Strategies to prevent severe Respiratory Syncytial Virus (RSV) infections in infants: the Belgian expert opinion

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Abstract

Respiratory syncytial virus (RSV) causes a significant burden of disease in children, particularly in young infants or those with comorbidities. Recently, two new effective options have been approved for the prevention of RSV-related lower respiratory tract disease in infants: a long-acting monoclonal antibody (nirsevimab, Beyfortus®) and a maternal vaccine (RSVpreF; Abrysvo®). A Belgian group of paediatric RSV experts (members of the Belgian Society of Paediatrics) recommends an immunization strategy targeting all infants aged <1 year, at the start of their first RSV season and infants with risk factors aged <2 years at the start of their second RSV season. The choice of one or a combination of these two complementary preventive options will depend on maternal and infant factors, taking into account the advantages and disadvantages of potential strategies, as well as costs and reimbursement. The expert group recommends a low cost to parents and rapid reimbursement to avoid health inequalities. Adequate supply should also be ensured. Implementation should include data collection to conduct a real-world observational survey of effectiveness over the first 5 years of use. Awareness campaigns need to be organised for all stakeholders.

Introduction

Respiratory syncytial virus (RSV) infections are important in paediatrics and one of the main causes of infant hospitalisation and mortality (1-3). By the age of 2 years, 95% of all the infants worldwide will have been infected (4). The vast majority (75% up to 90 %) of infants hospitalised for severe RSV infection were previously healthy infants (5, 6). Most cases of hospital admissions occur in infants less than 1 year of age (2, 3, 6). The Belgian RSV expert group was formed on the basis of an analysis by the Belgian Society of Paediatrics, taking into account expertise in paediatric pulmonology, infectiology or neonatology. All have been involved in the evaluation of the burden and surveillance of RSV disease in young infants in Belgium (7). As new prevention strategies are now available, RSV prevention is being reviewed in several countries. In this context, this group of Belgian experts took the opportunity to give their opinion on the subject.

Burden of disease

The Belgian Knowledge Centre for Health Care (KCE) recently published a report on the organisation of paediatric hospital care in Belgium (8). Hospital admissions of patients with RSV infection were defined by one of four diagnostic codes: 1) RSV as the cause of diseases classified elsewhere, 2) RSV pneumonia, 3) acute RSV bronchiolitis, or 4) bronchitis, mentioned either as a primary or secondary diagnosis in an upper or lower limit definition.

In 2018, there were 9,047 to 10,675 (depending on the definition) RSV hospitalisations of children in paediatric services. There were 260 to 313 (depending on the definition) stays of children in non-paediatric services for whom an RSV diagnosis was identified.

Depending on the definition used, 75.6% to 77.8% of children hospitalised in paediatric units with a diagnosis of RSV were aged < 1 year. A diagnosis of RSV was made in 452 (10.0%) to 533 (11.8%) hospitalisations of children in a paediatric intensive care unit (PICU) (8). RSV-related hospitalisations cause a peak in bed occupancy rates. During the seasonal peak, RSV-related hospitalisations account for 30% to 40% of bed occupancy in paediatric wards. In 2018, the national average bed occupancy rate exceeded 80% during the peak period. Without RSV, the rate would not have exceeded 70% (8). The annual incidence of RSV-associated hospitalisations was 68.3 per 1,000 children younger than 1 year and 5.0 per 1,000 children aged 1-4 years (9). Admission to the PICU is very stressful for the patient and demanding for the health care system and society. According to a Belgian PICU registry, which included 2,364 admissions of various aetiologies (age group: 0-15 years) in 2018, the main reason for PICU admission was severe and/or life-threatening lung or airway pathology (27.92%); 5.46% of PICU admissions were RSV-associated (10).

