Superior Health Council

PREVENTIVE STRATEGIES AGAINST RSV DISEASE IN CHILDREN

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Preventive strategies against RSV disease in children

In this scientific advisory report, which offers guidance to public health policy-makers, the Superior Health Council of Belgium provides recommendations on the use of preventive tools against RSV disease in children.

This version was validated by the Board on
December 6, 2023[1]

I   INTRODUCTION AND QUESTION

Respiratory Syncytial Virus (RSV) is the leading cause of viral lower respiratory tract infections (LRTI) in children under two years of age. Especially in infants, clinical manifestations including bronchiolitis and pneumonia due to RSV are most severe. Worldwide, RSV is the second leading cause of death in children under one year of age. In the adult population over 65 years and in people at risk, RSV is an important agent of respiratory infections.

After decades of research, new tools will shortly arrive on the Belgian market to prevent RSV disease. On one hand, a new monoclonal antibody (mAb) with a long-acting preventive effect against RSV infection, nirsevimab, was approved in 2022 by the European Medical Agency. It should be administered only once per season as opposed to palivizumab, the only preventive measure currently available that is kept for high risk groups only due to high costs and heavy monthly administration procedure.

The Superior Health Council (SHC) received an official request from the federal Minister of Health in March 2023 to provide recommendations on the use of monoclonal antibodies (mAb), nirvesimab (Beyfortus®) and Palivizumab (Synagis®), for the prevention of RSV infections in young children.

On the other hand, a maternal vaccine against RSV (Abrysvo®) will be available in January 2024 (EMA 07 2023) in Belgium for use in pregnant women to protect their infants against LRTI caused by RSV from birth to at least 6 months of age.

This report aims to provide recommendations and different strategies using each new preventive tool (mAb and maternal vaccination) that will be available for protection against RSV disease for young children in Belgium.

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[1] The Council reserves the right to make minor typographical amendments to this document at any time. On the other hand, amendments that alter its content are automatically included in an erratum. In this case, a new version of the advisory report is issued.

II CONCLUSIONS AND RECOMMENDATIONS

1) Due to its huge burden of disease in infants in terms of frequency and severity of infection, the SHC **supports the prevention of RSV disease for every infant < 1 year** of age entering its first RSV season, regardless of the presence of comorbidities. Moreover, the prevention is also indicated for **children between 1 and 2 years** of age during their second RSV season in case of **risk factors for severe infections** (see **Table 1**).

2) So far, **only passive immunization with specific monoclonal antibodies (palivizumab)** has been available and reimbursed for high-risk infants, but is associated with a heavy procedure of administration (monthly intramuscular injections during five months). Children eligible for palivizumab administration in Belgium are listed in **Table 2**.

3) **Two new preventive tools directed against the preF protein of RSV A and B have emerged (**results from KCE report**):**
    a) A F-protein based bivalent vaccine administered to pregnant women to protect their babies from birth up to 6 months (Abrysvo®). Based on the interim analysis of one RCT (N = 7 538), vaccine efficacy for severe medically assisted RSV related lower respiratory tract infection spans from 81.8 % (99.5 % CI: 40.6; 87.1) within 90 days of life to 69.4 % (97.6 % CI: 44.3; 84.1) within 180 days of life (high quality evidence). RSV-associated hospitalisations were reduced by 67.7 % (99 % CI: 15.9; 89.5) at 90 days and 56.8 % (99 % CI: 10.1; 80.7) at 180 days (moderate quality evidence). No safety signal was detected.

    b) An extended half live monoclonal antibody nirsevimab (Beyfortus®) for passive immunization of the infant during 5 months after a single intramuscular injection. In the meta-analysis of the 2 available RCTs (1 in infants born prematurely, 1 in late-preterm and term infants; N = 4 465), the efficacy against medically attended RSV-confirmed LRTI through 150 days is 75 % (95 % CI: 66; 82), and efficacy against RSV-related hospitalisations is 79 % (95 % CI: 63; 88) (high quality evidence). The evidence available so far indicates that nirsevimab has a favorable safety profile, although safety follow-up data beyond 360 days are limited.

    Both products have been recently approved by EMA and FDA.

4) **For this winter 2023 - 2024**, only **palivizumab** will be available in Belgium, as well as the **maternal vaccine (Abrysvo)** which should be available from January 2024 onwards. The SHC supports therefore the administration on an individual level of the **maternal vaccine for every woman expected to deliver before end of March 2024.** We also recommend to **keep using palivizumab for infants at high risk of RSV** infection during the RSV season, as previously recommended and according to applicable reimbursement criteria (see Table 2).

5) **For season 2024 - 2025**, both new preventive interventions (**nirsevimab and the maternal vaccine**) are expected to be on the Belgian market. Several strategies of prevention could then be proposed, using both interventions in combination or a single one, each on a year-round or seasonal program with or without a catch up at the start of the season.

    Considering:
    - the theoretical advantages and inconvenience of each immunization strategy,
    - the safety and efficacy data from phase 3 clinical trials available at this time,

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- the lack of data on co-administration of both products,
- and the impossibility to directly compare one tool to another,

the SHC aligns with the recommendations from other expert societies (ACIP or JCVI) and supports the use of each product, leaving the choice at the discretion of healthcare providers and parents and pending other data from cost-effectiveness analysis/reimbursement options.

Of note, **these recommendations are temporary and will be updated** once further relevant data on both preventive tools (in terms of co-administration, duration of protection and cost-effectiveness) will be available.

The SHC recommends the use of preventive RSV tools as follows:

- Either **maternal vaccine (Abrysvo)** for women **expected to deliver between early September and end of March.** The maternal vaccine is approved for use in Europe from 24 weeks of gestational age. However, considering all data available at the moment and the interval that should be respected with administration of Tdap vaccine, we consider **28 to 36 weeks of gestation as a preferential window for maternal vaccination** (see details below).
  Moreover, for pregnant women expected to have a premature delivery or an inadequate immune response to vaccination (immunocompromised status) or decreased transplacental antibody transfer (people living with HIV infection or membrane diseases), the maternal vaccination may not be the best preventive option and the use of monoclonal antibodies should be favored (see below).

- Or **nirsevimab (Beyfortus) for all babies born from unvaccinated mothers** or **born prematurely** (< 30 w) **or within the two weeks** following the vaccine administration.

  ➢ Nirsevimab could be provided:
    ▪ At birth (maternity ward) for babies born during the RSV season (October to March) using a single dose of 50 mg (as < 5 kg).
    ▪ During the regular immunization program (catch up) for those being ≤ 6 months old at the start of RSV season, using the dose of 50 mg if < 5 kg; and 100 mg if > 5 kg.
    ▪ Nirsevimab could be administered with other vaccines.
  ➢ Nirsevimab should replace palivizumab for high-risk children, considering its easier schedule of administration, similar safety profile and the pharmacokinetic data similar to other populations [1] Children who already started on palivizumab should not receive nirsevimab during the same RSV season.

  For most infants, **administering both products is not indicated and would not be a reasonable and efficient allocation of resources.** It is not currently known whether nirsevimab may provide additional protection to infants born from vaccinated mothers, and we do not have safety data on the use of nirsevimab in this specific population.

  In some specific cases however, administration of nirsevimab to infants born from vaccinated mothers could be considered:
  ➢ Infants with sufficiently increased risk for severe RSV disease (see **Table 1**) and born from mothers vaccinated at the end of the season (between January and March).

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> ➤ Infants from vaccinated mothers born within the two weeks following the vaccine administration in pregnancy.
> ➤ Pregnant women expected to have an inadequate immune response to vaccination (immunocompromised status) or decreased transplacental antibody transfer (people living with HIV infection or membrane diseases).
> ➤ Infants who have undergone cardiopulmonary bypass or neonatal blood exchange leading to loss of maternal antibodies.

6) **Specific populations (season 2024 - 2025):**

- <u>For premature babies</u>, nirsevimab should be administered 48 hours before discharge home (if discharged during the RSV season or during the month before), with dose adjusted to weight [50 mg if < 5 kg or 100 mg > 5 kg].
  Of note, administration of nirsevimab during NICU stay is not recommended, and there are no clinical data available in infants with a body weight from 1.0 kg to < 1.6 kg.

- <u>For Children at increased risk of severe disease</u> (**Table 1**):
  - Nirsevimab is recommended **during their first RSV** season until age of 11 months at start of the season and if the mother has not been vaccinated or has been vaccinated at the end of the season (January - March) (see criteria above). Dose is 50 mg or 100 mg depending on weight.
  - Nirsevimab is also recommended **during their second RSV season** (regardless of the vaccination status of the mother). The recommended dose is then 200 mg of nirsevimab, administered as two 100 mg injections given at the same time at different injection sites. Only one administration of nirsevimab is recommended per season (with exception for children who undergo cardiac surgery with cardiopulmonary bypass as explained in the product instruction).

Table 1: Children at increased risk of severe RSV disease
Children with: - Chronic lung disease of prematurity who required medical support (chronic corticosteroid therapy, diuretic therapy, or supplemental oxygen) any time during the 6 months period before the start of the second RSV season.   - Hemodynamically significant congenital heart disease.   - Immunocompromised states.   - Down syndrome.   - Cystic fibrosis.   - Neuromuscular disease.   - Congenital airway anomalies.

Table 2: Children eligible for palivizumab® reimbursement in Belgium
- Preterm infant born at < 28 WGA and being less than 1 year old at the beginning of RSV season.   - Preterm infant born between 28 to 35 WGA who required ventilation for at least 48 hours and being less than 6 months old at the beginning of the RSV season.   - Infant suffering from chronic respiratory insufficiency who requires oxygen-therapy or another ventilatory support at home and being less than 2 years postnatal at the start of RSV season.   - Infant less than two year of age presenting with a congenital cardiopathy with hemodynamic impact: reimbursement allows from the period before and the month following the cardiac surgery when this occurs during the RSV season and if the child has at least either congestive heart failure or desaturation (< 90 % FiO2) or pulmonary hypertension.

Research recommendations:

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- The Belgian population-based RSV surveillance should be improved, and a hospital-led reporting system should be put in place to enable the evaluation of the true burden of RSV disease in Belgium and to improve disease management in the future.
- Studies on the duration of immunity and efficacy of nirsevimab injections across several RSV seasons are needed, as well as data in children born from vaccinated mother and exposed to nirsevimab.
- Data on duration of protection acquired through maternal vaccination as well as of the need of booster during consecutive pregnancies and benefits for mothers themselves will also be important.
- Impact of preventive strategies on the overall burden of RSV in the community (not only on the number of hospitalizations) and in older age categories of children should be also evaluated once the measures will be in place.

