Rapid Response Report

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

RAPID RESPONSE REPORT

EVALUATION OF ABRYSVO® MATERNAL VACCINE AGAINST RSV INFECTION IN INFANTS

15 December 2023

ELENA COSTA, DOMINIQUE ROBERFROID

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AE	Adverse Event
EMA	European Medicines Agency
EudraCT	European Union Drug Regulating Authorities Clinical Trials,
FDA	Food and Drug Administration
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
GSK	GlaxoSmithKline
HAS	Haute Autorité de Santé
HTA	Health Technology Assessment
ICU	Intensive Care Unit
IRT	Interactive Response Technology
JCVI	Joint Committee on Vaccination and Immunisation
KCE	Belgian Health Care Knowledge Center
LRTI	Lower Respiratory Tract Infection
MA-LRTI	Medically Assisted Lower Respiratory Tract Infection
MA-RSV-LRTI	Medically Assisted RSV Related Lower Respiratory Tract Infection
MA-RSV-RTI	Medically Assisted RSV Related Respiratory Tract Infection
NNH	Number Needed to Harm
NNV	Number Needed to Vaccinate
RCT	Randomized Controlled Trial
RoB	Risk of Bias
RR	Respiratory Rate
RSV	Respiratory Syncytial Virus
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SAE	Severe Adverse Events
SHC	Superior Health Council
SpO2	Peripheral Capillary Oxygen Saturation
VE	Vaccine Efficacy

ABSTRACT

BACKGROUND

We performed a rapid review of the evidence of Abrysvo®, a maternal vaccine against respiratory syncytial virus (RSV) infections in infants <6 months. Based on the interim analysis of one RCT (N=7538), vaccine efficacy for severe medically assisted RSV related lower respiratory tract infection (LRTI) spans from 81.8% (99.5% CI: 40.6; 87.1) to 69.4% (97.6% CI: 44.3; 84.1) within 90 days and 180 days of life, respectively (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). There was no data on RSV-related mortality or admission in Intensive Care Unit (ICU). No safety signal was detected, but statistical power was limited.

1 BACKGROUND

Respiratory syncytial virus (RSV) stands out as the predominant etiological agent responsible for acute lower respiratory infections in the paediatric population with RSV representing 0.7% (95%CI: 0.6-0.9) of all-cause deaths in children younger than 5 years in industrialised countries. RSV has the highest burden in children aged 0 to 6 months of age, among whom, globally, 60% of cases occur in the first three months of age. In industrialised countries, the incidence of RSV-related acute lower respiratory infections hospital admissions in infants 0-6 months are an estimated 29.3 (95%CI: 20.0-42.8) per 1000 children per year. The hospital admission rate is higher in the age bracket 0-3 months and corresponds to 36.9 (95%CI: 20.9-65.0) per 1000 children per year.[1]

To feed into the advisory report of the Superior Health Council (SHC) on preventive strategies against RSV disease in infants, the Belgian Health Care Knowledge Center (KCE) reviewed the evidence on the efficacy and safety of nirsevimab (Beyfortus®, Sanofi) and a maternal vaccine (Abrysvo®, Pfizer). Beyfortus® is an extended half live monoclonal antibody indicated for the prevention of RSV lower respiratory tract disease in neonates and infants during their first RSV season. Abrysvo® is indicated for passive protection against LRTI caused by RSV in infants from birth through 6 months of age through maternal immunisation during pregnancy. Both products were granted a marketing authorization from EMA. The final SHC report can be found on SHC website.[a].

The current report evaluates the efficacy and safety of Abrysvo® vaccine. Passive immunity of infants through transfer of IgG antibodies from immunized pregnant women has been established for the prevention of tetanus, pertussis, influenza and COVID-19. Similarly, the hypothesis underlying RSV vaccination during pregnancy is that maternal immunization might confer passive immunity to the newborn, thereby reducing the risk of severe RSV-related outcomes during the early months of life. Pfizer‘s RSV preF vaccine 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. The neutralising antibodies cross the placenta, providing infants with protection up to 6 months after birth. The recommended dose is one single injection into the muscle of the upper arm. The vaccine has been approved by EMA for the use in pregnant individuals between weeks 24 and 36 of gestation. Abrysvo® is also approved for active immunisation of individuals 60 years of age and older for the prevention of LRTI caused by RSV.

