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ASSESSMENT

A living systematic review and meta analysis on the efficacy and safety of respiratory syncytial virus vaccines

Search period 18 May 2023 to 8 April 2024

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Abbreviations

ARI	Acute respiratory infections
EU/EEA	European Union/European Economic Area
GBS	Guillain-Barré syndrome
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
ILI	Influenza-like illness
mAbs	monoclonal antibodies
NRSI	Nonrandomized studies of interventions
RCT	Randomised controlled trial
RSV	Respiratory syncytial virus
RSV F	Respiratory Syncytial Virus Fusion (F) protein
SARI	Severe acute respiratory infection
VE	Vaccine Effectiveness

Executive summary

Background

Respiratory syncytial virus (RSV) is a prevalent and pervasive highly transmissible virus within the family *Pneumoviridae*, leading to respiratory illness of varying severity in humans. Most individuals experience their initial infection during early childhood, with near universal exposure by age two.

Since the discovery of RSV in 1956, vaccine development for the disease has been a major global health priority. Several clinical trials have taken place for nanoparticle-based and virus-like particles (VLP) RSV vaccines, which self-assemble to display several relevant viral epitopes, such as the prefusion F protein [1, 2]. In the EU/EEA, two RSV vaccines have been authorised for older adults 60+ years: Arexvy by GSK ([3,4)], and mResvia by Moderna [6], one RSV vaccine has been authorised for adults 18+ years (Abrysvo by Pfizer [5]) and one has been authorised as a maternal vaccine (Abrysvo by Pfizer) [7,8].

Live-attenuated candidate vaccines are also under development which target the paediatric population via intranasal administration. These vaccines are attenuated through various approaches [9-13] such as by deletion of the RSV RNA regulatory protein M2-2.

Understanding the different RSV vaccine subtypes and their safety, efficacy and effectiveness is essential for considerations related to implementation of vaccination programmes.

Objective

This report is an update of the primary systematic review, produced by the same authors within the same project and is similar to the published version [14]. The aim of both reviews is to assess different RSV vaccine efficacy, effectiveness, and safety compared to placebo, no intervention, vaccines for other respiratory infections, other RSV vaccines or monoclonal antibodies (mAbs) across all human populations.

Methods

Both the primary systematic review and this first update is informed by methodological standards outlined in the Cochrane Handbook [15]. All study selection, data extraction and risk of bias assessments were conducted independently and in duplicate. The reviews followed the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement (prisma-statement.org). The primary systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42023439128).

The initial literature search in the primary systematic review covered the period from 1 January 2000 to 18 May 2023. The first update search, which is presented in the current report covered the period from 19 May 2023 to 8 April 2024. The detailed description of the methods are presented in the primary systematic review [14]; this update provides only a brief overview.

This update involved:

- Conducting a literature search;
- Screening articles for inclusion;
- Extracting data from included studies;
- Performing a meta-analysis, when appropriate, and incorporating newly included studies;
- Assessing risk of bias for outcomes;
- Evaluating the certainty of evidence.

Results

The first search (primary systematic review) was conducted on 18 May 2023 and updated (first update of the living systematic review) on 8 April 2024. Only efficacy and safety data through clinical trials were identified in this first update of the living systematic review. Effectiveness and safety data from non-randomised studies of the effects of interventions (NRSI) were not available at the time of the updated living systematic review search.

In the updated review reported here, four new records [3,6,16,17] were included, including one new trial [6] and three additional analyses [3,16,17] of a previously included trial [4].

The newly-included trial is of an mRNA-based RSV prefusion vaccine in older adults (newly authorised vaccine mResvia by Moderna) [6] and updated results from a previously included trial which now covers two RSV seasons in older adults (authorised vaccine, Arexvy by GSK) [3].

The results on the efficacy and safety of RSV prefusion vaccines versus placebo in older adults have been updated. The direction of effects on outcomes and certainty of the evidence remains unchanged.

In this first update, we did not identify any new trials on RSV post-fusion F protein-based vaccines, maternal RSV F protein-based vaccines, RSV vaccines for women of childbearing age, or live attenuated RSV vaccines for infants and children.

The results on the efficacy and safety of RSV prefusion vaccines versus placebo in older adults have been updated to include four trials with 99 931 participants. However, the direction of effects on outcomes and certainty of the evidence remains unchanged.

In summary when taking results from both reviews, RSV prefusion vaccines effectively reduced both RSV-associated lower respiratory tract infections and acute respiratory illness in older adults (with trial results covering two RSV seasons post–dose 1). These findings were consistent for authorised vaccines and when analysing data from both authorised and unauthorised vaccines combined. In infants, maternal vaccination with RSV F protein-based vaccines led to a reduction in RSV-associated lower respiratory tract infections and severe RSV-associated lower respiratory tract infections (with trial results covering four RSV seasons from two hemispheres).

Efficacy results from review update

- RSV prefusion vaccines reduced RSV-associated lower respiratory tract infection (VE: 77%, high certainty of evidence) and acute respiratory illness (VE: 67%, high certainty of evidence) in older adults.
- Individual analysis of authorised vaccines showed similar efficacy.
- One trial (Arexvy) reported hospitalisations due to RSV (one in the vaccine arm of the trial and five in the placebo arm of the trial).
- Two trials (Arexvy, mResvia) found no RSV-related deaths in either group.
- RSV vaccines may result in little to no difference in RSV-related and all-cause mortality (low certainty of evidence).

Safety results from review update

- Serious adverse events were measured in all trials.
- RSV prefusion vaccines may result in little to no difference in serious adverse events related to vaccination in older adults (low certainty of evidence).
- Maternal RSV F vaccine is likely to have little to no difference in serious adverse events in both infants and mothers (low certainty of evidence).