Keywords[2]

Keywords	Sleutelwoorden	Mots clés	Schlüsselwörter
Vaccination	Vaccinatie	Vaccination	Impfung
Respiratory Syncytial Virus	Respiratoir Syncytieel Virus	Virus respiratoire syncytial	Respiratorisches Synzytialvirus
Vaccine efficacy	Werkzaamheid van het vaccin	Efficacité vaccinale	Wirksamkeit des Impfstoffs
Infant	Zuigeling	Nourrisson	Säugling
Pregnancy	Zwangerschap	Grossesse	Schwangerschaft
Monoclonal antibodies	Monoklonale antilichamen	Anticorps monoclonaux	Monoklonale Antikörper
LRTI	LRTI	IVRI	LRTI

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[2] The Council wishes to clarify that keywords are used for referencing purposes as well as to provide an easy definition of the scope of the advisory report. For more information, see the section entitled "methodology".

III TABLE OF CONTENT

IV METHODOLOGY

After analysing the request, the Board and the co-presidents of the NITAG identified the necessary fields of expertise. The KCE performed the literature review (link) on efficacy and safety of the vaccine and nirsevimab, and the corresponding GRADE appraisal of evidence quality. Sciensano provided data on epidemiology, burden of disease and risk factors.
The experts of this working group provided a general and an *ad hoc* declaration of interests and the Committee on Deontology assessed the potential risk of conflicts of interest.

This advisory report is based on a review of the scientific literature published in both scientific journals and reports from national and international organisations competent in this field (peer-reviewed), as well as on the opinion of the experts.

Once the advisory report was endorsed by the working group and NITAG it was ultimately validated by the Board.

V ELABORATION AND ARGUMENTATION

List of abbreviations

ADAs	Anti-Drug Antibodies
CI	Confidence Interval
FiO2	Fraction of inspired Oxygen
ICU	Intensive Care Unit
LRTI	Lower Respiratory Tract Infection
mAb	monoclonal Antibody
MA-RSV-LRTI	Medically Assisted RSV related Lower Respiratory Tract Infection
MA-RSV-RTI	Medically Assisted RSV related Respiratory Tract Infection
NITAG	National Immunization Technical Advisory Group
NNV	Number Needed to Vaccinate
RCT	Randomized Controlled Trial
RSV	Respiratory Syncytial Virus
SARI	Severe Acute Respiratory Infections
SAE	Serious Adverse Event
SHC	Superior Health Council
UR	Uncertainty Range
WGA	Weeks of Gestational Age

1 Respiratory Syncytial Virus (RSV)

Respiratory Syncytial Virus (RSV) is a pathogen causing a wide spectrum of respiratory illness. Globally, it is estimated that approximately 67 % of infants experienced an RSV infection in the first year of life and 90 – 95 % of infants within the first 2 years of life. RSV disease ranges from a mild upper respiratory tract infection to severe respiratory distress. RSV-associated lower respiratory tract infections (LRTIs) commonly present in young children as "bronchiolitis" and can progress to potentially life-threatening respiratory failure, apnoea and possibly death. Recent US data reported that hospitalizations directly related to RSV accounted for 9.3 % of all infant hospitalizations, being the primary cause of infants' hospitalization outside birth, and that 15 – 20 % of RSV hospitalized infants spend time in the ICU [2, 3]. Risk factors of poor outcome include prematurity/low birth weight, cardio-pulmonary congenital diseases and immunodeficiencies but the key issue with RSV is that 67 % to 79 % of hospitalized infants were previously healthy (even among those admitted to ICU) making those who will develop a life-threatening disease almost unpredictable [4, 5]. Moreover, RSV

LRTI has significantly been associated with increased odds of developing bacterial pneumonia, especially due to pneumococcus [6, 7]. Passive immunization with anti-RSV antibodies (palivizumab) is currently available but is restricted to some high-risk groups due its high cost and heavy procedure of delivery (**Table 2**). Until recently, no approved or recommended prophylaxis options were available for healthy term and preterm infants born beyond 29 weeks of gestation for RSV. However, experts agree now that every infant regardless of the presence of comorbidity as well as older adults deserve protection against such a virus [8, 9].

1.1 Burden of RSV infections (Sciensano)

RSV infections are a major source of disease burden in young children during their first years of life in Belgium. In high income countries, 26.2 % (24.0 – 28.6) of the children experiences an RSV-associated LRTI in the first year of life.

The incidence rate of RSV-associated LRTIs among infants during their first year of life is estimated around 23·7 per 1 000 infant-months (95 % CI 1 21·0 – 26·7). The incidence of medically attended RSV-LRTIs is estimated at 14·1 % (12·3 - 16·0), leading to incidence rate of 12·1 per 1 000 infant-months [11]. Among children younger than 5 years, the yearly incidence rate of RSV-associated LRTI is estimated at 24.3 (95 % UR 13.8 – 42.7) per 1 000 in children [10, 11].

The estimates of the incidence of RSV-associated hospitalisations range from 1·8 % (95 % CI 1·6-2·1) to 2.2 % (95 % UR 1,7 % – 2.8 %) in children younger than 1 year of age, 0.16 % (95 % UR 0.12 % – 0.21 %) among children aged 1 - 4 years and 0.6 % (95 % UR 0.47 % – 0.77 %) in children younger than 5 years [10, 11].

Applying these figures to the current Belgian population leads to a rough estimate of approximately 14 500 RSV infections and 3 200 – 3 600 hospital admissions annually in children under 5 years of age (including approximately 7 000 RSV infections and 2 300 – 2 700 hospital admissions annually in children under 2 years of age and 7 500 RSV infections and 600 hospital admissions annually in children aged 2 - 4 years).

This order of magnitude of hospitalization is corroborated by the Belgian sentinel SARI surveillance whose extrapolation of results led to an estimate of 3 044 hospitalisations for RSV infection in children aged 0 - 4 years in 2022 [12].

Median duration of hospitalisation was estimated to be 3 days (range 1 – 19 days, IQR 2 – 5 days) in the RESCEU birth cohort study, which was comparable to the findings in the Belgian SARI surveillance 4 days (range 1 - 18 days, IQR: 2 - 5 days) in children younger than 2 years and 3 days (range 1 - 18 days, IQR: 2 - 5 days) in children aged 2 - 4 years [11, 12].

Of importance, numbers of total admissions and impact of comorbidities provided by the Belgian SARI surveillance until 2022 might have been slightly underestimated, since the survey used a stricter case definition (based on adult clinical features) that excluded certain hospital admissions for RSV. Similarly, the report of important pediatric comorbidities like prematurity was missing. However, the surveillance has been adapted in the meanwhile and the results of future SARI seasons will be better representative of the true in-hospital situation in Belgium.

Because most infections occur during a seasonal peak of 8 - 12 weeks, the healthcare system is heavily burdened at that time and many children needing hospitalization have to be transferred to other centers far from their home because of lack of pediatric beds available.

1.2 Risk factors for severe infection (Sciensano)

Children at highest risk for a severe infection (and hence for hospital admission) are those with preterm birth, children aged less than 6 months (especially aged less than 3 months) and children with comorbidities (in particular congenital heart disease, chronic lung disease,

pulmonary hypertension and immunodeficiency) [13 - 20]. However, the issue with RSV is that the vast majority of hospitalized infants are previously healthy (even among those admitted to ICU) making it almost unpredictable who will develop a life-threatening disease [21 - 23]. Unpublished data from the Belgian SARI surveillance from the period 2012 - 2023 on 3 996 hospital admissions for LRTI in children aged less than 5 years (including 911 confirmed RSV patients) corroborates this finding, since most of the young children admitted to hospital for LRTI due to confirmed RSV had no pre-existing comorbidity: the percentage children without previous comorbidity admitted to hospital for LRTI due to confirmed RSV was 77 % (95 % CI 70 % – 84 %) in children younger than 2 years (out of which 20 % children were less than 3 months, 16 % children aged 3 - 5 months and 41 % between 6 and 2y) and 69 % (95 % CI 59 % – 80 %) in children aged 2 - 4 years [12]. Preterm birth was however not documented in this surveillance.

Moreover, among these hospitalised children aged 0 - 1 years old, those infected with RSV were significantly less likely to have pre-existing comorbidity than those not infected with RSV (Odds ratios: 0.71; 95 % CI 0.58 – 0.88 in 0 - 1 years old[12].

Repartition of comorbidities:
Among the 0-1 year old children reported with confirmed RSV and pre-existing comorbidity in the SARI surveillance, 15.1 % (95 % CI 9.6 % – 20.6 %) was suffering from chronic respiratory disease, 6.3 % (95 % CI 2.5 % – 10.0 %) from immunologic disorder, 3.8 % from cardiovascular disease (95 % CI 0.8 % – 6.8 %), 4.4% % from renal disease (95 % CI 1.2 % – 7.6 %), 0.6 % (95 % CI 0 % – 1.9 %) from liver disease and 6.3 % (95 % CI 3.4 % – 10.1 %) from neuromuscular disease (These percentages are not mutually exclusive as several children had more than 1 comorbidity specified.). For 64 % of these children who were reported to have comorbidities, no specific or other comorbidities were specified [12].

Among the 1 - 2 year old children reported with confirmed RSV and pre-existing comorbidity in the SARI surveillance 13.2 % (95 % CI 5.9 % – 30.3 %) was suffering from chronic respiratory disease other than asthma, 13.9 % (95 % CI 2.8 % – 27.2 %) from immunologic disorder, 1.3 % (95 % CI 0 % – 4.0 %) from cardiovascular disease, 1.3 % (95 % CI 0 % – 4.0 %) from renal disease, 9.2 % (95 % CI 2.5 % – 15.6 %) from neuromuscular disease and 10.5 % (95 % CI 3.3 % – 17.7 %) from asthma (These percentages are not mutually exclusive as several children had more than 1 comorbidity specified.).