Societal and financial burden

RSV has a significant impact on the health-related quality of life (HRQoL) of children and their parents and caregivers, and imposes a substantial economic burden on families, healthcare systems, governments and society (7). Forty-one studies reporting data from 1987 to 2017 were included in a systematic review and meta-analysis evaluating the global inpatient and outpatient costs of RSV healthcare management

in middle- and high-income countries. The average cost of RSV acute lower respiratory infection (ALRI) management was €3,452 (95% CI 3,265-3,639) and €299 (95% CI 295-303) per episode for inpatient and outpatient management without follow-up, respectively, and increased to €8,591 (95% CI 8,489-8,692) and €2,191 (95% CI 2,190-2,192) with follow-up to 2 years after the initial event (11). The global cost of RSV ALRI management in young children in 2017 was estimated to be approximately €4.82 billion (95% CI 3.47-7.93) (11).

A multi-country prospective cohort study conducted in Finland, the Netherlands, Spain and the United Kingdom (UK) prospectively measured costs and HRQoL of RSV in previously healthy term infants and their caregivers during the first RSV season in a community setting (12).The cohort of 1,041 infants experienced 265 RSV episodes with a mean symptom duration of 12.5 days. The mean costs per RSV episode were €399.5 (95 % CI 242.3-584.2) and €494.3 (95 % CI 317.7-696.1) from the perspective of healthcare payers (direct costs) and society (direct + indirect costs), respectively. The mean cost per hospitalised RSV episode was €4.587,9 (95% CI 3.085-6.229) from the perspective of the health care payer. The mean quality-adjusted life-day (QALD) loss per RSV episode of 1.9 (95 % CI 1.7-2.1) was independent of medical care. Caregivers' and children's HRQoL showed similar trends and correlated well (12).

Seasonality

In Belgium, based on a 13-year survey, the RSV season starts around week 41 (second week of October) and peaks between week 47 and 52 (13). After the emergence of COVID-19, a dramatic reduction in RSV activity was observed, coinciding with the implementation of public health and social measures (PHSMs). After the PHSMs were gradually lifted, a shift in seasonality and a delayed RSV outbreak with a higher number of infected patients were observed in many countries (14). In Belgium, an atypical seasonality was observed in 2021, with a reappearance of the epidemic pattern in 2022-2023 and 2023-2024 (15).

RSV prevention

Non-pharmaceutical interventions (NPI)

GENERAL MEASURES

Transmission of RSV occurs mainly by inoculation of the nasopharyngeal or ocular mucosa after direct contact with secretions containing the virus (16). General measures to prevent RSV infection focus on reducing inoculation and include hand washing, cough hygiene, avoiding exposure to tobacco and other smoke, restricting childcare attendance during the RSV season for high-risk infants, and possibly reducing air pollution (16). The types of infection control precautions in the healthcare setting depend on the setting and include appropriate use of gloves, surgical masks and disposable gowns, isolation or cohorting of RSV patients, and continuing education of staff (16).

Passive and active immunization

MONOCLONAL ANTIBODIES

Palivizumab (Synagis®)

Palivizumab is a recombinant humanised monoclonal antibody (mAb) indicated for the prevention of severe lower respiratory tract infection (LRTI) requiring hospitalisation due to RSV in children at high risk of RSV disease (17).

In a meta-analysis of three pre-licensure randomised trials comparing palivizumab prophylaxis with placebo in 2,831 high-risk infants with bronchopulmonary dysplasia (BPD) or other high-risk conditions, palivizumab reduced RSV hospitalisations from 101 to 50 per 1000 (relative risk [RR] 0. 49, 95% CI 0.37-0.64) and intensive care unit admissions from 34 to 17 per 1000 (RR 0.5, 95% CI 0.3-0.81) without increasing the risk of adverse events (16, 18). Palivizumab has a short half-life and requires monthly intramuscular administration during anticipated RSV risk periods (17).

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Nirsevimab (Beyfortus®)

Nirsevimab is a recombinant, long-acting human G1-kappa neutralising monoclonal antibody approved by the European Medicines Agency (EMA) for the prevention of RSV LRTI in neonates and infants during their first RSV season (19).

Unlike palivizumab, nirsevimab is administered as a single intramuscular dose. According to the label, the use of nirsevimab is not restricted to high-risk children, although it should be administered according to official local recommendations (19).