Conclusion

This first update of the living systematic review suggests that RSV prefusion vaccines and maternal RSV F protein-based vaccines reduce RSV-associated respiratory illnesses in older adults and infants, respectively. Only efficacy and safety data through clinical trials were included in this systematic review. Effectiveness and safety data from non-randomised studies of interventions (NRSI) were not available at the time of the systematic review search. More research is needed to establish the long-term safety and effectiveness of these vaccines, particularly in real-world settings and across different population groups. Real-world effectiveness studies are needed to provide evidence on the protection the vaccines provide against other severe disease outcomes, including hospitalisations and deaths, which has not been possible to show through clinical trial design and data. They are also needed to monitor long-term safety, especially to identify rare adverse events such as the slightly increased risk observed of developing Guillain-Barré syndrome (GBS) following Arexvy and Abrysvo vaccination which led to a US Food and Drug Administration (FDA) warning of GBS in the prescribing information for these vaccines [19].

In order to gather comprehensive data on RSV vaccine performance across various regions and populations, international collaboration is essential. It would also be useful to establish or enhance international surveillance networks and standardised protocols for monitoring vaccine effectiveness and safety.

Future areas of research and efforts should include:

- Detailed description of RSV epidemiology and burden in different national/local contexts;
- The duration of immunity provided by RSV vaccines;
- Further and continuous monitoring of vaccine safety;
- The effect of vaccination on the likelihood of future RSV infections and severe disease;
- Potential impacts of RSV vaccination on other respiratory pathogens;
- The effectiveness of RSV vaccination in specific populations at high risk of severe disease , such as immunocompromised individuals or those with chronic respiratory conditions;
- The cost-effectiveness of RSV vaccination programmes in different healthcare settings and populations.

This living systematic review is planned to include an additional analyses up to June 2025. Non-randomised studies of interventions will provide essential insights into the real-world effectiveness and safety of RSV vaccines, particularly as findings from these studies begin to emerge in published literature. These newly-available real-world studies will be included in upcoming updates of this review.

Introduction

RSV disease and epidemiology

Respiratory syncytial virus (RSV) is a prevalent and pervasive, highly contagious virus within the family *Pneumoviridae*, leading to respiratory illness of varying severity in humans. The first infection is typically encountered in early life, with almost all children becoming infected by two years of age. Subsequent infections are common [19].

There is a significant disparity in disease severity based on individual's geographical location and their comorbidities. In healthy infants, RSV infection can result in bronchiolitis and is generally short-lived, and for those infants in high-income countries, 1.8% of cases require hospitalisation [20]. A higher burden of illness is seen in premature infants and those with comorbidities such as congenital heart disease, neuromuscular disease, immunodeficiency and Down syndrome [21-23].

More frequent and more severe disease is encountered in resource-limited countries. Globally, over 95% of RSV-associated lower respiratory tract infection episodes and over 97% of RSV-attributable deaths in children occur in low and middle-income countries, where access to supportive therapies, including supplemental oxygen, is limited. RSV infection is estimated to account for 2% of deaths in infants up to the age of five years worldwide, with the bulk of severe diseases occurring in the first year of life [24].

RSV infection also has notable indirect health implications. It serves as a significant co-factor in childhood bacterial pneumonia and otitis media, exacerbating the severity of this common illness [25]. Additionally, RSV infection has been linked to chronic wheezing and asthma [26], suggesting its influence extends to long-term respiratory conditions. Initially considered an infection confined to infants and severely immunocompromised people, RSV is now recognised as a significant contributor to morbidity in older adults and adults with chronic conditions such as chronic heart and lung diseases and immunodepression, causing severe lower respiratory tract diseases (pneumonia, bronchiolitis) and increasing hospitalisations [27-29].

In Europe, RSV epidemics have an annual seasonality, occurring mostly between October and March. Based on historical RSV surveillance data from 15 EU/EEA countries, all RSV seasons from 2010/11 to 2015/16 had a similar timing and epidemic course across Europe, with some variation within and between countries. The RSV epidemic in Europe each year progressed rapidly in the beginning of October, after week 40 and the median start of the RSV season was in the beginning of December, in week 49, in sentinel and non-sentinel surveillance systems. The peak was at the end of January, around week 4 and the median length of the RSV season was 16–18 weeks [30]. At the season starts, the virus spreads in a West-to-East pattern, with the RSV season starting one month later in eastern European countries than western European countries [31]. Higher relative humidity and lower temperatures have also been associated with increased RSV activity [31].

With the wide circulation of SARS-CoV-2 during the pandemic and the implementation of non-pharmaceutical interventions (NPIs), the regular seasonality of RSV in Europe was altered. In February 2020, after the introduction of NPIs, RSV activity was interrupted, similar to other respiratory pathogens. In the following season (2020/21) the RSV epidemics, if they occurred, began several weeks later than usual [32, 33], while in the summer of 2021, interseason RSV activity was observed in several countries [33, 34]. Following a very early and intense RSV epidemic in 2022/23, trends in RSV activity in 2023/24 and the 2024/2025 season to date suggest a return to pre-pandemic seasonality. During season 2022/23, early and high RSV circulation affected mainly newborns and very young children, causing severe disease and mortality. Severe acute respiratory infection (SARI) surveillance data for the RSV epidemic in the 2023/2024 winter season (week 40, 2023 to week 20, 2024) in ERVISS showed children aged 0-4 years had the highest risk of hospitalisation for RSV, with over 60% of patients admitted due to SARI admissions in this age group testing positive for RSV at the peak of activity in December. This age group, followed by those aged 65 years and above, accounted for 71% and 19%, respectively, of the RSV-positive SARI admissions during this period.

Children aged 0-4 years, and in particular young infants, had the highest risk of hospitalisation for RSV (with over 40% of tests among SARI admissions in this age group positive for RSV since week 47, 2024). This age group, followed by those aged 65 years and above, accounted for 83% and 11%, respectively, of the RSV-positive SARI admissions between weeks 40-49, 2024. Subsequent intensive care unit admissions occurred most commonly in infants, while reported deaths tended to be concentrated in older age groups [35].