Among the 2 - 4 year old children reported with confirmed RSV and pre-existing comorbidity in the SARI surveillance, 18.2 % (95 % CI 7.1 % – 29.3 %) was suffering from chronic respiratory disease other than asthma, 15.9 % (95 % CI 4.7 % – 27.2 %) from immunologic disorder, 6.8 % (95 % CI 0 % – 14.9 %) from cardiovascular disease, 2.3 % (95 % CI 0 % – 7.0 %) from renal disease, 2.2 % (95 % CI 0 % – 7.0 %) from diabetes, 9.1 % (95 % CI 0 % – 18.4 %) from neuromuscular disease and 22.4 % (95 % CI 9.4 % – 36.0 %) from asthma (These percentages are not mutually exclusive as several children had more than 1 comorbidity specified.). For 30 % of these children who were reported to have comorbidity, no specific or other comorbidities were specified [12].

1.3 Severity of disease (Sciensano)

Respiratory distress and respiratory failure are common complications of an RSV infection in young children and are a common cause of hospitalization. According to the systematic analysis of Li et al [10], the RSV-associated LRTIs hospital admission with hypoxaemia rate was estimated at 8.9 (95 % UR 2.8 – 20.8) per 1 000 children younger than 1 year of age and 0.6 (95 % UR 0.1 – 1.6) per 1 000 children aged 1 - 4 years. The RSV-associated LRTI hospital admission with chest wall indrawing was estimated at 9.0 (4.8 – 17.0) per 1 000 children younger than 1 year of age and 3.1 (1.7 – 5.5) per 1 000 children younger than 5 years. The RESCEU birth cohort study reports admission to intensive care unit in 5·5 % of the RSV-associated hospitalisations and 0·09 % of the total cohort [11].

The results of the Belgian SARI surveillance corroborate these findings: among children aged less than 2 years who are hospitalised for RSV, 4.8 % (95 % CI 3.3 % – 6.3 %) need to be admitted to ICU, and 2.4 % (95 % CI 1.3 – 3.4 %) need invasive mechanical ventilation. Among the children aged 2 - 4 years who are hospitalised for RSV, 3.6 % (95 % CI 0.2 % – 7.0 %) need to be admitted to ICU, and 3.0 % (95 % CI 0 – 5.9 %) need invasive mechanical ventilation [12].

Extrapolating these findings to the Belgian population of children under 2 years of age, this amounts to annually approximately 1 100 children hospitalised for RSV suffering from hypoxemia, 1 200 children presenting with chest wall indrawing, 500 children developing pediatric acute respiratory distress syndrome, 130 children admitted to an intensive care unit and 65 children needing invasive mechanical ventilation (of which approximately 25 with pre-existing comorbidity).

Additionally, also older children aged 2 - 4 years are affected, as annually approximately 200 children hospitalised for RSV suffer from hypoxemia, 600 children present with chest wall indrawing, 90 children developing pediatric acute respiratory distress syndrome, 20 children admitted to an intensive care unit (of which approximately 8 with pre-existing comorbidity) and 17 children needing invasive mechanical ventilation (of which approximately 8 with pre-existing comorbidity).

In rare cases, a child may die as a result of the RSV infection. According to Li et al [10] the in-hospital CFR of RSV-associated acute LRTI is estimated respectively at 0.1 % (95 % UR 0.1 – 0.3) in children younger than 1 year of age, 0.2 % (95 % UR 0.1 – 0.4) in children aged 1 - 4 years and 0.1 % (95 % UR 0.1 – 0.2) in children younger than 5 years. Unpublished data from the Belgian SARI surveillance from the period 2012 - 2023 on 911 hospital admissions for acute LRTI with confirmed RSV, supports the order of magnitude of this in-hospital CFR: 0.1 % (95 % UR 0 – 0.4%) in children younger than 2 year of age and 0 % in children aged 2 - 4 years [12].

The proportion of RSV-attributable deaths in all-cause deaths (when RSV-attributable death is defined as RSV being anywhere in the causal chain of death) in high income countries was estimated at 1.4 % (95 % UR 1.0 – 2.0) in children younger than 1 year of age, 1.3 % (95 % UR 1.0 – 1.8) in children aged 1 - 4 years and 1.4 % (95 % UR 1.0 – 2.0) in children younger than 5 years [10].

Extrapolated to the Belgian population, this corresponds to annually 5 RSV-related deaths (of which 3 in hospital) among children younger than 2 years of age and 1 additional RSV-related death in children aged 2 - 4 years.

1.4 Acceptability of the population

According to a recent survey assessing knowledge of RSV disease and acceptability of new dedicated preventive tools among 244 pregnant women/future fathers and young parents in Brussels, 75 % were at first glance in favour of adopting a preventive measure against RSV and 25 % were against or doubtful. Although 90 % had already heard about bronchiolitis infection, less than half of them knew this was related to RSV virus [Blumental et al, manuscript in progress]. Almost 20 % of them had a relative already hospitalized because of bronchiolitis. After the reading of a very short informative text on RSV burden, 89 % declared to be for implementing prevention whereas 11 % remained con or hesitant. Among those ones in favour, 100 % said being ready to get a new vaccine during pregnancy if this will be recommended and for 60 % of them, the possibility of co-administration with the other injections was not of importance. Once asking the preference between a maternal vaccine and an antibody injection to the baby, 36 % said they don't care as soon as this will be recommended by the national schedule and/or by their health care workers. These results are in line with two previous investigations published in the pre-COVID-19 pandemic period, although 20 % of parents said the pandemic has negatively influenced their current attitude in

face of vaccination [24, 25]. Further investigation is now ongoing to assess opinion of gynaecologist and midwife and to find keys to improve adherence to the maternal vaccination program in general.

2 Vaccines

For a full description, we refer to the European Public Assessment Reports (EPAR) published at the [EMA website](), [FAGG/AFMPS website]() or [CBIP/BCFI website]().

2.1 Abrysvo®

Abrysvo is approved for:
- Passive protection against LRTI caused by RSV in infants from birth through 6 months of age through immunisation during pregnancy.
- Active immunisation of individuals 60 years of age and older for the prevention of LRTI caused by RSV.

The present advice only addresses maternal vaccination with Abrysvo® in the goal of children protection. The SHC has already issued another recommendation in September 2023 about RSV vaccination in adult patients [26].
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2.1.1 Type of vaccine

Abrysvo® is a bivalent RSV prefusion F-protein based vaccine. It contains 120 µg of stabilised prefusion RSV F glycoprotein from RSV A and RSV B strains (60 µg of each) in a lyophilised dosage form for reconstitution. There is no adjuvant.

2.1.2 Vaccine Efficacy and evidence quality ([adapted from KCE report]())

MATISSE trial [27]

The vaccine has been approved by EMA for the use in pregnant individuals between weeks 24 and 36 of gestation on the basis of the results of the MATISSE trial.

The main characteristics of the trial are presented in table below. In this phase 3, double-blind trial 3 682 maternal participants received vaccine and 3 676 received placebo. Medically attended severe RSV-associated lower respiratory tract illness in infants were evaluated at 90,120,150 and 180 days after birth.

Table: PICO of MATISSE trial

Patients	a. **Inclusion:**
	    ○ **Maternal participants**: healthy pregnant women age 49 or younger; gestational age 24 to 36 weeks (WG) the day of planned injection. Reassuring second trimester ultrasound.
	    ○ **Infant participants:** infants born to maternal participants who received the investigational product at least 14 days before birth.
	b. **Exclusion:** history of severe adverse reaction to a vaccine or vaccine component, major illness of the pregnant woman or of the foetus, pregnancy issue of in vitro fertilization, pregnancy complications or abnormalities at the time of consent. Other exclusion criteria are listed in footnote[3] **Infant participants**:

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[3] Participants were excluded if they had any of the following medical conditions: prior pregnancies with preterm delivery at 34 WG or less, prior stillbirth or neonatal death, previous infant with a genetic disorder or a congenital anomaly, having illnesses that required immunosuppressant medication, having received the following drugs 28 days prior to consent: monoclonal antibodies or systemic corticosteroids for more than 14 days, alcohol abuse or illicit drug use, bleeding diathesis, receipt of blood/plasma products or immunoglobulins within 60 days of investigational product administration, or planned receipt through delivery, they were excluded if they had already received any licensed or investigational RSV vaccine or if it was planned during study participation.

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	receiving a RSV monoclonal antibody, issue of a pregnancy with major protocol violations, transfusion of more than 20 mL/kg of any blood products before 180 days of life.
	Demographic and clinical characteristics of maternal participants were equally distributed in the intervention and control group. 64 % were white, 20 % Black and 12 % Asian. Median age was 29 years (14 to 47), median WG at injection was 31.3 weeks (24 to 36.9).
	Characteristics and obstetric outcomes of the infant participants were equally distributed in the intervention and control group. 51 % were males and 94 % were born at term.
Intervention	Maternal participants (n = 3 682) were randomly assigned in a 1:1 ratio to receive one intramuscular injection of unadjuvanted RSVpreF vaccine at a dose of 120 µg (containing 60 µg each of RSV A and RSV B antigens).
Comparators	Placebo (n = 3 676).
Outcomes	a. **First primary end point : medically attended *severe* RSV-associated lower respiratory tract illness in infants.** It was defined asa medically attended visit for Respiratory Tract Infection (RTI) and a RSV RT-PCR positive test result and at least one of the following: fast breathing[4], SpO2 < 93 % , high-flow nasal cannula or mechanical ventilation, ICU admission for more than 4 hours, unconscious infant, evaluated at 90,120,150 and 180 days after birth. b. **Second primary end point: medically attended RSV-associated lower respiratory tract illness in infants**. It was defined as a medically attended visit for Respiratory Tract Infection (RTI) and a RSV RT-PCR positive test result and at least one of the following: fast breathing[5], SpO2 < 95 %, chest wall indrawing, evaluated at 90,120,150 and 180 days after birth. c. **Secondary end points:**. Medically attended, RSV-related respiratory tract infection; RSV- associated hospitalization; Medically attended lower respiratory tract infection of any cause. d. **Safety** was measured in 7 357 maternal participants and 7 126 infant participants . Endpoints were in the **maternal participants** reactogenicity and adverse events (from the time of informed consent through 6 months after delivery) and in the **infant participants** adverse events and newly diagnosed chronic medical conditions (adverse events from birth to 1 month of age, chronic medical conditions from birth through 12 months - 24 months if enrolled in the first trial year).
Setting	77 % of patients were from: USA (n = 3 353) ; South Africa (n = 964); Argentina (n = 914); Japan (n = 462); others: Taiwan, Spain, Gambia, Netherlands, Chile, Finland, New Zealand, Philippines, Mexico, Brazil, Denmark, Canada, Australia, Republic of Korea.
Duration	Inclusion of maternal participants between June 17th 2020 and October 2nd 2022. Infant participants: 96 % completed the 1 month follow up, 79 % completed the 6 months follow-up and 46 % the 12-month follow-up.
Analysis	<u>This is a prespecified interim analysis</u>. Data monitoring committee recommended stopping the trial for efficacy. The primary efficacy analysis was performed in the eligible infant participants per-protocol. Missing laboratory results were the subject of a sensitivity analysis. Missing values were not imputed for the safety end-points. Vaccine efficacy was estimated with the use of binomial distribution of the number of cases of disease in the RSV vaccine group and given the total number of cases in both groups The probability of primary end-point coverage for confidence intervals was 99.5 % at 90 days (alpha-spending function and Bonferroni procedure) and 97.58 % at later intervals (two-sided alpha level of 0.0483 and Bonferroni procedure).

