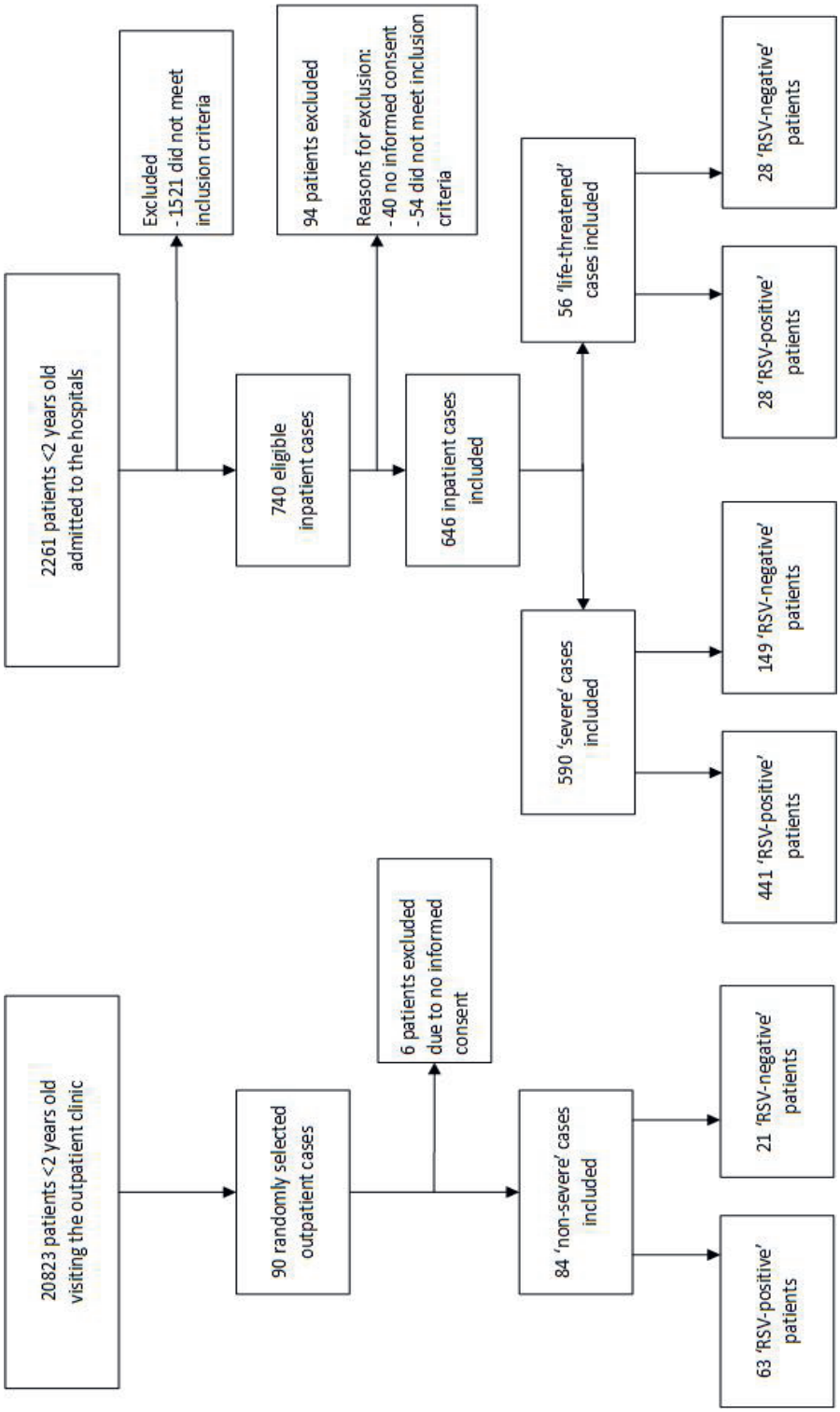

Figure 1. Flow diagram, showing the total numbers of outpatients and inpatients included and excluded from the study. RSV – respiratory syncytial virus.

Table 1. Demographics and clinical characteristics of RSV-positive and non-RSV (S)ARI patients <2 years old, by severity level.*

	RSV positive				Non-RSV (S)ARI				All patients
	Non-severe	Severe	Life-threatened	Total	Non-severe	Severe	Life-threatened	Total	Overall
Total number of participants	63	441	28	532	21	149	28	198	730
Age in months, x̄ (SD)	9.1 (5.2)	6.7 (5.6)	4.0 (5.0)	6.9 (5.6)	8.2 (5.3)	7.2 (6.5)	3.1 (4.5)	6.7 (6.3)	6.8 (5.8)
Female	25 (39.7)	178 (40.4)	9 (32.1)	212 (39.9)	7 (33.3)	44 (29.5)	10 (35.7)	61 (30.8)	273 (37.4)
Household size, MD (IQR)	4 (3–5)	4 (4–6)	5 (4–6)	4 (4–6)	4 (3–5)	4 (4–6)	4 (4–5)	4 (4–5)	4 (4–5)
Level of education of primary caregiver secondary school or higher	42 (66.7)	284 (64.4)	16 (57.1)	342 (64.3)	17 (81.0)	91 (61.1)	20 (71.4)	128 (64.7)	470 (64.4)
Distance to health care facility in km, x̄ (SD)	3 (4.8)	15 (3.4)	0 (0.0)	18 (3.4)	0 (0.0)	8 (5.4)	2 (7.1)	10 (5.1)	28 (3.8)
Physicians diagnosis									
Bronchiolitis	25 (39.7)	227 (51.5)	10 (35.7)	262 (49.3)	10 (47.6)	48 (32.2)	5 (17.9)	63 (31.8)	325 (44.5)
Pneumonia	6 (9.5)	170 (38.6)	17 (60.7)	193 (36.3)	4 (19.1)	76 (51.0)	22 (78.6)	102 (51.5)	295 (40.4)
URTI	2 (3.7)	0 (0.0)	0 (0.0)	2 (0.34)	3 (14.3)	0 (0.0)	0 (0.0)	3 (1.5)	5 (0.78)
Other LRTI	27 (42.9)	11 (2.5)	0 (0.0)	38 (7.1)	4 (19.1)	5 (3.4)	0 (0.0)	9 (4.6)	47 (6.4)
Other	3 (4.8)	23 (8.3)	11 (5.8)	37 (7.0)	0 (0.0)	20 (13.4)	1 (3.6)	21 (10.6)	58 (8.0)
Prematurity	0 (0.0)	27 (6.1)	2 (7.1)	29 (5.5)	0 (0.0)	12 (8.1)	5 (18.5)	17 (8.6)	46 (6.3)
Comorbidity	0 (0.0)	17 (3.9)	7 (25.0)	24 (4.5)	1 (4.8)	19 (12.8)	11 (39.3)	31 (15.7)	55 (7.5)
Length of stay in days, MD (IQR)	N/A	4 (3–5)	7 (4.5–10)	4 (3–6)	N/A	4 (3–6)	8 (5–12.5)	4 (3–7)	4 (3–6)
Previous medical consultation	21 (33.3)	214 (48.6)	14 (51.9)	249 (47.0)	6 (28.6)	65 (43.6)	15 (55.6)	86 (43.7)	335 (46.1)
Follow-up care	17 (27.0)	183 (42.2)	5 (21.7)	205 (39.4)	3 (14.3)	70 (47.3)	7 (31.8)	80 (41.9)	285 (40.1)
Mortality	–	–	2 (7.1)	2 (0.4)	–	–	10 (35.7)	10 (5.1)	12 (1.6)

IQR – interquartile range, MD – median, RSV – respiratory syncytial virus, (S)ARI – (severe) acute respiratory illness, LRTI – lower respiratory tract infection, URTI – upper respiratory tract infection, x̄ – mean. *Values presented as n (%) unless specified otherwise.

Table 2. Summary of societal cost (in 2023 USD) per lower respiratory tract infection episode for RSV-positive and non-RSV (severe) acute respiratory illness patients <2 years old, by severity level.

	RSV-positive (n = 532)			Non-RSV (S)ARI (n = 198)		
	Non-severe (n = 63)	**Severe (n = 441)**	**Life-threatened (n = 28)**	**Non-severe (n = 21)**	**Severe (n = 149)**	**Life-threatened (n = 28)**
Total costs						
x̄ (95% CI)	43.43 (24.77–62.09)	312.33 (292.81–331.85)	664.06 (381.39–946.73)	70.09 (20.68–119.51)	364.41 (317.25–411.57)	809.92 x(612.70–1,005.15)
MD (IQR)	28.30 (24.68–39.46)	260.90 (176.88–386.43)	486.82 (319.57–649.07)	31.00 (24.88–47.82)	295.99 (194.47–402.10)	629.88 (434.61–1,152.83)
Direct medical costs						
x̄ (95% CI)	21.61 (20.29–22.94)	125.78 (118.28–133.28)	305.63 (204.68–406.57)	24.66 (20.11–29.22)	145.59 (127.67–163.52)	471.27 (322.86–619.68)
MD (IQR)	20.43 (18.92–23.99)	107.07 (81.95–143.98)	236.27 (154.16–321.61)	19.04 (18.03–26.11)	113.70 (87.51–153.86)	277.93 (232.14–566.14)
Hospitality/facility-based fees						
x̄ (95% CI)	16.14 (15.53–16.75)	74.57 (70.07–79.07)	138.68 (104.61–172.75)	17.19 (15.97–18.42)	84.65 (74.12–95.18)	149.47 (108.10–190.84)
MD (IQR)	15.09 (15.09–18.59)	60.72 (45.63–81.44)	106.35 (75.80–155.74)	15.46 (15.09–18.59)	61.47 (47.76–90.89)	136.15 (90.51–182.75)
Medication costs						
x̄ (95% CI)	2.57 (2.16–2.98)	13.67 (12.59–14.74)	35.52 (22.82–48.22)	2.89 (1.61–4.17)	16.16 (13.53–18.79)	55.64 (35.01–76.27)
MD (IQR)	2.45 (1.20–3.65)	11.01 (7.38–16.55)	19.53 (13.86–42.97)	2.14 (0.90–3.38)	11.14 (7.98–17.58)	35.37 (16.45–81.37)

Table 2. Continued.

	RSV-positive (n = 532)			Non-RSV (S)ARI (n = 198)		
	Non-severe (n = 63)	**Severe (n = 441)**	**Life-threatened (n = 28)**	**Non-severe (n = 21)**	**Severe (n = 149)**	**Life-threatened (n = 28)**
Laboratory costs						
x̄ (95% CI)	1.00 (0.22–1.77)	12.61 (11.60–13.61)	33.99 (20.37–47.61)	3.04 (0.00–6.34)	17.38 (14.28–20.49)	73.38 (34.21–112.55)
MD (IQR)	0.00 (0.00–0.00)	9.96 (7.52–14.92)	21.81 (12.22–48.13)	0.00 (0.00–4.89)	11.09 (7.52–19.06)	33.79 (21.43–55.84)
Imaging costs						
x̄ (95% CI)	2.58 (2.16–3.01)	4.23 (3.85–4.61)	11.57 (0.90–22.23)	2.61 (2.09–3.13)	6.98 (4.41–9.55)	21.58 (11.20–31.96)
MD (IQR)	2.26 (2.26–3.16)	2.26 (2.26–4.51)	4.16 (2.26–8.50)	2.26 (2.26–3.16)	2.26 (2.26–6.77)	9.02 (4.51–30.53)
Procedure costs						
x̄ (95% CI)	0.16 (0.04–0.27)	7.19 (5.80–8.58)	58.24 (23.52–92.95)	0.86 (0.00–2.11)	5.52 (3.82–7.22)	84.13 (37.98–130.28)
MD (IQR)	0.00 (0.00–0.00)	3.76 (1.88–7.37)	27.26 (11.88–49.26)	0.00 (0.00–0.90)	2.19 (0.71–5.68)	24.82 (13.91–103.78)
Miscellaneous costs						
x̄ (95% CI)	0.46 (0.27–0.66)	14.68 (13.67–15.68)	37.93 (31.08–44.78)	3.31 (0.96–5.65)	16.38 (14.25–18.51)	82.41 (57.20–107.62)
MD (IQR)	0.19 (0.00–0.86)	11.78 (7.93–18.12)	37.26 (26.52–47.63)	1.03 (0.15–7.34)	12.42 (8.51–19.15)	58.28 (30.82–111.59)

Table 2. Continued.

	RSV-positive (n = 532)			Non-RSV (S)ARI (n = 198)		
	Non-severe (n = 63)	**Severe (n = 441)**	**Life-threatened (n = 28)**	**Non-severe (n = 21)**	**Severe (n = 149)**	**Life-threatened (n = 28)**
Direct non-medical costs*						
x̄ (95% CI)	8.32 (3.00–13.65)	63.85 (54.51–73.20)	118.92 (69.17–168.67)	34.98 (0.00–81.46)	65.23 (52.58–77.88)	153.74 (113.86–193.62)
MD (IQR)	1.80 (0.84–5.83)	36.10 (19.93–65.65)	79.49 (55.46–138.11)	7.52 (0.90–13.99)	39.14 (20.31–76.71)	137.47 (67.83–193.35)
Transport costs						
x̄ (95% CI)	6.37 (1.77–10.96)	37.22 (28.20–46.23)	46.33 (25.56–67.11)	32.69 (0.00–78.92)	32.09 (21.28–42.91)	79.83 (49.57–110.09)
MD (IQR)	1.35 (0.71–4.70)	8.27 (1.62–24.07)	19.89 (9.40–71.07)	5.26 (0.75–12.03)	8.80 (1.48–24.59)	52.04 (14.66–142.89)
Meal costs						
x̄ (95% CI)	1.92 (0.00–4.10)	26.33 (24.10–28.56)	51.33 (35.50–67.16)	2.25 (0.21–4.28)	32.05 (26.38–37.71)	72.39 (45.03–99.76)
MD (IQR)	0.00 (0.00–0.90)	21.66 (11.28–34.59)	45.91 (24.82–57.08)	0.00 (0.00–2.26)	24.82 (13.24–37.90)	45.72 (18.80–117.09)
Indirect costs						
x̄ (95% CI)	13.50 (0.00–27.20)	124.69 (112.75–136.75)	259.70 (106.02–413.39)	10.46 (2.24–18.67)	153.59 (122.18–185.00)	201.37 (131.96–270.78)
MD (IQR)	3.40 (0.63–9.61)	90.50 (48.41–157.27)	156.71 (99.27–265.39)	2.27 (1.51–7.63)	106.13 (48.41–187.63)	143.86 (42.36–295.54)

Table 2. Continued.

	RSV-positive (n = 532)			Non-RSV (S)ARI (n = 198)		
	Non-severe (n = 63)	**Severe (n = 441)**	**Life-threatened (n = 28)**	**Non-severe (n = 21)**	**Severe (n = 149)**	**Life-threatened (n = 28)**
Lost income						
x̄ (95% CI)	1.66 (0.00–4.08)	11.16 (8.70–13.61)	17.47 (5.91–29.03)	2.67 (0.14–5.20)	19.54 (14.13–24.95)	21.51 (6.34–36.69)
MD (IQR)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–35.09)	0.00 (0.00–0.00)	0.00 (0.00–35.09)	0.00 (0.00–37.60)
Lost productivity						
x̄ (95% CI)	8.73 (0.00–18.94)	54.67 (45.52–63.82)	141.47 (10.15–272.79)	4.30 (0.30–8.30)	71.17 (44.57–97.76)	72.97 (39.57–106.36)
MD (IQR)	0.00 (0.00–6.65)	20.99 (0.00–66.37)	55.97 (4.37–96.19)	0.00 (0.00–3.85)	35.16 (0.00–78.70)	55.97 (5.25–100.56)
Lost leisure						
x̄ (95% CI)	3.11 (1.86–4.37)	58.86 (55.05–62.67)	100.76 (73.36–128.17)	3.49 (0.67–6.31)	62.88 (55.20–70.56)	106.89 (62.08–151.69)
MD (IQR)	2.27 (0.25–4.16)	60.51 (36.31–72.62)	96.82 (60.51–128.97)	1.51 (0.00–3.40)	60.51 (30.64–72.62)	66.57 (18.15–136.16)

CI – confidence interval, IQR – interquartile range, MD – median, RSV – respiratory syncytial virus, (S)ARI – (severe) acute respiratory illness, x̄ – mean *Besides transport and meals, caretaker costs and lodging costs are included here; however, only few cases have costs here and are therefore not shown in the table.

Table 3. Direct medical cost (in 2023 USD) covered by the health system per lower respiratory tract infection episode for RSV-positive and non-RSV (severe) acute respiratory illness patients <2 years old, by severity level.

	RSV-positive (n = 532)			Non-RSV (S)ARI (n = 198)		
	Non-severe (n = 63)	**Severe (n = 441)**	**Life-threatened (n = 28)**	**Non-severe (n = 21)**	**Severe (n = 149)**	**Life-threatened (n = 28)**
Direct medical costs*						
x̄ (95% CI)	15.78 (15.04–16.52)	58.09 (53.87–62.31)	57.38 (31.86–82.90)	15.93 (15.26–16.60)	67.89 (59.05–76.73)	68.04 (40.47–95.60)
MD (IQR)	14.71 (14.71–17.84)	49.11 (39.39–65.70)	40.41 (13.66–67.33)	14.71 (14.71–17.84)	58.09 (42.29–74.30)	52.44 (5.40–89.89)
Hospitality/facility-based fees						
x̄ (95% CI)	15.40 (14.80–16.00)	55.23 (51.67–58.79)	52.63 (34.19–71.07)	15.93 (15.26–16.60)	65.84 (57.39–74.30)	56.72 (37.25–76.19)
MD (IQR)	14.71 (14.71–17.84)	46.75 (38.49–61.65)	40.36 (21.94–67.33)	14.71 (14.71–17.84)	58.09 (41.54–73.17)	45.41 (5.40–80.87)
Medication costs						
x̄ (95% CI)	0.13 (0.00–0.27)	1.02 (0.46–1.57)	1.19 (0.11–2.26)	0.00 (0.00–0.00)	0.63 (0.22–1.05)	3.04 (0.00–8.44)
MD (IQR)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)
Laboratory costs						
x̄ (95% CI)	0.23 (0.00–0.69)	0.68 (0.24–1.12)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.82 (0.04–1.60)	0.62 (0.00–1.62)
MD (IQR)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)

Table 3. Continued.

	RSV-positive (n = 532)			Non-RSV (S)ARI (n = 198)		
	Non-severe (n = 63)	**Severe (n = 441)**	**Life-threatened (n = 28)**	**Non-severe (n = 21)**	**Severe (n = 149)**	**Life-threatened (n = 28)**
Imaging costs						
$\bar{x}$ (95% CI)	0.18 (0.00–0.38)	0.15 (0.06–0.24)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.33 (0.00–0.66)	0.72 (0.00–2.06)
MD (IQR)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)
Procedure costs						
$\bar{x}$ (95% CI)	0.00 (0.00–0.00)	1.06 (0.41–1.71)	5.77 (0.00–14.71)	0.00 (0.00–0.00)	0.27 (0.05–0.48)	6.66 (0.00–13.71)
MD (IQR)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)

CI – confidence interval, IQR – interquartile range, MD – median, RSV – respiratory syncytial virus, (S)ARI – (severe) acute respiratory illness, $\bar{x}$ – mean
*Miscellaneous costs are part of direct medical costs; however, those costs are >95% covered by the households and are therefore not shown in the table.

Table 4. Household costs (in 2023 USD) per lower respiratory tract infection episode for RSV-positive and non-RSV (severe) acute respiratory illness patients <2 years old, by severity level.

	RSV-positive (n = 532)			Non-RSV (S)ARI (n = 198)		
	Non-severe (n = 63)	**Severe (n = 441)**	**Life-threatened (n = 28)**	**Non-severe (n = 21)**	**Severe (n = 149)**	**Life-threatened (n = 28)**
Total costs						
x̄ (95% CI)	18.92 (9.92–27.93)	200.48 (186.54–214.43)	472.31 (324.44–620.19)	49.86 (1.01–98.72)	225.35 (197.93–252.77)	670.44 (485.34–855.55)
MD (IQR)	11.00 (7.36–16.79)	165.49 (109.23–246.14)	362.36 (265.49–503.16)	13.15 (9.88–33.11)	184.89 (119.50–270.86)	515.62 (314.32–842.39)
Direct medical costs						
x̄ (95% CI)	5.83 (4.61–7.05)	67.70 (62.35–73.04)	248.25 (168.00–328.49)	8.73 (4.45–13.02)	77.70 (66.18–89.22)	403.23 (266.92–539.54)
MD (IQR)	5.23 (3.03–7.45)	52.27 (33.86–85.41)	189.19 (124.55–321.61)	4.14 (2.63–8.27)	55.62 (37.14–88.67)	233.66 (166.23–534.39)
Hospitality/facility-based fees						
x̄ (95% CI)	0.74 (0.49–0.99)	19.34 (16.78–21.90)	86.05 (63.92–108.18)	1.27 (0.54–1.99)	18.81 (14.49–23.12)	92.75 (60.16–125.34)
MD (IQR)	0.38 (0.38–0.75)	9.02 (2.26–25.95)	65.24 (45.88–103.03)	0.38 (0.38–1.13)	4.89 (2.26–27.07)	68.81 (53.40–92.13)
Medication costs						
x̄ (95% CI)	2.44 (2.04–2.83)	12.65 (11.66–13.64)	34.33 (21.93–46.74)	2.89 (1.61–4.17)	15.53 (12.93–18.13)	52.60 (32.95–72.25)
MD (IQR)	2.41 (1.17–3.37)	10.50 (6.84–15.67)	19.53 (13.86–42.97)	2.14 (0.90–3.38)	10.77 (7.75 –17.28)	34.61 (16.45–76.63)

Table 4. Continued.

	RSV-positive (n = 532)			Non-RSV (S)ARI (n = 198)		
	Non-severe (n = 63)	**Severe (n = 441)**	**Life-threatened (n = 28)**	**Non-severe (n = 21)**	**Severe (n = 149)**	**Life-threatened (n = 28)**
Laboratory costs						
x̄ (95% CI)	0.76 (0.12–1.40)	11.93 (10.97–12.88)	33.99 (20.37–47.61)	3.04 (0.00–6.34)	16.57 (13.48–19.66)	72.75 (33.88–111.63)
MD (IQR)	0.00 (0.00–0.00)	9.78 (7.52 –13.72)	21.81 (12.22–48.13)	0.00 (0.00–0.00)	10.30 (7.52–17.49)	33.79 (21.43–55.84)
Imaging costs						
x̄ (95% CI)	2.41 (1.96–2.85)	4.08 (3.70–4.47)	11.57 (0.90–22.23)	2.61 (2.09–3.13)	6.65 (4.16–9.14)	20.86 (10.58–31.14)
MD (IQR)	2.26 (2.26–2.26)	2.26 (2.26–4.51)	2.26 (2.26–8.50)	2.26 (2.26–3.16)	2.26 (2.26–6.77)	9.02 (4.51–27.30)
Procedure costs						
x̄ (95% CI)	0.16 (0.04–0.27)	6.14 (4.84–7.44)	52.46 (25.32–79.61)	0.86 (0.00–2.11)	5.30 (3.59–7.01)	77.47 (34.52–120.41)
MD (IQR)	0.00 (0.00–0.00)	2.73 (1.50–5.81)	27.07 (11.88–49.26)	0.00 (0.00–0.00)	1.88 (0.66–5.64)	24.82 (13.91–90.25)
Miscellaneous costs						
x̄ (95% CI)	0.46 (0.27–0.66)	14.56 (13.55–15.57)	37.93 (31.08–44.78)	3.31 (0.96–5.65)	16.30 (14.19–18.42)	81.89 (56.97–106.82)
MD (IQR)	0.19 (0.00–0.86)	11.72 (7.86–18.04)	37.26 (26.52–47.63)	1.03 (0.15–7.34)	12.42 (8.44–19.15)	58.28 (30.82–111.59)

Table 4. Continued.