The RSV epidemics that coincide with the circulation of other respiratory viruses in Europe, like seasonal influenza and SARS-CoV-2, result in acute pressure on healthcare systems, primary care providers, emergency services and paediatric hospitals. In most EU/EEA countries, surveillance of mild acute respiratory infections (ARI) or influenza-like illness (ILI) in primary care, primarily caused by RSV, influenza, or SARS-CoV-2, relies on nationally coordinated sentinel networks of primary care physicians, typically general practitioners (GPs), covering 1–6% of the population. Physicians may report the weekly number of ILI and/or ARI cases they encounter, and in some cases,

data on RSV testing. For severe disease linked to RSV, influenza, or SARS-CoV-2, many countries conduct sentinel surveillance for hospitalised cases with severe acute respiratory infection (SARI) based on case definitions, with all or a subset of SARI patients undergoing testing. Additionally, laboratory-based non-sentinel surveillance systems are established in many EU/EEA countries. However as of today, RSV is not an EU notifiable disease by legislation. ECDC collects weekly surveillance data from EU/EEA countries through the European Surveillance System platform, and data are presented and analysed in the weekly bulletin at ERVISS.org.

RSV vaccines

RSV was first discovered in 1956 and attempts to develop a vaccine [36] has been a major global health priority for many years. However, the journey towards its creation has been fraught with considerable challenges. Indeed, lessons learned in the early stages of RSV vaccine development have informed vaccine strategies for several other infectious diseases, such as SARS-CoV-2 [37]. RSV vaccines which have been recently authorised are targeted towards three separate populations: infants, pregnant women to protect newborns, and older adults, with specific candidates indicated for more than one group and other agents being population specific.

Several extended half-life monoclonal antibodies are also in development or recently approved, which have demonstrated efficacy against RSV disease, including clesrovimab and nirsevimab. Nirsevimab is also approved in the EU. Another monoclonal antibody, palivizumab, is authorised for use in the EU for children who are at high risk for the disease. These monoclonal antibodies have been reviewed in a recent systematic review and meta-analysis [38] and are not within the scope of this review.

There are three approved RSV vaccines (Arexvy by GSK for those 60+ years, Abrysvo by Pfizer for those 18+ years and mResvia by Moderna for those 60+ years) and one approved maternal RSV vaccine (Abrysvo by Pfizer). Understanding the various RSV vaccine subtypes and their safety, efficacy and effectiveness is essential for considerations in relation to implementation.

Vaccine Product	Manufacturer	Product type/platform	Indication	Posology	Date of authorisation
Arexvy [3,4, 39]	GlaxoSmithKline Biologicals (GSK)	Recombinant RSV virus pre-fusion F protein, adjuvanted with AS01E	Arexvy is indicated for active immunisation for the prevention of lower respiratory tract disease (LRTD) caused by respiratory syncytial virus in: • adults 60 years of age and older; • adults 50 through 59 years of age who are at increased risk for RSV disease.	For adults 60 years and above, and 50 to 59 years of age with increased risk for RSV disease: A single dose of 0.5 mL should be administered.	6 June 2023
Abrysvo [5, 40]	Pfizer	RSV pre-fusion F protein-based vaccine (bivalent, recombinant)	Abrysvo is indicated for: - Passive protection against lower respiratory tract disease caused by respiratory syncytial virus (RSV) in infants from birth through 6 months of age following maternal immunisation during pregnancy. -Active immunisation of individuals 18 years of age and older for the prevention of lower respiratory tract disease caused by RSV.	Pregnant women: A single dose of 0.5 mL should be administered between weeks 24 and 36 of gestation. Individuals 18 years of age and older: A single dose of 0.5 mL should be administered.	23 August 2023 (authorised for use in individuals 60 years and over) 1 April 2025 (authorised for extension of indication for use in individuals 18 years and over)
mResvia [6, 41]	Moderna Biotech Spain	Respiratory Syncytial Virus mRNA vaccine. (Single-stranded 5' capped mRNA encoding the Respiratory syncytial virus glycoprotein F stabilized in the prefusion conformation)	mResvia is indicated for active immunisation for the prevention of lower respiratory tract disease (LRTD) caused by Respiratory Syncytial Virus in adults 60 years of age and older.	Adults 60 years of age and older: one single dose of 0.5 mL should be administered.	22 August 2024

Methods

This first update of the living systematic review is informed by methodological standards outlined in the Cochrane Handbook [15]. All study selection, data extraction and risk of bias assessments were conducted independently and in duplicate. This report followed the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement (prisma-statement.org). The primary systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42023439128).

Criteria for considering studies for this review

Types of studies

Inclusion criteria

- Vaccine efficacy:
  - Randomised controlled trials (RCTs), where participants are randomly allocated to receive either the vaccine or a control (placebo or an alternative vaccine).
- Vaccine effectiveness
  - Cohort studies with at least one exposed group (e.g. individuals receiving the vaccine of interest) and one unexposed or comparison group (e.g. individuals not receiving the vaccine, receiving a placebo, or receiving a different vaccine).
  - Case-control studies comparing individuals with the disease (cases) to individuals without the disease (controls) and assesses the differences in vaccination status between the two groups.
  - Test-negative case-control studies where individuals presenting with symptoms similar to the disease of interest are tested. Cases are those with a positive test. Controls are those with a negative test. The differences in vaccination status between the two groups are assessed.
- Vaccine safety
  - Safety was evaluated for any vaccine with efficacy and/or effectiveness studies by examining any study design that includes a valid comparison group, such as a placebo, people who are unvaccinated, or an alternative vaccine group. These designs provide complementary information on the safety profile of vaccines across different populations and settings. These include, but are not limited to, Phase I and Phase II clinical trials.
- Intended to capture and listed any ongoing Phase III or IV trials related to RSV vaccines.

Exclusion criteria

- Studies focused on dose-finding schedules and immunogenicity assessment;
- Single-arm studies, including case reports and case series;
- Review articles;
- Thesis, editorials, letters, editorials, commentaries, etc.
- Results reported in an abstract form only (due to limited information on study methods);
- Laboratory and animal studies.