[4] RR superior or equal to 60 bpm for < 2 months of age, superior or equal to 50 bpm from 2 to less than 12 months of age, or equal or more than 40 bpm in 1 to 2 years of age.
[5] RR superior or equal to 70 bpm for < 2 months of age, superior or equal to 60 bpm from 2 to less than 12 months of age, or equal or more than 50 bpm in 1 to 2 years of age.

Results of MATISSE trial

Outcome	Intervention (N = 3 495) n (%)	Control (N = 3 480) n (%)	Vaccine efficacy (99.5 or 97.58 % CI)	Absolute risk difference (95 % CI)	NNV (95 % CI)
Severe MA-RSV-LRTI within 90 days	6 (0.2)	33 (0.9)	81.8 (40.6 - 96.3)	0.8 (0.4 - 1.1)	129 (89 - 234)
Severe MA-RSV-LRTI within 120 days	12 (0.3)	46 (1.3)	73.9 (45.6 - 88.8)	1 (0.5 - 1.4)	102 (71 - 181)
Severe MA-RSV-LRTI within 150 days	16 (0.5)	55 (1.6)	70.9 (44.5 - 85.9)	1.1 (0.6 - 1.6)	89 (63 - 153)
Severe MA-RSV-LRTI within 180 days	19 (0.5)	62 (1.8)	69.4 (44.3 - 84.1)	1.2 (0.7 - 1.7)	81 (57 - 136)
MA-RSV-LRTI within 90 days	24 (0.7)	56 (1.6)	57.1 (14.7 - 79.8)	0.9 (0.4 - 1.4)	108 (70 - 236)
MA-RSV-LRTI within 120 day	35 (1)	81 (2.3)	56.8 (31.2 - 73.5)	1.3 (0.8 - 1.9)	75 (52 - 138)
MA-RSV-LRTI within 150 days	47 (1.3)	99 (2.8)	52.5 (28.7 - 68.9)	1.5 (0.8 - 2.1)	67 (47 - 121)
MA-RSV-LRTI within 180 days	57 (1.6)	117 (3.4)	51.3 (29.4 - 66.8)	1.7 (1 - 2.5)	58 (41 - 100)
Secondary outcomes					
MA-RSV-TRI within 90 days	67 (1.9)	110 (3.2)	39.1 (16.7 - 55.7)	1.3 (0.5 - 1.9)	80 (50 - 197)
RSV-associated hospitalization within 90 days	10 (0.3)	31 (0.9)	67.7 (15.9 - 89.5)	0.6 (0.2 - 1.0)	165 (104 - 407)
MA-LRTI of any cause within 90 days	186 (5.3)	200 (5.7)	7 (-22.3 - 29.3)	0.4 (-0.5 - 1.5)	-

MA-RSV-LRTI: Medically Assisted RSV related Lower Respiratory Tract Infection; MA-RSV-RTI: Medically Assisted; NNV: Number Needed to Vaccinate; RSV related Respiratory tract infection.

The trial was judged good quality, with low risk of bias. Vaccine efficacy for severe medically assisted RSV related lower respiratory tract infection spanned from 81.8 % (99.5 CI 40.6 - 87.1) within 90 days of life to 69.4 % (97.58 CI 44.3 - 84.1) within 180 days of life. For this outcome, the predefined criterion for vaccine efficacy was met (lower 99.5 % CI boundary > 20 %). Waning of vaccine efficacy was rapid, going from 82 % at 90 days to 69 % at day 180 for severe MA-RSV-LRTI.

The vaccine efficacy for medically assisted RSV related lower respiratory tract infection did not meet the criterion for vaccine efficacy at 90 days.
The point estimates of all primary and secondary outcomes (with the exception of MA-LRTI of any cause after 90 days of life) favored intervention.

To be noted that the trial was conducted during the COVID-19 pandemic and in this context RSV-associated LRTI was only 22 % of medically attended LRTIs, whereas in prepandemic studies RSV was the most frequent pathogen in areas where pneumococcal vaccination was used, responsible of 50 – 80 % of cases of hospitalization for bronchiolitis. The Number needed to vaccinate (NNV) must be computed.

The frequency of SAEs in the maternal and infant populations was similar between the vaccine group and the control group. There was one RSV-related infant death, in the placebo group.

Evidence quality

GRADE methodology was used for judging the evidence on vaccine efficacy. The evidence quality was judged high. However, two aspects required more discussion. First, vaccine efficacy for severe medically assisted RSV related lower respiratory tract infection spanned from 81.8 % (99.5 % CI: 40.6 - 87.1) within 90 days of life to 69.4 % (97.58 % CI: 44.3 - 84.1) within 180 days of life. The confidence intervals are wide and downgrading evidence quality by one degree could be envisioned according to GRADE methodology. However, we consider that most clinicians would still be in favor of vaccinating pregnant women even if its true efficacy would correspond to the lower bound of the confidence interval. Therefore, downgrading quality for imprecision is not relevant, and the certainty of evidence can be considered high. The discussion on this point is less straightforward for RSV-associated hospitalization at 90 days (VE = 67.7 %; 99 % CI: 15.9 - 89.5) and 180 days (VE = 56.8 %; 99 % CI: 10.1 - 80.7). For this outcome, downgrading the evidence by one degree for imprecision seems to be justified. Second, the results presented are from the interim analysis of one unique trial, and it has been demonstrated that such analysis can yield more positive results than observed in subsequent trials or in real world data. Downgrading the evidence quality by one level could be considered (moderate quality), until final robust results are published.

2.1.3   Dosage and administration

According to EMA a single dose of 0.5 mL should be administered between weeks 24 and 36 of gestation but the SHC recommends a narrower window between 28 and 36 weeks of gestation as a preferential window for vaccination.

2.1.4   Adverse reactions

In pregnant women at 24 - 36 weeks of gestation the most frequently reported adverse reactions are mild to moderate (vaccination site pain (41 %), headache (31 %) and myalgia (27 %)) and resolve within 2 - 3 days of onset.

No significant safety signal was detected in the **Matisse trial** neither in the maternal nor infant participants. Frequency of AEs in the maternal participants within a month from injection) was 13.8 % in the vaccine group and 13.1 % in the control group. Frequency of AEs in infant participants within one month of life was 37.1 % in the vaccine group and 34.5 % in the control group. Maternal participants had a higher frequency of reported muscle pain and headache (27 % in the vaccine population vs 17 % in the control population

The frequency of SAE in maternal participants within 6 months of giving birth is reported to be similar between the vaccine and control group, the most frequent SAE was pre-eclampsia (1.8 % in the vaccine group and 1.6 % in the control group). One maternal death in the vaccine group was due to obstetric haemorrhage and evaluated as non-related to the vaccine. Premature birth was 0.8 % in the vaccine group and 0.6 % in the control group. 4 SAEs in the vaccine group and 1 in the control group were assessed to be related to the injection.

The frequency of SAEs in the infant population was similar between the vaccine group and the control group. None were assessed as being related to the injection. There were a total of 17 infant deaths, 5 in the vaccine group and 12 in the placebo group.

The published Pfizer results showed an excess of preterm births in the vaccinated group confined to the study sites in Upper Middle Income Countries (UMIC) more specifically in South Africa and Brazil. Further scrutiny showed that gestational age at vaccination was similar between the 2 income settings and that this was unlikely to be the reason for the observed disparity in premature births. Further plots of gestational age at vaccination against gestational age at birth stratified by income setting did not show a relationship between time of vaccination and prematurity.

The SHC is relatively reassured that there is not a clear signal of an increase in preterm births in high income countries following administration of Abrysvo in pregnancy. There is not a full understanding of the cause of the signal in UMIC settings and whether this was driven by data from South Africa alone or South Africa and Brazil. No difference in neonatal deaths was observed between the vaccine and control group, and in fact deaths were lower in the vaccine group compared with the control group. Potentially, vaccinating later in pregnancy might mitigate potential risks of prematurity.

2.1.5 Concomitant administration

Abrysvo can be administered **concomitantly with seasonal influenza** vaccine but a minimum **interval of two weeks is recommended** between administration of Abrysvo and administration of a tetanus, diphtheria and acellular pertussis vaccine (Tdap recommended in Belgium to all pregnant women between 24 – 32 weeks, see advice 8754). There were no safety concerns when Abrysvo was co-administered with Tdap in healthy non-pregnant women. However, whereas immune responses to RSV A, RSV B, diphtheria and tetanus on co-administration were non-inferior to those after separate administration, the immune responses to the pertussis components were lower on co-administration compared to separate administration and did not meet the criteria for noninferiority. No data are available yet on the coadministration of abrysvo and COVID 19-vaccine, nor have we immunogenicity data when abrysvo is co-administred with influenza vaccine (only safety data published).Further data on co-administration of abrysvo with other vaccines will be of importance.

3 Monoclonal antibodies

For a full description, we refer to the European Public Assessment Reports (EPAR) published at the [EMA website](#), [FAGG/AFMPS website](#) or [CBIP/BCFI website](#).

3.1 Palivizumab (Synagis®)

Palivizumab is a humanised IgG1 monoclonal antibody directed to an epitope in the A antigenic site of the fusion protein of RSV. It has potent neutralising and fusion-inhibitory activity against both RSV subtype A and B strains.

The product received the first authorization in August 1999.

Based on the SMC, Synagis is indicated for the prevention of serious lower respiratory tract disease requiring hospitalisation caused by RSV in children at high risk for RSV disease:

- Children born at 35 weeks of gestation or less and less than 6 months of age at the onset of the RSV season.
- Children less than 2 years of age and requiring treatment for bronchopulmonary dysplasia within the last 6 months.
- Children less than 2 years of age and with haemodynamically significant congenital heart disease.