	RSV-positive (n = 532)			Non-RSV (S)ARI (n = 198)		
	Non-severe (n = 63)	**Severe (n = 441)**	**Life-threatened (n = 28)**	**Non-severe (n = 21)**	**Severe (n = 149)**	**Life-threatened (n = 28)**
Direct non-medical costs*						
x̄ (95% CI)	8.32 (2.99–13.65)	63.85 (54.51–73.20)	118.92 (69.17–168.67)	34.98 (0.00–81.46)	65.23 (52.58–77.88)	153.74 (113.86–193.62)
MD (IQR)	1.80 (0.84–5.83)	36.10 (19.93–65.65)	79.49 (55.46–138.11)	7.52 (0.90–13.99)	39.14 (20.31–76.71)	137.47 (67.83–193.35)
Transport costs						
x̄ (95% CI)	6.37 (1.77–10.96)	37.22 (28.20–46.23)	46.33 (25.56–67.11)	32.69 (0.00–78.92)	32.09 (21.28–42.91)	79.83 (49.57–110.09)
MD (IQR)	1.35 (0.71–4.70)	8.27 (1.62–24.07)	19.89 (9.40–71.07)	5.26 (0.75–12.03)	8.80 (1.48–24.59)	52.04 (14.66–142.89)
Meal costs						
x̄ (95% CI)	1.92 (0.00–4.10)	26.33 (24.10–28.56)	51.33 (35.50–67.16)	2.25 (0.21–4.28)	32.05 (26.38–37.71)	72.39 (45.03–99.76)
MD (IQR)	0.00 (0.00–0.00)	21.66 (11.28–34.59)	45.91 (24.82–57.08)	0.00 (0.00–0.00)	24.82 (13.24–37.90)	45.72 (18.80–117.09)
Indirect costs						
x̄ (95% CI)	4.77 (1.23–8.32)	70.02 (64.85–75.19)	118.24 (86.22–150.25)	6.16 (1.50–10.81)	82.42 (71.32–93.53)	128.40 (82.00–174.81)
MD (IQR)	2.27 (0.44- 4.54)	60.51 (36.50–86.84)	96.82 (60.51–159.06)	2.27 (1.51–4.54)	62.40 (36.56–104.52)	87.90 (36.31–222.08)

Table 4. Continued.

	RSV-positive (n = 532)			Non-RSV (S)ARI (n = 198)		
	Non-severe (n = 63)	**Severe (n = 441)**	**Life-threatened (n = 28)**	**Non-severe (n = 21)**	**Severe (n = 149)**	**Life-threatened (n = 28)**
Lost income						
x̄ (95% CI)	1.66 (0.00–4.08)	11.16 (8.70–13.61)	17.47 (5.91–29.03)	2.67 (0.14–5.20)	19.54 (14.13–24.95)	21.51 (6.34–36.69)
MD (IQR)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–35.09)	0.00 (0.00–0.00)	0.00 (0.00–35.09)	0.00 (0.00–37.60)
Lost leisure						
x̄ (95% CI)	3.11 (1.86–4.37)	58.66 (55.05–62.67)	100.76 (73.36–128.17)	3.49 (0.67–6.31)	62.88 (55.20–70.56)	106.89 (62.08–151.70)
MD (IQR)	2.27 (0.25–4.16)	60.51 (36.31–72.62)	96.82 (60.51–128.97)	1.51 (0.00–3.40)	60.51 (30.64–72.62)	66.57 (18.15–136.16)

CI – confidence interval, IQR – interquartile range, MD – median, RSV – respiratory syncytial virus, (S)ARI – (severe) acute respiratory illness, x̄ – mean
*Besides transport and meal costs, caretaker and lodging costs are included here; however, only a few cases have costs and are therefore not shown in this table.

DISCUSSION

Our findings show substantial direct medical, non-medical, and indirect costs of (S)ARI-related illness in children <2 years old visiting two public hospitals in Kathmandu, Nepal. The medical costs of RSV-related hospital admissions have a substantial economic impact not only on the health system, but also on households in Nepal.

Existing literature highlights significant variability in the total costs associated with RSV-related hospital admissions across different countries and regions.[17] In our study, the total inpatient costs for RSV-positive children were USD 312 for severe cases and USD 664 for life-threatened cases, which are much higher compared to other Asian LMICs such as Bangladesh (USD 94 in 2010; USD 131 when adjusted for inflation to 2023) and Vietnam (USD 165 in 2022; USD 172 when adjusted for inflation to 2023). Outpatient costs for RSV-positive cases in our study were USD 43, and while these findings are comparable to data from Vietnam (USD 52; USD 54 when adjusted for inflation to 2023), the costs for hospitalised RSV patients in Nepal were significantly higher across all cost categories. Higher cost per RSV illness episode observed in our study could potentially be linked to several factors, including the following: the availability of ICUs at the study hospitals, which tend to be more expensive; a high proportion of enrolled children being admitted to HDU; and the completeness and quality of data collection. An unpublished study on the costs of pneumonia treatment in children 0–59 months of age conducted across five hospitals in Nepal reported an average cost of USD 177 in 2016 (USD 225 when adjusted for inflation to 2023) per pneumonia case.[18] This study suggests that, despite potential regional cost variations, our estimate for the cost of RSV illness adds a valuable perspective on the economic burden of RSV disease in Nepal.

Differences in indirect costs, mostly driven by lost income, are also much higher in our study (USD 125 for severe cases and USD 260 for life-threatened cases) when compared to Bangladesh (USD 19; USD 27 when adjusted for inflation to 2023) and Vietnam (USD 19; USD 20 when adjusted for inflation to 2023). These differences could reflect varying salary levels across countries but could also be influenced by the presence of different caregivers accompanying patients to the hospital. For instance, in Nepal, fathers, who are typically the primary income earners, often also accompany patients; whereas elsewhere, mothers, who may not be working, more commonly serve as the primary caregiver. These findings underscore the broader economic impact of RSV, extending beyond direct medical expenses. They also highlight the need for a comprehensive country-specific evaluation that encompasses the direct and indirect burden of RSV to inform health policy and effective resource allocation.

Household out-of-pocket costs for inpatients in our study were substantial, placing a significant financial burden on families. The mean direct medical costs for caregivers reporting inpatient care costs accounted for 73.9% of Nepal's all-source health expenditure per capita, which was USD 65 in 2021 (USD 73 when adjusted for inflation to 2023 USD).[19] This finding highlights the significant burden that RSV imposes on households. Previous research has defined catastrophic health expenditure as healthcare costs exceeding 10% of a household's annual income.[20] Keeping this in mind, if caregivers reporting income loss were the only income earners in their household, the mean direct medical and non-medical costs per RSV illness episode for those requiring inpatient care would likely qualify as catastrophic. Although we did not measure household income in this study, projecting the annual cost of RSV illnesses in Nepal using an ARI incidence rate of approximately 2.1%[3] can provide insight into the national household economic burden and the potential risk of impoverishment due to RSV illnesses. Reducing the burden of RSV, and thereby reducing the financial strain on households, is crucial for advancing efforts to lower childhood mortality and combat poverty.

Medical costs are a substantial part of our study and are slightly higher in the non-RSV (S)ARI group compared to the RSV patients. The largest difference is for medication and laboratory costs. This difference could be because healthcare providers have access to the point-of-care test results, leading to changes in their prescribing behaviour (*e.g.* reducing antibiotic prescriptions and not testing for other pathogens). This finding indicates the potential of point-of-care testing in influencing clinical decision-making and improving patient management by minimising unnecessary antibiotic use and testing procedures, thereby lowering medical and laboratory costs.

The overall cost in 2023 accounted for 3.3% of GDP per capita for non-severe cases, 23.6% for severe cases, and 50.2% for life-threatened cases of RSV infection. The high cost, particularly for severe and life-threatened cases, suggests a significant financial burden on both households and the government. For low-income families, where GDP per capita is already limited, these healthcare costs could exacerbate poverty, pushing households into financial distress or forcing them to forego necessary medical care. Additionally, the high governmental costs associated with treating severe cases could strain public healthcare budgets, potentially limiting resources available for other critical services.

This is the first prospective study to evaluate direct medical, direct non-medical, and indirect costs for households and the health system related to (S)ARI in Nepal. While it provides valuable data for public health decision-making, it also has several limitations. First, the study population consists of patients from two public hospitals in

the capital of Nepal, limiting the generalisability of the findings to the whole country. Second, the fact that we include fewer outpatients than required by the sample size calculations may mean that costs incurred by outpatients are not fully representative. Third, the results presented here likely underestimate the total economic burden of RSV illness in Nepal. Our study was limited to inpatients and outpatients at secondary and tertiary public facilities and did not capture costs associated with milder cases treated in an outpatient setting, at smaller health facilities, or at private facilities. Fourth, follow-up conducted via phone calls may have contributed to lower response rates when compared to regular in-person follow-up visits. We note, however, the high study adherence among our participants. Fifth, reliance on self-reported cost data from parents/caregivers may compromise the validity of the findings. Sixth, costs in private health facilities may potentially be higher due to factors such as specialised services, greater use of advanced medical technology, and the inclusion of overhead expenses not typically covered in public facilities.[21] Finally, we did not account for genetic factors that influence susceptibility to RSV, and we only captured incurred costs without considering the quality of care received.

CONCLUSION

Our study provides a detailed description of the cost and economic burden of RSV and non-RSV (S)ARI in children <2 years old in Kathmandu, Nepal. The burden on the health system and on households is substantial. Medical costs associated with severe and life-threatening RSV in urban Nepal are particularly high for its households. Detailed quantification of RSV-related costs is essential for informed decision-making, prioritising future preventive interventions, and achieving effective health resource allocation. Additionally, these data could be valuable for estimating the overall benefit of potential RSV immunisation strategies (e.g., with maternal vaccine and/or monoclonal antibody) in Nepal and other settings and will support cost-effectiveness modelling for RSV prevention strategies. Furthermore, future studies should investigate the economic burden in rural areas of Nepal, as well as the impact of (S)ARI illness in the private healthcare sector.

Supplementary files can be downloaded from:



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7

Cost-Effectiveness of Respiratory Syncytial Virus Prevention Strategies in Mozambique: A Modelling Study

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ABSTRACT

Background. Respiratory syncytial virus (RSV) is a leading cause of severe acute lower respiratory infections in children. The World Health Organization recently recommended two passive RSV immunisation strategies for global use, but prices are yet to be determined in low- and middle-income countries (LMICs).

Methods. We used a static cohort model to generate preliminary estimates of the potential health impact and cost-effectiveness of a maternal vaccine (RSVPreF, Abrysvo®, Pfizer) and a long-acting infant mAb (Nirsevimab, Beyfortus®, AstraZeneca, and Sanofi) over a 10-year period (2025–2034) in Mozambique. We incorporated cost-of-illness data from a recent study conducted in Maputo, Mozambique, and efficacy data from recent clinical trials. We compared each RSV prevention strategy to the current status quo (no pharmaceutical RSV prevention strategy). The primary outcome was the cost per disability-adjusted life year (DALY) averted from a government perspective, assuming year-round dose administration. We ran a range of deterministic scenarios, including a societal health perspective and a seasonal dose administration strategy. We also ran probabilistic uncertainty analyses and estimated the probability that each intervention would be cost-effective over a range of cost-effectiveness thresholds.

Results. Year-round administration of a maternal vaccine (USD 5/dose, 69% efficacy, 87% coverage, 6 months protection) could cost USD 80 million and prevent 4,671 RSV deaths. Year-round administration of the long-acting infant mAb (USD 5/dose, 77% efficacy, 94% coverage, 5 months protection) could cost USD 85 million and prevent 5,128 RSV deaths. Over half the cost of the respective programmes would be offset by healthcare cost savings. Compared to the current status quo, the cost per DALY averted from a government perspective was USD 288 (95% uncertainty interval 140–574) for the maternal vaccine and USD 289 (95% uncertainty interval 160–583) for the mAb. At an intervention price of USD 5 per dose, the probability is around 20% that either intervention is cost-effective at a threshold of 0.4 times the national GDP per capita.

Conclusion. New passive immunisation interventions have the potential to prevent a substantial number of infant deaths in Mozambique. Both interventions have the potential to be cost-effective if priced below USD 5 per dose. A seasonal strategy could further improve cost-effectiveness if feasible to implement.

INTRODUCTION

Respiratory Syncytial Virus (RSV) is a common viral pathogen that can lead to acute lower respiratory infections (ALRI) in young children.[1] In 2019, an estimated 101 400 RSV-associated deaths occurred in children aged under five years of age worldwide. Over 95% of the RSV-ALRI cases and deaths occurred in low- and middle- income countries (LMICs).[2] In Mozambique, respiratory diseases are responsible for around one in five deaths in children under 5 years old.[3] Evidence on RSV in Mozambique is limited. However, in Maputo City, RSV has been detected in 23–27% of inpatients under 2 years of age with ALRI,[4] and in 35% of patients of the same age with ALRI admitted to the intensive care unit (ICU).[5]

Forthcoming pharmaceutical interventions have the potential to significantly reduce the burden of RSV-ALRI. Currently, more than 20 vaccines and monoclonal antibody (mAb) candidates are at different stages of development.[6] Recently, the World Health Organization (WHO) Strategic Advisory Group of Experts on Immunization recommended two interventions, a maternal vaccine (RSVPreF, Abrysvo®, Pfizer) and a long-acting infant mAb (Nirsevimab, Beyfortus®, AstraZeneca, and Sanofi) for global use. These interventions are starting to be introduced in the Americas and Europe.[7] With maternal vaccination, RSV-neutralising antibodies are transferred across the placenta to the infant, offering protection to newborns.[8] Phase III trials for the bivalent prefusion F protein-based maternal vaccine, RSVpreF, showed 82% efficacy against severe medically attended ALRI due to RSV after 3 months post birth, and 69% efficacy after 6 months post birth.8 In addition, the long-acting infant mAb, administered at birth in a single dose has shown 79% efficacy against medically attended RSV-associated ALRI after 5 months of follow-up.[9]

RSV interventions, including both the maternal vaccine and long-acting infant mAb, were considered by Gavi, the Vaccine Alliance, as one of six priorities of its vaccine investment strategy for the 2021–2025 funding period and beyond.[10] One of the criteria Gavi considers is whether interventions offer good value for money. Mozambique is a low-income country where healthcare budget limitations and healthcare access inequalities are evident[11] so it is particularly important to assess the health and economic impact of health spending decisions. There are currently few economic evaluations of RSV interventions in the African context. An assessment of the potential cost-effectiveness of these interventions in Mozambique is therefore needed to help inform decisions about whether they should be considered for inclusion in the national Expanded Programme on Immunization (EPI), considering health priorities and budget limitations in the country.

This study aims to assess the potential health and economic impact of the recently prequalified maternal vaccine and long-acting infant mAb in Mozambique. This should provide important evidence to inform national policy decisions on the use of these interventions.

METHODS

Study Design and Model

In the base case scenario, we estimated the potential health impact and cost-effectiveness of a single dose of a maternal vaccine and a single dose of long-acting infant mAb from a government health perspective, including all costs borne by the public health system. We also ran a separate scenario analysis from a societal health perspective, which included additional direct medical and non-medical costs borne by households, as well as indirect costs. The health benefits were quantified using DALYs averted. We chose to use DALYs because they account for years lost due to premature mortality and years lived with the disability due to the disease, facilitating comparison with other potential public health interventions and results from other jurisdictions.[12] We used the universal vaccine decision support model (UNIVAC version 1.7) to calculate the potential impact and cost-effectiveness of implementing each intervention over ten successive birth cohorts (2025–2034). UNIVAC is a proportionate outcomes static cohort model specifically designed for ease of use by country-led multidisciplinary teams in LMICs. It allows users to supplement default data with local information and provides a context-specific assessment of cost-effectiveness in settings with limited time, capacity, and resources. The model was developed in Microsoft Excel (Excel, Microsoft Corp, Redmond, Washington, United States). Detailed methods have been described elsewhere.[13] Although the core methodology aligns with previous studies, we adjusted the input parameters to reflect the conditions in Mozambique.[14,15]

We compared both interventions to the current status quo (no RSV pharmaceutical prevention strategy) and to each other. In the base case scenario, we assumed both interventions were administered year-round, but also ran a separate scenario assuming seasonal administration. We analysed the new long-acting infant mAb, rather than Synagis® (Palivizumab; short-acting mAb), because the new mAb is suitable for use in LMICs in all infants, not just those at high-risk, and is likely to have a lower price per course,[16] while Palivizumab is a short-lasting mAb that requires up to five monthly doses to protect throughout the RSV season—making it an expensive and impractical prospect for most countries.[17]

We estimated the number of RSV severe and non-severe disease cases, outpatients, hospital admissions and deaths, with and without each RSV intervention, between birth and five years of age, using rates per 100 000 children aged < 5 years and assuming a range of possible pathways of the disease (Supplementary Figure 1). DALYs were calculated over the lifetimes of all ten birth cohorts evaluated. In addition, we calculated the programme costs associated with each RSV prevention strategy and the healthcare costs averted.

The primary outcome measure was the cost per DALY averted, which reflected the lifetime costs and consequences calculated for all ten birth cohorts combined (2025–2034), from the government health perspective. We used 2023 USD for all costs. Future health outcomes and costs were discounted at 3% per year to reflect their present value in the first year of the RSV intervention programme (2025).[18] In addition to analysing cost-effectiveness from a government health perspective, we also evaluated the costs per DALY averted (in 2023 USD) from a societal health perspective, which included costs borne by households.

To interpret the cost-effectiveness ratios (USD per DALY averted) we compared them to a range of willingness-to-pay (WTP) thresholds (ie, what the government might be prepared to pay for each DALY averted).[19] Since Mozambique has not yet defined a country-specific WTP threshold, we assumed 0.4 times the national gross domestic product (GDP) per capita based on a study that estimated national cost-effectiveness thresholds using data on health spending and outcomes in Mozambique.[20] This is equivalent to USD 249, considering the national GDP per capita of USD 608.4 in 2023.21 Further we also calculated the probability that the RSV interventions would be cost-effective over a range of thresholds (0.5 and 1.0 GDP per capita) expressed as proportions of the Mozambican GDP per capita.

To build consensus on the inputs used in the analysis, we invited 12 multidisciplinary experts to attend a one-day stakeholder consultation workshop in Maputo City, Mozambique on October 23, 2023. Participants included stakeholders from the EPI, the National Immunization Technical and Advisory Group (known in Mozambique as Comité de Peritos de Imunização), the Maternal and Child Health Programme, the Medicine School of the Eduardo Mondlane University, PATH, Wilhelmina Children's Hospital–UMC Utrecht (The Netherlands), WHO, and the United Nations Children's Fund.

Burden of Disease

The disease burden inputs are presented in Table 1. For the rate of RSV-ALRI community cases (per 100 000 per year aged under five years of age) we used estimates

for Mozambique as reported in a systematic review by Li et al.[2] Using the same review, we assumed 10% of RSV-ALRI cases would be severe (require hospital admission) based on the proportion of RSV-ALRI cases with chest-wall indrawing from the low-income stratum. To estimate the rate of RSV-ALRI hospitalisation, we multiplied the rates of RSV-ALRI severe cases by the coverage of Bacillus Calmette-Guerin (BCG) vaccine (94%), assuming this would be a reasonable proxy for access to public hospitals for severe conditions[22] and further assumed that each hospital admission would have had at least one clinic visit (either before or after admission). For the non-severe cases, we multiplied the rates of RSV-ALRI by the percentage (73%) of children under five years old with non-severe acute respiratory infection symptoms that received healthcare from the public sector, as reported in the 2023 Mozambique Demographic and Health Survey (DHS).[11] We multiplied the number of severe RSV-ALRI hospitalisations by the in-hospital fatality ratio reported for children under five years old in a systematic review study that included 19 LMICs (1.5%), including Mozambique.[23] Consistent with an RSV mortality study from Zambia, we assumed that around two-thirds of RSV deaths before five years of age would occur in the community rather than in hospitals. This assumption, combined with other burden parameters gave a fatality ratio of around one-third for severe cases that did not have hospital access. We cross-checked our estimates of the number of RSV deaths (around 1200 each year), with those derived by assuming that 2% of all under-five deaths would be attributed to RSV. This proportion, estimated in Child Health and Mortality Prevention Surveillance (CHAMPS)[23] and Li et al.,[2] resulted in slightly higher estimates of RSV deaths (around 1,600 each year), and suggested our base case estimates were slightly conservative. Different burden input sources are shown in Supplementary Figure 2. We conservatively assumed that RSV mortality rates would decline each year in the absence of pharmaceutical RSV interventions, and assumed this trend would be consistent with the overall trend in projected under-five mortality rates from the United Nations World Population Prospects.[24]

For the age distribution of RSV disease, we used data from a cost-of-illness (COI) study conducted in Maputo during the 2023 RSV season[28] and fit parametric Burr curves to these data to generate estimates by week of age under five years. This study included all children under two years of age with ALRI that visited an outpatient clinic or were admitted to the Maputo Central Hospital. The age distribution for RSV outpatient cases was used for non-severe RSV cases and clinic visits, while the age distribution for RSV inpatient cases (excluding ICU cases) was used for severe RSV cases, clinic visits and hospital admissions. We used the age distribution among RSV cases admitted to the ICU as a proxy for the age distribution of RSV deaths. We estimated the proportion of RSV counts expected to occur in the missing age range (24–59 months) based on preliminary estimates from a review of datasets in LMICs.[34] We compared the age

distributions obtained from the COI study with age distributions reported in a study by Pale et al. in 2017 and 20184 (see Supplementary Figure 3).

RSV Intervention Impact

We estimated the health impact of each intervention for each week of age based on the expected RSV burden, intervention coverage, and efficacy assumed for each week of age (Table 1). For the maternal vaccine, coverage for year-round administration was assumed to be 87%, based on at least one antenatal care (ANC) attendance, as recorded in Mozambique during the 2022 Demographic and Health Survey (DHS). The national tetanus vaccine coverage estimate of 48% was used as the lower bound,[11] while the upper bound was assumed to be at 95%. For simplicity, we did not adjust for gestational age and assumed efficacy would be consistent with the results from the recent clinical trial.

For year-round administration of the long-acting infant mAb we assumed coverage would be equivalent to the mean coverage of BCG vaccine (94%) in Mozambique from 2015 to 2019, as reported by WHO/UNICEF estimates of national immunisation coverage (WUENIC).[29] We used coverage data from this period because the COVID-19 pandemic negatively impacted health services delivery, including immunisation services[35]; in Mozambique, BCG vaccine coverage saw an average decrease of 10% during the pandemic. We assumed an uncertainty range from 79% (the current coverage estimate)[29] and 98%. We also assumed real-world delays in the administration of the long-acting infant mAb, consistent with the timeliness of BCG as reported in the DHS 2011[36] (ie, the cumulative coverage at each week of age after birth).

We based efficacy estimates for each RSV intervention on evidence obtained from Phase III clinical trials. For the maternal vaccine, an efficacy of 69.4% was observed in preventing severe ALRI associated with RSV during the infant´s first six months of life.[8] In contrast, the long-acting infant mAb demonstrated an efficacy of 78.6% against very severe disease during five months following immunisation.[9] For non-severe presentations, we assumed the efficacy to be 51.3% (97.58% CI: 29.4–66.8) for the maternal vaccine and 76.4% (95% CI: 62.3–85.2) for the long-acting infant mAb based on the reported efficacy against medically attended RSV.

RSV Intervention Programme Cost

The immunisation programme cost comprises the vaccine price per dose, wastage, international transportation and handling, and incremental health system costs. Mozambique is currently in the initial self-financing Gavi phase, which normally allows the payment of USD 0.20 per dose of vaccine; however, the dose price and level of Gavi support for RSV interventions is currently uncertain. We therefore assumed a base

case price of USD 5 per dose and considered two additional dose price scenarios of USD 2.5 and 15. We assumed these prices for both interventions14 and assumed they would remain fixed for the duration of the analysis.

Healthcare Costs Associated with the Treatment of RSV Disease

In the base case scenario, we used cost data obtained from a recent COI study on RSV in Maputo City. This study took place during one respiratory season from February 2023 to August 2023.[28] Costs borne by the government included general operational costs per illness episode and direct medical costs (e.g., medication and imaging). Costs borne by households included any out-of-pocket direct medical costs not covered by the government as well as direct non-medical costs (e.g., transportation) and indirect costs (e.g., income lost) that occurred during the initial visit to a governmental facility or prior/post initial visit at any healthcare facility. Since the costs were all collected at a tertiary-level hospital, we adjusted them to account for the distribution of primary, secondary, and tertiary facilities across the country, and used cost estimates from WHO-CHOICE for Mozambique to inform the relative cost of care at primary, secondary, and tertiary hospitals. From the governmental perspective the study estimated USD 6.98 (IQR: 6.97–6.99) per outpatient clinic visit and USD 465.30 (IQR: 411.05–519.55) per RSV hospital admission. From the societal perspective, the study estimated USD 41.79 (IQR: 10.91–72.66) per RSV outpatient case and USD 523.01 (IQR: 466.07–579.94) per RSV hospital admission.[37] We assumed the same outpatient cost per visit for severe and non-severe RSV cases (Table 1).