Subgroups

- Demographic characteristics: adults, older adults, infants, high-risk infants, immunocompromised individuals, and pregnant individuals.
- Geographic location: low- and middle-income countries and high-income countries.
- Vaccines: number of doses (e.g. once, twice, three times) and different types of RSV vaccines

Types of participants

Inclusion criteria

- All human populations
- Any age, sex, gender, ethnicity, or geographic location
- No restriction on medical history, i.e. healthy individuals, immunocompromised individuals, pregnant people, and participants with co-morbidities were considered.

Exclusion criteria

- None.

Types of interventions

Inclusion criteria

- Respiratory syncytial virus (RSV) vaccines**.**

Exclusion criteria

- None.

Comparator

Inclusion criteria

- Placebo or no intervention or vaccine not directed against RSV (e.g. MMR vaccine);
- One RSV vaccine with another RSV vaccine/other vaccine(s);
- Same RSV vaccine at different dosages and the same dosing schedule;
- Same RSV vaccine with different dosing schedules and the same dosages;
- An RSV vaccine with monoclonal antibodies (MAbs).

Exclusion criteria:

- None.

Types of outcome measures

Primary outcomes

Efficacy (randomised controlled trials) and effectiveness (non-randomised studies of interventions) primary outcomes

- Frequency of RSV infection (both lower and upper respiratory infection) confirmed by laboratory test (i.e. polymerase chain reaction (PCR) testing, culture, antigen tests, etc.);
- Hospitalisation due to RSV disease (both lower and upper respiratory infection) confirmed by laboratory tests (i.e. antigen tests, direct antibody (DFA), polymerase chain reaction (PCR) testing, culture, etc.);
- Mortality from illness caused by RSV (confirmed by laboratory test);
- All-cause mortality;
- Admission to an intensive care unit (ICU) (including duration of ICU admission and duration of invasive ventilation);
- Requirement for invasive ventilation;
- Duration of hospitalisation.

Primary safety outcomes

- Number and type of all serious adverse events[i] related to vaccination, including neurological disorders such as Guillain-Barre Syndrome.

Secondary outcomes

Efficacy (randomised controlled trials) and effectiveness (non-randomised studies of interventions) secondary outcomes

- Measures of symptomatology (i.e. symptom scores, duration of symptoms);
- Antibiotic usage
  - Reported as prescription rate, clinician or self-reported antibiotic use, antibiotic purchases, or the number of antibiotic days/courses.
- Acute otitis media (AOM) (children only);
- Duration of stay in an intensive care unit;
- Duration of protection (against any of the outcomes mentioned above);
- Long term outcomes
  - Development of asthma (children)
  - Reduced functional capacity
  - Requirement for rehabilitation stay due to potential adverse events.

[i] A serious adverse event that results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

Secondary safety outcomes

- Unsolicited adverse events (spontaneously reported/ other adverse events);
- Adverse events of particular interest (AESI): breakthrough infections;
- Solicited adverse events;
- Local (redness, swelling, pain/tenderness);
- Systemic reactions (fever, fatigue, etc.).

Setting

Inclusion criteria

- Any setting (inpatients, outpatients) in any geographic location.

Subgroups

- Geographic location (e.g. low-middle income and high-income countries).

Search methods

The initial literature search in the primary systematic review covered the period from 2000 to 18 May 2023. The first update search, conducted on 8 April 2024, covered the period from 19 May 2023 to 8 April 2024. The search encompassed the following databases: Medline (via Ovid MESZ segment), Cochrane Library/Central (via Wiley), Embase (via Embase.com/Elsevier), ClinicalTrials.gov (www.clinicaltrials.gov), and the International Clinical Trials Registry Platform (ICTRP). Additionally, supplementary references were identified through forward citation tracking.

Selection criteria

The analysis included all human populations without restrictions on age, sex, ethnicity, comorbidities, or geographic location. The intervention focused on RSV vaccines. Eligible comparisons were placebo or no intervention, one RSV vaccine against another RSV vaccine or another type of vaccine, the same RSV vaccine at different dosages and schedules or mAbs. Primary outcomes examined included RSV infection frequency, hospitalisation rates and duration, RSV-related and all-cause mortality, intensive care unit admission, invasive ventilation requirement, and serious adverse events. Both randomised trials and non-randomised studies of RSV vaccines were considered.

Risk of bias assessment

Two authors independently assessed the risk of bias for each of our specified outcomes in each included study. Any disagreement was resolved by consensus, moderated by a third reviewer where necessary. Consensus assessments were presented in 'risk of bias' tables.

Bias in RCTs was assessed using the Cochrane risk of bias tool for randomised trials (RoB version 2.0), which considers five domains: (i) bias arising from the randomisation process; (ii) bias due to deviations from intended interventions; (iii) bias due to missing outcome data; (iv) bias in the measurement of the outcome; and (v) bias in the selection of the reported result [42]. These domains were judged as 'low risk of bias', ' some concerns', or 'high risk of bias'.

We did not include any NRSIs. Had we done so, we had planned to evaluate their risk of bias using the 'Risk of Bias in Non-randomised Studies of Interventions' tool (ROBINS-I) [43].

Data collection and analysis

Two reviewers independently extracted information on study and participant characteristics along with the results obtained. When appropriate, a random-effects model meta-analysis was performed. Despite study variation, a random-effects model for data pooling was employed. This model allows for the possibility that the true effect size might vary across studies due to differences in factors such as study populations, interventions, or methodologies. It provides a more conservative estimate of the effect size and its uncertainty, which is more appropriate when there is potential heterogeneity among the included studies.

The risk ratio (RR) was calculated using the Cochran-Mantel-Haenszel method to estimate the between-study variance and the pooled effect size across strata.

Different types of heterogeneity (owing to different clinical characteristics, methodological diversity or small study effects) were evaluated and statistically quantified based on I^2 and chi-square. The following thresholds were used to interpret I^2:

- 0% to 40%: might not be important;
- 30% to 60% may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- ≥ 75% represents considerable heterogeneity.