Nevertheless in Belgium Synagis is reimbursed under certain more restrictive conditions (see Table 2)

3.1.1 Posology and method of administration

The recommended dose of palivizumab is 15 mg/kg of body weight, given once a month during anticipated periods of RSV (risk in the community (October to March)). The product is reimbursed for a maximum of 5 injections. For premature infants the first injection is done before discharge.

Palivizumab is administered intramuscularly, preferably in the anterolateral aspect of the thigh. The gluteal muscle should not be used routinely as an injection site because of the risk of damage to the sciatic nerve. The injection should be given using standard aseptic technique.

3.1.2 Adverse reactions

The most serious adverse reactions occurring with palivizumab are anaphylaxis and other acute hypersensitivity reactions. Common adverse reactions occurring with palivizumab are fever, rash, and injection site reaction.

3.2 Nirsevimab (Beyfortus®)

Beyfortus® is indicated for the prevention of RSV lower respiratory tract disease in neonates and infants during their first RSV season. Beyfortus® should be used in accordance with official recommendations.

3.2.1 Posology and method of administration

The recommended dose is a single dose of 50 mg administered intramuscularly for infants with body weight < 5 kg and a single dose of 100 mg administered intramuscularly for infants with body weight $\geq$ 5 kg.

Beyfortus® should be administered prior to commencement of the RSV season, or from birth for infants born during the RSV season.

Dosing in infants with a body weight from 1.0 kg to < 1.6 kg is based on extrapolation, no clinical data are available. Exposure in infants < 1 kg is anticipated to yield higher exposures than in those weighing more. The benefits and risks of nirsevimab use in infants < 1 kg should be carefully considered.

It is administered intramuscularly, preferably in the anterolateral aspect of the thigh. The gluteal muscle should not be used routinely as an injection site because of the risk of damage to the sciatic nerve.

For the full description, we refer to the EPAR

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3.2.2   Concomitant administration with vaccines

Since nirsevimab is a monoclonal antibody, a passive immunisation specific for RSV, it is not expected to interfere with the active immune response to co-administered vaccines. There is limited experience of co-administration with vaccines. In clinical trials, when nirsevimab was given with routine childhood vaccines, the safety and reactogenicity profile of the co-administered regimen was similar to the childhood vaccines given alone. Nirsevimab can therefore be given concomitantly with childhood vaccines. Nirsevimab should not be mixed with any vaccine in the same syringe or vial. When administered concomitantly with injectable vaccines, they should be given with separate syringes and at different injection sites.

3.2.3   Adverse reactions

The most frequent adverse reaction was rash (0.7 %) occurring within 14 days post dose. The majority of cases were mild to moderate in intensity. Additionally, pyrexia and injection site reactions were reported at a rate of 0.5 % and 0.3 % within 7 days post dose, respectively. Injection site reactions were non-serious.

In the Nirsevimab NCT02878330 trial (see KCE report), adverse events of grade 3 or higher were similar in the two groups, the investigator considered none to be related to the investigational product. Serious adverse events were reported in 11.2 % (108 of 968) of the participants who received nirsevimab and in 16.9 % (81 of 479) of those who received placebo. Five deaths occurred through day 361 (two deaths in the nirsevimab group and three in the placebo group), no deaths were known to be due to RSV or were considered by the investigator to be related to nirsevimab or placebo. In the nirsevimab group, 1 death on day 97 was caused by previously undiagnosed pulmonary vein stenosis, and 1 death of unknown cause occurred on day 123. In the placebo group, 1 death on day 343 was caused by pericardial effusion, and 2 deaths (on days 26 and 109) were caused by pneumonia. Five participants required an ICU admission, all in the placebo group.

In the Melody trial [28, 29](see KCE report), Adverse events related to nirsevimab or placebo were reported in 1.3 % of the nirsevimab recipients and 1.5 % of the placebo recipients through 360 days after injection. Adverse events of grade 3 or higher were similar in the two groups. Four adverse events of special interest were reported in the nirsevimab group: a grade 1 maculopapular rash reported in 2 participants (Study Day 1), a grade 1 papular rash in 1 participant (Study Day 1), and a grade 3 erythematous macular rash (Study Day 7, 6 days post-dose). No anaphylaxis or other serious hypersensitivity was reported. Four deaths occurred through day 361, all among nirsevimab recipients. One death of unknown cause occurred on day 140, two deaths (on days 143 and 338) were attributed to gastroenteritis in infants who did not have a health care visit for the illness, one death occurred after skull base fracture following road traffic accident.

3.2.4   Long-term impact

The protection conferred through nirsevimab is monoclonal, compared to maternal vaccination which provides a more polyclonal immunization. Of concern is therefore the possibility of emergence of escape variants acquiring resistance under the selective pressure of an extended half-life mAb targeting single epitopes. So far, palivizumab-resistant strains have been very rare, with resistance reported in only 5 % of children who were hospitalized with breakthrough RSV infection despite receiving palivizumab prophylaxis [30, 31]. However, genomic surveillance of RSV circulating strains would be of utmost importance to monitor emergence of mutations and resistances once the use of monoclonal antibodies will be broadened to a bigger part of the pediatric population.

Another concern is the possibility of formation of anti-drug antibodies (ADAs), which can lead to more or less serious immune complex diseases or can disturb mAb pharmacokinetic and pharmacodynamic properties as well as its neutralizing capacities [30]. Presence of ADAs has been detected in a low but unneglectable proportion of palivizumab and nirsevimab immunized children (6 % in phase2b and 3 nirservimab clinical trials) but was until now not related to clinical adverse events or loss of efficacy [28, 32]. This point should nevertheless be carefully followed up in immunized cohorts, especially in those receiving nirsevimab on two consecutive seasons.

3.2.5 *Protective effectiveness and evidence quality (adapted from KCE report)*

3.2.5.1 Nirsevimab in mid and high preterm infants

The Nirsevimab trial (NCT02878330) is 2:1 randomised double-blind placebo-controlled trial including healthy infants who had been born preterm with a gestational age from week 29 to week 35 and who were 1 year of age or younger and entering their first RSV season [32]. Participants received one intramuscular injection of 50 mg of nirsevimab or normal saline placebo during a 2-month period immediately before the RSV season.

PICO of Nirsevimab NCT02878330 trial

Patients	a. **Inclusion:** preterm infants born between 29 weeks 0 days and 34 weeks 6 days gestational age; age: ≤ 1 y (≤ 8 mo for infants born in Europe); entering their first full RSV season. b. **Exclusion:** infants who are recommended to receive palivizumab per local or national guidelines; other exclusion criteria are listed in footnote[6]. The mean gestational age of the participants was 33 weeks; the mean age was 3.3 months; 72 % were White; 48 % were of female sex; the majority (61 %) had a weight ≤ 5 kg. The demographic characteristics were broadly similar across the trial groups. Randomization was stratified by subject age at randomization (i.e. < 3 months, > 3 to < 6 months, > 6 months).
Intervention	Participants (n =1 453) were randomly assigned in a 2:1 ratio to receive one intramuscular injection of nirsevimab at a dose of 50 mg.
Comparators	Placebo
Outcomes	a. **Primary end point: incidence of medically attended RSV-confirmed LRTI (inpatient and outpatient) through 150 days post dose.** A diagnosis of RSV LRTI requires having a respiratory sample positive for RSV by RT-PCR performed at a central laboratory AND a physical examination finding indicating involvement of the lower respiratory tract (rhonchi, rales, crackles, or wheeze) AND at least one indicator of clinical severity[7]. b. **Secondary end point: hospitalization for RSV-confirmed LRTI through 150 days post dose.** A RSV hospitalization is defined as either.

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[6]   Participants were excluded in case of any of the following: any fever (≥ 38.0 °C, regardless of route) or lower respiratory illness within 7 days prior to randomization; acute illness (defined as the presence of moderate or severe signs and symptoms) at the time of randomization; active RSV infection (a child with signs/symptoms of respiratory infection must have negative RSV testing) or known prior history of RSV infection; Any drug therapy (chronic or other) within 7 days prior to randomization (with some exceptions); any current or expected receipt of immunosuppressive agents including steroids; receipt of any investigational drug; known renal impairment; known hepatic dysfunction including known or suspected active or chronic hepatitis infection; history of CLD/bronchopulmonary dysplasia; clinically significant congenital anomaly of the respiratory tract; chronic seizure or evolving or unstable neurologic disorder; congenital heart disease, except for children with uncomplicated CHD (eg, patent ductus arteriosus, small septal defect); prior history of a suspected or actual acute life-threatening event; known immunodeficiency; mother with HIV infection; any known allergy; receipt of palivizumab or other RSV monoclonal antibody or any RSV vaccine; receipt of any monoclonal or polyclonal antibody (for example, Hepatitis B immune globulin, intravenous immunoglobulin), including maternal RSV vaccination.

[7]   - Increased respiratory rate at rest (age: < 2 months, ≥ 60 breaths/min; 2 – 6 months, ≥ 50 breaths/min; > 6 months – 2 years, ≥ 40 breaths/min), OR
- Hypoxemia (in room air - oxygen saturation < 95 % at altitudes ≤ 1 800 meters or < 92 % at altitudes > 1 800 meters), OR
- Clinical signs of severe respiratory disease (e.g. acute hypoxic or ventilatory failure, new onset apnea, nasal flaring, intercostal, subcostal or supraclavicular retractions, grunting) or dehydration secondary to inadequate oral intake due to respiratory distress (need for intravenous fluid).

	-	A respiratory hospitalization with a positive RSV test within 2 days of hospitalization (primary), OR
	-	A new onset of respiratory symptoms in an already hospitalized child, with an objective measure of worsening respiratory status and positive RSV test (nosocomial).
	c.	**Exploratory** end point: incidence of hospitalizations with supplementary oxygen (**severe RSV**); number of admissions to hospitals and intensive care units (ICUs) and duration of stay.
	d.	**Safety** was measured in 968 participants through 360 days post dose.
	e.	Determination of **pharmacokinetics** of nirsevimab and the incidence of antidrug antibodies.