Uncertainty Analysis

We ran a number of deterministic scenarios to understand how variations in the input parameters and assumptions might influence the cost-effectiveness results.[12] The scenarios were defined based on parameters reported to be influential in previous studies:[14,38,39]

i) Dose price of USD 2.5
ii) Dose price of USD 15
iii) Dose price of USD 25
iv) Excluding indirect costs
v) Lower vaccine coverage
vi) High efficacy (upper bound of 95% CI)
vii) Low efficacy (lower bound of 95% CI)
viii) High healthcare costs (75th percentile)
ix) Low healthcare costs (25th percentile)
x) Higher initial efficacy but reduced duration of protection for maternal vaccine (assuming efficacy of 81.8% and 57.1% for severe and non-severe RSV disease, respectively, for a fixed 3-month period).

xi) Gradual waning protection for both interventions (assuming a gamma function described elsewhere to assume efficacy is initially very high, then gradually approaches zero by age 12 months).[14]

xii) Seasonal dose administration

For scenario xi regarding seasonal dose administration specifically, we took into account the seasonal burden of RSV disease in the southern part of Mozambique, wherein much of the burden occurs between February and July.[4,28] We evaluated various scenarios targeting specific months of the year (rather than year-round strategies) as well as various potential months of birth that could be targeted for protection using either intervention. Each combination of the expected health impact (percent reduction in RSV hospital admissions) and dose efficiency (doses required to achieve a 1% reduction in RSV hospital admissions) was compared to a year-round preventive strategy. Estimates of health impact by month of birth were calculated using a database of RSV hospital admissions, using the interval between birth and age of admission to determine the protection that could have been provided by either intervention, assuming different months of birth would qualify for protection. This analysis assumes protection from birth and no catch-up in dose administration at older ages. The database included data from a recent COI Study in Maputo, Mozambique, where during one respiratory season (from February to August 2022) all hospitalised children under two years of age were tested for RSV.19 In total, 109 RSV positive hospital admissions were recorded. Since children in the described study were only tested during a certain period of the year, we also repeated the analysis using data from another study by Pale et al. that was conducted in Maputo from 2017 to 2018.[4]

In addition to the aforementioned scenarios, we also ran a probabilistic sensitivity analysis (PSA) simultaneously varying all parameters within their ranges, using 1,000 Monte Carlo simulations. For both intervention options we ran a separate PSA for the base case (USD 5 per dose) and two alternative fixed price scenarios (USD 2.5 and USD 15 per dose). For simplicity, we assumed a transparent Beta-PERT distribution for all parameters and their respective ranges. The probabilistic results were presented on a cost-effectiveness plane. To estimate the probability that the intervention would be cost-effective at different WTP thresholds, the results were presented using cost-effectiveness acceptability curves. Finally, we estimated the maximum price per dose at which each intervention would be considered cost-effective at various thresholds, based on the base-case assumptions.

Table 1. Input parameters for estimating the impact and cost-effectiveness of maternal and long-acting infant mAb for RSV disease prevention in Mozambique.

Input parameters	Central value	Uncertainty range	Sources
Incidence (per 100 000 children under 5 years old per year) a			
Non severe RSV cases	5247	3870–7110	2
Non severe RSV visits	3841	2941–5404	11
Severe RSV cases	583	430–790	2
Severe RSV visits	583	430–790	2
Severe RSV hospitalisations	542	400–735	22
RSV deaths	23	12–31	Assumed based on2,23,25
Disability weights (%)			
Non-severe RSV	5.1	3.2–7.4	26
Severe	13.3	8.8–19	26
Mean duration of illness (days)			
Non-severe RSV	5	3–7	27
Severe	10	7–14	27
Cumulative age-specific burden (non-severe)		28	
<1 month	4%	NA	
<2 months	4%		
<3 months	12%		
<6 months	24%		
<1 year	44%		
<2 years	71%		
<3 years	87%		
<4 years	95%		
<5 years	100%		
Cumulative age-specific burden (severe)			28
<1 month	7%	NA	
<2 months	10%		
<3 months	29%		
<6 months	53%		
<1 year	77%		
<2 years	92%		
<3 years	97%		
<4 years	99%		
<5 years	100%		

Table 1. Continued.

Input parameters	Central value	Uncertainty range	Sources
Cumulative age-specific burden (death)			28
<1 month	2%		
<2 months	13%		
<3 months	39%		
<6 months	72%		
<1 year	89%		
<2 years	96%		
<3 years	98%		
<4 years	99%		
<5 years	100%		
Maternal immunisation impact			
Expected coverage (ANC proxy) (%)	87	48.0–95.7	Assumed based on11
Efficacy against RSV severe cases (%)	69.4	44.3–84.1	8
Efficacy against RSV non-severe cases (%)	51.3	29.4–66.8	8
Duration of protection (months)	6	3–7	8
Infant mAb immunisation impact			
Expected coverage (BCG proxy) (%)	94	79–98	29
Efficacy against RSV severe cases (%)	78.6	48.8–91.0	9
Efficacy against non-severe RSV (%)	76.4	62.3–85.2	9
Duration of protection (months)	5	4–6	9
Costs of intervention			
Price per dose (USD)	5	NA	Assumption
Syringe price per dose	0.000	NA	Assumed pre-filled syringe
Safety box price per dose	0.012	NA	30
International handling (% price per dose)	3%	NA	31
International delivery (% price per dose)	6%	2%–15%	32
Incremental system cost per dose (USD)	2.21	1.72–2.93	33
Wastage assumptions (% per dose)			
Dose and pre-filled syringe	5%	NA	Assumption
Safety boxes/bags	5%	NA	Assumption
Costs of RSV related care Governmental perspective			
Non-severe disease (USD)			
Outpatient visit cost	6.98	6.97–6.99	28

Table 1. Continued.

Input parameters	Central value	Uncertainty range	Sources
Severe disease (USD)			
Outpatient visit cost	6.98	6.97–6.99	28
Hospitalisation cost	465.30	411.05–519.55	28
Costs of RSV related care Societal Perspective			
Non-severe disease (USD)			
Outpatient visit cost	41.79	10.91–72.66	28
Severe disease (USD)			
Outpatient visit cost	41.79	10.91–72.66	28
Hospitalisation cost	523.01	466.07–579.94	28

All future costs and benefits are discounted at a 3% discount rate per year. Costs and GDP percentage are expressed in 2023 USD. Abbreviations: ANC, antenatal care; BCG, Bacillus Calmette-Guerin; GDP, gross domestic product; mAb, monoclonal antibody; RSV, respiratory syncytial virus.

RESULTS

All the base-case results are presented in Table 2. Without any pharmaceutical RSV intervention in Mozambique, we estimated 3.6 million RSV disease cases, 339 343 hospital admissions, and 10 816 deaths in ten birth cohorts of children (2025–2034). The long-acting infant mAb was estimated to have slightly more health benefit than the maternal vaccine, primarily due to the higher intervention coverage assumed for the mAb (Table 2). Either intervention was estimated to prevent more than 30% of the severe RSV disease cases and hospital admissions and more than 40% of RSV deaths in children under five years of age. Either intervention could prevent more than 4500 RSV deaths over a 10-year period.

The maternal vaccine programme could cost around USD 80 million over ten years, but this would be offset by USD 46 million healthcare costs averted from a government perspective (or USD 63 million from a societal perspective) (Table 2). The long-acting infant mAb could cost around USD 85 million over ten years, but this would be offset by USD 48 million healthcare costs averted from a government perspective (or USD 67 million from a societal perspective) (Table 2). Both interventions had a very similar cost per DALY averted (from a government perspective) when compared separately to no intervention. The cost per DALY averted was USD 288 (95% uncertainty interval 140–574) for the maternal vaccine and USD 289 (95% uncertainty interval 160–583) for the long-acting infant mAb, corresponding to around 48% of the national GDP per capita (Table 2).

Table 2. Estimated health impact and costs of RSV preventive interventions (MI: USD 5/dose 87% coverage, 69.4% efficacy, 6 months protection; and mAb immunisation: USD 5/dose, 94% coverage, 78.6% efficacy, 5 months protection) compared to no pharmaceutical intervention in Mozambique (2025–2034).

Outcomes	No intervention	Maternal vaccine	Long-acting infant mAb
Lifetime costs and effects			
RSV cases	3 650 126	3 186 112	3 067 442
RSV severe cases	365 013	247 337	244 023
RSV visits	2 769 838	2 398 630	2 310 871
RSV hospitalisations	339 343	229 943	226 861
RSV deaths	10 816	6 145	5 688
DALYs (discounted* in USD)	268 936	152 931	141 555
Vaccine programme costs (discounted* in USD)	0	79 608 014	84 813 864
Government healthcare costs (discounted* in USD)	151 113 622	104 940 864	103 175 597
Societal healthcare costs (discounted* in USD)	248 823 930	186 048 717	181 494 226
Differences (comparator = no vaccine)			
RSV total cases	-	464 014	582 684
RSV severe cases	-	117 675	120 990
RSV visits	-	371 208	458 967
RSV hospitalisations	-	109 400	112 481
RSV deaths	-	4 671	5 128
DALYs (discounted*)	-	116 004	127 380
Vaccine programme costs (discounted* in USD)	-	79 608 014	84 813 864
Government healthcare costs (discounted* in USD)	-	-46 172 757	-47 938 024
Societal healthcare costs (discounted* in USD)	-	-62 775 214	-67 329 704
Cost (USD) per DALY averted (comparator = no vaccine)			
Government cost perspective			
Cost (discounted* in USD)	-	33 435 257	36 875 840
DALYs averted (discounted* in USD)	-	116 004	127 380
Cost per DALY averted (discounted* in USD)	-	288	289
Societal cost perspective			
Cost (discounted* in USD)	-	16 832 800	17 484 160
DALYs averted (discounted* in USD)	-	116 004	127 380
Cost per DALY averted (discounted* in USD)	-	145	137

*All future costs and benefits are discounted at a 3% discount rate per year. Costs are in 2023 USD. Abbreviations: DALY, disability-adjusted life year; GDP, gross domestic product; mAb, monoclonal antibody; MI, maternal immunisation; RSV, respiratory syncytial virus.

The cost per DALY averted was sensitive to changes in the dose price and efficacy assumptions. All scenarios generated a ratio below one times the national GDP per capita with the exception of four: the lower bound estimate of efficacy, high maternal vaccine efficacy for only 3 months, a dose price of USD 15, and a dose price of USD 25 (Supplementary Figure 4 and 5). A nine-month strategy targeting births from September to April could generate the same impact as a year-round strategy and require 25% fewer doses (Supplementary Figure 6).

Both interventions were estimated to generate similar value for money compared to the status quo when assuming the same price per dose, with overlapping probabilistic clouds of uncertainty for costs and DALYs averted (Figure 1). At an intervention price of USD 5 per dose, the probability is approximately 20% that either intervention would be cost effective at a threshold of 0.4 times the national GDP per capita. This probability increases to 50% at 0.5 times the national GDP per capita and reaches 100% at a threshold of 1.0 times the national GDP per capita. If the dose price reduces to USD 2.5, the probability of being cost-effective at the 0.4 times the national GDP per capita threshold increases to almost 100%. If it rises to USD 15, however, the probability that either intervention could be cost-effective decreases to zero percent (Figure 2).

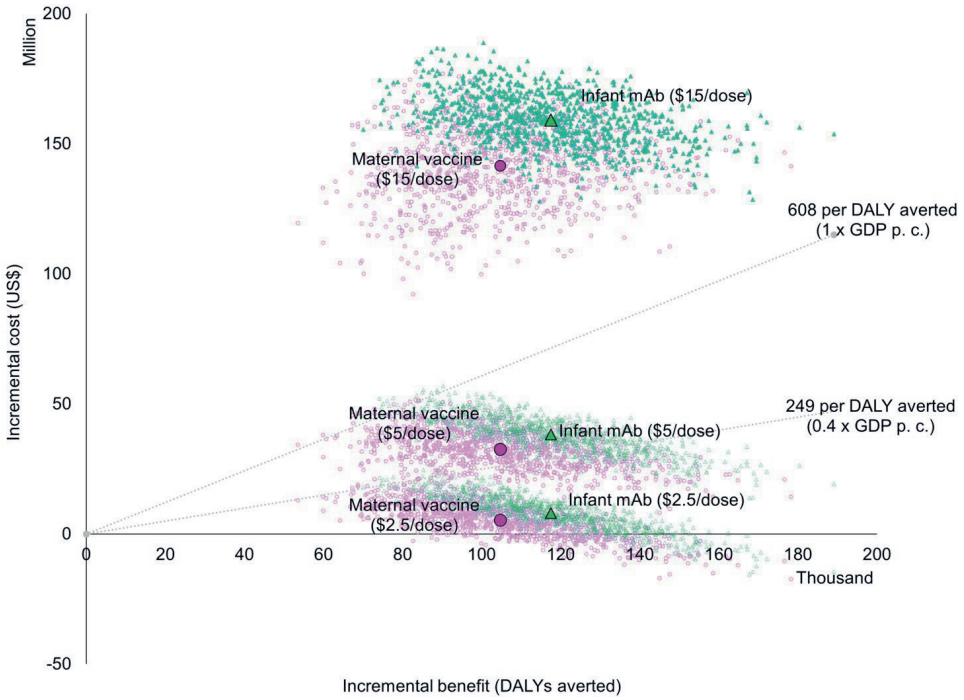

Figure 1. Probabilistic clouds of incremental costs and health benefits of both respiratory syncytial virus prevention strategies (maternal and long-acting infant monoclonal antibody immunisation) assuming dose price at USD 2.5, USD 5, and USD 15 from a government perspective.

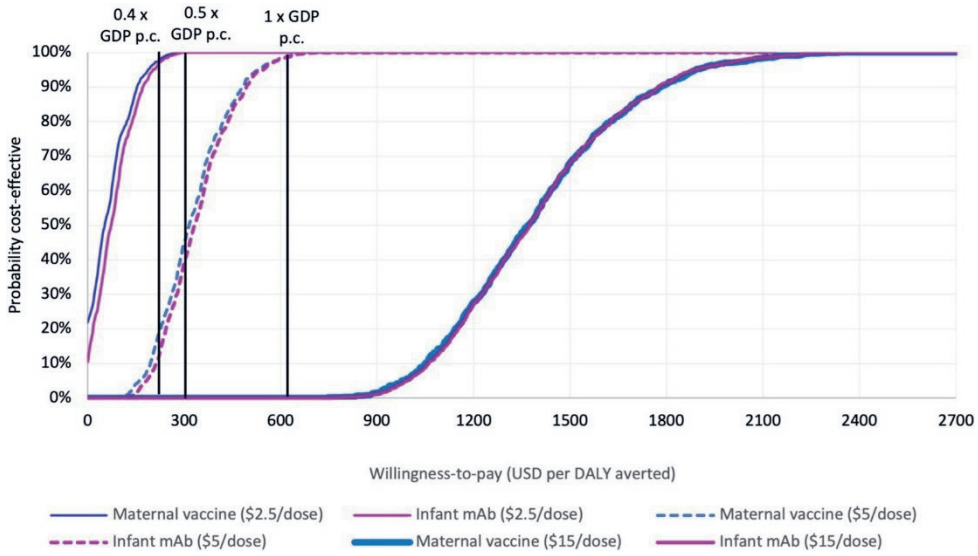

Figure 2. Probability that each respiratory syncytial virus prevention strategy (either maternal vaccine or long-acting infant monoclonal antibody) will be cost-effective compared to no intervention, at different willingness-to-pay thresholds.

DISCUSSION

Both interventions included in our analysis were recently prequalified and recommended for global use by WHO and have started to be introduced in Argentina, Chile, Canada, the United Kingdom, and the United States.[40] Our estimates indicate that both interventions have the potential to reduce the RSV burden in Mozambique, potentially averting over 4500 deaths (a reduction of more than 40%) over a 10-year period. The impact was lower for non-severe RSV cases because a substantial proportion of these cases were estimated to occur in the six- to 59-month age range. A strength of our analysis is that we used model input parameters that were approved by local stakeholders, including estimates from Mozambique. In particular, we were able to incorporate the results of a recent cost-of-illness study conducted in Maputo.

While the market price per dose for LMICs has yet to be defined, the prices for the maternal vaccine and mAb are unlikely to be the same. mAb costs are likely to be higher than those of the maternal vaccine due to existing pricing agreements for vaccines in LMICs and lower production costs. Using the current study's price estimation, both interventions were estimated to have a reasonable probability of being cost-effective at a per-dose cost of USD 5 and a WTP threshold of 0.4 times the national GDP per capita;

however, the cost-effectiveness was more favourable when the dose price was reduced to USD 2.5. These results are conservative (from a government health perspective) because they assume the government will cover the full cost of the vaccine, and do not account for anticipated support from Gavi.

We did not evaluate a combined strategy (e.g., using long-acting infant mAb for newborns that were not previously protected by maternal vaccination), but this could be an effective way to increase protection of the birth cohort by providing two opportunities to provide protection. In Mozambique, a high number of zero dose children and women who have not had ANC visits remains.[41] Addressing these gaps may require further analyses of how disease risk and access to care varies in different groups of the population.

Our results are comparable with previously published costs-effectiveness analyses in Vietnam and sub-Saharan African countries.[14,38,39] In our analysis, the long-acting infant mAb was estimated to have a higher health impact, which was primarily due to the higher coverage assumed compared to the maternal vaccine. Other studies reveal a similar pattern.[14] We considered a range of acceptable thresholds to interpret the results. In Vietnam, Do et al. assessed both preventive strategies and demonstrated that they have the potential to be cost-effective at USD 5 per vaccine dose, with a WTP threshold of 0.5 times the national GDP per capita.[15] Koltai et al. conducted a study on the cost-effectiveness of both interventions in Kenya and South Africa, and found that the interventions were cost-saving in South Africa and cost-effective in Kenya at a price of USD 5.[39] Baral et al. performed a similar study across several LICs, including in sub-Saharan Africa, which found that the cost per DALY averted was USD 949 for maternal vaccine and USD 257 for the long-acting infant mAb, based on a dose price of USD 3. This study, however, was based on earlier information about the clinical efficacy of the maternal vaccine. More recent estimates show equivalent cost-effectiveness for each option at equivalent prices.[38] Other infant immunisation programmes in Mozambique, such as for rotavirus vaccine, have recently been shown to be cost-effective in young children (USD 70 per DALY averted).[42] The introduction of an RSV preventive intervention in Mozambique would also mitigate any future RSV outbreaks that might be associated with climate change i.e. higher temperatures and increased rainfall,[43] as reported in the Americas[44,45] and Madagascar (Africa).[45]

Our study had some limitations. First, we used a static cohort model that did not account for transmission dynamics. However, there is currently limited evidence on the extent to which either intervention will interrupt transmission. Second, we used data from the south of the country (Maputo) to estimate the age profile of RSV outpatients and inpatients, costs of RSV illness and seasonality. While we have no a priori reason

to assume the age profile or seasonality would be different in the north and central regions, it is possible that the costs of illness could vary in different regions. However, deterministic scenarios with lower and higher healthcare costs did not alter the cost-effectiveness conclusions. It is also important to note that several other influential inputs and adjustments (e.g., RSV disease burden rates, DHS access to care, BCG and ANC coverage) were taken from national estimates, so we believe the analysis is as representative as it is possible to be at the present time. Third, clinical trials for both interventions have predominantly been conducted in high-income countries with lower rates of severe RSV outcomes compared to LMICs, such as Mozambique. Participants in controlled clinical trials often differ significantly from the average populations in LMICs, which may limit the generalisability of the findings. Fourth, we did not explore the potential balance of benefits to risks. In the Phase III trial, a numerical increase in preterm births was observed in some groups that received the maternal vaccine.[46] In response to this safety signal, an ongoing randomised controlled study is investigating the effectiveness and safety of the maternal vaccine in several African countries.

We investigated seasonal administration of either the maternal vaccine or long-acting infant mAb to assess the impact and cost-effectiveness of a seasonal programme rather than a year-round programme. Our analysis shows that a nine-month seasonal administration strategy could give the same overall impact, but better dose efficiency, as compared to a year-round strategy. Introducing a seasonal approach could therefore optimise resource allocation; however, no seasonal administration of any vaccine currently occurs in Mozambique and the feasibility of this approach is unclear. This seasonal approach also assumes that the dose price negotiated for a year-round programme would the same as the price negotiated for a seasonal programme. Seasonal administration implementation poses several challenges because it would require healthcare personnel training as well as investment in education, logistics, and monitoring systems. These factors imply a substantial increase in system and delivery costs per dose. South Africa has adopted seasonal approaches for influenza,[47] and several countries in Europe and America are following similar approaches for RSV vaccine administration.[48,49] The experience of these countries could provide valuable insights, since they registered positive results on reducing burden of both diseases especially in high risk people.[50,51] Further investigation in other African countries using similar strategies could also enhance the understanding of this approach in similar contexts.

The evidence generated is aligned with the current priority of the National Research Agenda 2024–2028,[52] which supports the introduction of impactful and cost-effective interventions. Passive RSV immunisation has the potential to prevent a substantial number of RSV cases in infants, and to be cost-effective at prices below USD 5/dose.

Although both interventions have undoubted potential to reduce disease burden and be cost-effective in Mozambique, the decision to introduce them would depend on several other criteria including acceptability, safety, government health priorities, and budget availability. Our existing model and evaluation should provide a convenient basis for updating estimates of cost-effectiveness as updated national data emerges, particularly on the price of each intervention.

CONCLUSION

A maternal vaccine or long-acting infant mAb could prevent a substantial number of infant deaths in Mozambique. Both interventions have the potential to be cost-effective in Mozambique if appropriately priced. Policymakers should consider introducing these interventions as part of the national immunisation strategy and explore the potential for seasonal administration to maximise efficiency.

Supplementary files can be downloaded from:



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8

Cost-Effectiveness of Introducing a Maternal Vaccine or Long-Acting Monoclonal Antibody to Prevent Infant Respiratory Syncytial Virus Disease in Nepal

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ABSTRACT

Background: The World Health Organization recommends two passive immunisation strategies to prevent respiratory syncytial virus (RSV) disease in young infants. Both are being introduced in high-income settings, but their affordability and cost-effectiveness have not been evaluated in many low- and middle-income countries. Preliminary estimates of cost-effectiveness are needed to guide immunisation policy and planning in Nepal.

Methods: We estimated the potential health impact and cost-effectiveness of introducing a maternal vaccine (RSVpreF) or long-acting infant monoclonal antibody (mAb) (nirsevimab) over the period 2025–34 in Nepal. We compared both interventions to the status quo (no intervention) and to each other. Model inputs included health care cost estimates from a recent prospective cost-of-illness study in Kathmandu, as well as the latest efficacy data from clinical trials. The primary outcome measure was the incremental cost (2023 USD) per disability-adjusted life year (DALY) averted from a governmental health perspective. We conducted a range of deterministic analyses, including scenarios that incorporated a societal perspective and a seasonal approach. Additionally, we performed probabilistic uncertainty analyses to assess decision uncertainty and estimated the likelihood of cost-effectiveness for each intervention across a range of willingness-to-pay thresholds.

Results: Introducing a maternal vaccine (USD 5/dose, 81% coverage, 69% efficacy, 6 months protection) or long-acting infant mAb (USD 5/dose, 97% coverage, 77% efficacy, 5 months protection) could prevent >2300 deaths and >50000 hospital admissions over ten years. The discounted immunisation programme costs were estimated to be USD 30 and USD 35 million, respectively. Compared to the status quo, the maternal vaccine and the long-acting infant mAb were estimated to cost USD 387 and USD 486 per DALY averted, respectively, which is around 0.3 times and 0.4 times the national gross domestic product (GDP) per capita. There was a 95% probability that the maternal vaccine would be cost-effective at USD 5 per dose, assuming a willingness-to-pay threshold of 0.5 times the national GDP per capita. With our base case assumptions, the maternal vaccine dominated the mAb (i.e. generated more health benefits at a lower cost). However, the results (and the rank order of interventions) were sensitive to the dose price, efficacy, duration of protection, and RSV disease burden estimates. Cost-effectiveness of the mAb improves with timely administration or when a seasonal approach is implemented.

Conclusion: New passive immunisation strategies have the potential to prevent a substantial number of RSV-related hospitalisations and deaths in Nepal. Cost-effectiveness and product choice will heavily depend on the price negotiated for each product.