Using the random-effects model, the 95% confidence intervals for meta-analyses were calculated. Sensitivity and subgroup analyses (for different clinical characteristics, including different populations, interventions and comparators) were planned irrespective of the measured statistical heterogeneity. However, subgroup analyses were performed based on the types of vaccines and sensitivity analyses based on the risk of bias in the included studies.

Additionally, the certainty of the evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.

Certainty of evidence

The certainty of evidence of selected patient-relevant outcomes was assessed using the GRADE approach [44, 45]. We included the following outcomes in the Summary of Findings Tables:

Efficacy (randomised controlled trials) and effectiveness (non-randomised studies of interventions) outcomes

- The frequency of RSV infection (both lower and upper respiratory infection) was confirmed by laboratory tests (i.e. polymerase chain reaction (PCR) testing, culture, antigen tests, etc.);
- Hospitalisation due to RSV disease (both lower and upper respiratory infection) was confirmed by laboratory tests (i.e. antigen tests, direct antibody (DFA), polymerase chain reaction (PCR) testing, culture, etc.);
- Mortality from illness caused by RSV (confirmed by laboratory test);
- All-cause mortality;
- Admission to an intensive care unit;
- Requirement for invasive ventilation;
- Duration of hospitalisation.

Safety

- All serious adverse events related to vaccination, including neurological disorders such as Guillain-Barre Syndrome.

GRADE assessment

In brief, the GRADE assessment considers five domains, including:

- Study limitations (risk of bias);
- Imprecision (when 95% confidence intervals are wide and/or are close to null effect around the point estimate or evidence was derived from only a few studies with a small number of participants);
- Inconsistency (that is, differences in effect estimates across studies that assessed the same comparison);
- Indirectness (that is, differences in patient characteristics, differing [co-] intervention, differing extent to which the intervention of interest is optimally conducted, differing comparator, and differences in measurement of outcome);
- Publication bias.

These domains are considered in addition to the underlying study design to rate the certainty of evidence for each outcome [46]. For each of the assessed domains, we downgraded our certainty by one level in case of serious concerns or by two levels in case of very serious concerns, resulting in the overall rating of high, moderate, low or very low for each evaluated outcome [46]. We did not identify any NRSIs. Had we included any NRSIs, in accordance with the GRADE guidelines for NRSI assessed with ROBINS-I, we would have also started with a high certainty of evidence [47].

The GRADE assessment was conducted by one review author and cross-checked by another author. Any disagreements were resolved by discussion and consensus involving a third person as needed.

Results

Main results from the primary systematic review

RSV prefusion F protein-based vaccines effectively reduced both RSV-associated lower respiratory tract infections and acute respiratory illness in older adults (with trial results covering one RSV season). These findings were consistent for authorised vaccines and when analysing data from both authorised and unauthorised vaccines combined. The sole trial investigating an unauthorised RSV post-fusion F protein-based vaccine showed little to no difference in RSV-associated lower respiratory tract infection and RSV-associated acute respiratory illness in older adults. In the case of infants, maternal vaccination with RSV F protein-based vaccines led to a reduction in medically attended RSV-associated lower respiratory tract infections and severe cases of the same (with trial results covering four RSV seasons two in the Northern Hemisphere and two in the Southern Hemisphere). This reduction was evident in studies involving authorised vaccines and when considering the combined data from trials of both authorised and unauthorised vaccines.

However, the effect of the RSV vaccine for the protection of women of childbearing age, as well as the effects of live attenuated RSV vaccines on infants and children, remain uncertain. These trials are being conducted with vaccines that have not yet been authorised. Summary of Findings tables are available in Annex 1.

Main changes from the primary systematic review and the first update

The first search (primary systematic review) was conducted on 18 May 2023 and updated on 8 April 2024. In the living systematic review, only phase two/three trials reporting safety, efficacy, and effectiveness data, as well as non-randomised studies of interventions (NRSIs) reporting safety and effectiveness data were included. In this first update, we identified 1 224 new citations and screened 873 citations after removing 351 duplicates. Four new records [3,6,16,17], including one new trial [6] and three additional analyses [3,16,17] of a previously included trial [4] were added.

- The newly-included trial is of an mRNA-Based RSV prefusion vaccine in older adults (newly authorised vaccine mResvia by Moderna) [6] and updated results from a previously included trial which now covers two RSV seasons in older adults (authorised vaccine, Arexvy by GSK) (3).
- The results on the efficacy and safety of RSV prefusion vaccines; three trials with authorised vaccines (Arexvy by GSK [3,4], Abrysvo by Pfizer [5], and mResvia by Moderna) [6] and one with unauthorised vaccine by Janssen Vaccines [48] versus placebo in older adults have been updated. The pooled analysis now includes data from four trials (n=99 931) [3,5,6,50,]. The direction of effects on outcomes and certainty of the evidence remains unchanged.
- In this first update, we did not identify any new trials on RSV post-fusion F protein-based vaccines, maternal RSV F protein-based vaccines, RSV vaccines for women of childbearing age, or live attenuated RSV vaccines for infants and children.
- The results on the efficacy and safety of RSV post-fusion F protein-based vaccines (unauthorised vaccine by MedImmune) [49] versus placebo in older adults remain unchanged.
- The efficacy and safety results for maternal RSV F protein-based vaccines, including two trials with the authorised vaccine Abrysvo by Pfizer [7,8] and one with an unauthorised vaccine by Novavax [50], versus placebo in infants, remain unchanged.
- The results on the efficacy and safety of live attenuated RSV vaccines (unauthorised vaccines such as RSV/ΔNS2/Δ1313/I1314L, RSV/276, etc.) [9-13] versus placebo in infants and children remains unchanged
- The efficacy and safety results of RSV recombinant F nanoparticle vaccine (unauthorised vaccine by Novavax) [51] versus placebo in women of childbearing age remains unchanged.