Setting	164 sites in 23 countries in both hemispheres: 68 % of participants in the Northern Hemisphere (Bulgaria, Canada, Czech Republic, France, Hungary, Italy, Poland, Russian Federation, Spain, United Kingdom, and USA), and 32 % in the Southern Hemisphere (Argentina, Australia, Brazil, Chile, New Zealand, and South Africa). The sample size was aiming at 99 % power to detect a 70 % relative risk reduction. The incidence rate in the placebo group was assumed to be 8 %.
Duration	Between November 2016 and December 2017, a total of 1 453 participants underwent randomization.
Analysis	Efficacy analyses were performed in the intention-to-treat population, safety analyses were based on the as-treated population. A hierarchical approach was used; the secondary end point would be tested only if statistical significance for the primary end point was shown. For subjects who do not have an event (RSV LRTI) prior to discontinuation from participation, their event status was imputed assuming the observed placebo RSV LRTI rate.

Results of Nirsevimab NCT02878330 trial

Outcome	Intervention group (N = 969)	Control group (N = 484)	Vaccine efficacy* (95 % CI)	Absolute risk difference** (95 % CI)	NNT (95 %CI)
Incidence of medically attended RSV-confirmed LRTI through 150 days***	2.6 % (25)	9.5 % (46)	70.1 % (52.3; 81.2)	6.7 % (5.0; 7.7)	15 (13; 20)
Incidence of hospitalization for RSV-confirmed LRTI through 150 days	0.8 % (8)	4.1 % (20)	78.4 % (51.9; 90.3)	3.2 % (2.1; 3.7)	31 (27; 48)
Incidence of severe RSV (supplementary oxygen)	0.4 % (4)	3.3 % (16)	87.5 % (62.9; 95.8)	2.9 % (2.1; 3.2)	34 (31; 48)
Median hospitalisation length of stay in days (min, max)	6.5 (3,14)	7.0 (2,20)	-	-	-
Adverse events of grade 3 or higher	8.0 % (77)	12.5 % (60)	-	-	-

*: Vaccine efficacy measured by Poisson regression with robust variance, as reported in the paper; **: Absolute risk difference computed by us on the basis of the vaccine efficacy reported in the paper; ***: a case was defined as positive result for RSV in a real-time, reverse-transcriptase–polymerase-chain reaction assay performed at a central laboratory, a physical examination finding indicating involvement of the lower respiratory tract, and at least one indicator of clinical severity CI: Confidence Interval; LRTI: Lower Respiratory Tract Infection; NNT: Number Needed to Treat; RSV: Respiratory Syncytial Virus.

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The trial was at low risk of bias. Vaccine efficacy was 70.1 % (95 % CI: 52.3; 81.2) against medically attended RSV-confirmed LRTI and 78.4 % (95 % CI: 51.9; 90.3) against hospitalization for RSV-confirmed LRTI in the 150 days following hospitalization. The corresponding NNT were 15 (95 % CI: 13; 20) and 31 (95 % CI: 27; 48), respectively. Vaccine efficacy against severe RSV infection was 87.5 % (95 % CI: 62.9; 95.8).

3.2.5.2 Nirsevimab in late-preterm and term infants

The MELODY trial is a phase 3 trial evaluating Nirsevimab for the prevention of RSV in healthy infants who had been born late-preterm and term infants ≥ week 35 gestational age [28]. Based on results from the nirsevimab trials NCT02878330 showing suboptimal exposure to nirsevimab and lower efficacy in children > 5 kg, participants received one intramuscular injection of nirsevimab (at a dose of 50 mg if they weighed < 5 kg or at a dose of 100 mg if they weighed ≥ 5 kg) or placebo.

PICO of MELODY trial

Patients	a. **Inclusion:** infants born at term or late preterm ≥ week 35 gestational age; entering their first full RSV season. b. **Exclusion:** infants who are recommended to receive palivizumab per local or national guidelines; other exclusion criteria are listed in footnote[8] and are nearly the same as those in the Nirsevimab trial. 86 % of the participants had a gestational age of ≥ 37 weeks; the mean age of the participants was 2.6 months; 54 % were White; 48 % were of female sex; 40 % had a weight of < 5 kg, 15.6 % had a body weight ≤ 2.5 kg. The demographic characteristics were broadly similar across the trial groups. Randomization was stratified by subject age at randomization (i.e. < 3 months, > 3 to < 6 months, > 6 months).
Intervention	Participants (n = 3 012) were randomly assigned in a 2:1 ratio to receive one intramuscular injection of nirsevimab at a dose of 50 mg if they weighed < 5 kg or at a dose of 100 mg if they weighed ≥ 5 kg.
Comparators	Placebo
Outcomes	a. **Primary end point: incidence of medically attended RSV-confirmed LRTI (inpatient and outpatient) through 150 days post dose.** A diagnosis of RSV LRTI requires having a respiratory sample positive for RSV by RT-PCR performed at a central laboratory AND a physical examination finding indicating involvement of the lower respiratory tract (rhonchi, rales, crackles, or wheeze) AND at least one indicator of clinical severity[9]. b. **Secondary end point: hospitalization for RSV-confirmed LRTI through 150 days post dose.** A RSV hospitalization is defined as either: - A respiratory hospitalization with a positive RSV test within 2 days of hospitalization (primary), OR

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[8]   Participants were excluded in case of any of the following: any fever (≥ 38.0 °C, regardless of route) or lower respiratory illness within 7 days prior to randomization; any history of LRTI or active LRTI prior to, or at the time of, randomization; known history of RSV infection or active RSV infection prior to, or at the time of randomization; any drug therapy (chronic or other) within 7 days prior to randomization (with some exceptions); any current or expected receipt of immunosuppressive agents including steroids; history of receipt of blood, blood products, or immunoglobulin products, or expected receipt through the duration of the study; receipt of any investigational drug; known renal impairment; known hepatic dysfunction including known or suspected active or chronic hepatitis infection; history of CLD/bronchopulmonary dysplasia; clinically significant congenital anomaly of the respiratory tract; chronic seizure or evolving or unstable neurologic disorder; congenital heart disease, except for children with uncomplicated CHD (eg, patent ductus arteriosus, small septal defect); prior history of a suspected or actual acute life-threatening event; known immunodeficiency; mother with HIV infection; any known allergy; receipt of palivizumab or other RSV monoclonal antibody or any RSV vaccine; receipt of any monoclonal or polyclonal antibody (for example, Hepatitis B immune globulin, intravenous immunoglobulin), including maternal RSV vaccination.

[9]   - Increased respiratory rate at rest (age: < 2 months, ≥ 60 breaths/min; 2 – 6 months, ≥ 50 breaths/min; > 6 months – 2 years, ≥ 40 breaths/min), OR
- Hypoxemia (in room air - oxygen saturation < 95 % at altitudes ≤ 1 800 meters or < 92 % at altitudes > 1 800 meters), OR
- Clinical signs of severe respiratory disease (eg, acute hypoxic or ventilatory failure, new onset apnea, nasal flaring, intercostal, subcostal or supraclavicular retractions, grunting) or dehydration secondary to inadequate oral intake due to respiratory distress (need for intravenous fluid).

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	-	A new onset of respiratory symptoms in an already hospitalized child, with an objective measure of worsening respiratory status and positive RSV test (nosocomial).
	c.	**Exploratory** end point: RSV infection after 150 days; incidence of hospitalizations with supplementary oxygen (**severe RSV**); number of admissions to hospitals and intensive care units (ICUs) and duration of stay.
	d.	Safety was measured in 987 participants through 360 days post dose.
	e.	Determination of **pharmacokinetics** of nirsevimab and the incidence of antidrug antibodies.
Setting		Northern Hemisphere (Austria, Belgium, Bulgaria, Canada, Czech Republic, Estonia, Finland, France, Germany, Hungary, Israel, Italy, Japan, Latvia, Lithuania, Mexico, Poland, Republic of Korea, Russia, Spain, Sweden, Turkey, Ukraine, United Kingdom, and United States of America [USA]) and Southern Hemisphere (Argentina, Australia, Brazil, Chile, Colombia, New Zealand, Panama, and South Africa). The sample size was aiming at 99 % power to detect a 70 % relative risk reduction. The incidence rate in the placebo group was assumed to be 8 %. A pooled analysis of efficacy against hospitalization for RSV-LRTI in the nirsevimab trial involving was prespecified.
Duration		Between July 2019 and November 2019, a total of 1 027 participants were enrolled in the Northern Hemisphere. Between January 2020 and March 2020, a total of 462 participants were enrolled in South Africa. No other participants were enrolled in the Southern Hemisphere. One participant was enrolled in Japan in July 2020.
Analysis		Efficacy analyses were performed in the intention-to-treat population, safety analyses were based on the as-treated population. A hierarchical approach was used; the secondary end point would be tested only if statistical significance for the primary end point was shown. For subjects who do not have an event (RSV LRTI) prior to discontinuation from participation, their event status was imputed assuming the observed placebo RSV LRTI rate.

Results of MELODY trial

Outcome	Intervention group (N = 2 009)	Control group (N = 1 003)	Vaccine efficacy* (95 % CI)	Absolute risk difference** (95 % CI)	NNT (95 % CI)
Incidence of medically attended RSV-confirmed LRTI through 150 days*	1.2 % (24)	5.4 % (54)	76.4 % (62.3; 85.2)	4.1 % (3.4; 4.6)	24 (22; 30)
Incidence of hospitalization for RSV-confirmed LRTI through 150 days	0.4 % (9)	2.0 % (20)	76.8 % (49.4; 89.4)	1.5 % (1.0; 1.8)	67 (56; 100)
Incidence of severe RSV (supplementary oxygen)**	0.3 % (7)	1.7 % (17)	78.6 % (48.8; 91.0)	1.3 % (0.8; 1.5)	77 (67; 125)
Adverse events of grade 3 or higher	3.1 % (61)	3.8 % (38)	-	-	-

*: Vaccine efficacy measured by Poisson regression with robust variance, as reported in the paper; **: Absolute risk difference computed by us on the basis of the vaccine efficacy reported in the paper; ***: a case was defined as positive result for RSV in a real-time, reverse-transcriptase–polymerase-chain reaction assay performed at a central laboratory, a physical examination finding indicating involvement of the lower respiratory tract, and at least one indicator of clinical severity. CI: Confidence Interval; LRTI: Lower Respiratory Tract Infection; NNT: Number Needed to treat; RSV: Respiratory Syncytial Virus.*

The trial was at low risk of bias (see table). Vaccine efficacy against medically attended RSV-confirmed LRTI was 76.4 % (95 % CI: 62.3; 85.2), with a NNT of 24 (95 % CI: 22; 30). Vaccine efficacy against hospitalization for RSV-confirmed LRTI was 76.8 % (95 % CI: 49.4; 89.4).

