National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

Prevention of **respiratory syncytial virus** (RSV) disease in infants

Background information for the Health Council of the Netherlands

RIVM letter report 2023-0355
A.C. Teirlinck | P.B. van Kasteren

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DOI 10.21945/RIVM-2023-0355

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This investigation was performed by order, and for the account, of the Ministry of Health, Welfare and Sports and the Health Council of the Netherlands, within the framework of the project 'Epidemiologie en surveillance van Respiratoire infecties', project number V/150207/23/RI, and V/151103/23/RV, surveillance of the National Immunization Program.

Published by:
National Institute for Public Health and the Environment, RIVM
P.O. Box 1 | 3720 BA Bilthoven
The Netherlands
www.rivm.nl/en

Synopsis

Prevention of respiratory syncytial virus (RSV) disease in infants
Background information for the Health Council of the Netherlands

The respiratory syncytial virus (RSV) is a respiratory virus that is common in the Netherlands, especially in the winter. Most children are first infected with this virus before the age of two. This usually causes mild, cold-like symptoms. It is estimated that 1 in 5 to 10 children in the Netherlands with an RSV infection visit the GP. But some children become seriously ill: around 1 in 100 babies with RSV is hospitalized for this infection. A number of them even have to be treated in the intensive care unit, for example because they need mechanical ventilation.

In recent years, efforts have been made to develop drugs and vaccines to prevent children from becoming seriously ill from an infection with this virus. The Ministry of Health, Welfare and Sport asked the Health Council of the Netherlands to issue advice on these products. To support this advice, RIVM gathered background information for the Health Council.

Some children are at a higher risk of becoming seriously ill from RSV. These include children who were born prematurely or who have a congenital heart or lung condition. They are therefore given a medication (palivizumab) that reduces the chance of becoming seriously ill. However, most children who are hospitalized for RSV do not belong to these risk groups. That means they are not eligible for this medication.

In October 2022, the European Medicines Agency (EMA) approved a new medication (nirsevimab) for use in Europe. This drug can also reduce illness in children, but it works better and longer than palivizumab. In addition, a vaccine against RSV for pregnant women may become available. This 'maternal vaccine' protects infants against serious illness from birth, as the mother passes on antibodies to the child during pregnancy. The Food and Drug Administration (FDA) is expected to advise on the approval of this vaccine in the United States soon.
The information gathered concerns both RSV and nirsevimab and the maternal vaccine against this virus. Examples include how many young children in the Netherlands become infected with the virus, how the body builds its defences against the virus and how well the products work.

Keywords: RS-virus, RSV, respiratory infection, bronchiolitis, antibodies, vaccination, cost-effectiveness

Publiekssamenvatting

Preventie van RSV bij jonge kinderen

Actuele achtergrond informatie voor de Gezondheidsraad

Het respiratoir syncytieel (RS-)virus is een luchtwegvirus dat in Nederland veel voorkomt, vooral in de winter. De meeste kinderen krijgen vóór hun tweede jaar een eerste infectie met dit virus. Deze verloopt vaak mild, met vooral verkoudheidsklachten. Naar schatting gaat 1 op de 5 tot 10 kinderen met een RS-virus infectie naar de huisarts. Maar een deel van de kinderen wordt erg ziek: ongeveer 1 op de 100 baby's moet door een RS-virus infectie naar het ziekenhuis. Een aantal van hen moet zelfs op de intensive care worden behandeld bijvoorbeeld omdat ze moeten worden beademd.

De laatste jaren wordt gewerkt aan middelen om te voorkomen dat kinderen ernstig ziek worden van een infectie met dit virus. Het ministerie van VWS heeft de Gezondheidsraad gevraagd advies te geven over deze middelen. Het RIVM heeft als ondersteuning voor dit advies bestaande achtergrondinformatie verzameld voor de Gezondheidsraad. Sommige kinderen hebben een grotere kans om erg ziek te worden van het RS-virus. Dat zijn kinderen die te vroeg geboren zijn of een aangeboren ziekte hebben aan de longen of het hart. Zij krijgen daarom een medicijn dat de kans verkleint om erg ziek te worden (palivizumap). Maar de meeste kinderen die met het RS-virus in het ziekenhuis terechtkomen, horen niet bij deze risicogroepen. Zij komen daarom niet in aanmerking voor dit medicijn.

In oktober 2022 heeft de EMA (Europees Geneesmiddelen Agentschap) een nieuw medicijn (nirsevimab) goedgekeurd voor Europa. Ook dit middel kan ervoor zorgen dat kinderen minder ziek worden, maar het werkt beter en langer dan palivizumap. Verder komt er mogelijk een vaccin voor zwangere vrouwen tegen het RS-virus. Zo'n 'maternaal vaccin' beschermt het kind vanaf de geboorte tegen ernstige ziekte doordat de moeder tijdens de zwangerschap antistoffen aan het kind doorgeeft. Naar verwachting adviseert de Food and Drug Administration (FDA) binnenkort over de goedkeuring van dit vaccin in de Verenigde Staten.

De verzamelde informatie gaat over zowel het RS-virus als nirsevimab en het maternale vaccin tegen dit virus. Bijvoorbeeld hoeveel jonge kinderen in Nederland een infectie met het virus krijgen, hoe het lichaam de afweer tegen het virus opbouwt en hoe goed de middelen werken.

Kernwoorden: RS-virus, RSV, luchtweginfectie, bronchiolitis, antilichaam/antistoffen, vaccinatie, kosteneffectiviteit

Contents

Summary

Respiratory syncytial virus (RSV) causes respiratory disease in a wide spectrum, ranging from asymptomatic cases and mild 'common cold' symptoms, to severe disease that can be life-threatening if not medically attended. In a study prospectively assessing RSV-LRTI in the Netherlands in the first year of life, 14% developed RSV-LRTI and 9% visited a GP for RSV-LRTI. Another prospective study found an incidence proportion of 42% of infants that developed and RSV-ARI (more broadly defined than the first study) and 22% of medically-attended RSV-ARI in the first year of life in the Netherlands. About 0.84-1.5% of all infants is hospitalized in the Netherlands for an RSV infection in the first year of life. The number of young children <2 years in the Netherlands admitted to the pediatric intensive care unit (PICU) for RSV bronchiolitis showed an increasing trend from 2003-2016, with 48 PICU admissions per 100.000 children in 2016. In a European study, 5.5% of the children that were hospitalized with RSV, were admitted to the PICU. In contrast to low- and middle-income countries, RSV is rarely fatal in the Netherlands. Medical risk groups for severe RSV disease are prematurely born infants, and children with certain underlying diseases. However, the majority of the infants admitted to the hospital has no such risk factor. Age and birthdate are strong predictors of (severe) RSV infection in the first years of life. Children born in summer have the highest probability of infection in the first year of life, but children <3 months born in autumn are most at risk for RSV hospitalization. Currently, the monthly administered prophylactic monoclonal antibody palivizumap is only recommended for a small specific risk profile in the period September - April, for the prevention of severe disease. The current hospital treatment is mainly supportive and antiviral drugs is only rarely used.

In the Netherlands, RSV typically circulates in the winter period, but the classical seasonal pattern has (temporarily) changed due to the COVID-19 pandemic and the associated measures to prevent transmission of SARS-CoV-2. RSV has been associated with recurrent wheeze and asthma, but a causal relationship has not been established, as, for instance, genetic predisposition and a multifactorial nature complicates this association.

In the first few months of life, infants are to a certain extent protected against infection by the presence of naturally acquired maternally derived antibodies. Nevertheless, severe infections peak in the first months of life, which is likely due to incomplete protection by waning maternal antibodies, incompletely developed airways, and immature immune systems in these young infants. RSV infection results in the induction of neutralizing serum and local (secretory) antibodies, of which the latter show the best correlation with protection from infection. A definite correlate of protection has not been established for RSV. Re-infections with RSV occur already within 2-3 years even in healthy adults, suggesting a suboptimal induction of adaptive immune responses to this virus.

Nirsevimab is a novel monoclonal antibody for the prevention of RSV disease in infants and has been approved for market authorisation by EMA in October 2022. Compared to palivizumap, it has a longer half-life and higher efficacy in clinical studies. Nirsevimab was shown to have an acceptable safety profile in phase 1B/2A, phase 2B, and phase 3 clinical trials in healthy (preterm) infants. Potential concerns that could be consequences of wider use of nirsevimab are emergence of escape mutants, replacement of RSV by other pathogens, and that development of natural immunity in treated children will be affected. These concerns have not been observed in clinical trials but should be monitored carefully in future studies and post-marketing surveillance. While other newly developed monoclonal antibodies have been discontinued due to either safety concerns or failing efficacy, one additional monoclonal antibody is currently in a phase 2B/3 clinical trial.

Several maternal vaccines have been developed and been through clinical trials. One vaccine (Novavax) was discontinued for not meeting the efficacy criteria in a Phase 3 clinical trial and one vaccine (GSK) was recently discontinued due to safety concerns. Another vaccine (Pfizer) has met the success criteria for efficacy and has been filed for marketing approval with an expected decision in the second half of 2023. In response to the GSK trial results, concerns were raised however by some scientists regarding the safety of the Pfizer vaccine.

With the market approval of nirsevimab and possibly also of the first maternal vaccine in the foreseeable future, various scenarios can be envisioned for the prevention of RSV disease in infants in the Netherlands, including various combinations of maternal vaccine and monoclonal antibody. Surveillance platforms should be in place to monitor the impact of the implemented immunization strategy. A national vaccination register would be crucial for appropriately monitoring vaccination/immunization effectiveness.

Few studies have been published on the cost-effectiveness of the nirsevimab so far, comparing seasonal administration and year-round administration. For the Netherlands, seasonal administration of one dose at birth for infants born in October to and including January is expected to be cost-effective to a threshold of €20,000 per QALY gained if the intervention costs are assumed at €64 (immunization plus administration). Seasonal administration plus a catch-up in October for cohorts born outside the RSV season was more effective and less costly than all-year round immunization, but not cost-effective compared to seasonal immunization. However, the optimal target group of the most effective birth cohort for seasonal administration and potential catch-up requires further analysis. Given the similar vaccine efficacy profiles to nirsevimab, the impact of seasonal maternal vaccination is expected to be comparable to seasonal administration of nirsevimab if the immunization uptake is the same. The optimal alternative from a cost-effectiveness point of view would highly depend on the total intervention costs per child.

1 Background

In October 2022, the European Medicines Agency (EMA), has recommended a marketing authorization in the European Union (EU) for Beyfortus (nirsevimab) for the prevention of Respiratory Syncytial Virus (RSV) lower respiratory tract disease in newborn babies and infants during their first RSV season (when there is a risk of RSV infection in the community) (1). Furthermore, maternal vaccination to prevent RSV in newborn babies and infants are currently in (late-stage) clinical development. The Ministry of Health and Welfare has requested advice on this topic to the health council of the Netherlands.
This document provides a background for the Health Council on information that is available on the epidemiology of RSV (including seasonality, burden, risk groups, long term effects), immunological aspects, current clinical practice, information on the different (future) immunization strategies and current literature on cost-effectiveness. We furthermore draft potential scenarios for implementation of immunization strategies.