The efficacy and safety of nirsevimab for the prevention of medically attended (MA) RSV LRTI in term and preterm infants entering their first RSV season was evaluated in two randomised, double-blind, placebo-controlled, multicentre trials (D5290C00003 [phase IIb] and MELODY [phase III]) (14). The results of these trials are summarised in Table 1.

D5290C00003 randomised a total of 1,453 very and moderately preterm infants (gestational age [GA] ≥ 29 to < 35 weeks; median age 3.3 months) (2:1) to receive a single intramuscular dose of nirsevimab or placebo.

MELODY (primary cohort) randomised a total of 1,490 term and late preterm infants (GA ≥ 35 weeks; mean age 2.6 months) (2:1) to receive a single intramuscular dose of nirsevimab or placebo (19).

The primary endpoint for D5290C00003 and MELODY was the incidence of MA LRTI (including hospitalisation) caused by reverse transcription polymerase chain reaction (RT-PCR)-confirmed RSV up to 150 days after dosing (19). Hospitalisation for RSV-associated LRTI up to 150 days was a secondary endpoint. Very severe MA RSV LRTI (MA RSV LRTI with hospitalisation and need for supplemental oxygen or intravenous fluids) was also evaluated.

The primary endpoint was statistically significant in both studies. The relative risk reduction for MA RSV LRTI was 70.1% (95% CI 52.3-81.2; $p < 0.001$; incidence 2.6% with nirsevimab vs. 9.5% with placebo) in D5290C00003 and 74.5% (95% CI 49.6-87.1; $p < 0.001$; incidence 1.2% with nirsevimab vs. 4.1% with placebo) in MELODY (19, 20).

In D5290C00003, the incidence of hospitalisation for RSV LRTI was 0.8% with nirsevimab and 4.1% with placebo (efficacy 78.4%; 95% CI 51.9-90.3; $p < 0.001$) (21). Very severe MA RSV LRTI occurred in 0.4% and 3.3% of infants with nirsevimab and placebo, respectively (efficacy 87.5%; 95% CI 62.9-95.8) (19, 21).

In MELODY, hospitalisation for RSV LRTI occurred in 0.6% and 1.6% of infants in the nirsevimab and placebo groups, respectively (efficacy 62.1%; 95% CI -8.6-86.8; $p = 0.07$) (20). Very severe MA RSV LRTI up to 150 days post-dose occurred in 0.5% and 1.4% of infants in the nirsevimab and placebo groups, respectively (efficacy 64.2%; 95% CI -12.1-88.6) (19, 20).

Due to the COVID-19 pandemic, enrolment in the MELODY study was stopped early. Due to the very low number of RSV cases in both groups, the initial analysis of the study was underpowered to determine the

efficacy of nirsevimab against hospitalisation for RSV LRTI. After the pandemic, full enrolment was achieved (3012 infants) and efficacy against hospitalisation for RSV LRTI up to 150 days after injection was 76.8% (95% CI 49.4-89.4) and efficacy against very severe MA RSV LRTI was 78.6% (95% CI 48.8-91.0). Efficacy against MA RSV LRTI (primary endpoint) (76.4%; 95% CI 62.3-85.2) was consistent with that seen in the primary cohort of the study (22).

Safety was the primary endpoint in the phase II/III MEDLEY trial, in which 925 infants at higher risk of severe RSV disease and preterm infants (GA < 35 weeks) entering their first RSV season were randomised (2:1) to receive either a single intramuscular dose of nirsevimab and 4 placebo injections or 5 monthly intramuscular doses of palivizumab (19, 23). The primary endpoint was met as the incidence of adverse events was similar between treatment groups and cohorts. The incidence of MA RSV LRTI up to 150 days post-dose was 0.6% with nirsevimab and 1.0% with palivizumab (19, 22).

Nirsevimab has a favourable safety profile. The most common adverse reaction was rash (0.7%) occurring within 14 days of treatment. The majority of cases were mild to moderate. In addition, pyrexia and non-serious injection site reactions were reported at a rate of 0.5% and 0.3% within 7 days post dose, respectively (19).