[a] https://www.health.belgium.be/en/superior-health-council

2 METHODS

We performed a rapid review of the evidence based on retrieval and critical appraisal of the pivotal randomised controlled trials (RCTs). This document summarises evidence coming from RCTs investigating the use of RSV vaccination in pregnant women compared to a placebo and its effects on RSV-related mortality (critical outcome), RSV-related ICU admission (critical outcome), RSV-related hospitalisation (critical outcome), severe RSV-related illness cases (critical outcome), RSV-related illness (important outcome) and serious adverse events in pregnant women and in infants (critical outcomes) (see Table 1).

Table 1 – Review inclusion criteria

PICO	Inclusion
Patients	Pregnant women
Intervention	Maternal vaccine (Abrysvo®, Pfizer)
Comparators	Placebo
Outcomes	a. Critical outcomes in infants: - RSV-related mortality rate - RSV-related ICU admission - RSV-related hospitalisation rate - Hospitalisation length of stay (LOS) - Rate of severe RSV-related lower respiratory tract illness (LRTI) - Rate of serious adverse events in mothers and infants b. Important outcomes in infants: - Rate of RSV-related LTRI - Rates of acute respiratory illness (ARI) - Reactogenicity
Setting	High-income countries
Type of studies	Phase 3 RCT

We searched for pivotal RCTs by searching RCTs taken into consideration in RSV-related maternal vaccination advice given from regulatory agencies and Health Technology Assessment (HTA) agencies abroad.[2-5] It was completed via a Medline search and search of the website Clinicaltrials.gov.[b]

Retrieved evidence was assessed for quality using the Risk of Bias 2 (RoB 2) tool,[6] in order to assess various aspects of the trial design, conduct, and reporting to determine the level of bias in the study. The purpose is to identify any methodological flaws that may affect the validity of the trial results.

In order to draw conclusions based on the overall confidence in the evidence retrieved, we applied the GRADE methodology.[7] This assessment is based on several factors, including risk of bias, inconsistency in results, indirectness of evidence, imprecision, and publication bias.

[b] Search strategy: ("Infant"[Mesh] OR "Infant, Extremely Premature"[Mesh] OR "Infant, Extremely Low Birth Weight"[Mesh]) AND (("Pregnancy"[Mesh]) AND ("Respiratory Syncytial Virus Vaccines"[Mesh] OR "RSV vaccine" OR "Respiratory Syncytial Virus Vaccine" OR ("RSV" AND "Vaccine") OR ("Respiratory Syncytial Virus" AND "vaccine")))

3 RESULTS

We report below the results of the Matisse trial on Abrysvo®.[8] It was sponsored by Pfizer and was the basis of the recommendations given by the French Haute Autorité de Santé (HAS)[4] and the Joint Committee on Vaccination and Immunisation (JCVI).[5]

Of note, we retrieved another RCT sponsored by Novavax and published in 2020. [9] Novavax vaccine was excluded from the clinical evaluation process since the use of their RSV vaccine in pregnant women did not meet the pre-specified success criterion for efficacy against RSV-associated, medically significant Lower Respiratory Tract Infection (LRTI) within 90 days of birth.[9] A third vaccine trial, sponsored by GSK, was withdrawn from further development since the clinical trial involving the GSK maternal vaccine candidate documented a 1.5-fold higher risk of preterm births in the group that received the vaccine.[5]

3.1 Matisse trial results

The main characteristics of the trial are presented in Table 2. In this phase 3, double-blind trial 3682 maternal participants received vaccine and 3676 received placebo. The final sample size is 14763 maternal participants, but results are not yet published. Medically attended severe RSV-associated lower respiratory tract illness in infants were evaluated at 90,120,150 and 180 days after birth.