Main results from the first update

In this first update of the living systematic review, we identified 1 224 records. After removing 351 duplicates, we screened 873 records and selected 14 for full-text screening. We excluded eight records for the following reasons: studies focused on dose-finding schedules and immunogenicity assessment (n = 2), trials terminated and not continued (n = 5), and registration of a published study (n = 1) (Annex Table 15). We included six records, comprising one new trial, three providing updated results of previously included trials, and two registrations of ongoing trials with no published results (see Annex Figure1).

We identified efficacy and safety data from clinical trials. Effectiveness and safety data from NRSI were not available at the time of the initial or updated search. In this update, we identified one new trial on RSV prefusion vaccines in older adults (newly authorised vaccine mResvia by Moderna) over one season [6] and updated results

from a previously included trial which is now covering two RSV seasons (authorised vaccine, Arexvy by GSK) [3,4]. We have combined the updated results with the previous findings.

Through the primary systematic review and this update, we identified five trials [3,5,6,48,49] on older adults (one trial added in this update [6]), three on maternal vaccination and its effect on infants [7,8,50], one on women of childbearing age [51], and five on infants and children [9-13].

This update presents updated findings on the efficacy and safety of RSV prefusion vaccines versus placebo in older adults.

Efficacy and safety of RSV prefusion vaccines vs. placebo in older adults (covering two RSV seasons post–dose 1)

In a meta-analysis of four trials involving 99 931 older adults (mean age 68.1 to 69.5 years across studies), the efficacy and safety of RSV prefusion vaccines against placebo were assessed. These trials included three with authorised vaccines (Arexvy by GSK [3,4], Abrysvo by Pfizer [5] and mResvia by Moderna) [6] and one with an unauthorised vaccine by Janssen Vaccines [48].

Efficacy

All four trials reported outcomes on RSV-associated lower respiratory tract infection, and three of them reported RSV-associated acute respiratory illness. Overall, RSV prefusion vaccines reduced RSV-associated lower respiratory tract infection (Annex Figure 2) with a Vaccine Efficacy (VE) of 77% (high certainty of evidence) and RSV-associated acute respiratory illness (Annex Figure 3) with a VE of 67% (high certainty of evidence). Analysis of each of the authorised vaccines (Arexvy, Abrysvo, and mResvia) demonstrated similar efficacy rates to the overall analysis.

One trial (authorised vaccine, Arexvy by GSK) [3,4] reported hospitalisations due to RSV disease: one in the vaccine arm and five in the placebo arm.

Two trials (authorised vaccines, Arexvy by GSK [3,4] and mResvia by Moderna [6]) which reported mortality from illness caused by RSV in older adults found no deaths attributed to RSV-related disease (in either the vaccinated or placebo groups).

Regarding all-cause mortality, the same trials reported 73 deaths in the vaccine group and 153 deaths in the placebo group. Based on the clinical trial results we concluded that RSV prefusion vaccines may result in little to no difference in all-cause mortality (low certainty of evidence). Admission to an intensive care unit, requirement for invasive ventilation and duration of hospitalisation were pre-specified outcomes for this systematic review; however, the trial did not report any information related to these outcomes. It was concluded that RSV prefusion vaccines may result in little to no difference in mortality from illness caused by RSV (low certainty of evidence).

Safety

All four trials measured serious adverse events (Annex Figure 4). In one trial (Arexvy by GSK) [3,4], it was reported that there were 10 vaccine recipients (0.1%) and seven placebo recipients (0.1%) who had a serious adverse event that the investigator considered to be related to the vaccine or placebo. The investigator assessed four fatal serious adverse events (with group allocation blinded) as potentially related to the placebo or vaccine, these included pulmonary embolism, cardiopulmonary failure, myocardial ischemia, and unknown cause (not specified). Nonetheless, study researchers also found alternative explanations for these deaths plausible, given the participants' pre-existing and concurrent medical conditions [3].

In the Abrysvo (Pfizer) trial, at the data-cutoff date, 2.3% of the vaccine recipients and 2.3% of the placebo recipients had reported serious adverse events which were considered by the investigators to be injection-related: a delayed allergic reaction, Miller-Fisher syndrome (a Guillain-Barré variant), and a myocardial infarction followed by Guillain-Barré syndrome. Although all participants recovered, the study investigators suggested that these adverse events of Guillain-Barré syndrome and Miller-Fisher syndrome warrant close monitoring in future studies and real-world data to discern any potential relatedness to the vaccine. In the mResvia (Moderna) trial, serious adverse events that were assessed by the investigator as being related to the trial injection were reported in four participants compared to three in the placebo group, which was equal to <0.1% in each group (the serious adverse events were unspecified).

RSV prefusion vaccines may result in little to no difference in serious adverse events related to vaccination in older adults (low certainty of evidence).

The flow diagram (Annex 1, Figure 1) illustrates updated Summary of Findings Tables 1A and 1B, characteristics of the newly-included trial (Annex tables 1-7), updated meta-analyses (Annex 1, Figures 2-4) and risk of bias (Annex 1, Figure 5) demonstrating the evidence.

The results regarding the efficacy and safety of RSV post-fusion F protein-based vaccines compared to placebo in older adults, maternal RSV F protein-based vaccines compared to placebo in infants, RSV recombinant F nanoparticle vaccines compared to placebo in women of childbearing age, and live attenuated RSV vaccines compared with placebo in infants and children remain unchanged, as no new trials were identified. The results are provided here for completeness (see also Summary of Findings Tables 1C, 2A, 2B, 3 and 4).

Efficacy and safety of RSV post-fusion F protein-based vaccine vs. placebo in older adults (covering one RSV season)

We evaluated the efficacy and safety of RSV post-fusion F protein-based vaccine compared to a placebo in 1 894 older adults. This analysis draws from a single trial using an unauthorised vaccine by MedImmune [49]. This Phase 2b trial was carried out to evaluate the immune response and efficacy of this experimental RSV vaccine.