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When results of the Nirsevimab NCT02878330 trial and the final results of the MELODY trial are pooled (see **Fout! Verwijzingsbron niet gevonden.** and **Fout! Verwijzingsbron niet gevonden.**), the vaccine efficacy against medically attended RSV-confirmed LRTI is 75 % (95 % CI: 66; 82), and vaccine efficacy against RSV-related hospitalisations is 79 % (95 % CI: 63; 88).

Figure 1: Meta-analysis of nirsevimab efficacy medically attended RSV-confirmed LRTI through 150 days.
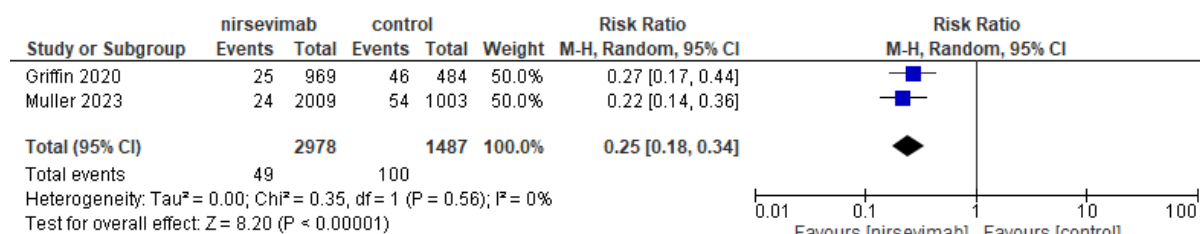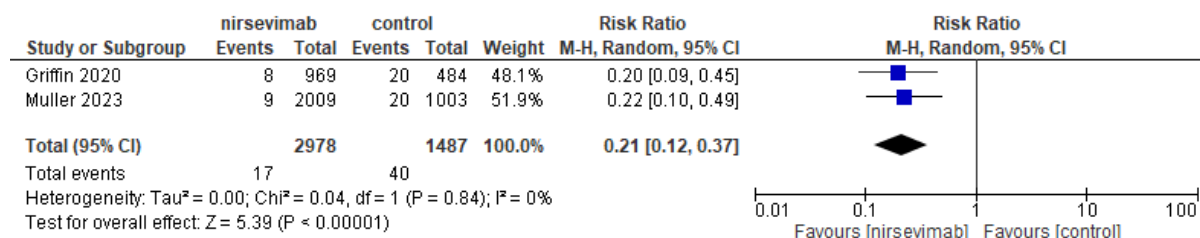
Study or Subgroup	nirsevimab Events	Total	control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Griffin 2020	25	969	46	484	50.0%	0.27 [0.17, 0.44]
Muller 2023	24	2009	54	1003	50.0%	0.22 [0.14, 0.36]
Total (95% CI)		2978		1487	100.0%	0.25 [0.18, 0.34]
Total events	49		100			

Heterogeneity: Tau² = 0.00; Chi² = 0.35, df = 1 (P = 0.56); I² = 0%
Test for overall effect: Z = 8.20 (P < 0.00001)

Figure 2: Meta-analysis of nirsevimab efficacy against hospitalization for RSV-confirmed LRTI through 150 days.

Study or Subgroup	nirsevimab Events	Total	control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Griffin 2020	8	969	20	484	48.1%	0.20 [0.09, 0.45]
Muller 2023	9	2009	20	1003	51.9%	0.22 [0.10, 0.49]
Total (95% CI)		2978		1487	100.0%	0.21 [0.12, 0.37]
Total events	17		40			

Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.84); I² = 0%
Test for overall effect: Z = 5.39 (P < 0.00001)

3.2.5.3: High risk preterm infants: MEDLEY trial

This phase 2/3 trial evaluated safety of nirsevimab in comparison to palivizumab in preterm infants born < 35 weeks gestational age without chronic lung disease (CLD) or congenital heart disease (CHD) and term and preterm infants with CLD or CHD. The primary endpoint in the MEDLEY trial was safety, secondary efficacy endpoints are extrapolated as palivizumab was the comparator. In total, 925 children under 12 months were randomised in a 2:1 ratio, 615 in the cohort of preterm infants and 310 in the cohort of patients with CLD or CHD. The latter cohort were followed through a consecutive RSV season: nirsevimab recipients received a second dose of nirsevimab in the consecutive season, whereas palivizumab recipients were re-randomised to receive a nirsevimab or second palivizumab dose.

The incidence of adverse events was similar across treatment groups and cohorts. Five deaths occurred in the nirsevimab group: two in the preterm cohort and three in the CHD–CLD cohort. One death occurred in the palivizumab group (CHD–CLD cohort), all deaths were thought to be unrelated to the treatment by the investigator.

3.2.5.4: HARMONIE trial (preliminary data) [33]

This pragmatic trial (phase 3b) is conducted in the UK, France, and Germany, evaluating nirsevimab for the prevention of hospitalization due to RSV-associated LRTI in infants. Infants (≥ 29 weeks gestational age) were randomised in an open label 1:1 ratio to receive a single intramuscular injection of nirsevimab (< 5 kg 50 mg; ≥ 5 kg 100 mg), or no intervention (standard of care) before or during the RSV season.

At the time of the primary analysis, 8 058 infants were randomized, 4 037 in nirsevimab group and 4 021 in the no intervention group. Of these, 3 916 (48.6 %), 1 912 (23.7 %) and 2 230 (27.7 %) were ≤ 3.0, > 3.0 and ≤ 6.0, and > 6.0 months of age. Efficacy against RSV LRTI

hospitalization was 83.21 % (95 % CI: 67.77 %, 92.04 %) and 75.71 % (32.75 %, 92.91 %) against severe RSV LRTI.

3.2.5.6: Evidence quality

The quality of evidence was judged high. Both the Nirsevimab NCT02878330 trial and the MELODY trial ere at low risk of bias, and their results (together with the unpublished preliminary results of the HARMONIE trial) were consistent. There were some degree of indirectness. First, infants with any history of LRTI were excluded whereas they may have represented a group of more fragile individuals. Second, there were no results on mortality reduction. But we considered that 2 elements did not justify downgrading the evidence. Finally, the results had sufficient precision to decide on their minimum clinical benefits, and no publication bias was apparent.

Either in infants who had been born premature or in late-preterm and term infants, there is good quality evidence that a single dose of nirsevimab resulted in a lower incidence of medically attended RSV-associated lower respiratory tract infection and of hospitalization than placebo for 150 days — the length of a typical RSV season — after administration of the dose. The unpublished preliminary results of the HARMONIE trial seem to confirm these results.

4 Other country recommendations (last consulted mid-November 2023)

4.1 US (ACIP and AAP)

https://www.cdc.gov/mmwr/volumes/72/wr/mm7241e1.html

Nirsevimab is recommended for:
- All infants younger than 8 months born during or entering their first RSV season, including those recommended by the American Academy of Pediatrics (AAP) to receive palivizumab;
- Infants and children aged 8 through 19 months who are at increased risk of severe RSV disease and entering their second RSV season, including those recommended by the AAP to receive palivizumab.

Per the FDA label, children who have received nirsevimab should not receive palivizumab for the same RSV season.

Some considerations for the 2023 – 2024 RSV season with regard to palivizumab versus nirsevimab administration for high-risk infants during the same RSV season

1. If nirsevimab is administered, palivizumab should not be administered later that season.
2. If palivizumab was administered initially for the season and < 5 doses were administered, the infant should receive 1 dose of nirsevimab. No further palivizumab should be administered.
3. If palivizumab was administered in season 1 and the child is eligible for RSV prophylaxis in season 2, the child should receive nirsevimab in season 2, if available. If nirsevimab is not available, palivizumab should be administered as previously recommended.

On September 22 2023, ACIP recommended seasonal administration of one dose of RSV vaccine for pregnant people during weeks 32 through 36 of pregnancy.

4.2 France (HAS)

Recommendation issued by HAS on Nirsevimab: https://www.has-sante.fr/jcms/p_3461236/fr/nirsevimab-beyfortus-dans-la-prevention-des-bronchiolites-a-virus-respiratoire-syncytial-vrs-chez-les-nouveau-nes-et-les-nourrissons

As part of this national immunisation campaign, nirsevimab is intended for children during their first year of exposure to RSV circulation, i.e.:
- all newborns and infants born after 6 February 2023;
- all newborns from birth, preferably before leaving the maternity hospital.

The 2023 - 2024 immunisation period will begin on 15 September 2023 and will last until the end of the epidemic, usually at the end of January. The end of the epidemic is determined annually by *Santé publique France*. The epidemic period varies from year to year and from region to region.

4.3 UK (JCVI)

https://www.gov.uk/government/publications/rsv-immunisation-programme-jcvi-advice-7-june-2023/respiratory-syncytial-virus-rsv-immunisation-programme-for-infants-and-older-adults-jcvi-full-statement-11-september-2023#programme-for-older-adults

Programme to protect neonates and infants:
- The committee notes a seasonal, seasonal with catch-up or year-round passive immunisation (monoclonal antibody) programme for newborns could be cost effective over a range of potential prices that combine the cost of the product and its administration.
- The committee notes a seasonal or year-round maternal active immunisation programme could be cost effective over a range of potential prices that combine the cost of the product and its administration.
- JCVI advises that both products are suitable for a universal programme to protect neonates and infants from RSV.
- JCVI does not have a preference for either product or whether a maternal vaccination or a passive immunisation programme should be the programme chosen to protect neonates and infants. Therefore, subject to licensure of the maternal vaccine, both options should be considered for a universal programme.
- JCVI advises a preference for a year-round offer for a passive immunisation or maternal immunisation programme to ensure high uptake and for reasons of operational effectiveness because this would be less complex and resource intensive to deliver, compared with running seasonal campaigns.
- However, the most cost-effective programmes were seasonal, for either product, followed by seasonal + catch up for the monoclonal product and then year-round programmes for either product. If the products were priced similarly, then it was difficult to differentiate between the two, based on cost-effectiveness.

JCVI advises that a RSV immunisation programme, that is cost effective, should be developed for both infants and older adults.