Finally, HARMONIE is a real-world phase 3b study in which 8058 infants (>29 weeks GA and ineligible for palivizumab) were randomised (1:1) to receive nirsevimab or standard of care (SOC) before or during their first RSV season (24). The efficacy of nirsevimab against RSV LRTI hospitalisation (primary endpoint) and very severe RSV LRTI (secondary endpoint) was 83.21% (95% CI 67.77- 92.04) and 75.71% (32.75-92.91), respectively (24).

VACCINES

Respiratory syncytial virus vaccine (bivalent, recombinant) (RSVpreF; Abrysvo®)

RSVpreF contains two recombinant, stabilised RSV prefusion F antigens representing the RSV-A and RSV-B subgroups. RSVpreF is licensed by the EMA from July 2023 for (a) passive protection against RSV LTRI in infants from birth to 6 months of age following maternal immunisation during pregnancy and (b) active immunisation of persons > 60 years of age for prevention of RSV LTRI (25). The latter indication is beyond the scope of this paper. For infant protection, RSVpreF should be given as a single dose between 24 and 36 weeks of gestation (25).

The approval for passive protection against RSV LTRD (lower respiratory tract disease) in infants was based on the results of the MATISSE study, a phase 3, multicentre, randomised (1:1), double-blind, placebo-controlled trial in which 7,392 pregnant women with uncomplicated singleton pregnancies were randomised to receive either RSVpreF or placebo (25). Co-primary endpoints assessed in parallel were severe MA RSV LRTD and PCR-RT confirmed RSV LRTD in infants at 90, 120, 150 and 180 days of age. Vaccine efficacy (VE) was defined as the relative risk reduction of the endpoint in the RSVpreF group compared with the placebo group (20, 21). A lower limit of the CI for VE (99.5% CI at 90 days; 97.58% CI at later intervals) > 20% was considered to meet the success criterion for vaccine efficacy with respect to the primary endpoints (25, 26).

At the time of the prespecified interim analysis, the VE success criterion for the severe MA RSV LRTD endpoint was met with a VE of 81.8% (99.5% CI 40.6% to 96.3%) at 90 days and 69.4% (97.58% CI 44.3% to 84.1%) at 180 days after birth. The VE of 57.1% (99.5% CI 14.7%

Table 1: Efficacy of nirsevimab in term and preterm infants entering their first RSV season.

Group	Treatment	N participants	Incidence N (%)	Efficacy [a] (95% CI) NNT
Efficacy in infants against MA RSV LRTI through 150 days post dose				
Very and moderately preterm GA ≥29 to <35 weeks (D5290C00003) [b]	Nirsevimab	969	25 (2.6)	70.1% (52.3, 81.2) c p <0.001
	Placebo	484	46 (9.5)	NNT= 14.5
Term and late preterm GA ≥35 weeks (MELODY Primary cohort)	Nirsevimab	994	12 (1.2)	74.5% (49.6, 87.1) c p <0.001
	Placebo	496	25 (5.0)	NNT=26.3
MELODY full cohort	Nirsevimab	2009	24 (1.2)	76.4% (62.3, 85.2) p <0.001
	Placebo	1003	54 (5.4)	NNT=23.8
Efficacy in infants against MA RSV LRTI with hospitalization through 150 days post dose				
Very and moderately preterm GA ≥29 to <35 weeks (D5290C00003) [b]	Nirsevimab	969	8 (0.8)	78.4% (51.9, 90.3) c p <0.001
	Placebo	484	20 (4.1)	NNT=30.3
Term and late preterm GA ≥35 weeks (MELODY Primary cohort)	Nirsevimab	994	6 (0.6)	62.1% (-8.6, 86.8) p = 0,07
	Placebo	496	8 (1.6)	NNT=100
MELODY full cohort	Nirsevimab	2009	9 (0.4)	76.8% (49.4, 89.4) p < 0.001
	Placebo	1003	20 (2.0)	NNT=62.5
Efficacy in infants against very severe MA RSV LRTI through 150 days post dose				
Very and moderately preterm GA ≥29 to <35 weeks (D5290C00003) [b]	Nirsevimab	969	4 (0.4)	87.5% (62.9, 95.8) [d]
	Placebo	484	16 (3.3)	
Term and late preterm GA ≥35 weeks (MELODY Primary cohort)	Nirsevimab	994	5 (0.5)	64.2% (-12.1, 88.6) [d]
	Placebo	496	7 (1.4)	
MELODY full cohort	Nirsevimab	2009	7 (0.3)	78.6% (48.8, 91.0)
	Placebo	1003	17 (1.7)	

a: based on relative risk reduction versus placebo. / b: All subjects who received 50 mg irres

Table 2: Efficacy of RSVpreF against RSV LRTI in infants.