2 Epidemiology of RSV in the Netherlands

2.1 Seasonality and virus circulation

In countries with a temperate climate, such as the Netherlands, RSV typically circulates in the winter period (2). The majority of RSV cases in the Netherlands are detected from November until March (3, 4), see figure 2.1. RSV causes respiratory infections. Severe infections may occur in very young children, including preterm born children and with underlying disease (5), but also in the elderly, especially immunocompromised or with an underlying disease such as congestive heart failure and COPD (6). As a result of the COVID-19 pandemic and associated measures to prevent transmission of SARS-CoV-2, the incidence and seasonality pattern of RSV, and many other respiratory viruses, drastically changed (7). While in the winter of 2020/2021 hardly any RSV was detected, a high surge of RSV caused an RSV-epidemic starting in June 2021. Since this summer peak in 2021, RSV had been circulating continuously for a long time, with mild peaks in the winter of 2021/2022 and spring/summer of 2022. Changes in seasonality have been observed across the world in the winter seasons of 2020/2021 and 2021/2022 (8, 9, 10, 11). Whether and how fast RSV circulation will return to its usual pre-pandemic seasonal pattern is uncertain, and will depend on the susceptibility dynamics in the population (12, 13). Also, it is yet unknown whether and how a new balance of dynamics between influenza virus, RSV, SARS-CoV-2 and other respiratory pathogens, will evolve. This will depend on potential viral interference between viruses (14, 15) and also on the future pattern of SARS-CoV-2 (16). In Europe, many countries experienced higher transmissions rates of RSV than usual and an early start of the season in winter 2022/2023 (10, 17, 18), but RSV circulation seemed to start moving back to its pre-pandemic patterns (11, 17, 18). In the Netherlands, in fall of 2022, RSV peaked according to its usual timing, although the number of detections of RSV was much higher than previously observed. These higher number of cases are possibly due to a combination of more RSV circulation and more diagnostic testing, as multiplex testing of Influenza virus, SARS-CoV-2 and RSV has seemed to become more generic in hospitals. Since spring 2023, RSV detections declined and are back to its usual low out-of-season circulation, see figure 2.1.

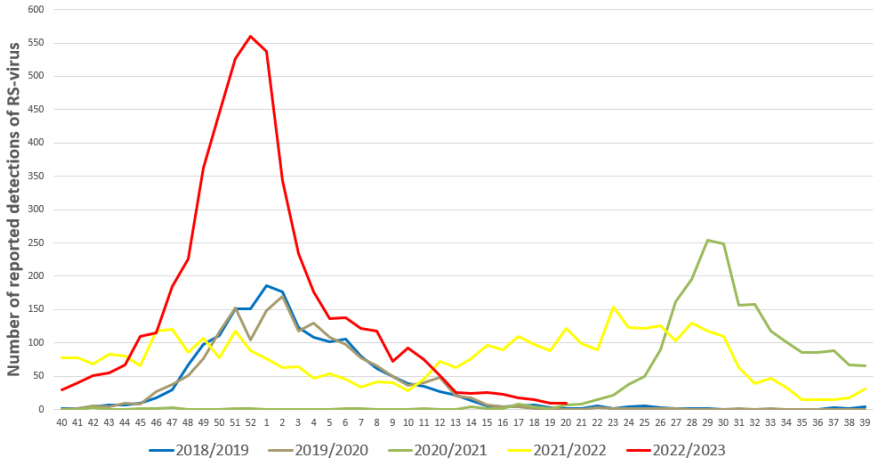

Figure 2.1 RSV detections reported by the laboratories of the virological laboratory surveillance in the period of 2018/week40 up to and including 2023/week20.
Source: virologische diagnostiek rapportages Nederlandse Werkgroep voor Klinische Virologie.

2.2 RSV-types

RSV is divided into two subtypes (RSV-A and RSV-B), based on the different antigenic properties of their attachment glycoprotein G. These two serotypes may circulate simultaneously in the population, and either type can be dominating during the season (19). Both serotypes are evolutionary lineages which diverged approximately 350 years ago with considerable genotypic variability within each lineage. The major differences are found in the attachment glycoprotein G, which has only 53% amino acid sequence conservation across strains (20). Currently, 13 RSV genotypes have been defined among the subgroup A strains and 20 genotypes for the subgroup B strains, but this method of genotyping is currently undergoing revision in hopes of providing an updated, unified method for globally genotyping RSV (21, 22). Reports are conflicting in their conclusions on the correlation of RSV infection severity with RSV serotype and specific genotypes (23).

2.3 Pathogenesis of RSV infection in infants and children

The spectrum of disease severity caused by RSV is very broad, ranging from asymptomatic cases to deaths due to respiratory insufficiency when developing bronchiolitis or pneumonia. Apart from the COVID-19 period, the majority of bronchiolitis cases in infants and children, presented at the GP and hospital is caused by an RSV infection (24). In general, infection with RSV in the upper respiratory tract as porte d'éntree leads to destruction of the ciliated epithelial cells in the airways, and the characteristic formation of syncytia (hence the name of the virus). This may remain confined to the upper airways, with mostly relatively mild symptoms of common cold. But in naïve persons (mostly very young children) or immunocompromised persons, the virus can descend in the airways and cause a lower respiratory infection like bronchiolitis and pneumonia. The destruction of the epithelial cells can start a cascade of pro-inflammatory immune responses, capillary leakage, interstitial swelling, inhibited pulmonary surfactant function and

bronchoconstriction leading to severe respiratory symptoms requiring hospital admission and sometimes intensive care for respiratory support (24, 25, 26). Death rates in the Netherlands are however small, see the paragraph on mortality. Recognized complications of an RSV infections are otitis media (27) and bacterial superinfections (28, 29).

2.4 Mild disease and GP consultations for RSV

Mild disease due to RSV is very common, especially in young children. As part of the Wheezing Illnesses Study Leidsche Rijn (WHISTLER), infants were followed in the first year of life in a prospective cohort and tested for respiratory pathogens when having symptoms (30) in a total study period from October 2003-September 2006. A median of 5 episodes of respiratory illness per infant in the first year (range: 1–35 episodes) was reported by the parents. Eleven percent of the tested samples were positive for RSV, the vast majority of these positive detections were in November, December and January. In another prospective birth cohort study in the Netherlands (Houben et al.) between January 2006 and December 2008, 298 healthy term new-borns were followed in the first year of life, of which 42 (14%) developed RSV LRTI and 27 (9%) visited a GP for RSV LRTI (31). In an active surveillance cohort, as part of a larger observational birth cohort of healthy term-born infants, born between July 2017 and March 2020 in five high income European countries (Scotland, England, Spain, Finland, Netherlands), the incidence proportion of infants that had an RSV-associated acute respiratory infection (ARI) episode (using a broader case definition than Houben et al.) in the first year of life was 42% (95% CI 36%-48%) in the 187 infants that were actively followed up in the Netherlands. The incidence proportion of medically attended (both outpatient and hospitalization) RSV-positive ARI was 22% (95% CI 17%-27%) in the Netherlands (32). These estimates were higher than the other four countries (point estimates ranging from 11%-30% for ARI and 7%-14% for medically attended ARI). A regression analysis combining Dutch GP sentinel surveillance data (by Nivel and RIVM) on ILI consultations and the corresponding virology, together with Dutch laboratory confirmations of diagnostic laboratories (Virologische Weekstaten), estimated a seasonal average of 16.345 GP consultations for RSV-attributed influenza-like illness (ILI) in children 0-4 years of age (176/10.000 children) in the period 2004-2014 (33). As many children present to the GP without fever, which is required for the definition of ILI syndrome, this is an underestimation of all GP visits for RSV infection. In infants below one years old that were sampled for ARI for the Dutch GP sentinel surveillance (by Nivel and RIVM), 22-39% of the samples collected in the winter season (week 40- week 20) in the seasons 2017/2018 up to 2021/2022 (excluding 2020/2021) was positive for RSV (3, 34, 35, 36, 37).

2.5 Hospitalization, including intensive care units (ICU) for RSV

Globally, RSV is the major cause of hospitalizations for respiratory tract infections in infants and young children (26). In an international pre-pandemic study, RSV was the most common individual pathogen in children that were hospitalized with pneumonia in study sites in Africa and Asia, in areas where pneumococcal conjugate vaccine was used (38), and was shown to be responsible for 50% to 80% of

hospitalizations for bronchiolitis of children during seasonal epidemics in North-America (39).
Several studies in Europe and the Netherlands have provided further insight in the number of hospital admissions due to RSV. In the previously described WHISTLER study, out of 2133 term healthy new-borns that had a successful lung function measurement, 18 (0.84%) were hospitalized for RSV bronchiolitis in their first year of life (40). In the prospective cohort study of Houben et al., 3/298 (1.0%) healthy term newborns were hospitalized for RSV LRTI (31). A Dutch cohort study as part of the LOLLIPOP cohort, comparing full-term born to preterm born children in 2002 and 2003, the hospitalization for confirmed RSV was 1.2% (7/563) of the full-term born children that were included in the cohort, as reported by the parents at the child age of 43-49 months, and confirmed in medical records (41).
In the above mentioned observational birth cohort of healthy term-born infants, born between July 2017 and March 2020 in five European countries (32), the incidence proportion of RSV-associated hospitalized infants with ARI was 1.47% (1.07-2.03) of all infants up to one year of age in the Netherlands. The observed duration of hospitalisation in the Netherlands was a median of three days (IQR 2-6 days). Despite the fact that infants are (partially) protected by their maternally derived IgG antibodies (see chapter 3), infants are at highest risk for severe disease. The incidence proportion of RSV-associated hospitalization in the Netherlands was at least 3 times higher in the youngest children < 3 months (0.97% (0.65-1.43)) compared to children 3- <6 months (0.26% (0.12-0.57) and further declined at age 6 to <12 months (0.25% (0.11-0.56)), see Table 2.1. When (for all five countries together) comparing age and season of birth, the authors found the highest incidence among <3-month-olds born in autumn (8.53 per 1000 infant-months), followed by 3- to <6-month-olds born in summer (4.24 per 1000 infant-months), and <3-month-olds born in winter (2.03 per 1000 infant-months). In the five European countries that were studied together, eight out of 145 (5.5%) of the hospitalized RSV cases (0.09% of the total cohort of 9154 infants) was admitted to the paediatric intensive care unit (PICU) in the first year of life.
In a register based study in the Netherlands, the number of all RSV admissions were assessed retrospectively over the period of 2013-2017, using ICD-10 codes (42). In this study, where only acute clinical admissions were selected, an average hospitalization rate of 0.97% of children <1 years old was found in this period, see Table 2.2. The number of RSV-coded respiratory tract infection (RTI) admissions was highest in children of 1 month of age. The duration of RSV-RTI admission was median 4 days (IQR 2-6 days) (43). In this study, the admission rates for RSV-RTI were highest in infants that were born in October to December, and lowest in infants born in March and April, see figure 2.2 . Important to note that the entire study period was pre-COVID-19 pandemic (2013-2017), when RSV circulation had a strong seasonal pattern (see paragraph 2.1).