INTRODUCTION

Acute lower respiratory infections (ALRIs) caused by respiratory syncytial virus (RSV) are a major cause of death and hospital admissions among young children. In 2019, RSV was estimated to cause 33 million cases and 118 000 deaths in children under five years, with more than 95% of the burden in low- and middle-income countries (LMICs).[1] In 2017, the global economic burden of managing RSV infections in young children was estimated to be USD 5.5 billion (EUR 4.82 billion (95% confidence interval (CI) = EUR 3.47–7.93 billion)), with 65% of the economic burden in LMICs.[2] Despite this, most cost-effectiveness studies to date have been conducted in high-income countries, limiting their relevance for health policy decision-making in LMICs.

Two passive RSV immunisation strategies have recently received market approval and are recommended for global use by the World Health Organization (WHO).[3] A maternal vaccine (RSVpreF, Abrysvo, Pfizer) has demonstrated efficacy of 69.4% (97.58% CI = 44.3–84.1) against severe medically attended RSV-ALRI after 180 days of follow-up.[4] In addition, a long-acting infant monoclonal antibody (mAb) (nirsevimab, Beyfortus, AstraZeneca and Sanofi)[5] has demonstrated efficacy of 76.8% (95% CI= 49.4–89.4) against hospitalisation for RSV-associated lower respiratory tract infection after 150 days of follow-up.[6] Both intervention strategies have already been introduced in national immunisation programmes in parts of the Americas and Europe and are starting to be considered for introduction in LMICs.

Health systems in LMICs vary widely in terms of service delivery, health care financing, disease burden, and available infrastructure. These differences influence how interventions are implemented, how costs are incurred, and how health outcomes are realised. As a result, cost-effectiveness findings from high-income countries, and even from other LMICs, may not be directly applicable, underscoring the need for country-specific analyses to support evidence-based policy decisions.

In Nepal, RSV is one of the leading respiratory viral pathogens among young children presenting with respiratory symptoms, both in rural and urban areas.[7–9] In a semi-urban region, 15% of all pneumonia cases in children under three years of age were associated with RSV. In urban areas, 28% of ALRI patients in intensive care units (ICUs) tested positive for RSV,[10] and a recent study detected RSV in 73% of hospitalised children with severe ALRI during the respiratory season.[9]

Nepal's National Immunisation Programme has recently integrated several new vaccines into the national immunisation schedule, including the rotavirus and typhoid conjugate vaccine.[11] The country's vaccination initiatives are strongly supported by

Gavi, the Vaccine Alliance, and the United Nations Children's Fund (UNICEF), which provide both financial and technical assistance. In February 2025, Nepal launched a nationwide human papillomavirus vaccination campaign with support from Gavi [12]. Since Gavi's Vaccine Investment Strategy has prioritised RSV vaccines for the 2021–25 funding period and beyond, RSV is considered a potential candidate for future inclusion in Nepal's National Immunisation Programme. In March 2025, the first maternal RSV vaccine received WHO prequalification, and shortly thereafter, Gavi approved funding for country introductions.[13,14] These developments highlight the need for national decision-makers in Nepal to have timely estimates of the potential health impact and cost-effectiveness of both the maternal vaccine and long-acting infant mAb.

We aim to evaluate the potential health and economic impact of a maternal vaccine and a long-acting infant mAb, utilising the best available evidence for the Nepali context. The findings are expected to provide essential information for informed national policy decisions on implementing these interventions.

METHODS

Study Design

We estimated the potential health impact and cost-effectiveness of two passive RSV immunisation strategies for children under five years of age in Nepal over 10 years (2025–34). We compared a maternal vaccine (RSVpreF, Abrysvo, Pfizer) and long-acting infant mAb (nirsevimab, Beyfortus, AstraZeneca and Sanofi) to the status quo (no pharmaceutical intervention) and to each other. The primary outcome measure was the cost (2023 USD) per disability-adjusted life year (DALY) averted, from a governmental health perspective. We applied a 3% discount rate to both the costs and benefits of immunisation following WHO guidelines.[15] To interpret the cost-effectiveness ratios (USD per DALY averted) we used a willingness-to-pay (WTP) threshold to represent what the government might be willing to pay for each DALY averted by the intervention. In the absence of a country-specific WTP threshold for Nepal, we used 0.34 times the national gross domestic product (GDP) per capita. This value represents the midpoint of the 0.28–0.39 range estimated by Ochalek et al., who estimated opportunity costs specific to Nepal by using data on current health expenditures and health outcomes.[16] This approach seeks to quantify the marginal productivity of health spending, to account for the health that is forgone elsewhere in the system when resources are reallocated. This threshold is consistent with the estimates from Pichon-Riviere et al., who used an independent, but similar, methodology and estimated a threshold of 0.35 (95% CI = 0.18–0.44) for Nepal.[17] To reflect broader global health decision-making practices and account for uncertainty in

the threshold, we also evaluated the probability that the RSV intervention strategies would be cost-effective at two alternative thresholds of 0.5 and 1 times the GDP per capita.[18] We assumed a GDP per capita of USD 1324 for Nepal, based on estimates from the World Bank for the year 2023.[19] We reported all costs in 2023 USD (USD 1 = NPR 132.12).[20]

Model

To calculate the potential health impact and cost-effectiveness of both RSV intervention strategies, we used the universal vaccine decision-support model (UNIVAC, version 1.7) a static proportionate outcomes cohort model. The model can be used to provide transparent and conservative estimates of the projected impact and cost-effectiveness of the maternal vaccine and long-acting infant mAb.[21] It was recently applied in Argentina, Mozambique, and Vietnam.[22–24] The model is populated with parameters on population demographics, rates of RSV disease (cases, clinic visits, hospital admissions, and deaths before the age of five), RSV health care costs, intervention efficacy, coverage, timeliness, and programme costs.

To build consensus on the inputs used in the UNIVAC model, we consulted key national stakeholders, including representatives from Nepal's Ministry of Health and Population (Family Welfare, Epidemiology and Disease Control, Logistics, Procurement and Management, Finance, and Policy and Planning Divisions), the National Immunization Technical Advisory Group, and international partners (WHO and UNICEF) (Table 1). Professional bodies, including the Nepal Paediatric Society and paediatric nursing associations, also contributed. Stakeholder engagement was conducted between September 2023 and August 2024 through a combination of both in-person meetings and structured discussions. These interactions provided critical insights into available country-specific data and guided decisions on treatment-seeking behaviour, health care utilisation patterns, and the operational feasibility of vaccine delivery. We iteratively incorporated stakeholder feedback to ensure that the model inputs accurately reflect the local context.

Burden of RSV Disease

We estimated the rate of RSV disease events (cases, visits, clinic visits, hospital admissions, deaths) per 100 000 per year (<5 years) and applied these to United Nations World Population Prospects estimates of life-years lived between birth and five years in each evaluated birth cohort. We assumed these rates would remain fixed in the absence of new pharmaceutical interventions (except RSV deaths), which we conservatively assumed would decrease at the same rate as the United Nations World Population Prospects projected improvements in overall under-five mortality.

Table 1. Input parameters for estimating the impact and cost-effectiveness of a maternal vaccine and a long-acting infant mAb for RSV prevention in Nepal.

	Central value	UR	Sources
Incidence rate per 100000 under-five children per year			
Non-severe RSV cases	7313	3269–9140	Chu et al. [7], Li et al. [1]
Non-severe RSV visits	1901	850–2377	DHS 2022 [25], MICS 2019 [26]
Severe RSV cases	963	431–1204	Chu et al. [7], Li et al. [1]
Severe RSV visits	2167	969–2708	DHS 2022 [25], MICS 2019 [26]
Severe RSV hospitalisation	722	323–903	DHS 2022 [25]
RSV deaths	44	19–54	Li et al. [1], GOLD-ICU [10]
Non-severe cumulative age-specific burden, %			
<1 month	1	NA	GOLD-COI [9]
<2 months	3		
<3 months	8		
<6 months	21		
<1 year	47		
<2 years	77		
<3 years	90		
<4 years	96		
<5 years	100		
Severe cumulative age-specific burden (severe), %			
<1 month	7	NA	GOLD-COI [9]
<2 months	8		
<3 months	24		
<6 months	44		
<1 year	69		
<2 years	89		
<3 years	96		
<4 years	99		
<5 years	100		
Cumulative age-specific mortality burden, %			
<1 month	16	NA	GOLD-COI [9]
<2 months	15		
<3 months	44		
<6 months	64		
<1 year	80		
<2 years	91		
<3 years	96		

Table 1. Continued.

<4 years	98		
<5 years	100		
Disability weights, %			
Non-severe RSV	5.1	3.2–7.4	GBD 2019 [27]
Severe	13.3	8.8–19.0	GBD 2019 [27]
Mean duration of illness, in days			
Non-severe RSV	5	3–7	Graham and Anderson [28]
Severe RSV	10	7–14	Graham and Anderson [28]
Maternal immunisation impact			
Expected coverage (ANC proxy), %	81.0	77.8–92.0	DHS 2022 [25]
Efficacy against RSV severe cases, %	69.4	44.3–84.1	Kampmann et al. [4]
Efficacy against RSV non-severe cases, %	51.3	29.4–66.8	Kampmann et al. [4]
Duration of protection (months)	6	5–7	Kampmann et al. [4]
Infant mAb impact			
Expected coverage (BCG proxy), %*	97	95–99	WHO and UNICEF [29]
Efficacy against RSV severe cases, %	76.8	49.4–89.4	Muller et al. [6]
Efficacy against non-severe RSV, %	76.4	62.3–85.2	Muller et al. [6]
Duration of protection (months)	5	4–6	Muller et al. [6]
Costs of intervention, in USD			
Price per dose†	5	NA	Assumption
Syringe price per dose	0.000	NA	Assume pre-filled syringe
Safety box price per dose	0.005	NA	UNICEF [30]
International handling (% price per dose)	3	3–5	UNICEF [31]
International delivery (% price per dose)	6	2–15	Debellut [32]
Incremental delivery cost per dose†	1.66	1.00–2.75	Janoch et al. [33]
Wastage assumptions, % per dose			
Wastage of vaccines and syringes	5	NA	Assumption
Safety boxes/bags	5	NA	Assumption
Costs of RSV-related care governmental perspective, in USD†			
Non-severe disease			
Outpatient visit cost	15.22	14.51–15.94	GOLD-COI [9], MoHP [34]
Severe disease			
Outpatient visit cost	15.22	14.51–15.94	GOLD-COI [9], MoHP [34]
Hospitalisation cost	47.65	44.21–66.38	GOLD-COI [9], MoHP [34]
Costs of RSV-related care societal perspective, in USD†			
Non-severe disease			
Outpatient visit cost	41.90	23.90–59.91	GOLD-COI [9], MoHP [34]

Table 1. Continued.

Severe disease			
Outpatient visit cost	41.90	23.90–59.91	GOLD-COI [9], MoHP [34]
Hospitalisation cost	273.61	251.22–295.99	GOLD-COI [9], MoHP [34]

ANC – antenatal care, BCG – Bacillus Calmette-Guerin, COI – cost-of-illness, DHS – Demographic and Health Surveys, mAb – monoclonal antibody, ICU – intensive care unit, MICS – Multiple Indicator Cluster Surveys, MoHP – Ministry of Health and Population, RSV – respiratory syncytial virus, UNICEF – United Nations Children's Fund, UR – uncertainty range, WHO – World Health Organization

*BCG vaccination real-world timeliness is applied to the coverage assumption for the long-acting infant mAb. For simplicity, no age restriction was assumed for the long-acting infant mAb administration.

†All future costs and benefits are discounted at a 3% discount rate per year. Costs and gross domestic product per capita are expressed in 2023 USD.

We assumed annual incidence of 7313 per 100 000 < 5 years for non-severe RSV cases, and 963 for severe RSV cases based on a cohort study by Chu et al. in the rural sub-tropical plains of Nepal.[7] This study captured incidence in children under six months of age, so we adjusted the incidence rate to reflect children under five by assuming that 22% of under-five cases would be aged under six months, based on preliminary estimates from a systematic review evaluating RSV age distribution in LMICs (data not published). We assumed that 12% of RSV cases would be severe, consistent with estimates from Chu et al.[7] and Li et al.[1] We assumed 0.26 clinic visits per non-severe RSV case based on the proportion of acute respiratory infection cases with access to public sector providers, as reported in the 2019 Nepal Multiple Indicator Cluster Surveys (MICS 2019) and the 2022 Demographic and Health Survey (DHS 2022).[25,26] For severe RSV cases, we assumed that 75% would have access to a hospital, based on the reported access to care for acute respiratory infections in the DHS 2022.[25] We further assumed three clinic visits per hospital admission because caregivers in Nepal often return to health care facilities multiple times when symptoms persist or worsen, and follow-up care is typically provided after hospital discharge. We assumed a hospital fatality ratio of 2%, reflecting the average of two hospital fatality ratio estimates from LMICs[1,8] and that 67.5% of RSV deaths would occur in the community, reflecting the average of two separate estimates from LMICs.[1,24] Our estimates of the annual number of RSV deaths were higher than estimates derived using a separate 'top-down' (proportionate mortality) approach (1285 vs. 643). We used the higher burden estimate derived from the 'bottom-up' (incidence-based) approach in the base case scenario to avoid underestimating the potential impact of RSV, assuming that registration systems are often incomplete and community deaths may be underreported. To account for this uncertainty, we ran a scenario analysis using both the lower and higher mortality estimates, including an even more conservative lower bound of 561 based on Li et al. We incorporated these mortality bounds into the lower and higher burden scenarios, respectively, and formed the range used in the

probabilistic uncertainty analysis (Appendix S1 in the Online Supplementary Document).

We obtained the RSV age-burden distribution from a recent cost-of-illness (COI) study [9] and an associated study on high-dependency units and ICUs in Kathmandu, Nepal [10] (Appendix S2 in the Online Supplementary Document). The COI study included all children under two years with ALRI who visited Kanti Children's Hospital or Tribhuvan Teaching Hospital between July and November 2023. The ICU study focused on life-threatening cases being admitted to the high-de- pendency units/ICUs during two local RSV seasons. We estimated the proportion of under-five RSV counts that were under two years of age based on estimates from a systematic review of RSV age distributions in LMICs (data not published). We used the age distribution of RSV outpatients from the COI study to estimate the age distribution of non-severe RSV cases and clinic visits. We used the age distribution of RSV inpatients from the same study to estimate the age distribution of severe RSV cases, clinic visits, and hospital admissions, and the age distribution of RSV ICU cases from the ICU study as a proxy for the age distribution of RSV deaths. The age distribution for RSV non-severe disease was consistent with that obtained for community cases in more rural areas of southern Nepal and Bhaktapur.[7,8]

Economic Burden of RSV Disease

In the base-case scenario, we used cost data from a recent COI study on RSV conducted in Kathmandu from July 2023 to November 2023 [9] (Appendix S3 in the Online Supplementary Document). Governmental costs included all expenses incurred by the government in providing services and infrastructure for children with an RSV infection during the full illness episode, as well as direct medical costs borne by the government. We conducted separate scenario analyses from the societal health perspective for completeness. From a societal health perspective, the costs included all government health costs as well as direct medical expenses (e.g., medication, imaging), direct non-medical expenses (e.g., transportation, food), and indirect costs (e.g., lost income) that were borne by households during the initial visit at a governmental health facility and prior/post visit at any health care facility (public or private).

RSV Intervention Impact

We calculated the health impact of each intervention by multiplying the expected number of RSV disease events in each week of age under five years by the corresponding coverage and efficacy in the same week of age. In the base-case scenario, we assumed year-round immunisation and maternal vaccine coverage of 81.0% based on antenatal care attendance reported by women who attended four or more antenatal care visits, as documented in DHS 2022.[25] For the uncertainty range,

we assumed a lower coverage of 77.8%, based on the MICS 2019,[26] and an upper coverage of 92%, based on the second dose of diphtheria-tetanus-pertussis vaccine.[28]

To estimate the coverage of year-round administration of a long-acting infant mAb, we used the coverage of the Bacillus Calmette-Guérin (BCG) vaccine as a proxy (97%), based on WHO and UNICEF estimates of immunisation coverage for the year 2023.[28] We assumed an uncertainty range of 2% above and below the point estimate. Birth doses that are not administered on time could result in a reduced impact of the infant mAb; therefore, we assumed that the long-acting infant mAb would be administered with the same delays (coverage by week of age) as reported for BCG in DHS 2022.

We derived efficacy estimates for each RSV intervention from evidence obtained in phase III clinical trials. For the maternal vaccine, an efficacy of 69.4% (97.58% CI = 44.3–84.1) was observed in preventing severe lower respiratory tract infection associated with RSV during the first six months of life.[4] For the long-acting infant mAb, efficacy against very severe disease was assumed to be 76.8% (95% CI: 49.4–89.4) five months after immunisation.[6] For non-severe cases, we assumed the efficacy to be 51.3% (97.58% CI = 29.4–66.8) for the maternal vaccine[4] and 76.4% (95% CI = 62.3–85.2) for the long-acting infant mAb based on any medically attended RSV.[6] Mahmud et al.[21] described the efficacy and waning assumptions we applied in our analysis in detail.

RSV Intervention Programme Costs

The price of both interventions is highly uncertain in LMICs. Therefore, we evaluated three different price scenarios, with USD 5 per dose for the base-case scenario, as well as USD 15 and USD 25 per dose. We assumed these prices would stay constant throughout the ten years. Both the long-acting infant mAb and maternal vaccine are available in a pre-filled syringe,[35,36] so we assumed no additional syringe costs. Programme costs included all expenses related to procuring and administering either the maternal vaccine or the long-acting infant mAb. We assumed a 5% wastage for doses and safety boxes.

Uncertainty Analysis

To assess the influence of different parameters and assumptions on the cost-effectiveness results, we ran the following deterministic scenarios:

i) Lower and higher bound rates of annual RSV burden;
ii) Lower and higher bound rates of immunisation efficacy (95% CI);
iii) High initial immunisation efficacy that gradually decreases to zero by age 12 months;[21]

iv) Lower and higher bound rates of the incremental health system cost per dose (25th and 75th percentile);

v) Lower and higher bound rates of the RSV cost per visit/admission;

vi) Dose prices of USD 15 and USD 25;

vii) A societal perspective, taking access to private health facilities into account (overall access: 82%)[26] and including all scaled societal costs from the COI study;[9]

viii) A societal perspective, taking access to private health facilities and societal costs into account, while excluding indirect costs (i.e. lost wages), which accounted for 31% of outpatient costs and 39% of inpatient costs in the COI study[9]; and

ix) A seasonal dose administration for both interventions (Appendix S4 in the Online Supplementary Document).

We used burden estimates from Li et al.[1] as the lower bound and a value of 25% above the adjusted estimate from Chu et al.[7] as the upper bound, to reflect uncertainty in incidence rates (Table 1). We also conducted a probabilistic sensitivity analysis by simultaneously varying all parameters within their respective ranges through 1000 Monte Carlo simulations. For both interventions, we performed a separate probabilistic sensitivity analysis for three fixed price scenarios (USD 5, USD 15, and USD 25 per dose). For simplicity, we assumed a consistent Beta-PERT distribution for all parameters and their respective ranges. We displayed the probabilistic results on a cost-effectiveness plane. We generated cost-effectiveness acceptability curves to calculate the probability that each intervention would be cost-effective at various WTP thresholds.

RESULTS

Lifetime Costs and Effects Based on Central Input Parameters

Over ten years, either the maternal vaccine (USD 5/dose, 81% coverage, 69% efficacy, 6 months protection) or a long-acting infant mAb (USD 5/dose, 97% coverage, 77% efficacy, 5 months protection) could prevent over 2300 deaths and 50 000 hospital admissions, compared to the status quo (Table 2). The long-acting infant mAb would prevent more visits and hospitalisations compared to the maternal vaccine. Accounting for real-world delays in mAb administration and the fact that RSV mortality peaks early in infancy, the maternal vaccine was estimated to prevent a greater number of RSV deaths (n = 2507; 35.8%) than the long-acting infant mAb (n = 2369; 33.8%), despite the lower coverage assumed for the maternal vaccine. The maternal vaccine, therefore, dominated the mAb (generated more health benefits at lower cost) under our base case assumptions.

Introducing each intervention would have discounted programme costs of USD 30 and USD 35 million in ten years, respectively. Approximately 15% of the programme costs were estimated to be offset by government health care cost savings. From a societal health perspective, 60% of the programme costs would be offset by health care cost savings. Compared to the status quo, the maternal vaccine would cost USD 387 per DALY averted, corresponding to 0.29 of the national GDP per capita, and the long-acting infant mAb would cost USD 486 per DALY averted, corresponding to 0.37 of the national GDP per capita.

Table 2. Estimated health impact and costs of RSV preventive interventions compared to no pharmaceutical intervention in Nepal (2025–34)*.

	No intervention	**Maternal vaccine**	**mAb**
Lifetime costs and effects			
Non-severe RSV cases	2 040 658	1 860 216	1 741341
Non-severe RSV clinic visits	530 465	483 560	452 658
Severe RSV cases	268 721	20 1983	196843
Severe RSV clinic visits	604 691	454 513	442948
Severe RSV hospital admissions	201 471	151 435	147581
Severe RSV deaths	7002	4494	4633
DALYs†	181 489	116 210	119 705
Vaccine programme costs†	0	29 938 203	35 397 868
Governmental healthcare costs†	2 261 0244	17 935 236	17215 204
Societal healthcare costs†	85 589 768	67 531 229	65 073 041
Differences‡			
Non-severe RSV cases		180 441	299 317
Non-severe RSV clinic visits		46 905	77 807
Severe RSV cases		66 738	71 878
Severe RSV clinic visits		150 178	161 743
Severe RSV hospital admissions		50 036	53 889
Severe RSV deaths		2507	2369
DALYs†		62 279	61 784
Vaccine programme costs†		29 938 203	35 397 868
Government healthcare costs†		4 675 008	5 395 040
Societal healthcare costs†		19 058 538	21 516 726

Table 2. Continued.

Cost per DALY averted†‡		
Government cost perspective		
Cost, in USD	29 938 203	35 397 868
DALYs averted	65 279	61 784
Cost per DALY averted, in USD	387	486
Societal cost perspective		
Cost, in USD	29 938 203	35 397 868
DALYs averted	65 279	61 784
Cost per DALY averted, in USD	167	225

DALY – disability-adjusted life year, GDP – gross domestic product, mAb – monoclonal antibody, RSV – respiratory syncytial virus

*Maternal vaccine is USD 5 per dose, 81% coverage, 69.4% efficacy, and six months protection, while infant mAb is USD 5 per dose, 97% coverage, 76.8% efficacy, and five months protection.

†All future costs and benefits are discounted at a 3% discount rate per year. Costs and gross domestic product per capita are expressed in 2023 USD.

‡No pharmaceutical intervention was used as a comparator.

Scenario and Sensitivity Analysis

In the base-case scenario, the long-acting infant mAb had a less favourable cost-effectiveness ratio compared to status quo than the maternal vaccine (USD 486 vs. USD 387 DALYs averted) (Figure 1, Panels A and B). Only the maternal vaccine was cost-effective at a WTP threshold of 0.34 times GDP per capita, while the long-acting infant mAb was cost-effective at 0.5 times the GDP per capita in Nepal. However, when adjusting for timely immunisation coverage (no delay), the long-acting infant mAb had more favourable cost-effectiveness compared to status quo than the maternal vaccine (USD 371 vs. USD 387). When assuming high initial efficacy that waned to zero by 12 months of age, the cost-effectiveness for both interventions decreased to 0.23 times the GDP per capita and 0.27 times the GDP per capita, respectively. Stepwise increases in the price per dose (USD 15 and USD 25) reduced cost-effectiveness, and neither of these dose prices was cost-effective at 0.34 times the GDP per capita.

Cost-Effectiveness at Different WTP Thresholds

At all dose prices, the maternal vaccine demonstrated greater incremental health benefits compared to the long-acting infant mAb (Figure 2, Panels A and B). At a WTP threshold of 0.34 times GDP per capita, the most cost-effective intervention strategy would need to be priced ≤USD 5 per dose to achieve >55% probability of being considered cost-effective (Figure 3, Panels A and B).