Efficacy

The trial reported on both RSV-associated lower respiratory tract infection and acute respiratory illness. RSV post-fusion F protein-based vaccine (unauthorised vaccine by MedImmune) resulted in little to no difference in RSV-associated lower respiratory tract infection (moderate certainty evidence) or RSV-associated acute respiratory illness in older adults (moderate certainty of evidence). Hospitalisation due to RSV disease were pre-specified outcomes for this systematic review; however, the trial did not report any information related to these outcomes.

The trial reported mortality from illness caused by RSV in older adults, with no deaths attributed to RSV-related disease. For all-cause mortality, the trial reported three deaths in the vaccine group and five deaths in the placebo group. We concluded that RSV post-fusion F protein-based vaccine may result in little to no difference in mortality from illness caused by RSV (low certainty of evidence) or all-cause mortality (low certainty of evidence) in older adults.

Admission to intensive care units, requirement for invasive ventilation, and duration of hospitalisation were pre-specified outcomes for this systematic review; however, the trial did not report any information related to these outcomes.

Safety

The trial also reported on safety and found no vaccine-related serious adverse events although there was one adverse event of special interest that the investigator deemed related to the RSV vaccine (autoimmune thyroiditis). It was concluded that the RSV post-fusion F protein-based vaccine may result in little to no difference in serious adverse events related to vaccination in older adults (low certainty of evidence).

Efficacy and safety of maternal RSV F vs. placebo in infants (covering four RSV seasons)

In a combined analysis of three trials totalling 12 010 participants, the efficacy and safety of maternal RSV F protein-based vaccines versus placebo were evaluated. These trials included two with authorised vaccines (Abrysvo by Pfizer) [7,8] and one with an unauthorised vaccine by Novavax [50].

Efficacy

All three trials reported medically attended RSV-associated lower respiratory tract infection and severe RSV-associated lower respiratory tract infection in infants. The findings showed that maternal RSV F protein-based vaccines reduced:

- medically attended RSV-associated lower respiratory tract infection with VE 54% (high certainty of evidence);
- severe RSV-associated lower respiratory tract infection with VE 74% (high certainty of evidence);
- hospitalisation due to RSV disease with VE 54% (high certainty of evidence) in infants.

One trial (authorised vaccine, Abrysvo by Pfizer) [7] reported five deaths in the vaccine group and 12 deaths in the placebo group, of which one death in the placebo group was related to RSV disease. Another trial (unauthorised vaccine by Novavax) [50] reported 17 deaths in the vaccine group and 12 deaths in the placebo group, of which one in the vaccine group was related to RSV disease. This suggests that maternal RSV F protein-based vaccine may result in little to no difference in mortality caused by RSV (low certainty evidence) or all-cause mortality (low certainty of evidence) in infants.

Admission to intensive care units, requirement for invasive ventilation, and duration of hospitalisation were pre-specified outcomes for this systematic review; however, the trial did not report any information related to these outcomes.

Two trials evaluated the authorised vaccine, Abrysvo by Pfizer [7,8]. They reported RSV-associated lower respiratory tract infection, medically attended severe RSV-associated lower respiratory tract infection, and hospitalisation due to RSV disease in infants. The authorised vaccine reduced:

- medically attended RSV-associated lower respiratory tract infection with VE of 68% (high certainty of evidence);
- severe cases with a VE of 84% (high certainty of evidence) in infants;
- hospitalisation due to RSV disease in infants with VE of 68% (high certainty of evidence).

Only one trial [7] reported mortality caused by RSV and all-cause mortality. The analysis of the authorised vaccine alone indicated one death due to RSV in the placebo group. It highlighted that maternal RSV prefusion F protein-based vaccine might have little to no impact on RSV-caused mortality (low certainty of evidence). This vaccine also showed minimal impact on all-cause mortality (low certainty of evidence) in infants, with a total of five deaths in the vaccine group and 12 in the placebo group.

As with the broader analysis, there was no report on intensive care unit admissions, invasive ventilation, or hospitalisation duration.

Safety

All three trials reported serious adverse events related to vaccination. In the Abrysvo (Pfizer) trial, the events related to vaccination were measured in maternal participants and in infants. Events assessed by the investigator as related to the injection occurred in four vaccine recipients (arm pain with bilateral lower-extremity pain, premature labour, systemic lupus erythematosus, and eclampsia) and one placebo recipient (premature placental separation). The number of preterm birth or delivery (categorised as adverse events of special interest) was higher in the RSV vaccine recipients compared to the placebo group, but the differences were not statistically significant (229 preterm deliveries in the vaccine recipient group compared to 198 in the placebo group). No serious adverse events in infants were considered by the investigators to be related to the vaccine.

The other trial (unauthorised vaccine by Novavax) reported two unsolicited serious adverse events (not specified) in the vaccine group and four in the placebo group that were deemed related to vaccination.

These vaccines may result in little to no difference in serious adverse events related to vaccination in both mothers and infants (low certainty of evidence).

Both trials reported serious adverse events related to vaccination. The vaccine is likely to have little to no difference in these events in both infants and mothers (low certainty of evidence).

Efficacy and safety of live attenuated RSV vaccines vs. placebo in infants and children (covering one RSV season)

A meta-analysis of five trials involving 192 infants and children to evaluate the efficacy and safety of various live attenuated vaccines compared to a placebo was conducted. These phase 1 trials collectively featured six live attenuated vaccines (RSV/ΔNS2/Δ1313/I1314L, RSV/276, etc)., none of which were authorised [9-13].

Efficacy

All five trials reported all-cause medically attended acute respiratory illnesses (MAARI) and RSV associated MAARI in infants and children. The evidence on the effect of live attenuated RSV vaccines on RSV-associated MAARI (very low certainty of evidence) and all-cause MAARI in infants and children is very uncertain (very low certainty of evidence).

Hospitalisation due to RSV disease, mortality from illness caused by RSV disease, all-cause mortality, admission to intensive care units, requirement for invasive ventilation, and duration of hospitalisation were pre-specified outcomes for this systematic review; however, the trial did not report any information related to these outcomes.

Safety

All five trials measured serious adverse events and there were no events reported in any of the trials. Live attenuated RSV vaccines may result in little to no difference in serious adverse events related to vaccination (low certainty of evidence).