4.4 Luxembourg

https://gouvernement.lu/en/actualites/toutes_actualites/communiques/2023/09-septembre/22-immunisation-bronchiolite-nourrissons.html

This new immunisation, administered by intramuscular injection and consisting of the monoclonal antibody Nirsevimab, can be offered to newborns from birth in maternity wards, starting with the autumn-winter 2023 - 2024 season.
It is recommended for the following categories of children:
- All newborns born during the period of high RSV circulation (from October 1 to March 30 each year) with an intramuscular injection preferably before discharge from the maternity hospital.
- For the 2023 - 2024 season, non-immunised children born after 1 January 2023 will receive an intramuscular injection at the start of the RSV high circulation season (from October 2023).
- From 2024, all infants under 6 months of age born outside the RSV high circulation period (April to September) with an intramuscular injection at the start of the RSV high circulation season.
- Children aged over 12 months with underlying conditions that increase the risk of serious RSV infection (one intramuscular injection per year up to the age of 2 years).

4.5 Spain

Following a review of the scientific literature and an evaluation of the use of Nirsevimab in the population under 1 year of age, it is recommended in order of priority, and only for this season 2023 - 2024, in the following population groups:

Infant population at high risk of severe RSV disease, including:
a) preterm infants with gestational age < 35 weeks (single dose administration before 12 months of age);
b) patients with cyanosing or non-cyanosing congenital heart disease with significant
c) haemodynamic involvement;
d) (patients with bronchopulmonary dysplasia and
e) patients with other underlying conditions that pose a high risk for severe RSV bronchiolitis (see conditions in recommendations section).

In patients with risk conditions b, c and d, nirsevimab will be administered prior to each RSV season before reaching 24 months of age at the time of immunisation.

Children under 6 months of age at the start of or during the RSV season: **For the 2023 - 2024 season,** nirsevimab is recommended for children under 6 months of age born from 1 April 2023 to 31 March 2024. Priority will be given to immunise those born during the season and those born previously will be immunised as early as possible (October).

Efforts should be made to immunise the majority of the target population at the beginning of the RSV season (in October). In addition, those born during the season (October - March) should receive nirsevimab very early (preferably within 24 - 48 hours of birth) due to the increased severity of RSV disease in the first days of life.

Other prevention strategies, such as vaccines for pregnant women, are expected to become available in the near future. Therefore, these recommendations and target groups will be reviewed for the following seasons.

4.6 Sweden

Recommendations by the Medicines Product Agency targeting in priority preterm birth < 32 GW or children with underlying medical conditions for Nirsevimab for the winter season 2023/2024.

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VII COMPOSITION OF THE WORKING GROUP

The composition of the Committee and that of the Board as well as the list of experts appointed by Royal Decree are available on the following website: About us.

All experts joined the working group *in a private capacity*. Their general declarations of interests as well as those of the members of the Committee and the Board can be viewed on the SHC website (site: conflicts of interest).

The ad hoc working group was chaired by **David TUERLINCKX and Sophie BLUMENTAL**; the scientific secretary was Veerle MERTENS.
Based on the discussions within the *ad hoc* working group and in collaboration with KCE and Sciensano, the advisory report was drafted.

BEUTELS Philippe	Social sciences, health care economics and organizations, infectious disease medicine	*UAntwerpen*, CHERMID, SIMID
BLUMENTAL Sophie	Pediatrics, infectious disease medicine, vaccinology, primary immunodeficiency diseases, pneumococcal infections, tuberculosis	ULB, CHIREC
BOIY Tine	Pediatrics, rare diseases, congenital hereditary and neonatal diseases and abnormalities, down syndrome	*UAntwerpen*, UZA
BOSSUYT Nathalie	Epidemiology of infectious diseases	Sciensano
CARRILLO SANTISTEVE Paloma	General Practice, infectious disease medicine, vaccinology, preventive medicine, public health	ONE
CHATZIS Olga	Pediatrics, infectious disease medicine, congenital hereditary and neonatal diseases and abnormalities, vaccinology	*UCLouvain, Cliniques universitaires Saint-Luc*
CORNELISSEN Laura	Obstetrics, gynecology, epidemiology, infectious disease medicine, maternal health, public health	Sciensano
COSTA Elena	Obstetrics, gynecology	KCE
MAERTENS Kirsten	Vaccinology and maternal immunization	*UAntwerpen*
MALFROOT Anne	Pediatrics and infectiology	*UZ Brussel*
ROBERFROID Dominique	Epidemiology, anthropology and health sciences	KCE, *UNamur*
SMEESTERS Pierre	Pediatrics, infectiology, vaccinology	HUDERF
SPODEN Julie	General medicine	SSMG
SWENNEN Béatrice	Epidemiology and vaccinology	ULB
TILMANNE Anne	Pediatrics and infectiology	CHU Tivoli
TUERLINCKX David	Pediatrics and vaccinology	*CHU UCL Namur*

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VAN DER LINDEN Dimitri	Pediatrics, infectiology, travel medicine and HIV	UCL

The following experts agreed on the conclusions at the NITAG meeting of November 16 2023 and/or approved the advisory report by mail on November 24 2023. The NITAG was co-chaired by **David TUERLINCKX** and **Steven CALLENS.** The scientific secretariat were Fabrice PETERS and Veerle MERTENS.

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BLUMENTAL Sophie	Pediatrics, infectious disease medicine, vaccinology, primary immunodeficiency diseases, pneumococcal infections, tuberculosis.	ULB, CHIREC
CALLENS Steven	Internal medicine, infectious disease medicine, emerging communicable diseases, travel medicine, vaccinology, tuberculosis, AIDS-HIV, ebola, COVID-19.	*UGent, UZ Gent*
CARRILLO SANTISTEVE Paloma	General practice, infectious disease medicine, vaccinology, preventive medicine, public health.	ONE
CHATZIS Olga	Pediatrics, infectious disease medicine, congenital hereditary and neonatal diseases and abnormalities, vaccinology.	*UCLouvain, Cliniques universitaires Saint-Luc*
DE LOOF Geert	General practice, Pharmacology.	Private Practice, ex-CBIP-BCFI
DE SCHRYVER Antoon	Occupational and environmental medicine	*UAntwerpen*
DOGNE Jean Michel	Pharmacy and pharmacovigilance	*UNamur*, AFMPS, EMA
MAERTENS Kirsten	Vaccinology and maternal immunization	*UAntwerpen*
MALFROOT Anne	Pediatrics and infectiology	*UZ Brussel*
MENDEZ Murielle	Public and environmental health, economics	Kaleido
MICHIELS Barbara	General medicine	*UAntwerpen*
PELEMAN Renaat	Pediatrics, infectiology, vaccinology healthcare services management	*UZ Gent*
ROBERFROID Dominique	Epidemiology, anthropology and health sciences	KCE, *UNamur*
ROSSI Camelia	Infectiology, HIV, travel and internal medicine	*CHU Ambroise Paré*
SPODEN Julie	General medicine	SSMG
SWENNEN Béatrice	Epidemiology and vaccinology	ULB
TILMANNE Anne	Pediatrics and infectiology	CHU Tivoli
TUERLINCKX David	Pediatrics and vaccinology	*CHU UCL Namur*
VAN DAMME Pierre	Epidemiology, vaccinology, infectiology, public health	*UAntwerpen*
VAN DER LINDEN Dimitri	Pediatrics, infectiology, travel medicine and HIV	UCL

VAN LAETHEM Yves	Infectiology, vaccinology and travel medicine	*ex-CHU Saint-Pierre*, ULB
VEKEMAN Veerle	General medicine	*Kind en Gezin*
VERHAEGEN Jan	Immunology, clinical microbiology, transplantation	*UZ Leuven*
WAETERLOOS Geneviève	Quality of vaccines and blood products	Sciensano

The following experts were heard but did not take part in endorsing the advisory report:

DAEMS Joêl	Directorate Drugs	RIZIV-INAMI
DAELEMANS Siel	Pediatrics, infectious disease Medicine, pulmonary medicine, cystic fibrosis, RSV, COVID-19.	VUB, *UZ Brussel*
DOCHEZ Carine	Coordinator of the Spearhead Domain Vaccines	FAGG-AFMPS
FRERE Julie	Pediatrics and infectiology	*CHR Citadelle*
GOETGHEBUER Tessa	Pediatrics and infectiology	*CHU St Pierre*, ONE
LEROUX-ROELS Isabel	Vaccinology, infection prevention and microbiology	*UZ Gent*
PERIN Belinda	General medicine, vaccinology	AVIQ - ONE
SCHELSTRAETE Petra	Pediatrics, pneumology and infectiology	*UZ Gent*
THEETEN Heidi	Vaccinology	VAZG
VANDEN DRIESSCHE Koen	Pediatrics and infectiology	UZA

The following companies were heard: Pfizer and Sanofi.

About the Superior Health Council (SHC)

The Superior Health Council is a federal advisory body. Its secretariat is provided by the Federal Public Service Health, Food Chain Safety and Environment. It was founded in 1849 and provides scientific advisory reports on public health issues to the Ministers of Public Health and the Environment, their administration, and a few agencies. These advisory reports are drawn up on request or on the SHC's own initiative. The SHC aims at giving guidance to political decision-makers on public health matters. It does this on the basis of the most recent scientific knowledge.

Apart from its 25-member internal secretariat, the Council draws upon a vast network of over 500 experts (university professors, staff members of scientific institutions, stakeholders in the field, etc.), 300 of whom are appointed experts of the Council by Royal Decree. These experts meet in multidisciplinary working groups in order to write the advisory reports.

As an official body, the Superior Health Council takes the view that it is of key importance to guarantee that the scientific advisory reports it issues are neutral and impartial. In order to do so, it has provided itself with a structure, rules and procedures with which these requirements can be met efficiently at each stage of the coming into being of the advisory reports. The key stages in the latter process are: 1) the preliminary analysis of the request, 2) the appointing of the experts within the working groups, 3) the implementation of the procedures for managing potential conflicts of interest (based on the declaration of interest, the analysis of possible conflicts of interest, and a Committee on Professional Conduct) as well as the final endorsement of the advisory reports by the Board (ultimate decision-making body of the SHC, which consists of 30 members from the pool of appointed experts). This coherent set of procedures aims at allowing the SHC to issue advisory reports that are based on the highest level of scientific expertise available whilst maintaining all possible impartiality.

Once they have been endorsed by the Board, the advisory reports are sent to those who requested them as well as to the Minister of Public Health and are subsequently published on the SHC website (www.shc-belgium.be). Some of them are also communicated to the press and to specific target groups (healthcare professionals, universities, politicians, consumer organisations, etc.).

In order to receive notification about the activities and publications of the SHC, please contact: info.hgr-css@health.fgov.be.

.be

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