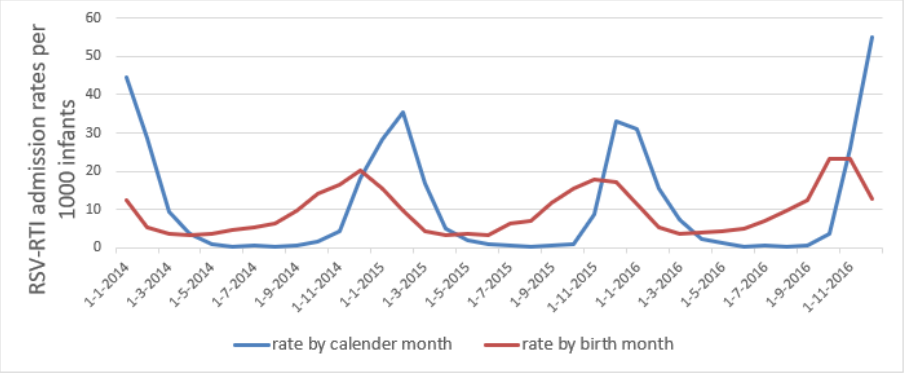

Figure 2.2 Dutch data figure, derived from Wang et al (43), figure 1. Respiratory syncytial virus–associated respiratory tract infection (RSV-RTI) admission rates per 1000 infants <1 year by birth month and calendar month in the Netherlands. The red line displays hospital admission rates of RSV-RTI per 1000 live births by birth month. the blue line displays annualized rates of RSV-RTI per 1000 infants by calendar month.

During the winter season of 2016/2017, RSV was the most often detected pathogen in children that were admitted to Dutch paediatric intensive care units (PICU) with a severe acute respiratory infection; over the winter season, 68% was positive for RSV, with a peak positivity of 80% during the epidemic peak (44). One other study in the Netherlands specifically addressing paediatric intensive care (PICU) hospitalization between 2003 and 2016, found that yearly 13,5 – 48 per 100,000 children <2 years were admitted because of RSV bronchiolitis, with an increasing trend in time and and this increase was mostly driven by increased admissions in children up to 3 months old (45), see also Table 2.3. According to the authors, the increase in PICU disease burden was concurrent with change in clinical management with a significant increase in the use of high flow nasal cannula at the PICU. Importantly, the use of invasive mechanical ventilation, representing the most severe patients, remained stable (45). How these ICU admission numbers continue after 2016 is currently under investigations (BRICK study, personal communication L. Bont and J. van Woensel). BRICK is a prospective national study aiming to define the full burden of RSV infection, including health-economic consequences, at the ICU in the Netherlands.

Table 2.1 RSV-associated hospitalised acute respiratory tract infections (ARI) from prospective cohort study (period July 2017 – April 2020)*

	RSV incidence proportion
<3 months	0.97% (0.65-1.43)
3 - 5 months	0.26% (0.12-0.57)
6 - 11 months	0.25% (0.11-0.56)
cumulative < 12 months	*1.47% (1.07-2.03)*

Source: Wildenbeest et al. (32)
NB. In the introduction paper of this study (46), the authors refer to ARTI (acute respiratory tract infections), but the definition is the same.

Table 2.2 Dutch data (DHD) on RSV coded hospital admissions in period 2013/2014 - 2016/2017

Age group	Average yearly number of RSV coded hospital admissions (min-max)	Per 1000 population (min-max)
<3 months	994 (85-1144)	23.1 (20.8-26.8)
3 - 5 months	384 (347-439)	8.9 (8.1-10.3)
6 - 11 months	299 (232-390)	3.5 (2.7-4.6)
total < 12 months	*1676 (1464-1973)*	*9.7 (8.6-11.5)*
1 - 4 years	242 (208-321)	0.3 (0.3-0.4)

Source: Reeves at al. (42) and RIVM/DHD.

Table 2.3 PICU admission for RSV bronchiolitis in the Netherlands in children <24 months

Year	Number of PICU admissions RSV bronchiolitis	PICU admissions RSV bronchiolitis per 100.000 children
2003	83	13.5
2004	131	21.5
2005	128	21.4
2006	149	25.6
2007	158	28.0
2008	160	29.0
2009	101	18.3
2010	147	26.6
2011	133	24.0
2012	191	34.7
2013	151	27.9
2014	172	32.6
2015	208	39.8
2016	249	48.0

Source: Linssen at al. (45), derived from table 1

2.6 Mortality

In a large part of the world, especially in low-and middle-income countries, RSV is a major cause of infant mortality, both in hospitals and in the community (47, 48). On the contrary, the mortality caused by RSV in high income countries with high quality healthcare, such as the Netherlands, is very low (5, 48). In the Netherlands, severe comorbidity (see risk groups described in paragraph below) is almost always underlying RSV-related infant death. In the 14 years study period (2003-2016) of the above described ICU study (45), 37 children died (1.7%). Of these children, 27 had at least one comorbidity and 11 were born prematurely.

2.7 Medical Risk groups for severe RSV infection in infants

Classical recognized medical risk groups for severe RSV infections and longer hospital stay in Western countries are premature infants (49), individuals with Down syndrome (50, 51), congenital heart disease patients (52), Chronic Lung Disease patients (CLD, formerly called BPD) (53), immunocompromised children (51), Cystic Fibrosis patients (51), and those with other (congenital) chronic diseases (51). However, as the number of infants in these risk groups are relatively small compared to healthy born infants, the majority of the hospitalized infants with RSV is previously healthy. A review on RSV hospitalization in Western countries (defined as US, Canada and Europe) in 2016 concluded that in general, more than 70% of the RSV-related hospitalized infants have no underlying medical condition (5). In the register-based study in Europe, in 1546 out of 1918 (81%) of the RSV admissions in the Netherlands, no risk factor was identified (43). This is an overestimation, because not all risk factors could be identified or were registered. In a large active surveillance study in the US, 33% of the RSV infected hospitalized children had either any underlying comorbidity (21%) or preterm birth (18%). Only a little more than 2% of these children had received palivizumab (see paragraph 4.1). If hospitalized, children with underlying comorbidity or preterm birth were more likely to be admitted to ICU than the children without these conditions (54). A double-blind placebo controlled trial on palivizumab in healthy preterm infants born at a gestational age of 33-35 weeks in hospitals in the Netherlands in 2008-2010 (MAKI trial), found that in the control group (receiving the placebo) 11/215 (5.1%) were hospitalized for RSV infection in their first year of life (compared to 2/214=0.9% in the intervention group) (55). In the Netherlands, out the 2.161 children ≤ 2 years old that were admitted to ICU with a confirmed RSV bronchiolitis in the period of 2003-2016, 57% were male. 40% of the children had a pre-existing comorbidity and/or were born prematurely. 26% of children were born preterm without comorbidity (45). Apart from the anatomy (small airways that are easily plugged) or an already compromised respiratory or cardiac situation, the immune response has a major role in disease severity after RSV infections, not only in defense against the virus and viral clearance, but also by inducing the inflammatory response causing disease exacerbation. Therefore, risk factors affecting the immune system can influence disease progression and severity (56, 57)). Other (medical or non-medical) risk factors that have been reported globally as risk factor for severe RSV disease are low birth weight, male sex,

maternal smoking, history of atopy, presence of siblings, no breastfeeding and large households (58).

In the Netherlands, the preterm birth percentage was 6.9% in 2015, with a decreasing trend in the percentage of preterm birth <37 weeks in singletons in the period 2008-2015 (5.6% to 5.3%) but a slight increase in preterm birth <27 weeks (0.40% to 0.45%). In multiple gestations, the percentage of preterm birth is much higher and had a slight increase over time in preterm birth <37 weeks (50.9% to 52.5%) and a slight decrease in preterm births <32 weeks (9.3% to 8.6%) (59). Although prematurity is a well described risk factor, the effect of gestational age on RSV severity within the premature risk group is less established, because of small study numbers and differential care (e.g. palivizumab use) and environmental factors (49). The Dutch LOLLIPOP cohort-study (see also paragraph 2.5), comparing full-term born (gestational age 38-42 weeks), moderately preterm (gestational age 32-36 weeks), and early preterm (gestational age < 32 weeks), found no difference in hospitalization rates between early term and moderately term born children (41); 3.9% (38/964) and 3.2% (17/524) respectively. Palivizumab had been provided to 56.6% of all early preterms, 2.2% of moderate preterms and to none of the full-terms of the children in this study. When immunized children were excluded, the proportion of hospitalized children was 5.3% and 3.8% and for early preterm and moderate preterm respectively, although not statistically significant different. The hospitalization rates of the early preterm and moderate preterm were statistically significant higher than the full-term born children, even after excluding the immunized children (41). In the active surveillance study in the US in 2015-2016 (54), among children <24 months, the point estimates of the RSV-associated hospitalization gradually decreased with a longer gestational age, but also here groups were too small to be able to compare.

2.8 Debate on asthma as long-term consequences of RSV

One major and impactful point of discussion and uncertainty is whether a *causal* relation exists between lower respiratory illness caused by RSV in early life and recurrent wheeze of early childhood and asthma. Many studies have been performed to address this question, but the evidence remains inconclusive. An important factor complicating this issue is the genetic predisposition that can both affect the development of (more severe) RSV illness, and also recurrent wheeze or asthma (60). In order to get across this issue, the WHO had called for a systematic review and meta-analysis in 2018 (60) and convened an expert meeting in 2019 (61). In the systematic review and meta-analysis, observational exposure studies and immunoprophylaxis studies were evaluated (final search on August 28, 2018). In the meta-analysis of exposure studies adjusting for genetic influences, an adjusted OR estimate of 2.45 (95% CI 1.23–4.88) was found for the direct effect of RSV-LRTI on wheezing illness. The immunoprophylaxis RCT meta-analysis resulted in a non-significant OR of 1.21 (95% CI 0.73–1.99) of *not* receiving immunoprophylaxis on wheezing illness. The authors warn for high risk of bias due to missing outcome data in both studies and conclude that the current evidence does not sufficiently support the assumption that prevention or RSV-LRTI will reduce recurrent chronic wheezing illnesses.

The authors therefore discourage using this assumption for policy decisions. The WHO expert meeting (with overlapping authors from the systematic review) (61), evaluating observational studies, randomized intervention studies and systematic review, also concluded that the current evidence is inconclusive in establishing a causal association between RSV LRTI and recurrent wheeze of early childhood /asthma. They state that the evidence does not establish that RSV mAbs or future vaccines will have a substantial effect on these outcomes and recommend basing policy decisions on the impact against acute illness, with the focus on severe disease. Also more recent publications, such as a large population based prospective birth cohort (62) that provided evidence for an age-dependent and severity dependent association between RSV infection during infancy and 5-year current asthma, can by design not formally establish a causal relationship. The temporality changed epidemiology of RSV due to the corona pandemic might shed more light on this question (63, 64), although many other respiratory viruses that have been associated with wheezing (65) also had an altered circulation during the pandemic, complicating interpretation. Alternatively, intervention studies with RSV-preventive products (antibodies or vaccinations, such as described in this report) might be able to assess such causal relationships. The large sample size needed for proving a potential causal relationship will however complicate deriving an answer by clinical trials of maternal RSV immunization trials (66).