Time period	Abrysvo® (N subjects =3 495)	Placebo (N subjects =3480)	VE% (CI) [a]
Severe MA LRTI due to RSV in infants from birth to 6 months of age (N (%))			
90 days	6 (0.2)	33 (0.9)	81.8 (40.6, 96.3)
120 days	12 (0.3)	46 (1.3)	73.9 (45.6, 88.8)
150 days	16 (0.5)	55 (1.6)	70.9 (44.5, 85.9)
180 days	19 (0.5)	62 (1.8)	69.4 (44.3, 84.1)
MA LRTI due to RSV in infants from birth through 6 months of age (N (%))			
90 days	24 (0.7)	56 (1.6)	57.1 (14.7, 79.8)
120 days	35 (1)	81 (2.3)	56.8 (31.2, 73.5)
150 days	47 (1.3)	99 (2.8)	52.5 (28.7, 68.9
180 days	57 (1.6)	117 (3.4)	51.3 (29.4, 66.8)

a= 99.5% CI at 90 days; 97.58% CI at later intervals.

to 79.8%) at 90 days and 51.3% (97.58% CI 29.4% to 66.8%) at 180 days after birth did not meet the success criterion for the endpoint MA RSV LRTD (25, 26).

Vaccine efficacy (VE) is shown in Table 2.

In MATISSE, maternal adverse events reported within 1 month after vaccination were similar in the RSVpreF group (14%) and the placebo group (13%). In pregnant women at 24-36 weeks of gestation the most frequently reported adverse reactions were vaccination site pain (41%), headache (31%) and myalgia (27%). The majority of local and systemic reactions in maternal participants were mild to moderate in severity and resolved within 2-3 days of onset (27). No safety signals were observed in infants up to 24 months of age. The incidence of adverse events reported in infants within 1 month after birth was similar in the RSVpreF group (37%) and the placebo group (35%). Major birth outcomes assessed in the RSVpreF group compared to placebo included premature birth (6% and 5%, respectively), low birth weight (5% and 4%, respectively) and congenital anomalies (5% and 6%, respectively) (25). In a subgroup analysis, a difference in the rate of preterm birth was found between vaccine recipients (8.3%) and placebo recipients (4.0%) in South Africa and Brazil (upper middle income economies) (27). This difference was not observed in cohorts from high-income countries.

The Food and Drug Administration (FDA) prescribing information for RSVpreF includes a warning to inform that there was a numerical imbalance in preterm births in those receiving RSVpreF (5.7%) compared with those who received placebo (4.7%). Therefore, the FDA restricts administration of RSVpreF to pregnant women between 32 and 36 weeks of gestation (28). According to the Medicines and Healthcare Products Regulatory Agency (UK), RSVpreF should not be used in pregnant women at less than 28 weeks of gestation (29). In contrast, according to the EMA, RSVpreF can be administered between weeks 24 and 36 of gestation (25). The Superior Health Council (SHC) is relatively reassured that there is no clear signal of an increase in preterm births in high-income countries following administration of Abrysvo in pregnancy. According to the SHC, vaccination later in pregnancy may reduce the potential risk of preterm birth. In addition, an interval of at least two weeks is recommended between the administration of RSVpreF and the administration of tetanus, diphtheria and acellular pertussis vaccine (Tdap), which is recommended in Belgium for all pregnant women between 24 and 32 weeks. Therefore the SHC favours administration during weeks 28-36 of pregnancy) (30).