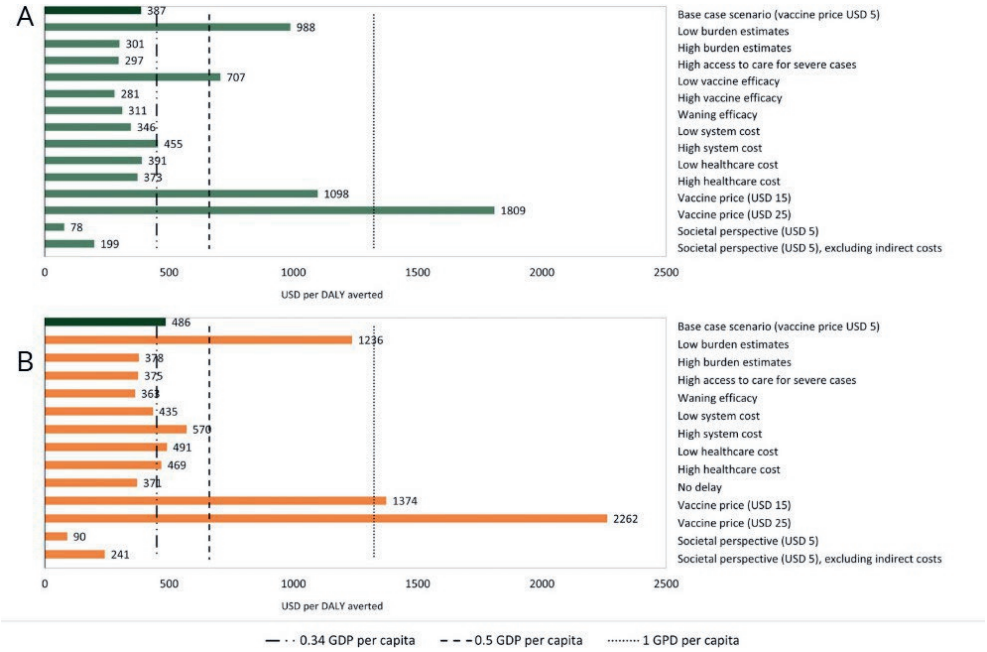

Figure 1. USD per DALY averted for several alternative scenarios. Panel A. Maternal vaccine. Panel B. Long-acting infant mAb. DALY – disability-adjusted life year, GDP – gross domestic product.

DISCUSSION

Our study shows that either the maternal vaccine or long-acting infant mAb have the potential to substantially reduce the total number of RSV cases, clinic visits, hospital admissions, and deaths in Nepal. Our estimates suggest that year-round RSV passive immunisation strategies would need to be priced <USD 5 per dose to be considered cost-effective at the most conservative WTP thresh- old of 0.34 times the GDP per capita in Nepal.

While the maternal vaccine generated greater health benefits at a lower cost under our base-case assumptions, this result was influenced by key variables, including product efficacy, duration of protection, dose price, and disease burden. The mAb may become more cost-effective under alternative assumptions, particularly if timely administration at birth or a seasonal approach is implemented. Given the uncertainties around real-world implementation, both strategies should be considered if they are affordable and priced <USD 5 per dose. Programmatic priorities, including coverage, feasibility, and equity, should also inform the final product choice.

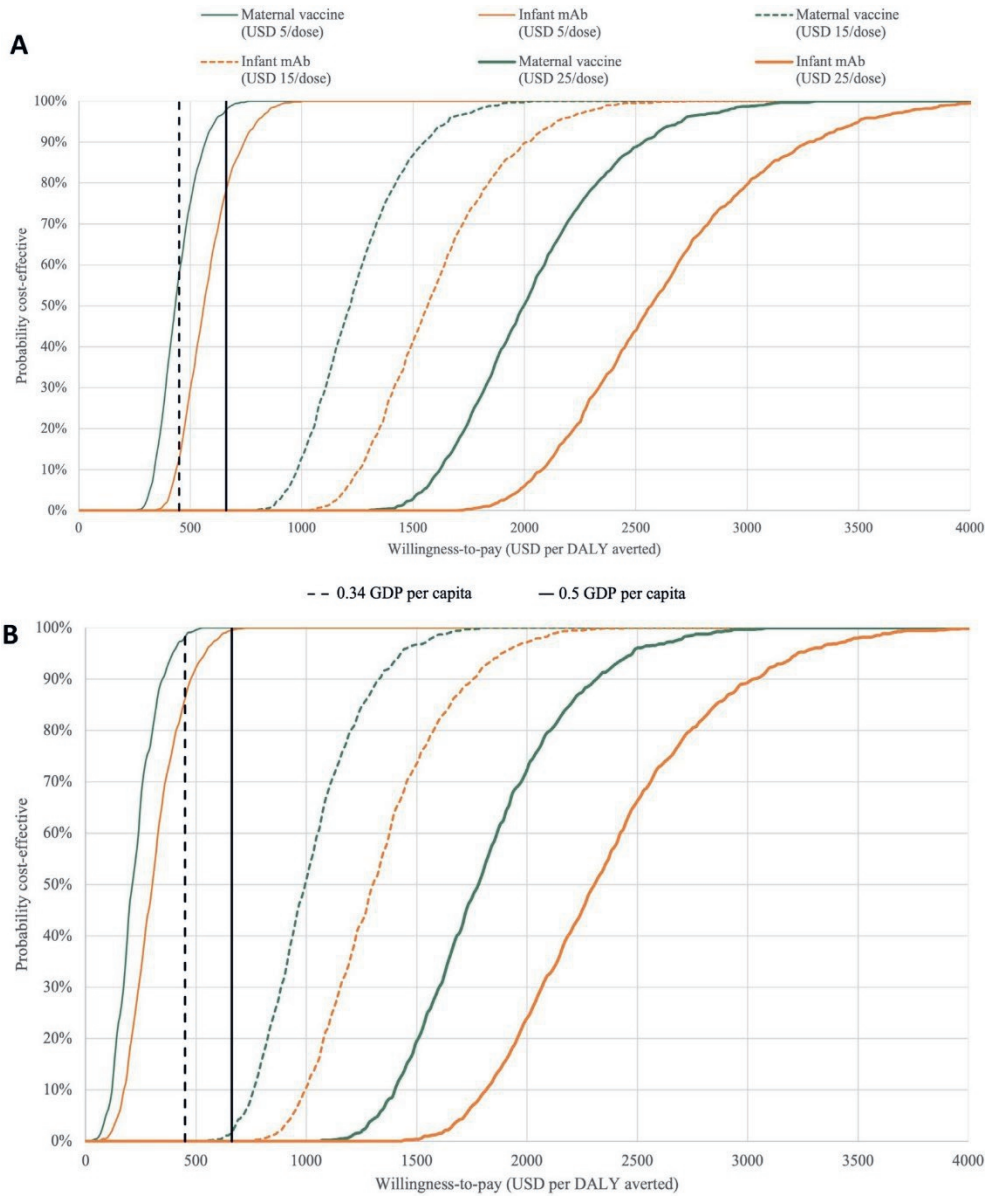

Figure 2. Probabilistic clouds of incremental costs and benefits of both RSV intervention strategies, assuming three different dose prices. Panel A. Governmental health perspective. Panel B. Societal health perspective. DALY – disability-adjusted life year, mAb – monoclonal antibody, RSV – respiratory syncytial virus.

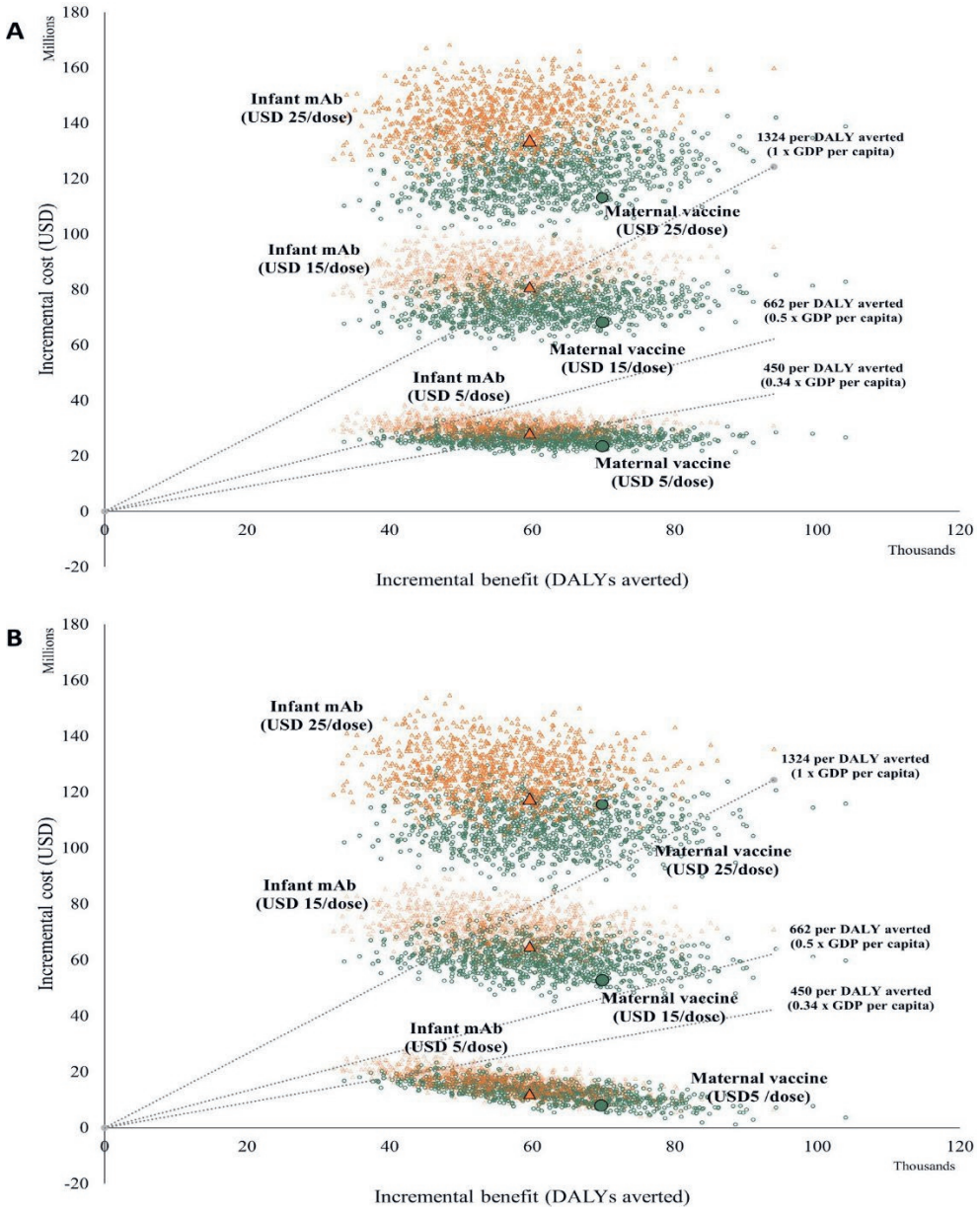

Figure 3. Cost-effectiveness acceptability curves for introducing a maternal vaccine or the long-acting infant mAb for RSV prevention over a range of prices per dose and cost-effectiveness thresholds. Panel A. Governmental health perspective. Panel B. Societal health perspective. DALY – disability-adjusted life year, mAb – monoclonal antibody, RSV – respiratory syncytial virus. The curves are the result of 1000 Monte Carlo simulations given base-case assumptions for the maternal vaccine and the long-acting infant mAb. The dashed black line indicates 0.34 times the gross domestic product per capita, while the solid black line shows 0.5 times the gross domestic product per capita.

Our findings align with a cost-effectiveness analysis conducted in Vietnam,[24] which also found that both the maternal vaccine and long-acting infant mAb have the potential to be cost-effective at USD 5 per dose, with a WTP threshold of 0.5 times the national GDP per capita. However, they found that the long-acting infant mAb is potentially more cost-effective in Vietnam, highlighting how local context can shift comparative advantages.

The seasonal approach shows that restricting administration to an eight-month window achieves comparable reductions in RSV-associated disease burden when compared to a year-round programme, while improving dose efficacy for both maternal vaccine and long-acting infant mAb. In Nepal, targeting birth months between February and September (or January to August for maternal vaccination) could result in significant cost savings. These results are in line with modelling analyses from Argentina and Mozambique, which found that implementing a seasonal approach preserved most of the health gains of year-round administration while reducing the number of doses needed.[22,23]

To model mAb uptake, we used BCG coverage as a proxy, given that both interventions are delivered in early infancy through standardised immunisation programmes. In Nepal, children do not typically receive BCG immediately at the time of hospital discharge, as many health facilities provide routine immunisation only on selected days of the month due to programmatic constraints. While mAb delivery may require additional logistical inputs such as enhanced cold chain and staff training, Nepal has longstanding experience with vaccine introduction, and vaccine acceptance is generally strong.[37] Therefore, BCG coverage remains the most appropriate proxy in the absence of real-world implementation data from LMICs. This assumption was influential in the analysis and explains why the maternal vaccine appeared to be the more cost-effective option when the same dose price was assumed for both products. Both products, however, had similar cost-effectiveness when the mAb was assumed to be administered on time at birth. Realising the full benefit of the long-acting infant mAb, innovative strategies for achieving high and timely coverage of newborns are essential. Possible approaches include targeting mAb administration based on risk factors, seasonal administration, or using the mAb selectively among newborns who did not receive passive immunisation from a maternal vaccine.

We based our input parameters on the most recent clinical trial results available during the study period. Since then, an updated efficacy estimate from the MATISSE trial for the maternal vaccine has been published,[38] reporting the following efficacy rates: 70.0% for severe medically attended RSV-ALRI (compared to 69.4% in our analysis) and 49.2% for non-severe RSV-ALRI (compared to 51.3% in our study). Considering the

close alignment between the updated values and the input parameters we used, we do not anticipate any substantial impact on the model's outcomes.

Mortality estimates remain one of the more uncertain parameters in modelling, particularly in LMICs where vital registration systems are incomplete. We selected the higher mortality estimate from the bottom-up approach for the base case to better reflect the likely true burden of disease in this context. To assess the impact of this assumption, we conducted scenario analyses using both the lower and higher mortality estimates based on an even more conservative lower bound from Li et al. As expected, using lower mortality assumptions reduced projected health gains and led to a moderately less favourable cost per DALY averted. However, the overall conclusions regarding the relative cost-effectiveness of the two strategies remained consistent. These findings underscore the importance of strengthening mortality surveillance to better inform future evaluations.

Nepal has made substantial progress in enhancing its immunisation programme by integrating the typhoid conjugate vaccine into its routine vaccination schedule. Following a major earthquake in November 2023, targeted vaccination campaigns reached over 118 000 children with the Measles-Rubella vaccine and 520,000 individuals with the typhoid conjugate vaccine. The country's vaccine delivery infrastructure, built on strong leadership and governance, healthcare finance, and human resources, provides a solid foundation for introducing RSV immunisation strategies. Integrating maternal RSV vaccination with existing maternal immunisation (e.g., tetanus, diphtheria, and pertussis) may further enhance coverage and increase community acceptance. Moreover, Nepal's high routine immunisation coverage and previous success in introducing vaccines against Haemophilus influenzae type b, pneumococcal and, most recently, cervical cancer, demonstrate the system's capacity and public willingness to accept new vaccines.

We assumed moderate coverage estimates for the maternal vaccine. We believe, however, that coverage rates are likely to improve significantly with comprehensive education and outreach about the vaccine's potential benefits, specifically its role in preventing early infant pneumonia. As awareness grows, these conservative assumptions may no longer hold true. In Nepal, where health expenditures are primarily paid out-of-pocket and insurance coverage remains low, RSV immunisation strategies must consider household financial burden. Preventive strategies, such as immunisation programmes fully financed by the government (which allocates about 5.8% of its annual budget to health sector spending [39]) and supported by Gavi and other international organisations, can not only reduce disease incidence, but also prevent

household impoverishment as demonstrated in our analysis from a societal health perspective.

Cost-Effectiveness of RSV Immunisation Strategies in Nepal

Although both immunisation strategies have so far been primarily introduced in high- and middle-income countries, new WHO guidance and Gavi support aim to support their rollout in LMICs like Nepal. Following WHO prequalification in March 2025, the maternal vaccine became eligible for Gavi support in July 2025.[13,14] While Gavi support remains critical for vaccine introduction, it is temporary. The Government of Nepal has consistently increased its share of immunisation programme costs, and with the planned graduation to middle-income status by 2030, Gavi support will change. To prepare for this transition, the government has outlined strategies for diversifying resources in its National Health Financing Strategy 2023–33.[40] Sustainability strategies may involve integrating RSV immunisation into the national health insurance scheme, increasing domestic funding of immunisation and exploring co-financing opportunities with other donors. Our study represents the first comprehensive evaluation of the health impact and cost-effectiveness of RSV intervention strategies in Nepal. We employed a diverse range of country-specific data with international estimates for LMICs to estimate the burden of RSV. Additionally, we incorporated local COI data from both governmental and societal health perspectives, reflecting the multifaceted economic consequences of RSV in the Nepalese context. Furthermore, we used the UNIVAC decision-support model, a user-friendly tool that allows local stakeholders to update the evaluation as more data become available.

We used a static cohort model that does not account for transmission dynamics, which is appropriate given that both RSV immunisation strategies evaluated provide passive immunisation to infants, and there is currently limited evidence suggesting that either of the interventions would interrupt transmission patterns. However, as the RSV vaccine landscape evolves, this modelling approach may need to be revisited. A dynamic model would require high-quality RSV transmission data from Nepal, particularly in a future context where additional vaccines, such as those targeting toddlers or older children become available, as these are more likely to influence RSV transmission dynamics.

In addition to the direct health and economic benefits we captured in the cost-effectiveness analysis, RSV immunisation strategies may provide important broader health system advantages. By reducing RSV-related respiratory illness, these interventions could help decrease inappropriate antibiotic use, which is a recognised contributor to antimicrobial resistance. Furthermore, reducing the RSV burden during

peak seasons may ease pressure on paediatric wards, improving health-care capacity and resource allocation.

Additionally, it is important to note that in two upper-middle-income country sites (Argentina and South Africa) of the phase III trial, a numerical non-significant increase in preterm births was observed in women who received the RSV maternal vaccine. Although the difference was not statistically significant, this safety signal led regulatory agencies to restrict vaccine administration to ≥32 weeks of gestational age. For countries like Nepal, where preterm birth rates are already high, these findings underscore the need for cautious policy consideration. Importantly, an ongoing randomised controlled trial (NCT06955728) is currently investigating the effectiveness and safety of the maternal vaccine in several African countries, providing additional valuable evidence on vaccine safety.[3] Findings from this trial will be critical in informing future regulatory and programmatic decisions.

Recent research has also identified RSV as a contributing factor to long-term respiratory conditions, including asthma and allergic disorders [41]. Furthermore, toddlers can play a significant role in spreading RSV to older adults, particularly those with Chronic Obstructive Pulmonary Disease, where RSV can lead to severe exacerbations.[42] Considering these factors may further support the societal value of RSV immunisation strategies beyond just immediate outcomes on infants. While both intervention strategies have clear potential to reduce RSV disease burden and demonstrate cost-effectiveness in Nepal, the decision to implement them will depend on various factors, such as acceptability, safety, alignment with government health priorities, and budget constraints. This analysis can help inform decision-makers of the economic consequences of introducing RSV interventions, especially once intervention prices are known.

CONCLUSION

Our analysis demonstrates that both the maternal vaccine and the long-acting infant mAb have the potential to substantially reduce RSV-related morbidity and mortality in Nepal. While the maternal vaccine was generally more cost-effective under the base-case assumption, this finding was highly sensitive to several key parameters, including coverage, product efficacy and timing of administration. A seasonal approach, particularly one that aligns with Nepal's RSV epidemiology, can further improve efficiency and reduce costs.

Given the uncertainties around real-world implementation and evolving clinical data, both strategies remain viable options. The ultimate decision will require careful consideration of programmatic feasibility, equity, safety and long-term sustainability, especially as Nepal plans to transition to middle-income status by 2030 and prepares for the eventual phase-out of Gavi support. As vaccine prices and delivery strategies become clearer, this study provides a critical foundation for informing national immunisation policy.

Supplementary files can be downloaded from:



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PART IV

General Discussion & Appendices

9

Contextual Framework and General Discussion



CONTEXTUAL FRAMEWORK

The successful introduction of new vaccines depends on more than their availability or efficacy. It also requires a strong evidence base, structures for evaluation and alignment between scientific, societal and political priorities. In most high-income countries, such as the Netherlands, this process is highly structured, and evidence-driven. To ensure consistent decision-making about the addition of new vaccines to the National Immunisation Programme (NIP), the Dutch Health Council uses a clearly defined assessment framework (Figure 1). This framework outlines the **five key criteria a vaccine must meet for a positive recommendation** from the council. These criteria include a significant disease burden in the population, sufficient vaccine effectiveness and safety and an acceptable vaccination burden for individuals and society. Additional points that may be considered include cost-effectiveness, feasibility of implementation, ethical and social aspects and alignment with international practices.[1]

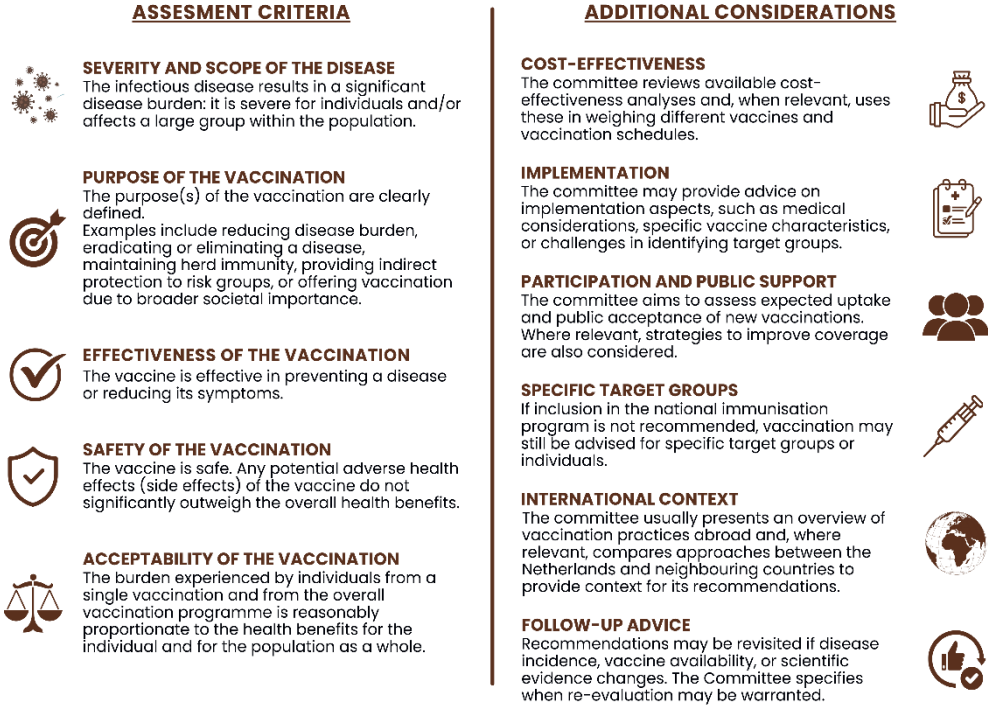

Figure 1. Dutch Framework for Vaccine Introduction based on the Dutch Health Council (De Gezondheidsraad).[1]

After careful evaluation within this framework, on February 14, 2024, the Dutch Health Council advised that **all infants in the Netherlands should be protected against Respiratory Syncytial Virus (RSV) through passive immunisation**.[2] Subsequently, in October 2024, the Ministry of Health, Welfare and Sport decided to add RSV immunisation to the Dutch NIP with the start of implementation in autumn 2025.[3] The National Institute for Public Health and the Environment (RIVM) has since developed a vaccination pathway for this new immunisation programme.[4]

In contrast, vaccine introduction in low- and middle-income countries (LMICs) often occurs in more resource-constraint settings, where institutional mechanisms such as National Immunisation Technical Advisory Groups (NITAGs) may have limited capacity and where donor funding and global initiatives play a larger role.[5] In these contexts, **local data on disease burden, healthcare utilisation and economic impact are essential for translating global recommendations into national realities**. The World Health Organization (WHO) provides guidance for vaccine development and implementation, ranging from prioritising diseases with a high burden to manufacturing, approval and implementation.[6] The process is often highly collaborative, involving international stakeholders, national regulatory authorities and public health institutions. The Strategic Advisory Group of Experts on Immunization (SAGE) reviews global disease burden to set immunisation priorities and identifies key pathogens for vaccine research and development, which can then be adapted by countries through their NITAGs. Vaccine candidates progress from preclinical research, through clinical trial phases evaluating safety, immunogenicity and efficacy.

Once sufficient evidence has been generated, national regulatory authorities (NRAs), such as the U.S. Food and Drug Administration (FDA) or the European Medicines Agency (EMA), provide market approval. After regulatory approval from national authorities that are 'functional' or listed by the WHO as operating at level 3 or above, such as FDA and EMA, WHO prequalification ensures that the vaccine meets international standards for use in global procurement by United Nations agencies and Gavi, the Vaccine Alliance. Gavi is a global health partnership that aims to increase access to immunisation in LMICs.[7] Through its financial and technical support, Gavi helps ensure that vaccines are affordable and available, particularly for the most vulnerable populations.