3 Immune responses and serology

3.1 Immune response characteristics of primary RSV infection

Most children get infected with RSV before the age of 2-3 years, based on specific seroconversion rates in population-based cross-sectional seroprevalence studies in the Netherlands (PIENTER) (67). Further analysis of two of these seroprevalence studies that were performed in 2006/2007 and 2016/2017, found infection estimates of 44% after one year and 85% in two years. Age and birthdate are strong predictors of RSV infection in the first years of life, and children born in summer have substantially higher estimated probability of infection than those born in winter; e.g., 0.56 (95% CI 0.45–0.66) vs. 0.32 (0.21–0.45) at age 1 year (68), possibly because around the timing of the usual epidemic peak, their maternal antibodies have substantially waned (67, 68).
Although most children experience a mild respiratory infection, infections early in life as well as infections in premature or immunocompromised children or other high-risk neonates can be associated with severe disease. Hence, for premature neonates under 32 weeks of gestation, immunoprophylaxis is indicated and reimbursed, as well as for newborns with certain specified underlying diseases (see chapter 4).
Although in the first few months of life, infants are to a certain extent protected against infection via the presence of naturally acquired maternally derived IgG antibodies (67), severe lower respiratory tract illness peaks in the first 2-3 months of life (32, 42). This can be explained by the smaller and not yet fully developed airways and immature immune system of these young children (69). The (functional) neutralizing capacity of these antibodies, rather than quantitative antibody levels against RSV, is regarded fundamental for providing immune protection. However, the effectiveness of these antibodies against infection declines rapidly after birth, but it is not exactly known which levels are required for protection (70, 71, 72, 73).
RSV infection results in the induction of neutralizing serum antibodies of the IgG and IgA isotype and of local (secretory) IgA antibodies, both of which are involved in the clearance/resolution of RSV infection and are considered important humoral correlates of immune protection, based on many observational studies in children (74, 75, 76, 77, 78, 79, 80, 81, 82, 83). IgA antibodies are not transferred via the placenta, and detection of RSV-specific IgA antibodies presents a serological hallmark for primary RSV infection, often detected as early as 3-6 months of age (67). Current knowledge on the humoral correlates of protection in RSV is limited and cannot be understood solely by antibody concentrations. In this respect, community-based serological surveys are also limited (67, 84). Notably, in experimental infection studies in healthy adults, high pre-inoculation nasal RSV IgA levels are linked to protection from infection and reduced viral replication (85). Both neutralizing antibodies as well nasal IgA predicted lower infectivity, but neither were fully protective once individuals were infected, implying they act as independent co-correlates of protection against RSV infection (86).
While RSV A and B type infections are accompanied by a group-specific

neutralizing antibody response, both nasal (IgA) as well as systemic (IgG) antibodies directed at the fusion (F) glycoprotein are shown to be cross-protective. Antibodies against the F glycoprotein predominate overall RSV-neutralizing capacity, where in particular antibodies directed against epitopes present on the prefusion conformation of this protein - which is found on infectious virus particles - are important for neutralization. Immune protection after primary RSV infection is not sustained and antibody titers have been found to decrease as early as 8 weeks after infection in older adults (87). Antibody maturation and longevity of antibodies may differ according to age of first infection. Individuals with low antibody levels appear more susceptible to a RSV re-infection, but even individuals with higher antibody levels can be reinfected after which antibody levels are boosted, which occurs frequently throughout life (77). Additionally, neutralizing capacity of antibodies is not long-lasting, not even after natural re-infection (88, 89).

3.2 Immune response characteristics of RSV re-infection, population dynamics

Transmission of RSV happens during seasonal epidemics in the winter months, leading to high rate of infections in susceptible children, which experience a primary infection. Consecutive re-infections occur already within 2-3 years, which are mostly less severe or even subclinical (72, 90, 91). Reinfection triggers a strong boosting of naturally-acquired antibodies after a first infection, leading to better protection against subsequent RSV infection. In adults who were experimentally infected with live RSV, investigators found that while nasal IgA correlates with protection, only IgG (and no IgA) RSV-specific memory B cells were detectable in peripheral blood which contrasted with natural influenza infection. This suggests that IgA memory may be relatively limited, and this might offer a possible explanation for RSV to cause recurrent symptomatic infections (85).
During the COVID-19 pandemic, due to the absence of RSV circulation for more than a year, more newborns without first infection are present as well as the fact that children may have been become susceptible for RSV again due to absent boosting, when enforced social distancing measures due to COVID-19 were released. The noted out-of-season RSV activity might have been caused by declining antibodies in the population during the COVID-19 social distancing measures. Interestingly, all age groups in a prospective nationwide study in the Netherlands showed a decline of anti-RSV post-fusion F antibodies one year in the pandemic (92). Also, a study in Canada showed a reduction of anti-RSV pre-fusion F antibody levels and also anti-RSV antibody function in women and infants, in the period without RSV circulation in the population (89). It is likely that infants were unable to acquire T- and B-cell immunity in the absence of viral exposure and therefore remained susceptible at an older age.

4 Current clinical practice

4.1 Prevention – Palivizumab/Synagis

In august 1999, Synagis (MEDI-493) was approved for marketing in the European Union by the European Medicines Agency (EMA) (93). Synagis contains the RSV-specific monoclonal antibody palivizumab as an active substance and is injected intramuscular in monthly doses during the 5 months of the RSV season (93). For European countries this is generally from November to April (see paragraph on seasonality). Palivizumab was originally developed by MedImmune, and the current marketing-authorization holder is AstraZeneca AB. Palivizumab can be only obtained with a prescription. The EMA has described the target groups for palivizumab, but in practice there are quite some differences between European countries, e.g. on the definition of prematurity and recommendations for risk groups (94). In the Netherlands, palivizumab is used at the recommended dose of 15 mg/kg/dose, and recommended 1 x per 4 weeks, to start before the RSV season (October-March) and continue through the season (95).
The guideline for reimbursement of palivizumab in the Netherlands is as follows (96):

a. Children born with a gestational age of 32 weeks or less, and that were younger than six months at the beginning of the RSV season.
b. Children <1 year of age with bronchopulmonary dysplasia.
c. Children <2 years of age that are in need for oxygen therapy for the treatment of bronchopulmonary dysplasia.
d. Children <2 years of age with a congenital heart disease of hemodynamic significance.
e. Children <1 year of age with severe immunodeficiency.
f. Children <1 year of age with severe lung pathology due to Cystic Fibrosis.

N.B. The Summary of Product Characteristics (SPC) lists a gestational age of 35 weeks or less. Palivizumab is however only reimbursed in children with a gestational age of 32 weeks or less (see *Commissie Farmaceutische Hulp* (CFH) advise of 29 June 2009) (95).
Furthermore, the NVK (Nederlandse Vereniging voor Kindergeneeskunde) recommended in November 2021 to advise subscribing palivizumab for children with Down syndrome, although this is not reimbursed, unless they have congenital heart disease (97).

The efficacy of palivizumab has been studied in clinical trials pre-marketing, where an overall reduction of 55% in hospitalization was found. Efficacy was higher in premature children without CLD/BPD (78% reduction) than in children with CLD/BPD (39% reduction) (98). In infants with congenital heart disease, a reduction in hospitalization of 45% was observed (99). A systematic review in the Cochrane Database of Systematic Reviews in 2021 (100), found five RTCs that compared palivizumab with placebo (among which the above mentioned study) and showed significant effect of palivizumab on hospitalization for RSV

infection (RR 0.44, 95% CI 0.30-0.64, 2 years follow up), and on the number of wheezing days (RR 0.33, 95% CI 0.20-0.55, 12 months follow up) and a non-significant effect on mortality (RR 0.69, 95% CI 0.42-1.15). The real-world effectiveness of palivizumab is more complicated to establish and dependent on the uptake of palivizumab. A review published in 2014 found most evidence for effectiveness in very preterm infants (gestational age until 32 weeks) and children with chronic lung and heart diseases, but with lower effect than reported in the clinical trials (101). Effectiveness for other risk groups is more inconclusive due to limited data. Based on a literature review with data until 2018, an expert group has drafted guidelines for the use of palivizumab for use in developed countries, focusing on very premature and the high-risk groups (102).

4.2 Therapeutics

While many therapeutic and non-therapeutic therapies have been used and trialed (and often disregarded) in the past, the current hospital treatment for RSV infections is mainly supportive (69, 103). Supportive care consists of (intravenous) hydration, oxygenation if needed and airway clearance (103, 104, 105). Current treatments that are still in use without convincing evidence are the use of corticosteroids, beta agonist bronchodilators and the more recently introduced High Flow Nasal Cannula (HFNC).

4.3 Antivirals

Monoclonal antibodies as antiviral drugs are discussed above and in chapter 5. There are hardly any chemical compounds as antiviral drugs available for prevention or treatment of RSV infection (106). The first and only approved antiviral drug is Ribavirin- for treatment of hospitalized infants with RSV bronchiolitis and pneumonia, although it is rarely used for that purpose due to limited evidence of benefit, high costs and potential for toxicity (107, 108). However, Ribavirin is incidentally being used for treatment of RSV-infected immunocompromised patients to prevent progression to lower respiratory tract disease and mortality (109, 110, 111). Targeted development of new antiviral drugs for treatment of RSV infection has provided a number of candidates (112). The emergence of SARS-CoV-2 has stimulated the search for broad-spectrum therapeutics against respiratory viruses, e.g. Thapsigargin and 4’-fluorouridine (4’-FlU, EIDD-2749) that included activity against RSV (112, 113, 114). However, despite these efforts none of these drugs have made it to marketing authorization, yet.

5 Nirsevimab

5.1 Characteristics and mechanism of action

Nirsevimab (MEDI8897) is a recombinant human IgG1 monoclonal antibody for the prevention of RSV disease in infants by passive immunization that has been developed by AstraZeneca/MedImmune and Sanofi. It obtained marketing authorization from EMA in October 2022 under the brand name Beyfortus. Nirsevimab is the result of the in vitro optimization of an RSV-specific antibody (D25) previously identified in a functional screen in human donors (115, 116). Similar to palivizumab (AstraZeneca), the main mechanism of action of nirsevimab is to prevent entry of RSV into host target cells by binding to the viral fusion (F) protein, i.e. virus neutralization. Two important improvements compared to palivizumab are nirsevimab's increased potency for neutralization and extended in vivo half-life.

The RSV F protein is essential for infection by means of mediating the fusion between the viral and target cell membranes which it accomplishes through a conformational change. For this reason, the F protein exists in a metastable prefusion and a highly stable postfusion conformation which have both common and distinct antigenic sites to which antibodies may bind (117). Nirsevimab recognizes antigenic site Ø which is only present on the prefusion conformation of the F protein and is very important for potent neutralization (115). In contrast, palivizumab binds to antigenic site II which is present on both the prefusion and postfusion conformations of the F protein (98). Using in vitro microneutralization assays, nirsevimab was shown to have a 50-fold increased potency against a panel of clinical RSV isolates compared to palivizumab (115).

Due to its relatively short half-life in vivo, palivizumab requires 5 monthly administrations to retain sufficiently high serum concentrations needed for protection throughout a typical RSV season. To enable a reduced dosing scheme, the Fc domain of nirsevimab was engineered to include three amino acid substitutions (M252Y/S254T/T256E or YTE) which led to a prolonged in vivo half-life by increasing binding affinity for the neonatal Fc receptor (115). In the clinical trials described in more detail below, the mean (±SD) half-life of nirsevimab was 59.3±9.6 days in preterm infants (29-35 weeks gestational age) and 68.7±10.9 days in late preterm and term infants (≥35 weeks gestational age), which was found to be sufficient to retain an effective serum concentration throughout a typical RSV season with a single administration (118, 119).