IMPLEMENTATION STRATEGIES

There are no head-to-head comparisons between passive infant immunisation with nirsevimab and maternal immunisation with RSVpreF. Therefore, the RSV subcommittee of the Joint Committee on Vaccination and Immunisation (JVCI) (UK) sought expert opinion on the comparison of the endpoints of the MELODY (nirsevimab) and MATISSE (RSVpreF) trials (31). The Committee noted that the background attack rates in the control groups for RSV MA LRTI and RSV hospitalisations were higher in MELODY than in MATISSE. Seasonal recruitment in MELODY versus year-round recruitment in MATISSE, interruptions in RSV transmission during the pandemic, and the different populations included may all have contributed to the difference in background rates. The median age at passive immunisation of infants in MELODY was 2.6 months (range 0.03-11). In the maternal vaccine trial, babies were born with maternal antibody and therefore protected from birth (26). The primary endpoints for RSV MA LRTI were considered similar between the trials. However, the definitions for severe or very severe LRTI and the secondary endpoints of hospitalisation were considered to be very different (31).

Modellers at the London School of Hygiene & Tropical Medicine (LSHTM) simulated 2 options for RSVpreF:

- a seasonal programme between July and the end of December and
- a year-round programme.

Coverage was estimated to be 60% based on pertussis vaccination uptake data (31).

Three scenarios were modelled for nirsevimab with a 90% uptake:

- seasonal from September to February;
- seasonal with catch-up for children aged < 6 months at the beginning of the season; and
- a year-round birth dose offer from March to February.

The impact of each programme was compared in terms of QALYs and costs averted, and the number needed to vaccinate (NNV) for

- a seasonal and a year-round maternal programme, and
- a seasonal, a seasonal with catch-up, and a year-round monoclonal programme.

The greatest impact was seen with the seasonal catch-up and year-round monoclonal programmes, while the most efficient in terms of NNV was the seasonal programme, both maternal vaccination and monoclonal antibodies (without catch-up). For both products, estimates for weaning immunity beyond the published data are highly uncertain and could have major impacts on their cost effectiveness (31).

The most cost-effective programme was seasonal for either product, followed by seasonal with catch-up for nirsevimab, followed by the year-round programme for either product. When the products were similarly priced, it was difficult to differentiate between the 2 on the basis of cost-effectiveness.

Following modelling of the impact and cost-effectiveness of potential immunisation strategies undertaken by the London School of Hygiene and Tropical Medicine (LSHTM), the Joint Committee on Vaccination and Immunisation (JVCI, UK) requested the University of Antwerp (UA) to conduct a second opinion modelling using a model developed for the REspiratory Syncytial virus Consortium EUrope (RESCEU) project. Overall, despite the different approaches used, the cost-effectiveness results were similar between the two models, ensuring that the

Table 3: Published RSV prevention Guidelines.