Following approval by NRAs, countries plan national introduction and establish systems to monitor coverage, safety and real-world effectiveness. SAGE provides policy guidance to member states, which can be reviewed and adapted by each country's NITAG based on local epidemiology and programmatic capacity. In parallel, the WHO Immunization Agenda 2030 provides a global framework to support countries

in developing multi-year plans for budgeting, logistics, cold-chain management and community engagement, aiming to reduce vaccine hesitancy.[8, 9] For many LMICs, financial and technical support from UNICEF, Gavi and other agencies remains essential for vaccine rollout. Through co-financing arrangements and technical assistance, agencies such as Gavi facilitate the inclusion of new vaccines in the Extended Programme on Immunization (EPI), bridging the gap between global recommendations and local implementation. However, sustainable introduction depends on domestic commitment, integration into national health budgets and continuous monitoring of impact and cost-effectiveness.

Recent developments in the RSV research field have led to the approval and implementation of new RSV immunisation strategies, including a maternal vaccine and a long-acting monoclonal antibody (mAb) for infants. Although mAbs represent a form of passive immunisation rather than vaccination, they are considered within the scope of vaccine implementation in this discussion, reflecting their programmatic overlap with vaccine policy, delivery and financing frameworks.

By 2025, most high-income countries have successfully integrated one or both interventions into their immunisation programmes. In contrast, many LMICs, where RSV burden is highest, continue to lag behind. Although most of these countries have established EPI structures, decisions regarding the introduction of new vaccines are often constrained by multiple factors, including affordability, logistics and competing health priorities. Moreover, limited availability of country-specific data on disease burden, healthcare utilisation and cost-effectiveness further complicates national decision-making. Without robust local evidence, global recommendations may be difficult to translate into actionable policies. Strengthening such evidence is therefore essential to ensure that global advances in RSV prevention lead to equitable protection for infants worldwide. Yet, an important question remains: **does generating country-specific evidence on RSV disease burden and health economics truly bring us closer to the introduction of RSV immunisation strategies in LMICs?**

GENERAL DISCUSSION

PART I – Clinical Characteristics and Seasonality of RSV in the Netherlands: Implications for Immunisation Strategies

RSV Burden in the Netherlands

Without disease burden, there is no need for a vaccine. All vaccines are developed with the idea of preventing an existing or potential disease. To understand which populations should be protected by a new vaccine and to assess the (potential) impact of new immunisation strategies, it is important to understand the current disease burden. Although much is already known about RSV burden in the Netherlands,[10-12] country-specific data, especially in a period of pandemic disruption, are of great value. **Chapter 2** of this thesis contributes to a deeper understanding of the burden of RSV in the Netherlands and its disruption during the COVID-19 pandemic. We found that following the absence of RSV activity in the winter of 2020/2021, most likely due to the implementation of non-pharmaceutical interventions (NPIs), RSV re-emerged in the summer of 2021. This unusual summer epidemic was followed by year-round (endemic) circulation in 2022, after which RSV activity returned to its typical winter pattern in 2022/2023 and 2023/2024. Our study shows that **epidemiological and clinical characteristics of RSV have largely returned to a pattern consistent with the pre-COVID period**. Shifts in age distribution and severity of infection are most likely related to changes in social dynamics and public health practices. Following the COVID-19 pandemic, severe RSV cases in the Netherlands occurred predominantly in children younger than six months of age. This pattern closely reflects observations from the pre-pandemic period. These findings support the current immunisation strategy in the Netherlands under which all children under the age of one year are offered RSV immunisation. In addition, our findings provide an important reference point for interpreting potential future disruptions, such as a pandemic, where RSV circulation may temporarily shift. Finally, in the absence of a standardised national RSV surveillance system, our findings highlight the added value of establishing baseline data. Such data could strengthen ongoing monitoring efforts by the National Institute for Public Health and the Environment and contribute to a more comprehensive understanding of RSV dynamics in the Netherlands.

RSV Immunisation in the Netherlands

Since September 2025, all children born on or after April 1, 2025, are eligible to receive immunisation against RSV within their first year of life. The programme targets two groups. The first group includes children born during the respiratory season (October–March), who receive RSV immunisation as soon as possible after birth and no later than

14 days. The second group, the catch-up group, includes children born outside the RSV season (April–September), who are offered immunisation in September–October, prior to the start of the upcoming RSV season.

While the current RSV prevention strategy is based on clinical evidence, expert recommendations and feasibility in the Dutch context, it does not take into account potential differences in hospitalisation risk by birth month or by age during the first weeks of life. Using data collected as part of the SPREAD study (**Chapter 2**), as well as findings from our research group within the Dutch intensive care RSV burden study (BRICK study, unpublished data), we estimated how these factors influence the risk of RSV-related hospitalisation. Based on these multicentre data from the Netherlands, we found that the **risk of hospitalisation in the first months after birth for children born in March is relatively low**. Nine of 58 (15.5%) children born in March were admitted during the same season, eight of whom were admitted in the 2022/2023 post-COVID season, a period during which slight shifts in seasonality were still observed. **Chapter 3** shows that children born in March would be more effectively protected if included in the catch-up round in September–October, prior to the start of the next RSV season. In addition to the timing of immunisation, the current 14-day time window between birth and vaccination during the season seems unnecessarily long. We showed that **one in 17 hospital admissions and one in 10 paediatric intensive care unit (PICU) admissions occurred between 7 and 14 days of age.** While practical considerations are recognised, **aligning RSV immunisation in the Netherlands with the first routine postnatal contact with a healthcare provider,** most likely during the heel prick (neonatal screening) visit, typically between 4 and 7 days after birth, could reduce this early burden.

In addition, as shown in **Chapter 2**, RSV seasonality appears to shift over time and such variation should be taken into account as well. Regular evaluation of the timing and duration of RSV immunisation for the primary target group (infants born during the RSV season) based on an established age-stratified surveillance system could help ensure optimal protection, even in years with atypical RSV circulation. In this context, the current seasonal approach and catch-up campaign may need flexible adaptation to align with shifts in epidemic timing. Looking forward, it is important to maintain robust and continuous RSV surveillance to detect deviations from expected patterns immediately and to enable timely adjustment of immunisation strategies when needed.

PART II – Paediatric RSV Burden in LMICs: Guiding the Path to Vaccine Introduction

RSV Burden in 10 Low- and Middle-Income Countries

RSV burden is highest in LMICs. Although the global evidence base of RSV burden in LMICs has advanced considerably over the past decade, and an increasing amount of data are available for RSV-associated lower respiratory tract infection (LRTI) incidence, hospital admissions and mortality, important gaps remain.[13] There is limited understanding of the burden and clinical outcomes of severe RSV disease among children admitted to PICUs in these settings. Limited availability of detailed clinical and virological data from critical care settings constrains our ability to fully characterise the severity of RSV disease, identify high-risk groups and tailor prevention strategies to capacities and constraints of LMIC health systems. In **Chapter 4**, we address parts of this gap by examining the burden of RSV in PICUs across ten LMICs. This multi-country analysis demonstrates that **RSV accounts for a substantial proportion of severe respiratory infections in young children, with 29% of admissions testing positive for RSV during the local RSV season**. These findings confirm the substantial burden that RSV poses in LMIC settings. Importantly, **most life-threatening RSV infections occurred within the first six months of life**, and almost half of the affected children were younger than three months. This age pattern underscores both the vulnerability of young infants in these settings and the potential impact that currently available immunisation strategies could have in preventing severe RSV disease in the high-risk age groups.

Although **Chapter 5 and 7** were primarily designed to study the financial burden of RSV, they also provide important insights into the broader burden of medically attended RSV in two low-income countries, Mozambique and Nepal. **In Mozambique, 29.2% of the children presenting with (severe) acute respiratory illness during the respiratory season** (February to August 2023) tested positive for RSV. **In Nepal, RSV positivity among children with (severe) acute respiratory illness was even higher, reaching 72.9%** across two healthcare facilities during the local RSV season (June to November 2023). These findings demonstrate that **RSV represents a substantial health challenge not only in intensive care settings, but also across all levels of care, including hospital wards and outpatient clinics**. The marked differences observed between Mozambique and Nepal underscore the importance of country-specific data. While combining data from ten different study sites in the RSV GOLD III–ICU Network offers a powerful overview of RSV burden in critically ill children, such **pooled data may overlook local variability in disease dynamics, healthcare access and health system capacity**. The country-specific cost-of-illness (COI) studies therefore complement this multi-country work by providing the contextual depth needed to

interpret such heterogeneity. They highlight how factors such as climate, healthcare-seeking behaviour, service availability and social determinants shape both the incidence and clinical presentation of RSV in different settings. The strength of the two COI studies lies in their detailed country-level observations, which, despite being conducted in the capital, provide essential country-specific insights for national policy and planning.

These national burden data contribute to several stages of the vaccine implementation process. First, and most fundamentally, these data **support the justification for vaccine development and investment**. Without robust data on the national disease burden, policymakers and funders cannot prioritise RSV among competing public health needs. Although the global prioritisation undertaken by WHO's SAGE occurred before the availability of our findings, such national data remain highly relevant for NITAGs to recognise RSV as a priority pathogen within the local context. Second, country-specific burden data **provide essential inputs for health economic evaluations**, as demonstrated in **Chapter 6 and 8.** Having local evidence allowed us to avoid reliance on extrapolated global assumptions and to generate economic estimates that are more relevant for national decision-making. Third, **national burden data inform the design and delivery of immunisation programmes**. Insight into age distribution, seasonal pattern and risk factors for severe RSV infection is critical for optimising vaccine strategies, determining the timing of administration and identifying priority groups. Finally, country-specific burden data are **essential for post-introduction monitoring and evaluation**. The findings from our studies provide a pre-implementation baseline against which future reductions in RSV-associated hospitalisation and deaths can be measured, enabling assessment of the real-world impact of RSV immunisation once implemented.

PART III – Economic Burden and Cost-Effectiveness of RSV Immunisation Strategies in LMICs

Financial Burden of RSV

Beyond characterising clinical burden, our work provides essential insights into the economic consequences of RSV in two low-income settings, highlighting why country-specific financial data are indispensable for informing immunisation decisions. Although Mozambique and Nepal both experience a substantial RSV burden, the financial implications for families differ markedly. In Mozambique, where most healthcare services are publicly funded, the financial burden for households remains considerably high. As presented in **Chapter 5**, the mean cost per RSV-associated hospital admission for severe acute respiratory illness was USD 612, while the cost for children admitted to the intensive care unit was nearly double (USD 1161). Although most of these costs were covered by the public health system, out-of-pocket household expenses per RSV admission remained substantial, averaging USD 39 for hospital admissions and USD 132 for ICU admissions, presenting a significant economic burden relative to the average monthly household income (USD 91 in 2023). In contrast, in Nepal, as shown in **Chapter 6**, out-of-pocket expenses for RSV-related care were substantially higher, reflecting the more limited government coverage of healthcare services. The mean total cost per RSV-related hospital admission was USD 312, compared to USD 664 for ICU admissions. Household out-of-pocket costs were USD 200 for hospital admissions and USD 472 for ICU, representing a considerable financial burden relative to the minimum monthly wage (USD 118 in 2023).

These contrasts illustrate that **the relative economic burden of RSV is shaped not only by disease severity, but also by health system financing structures, service availability and the presence or absence of social protection mechanisms**. Such contextual differences cannot be captured through pooled global estimates. To situate our findings within the broader RSV costing landscape in LMICs, Figure 2 shows a schematic overview, integrating existing RSV costing data previously published and shown in the introduction of this thesis with country-specific data generated as part of the RSV GOLD III–Health Economics Study. By displaying both the existing literature and our derived estimates side by side, the substantial heterogeneity in cost structures and affordability becomes visible. This cross-country perspective underscores why reliance on global averages is insufficient and why tailored national evidence is essential for robust economic evaluations and informed policy decisions.

Cost-Effectiveness Analysis of RSV Immunisation Strategies

Building on the COI data, we conducted CEAs in Mozambique and Nepal, using the Universal Vaccine Decision Model (UNIVAC, version 17.1) to evaluate maternal RSV vaccination and infant prophylaxis with a long-acting monoclonal antibody (mAb) compared to no intervention. Multiple dose-price scenarios were explored to assess affordability and value for money. **At a hypothetical dose price of USD 5, both interventions showed favourable probabilities of being cost-effective relative to country-specific willingness-to-pay (WTP) thresholds**, which were derived from estimates based of health spending and health outcomes across LMICs.[14] In Mozambique, as shown in **Chapter 7**, the probability of cost-effectiveness at USD 5 was approximately 40% for both interventions at a threshold of 0.5 times the national GDP per capita. In Nepal (**Chapter 8**), the probability was substantially higher, at 95% for maternal vaccination and 80% for the infant mAb using a WTP threshold of 0.5 times GDP per capita. Although the mAb averted more deaths in Mozambique, it required an additional USD 5 million in programme costs, highlighting the trade-off between incremental health gains and affordability. A similar pattern was observed in Nepal, where both interventions offered substantial health impact but differed in required investment.

These findings demonstrate that **the economic value of RSV immunisation strategies is highly context-specific, shaped by local epidemiology, healthcare utilisation and economic conditions.** Country-specific evidence is therefore essential to ensure that CEAs support realistic, equitable and nationally relevant decision-making.

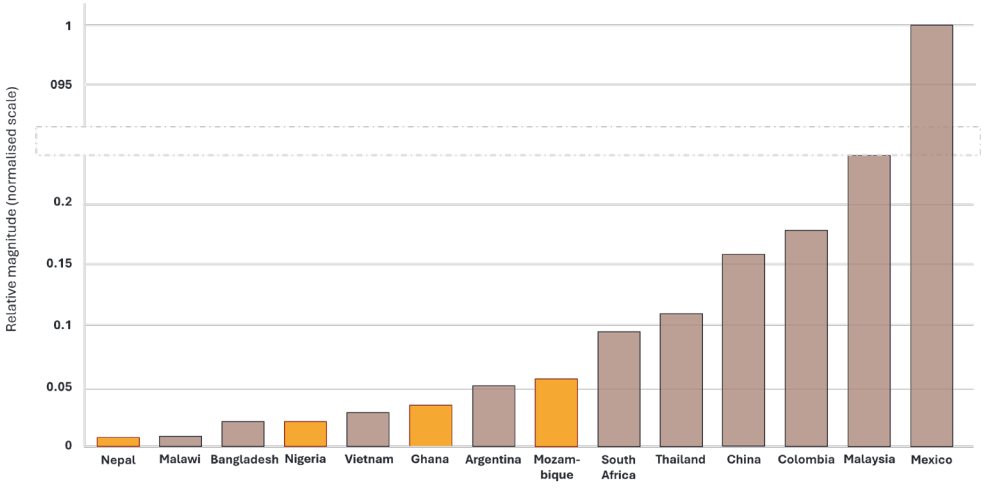

Figure 2. Schematic illustration on how the findings from this thesis expand the existing landscape of RSV-related medical cost estimates across LMICs. Values are shown on a normalised scale for schematic comparison across countries.

Study Site Selection and Contextual Considerations in Health Economics Research in LMICs

The COI and CEA analyses conducted in Mozambique and Nepal were part of the RSV GOLD III–Health Economics Study, which followed the RSV GOLD III–ICU Network Study. Study sites were initially selected from network partners in Ghana, Mozambique, Nepal and Nigeria, with Cameroon later being included to compensate for limited CEA capacity in Ghana. In total, the project included four COI and four CEA studies. Although the study design was consistent across all sites, **marked differences in the structure of national health systems and data availability resulted in substantial variability across sites**. To ensure country-specific relevance, all analyses were therefore conducted separately.

During start-up visits, important differences in the availability and quality of costs data were observed. For the COI studies, medication documentation and availability varied substantially. In Mozambique, medications are generally provided by the hospital but often rely on international donations. While prescriptions were recorded, it was often unclear whether full treatment courses were administered. In contrast, in Nepal, medication use was captured more precisely. Prescriptions were documented in patient files and parents frequently retained payment slips organised in patient-specific folders, enabling more granular estimation of direct medical costs. Differences also emerged in overhead cost reporting. Mozambique provided only aggregated hospital-level overhead data, while one Nepalese site, a specialised paediatric hospital, offered detailed paediatric-specific overhead and staffing information. The second Nepalese site, a university teaching hospital, also allowed for robust patient-level costing due to more structured administrative records.

For the CEA studies, additional contextual challenges arose. **Stakeholder availability varied across countries, affecting the identification and validation of model parameters**. Moreover, essential data such as rural health service utilisation were limited in both settings, highlighting the difficulties in capturing heterogeneity in healthcare access and resource use. These observations underscore that conducting CEAs in LMICs requires careful navigation of data constraints and explicit justification of assumptions to preserve local relevance and scientific integrity.

A key advantage of the study was that all selected sites were part of the established RSV GOLD III–ICU Network Study Group. Prior collaboration with local teams and familiarity with institutional practices facilitated tailored study design, efficient data

collection and increased confidence in data quality. More broadly, these experiences demonstrate that **understanding the local context is fundamental to the validity, interpretability and policy relevance of health economics analyses.** By engaging closely with local health systems, administrative structures and stakeholders, we were able to generate COI and CEA evidence that is scientifically robust, locally relevant. In the future, it will support informed policy decisions in countries such as Mozambique and Nepal.

The Importance of Health Economic Evidence

Beyond methodological challenges and contextual differences, the value of our work lies in its contribution to the broader pathway that connects disease burden assessment, clinical research and the potential introduction of RSV immunisation strategies in LMICs. Our health economic studies conducted in Mozambique and Nepal address a critical evidence gap by providing country-specific economic insights that are essential for translating global immunisation strategy development into national decision-making.

The COI analyses represent the first foundational component of this economic evidence. By quantifying both direct medical costs (e.g., hospitalisation, medication and diagnostics) and indirect costs (e.g., transport and lost income), these studies capture the full societal and household burden of RSV. Such evidence strengthens priority setting by demonstrating the financial hardship caused by RSV and highlighting the potential economic benefits of preventive strategies. It also provides the foundation upon which further economic evaluations can be built.

Health economic evidence additionally informs the immunisation strategy pathway. Funders such as Gavi use such data to prioritise investments and assess the expected return on financing decisions. Insights into affordability and feasibility in LMICs can also guide product design considerations, such as vial size, shelf life or cold-chain requirements, ultimately improving the practical viability of immunisation strategies in resource-constrained settings.

CEA analyses form the next step in this “economic bridge”. By linking disease burden, intervention costs and health outcomes, CEAs evaluate whether immunisation strategies provide value for money compared to no intervention. These results are central for NITAG deliberations and also inform global decision-makers such as WHO and Gavi. Although this thesis did not include a formal budget impact analysis, such assessments often complement CEAs by assessing the affordability of large-scale introduction within national health budgets.

While cost-effectiveness analyses are not a mandatory requirement for vaccine introduction in high-income countries such as the Netherlands, they are often essential in LMICs, where economic evidence is a key component of vaccine introduction decisions. Health systems in low-resource settings operate under severe financial constraints, where multiple interventions compete for limited resources. Economic analyses help quantify opportunity costs and ensure that limited resources are directed towards interventions that provide the greatest health benefit. Equally important, local economic evidence ensures that decisions reflect national realities rather than global averages that may not be applicable.

Taken together, these components show how health economics can function as a bridge to vaccine implementation in LMICs (Figure 3). However, a bridge alone cannot fulfil its purpose. It requires roads that connect to it and pillars that support it. Similarly, economic evaluations are necessary, they are not sufficient on their own. Successful implementation also requires adequate health system capacity, equity considerations, context-specific epidemiology and the structural and social infrastructure to deliver vaccines effectively. Strengthening cold-chain capacity, ensuring reliable supply-chain management, investing in trained health workers and fostering community engagement are all essential to translate economic evidence into action.

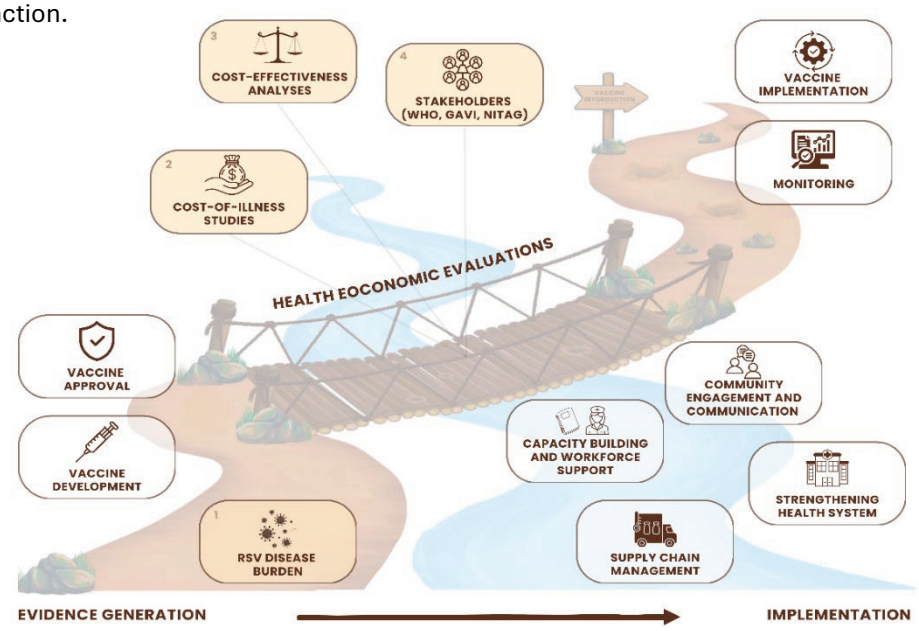

Figure 3. Health Economics as a Bridge in Vaccine Implementation in LMICs.
Schematic representation of the major steps in the LMIC vaccine implementation process. Dark beige boxes indicate components directly supported by data from this thesis. 1: Disease burden assessment (Chapters 4, 5 and 7), 2: Cost of illness (COI) analyses (Chapter 5 and 6), 3: Cost-effectiveness analyses (CEA) (Chapters 7 and 8), 4: Stakeholder engagement and dissemination.

Looking ahead, this thesis contributes to the growing body of evidence on RSV burden and health economics across countries of varying income levels. Importantly, this does not imply that each country must conduct its own new COI or CEA study. Leveraging existing evidence from countries with comparable health systems can offer a more efficient, feasible and sustainable approach, allowing limited national resources to focus on implementation rather than analysis.

The dissemination workshops held in Mozambique and Nepal demonstrate the practical value of health economic evidence. By bringing together the Ministry of Health, NITAG members, clinicians, donor agencies and international partners, the findings stimulated discussions on preparedness, prioritisation and system readiness, even before vaccine introduction is imminent. These discussions highlighted the importance of early planning around cold-chain capacity, supply-chain logistics, workforce training and community engagement.

More broadly, these experiences demonstrate how health economics form a bridge between research and policy. Economic evidence provides the contextual foundation for equitable, data-driven decisions and supports countries in planning for future introduction when policy priorities and resources align. Integrating economic perspectives early in the vaccine pathway ensures that innovations such as maternal RSV vaccination can eventually be introduced in ways that are both feasible and financially sustainable, thereby maximising their long-term public health impact.

PART IV – The Added Value of Country-Specific Evidence in a Global Context

Comparative analysis: country-specific versus pooled data

Pooled data are highly valuable for global advocacy and for informing vaccine manufacturers and international organisations such as the WHO and SAGE. By combining multiple study sites, pooled analyses offer stronger statistical power and a broader, more generalisable understanding of RSV burden and intervention impact. Such insights also support global prioritisation and vaccine price negotiations and provide crucial inputs for modelling the potential impact of new immunisation strategies across regions.

For national decision-making, however, country-specific data are essential. Differences in healthcare infrastructure, access to care, disease surveillance capacity and the socio-economic circumstances strongly influence the epidemiological and economic burden of RSV. As shown in our studies in Mozambique and Nepal, aggregated multi-country data cannot capture these critical contextual nuances. **Country-specific evidence allows policymakers not only to estimate the true local burden of a disease, but also to evaluate feasibility, cost-effectiveness and operational requirement of new immunisation strategies within the realities of their own health systems.** A balanced approach where global pooled analyses guide overall prioritisation and country-specific studies inform local implementation is crucial for translating evidence into equitable and sustainable immunisation strategies.