5.2 Summary of clinical trial results

5.2.1 *Efficacy*

To assess the efficacy of nirsevimab in healthy infants, two randomized double-blind placebo-controlled clinical trials were performed in 2016/2018 at 164 sites in 23 countries* and 2019/2022 at 211 sites in

* Northern hemisphere: Belgium, Bulgaria, Canada, Czech Republic, Estonia, Finland, France, Hungary, Italy, Latvia, Lithuania, Poland, Spain, Sweden, Turkey, United Kingdom, United States; Southern hemisphere: Argentina, Australia, Brazil, Chile, New Zealand, South Africa.

31 countries** (118, 119, 120). The primary efficacy endpoint in both studies was medically attended RSV-associated lower respiratory tract infection through 150 days post administration and the secondary efficacy endpoint was hospitalization due to the same condition during the same period. A summary of the efficacy results can be found in Table 5.1.

** Northern hemisphere: Austria, Belgium, Bulgaria, Canada, Czech Republic, Estonia, Finland, France, Germany, Israel, Italy, Japan, Republic of Korea, Latvia, Lithuania, Mexico, Panama, Poland, Russian Federation, Spain, Sweden, Turkey, Ukraine, United Kingdom, United States; Southern hemisphere: Argentina, Australia, Chile, Colombia, New Zealand, South Africa.

Table 5.1 Overview of nirsevimab efficacy in different clinical trials.

Study	Sponsor	Population and trial period	Dose	Study size	Nirsevimab n (%)	Placebo n (%)	Efficacy (95% CI)	P value	Ref
NCT02878330 Full enrollment	MedImmune/ AstraZeneca	29-35W GA, healthy preterm infants 2016-2018	50 mg	1453	969	484			(118)
Primary endpoint	Medically attended RSV-associated lower respiratory tract infection through 150 days p.a.				25 (2.6)	46 (9.5)	70.1% (52.3-81.2)	<0.001	
Secondary endpoint	Hospitalization due to RSV-associated lower respiratory tract infection through 150 days p.a.				8 (0.8)	20 (4.1)	78.4% (51.9-90.3)	<0.001	
NCT03979313 Primary analysis	AstraZeneca	≥35W GA, healthy late preterm and term infants 2019-2020	50/100 mg	1490	994	496			(119)
Primary endpoint	Medically attended RSV-associated lower respiratory tract infection through 150 days p.a.				12 (1.2)	25 (5.0)	74.5% (49.6-87.1)	<0.001	
Secondary endpoint	Hospitalization due to RSV-associated lower respiratory tract infection through 150 days p.a.				6 (0.6)	8 (1.6)	62.1% (-8.6-86.8)	0.07	
NCT02878330 NCT03979313 Pooled analysis	MedImmune/ AstraZeneca	>29W GA, healthy preterm and term infants 2016-2020	50/100 mg	2350	1564	786			(121)
Primary endpoint	Medically attended RSV-associated lower respiratory tract infection through 150 days p.a.				19 (1.2)	51 (6.5)	79.5% (65.9-87.7)	<0.0001	
Secondary endpoint	Hospitalization due to RSV-associated lower respiratory tract infection through 150 days p.a.				9 (0.6)	21 (2.7)	77.3% (50.3-89.7)	0.0002	
NCT03979313 Full enrollment	AstraZeneca	≥35W GA, healthy late preterm and term infants 2019-2022	50/100 mg	3012	2009	1003			(120)
Primary endpoint	Medically attended RSV-associated lower respiratory tract infection through 150 days p.a.				24 (1.2)	54 (5.4)	76.4% (62.3-85.2)	n.r.	
Secondary endpoint	Hospitalization due to RSV-associated lower respiratory tract infection through 150 days p.a.				9 (0.4)	20 (2.0)	76.8% (49.4-89.4)	n.r.	

Abbreviations: p.a., post administration; n.r., not reported.

The first study was a phase 2B clinical trial in which healthy preterm infants (29-35 weeks gestational age) under 1 year of age and entering their first RSV season were randomly assigned to receive a single 50 mg intramuscular dose of nirsevimab or 0.9% (w/v) saline placebo (NCT02878330, MedImmune, 2016-2018). This trial included a total of 1453 participants (969 in the nirsevimab group and 484 in the placebo group) and was conducted at 164 sites in 23 countries (118). In this cohort, nirsevimab was found to have an efficacy of 70.1% (95% CI 52.3 to 81.2, P value <0.001) against medically attended RSV-associated lower respiratory tract infection through 150 days post administration and 78.4% (95% CI 51.9 to 90.3, P value <0.001) against hospitalization for the same condition during the same period (118).

The second study was a phase 3 clinical trial in which healthy infants born at term or late preterm (>35 weeks gestational age) under 1 year of age and entering their first RSV season were randomly assigned to receive either nirsevimab or 0.9% (w/v) saline placebo (MELODY, NCT03979313, AstraZeneca, 2019-2023). Since the results of the phase 2B study suggested that a dosage of 50 mg was inadequate for infants weighing more than 5 kg, the dosing for the phase 3 trial was adapted to a weight-banded regimen in which children weighing <5 kg received a dose of 50 mg and children weighing ≥5 kg received a dose of 100 mg (119). The primary cohort of this study - which was used for the published primary analysis - included a total of 1490 participants (987 in the nirsevimab group and 491 in the placebo group) from 150 sites in 20 countries in the Northern hemisphere and 10 sites in 1 country (South Africa) in the Southern hemisphere. Notably, the 462 participants from South Africa contributed no events to the primary efficacy estimate due to reduced circulation of RSV during the COVID-19 pandemic. In this primary cohort, nirsevimab was found to have an efficacy of 74.5% (95% CI 49.6 to 87.1, P value <0.001) against medically attended RSV-associated lower respiratory tract infection through 150 days post administration and 62.1% (95% CI -8.6 to 86.8, P value 0.07) against hospitalization for the same condition during the same period (119).

Upon completion of full enrollment for the phase 3 study, efficacy analysis of the full cohort consisting of 3012 participants (2009 in the nirsevimab and 1003 in the placebo group) from 211 sites in 31 countries was performed (120). In this cohort, nirsevimab was found to have an efficacy of 76.4% (95% CI 62.3 to 85.2) against medically attended RSV-associated lower respiratory tract infection through 150 days post administration and 76.8% (95% CI 49.4 to 89.4) against hospitalization for the same condition during the same period. These results are largely in line with the primary analysis, with a higher efficacy estimate against hospitalization in the complete analysis.

To further assess the efficacy of nirsevimab, a pooled analysis of the phase 2B and primary cohort of the phase 3 trials was additionally performed, from which those children from the phase 2B trial that weighed ≥5 kg were excluded because the 50 mg dose they had received was deemed insufficient after evaluating the trial results (121). The pooled analysis included a total of 2350 participants (1564 in the

nirsevimab group and 786 in the placebo group) consisting of healthy infants with a gestational age >29 weeks. In this pooled analysis of the weight-banded dose regimen, nirsevimab was found to have an efficacy of 79.5% (95% CI 65.9 to 87.7, P value <0.0001) against medically attended RSV-associated lower respiratory tract infection through 150 days post administration and 77.3% (95% CI 50.3 to 89.7, P value 0.0002) against hospitalization for the same condition during the same period (121).

Of note, a phase 3B randomized open-label study to assess the efficacy and safety of nirsevimab with an estimated enrollment of 22000 participants (gestational age ≥29 weeks) and estimated primary completion date in 2023 is currently ongoing in France, Germany, and the UK (HARMONIE, NCT05437510, Sanofi/AstraZeneca). To date, no published data are available for this study.

Drug-resistant virus variants
For a monoclonal antibody against RSV to be effective it is important that it has neutralizing activity against both RSV A and B strains. Importantly, another monoclonal antibody (suptavumab) failed to meet its primary efficacy endpoint in a phase 3 trial due to its inability to neutralize a newly circulating RSV B strain (122). Based on *in vitro* evidence, nirsevimab is able to neutralize a broad range of both RSV A and B clinical isolates (115). During the phase 2B trial however, two RSV B clinical isolates with reduced nirsevimab susceptibility were identified in nirsevimab recipients with breakthrough infections (118). The primary analysis of the MELODY trial reported that no clinical isolates with reduced susceptibility to nirsevimab were identified (119). An analysis of fusion protein sequences from viruses circulating between 2015 and 2021 showed that nirsevimab-resistant variants occurred mainly in RSV B strains but were generally rare (123). It is currently unknown what the impact of widespread nirsevimab use on the emergence of escape variants and their onward transmission will be and ongoing surveillance will be essential to monitor RSV evolution over time.

Antidrug antibodies
Administration of non-self, recombinant monoclonal antibodies such as nirsevimab might lead to the induction of endogenous antibodies that can specifically bind the administered monoclonal antibodies. These so-called antidrug antibodies (ADA) potentially interfere with the functionality of the administered monoclonal antibodies by steric hindrance or by facilitating clearance. In addition, the presence of ADA might result in inflammatory reactions. In the nirsevimab phase 2B trial, postbaseline ADA was detected in 5.6% of nirsevimab recipients and 3.8% of placebo recipients (118). In the nirsevimab phase 3 trial, 6.1% of nirsevimab recipients and 1.1% of placebo recipients had detectable postbaseline ADA (119). Although ADA did not appear to affect nirsevimab pharmacokinetics up until 151 days post administration, on day 361 post administration serum nirsevimab concentrations were found to be lower in those participants that were positive for ADA than in those who tested negative (119). The MEDLEY trial (NCT03959488, AstraZeneca) might provide information on the effect of ADA on

repeated administration of nirsevimab to high risk infants, but no published data are available yet.

5.2.2 *Safety*

Nirsevimab was shown to have an acceptable safety profile in phase 1B/2A, phase 2B, and phase 3 clinical trials in healthy (preterm) infants (118, 119, 120, 124). Similar types and frequencies of adverse events were observed in the nirsevimab and placebo groups and no anaphylaxis or other notable hypersensitivity reactions were reported. In the analysis of the phase 2B trial and the primary cohort of the phase 3 trial, no difference in the safety profile was observed between participants with and without ADA, although no data was presented to support this claim (119). In the primary analysis of the phase 3 trial a single adverse event of special interest was reported: one nirsevimab recipient had a grade 3 generalized macular rash without any systemic features 6 days after administration which resolved after 20 days without treatment and was considered related to nirsevimab by the investigator (119). Adding to the primary analysis, full enrollment for the phase 3 trial encompassed an additional cohort of 1500 infants (120). Also in the full cohort, similar types and frequencies of adverse events were observed between nirsevimab and placebo recipients, for a selection see Table 5.2. To date, safety monitoring for nirsevimab was reported up to 360 days post administration, no published data is therefore available on potential adverse events during the second RSV season post administration.