Table 2 – PICO of MATISSE trial

Patients	a. **Inclusion:** o **Maternal participants**: healthy pregnant women age 49 or younger; gestational age 24 to 36 weeks the day of planned injection, reassuring second trimester ultrasound. o **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[c] **Infant participants**: 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 gestational age 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=3682) 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=3676)
Outcomes	a. **First primary end point: medically attended *severe* RSV-associated lower respiratory tract illness (RSV-MA-LRTI) in infants <6 months.** 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

[c] 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.

	breathing[d], 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 (RSV-MA-LRTI)**. 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[e], 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 7357 maternal participants and 7126 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=3353); 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	This is a prespecified interim analysis. According to the study protocol, interim analysis may be performed to assess efficacy and safety after at least 50% of the planned number of cases of MA-LRTI due to RSV have occurred (62 cases).. 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).

[d] 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.

[e] 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.

Table 3 – Quality appraisal of MATISSE trial

	RoB	Explanation
Randomization	Low	Allocation (randomization) of participants to vaccine groups proceeded through the use of a web-based Interactive Response Technology (IRT) system (see protocol)
Allocation concealment	Low	No imbalances between the intervention and control populations were observed at baseline
Blinding of participants and personnel	Low	The maternal participants, investigator, study coordinator, and all site staff were blinded (protocol)
Blinding of outcome assessors	Low	The maternal participants, investigator, study coordinator, and all site staff were blinded (protocol)
Incomplete outcome data	Low	In a sensitivity analysis for missing laboratory results for RSV-MA-LRTI multiple imputation examined the impact of missing nasal swab results on vaccine efficacy assumptions, including unfavorable ones. There was no impact on conclusion
Selective reporting	Low	MATISSE was registered in ClinicalTrials.gov (number, NCT04424316) and EudraCT (number, 2019-002943-85)
Other	Unclear	-Prespecified interim analysis, planned to occur as 62 cases (50% of expected cases) of MA-LRTI due to RSV had occurred. -Funded by Pfizer

RoB: Risk of Bias

Table 4 – Results of MATISSE trial

Outcome	Intervention (N=3495) n (%)	Control (N=3480) 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-RTI within 90 days	67 (1.9)	110 (3.2)	39.1 (16.7-55.7)	1.2 (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)
RSV-associated hospitalization within 180 days	19 (0.5)	44 (1.3)	56.8 (10.1–80.7)	0.7 (0.2-1.1)	138 (85-361)
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)	235 (NS)
Severe Adverse Events (SAEs)					
Maternal SAEs	147 (4.2)	129 (3.7)		0.5 (-1.4-0.4)	NNH: 210 (NS)
Infant SAEs	553 (15.5)	541(15.2)		-0.3 (-1.9-1.4)	NNH:340 (NS)

CI: Confidence Interval; MA-RSV-LRTI: Medically assisted RSV related lower respiratory tract infection; MA-RSV-RTI: Medically assisted RSV related Respiratory tract infection; NNV: Number to Vaccinate

The trial was judged good quality, with low risk of bias (Table 2). 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 authors performed imputation on missing laboratory results of RSV nasal swabs, considering various scenarios ranging from assuming the missing data was random (Missing At Random) to considering scenarios where missing data could negatively affect efficacy conclusions (Missing Not At Random). Regardless of the assumptions made about the missing data, none affected the overall conclusions.

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.

No safety signal was detected in this 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 groups, the more frequent SAEs were 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 hemorrhage 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.[f]

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. There was one RSV-related infant death in the placebo group.

3.2 Evidence quality

Following GRADE methodology, the evidence quality was judged high, although there was no data on RSV-related mortality or admission in Intensive Care Unit (ICU) which were critical outcomes of our review. 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 for imprecision 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. 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.[10] Downgrading the evidence quality by one level could be considered (moderate quality), until final robust results are published. In spite of a possibility according to protocol for the trial to be stopped for efficacy, the trial continued and it has recruited 14763 maternal participants and was last updated on Clinicaltrials.gov on September 28th 2023, and is no longer recruiting.