Country	Nirsevimab	RSVpreF	
Spain	For the 2023-24 season: In order of priority: 1. Child populations at high risk of severe RSV disease, including: (a) premature infants with a GA<35 weeks (1 dose before 12 months of age); (b) patients with CHD with significant haemodynamic involvement; (c) with BPD and (d) with other underlying pathologies who are at a high risk of developing severe RSV bronchiolitis. In risk conditions b, c and d, administration prior to each RSV season up to 24 months of age 2. Children < 6 months of age at the beginning or during the RSV season: For the 2023-2024 season, the administration is recommended to children under 6 months of age born from April 1, 2023 to March 31, 2024. Immunisation of those born during the season will be prioritized and those born earlier will be immunised as soon as possible.	Not included.	Comité Asesor de Vacunas. Asociación Española de Pediatría. July 2023 (35, 36).
France	For 2023-2024 season: All infants < 6 months at the start of the RSV epidemic period. Vulnerable infants (GA < 32 weeks, chronic lung disease, CHD): extension to infants < 12 months at the start of the epidemic period. Nirsevimab could also be used during the second epidemic season for the most vulnerable infants currently affected by the second season of palivizumab.	The place of the maternal vaccine should also be considered in a combined strategy with nirsevimab	Société Française de Néonatologie (SFN) et du Groupe de Pathologie Infectieuse Pédiatrique (GPIP). June 5, 2023 (37). Avis des Sociétés Savantes Françaises de Pédiatrie (38).
Sweden	The Läkemedelsverket, with the support of the expert group, recommends the following order of priority: Prophylaxis up to 12 months of age (first RSV season) • Risk group level 1: nirsevimab, or palivizumab if nirsevimab is not available. Priority group for winter season 2023/2024. • Risk group level 2: nirsevimab, if available, in which case priority group for winter season 2023/2024. • Risk group level 3 and 4: nirsevimab, provided that the drug is available to all children in these risk groups and that an equitable national implementation can be achieved	Not included	Läkemedelsverket Swedish Medical Products Agency. September 22, 2023 (39).
Luxembourg	Nirsevimab is recommended for: • All newborns born during a period of high circulation of the RSV virus (from October 1 to March 30) preferably before the leaving the maternity ward. • As a catch-up in 2023, non-immunised children born after January 1, 2023 at the beginning of the season of high circulation of the RSV virus (from October 2023). • From 2024, all infants under 6 months of age, born outside the period of high circulation of RSV (April to September), at the start of the season of high circulation of the RSV virus. • Children aged over 12 months of age with underlying conditions that increase the risk of severe RSV infection, annual injection/year, up to 2 years of age	Not included	Conseil Supérieur des Maladies Infectieuses (CSMI). July 14, 2023 (40).
Italy	We should consider organising universal administration of nirsevimab before discharge from the maternity ward, for all children born during the October-March epidemic period. Children born between April and September should be passively immunised in October of the year of birth by the local services and their paediatrician of their choice.	Not included	Position Paper. Board del Calendario Vaccinale per la Vita e della Società Italiana di Neonatologia (41).
United Kingdom	Preference for year-round immunisation programme to ensure high uptake and for reasons of operational effectiveness, as it would be less complex and resource-intensive to deliver than running seasonal campaigns. No preference for either product.		Joint Committee on Vaccination and Immunisation (JCVI). September 11, 2023 (31).
United States	Maternal RSV vaccination or RSV mAb in infants. Most infants will not need both. Vaccination for pregnant women: • 1 dose of maternal RSV vaccine during weeks 32- 36 of pregnancy, immediately before or during the RSV season. Immunisation of infants and young children: • 1 dose of nirsevimab for all infants aged < 8 months born during or entering their first RSV season. • 1 dose of nirsevimab for infants and children aged 8-19 months who are at increased risk of severe RSV disease and entering their second RSV season.		Centers for Disease Control and Prevention (CDC) (42).
Belgium	Either maternal vaccine for women expected to give birth between early September and the end of March, preferably during weeks 28-36 of pregnancy; or nirsevimab (Beyfortus®) for all babies born to unvaccinated mothers or born prematurely (< 30 w) or within the two weeks following the vaccine administration. Nirsevimab could be offered: - At birth (maternity ward) for babies born during the RSV season (October to March) with a single dose of 50 mg (as < 5 kg) - During the regular immunisation programme (catch-up) for those aged ≤ 6 months at the start of the RSV season, using the dose of 50 mg if < 5 kg; and 100 mg if > 5 kg. - Nirsevimab could be administered with other vaccines. Administration of nirsevimab to infants born to vaccinated mothers could be considered for • infants with a sufficiently increased risk of severe RSV disease and born to mothers vaccinated at the end of the season (between January and March) • infants born to women expected to have an inadequate immune response to vaccination (immunocompromised status) or reduced transplacental antibody transfer • infants who have undergone cardiopulmonary bypass or neonatal blood exchange resulting in loss of maternal antibodies. In premature babies, nirsevimab should be administered 48 hours before discharge home (during the RSV season or during the month before). Nirsevimab is recommended for children at increased risk of severe disease nirsevimab 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) and during their second RSV season (regardless of the vaccination status of the mother).		Superior Health Council. December 2023.

Some of these recommendations are outside the EMA label (prevention of RSV LRTI in neonates and infants during their first RSV season)(14)

modelling was robust (31).