The MEDLEY trial (NCT03959488, AstraZeneca) involves two cohorts (preterm infants and infants with specific comorbidities) eligible for palivizumab treatment that are administered nirsevimab in two consecutive RSV seasons (125). In this study, nirsevimab was shown after primary analysis up to one year post administration to have a similar safety profile to palivizumab in healthy preterm infants and infants with congenital heart disease (CHD) or chronic lung disease (CLD) of prematurity (125). This study enrolled 310 participants in the CHD-CLD cohort (208 in the nirsevimab group and 98 in the palivizumab group) and 615 participants in the preterm cohort (406 in the nirsevimab group and 206 in the palivizumab group).

A concern related to the prevention of respiratory infections is that another pathogen (either a nirsevimab-resistant RSV strain or another virus) will fill the vacated niche. The results of the pooled analysis of the phase 2B and phase 3 studies showed an efficacy of 34.5% (95% CI 21.5 to 46.9, P value <0.0001) for nirsevimab against medically attended lower respiratory tract infections of any cause compared to placebo (121). The results of the analysis upon full enrollment of the phase 3 trial showed an efficacy of 38.9% (95% CI 6.3 to 60.2%) against hospitalization for all-cause lower respiratory tract infection (120). These findings do not preclude the replacement of RSV by another pathogen, but they do suggest that the benefit of RSV prevention outweighs the potential for pathogen replacement in the first months of life. Notably, these studies were partly performed during the COVID-19 pandemic, in which non-pharmaceutical interventions resulted in altered circulation patterns for a variety of respiratory pathogens.

Finally, the possibility has been raised that nirsevimab administration will affect the subsequent development of natural immunity against RSV in infants (115). The presence of a monoclonal antibody targeting a single epitope might influence this process differently than the presence of polyclonal maternal antibodies. As there are currently no examples of widespread use of monoclonal antibody prophylaxis in infants, it is unknown whether this would actually be a problem. A recent serologic analysis of the nirsevimab phase 2B and phase 3 MELODY trials shows that, at 361 days post administration, RSV postfusion F-specific antibody levels (representing naturally acquired antibodies to RSV) are slightly lower in nirsevimab recipients compared to controls (126).

Table 5.2 Occurrence of adverse events during nirsevimab phase 3 clinical trial.

Events, n (%)	**Placebo (n=996)**	**Nirsevimab (n=1998)**
≥1 AE	815 (81.8)	1673 (83.7)
≥1 Treatment-related AE	15 (1.5)	25 (1.3)
≥1 AE ≥Grade 3 severity	38 (3.8)	61 (3.1)
Deaths	0 (0.0)	4 (0.2)[#]
≥1 SAE	74 (7.4)	125 (6.3)
Pyrexia (grade 1)	90 (9.0)	223 (11.2)
Pyrexia (grade 2)	12 (1.2)	24 (1.2)

[#]All four deaths were assessed by the investigator as being unrelated to treatment.
Abbreviations: AE, adverse event; SAE, serious adverse event.
Source: Muller et al. 2023, NEJM, (120) Tables S6 and S7. For a complete overview of adverse events refer to source.

5.3 Other monoclonal antibodies in clinical development

Since the marketing approval of palivizumab for the prevention of RSV disease, several RSV-specific monoclonal antibodies - all targeting the F protein - have been developed in an attempt to provide enhanced and/or more durable protection. Of these, motavizumab (MedImmune/AstraZeneca) did not succeed in obtaining US food and drug administration approval due to concerns of increased hypersensitivity reactions compared to palivizumab (127). As mentioned above, the monoclonal antibody suptavumab (Regeneron) failed to meet its primary efficacy endpoint in a phase 3 trial due to its inability to neutralize a newly circulating RSV B strain (122). Development of both motavizumab and suptavumab has been discontinued. Currently, a phase 2B/3 clinical trial with an expected primary completion date in 2024 (NCT04767373, Merck) is assessing the safety and efficacy of clesrovimab (MK-1654) in infants. This human monoclonal antibody recognizes the highly conserved antigenic site IV which is present on both the prefusion and postfusion conformations of the F protein and to date only phase 1 data in adults have been published (128).

6 Maternal vaccination against RSV disease in infants

In addition to monoclonal antibodies, several other immunization strategies are currently in (late-stage) clinical development, an up-to-date overview of which can be accessed via www.path.org/resources/rsv-vaccine-and-mab-snapshot/. Furthermore, a recent complete overview is provided by Mazur et al. (129).

One alternative strategy for the prevention of RSV disease in infants is maternal vaccination, whereby antibodies produced by the mother are transferred to the unborn child via the placenta (130). Several years ago, maternal vaccination with an RSV F protein nanoparticle vaccine was assessed in a phase 3 clinical trial (NCT02624947, Novavax, 2015-2018) including 4527 infants (2980 in the vaccine and 1547 in the placebo group) (131). This vaccine was shown to have an efficacy against hospitalization for RSV-associated lower respiratory tract infection up to 150 days after birth of 41.7% (95% CI 19.0 to 58.0%), see Table 6.1. Its efficacy against medically significant RSV lower respiratory tract infection was even lower. Therefore, the vaccine did not meet its pre-specified success criterion for efficacy and development was discontinued.

Following recent structural insights into neutralizing epitopes for the RSV F protein, vaccine development has shifted focus to the use of F protein in the prefusion conformation as an antigen (117, 132). A phase 2B trial in pregnant women (NCT04032093, Pfizer) with a subunit vaccine containing prefusion F (RSVpreF) of both RSV A and B showed immunogenicity and transplacental transfer of antibodies without evident safety concerns (133, 134). Another phase 2B trial in nonpregnant women (NCT04071158, Pfizer) showed that co-administration of the RSVpreF vaccine with a tetanus, diphteria, and acellular pertussis (Tdap) vaccine was safe but resulted in inferior antibody responses to pertussis components but not RSV compared to vaccination with Tdap or RSVpreF alone (135). A subsequent phase 3 randomized placebo-controlled trial (MATISSE, NCT04424316, Pfizer, 2020-2022) assessed the safety and efficacy of this subunit vaccine in 6975 infants (3495 in the vaccine and 3480 in the placebo group) in 18 countries, including 194 (2.6%) maternal participants from the Netherlands (136). An interim analysis showed an efficacy against medically attended RSV-associated lower respiratory tract infection through 150 days after birth of 52.5% (97.58% CI 28.7-68.9%) and against medically attended severe RSV-associated lower respiratory tract infection through 150 days after birth of 70.9% (97.58% CI 44.5-85.9%), see Table 6.1. Since one of the two pre-specified success criteria for efficacy was met with these results (i.e. a lower bound of the confidence interval >20% for all timepoints assessed), the data monitoring committee recommended to stop the trial for efficacy. Pfizer has filed for marketing approval and a decision is expected in the second half of 2023. As the MATISSE study was not powered to assess efficacy in infants that were born preterm, there is currently no published data available on the efficacy of the Pfizer maternal vaccine for this subgroup. It is to be expected, however, that efficacy in preterm infants will be

lower than in term infants as less time was available for transfer of maternal antibodies to the unborn child (137). For this reason, preterm infants will likely require monoclonal antibody therapy for optimal protection from RSV disease even when born from vaccinated mothers (see chapter 7).

In contrast, several phase 3 studies (NCT04605159, NCT04980391, NCT05229068, all GSK) assessing maternal vaccination with an unadjuvanted RSV prefusion F protein subunit vaccine (RSVpreF3) were recently stopped due to safety concerns as an imbalance in preterm births and neonatal deaths was observed between the vaccinated arm as compared to the placebo arm (Table 6.2) (138, 139). GSK considers the imbalance in neonatal deaths to be a consequence of the imbalance in preterm births (139). The imbalance was more associated with low- and middle-income countries (RR: 1.57, 95% CI 1.17–2.10) than high-income countries (RR: 1.04, 95%CI 0.68–1.58) (139). The mechanism(s) underlying this imbalance remain unclear and development of this candidate for maternal vaccination has been discontinued. In response to the GSK trial results, concerns were raised by some scientists regarding a potential imbalance in preterm births between the vaccine and placebo arms in the Pfizer phase 3 MATISSE study as well (Table 6.3) (136, 138).

Table 6.1 Overview of maternal vaccination efficacy in phase 3 clinical trials.

Study	**Sponsor**	**Population and trial period**	**Vaccine**	**Study size**	**Vaccine n (%)**	**Placebo n (%)**	**Efficacy**	**P value**	**Ref**
NCT02624947 Full enrollment	Novavax	Pregnant women and their children 2015-2018	RSV F protein nanoparticle, 120 µg, adjuvanted	4527	2980	1547	**(95% CI)**		(131)
Secondary endpoint	RSV-associated medically significant lower respiratory tract infection up to 150 days p.p.				68 (2.3)	45 (2.9)	21.6 (-13.8-45.9)	n.r.	
Secondary endpoint	Hospitalization for RSV-associated lower respiratory tract infection up to 150 days p.p.				73 (2.4)	65 (4.2)	41.7 (19.0-58.0)	n.r.	
NCT04424316 Interim analysis	Pfizer	Pregnant women and their children 2020-2022	RSVpreF A/B subunit vaccine, 120 µg, non-adjuvanted	6975	3495	3480	**(97.58% CI)**		(136)
Primary endpoint	Medically attended RSV-associated lower respiratory tract infection through 150 days p.p.				47 (1.3)	99 (2.8)	52.5 (28.7-68.9)	n.r.	
Primary endpoint	Medically attended severe RSV-associated lower respiratory tract infection through 150 days p.p.				16 (0.5)	55 (1.6)	70.9 (44.5-85.9)	n.r.	

Abbreviations: p.p., postpartum; n.r., not reported.
Of note, the 150 days after birth efficacy endpoints are shown to allow for better comparison with the nirsevimab results.

Table 6.2 Occurrence of preterm births and neonatal deaths in GSK phase 3 maternal vaccination clinical trial (NCT04605159).

	Vaccine, n (%)	**Placebo, n (%)**	**Relative Risk (95% CI)**
Birth <37 weeks gestational age	238/3496 (6.8)	86/1739 (5.0)	1.38 (1.08-1.75)
Neonatal deaths	13/3496 (0.37)	3/1739 (0.17)	2.16 (0.62-7.55)

Source: GSK, RSVPreF3 OA sponsor briefing document, Vaccines and related biological products advisory committee (139)

Table 6.3 Occurrence of preterm births in Pfizer phase 3 maternal vaccination clinical trial (NCT04424316).