The added value of country-specific research beyond policy adoption

Beyond informing national policy, locally led research strengthens national analytic capacity and builds expertise in epidemiology, health economics and implementation research. It also fosters data ownership and empowers national teams to engage directly in study design, data collection, analysis and policy dialogues, rather than relying solely on external evidence.

Moreover, investing in locally generated evidence promotes equitable global health partnerships. Many LMICs remain underrepresented in the evidence base that shapes global vaccine policy, creating dependency on high-income settings. Strengthening national research capacity helps correct this imbalance, ensuring that evidence from diverse contexts informs both global models and local implementation.

CONCLUSION

Health economic evaluations play a critical role in the pathway from evidence generation to vaccine introduction, particularly in resource-constrained settings. Through the RSV GOLD III–ICU Network Study and the RSV GOLD III–Health Economics Study, we contributed to understanding the epidemiological, clinical and financial burden of RSV and provided insights into the potential impact and value-for-money of new RSV immunisation strategies.

In doing so, this thesis shows that generating country-specific evidence on RSV burden and health economics is a necessary step towards the introduction of RSV immunisation strategies in LMICs, as it informs prioritisation, investment decisions and context-appropriate programme design.

Our economic evidence also informs WHO SAGE recommendations, funding decisions from Gavi and other agencies and national policy development. However, economic evaluations alone are not sufficient for successful implementation. Vaccine introduction also depends on health system capacity, programme logistics, equity considerations and sustained political and financial commitment. In this sense, health economics serves as a bridge between scientific knowledge and policy action, whose true value emerges only when supported by operational readiness, societal engagement and sustainable financing.

Beyond its analytic function, economic evaluation should be embedded within the broader ethical framework that reflects the principles of human dignity, need, solidarity and cost-effectiveness. This ensures that resources are directed towards those with the greatest need and that the health gains achieved are proportional to investments made. Integrating such ethical considerations alongside economic evidence ensures that decisions about vaccine introduction are efficient, equitable, inclusive and socially just, particularly in settings such as Mozambique and Nepal where disparities in access, capacity, and opportunity are greatest.

Together, these findings underscore the overarching message of this thesis: while global evidence and guidance are essential, it is locally grounded epidemiological and economic data that ultimately enable effective, sustainable and equitable RSV immunisation strategies in LMICs.

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Appendices

ENGLISH SUMMARY

Respiratory syncytial virus (RSV) is a leading cause of lower respiratory tract infections in young children. Each year, RSV is estimated to cause 33 million infections, 3.6 million hospitalisations and more than 101 000 deaths, the majority of which occur in low- and middle-income countries (LMICs). The high disease burden, combined with the lack of effective treatments and immunisation strategies until recent years, places considerable pressure on hospitals and healthcare budgets.

Until the start of this PhD research project in 2022, palivizumab was the only approved preventive option for RSV infections in infants. Palivizumab is a monoclonal antibody that binds to the RSV F protein, preventing the virus from entering host cells. It must be administered monthly via intramuscular injection throughout the RSV season and, due to its high cost, has been available primarily to high-risk groups in high-income countries.

Recent developments, however, have enabled new immunisation strategies that can substantially reduce the risk of severe RSV infections in early childhood. The World Health Organization (WHO) currently recommends two options globally: maternal PreF protein vaccination (RSVpreF, Abrysvo®, Pfizer) and a long-acting monoclonal antibody (mAb) for infant prophylaxis (nirsevimab, Beyfortus®, AstraZeneca and Sanofi). The maternal vaccine is administered during the second or third trimester of pregnancy, allowing the mother to develop high levels of RSV-specific antibodies that are transferred to the infant via the placenta, providing passive protection during the first six months of life, the period when infants are most vulnerable to severe RSV infection. Nirsevimab, on the other hand, is administered as a single intramuscular injection to infants at the start of their first RSV season or at birth if born during the RSV season, providing direct passive protection. In September 2025, the European Medicines Agency (EMA) also issued a positive opinion for a new long-acting monoclonal antibody, clesrovimab (Enflonsia®, Merck), offering a promising additional option for RSV prevention in children.

In many high-income countries, some form of RSV immunisation has now been implemented into the National Immunisation Programme (NIP), ranging from exclusively maternal vaccination to nirsevimab, or a combination of both strategies. In contrast, access to RSV immunisation strategies remains very limited in low-income countries, meaning that the majority of the global RSV disease burden still occurs in these regions.

Following a general introduction on RSV and health economics, **Part I** of this thesis focuses on the seasonal patterns and clinical characteristics of RSV in the Netherlands, with particular attention to the impact of the COVID-19 pandemic. The pandemic had a major global effect on respiratory infections. Measures such as physical distancing, school closures and mask-wearing temporarily reduced transmission of many viral infections. During the winter of 2020–2021, RSV infections were almost absent, followed by an unusual summer peak in 2021. **Chapter 2** describes the burden of RSV in children under two years of age in the Netherlands, with special attention to the changes of the typical winter pattern during and after the pandemic. Our analyses indicate that both the epidemiological and clinical characteristics of RSV have largely returned to the pre-pandemic patterns. Differences in age distribution and severity appear to be related to changes in social interactions and public health measures. As before the pandemic, severe RSV infections after the pandemic occurred predominantly in children under six months of age.

During my PhD trajectory, RSV immunisation was incorporated into the Dutch NIP. **Chapter 3** reflects on this programme and explores opportunities for further optimisation. Since September 2025, RSV immunisation has been offered to all children born on or after April 1, 2025, during their first year of life, providing a crucial foundation for protection. Analyses suggest that consideration of birth month and timely administration remain important. A proportion of infants acquire RSV infection requiring hospitalisation within the first 14 days of life and are possibly outside the reach of the existing vaccination policy. Better alignment of the immunisation strategy with birth month and timely administration could further enhance the programme's effectiveness.

Part II shifts the focus to the impact of RSV infections in intensive care units (ICUs) in LMICs, where available data are often limited. In collaboration with ten LMICs, all children under two years of age admitted with severe respiratory symptoms were prospectively tested for RSV during two local RSV seasons. The results of this study, the RSV GOLD III–ICU Network Study, are described in **Chapter 4**. This multi-country study found that RSV accounts for a substantial proportion of severe respiratory infections in young children. During the local RSV season, 29% of hospitalised children tested positive for RSV. Notably, most life-threatening RSV infections occurred in children during the first six months of life, with almost half in infants under three months old. This age distribution underscores both the vulnerability of young infants in these settings and the potential of available immunisation strategies to prevent severe RSV infections in high-risk groups. Furthermore, this study served as the starting point for my PhD research and provided the basis for selecting study sites for the RSV GOLD

III–Health Economics Study, which later made the health economic evaluations in **Part III** possible.

Chapters 5 and 6 focus on cost-of-illness (COI) studies in Mozambique and Nepal. The studies estimated the costs of RSV infections in children under two years from the perspective of the healthcare system, households and society. Analyses showed that Mozambique had the highest total costs. Costs for life-threatening cases averaged USD 1161, nearly double that of severe cases (USD 612). Healthcare system costs were also highest in Mozambique: USD 7, USD 550 and USD 928 for non-severe, severe and life-threatening cases, respectively. In Nepal, healthcare system costs for life-threatening and severe cases were only USD 58. The data also highlight the substantial burden of RSV on households. In Mozambique, household costs associated with RSV-related hospitalisation represented 43 to 145% of the monthly minimum wage, whereas in Nepal, out-of-pocket expenses ranged from 168-400% of the monthly minimum wage. These studies provide some of the first insights into the economic burden of RSV in LMICs and emphasise the importance of RSV immunisation strategies to reduce both child mortality and poverty.

Chapters 7 and 8 present cost-effectiveness analyses of new RSV intervention strategies in Mozambique and Nepal. These analyses evaluated the introduction of maternal RSV vaccination (RSVPreF, Abrysvo®, Pfizer) and a long-acting monoclonal antibody (mAb) for infants (nirsevimab, Beyfortus®, AstraZeneca and Sanofi) over a ten-year period (2025–2034). Each intervention was compared with the current situation without pharmacological prevention. The analyses indicate that both maternal vaccines and mAbs can have a substantial impact on reducing RSV related infant mortality and hospitalisations. Both interventions can be cost-effective if appropriately priced and with potential support from Gavi, an organisation that financially supports low-income countries with vaccine implementation. mAbs are expected to be more expensive than maternal vaccines, making future pricing information critical for policy decisions. In Nepal, a maternal RSV vaccine priced at USD 5 per dose could potentially save an estimated 2500 child lives (36%) and prevent 50 000 hospitalisations (25%) over ten years. A mAb for infants, in contrast, could prevent slightly fewer deaths (over 2000, 33%) but slightly more hospitalisations (over 53 500, 27%). In Mozambique, the same maternal vaccine would cost approximately USD 80 million and could prevent an estimated 4700 deaths (43%) and 109 000 hospitalisations (32%). The mAb for infants would cost USD 85 million and could prevent 5000 deaths (47%) and 112 000 hospitalisations (33%). More than half of these costs could potentially be offset by savings to the healthcare system. In summary, both strategies have the potential to save numerous children's lives and prevent hospitalisations. They are likely to be affordable at low prices, particularly with international support from organisations

such as Gavi. Furthermore, aligning the timing of immunisation with local RSV seasonality could further enhance their impact.

Chapter 9, the general discussion, reflects on the role of health economic research in advancing the implementation of RSV immunisation strategies in LMICs. It demonstrates how health economics contributes to evidence on costs, health impact and value-for-money, supporting priority setting and resource allocation in settings where health system capacity and budgets are constrained. The chapter further highlights that such evidence is most informative when generated at the country-level, complementing insights from epidemiological and clinical studies on RSV burden and seasonality. While international guidelines and global models provide an essential framework for decision-making, local epidemiological data, cost structures and healthcare delivery practices can strongly influence economic outcomes and implementation feasibility. By integrating context-specific data with international evidence, health economic analyses can support context-appropriate and equitable policy decisions.

At the same time, the discussion recognises that in LMICs the translation of economic evidence into policy action is rarely linear. Although cost-effectiveness analyses are indispensable for prioritisation and investment justification, they cannot on their own overcome structural constraints such as competing health priorities, limited financing and system capacity. Health economic evidence should therefore be seen as a necessary enabling step that brings RSV immunisation strategies closer to implementation. Subsequent decisions, however, remain contingent on financing arrangements, health system readiness and sustained political and institutional commitment to translate evidence into action.

NEDERLANDSTALIGE SAMENVATTING

Respiratoir syncytieel virus (RSV) is een belangrijke oorzaak van lage luchtweginfecties bij jonge kinderen. Jaarlijks leidt RSV naar schatting tot 33 miljoen luchtweginfecties, 3,6 miljoen ziekenhuisopnames en meer dan 101.000 sterfgevallen, waarvan het merendeel voorkomt in lage- en middeninkomenslanden (LMICs). De hoge ziektelast in combinatie met het ontbreken van effectieve behandeling en immunisatie-strategieën zorgt voor grote druk op ziekenhuizen en zorgbudgetten.

Tot het begin van dit promotieonderzoek in 2022 was palivizumab de enige optie om RSV-infecties bij zuigelingen te voorkomen. Palivizumab is een monoklonaal antilichaam dat bindt aan het RSV F-eiwit en zo voorkomt dat het virus gastheercellen binnendringt. Het middel moet maandelijks intramusculair worden toegediend gedurende het RSV-seizoen en was vanwege de hoge kosten vooral beschikbaar voor hoogrisicogroepen in landen met hoge inkomens.

Recente ontwikkelingen zorgden voor nieuwe immunisatiestrategieën die het risico op ernstige RSV-infecties bij jonge kinderen aanzienlijk verminderen. De Wereldgezondheidsorganisatie (WHO) beveelt momenteel wereldwijd twee opties aan: maternale PreF-eiwitvaccinatie (RSVpreF, Abrysvo®, Pfizer) en een langwerkend monoklonaal antilichaam voor profylaxe bij zuigelingen (nirsevimab, Beyfortus®, AstraZeneca en Sanofi). Het maternaal vaccin wordt toegediend in het tweede of derde trimester van de zwangerschap, waardoor de moeder hoge levels van RSV-specifieke antistoffen ontwikkelt die via de placenta aan het kind worden doorgegeven. Dit biedt passieve bescherming in de eerste zes maanden van het leven, de periode waarin zuigelingen het meest kwetsbaar zijn voor ernstige RSV-infecties. Nirsevimab wordt daarentegen als een intramusculaire injectie toegediend aan zuigelingen aan het begin van hun eerste RSV-seizoen, of direct na de geboorte als ze geboren zijn tijdens het RSV-seizoen, en biedt directe passieve bescherming. In september 2025 gaf de European Medicines Agency (EMA) bovendien een positief advies voor een nieuw langwerkend antilichaam, clesrovimab (Enflonsia®, Merck), wat een veelbelovende aanvullende optie biedt voor RSV-preventie bij jonge kinderen.

In veel hoge-inkomenslanden is inmiddels een vorm van RSV-immunisatie ingevoerd, variërend van uitsluitend maternale vaccinatie of nirsevimab, of een combinatie van beide strategieën. In lage-inkomenslanden blijft de toegang tot RSV-preventie daarentegen zeer beperkt, waardoor het merendeel van de wereldwijde RSV-ziektelast nog steeds in deze regio's voorkomt.

Na een algemene introductie over RSV en gezondheidseconomie richt **Deel I** van dit proefschrift zich op seizoenspatronen en klinische kenmerken van RSV in Nederland, met bijzondere aandacht voor de invloed van de COVID-19-pandemie. De pandemie heeft wereldwijd een grote impact gehad op luchtweginfecties. Door maatregelen zoals fysieke afstand, schoolsluitingen en het dragen van mond-neusmaskers nam de transmissie van meerdere virale infecties tijdelijk drastisch af. In de winter van 2020-2021 waren er vrijwel geen RSV-infecties, gevolgd door een ongebruikelijke piek in de zomer van 2021. **Hoofdstuk 2** beschrijft de ziektelast van RSV bij kinderen onder de twee jaar in Nederland. Specifiek beschrijven wij de veranderingen van het gebruikelijke winter patroon tijdens en na de pandemie. Onze analyses laten zien dat zowel de epidemiologische als de klinische kenmerken van RSV grotendeels zijn teruggekeerd naar het pre-pandemische beeld. Verschillen in leeftijdsverdeling en ernst van infecties lijken samen te hangen met veranderingen in sociale interacties en volksgezondheidsmaatregelen. Net als voor de pandemie traden ernstige RSV-infecties na de pandemie vooral op bij kinderen jonger dan zes maanden.

Tijdens mijn promotietraject is RSV-immunisatie opgenomen in het Rijksvaccinatieprogramma in Nederland. **Hoofdstuk 3** reflecteert op dit programma en verkent mogelijkheden voor verdere optimalisatie. Sinds September 2025 wordt RSV-immunisatie aangeboden aan alle kinderen geboren op of na 1 april 2025 gedurende hun eerste levensjaar, wat een belangrijke basis voor bescherming biedt. Onderzoek suggereert dat aandacht voor geboortemaand en tijdige toediening relevant blijft. Een deel van de zuigelingen loopt al binnen de eerste 14 levensdagen een RSV-infectie op die ziekenhuisopname vereist en valt mogelijk buiten het bereik van het huidige vaccinatiebeleid. Het beter afstemmen van de immunisatiestrategie op de geboortemaand en het tijdig toedienen zou de effectiviteit van het programma nog kunnen verbeteren.

Deel II verschuift de focus naar de impact van RSV-infecties op intensive care-afdelingen (ICU's) in LMICs, waar beschikbare data vaak beperkt zijn. In samenwerking met tien LMICs werden alle kinderen jonger dan twee jaar, opgenomen met ernstige luchtwegklachten prospectief getest op RSV gedurende twee lokale RSV-seizoenen. De resultaten van deze studie, de RSV GOLD III–ICU Network Study, worden beschreven in **Hoofdstuk 4**. Uit deze internationale studie bleek dat RSV verantwoordelijk is voor een aanzienlijk deel van ernstige luchtweginfecties bij jonge kinderen. Tijdens het lokale RSV-seizoen testte 29% van de opgenomen kinderen positief op RSV. Belangrijk is dat de meeste levensbedreigende RSV-infecties optraden bij kinderen in de eerste zes maanden van hun leven en bijna de helft jonger was dan drie maanden. Deze leeftijdsverdeling benadrukt zowel de kwetsbaarheid van jonge zuigelingen als het potentieel van beschikbare immunisatiestrategieën om ernstige

RSV-infecties in hoogrisicogroepen te voorkomen. Daarnaast vormde deze studie het startpunt van dit promotieonderzoek en de basis voor de selectie van studielocaties voor de RSV GOLD III–Health Economics Study, wat later de uitvoering van gezondheids-economische evaluaties in **Deel III** mogelijk maakte.

Hoofdstuk 5 en 6 richten zich op de kostenstudies (cost-of-illness, COI) in Mozambique en Nepal. De studies schatten de kosten van RSV-infecties bij kinderen jonger dan twee jaar vanuit het perspectief van het gezondheidssysteem, huishoudens en de samenleving. Uit de analyses bleek dat de totale kosten het hoogst waren in Mozambique. Voor levensbedreigende gevallen lagen de gemiddelde kosten bij USD 1161, bijna twee keer zo hoog als voor ernstige gevallen (USD 612). Ook de kosten voor het gezondheidssysteem waren in Mozambique het hoogst: USD 7, USD 550 en USD 928 voor respectievelijk niet-ernstige, ernstige en levensbedreigende gevallen. In Nepal lagen de kosten voor levensbedreigende en ernstige gevallen daarentegen slechts bij USD 58. De gegevens laten daarnaast ook de aanzienlijke financiële belasting voor huishoudens zien. In Mozambique vertegenwoordigden de huishoudelijke kosten van RSV-gerelateerde ziekenhuisopnames 43–145% van het maandelijkse minimumloon, terwijl in Nepal de huishoudelijk kosten varieerden van 168-400% van het maandelijkse minimumloon. Deze studies bieden waardevolle eerste inzichten in de economische last van RSV in LMICs en benadrukt het belang van RSV-immunisatiestrategieën om zowel kindersterfte als armoede tegen te verminderen.

Hoofdstuk 7 en 8 laten kosteneffectiviteitsanalyses van nieuwe interventiestrategieën tegen RSV in Mozambique en Nepal zien. Hierbij werd gekeken naar de introductie van maternale RSV-vaccinatie (RSVPreF, Abrysvo®, Pfizer) en een langwerkend monoklonaal antilichaam (mAb) voor zuigelingen (nirsevimab, Beyfortus®, AstraZeneca en Sanofi) over tien jaar (2025–2034). Elke interventie werd vergeleken met de huidige situatie waarin geen preventieve optie beschikbaar is. De primaire uitkomstmaat was de incrementele kostprijs per gewonnen disability-adjusted life year (DALY) vanuit het perspectief van de overheid. Uit onze analyses blijkt dat zowel maternale vaccinaties als mAbs een aanzienlijke impact kunnen hebben op het verminderen van sterfte en ziekenhuisopnames bij zuigelingen. Beide interventies kunnen kosteneffectief zijn mits de prijs passend is en er mogelijke ondersteuning van Gavi, een organisatie die arme landen helpt bij het vaccineren van kinderen, beschikbaar is. Verwacht wordt dat mAbs duurder zijn dan maternale vaccins, waardoor toekomstige prijsinformatie cruciaal is voor beleidsbeslissingen. In Nepal zou een vaccin voor zwangere vrouwen tegen RSV, bij een prijs van US$5 per dosis, in tien jaar naar schatting 2.500 kinderlevens kunnen redden (36%) en 50.000 ziekenhuisopnames voorkomen (25%). Een langwerkend antilichaam voor zuigelingen

daarentegen, zou iets minder sterfgevallen kunnen voorkomen (meer dan 2.000, 33%) maar wel iets meer ziekenhuisopnames (meer dan 53.500, 27%). In Mozambique zou hetzelfde vaccin voor zwangere vrouwen ongeveer US$80 miljoen kosten en naar schatting 4.700 sterfgevallen (43%) en 109.000 ziekenhuisopnames (32%) kunnen voorkomen. De langwerkende antistof voor zuigelingen zou US$85 miljoen kosten en 5.000 sterfgevallen (47%) en 112.000 ziekenhuisopnames (33%) kunnen voorkomen. Meer dan de helft van deze kosten kan worden terugverdiend door besparingen in de gezondheidszorg. Kortom, beide strategieën kunnen veel kinderlevens redden en ziekenhuisopnames voorkomen. Bij een lage prijs en met internationale steun zoals van Gavi zijn deze strategieën betaalbaar. Door de vaccinatie slim af te stemmen op het RSV-seizoen kan het effect verder worden vergroot.

Hoofdstuk 9, de algemene discussie, gaat in op de rol van gezondheidseconomisch onderzoek bij de implementatie van RSV-immunisatiestrategieën in LMICs. Het hoofdstuk laat zien dat gezondheidseconomie bijdraagt aan inzichten in de kosten, baten en uitvoerbaarheid van nieuwe interventies. Deze informatie ondersteunt beleidsmarkers bij het prioriteren van middelen in settings met beperkte capaciteit. Het hoofdstuk benadrukt bovendien dat dit soort bewijs het meest waardevol is wanneer het op landniveau wordt verzameld, en zo een belangrijke aanvulling vormt op epidemiologische en klinische gegevens over de ziektelast en seizoenspatronen van RSV. Hoewel internationale richtlijnen en globale modellen een belangrijke kader bieden voor besluitvorming, kunnen lokale epidemiologische gegevens, kostenstructuren en zorgpraktijken de economische uitkomsten en uitvoerbaarheid van implementatie sterk beïnvloeden. Door contextspecifieke gegevens te combineren met internationale inzichten, kunnen gezondheidseconomische analyses bijdragen aan beleid dat beter is afgestemd op de lokale realiteit.

Tegelijkertijd wordt in de discussie besproken dat de vertaling van economische analyses naar beleidsactie in LMICs zelden lineair verloopt. Kosteneffectiviteitsanalyses zijn essentieel voor prioritering en onderbouwing van investeringen, maar kunnen op zichzelf structurele beperkingen zoals concurrerende gezondheidsprioriteiten en afhankelijkheid van externe financiering niet wegnemen. Gezondheidseconomisch bewijs moet daarom worden gezien als een noodzakelijke, faciliterende stap die RSV-immunisatiestrategieën dichter bij daadwerkelijke implementatie brengt. De beslissingen blijven echter afhankelijk van financieringsmogelijkheden, de paraatheid van het gezondheidssysteem en blijvende politieke en institutionele bereidheid om wetenschappelijke inzichten om te zetten in actie.

DEUTSCHE ZUSAMMENFASSUNG

Das Respiratorische Synzytial-Virus (RSV) ist ein weltweit verbreiteter Erreger akuter Atemwegsinfektionen, der insbesondere Säuglinge, Kleinkinder sowie ältere Erwachsene betrifft. Jährlich werden weltweit schätzungsweise 33 Millionen RSV-assoziierte Atemwegserkrankungen, 3,6 Millionen Krankenhausaufenthalte und über 101.000 Todesfälle verzeichnet, wobei ein Großteil in Ländern mit niedrigem und mittlerem Einkommen (LMICs) auftritt. Die hohe Krankheitslast in Kombination mit dem Mangel an wirksamen therapeutischen und präventiven Maßnahmen führt zu einer erheblichen Belastung der Gesundheitssysteme.

Bis zu Beginn dieser Doktorarbeit im Jahr 2022 war der monoklonale RSV-Antikörper Palivizumab (Synagis) die einzige zugelassene präventive Maßnahme gegen RSV-Infektionen bei Säuglingen. Palivizumab ist ein monoklonaler Antikörper, der an das RSV-F-Protein bindet und dadurch das Eindringen des Virus in Wirtszellen verhindert. Das Präparat muss während der RSV-Saison (meist Oktober bis März) in monatlichen Intervallen intramuskulär verabreicht werden und war aufgrund der hohen Kosten ausschließlich bei Kindern mit einem hohen Risiko für eine schweren Krankheitsverlauf in Ländern mit hohem Einkommen zugelassen.