The JVCI Committee raised the question whether existing and future maternal vaccines for other diseases might make maternal vaccination a crowded space (26).

The JVCI Committee agreed that, based on current data, no product can be preferred over the other and that at present there is a preference for a year-round programme of either maternal vaccine or mAb, but that a seasonal programme is also an option.

The JCVI had previously recommended that palivizumab should be replaced by nirsevimab for the currently eligible cohort (31).

Recommendations

Strategies for implementing preventive measures should be based on epidemiological and socioeconomic data (32). Recommendations will depend on the organisation of health care systems in different countries and settings. Issues for discussion include the optimal choice between available agents and their respective target population (i.e., only infants with risk factors or all infants in the first 6 or 12 months of life) and schedule (i.e., pre-seasonal, seasonal with catch-up, all year-round). Because all infants are at risk of developing MA RSV LRTI during their first year of life and more than 85 to 90 % of infants hospitalised for RSV infection are previously healthy, experts support universal pre-seasonal immunisation against RSV (33, 34).

Published recommendations about RSV prevention in children are summarised in Table 3 (30, 31, 35-42). Some of these recommendations are outside the EMA label (prevention of RSV LRTI in neonates and infants during their first RSV season).

The Belgian Paediatric RSV Experts Group opinion

Based on the literature review, available epidemiological data, guidelines from other countries and taking into account:

- the accumulating epidemiological data on the severe health burden
- the major social and economic impact of RSV infection, with high direct and indirect costs
- that virtually all infants are infected before the age of 2 years
- that most MA cases, including hospitalisations, occur in otherwise healthy term infants
- that most RSV-associated hospitalisations occur before the age of 1 year, with almost 25 % occurring between 6 and 12 months of age (2, 3, 6)
- the seasonality of RSV infections in infants
- the availability of a safe and effective long-acting mAb (nirsevimab) and an effective maternal vaccine (RSVpreF) for the prevention of MA RSV LRTD in newborns and infants from birth through their first RSV season,
- the recommendations and advice of many European paediatric societies, JVCI, CSMI, and CDC

<u>The Belgian Paediatric RSV Experts Group recommends:</u>

- an immunisation strategy for:
  - all infants aged < I year, at the start of their first RSV season
  - infants with risk factors aged < 2 years, also at the start of their second RSV season
- implementation both in and out of-hospital
- either
- passive immunisation with nirsevimab (Beyfortus®):
  - for neonates at the maternity/neonatal unit before discharge or at the paediatric outpatient come-back visit at one week of age during the epidemic season from October to March.
  - at the beginning of the season (October) for infants born outside epidemic seasons of:
    - all infants under one year of age,
    - infants with risk factors in the second year of life,
  - OR passive immunisation of the newborn with the maternal RSVpreF vaccine (Abrysvo®):
- strategy and implementation to be discussed and agreed with obstetricians, gynaecologists and experts on maternal immunisation. The Superior Health Council (SHC) recommends vaccination, preferably between 28 and 36 weeks of gestation, for mothers suspected to deliver between early September and the end of March (30).
- Administration of nirsevimab (Beyfortus®):to infants born from vaccinated mothers could be considered (30):
  - For infants at sufficiently increased risk of severe RSV disease and born from mothers vaccinated at the end of the season (between January and March)
  - For all babies born within 2 weeks following maternal RSVpreF vaccine administration
  - For infants who have undergone cardiopulmonary bypass or neonatal blood exchange, resulting in loss of maternal antibodies.
  - When pregnant woman is expected to have an inadequate immune response to vaccination or a reduced transplacental antibody transfer.
- a low cost to parents and quick refund, in order to avoid health inequalities
- a sufficient supply
- a well-coordinated referral system with clear communication channels to optimise interdisciplinary collaboration
- a practical, easily accessible online registration procedure to collect immunisation data in a national immunisation/vaccination database
- a real-world observational survey of efficacy during the first 5 years of use
- awareness campaigns with tailored messages addressed to health care professionals, parents, lay public and caregivers.

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Conflict of interest

The authors have no conflicts of interest to declare with regard to the topic discussed in this manuscript.

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