Gestational age	**Vaccine, n (%)**	**Placebo, n (%)**
24 to <34 weeks	21/3568 (0.6)	12/3558 (0.3)
24 to <37 weeks	201/3568 (5.6)	169/3558 (4.7)
≥37 weeks	3364/3568 (94.3)	3386/3558 (95.2)

Source: Kampmann et al., 2023, NEJM (136)

7 Potential scenarios for the prevention of severe RSV disease

7.1 Considerations for the prevention of RSV disease in the Netherlands

With the market approval of nirsevimab and possibly also of the first maternal vaccine in the foreseeable future, various scenarios can be envisioned for the prevention of RSV disease in infants in the Netherlands. The choice for a particular scenario (involving monoclonal antibody prophylaxis, maternal vaccination, or a combination of both) will depend on many factors including - but not limited to - efficacy, safety, cost-effectiveness, practicalities of implementation, and expected acceptance. Also, the direct effect of immunization on shifting the age of first infection, and the potential indirect effect of immunization of infants on the circulation of RSV in other age groups are points of consideration (140). Notably, the seasonality of RSV circulation in combination with the passive (waning) nature of immunization via monoclonal antibodies as well as maternal vaccination, necessitate careful thought on the timing of administration. The efficacy of maternal vaccination likely strongly depends on the timing of birth relative to vaccination (e.g. lower antibody levels are expected in preterm infants than in term infants) and the RSV season (e.g. infants born several months before the RSV season will likely benefit less from maternal vaccination than those born during the RSV season). In this respect, the timing of administration of a monoclonal antibody could be more straightforward, either directly at birth for those infants born during the RSV season or at a scheduled visit directly preceding the RSV season. Depending on whether the seasonality of RSV will change again at a certain point in the future due to (unexpected) circumstances (as happened during the COVID-19 pandemic), the timing of the administration of a monoclonal antibody could be adjusted to the timing of the RSV season. The choice for a particular scenario might determine which healthcare provider(s) will be responsible for administration and involved in providing information to (expecting) parents. An extensive overview of various considerations for the implementation of preventative measures against RSV disease is provided by Esposito et al. (141).

7.2 Potential scenarios for the prevention of RSV disease in the Netherlands

Examples of potential scenarios, including scenarios combining monoclonals and vaccination are:

1. A novel **monoclonal** antibody replaces palivizumab to protect high-risk infants only. The antibody is only administered at the beginning or during the RSV season and there is no program for the broader infant population. Depending on the date of birth, administration could be performed directly after birth (during the RSV season) or at a scheduled visit at an older age (directly preceding the RSV season, i.e., catch-up campaign)
2. A novel **monoclonal** antibody is offered to medical high-risk infants (as above) and all infants that are at higher risk for severe disease based on their birth months (see paragraph 2.5).

Depending on the date of birth, administration could be performed directly after birth (during the RSV season) or at a scheduled visit at an older age (directly preceding the RSV season, i.e., catch-up campaign)

3. A novel **monoclonal** antibody is offered to all infants up to a specific - to be further considered - age. Depending on the date of birth, administration could be performed directly after birth (during the RSV season) or at a scheduled visit at an older age (directly preceding the RSV season, i.e., catch-up campaign).
4. Maternal **vaccination** is offered to pregnant women year-round. High risk infants are offered the novel **monoclonal** antibody, as described in scenario 1, as the levels of transferred vaccine-induced antibodies are expected to be low. This scenario can be enhanced with additional options, e.g.:
    a. Newborns that were born several months before the start of the RSV season are also offered **monoclonal** antibody prophylaxis (preceding the RSV season) as their maternal antibodies might have substantially waned.
    b. Newborns that were born from mothers that declined maternal vaccination are offered novel **monoclonal** antibody prophylaxis (preceding or during the RSV season) as they did not receive vaccine-induced maternal antibodies.
5. Maternal **vaccination** is offered to pregnant women only when their expected delivery date is shortly preceding or during the RSV season. High risk infants are offered the novel **monoclonal** antibody, as described in scenario 1, as the levels of transferred vaccine-induced antibodies are expected to be low. This scenario can be enhanced with additional options, e.g.:
    a. Newborns that were born from mothers that were not offered maternal vaccination because of their expected delivery date are offered novel **monoclonal** antibody prophylaxis (preceding the RSV season) as they did not receive vaccine-induced maternal antibodies.
    b. Newborns that were born from mothers that declined maternal vaccination are offered novel **monoclonal** antibody prophylaxis (preceding or during the RSV season) as they did not receive vaccine-induced maternal antibodies.

N.B. In the following chapter on cost-effectiveness of RSV immunization, literature is described in which the following scenarios are considered:

1. seasonal administration of nirsevimab at birth for all infants born in October – April. (*this is a variant to scenario 2 above*)
2. year-round administration of nirsevimab at birth for all infants. (*not mentioned in scenarios above*)
3. seasonal administration of nirsevimab (option 1) plus a catch-up in October for cohorts born in May – September. (*this is a variant to scenario 3 above*)
4. Year-round administration of maternal vaccination. (*this is scenario 4 above, in the analysis high risk groups were not considered but assumed to follow the current protocol*)

7.3 Surveillance platforms to monitor RSV

When implementing RSV immunization strategies, it is important that surveillance systems are in place to monitor the seasonality of RSV, measure incidences and burden of RSV (both as baseline and after intervention(s)), to monitor potential virological changes, and to monitor impact of novel monoclonal antibody/vaccination and vaccine effectiveness (VE) (142, 143). In the Netherlands, surveillance of RSV is part of the respiratory sentinel surveillance by Nivel and RIVM, and RSV detections are reported by the virological laboratory surveillance (by NWKV and RIVM). At this moment, since the summer of 2021, RSV-bronchiolitis hospitalization of children <2 years is weekly assessed a part of a study by UMCU/WKZ (3). These current surveillance systems can well monitor seasonality and the sentinel surveillance is additionally important to monitor virological changes because swabs are taken from patients and further analysed. For establishing the burden or RSV and impact of immunization on severe cases, a sustainable surveillance to hospitalizations for several acute respiratory infections, including a strong virological component, is crucial. Furthermore, as the immunization strategies target the very young (and in the future probably also the older) age groups, focusing on these specific age groups and reporting age groups in more detail (e.g. 0-5 months, 6-11 months, 1-2 years, etc.) than currently is done for influenza is important (142, 143). In order to directly assess the vaccine/immunization effectiveness, the registration of the immunization status of the patients should be incorporated in the existing, or potential new developed surveillance platform (144) for respiratory infections. A national vaccination register (including, if applicable, both monoclonal antibody prophylaxis and vaccinations) would be crucial for appropriately monitoring vaccination/immunization effectiveness. The ECDC and WHO are also working on enhancing RSV surveillance, mostly as part of an integrated respiratory surveillance format, where RSV is one of the primary viruses of interest, in addition to influenza and SARS-CoV-2 (145, 146). Finally, the post-marketing monitoring of potential safety issues and side-effects of the monoclonal antibodies and vaccines, performed by Netherlands pharmacovigilance centre Lareb, is an essential part of the surveillance.

8 Cost effectiveness of RSV immunization

8.1 Nirsevimab

Few studies have been published on the cost-effectiveness of the nirsevimab so far. One study by Getaneh et al. (147) evaluated the cost-effectiveness of nirsevimab in infants for six different European countries, including the Netherlands. They used a static cohort model to follow 179 thousand Dutch infants from birth till 5 years of age in monthly cycles. The infants were stratified by month of birth, as the incidence of RSV hospitalizations varies with age in months and by month of the year (seasonality). No distinction between risk groups was made. The reference scenario of no RSV immunization was compared with the three following programs:

1) seasonal administration at birth for all infants born in October – April
2) year-round administration at birth for all infants
3) seasonal administration (option 1) plus a catch-up in October for cohorts born in May – September.

Infants were assumed to be born on the first day of the month and nirsevimab to be given on the day of birth. The analysis considered only averted medically attended (GP visit or hospitalization) cases. Non-medically attended cases were not included, and RSV mortality (rare and primarily in very high-risk groups) or the development of wheezing and asthma following RSV (no consensus on causal relationship, see paragraph 2.8). The model did also not incorporate secondary bacterial infections following RSV infection. The most important input values are given in Table 8.1. The incidence of RSV cases by calendar month in the Netherlands was based on a time-series analysis of hospitalizations attributed to RSV over the seasons 2013/14-2016/17 using virology data (148). In a sensitivity analysis, RSV-related hospitalizations rates based on ICD-10 codes were explored, being approximately 50% lower than the estimates of the time-series analysis. Vaccine-efficacy was derived from the randomized clinical trial, which had 5 months of follow up (119). In absence of a list price from the manufacturer, nirsevimab was assumed to cost €50 per dose. Administration costs at birth were €14, assuming that it could be implemented in a routine visit, and administration costs of a catch-up were assumed at €30 (separate appointment). Costs and health effects of adverse events were not included. The analysis was conducted from a healthcare payer's perspective and from the societal perspective (with and without the valuation of leisure time lost).

Table 8.1 Main input parameters of the cost-effectiveness analysis of nirsevimab in the Netherlands as estimated by Getaneh et al. (149)

Parameter	RSV hospitalization	RSV GP visit
Burden of disease		
Incidence (per 1000 persons per year):	0-2mo: 42.4; 3-5mo: 16.8; 6-11mo: 6.7; 12-23mo: 1.30; 23-59mo: 0	0-5mo: 5 GP visits per hospitalization; 6-59mo: 12.5 GP visits per hospitalization
QALY loss per hospitalization	0.01023*	0.00625*
Costs per hospitalization	€3,107 - €4,131**	€36
Intervention		
Vaccine efficacy	62.3%	74.5%
Duration of protection	5 months	
Immunization uptake	90%	
Nirsevimab cost per dose	€50 (assumption)	
Administration costs	€14 (assumed to be implemented in a regular visit)	

*equivalent to a loss of 3.7 days (hospitalization) and 2.3 days (GP visit) in perfect health.
** depending on age

The main results are shown in Table 8.2. Without immunization, RSV was estimated to cause 3,625 hospitalizations and 25,886 GP visits in children aged 0-59 months, resulting in a loss of 176 QALYs and in €15.2 million on treatment costs. Seasonal administration of nirsevimab to infants born in October – April would cost €5.9 million euros and would reduce the number of GP visits by 22% and the number of hospitalizations by 32%, saving 40 QALYs and €5.1 million on treatment costs. Seasonal administration of nirsevimab with a catch-up in October for children born outside the RSV season would avert a substantially higher burden of RSV disease than year-round administration at birth. The intervention costs of seasonal administration plus a catch-up in October would be €11.2 million, averting 42% of the hospitalizations and 39% of the GP visits compared to no immunization, and saving 69 QALYs and €6.6 million on treatment costs. The reason why seasonal immunization at birth plus a catch-up in October had a higher impact than year-round immunization at birth is because of the limited duration of protection of 5 months duration as assumed in the model. Consequently, children born in late spring and early summer who are immunized at birth are not protected anymore during (part of) the regular RSV season.

Table 8.2 Clinical and economic outcomes of the cost-effectiveness analysis of nirsevimab in the Netherlands as estimated by Getaneh et al. (149)

		Difference compared to no RSV immunization		
Outcome	No RSV immunization	Seasonal administration	Year-round administration	Seasonal + catch-up
GP visits	25,886	-5,663	-6,309	-10,091
Hospitalizations	3,625	-1,146	-1,298	-1,536
QALYs lost	176	-40	-45	-69
Treatment costs (€, thousands)	15,195	-5,094	-5,682	-6,617
Intervention costs (€, thousands)	0	5,942	10,186	11,243
Net costs (€, thousands)		848	4,504	4,626

The cost-effectiveness of nirsevimab from the healthcare payer's perspective is shown in Figure 8.1. The incremental cost-effectiveness ratio (ICER) of seasonal immunization with nirsevimab was estimated at €21,200/QALY gained compared to no immunization. Seasonal immunization plus a catch-up dominated all-year round immunization (extended dominance: higher QALY gain against a lower ICER) and had an ICER of €130,300 per QALY gained compared to seasonal immunization.
Sensitivity analyses pointed out that the ICER of seasonal immunization would decrease from €21.200/QALY gained to the range of €10,000-€20,000/QALY gained if productivity losses would be included (societal perspective small) and would become cost-saving if also the loss of leisure time was valued (societal perspective broad). The inclusion of RSV-related mortality would decrease the ICER from €21.200/QALY gained to a range of €10,000-€20,000/QALY gained, and the inclusion of the impact on wheezing and asthma to a range of €0-€10,000/QALY gained (referring to (150) and (151). When RSV-related hospitalization rates based on ICD-10 codes were used, the ICER of seasonal immunization would increase from €21.200/QALY gained to higher than €100,000/QALY gained.