[f] Vaccine group : pain in the arm followed by lower extremity pain, premature labor, lupus, eclampsia. Placebo group: abruptio placentae

Table 5 – GRADE Summary of findings table

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RSV vaccine in expectant mothers	Placebo	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
RSV-related mortality in infants												
1	RCT				[a]				not estimable		-	CRITICAL
RSV-related ICU admission in infants												
1	RCT				[b]				not estimable		-	CRITICAL
RSV-related hospitalisation in infants (follow-up: 180 days)												
1	RCT	not serious	not serious	not serious	serious[c]	none	19/3495 (0.5%)	44/3480 (1.3%)	**RR 0.43** (0.25 to 0.73)	**8 fewer per 1,000** (from 9 fewer to 3 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
Severe Medically Attended RSV-related Lower Respiratory Tract Infection (follow-up: 90 days)												
1	RCT	not serious	not serious	not serious	not serious	none	6/3495 (0.2%)	33/3480 (0.9%)	**RR 0.18** (0.08 to 0.43)	**8 fewer per 1,000** (from 9 fewer to 5 fewer)	⨁⨁⨁⨁ High	CRITICAL
Medically Attended RSV-related Lower Respiratory Tract Infection (follow-up: 90 days)												
1	RCT	not serious	not serious	not serious	not serious	none	24/3495 (0.7%)	56/3480 (1.6%)	**RR 0.42** (0.26 to 0.68)	**9 fewer per 1,000** (from 12 fewer to 5 fewer)	⨁⨁⨁⨁ High	IMPORTANT

CI: *confidence interval;* ***RR:*** *risk ratio*

Explanations

a. Only 1 RSV-related death. It happened in the control group

b. The data were collected but the outcome was not reported

c. A small amount of cases and large confidence intervals

3.3 Vaccination impact

The absolute difference in risk of events between intervention and control groups is small, i.e. 0.8% (95% CI: 0.4-1.1) for severe medically assisted RSV related lower respiratory tract infection within 90 days of life. This results in a high NNV of 129 (95% CI: 89-234) to avoid a new event at day 90, and a NNV of 81 (95% CI: 57-136) at day 180. Figures are quite similar for MA-RSV-LRTI, but the higher bound of the NNT is much bigger. For RSV-associated hospitalization within 90 days, the NNV was 165 (95%CI: 104-407). These big NNV numbers must be put in perspective with the low incidence rates of RSV-related respiratory infections observed in the trial during the COVID-19 epidemic.

4 CONCLUSION

Based on the interim analysis of the MATISSE trial (N=7538), vaccine efficacy for severe medically assisted RSV related lower respiratory tract infection (LRTI) 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). There was no data on RSV-related mortality or admission in Intensive Care Unit. No safety signal was detected, but statistical power was limited. Final analysis of all trial data is necessary to confirm those results.

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Colophon

The Rapid Response Reports aim to answer urgent questions from decision-makers. They apply expedited methods to produce timely evidence-based recommendations.

Title:	Evaluation of abrysvo® maternal vaccine against RSv infection in infants
Authors:	Elena Costa (KCE)
Reviewers:	Roberfroid Dominique (KCE)
Disclaimer:	• The validation of the report results from a consensus or a voting process between the authors. • Only the KCE is responsible for errors or omissions that could persist. The policy recommendations are also under the full responsibility of the KCE.
Publication date:	19 December 2023 (2nd edition; 1st edition: 12 March 2025)
Language:	English
Format:	Adobe® PDF™ (A4)
Legal depot:	D/2025/10.273/40
ISSN:	2684-5830
Copyrights:	KCE Rapid Response Reports are published under a “by/nc/nd” Creative Commons Licence http://kce.fgov.be/content/about-copyrights-for-kce-publications.
How to refer to this document?	Costa E. Evaluation of abrysvo® maternal vaccine against RSv infection in infants. Brussels: Belgian Health Care Knowledge Centre (KCE). 2023. KCE Rapid Response Reports 397. D/2023/10.273/40. https://doi.org/10.57598/R3.397C This document is available on the website of the Belgian Health Care Knowledge Centre.