Neuere Entwicklungen haben jedoch innovative Immunisierungsstrategien ermöglicht, die das Risiko schwerer RSV-Infektionen in den ersten Lebensjahren deutlich verringern können. Die Weltgesundheitsorganisation (WHO) empfiehlt derzeit zwei Optionen: die maternale PreF-Protein-Impfung (RSVpreF, Abrysvo®, Pfizer) sowie einen langwirkenden monoklonalen Antikörper (mAb) zur Prophylaxe bei Säuglingen (Nirsevimab, Beyfortus®, AstraZeneca und Sanofi). Der maternale Impfstoff wird im zweiten oder dritten Trimester der Schwangerschaft verabreicht, sodass die Mutter hohe Mengen an RSV-spezifischen Antikörpern bildet, die über die Plazenta an das ungeborene Kind weitergegeben werden. Dies gewährleistet einen passiven Schutz in den ersten sechs Lebensmonaten, der Phase, in der Säuglinge am anfälligsten für schwere RSV-Infektionen sind. Nirsevimab hingegen wird als einmalige intramuskuläre Injektion zu Beginn der ersten RSV-Saison eines Säuglings oder direkt nach der Geburt, wenn das Kind während der RSV-Saison geboren wurde, verabreicht und bietet direkt passiven Schutz. Im September 2025 erteilte die Europäische Arzneimittelagentur (EMA) zudem eine positive Stellungnahme für einen weiteren langwirkenden monoklonalen Antikörper, Clesrovimab (Enflonsia®, Merck), der als vielversprechende zusätzliche Option zur RSV-Prävention bei jungen Kindern gilt.

In vielen Ländern mit hohem Einkommen wurde mittlerweile eine Form der RSV-Immunisierung eingeführt, die von ausschließlich maternaler Impfung oder Nirsevimab

bis hin zu einer Kombination beider Strategien reicht. In Ländern mit niedrigem Einkommen bleibt der Zugang zu RSV-Prävention jedoch weiterhin stark eingeschränkt, sodass der Großteil der globalen RSV-Krankheitslast in diesen Regionen konzentriert bleibt.

Nach einer allgemeinen Einführung zu RSV und Gesundheitsökonomie konzentriert sich **Teil I** dieser Dissertation auf saisonale Muster und klinische Merkmale von RSV in den Niederlanden, wobei besonderes Augenmerk auf die Auswirkungen der COVID-19-Pandemie gelegt wird. Die Pandemie hatte weltweit erhebliche Auswirkungen auf Atemwegsinfektionen. Maßnahmen wie physische Distanzierung, Schulschließungen und das Tragen von Masken führte zu einem drastischen Rückgang der Übertragung vieler Virusinfektionen. Im Winter 2020–2021 traten RSV-Infektionen nahezu nicht auf, gefolgt von einem ungewöhnlichen Anstieg im Sommer 2021. **Kapitel 2** beschreibt die Krankheitslast von RSV bei Kindern unter zwei Jahren in den Niederlanden, mit einem besonderen Fokus auf die Veränderungen des typischen Wintermusters während und nach der Pandemie. Unsere Analysen zeigen, dass sowohl die epidemiologischen als auch die klinischen Merkmale von RSV weitgehend auf das prä-pandemische Muster zurückgekehrt sind. Unterschiede in Altersverteilung und Schweregrad scheinen mit Veränderungen sozialer Interaktionen und öffentlichen Gesundheitsmaßnahmen zusammenzuhängen. Wie vor der Pandemie traten auch nach der Pandemie schwere RSV-Infektionen vor allem bei Kindern unter sechs Monaten auf.

Während meiner Promotionsarbeit wurde die RSV-Immunisierung in das niederländische Nationale Impfprogramm integriert. **Kapitel 3** reflektiert die Umsetzung dieses Programms und untersucht Möglichkeiten zur weiteren Optimierung. Seit September 2025 wird allen Kindern, die am oder nach dem 1. April 2025 geboren wurden, eine RSV-Immunisierung mit dem monoklonalen Antikörper Nirsevimab im ersten Lebensjahr angeboten, was eine wesentliche Grundlage für den Schutz bietet. Analysen deuten darauf hin, dass die Berücksichtigung des Geburtsmonats, sowie eine rechtzeitige Verabreichung der Impfung nach wie vor relevant sind. Ein Teil der Säuglinge erleidet bereits innerhalb der ersten 14 Lebenstage eine RSV-Infektion, die eine Hospitalisierung erforderlich macht, und fällt möglicherweise außerhalb der Reichweite des bestehenden Impfprogrammes. Eine präzisere Abstimmung der Immunisierungsstrategie auf den Geburtsmonat und die rechtzeitige Verabreichung könnte die Effektivität des Programms weiter erhöhen.

Teil II verlagert den Fokus auf die Auswirkungen von RSV-Infektionen auf Intensivstationen (ICUs) in LMICs, wo verfügbare Daten häufig begrenzt sind. In Zusammenarbeit mit zehn Studienstandorten in LMICs wurden alle Kinder unter zwei Jahren, die mit schweren Atemwegssymptomen stationär aufgenommen wurden, über

zwei lokale RSV-Saisonen prospektiv auf RSV getestet. Die Ergebnisse dieser Studie, die RSV GOLD III–ICU Network Study, werden in **Kapitel 4** beschrieben. Die multinationale Studie zeigte, dass RSV einen erheblichen Anteil schwerer Atemwegsinfektionen bei Kleinkindern ausmacht. Während der lokalen RSV-Saison testeten 29% der hospitalisierten Kinder positiv auf RSV. Besonders auffällig war, dass die meisten lebensbedrohlichen RSV-Infektionen bei Kindern in den ersten sechs Lebensmonaten auftraten, wobei fast die Hälfte der Fälle bei Kindern unter drei Monaten verzeichnet wurden. Diese Altersverteilung hebt sowohl die erhöhte Anfälligkeit junger Säuglinge in diesen Ländern hervor als auch das Potenzial der verfügbaren Immunisierungsstrategien, schwere RSV-Infektionen in Hochrisikogruppen zu verhindern. Darüber hinaus bildete diese Studie den Ausgangspunkt dieser Dissertation und die Grundlage für die Auswahl der Studienstandorte für die RSV GOLD III–Health Economics Study, die später die Studien zur Gesundheitsökonomie in **Teil III** ermöglichte.

Kapitel 5 und 6 konzentrieren sich auf Kostenstudien (Cost-of-Illness, COI) zum RSV-Virus in Mosambik und Nepal. Die Studien bieten einen Einblick in die Kosten von RSV-Infektionen bei Kindern unter zwei Jahren aus der Perspektive des Gesundheitssystems, der Haushalte und der Gesellschaft. Die Analysen zeigten, dass Mosambik die höchsten Gesamtkosten für RSV-Infektionen bei Kindern unter zwei Jahren aufwies. Die Kosten für lebensbedrohliche Fälle, gekennzeichnet durch ICU-Aufnahmen, lagen im Durchschnitt bei 1161 USD, fast doppelt so hoch wie die Kosten bei schweren Fällen (612 USD). Auch die Kosten für das Gesundheitssystem waren in Mosambik hoch: jeweils 7 USD, 550 USD und 928 USD für nicht-schwere, schwere und lebensbedrohliche Fälle. In Nepal lagen die Kosten für das Gesundheitssystem für lebensbedrohliche und schwere Fälle nur bei 58 USD. Die Daten verdeutlichen auch die erhebliche Belastung von Haushalten durch RSV. In Mosambik entsprachen Haushaltskosten im Zusammenhang mit einer RSV-bedingte Hospitalisierung 43–145% des monatlichen Mindestlohns, während in Nepal die Eigenanteile zwischen 168 und 400% des monatlichen Mindestlohns lagen. Diese Studien bieten erste Einblicke in das wirtschaftliche Ausmaß von RSV-Infektionen bei Kindern unter 2 Jahren in LMICs und machen die Bedeutung RSV-Immunisierungsstrategien zur Reduzierung von sowohl der Kindersterblichkeit als auch der Armut deutlich.

Kapitel 7 und 8 präsentieren Kosten-Nutzen-Analysen neuer RSV-Immunisierungsstrategien in Mosambik und Nepal. Diese Analysen bewerten die Einführung der maternalen RSV-Impfung (RSVPreF, Abrysvo®, Pfizer) sowie eines langwirkenden monoklonalen Antikörpers (mAb) für Säuglinge (Nirsevimab, Beyfortus®, AstraZeneca und Sanofi) über einen Zeitraum von zehn Jahren (2025–2034). Jede Intervention wurde mit der aktuellen Situation ohne pharmakologische

Prävention verglichen. Die Analysen deuten darauf hin, dass sowohl maternale Impfstoffe als auch mAbs einen erheblichen Einfluss auf die Reduktion von RSV-bedingter Kindersterblichkeit und Krankenhausaufenthalten haben können. Beide Interventionen können kosteneffektiv sein, sofern der Preis angemessen ist und gegebenenfalls finanzielle Unterstützung durch Gavi möglich ist. Gavi ist eine Organisation, die die Einführung von Impfstoffen in armen Ländern finanziell unterstützt. Es wird erwartet, dass mAbs teurer als maternale Impfstoffe sein werden, weshalb zukünftige Preisinformationen für politische Entscheidungen von elementarer Bedeutung sind. Über zehn Jahre zeigen beide Strategien in Nepal und Mosambik substanzielle Effekte auf Todesfälle und Krankenhausaufenthalte. In Nepal ist die maternale Impfung kostengünstiger und stärker auf Todesfälle ausgerichtet, während mAbs etwas mehr Hospitalisierungen verhindern; in Mosambik sind Kosten und Wirkungen beider Interventionen vergleichbar. Mehr als die Hälfte dieser Kosten könnten potenziell durch Einsparungen im Gesundheitssystem ausgeglichen werden. Zusammenfassend lässt sich sagen, dass beide Strategien das Potential haben zahlreiche Kinderleben retten und Krankenhausaufenthalte verhindern können. Bei einem niedrigen Preis und internationaler Unterstützung durch Organisationen wie Gavi, sind diese Strategien voraussichtlich erschwinglich. Darüber hinaus könnte eine geschickte Abstimmung der Impfungen auf die lokale RSV-Saison ihre Wirkung noch weiter verstärken.

Kapitel 9, die allgemeine Diskussion, erklärt die Rolle der gesundheitsökonomischen Forschung bei der Umsetzung von RSV-Immunisierungsstrategien in LMICs. Es wird gezeigt, wie die gesundheitsökonomische Forschung hilft, Kosten, gesundheitliche Auswirkungen und das Preis-Leistungsverhältnis von RSV-Impfungen zu bewerten. Diese Erkenntnisse unterstützen dabei Prioritäten zu stellen und Ressourcen gezielt in den Ländern einzusetzen, in denen die Gesundheitsbudgets und -ressourcen begrenzt sind. Das Kapitel betont, dass solche Studien besonders nützlich sind, wenn sie auf Länderebene durchgeführt werden, da sie dann besser mit den Daten aus epidemiologischen und klinischen Studien zu RSV und der Virus-Saison in Einklang gebracht werden können. Obwohl internationale Empfehlungen und globale Modelle eine wichtige Grundlage für Entscheidungen bieten, können lokale Daten zu Infektionsraten, Kosten und Gesundheitsversorgung die Ergebnisse und die Umsetzung in jedem Land stark beeinflussen. Durch die Kombination dieser lokalen Informationen mit internationalen Erkenntnissen können wirtschaftliche Analysen helfen, faire und fundierte passende politische Entscheidungen zu treffen.

Gleichzeitig wird in der Diskussion darauf hingewiesen, dass in LMICs der Übergang von ökonomischen Erkenntnissen zu politischen Maßnahmen oft nicht linear verläuft. Obwohl Kosten-Nutzen-Analysen wichtig sind um zu entscheiden welche Investitionen

sinnvoll sind und priorisiert werden sollten, können sie allein nicht die strukturellen Herausforderungen in den Gesundheitssystemen lösen. Dazu gehören zum Beispiel konkurrierende Gesundheitsprioritäten, begrenzte finanzielle Mittel und ein Mangel an Kapazitäten im Gesundheitssystem. Gesundheitsökonomische Erkenntnisse sollten deshalb als ein notwendiger Schritt angesehen werden, um die Umsetzung von RSV-Impfstrategien voranzutreiben. Jedoch hängen die konkreten Entscheidungen immer noch von finanziellen Möglichkeiten, der Bereitschaft des Gesundheitssystems und dem kontinuierlichen politischen sowie institutionellen Engagement ab, um wissenschaftliche Ergebnisse tatsächlich in die Praxis umzusetzen.

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Other Publications

Sharma AK, Kattel HP, Chapagain RH, Shrestha R, Joshi P, Khadka NB. Sharma S, Löwensteyn YN, **Rave N**, Viveen MC, Bont LJ; Diagnostic accuracy of a molecular-based point-of-care test for rapid detection of respiratory syncytial virus in children admitted to high-dependency care in Nepal. *Accepted for publication in J Glob Health*.

Shaaban FL, Debellut F, Fuhngwa N, Mandi H, Clark A, **Rave N**, Pecenka C, Bont LJ; RSV GOLD III – Health Economics Study Group. Impact and cost-effectiveness of two interventions to prevent paediatric respiratory syncytial virus (RSV) disease in Cameroon: a modelling approach. *Accepted for publication in J Glob Health*.

Shaaban FL, Dame J, Nguyen A, **Rave N**, Pecenka C, Bont LJ; RSV GOLD III – Health Economics Study Group. The economic burden of respiratory syncytial virus and other acute respiratory infections among children <2 years old seeking care at a tertiary facility in Accra, Ghana. J Glob Health. 2026 May 29;16:04040. doi: 10.7189/jogh.16.04040. PMID: 42210648; PMCID: PMC13219970.

Shaaban FL, Fuhngwa N, Mandi H, Clark A, **Rave N,** Pecenka C, Bont LJ, Debellut F; RSV GOLD III – Health Economics Study Group. Impact and cost-effectiveness of two interventions to prevent paediatric respiratory syncytial virus disease in Cameroon: a modelling approach. J Glob Health. 2026 Apr 30;16:04051. doi: 10.7189/jogh.16.04051. PMID: 42060341; PMCID: PMC13132004.

Shaaban FL, Garba MA, Nguyen A, Pecenka C, **Rave N**, Bont LJ. Estimating the economic burden of respiratory syncytial virus infection among children <2 years old seeking care in North-West Nigeria. J Glob Health. 2025 Dec 12;15:04307. doi: 10.7189/jogh.15.04307. PMID: 41383167; PMCID: PMC12699286.

Mazur NI, Löwensteyn YN, Terstappen J, Leusen J, Schobben F, Cianci D, van de Ven PM, Nierkens S, Bont LJ; **Narsyn Study Group**. Daily intranasal palivizumab to prevent respiratory syncytial virus infection in healthy preterm infants: a phase 1/2b randomized placebo-controlled trial. EClinicalMedicine. 2023 Nov 25;66:102324. doi: 10.1016/j.eclinm.2023.102324. PMID: 38192587; PMCID: PMC10772232.

Löwensteyn YN, Zheng Z, **Rave N**, Bannier MAGE, Billard MN, Casalegno JS, Pitzer VE, Wildenbeest JG, Weinberger DM, Bont L; Surveillance of Pediatric REspiratory Admissions in Dutch hospitals (SPREAD) Study Group. Year-Round Respiratory Syncytial Virus Transmission in The Netherlands Following the COVID-19 Pandemic: A Prospective Nationwide Observational and Modeling Study. J Infect Dis. 2023 Nov

11;228(10):1394-1399. doi: 10.1093/infdis/jiad282. PMID: 37477906; PMCID: PMC10640768.

van Eenennaam RM, **Rave N**, Kruithof WJ, Kruitwagen-van Reenen ET, van den Berg LH, Visser-Meily JA, Beelen A. Control in the absence of choice: A qualitative study on decision-making about gastrostomy in people with amyotrophic lateral sclerosis, caregivers, and healthcare professionals. PLoS One. 2023 Sep 8;18(9):e0290508. doi: 10.1371/journal.pone.0290508. PMID: 37682899; PMCID: PMC10490981.

Streng BMM, Bont M, Delemarre EM, Binnendijk RS, Smit G, den Hartog G, Coppus AMW, de Vries E, Weijerman ME, Lamberts R, de Graaf G, van der Klis FR, Vidarsson G, **Rave N**, Bont LJ, Wildenbeest JG. Decreased Antibody Response After Severe Acute Respiratory Syndrome Coronavirus 2 Vaccination in Patients With Down Syndrome. J Infect Dis. 2022 Sep 4;226(4):673-677. doi: 10.1093/infdis/jiac235. PMID: 35748853; PMCID: PMC9278229.

Sommers-Spijkerman M, **Rave N**, Kruitwagen-van Reenen E, Visser-Meily JMA, Kavanaugh MS, Beelen A. Parental and child adjustment to amyotrophic lateral sclerosis: transformations, struggles and needs. BMC Psychol. 2022 Mar 17;10(1):72. doi: 10.1186/s40359-022-00780-1. PMID: 35300726; PMCID: PMC8929294.

Hulst RY, Pillen S, Voorman JM, **Rave N**, Visser-Meily JMA, Verschuren O. Sleep health practices and sleep knowledge among healthcare professionals in Dutch paediatric rehabilitation. Child Care Health Dev. 2020 Nov;46(6):703-710. doi: 10.1111/cch.12799. Epub 2020 Aug 12. PMID: 32706911; PMCID: PMC7589250.

PHD PORTFOLIO

Courses

2025	Global Health Masterclasses - NVTG
2022 - 2025	Utrecht University – Graduate School of Life Sciences courses: Responsible Conduct of Research - Year 1-4; Writing a Scientific Paper; Supervising MSc students: Starter Kit; Adobe InDesign
2023 - 2024	Utrecht University – MSc Epidemiology Postgraduate courses: Introduction to Statistics; Introduction to Epidemiology
2023	Collaborative Institutional Training Initiative (CITI): Biomedical Responsible Conduct Research; Protection of Human Subjects, Biomedical Research Investigators and Key Personnel;
2023	Basic Course on Regulations and Organisation for Clinical Investigators (BROK)

Conferences

2026	RSV Vaccines for the World (RSVVW'26) – A Global Conference on Novel RSV Preventive and Therapeutic Interventions; Rome, Italy (participant)
2024	RSV Vaccines for the World (RSVVW'24) – A Global Conference on Novel RSV Preventive and Therapeutic Interventions; Mumbai, India (poster; co-chairing session on Health Economics)
2023	13th World Society for Peadiatric Infectious Diseases (WSPID) Conference; Durban, South Africa (oral)
2023	RSV Vaccines for the World (RSVVW'24) – A Global Conference on Novel RSV Preventive and Therapeutic Interventions; Lisbon, Portugal (poster)
2022	40th European Society for Paediatric Infectious Diseases (ESPID) Conference; Athens, Greece (poster)

Supervision

2023 - 2024	Sophie ten Have (Bachelor Student Medical Science, University College Utrecht): The economic burden of RSV and the cost-effectiveness of RSV preventive strategies in children under 5 years: a systematic review from a low-income and middle-income country perspective.
2023	Anne Jasmijn Sellies (Master Student Epidemiology, University Utrecht) Barriers in respiratory syncytial virus vaccine implementation and uptake in LMICs
2022	Trisja Boon (Master Student Epidemiology, University Utrecht) Seasonal Patterns and burden of severe RSV among children in the Gambia: The Impact of COVID-19
2022	Michelle van Wijk (Master Student Pharmacy, University Utrecht): Bolivia SARI burden pilot study
2022 - 2025	Supervision of four (bio)medical students working on the SPREAD Study and eight (bio)medical students working on the RSV GOLD – ICU Network Study and the RSV GOLD – Health Economics Study.

Other experiences

2024/25	Participation in national stakeholder meetings on RSV prevention and immunisation implementation with representatives from the Ministry of Health and international health organisations, Maputo, Mozambique
2024	Co-chair, Health Economics Session, RSV Vaccines for the World Conference, Mumbai, India
2024	Health Economics Priority Setting, including visit to the World Health Organization (WHO), Geneva, Switzerland
2023	Study Start-up visits for the RSV GOLD III-Heatlh Economcis Study to Maputo, Mozambique; Kaduna, Nigeria; Kathmandu, Nepal

ABOUT THE AUTHOR



Neele Rave was born on the 3rd of June 1992 in Osnabrück, Germany and grew up in the nearby village of Schledehausen with her parents Marita and Holger. From an early age, she was encouraged to stay curious, care for others and never stop learning. She graduated from Gymnasium Ursulaschule in Osnabrück in 2011.

After finishing high school, Neele followed her intuition and spent a year volunteering in South Africa. At the Hantam Community Education Trust near Colesberg, she supported English and Mathematics education in a computer lab. What started as a gap year soon became a life-changing experience. It marked the beginning of a lasting connection with South Africa and awakened her interest in global health, health equity and working across cultures.

In 2012, she moved to the Netherlands to study (Medical) Biology at the Radboud University in Nijmegen, a path that allowed her to explore the possibility of a future in Medicine. During a Community Outreach Project in South Africa in 2015, organised by the university, her interest in Global Health continued to grow. Although she completed a pre-master in Medicine, she realised that her interests and ambitions lay elsewhere. After taking time to reflect during a gap year, she returned to biomedical research and enrolled in the two-year Research Master's programme in Biomedical Sciences at the Radboud University in Nijmegen, The Netherlands.

During her second research internship at the Hoogstraat Rehabilitation Centre in Utrecht, Neele discovered how much she enjoyed research that could make a difference in children's lives. After graduating in 2019, she joined the RSV Research Group at the Wilhelmina Children's Hospital (WKZ) in Utrecht as a research assistant. There, she gained experience in RSV research, epidemiology and quantitative methods, while learning the importance of collaboration and scientific curiosity.

A subsequent period of qualitative research within the ALS research group at the UMC Utrecht proved to be especially meaningful. This experience taught her valuable lessons about vulnerability, resilience and the importance of living in the present, while reinforcing her desire to contribute to improving lives of others, particularly those in vulnerable situations.

As the RSV research group expanded, Neele continued working with the team and contributed to several projects, including research on the effectiveness of COVID-19 vaccination in children and adults with Down syndrome during the pandemic. After more than two years as a research assistant, she started her PhD at the WKZ under the supervision of Prof. Dr. Louis Bont and Dr. Joanne Wildenbeest.

Alongside her PhD, Neele volunteered with the non-profit organisation *Let's Keep the Ball Flying*, which uses volleyball as a tool for social change and aims to make sport accessible to children around the world. Staying true to her connection with South Africa, she spent two months in Rustenburg in 2022 and almost four months in Stellenbosch in 2025, working remotely on her PhD while remaining closely connected to the communities that continue to inspire her.

Since May 2026, Neele has been working as an International Project Manager at the Institute of Virology at the Medical University of Innsbruck, Austria. In this role, she coordinates the European-African Vaccine Initiative (EAVI), an international consortium focused on advancing chikungunya vaccine research and strengthening seroepidemiological evidence in sub-Saharan Africa. This role brings together many of the themes that have shaped her journey so far: science, international collaboration, global health, and the ambition to translate research into meaningful impact.

Looking back, each step along the way has been guided by curiosity, meaning encounters and a genuine desire to contribute to improving peoples lives. She hopes to continue building bridges between research, policy and implementation, always with a special place in her heart for children, global health and the people and communities who have shaped her along the way.

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Dear **Andra,** I honestly miss a day with you. Your hilarious laugh, your energy, your whole vibe. Thanks for always keeping me in the loop about your life in China, for giving me a little glimpse in your new apartment and of course the legendary Lego castles and Christmas trees.

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Justyna, our shared love for volleyball and travelling brought us together and I still remember 2022 like it was yesterday. We met at the Volleyball World Championship and somehow ended up at the closing party of the FIVB Congress. Since then, we've made so many wonderful memories together in Italy, Poland, the Netherlands and Turkey. It's been far too long since our last adventure, but I treasure every single one of them. And let's not forget: the president of the Nepal Volleyball Federation still owes us that helicopter flight to Mount Everest... so I guess it's about time we start planning our next trip!

Lieve **Les**, ik weet niet eens waar ik moet beginnen. We spreken elkaar wekelijks, maar verliezen ons vaak in LKTBF-gerelateerde gesprekken. Samen met jou mogen 'werken' is soms best een uitdaging, maar tegelijkertijd zou ik niets liever willen dan dat. Jij hebt mij zo veel mooie dingen geleerd en bent in de loop der jaren een hele goede vriend geworden. Dankjewel dat je me regelmatig een spiegel voorhoudt, dat ik altijd alles zonder filter bij jou kwijt kan en dat jij nooit oordeelt.

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Liebe **Silke,** die „Dachlosen" stehen definitiv auf Platz eins in Neeles Wörterbuch – und ich bin sehr gespannt, welche weiteren legendären Begriffe es noch hineingeschafft haben. Jetzt wird es wohl Zeit, das Wörterbuch auch noch mit ein paar österreichischen Ausdrücken zu erweitern.

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Thank you!

♥