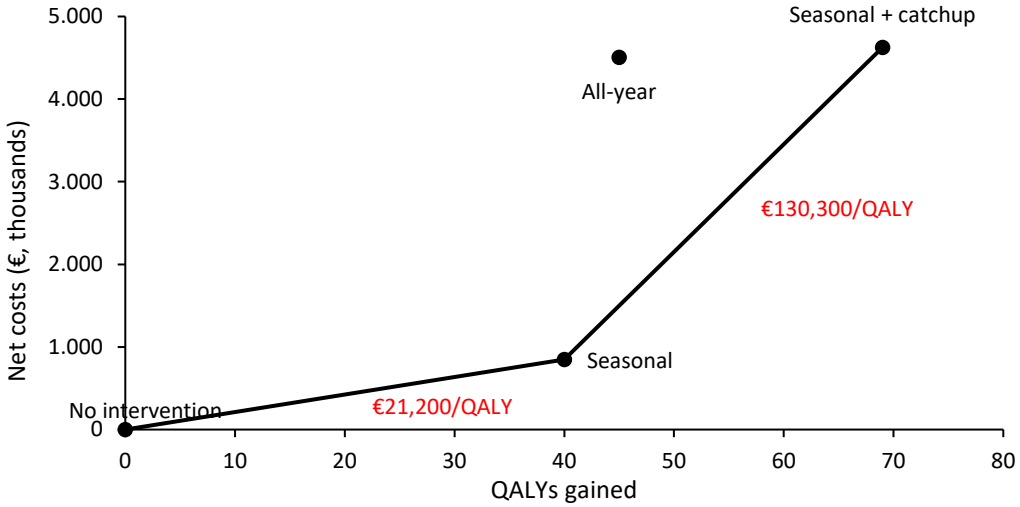

Figure 8.1 Cost-effectiveness of different RSV immunization programs in the Netherlands as estimated by Getaneh et al. from the healthcare payer's perspective

An important limitation of the study by Getaneh et al. is that they assessed the cost-effectiveness of nirsevimab for all infants born in the season October – April jointly, while the cost-effectiveness of nirsevimab could also differ by monthly birth cohort within this season. This is illustrated by a cost-effectiveness study of nirsevimab for Norwegian infants by Li et al. (152). This study used the same cohort model and methodological assumptions as Getaneh et al. used for the Netherlands, although the epidemiology of RSV differed, hospitalization costs were higher and administration cost were lower. This most likely explains why Li et al. found seasonal administration of infants born in October-April to be cost-saving from the healthcare payer's perspective in Norway, while this was estimated at €21.200 per QALY gained for the Netherlands. However, when the cost-effectiveness of nirsevimab was assessed by birth month, immunization was only found to be cost-saving for children born in the season November up to and including February, while the ICER was close to €100,000/QALY gained for extension of the target group to cohorts born in October or March, and over a million euros per QALY gained for a further extension to the cohort born in April (Figure 8.2).

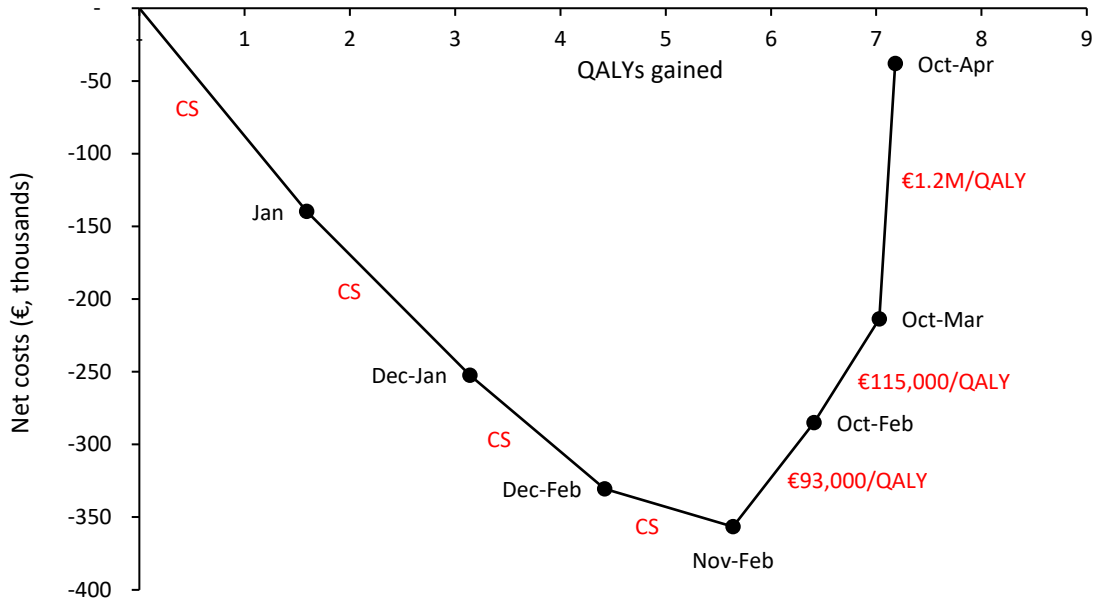

Figure 8.2 Cost-effectiveness of nirsevimab in Norwegian infants as estimated by Li et al. (152), showing the ICER of extending the target group with the next most cost-effective birth cohort by calendar month. Intervention costs were converted from Norwegian Krones (NOK) to euros using an exchange rate of €1 = 9.6 NOK (year 2019), while disease costs were converted from NOK to euros using the power purchasing parity of €1 = 8.8 NOK (year 2019). CS: Cost-saving. QALY: Quality-adjusted life year.

Cost-effectiveness outcomes of birth cohorts by calendar month cannot directly be transferred between countries due to differences in timing of the RSV season. In the Norwegian analysis, the incidence of RSV hospitalizations in the period 2008-2017 was on average the highest in January-February; hence, vaccination was estimated cost-effective for infants born during the peak of the epidemic or two months before the peak. In the Netherlands, the incidence of RSV hospitalizations in the period 2013-2017 was on average the highest in December-January, which would indicate that seasonal administration of nirsevimab would likely to be only cost-effective for children born in the months October up to and including January. Prioritization of infants born in autumn (including December) above infants born in winter is supported by a finding from Wildenbeest et al. (32) and Wang et al. (43), see paragraph 2.5 and figure 2.2. These results suggest that a catch-up program in October for children born in August and September may be prioritized above immunization at birth for children born in February and March, and perhaps also above children born in January. Unfortunately, the cost-effectiveness of a catch-up program specifically for children born in August and September was not included in the cost-effectiveness analyses for the Netherlands and Norway.

8.2 Maternal vaccination

The studies by Getaneh et al. for the Netherlands and Li et al. for Norway also considered an alternative with year-round maternal immunization. The used vaccine efficacy of maternal immunization against hospitalization of infants was assumed to be somewhat higher

than nirsevimab (70.1% *versus* 62.3%), but the duration of protection assumed to be somewhat shorter (4 months *versus* 5 months). Note that this modelling study did not use the most recently published efficacy data of the maternal vaccine from Pfizer, see chapter 7. The vaccine uptake of maternal vaccination and nirsevimab was assumed to be equal in the study. Given the similar efficacy profile, the impact of year-round maternal immunization on the number hospitalizations was estimated to be similar than year-round administration of nirsevimab and substantially lower than seasonal administration of nirsevimab plus a catch-up in October (see Table 8.2 for nirsevimab results). No scenarios with seasonal maternal immunization had been explored in the study, but given the similar vaccine efficacy profiles, the impact would be comparable with seasonal administration of nirsevimab. In reality, the immunization impact will also depend on the uptake; the current uptake of for instance maternal vaccination program for pertussis is lower than the uptake in the national immunization program for infants (65% versus >90%). Whether nirsevimab or maternal immunization is the most cost-effective strategy will highly depend on the total immunization costs (drug price plus administration).

8.3 Conclusion

Available cost-effectiveness studies for the Netherlands and Norway indicate that immunization with nirsevimab could be cost-effective to a threshold of €20,000 per QALY gained for infants born in October to and including January, provided that the intervention costs per child is not higher than €64 (immunization plus administration). Extending seasonal administration with a catch-up in October for all children born outside the RSV season averted the most hospitalizations (substantially more than year-round immunization at birth) but was not estimated to be cost-effective (ICER > €100,000/QALY) compared to seasonal immunization. Whether a catch-up for children born in August or September is cost-effective requires further analysis. These results are based on an average RSV season for the Netherlands with a peak incidence in early January, and with infants assumed to be born at the first of the month with immunization at birth. The target group for whom nirsevimab is cost-effective could be different for seasons with a different timing of the epidemic or when assumptions on the price of nirsevimab or on the administration costs do not hold. With an equal efficacy profile and immunization uptake, year-round maternal immunization would have similar impact than year-round administration of nirsevimab at birth, and therefore having less impact than seasonal administration of nirsevimab plus a catch-up in October. Seasonal maternal immunization could have similar impact than seasonal immunization with nirsevimab; the optimal alternative from a cost-effectiveness point of view would highly depend on the total intervention costs per child.

9 Acknowledgements

This report includes contributions from:

Anne Teirlinck (author Chapter 1, 2, 4, 7 and editor)
Puck van Kasteren (author Chapter 3, 5, 6, 7 and reviewer of the content)
Pieter de Boer (author Chapter 8)
Rob van Binnendijk, Channah Gaasbeek, Rutger Schepp (author Chapter 3)
Lance Presser, Adam Meijer (author Chapter 2.2 and 4.3)

Hester de Melker, Rianne van Gageldonk-Lafeber (editor)

Lieke Sanders, Nicoline van der Maas, Jacco Wallinga, Michiel van Boven, Femke Jongenotter, Albert Vollaard, Nynke Rots (Reviewers of the content)

Conflicts of interest

All authors and other contributors are from RIVM and report no potential conflicts of interest.

IMI Projects in which RIVM is partner

RIVM is partner in the RESCEU- and PROMISE-projects that have received funding from the Innovative Medicines Initiative 2 (IMI2) Joint Undertaking under grant agreement 116019 and 101034339. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and the European Federation of Pharmaceutical Industries and Associations (EFPIA).

RIVM is also partner in the Innovative Medicines Initiative 2 (IMI2) Joint Undertaking INNO4VAC. Funded under grant agreement No 101007799, this Joint Undertaking receives support from the European Union’s Horizon 2020 research and innovation programme and EFPIA.

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Published by:

National Institute for Public Health and the Enviroment, RIVM
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July 2023

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