Efficacy and safety of RSV recombinant F nanoparticle vaccine vs placebo in women of childbearing age

The efficacy and safety of RSV recombinant F nanoparticle vaccine compared to a placebo in 300 women of childbearing age was evaluated. This analysis draws from a single phase 2 trial using an unauthorised vaccine by Novavax [51].

Efficacy

The trial reported new RSV infection in women as an outcome. The evidence is very uncertain about the effect of RSV recombinant F nanoparticle vaccine (unauthorised vaccine by Novavax) on new RSV infection in women of childbearing age (VE 50%, very low certainty of evidence). Hospitalisation due to RSV disease was a pre-specified outcome for this systematic review; however, the trial did not report any information related to this outcome.

The trial reported no death from illness caused by RSV disease or all-cause mortality. We concluded that RSV recombinant F nanoparticle vaccine may result in little to no difference in mortality from illness caused by RSV (low certainty of evidence) or all-cause mortality (low certainty of evidence) in women of childbearing age.

Admission to intensive care units, requirement for invasive ventilation, and duration of hospitalisation were pre-specified outcomes for this systematic review; however, the trial did not report any information related to these outcomes.

Safety

The trial reported no serious adverse events related to vaccination and RSV recombinant F nanoparticle vaccine may result in little to no difference in serious adverse events related to vaccination (low certainty of evidence).

Conclusions

This systematic review adhered to standard methods, ensuring methodological rigour at each stage. A comprehensive search strategy was developed by an information specialist and peer reviewed. Major bibliographical databases and trial registries were searched thoroughly, and forward citation tracking of included trials was conducted. All critical steps, including citation screening, data extraction, and risk of bias assessment, were carried out independently by two review authors. Any discrepancies were resolved through discussion with the lead author. The lead author evaluated the certainty of evidence and finalised it through team discussion. A limitation of this living systematic review is the restriction to articles published in English.

We identified only efficacy and safety data through clinical trials. Effectiveness and safety data from non-randomised studies of interventions (NRSI) were not available at the time of the updated living systematic review search.

The results from this review indicate that RSV prefusion vaccines effectively reduced both RSV-associated lower respiratory tract infections and acute respiratory illness in older adults (trial results covering two RSV seasons). These findings were consistent for authorised vaccines and when analysing data from both authorised and unauthorised vaccines combined.

In infants, maternal vaccination with RSV F protein-based vaccines led to a reduction in RSV-associated lower respiratory tract infections and severe RSV-associated lower respiratory tract infections (trial results covering four RSV seasons). This reduction was evident in studies involving authorised vaccines and when considering the combined data from trials of both authorised and unauthorised vaccines. However, the effect of RSV vaccine on women of childbearing age, as well as the effects of live attenuated RSV vaccines on infants and children, remained uncertain. These findings are based on trials with vaccines that have not been authorised.

Implications for practice and research

This first update suggests that RSV prefusion F vaccines and maternal RSV F protein-based vaccines reduce RSV-associated respiratory illnesses in older adults and infants, respectively. However, more research is needed to establish the long-term safety and effectiveness of these vaccines, particularly in real-world settings and across different population groups. Real-world effectiveness studies are needed to provide evidence on the protection the vaccines provide against severe disease, including hospitalisations and deaths, which has been difficult to show through clinical trial design and data.

Studies with extended follow-up periods are necessary to assess the durability of immune responses, direct and indirect long-term effects, and long-term vaccine effectiveness. Post-licensure safety surveillance and studies are important to monitor any safety signals or rare adverse events especially for neurological disorders such as GBS in older adults and any safety signals in pregnant persons such as preterm births. Observational studies and post-marketing surveillance are also required to evaluate the effectiveness and safety of RSV vaccines in diverse, real-world populations and settings. This should include studies across different age groups, geographical regions, and population groups.

In order to gather comprehensive data on RSV vaccine performance across various regions and populations international collaboration is essential. Future efforts on establishing or enhancing international surveillance networks and standardised protocols for monitoring vaccine effectiveness and safety would be beneficial.

RSV viruses may continue to evolve, making it important to investigate how new variants could affect the efficacy and effectiveness of existing vaccines. Ongoing genetic and antigenic characterisation of circulating RSV strains should ideally be integrated into research efforts to adapt and update vaccines if needed.

Future research efforts should focus on new observational studies assessing the safety and effectiveness of these vaccines, along with further data collection for addressing knowledge gaps. Strengthening the evidence base will be essential to support policymakers in making informed decisions about the optimal strategies for using these new vaccines to prevent severe RSV disease and deaths in populations most at risk. Key areas for further evidence generation includes topics such as:

- The detailed description of RSV epidemiology and burden in different national/local contexts;
- The duration of immunity provided by RSV vaccines;
- Further and continuous monitoring of the safety of RSV vaccines;
- The effect of vaccination on the likelihood of future RSV infections and severe disease;
- Potential impacts of RSV vaccination on other respiratory pathogens;
- The effectiveness of RSV vaccination in specific high-risk populations, such as immunocompromised individuals or those with chronic respiratory conditions;
- The cost-effectiveness of RSV vaccination programmes in different healthcare settings and populations.

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Annex 1. Summary of findings tables

Table 1. Efficacy and safety of (both authorised and unauthorised) RSV prefusion (Respiratory Syncytial Virus prefusion F vaccine) vs placebo in older adults

Outcome No of participants (studies)	Vaccine efficacy (95% CI) Relative Risk) (95% CI)	Anticipated absolute effects (95% CI)			Certainty	Comments
		With placebo	With RSV vaccination	Difference		
RSV-associated lower respiratory tract infection No of participants: 99 931 (4 RCTs)	**VE 77%** (CI: 70% to 83%) **RR 0.23** (CI: 017 to 0.30)	0.5%	**0.1%** (0.1 to 0.2)	**4 fewer per 1 000** (4 fewer to 4 fewer)	⊕⊕⊕⊕ High	RSV prefusion vaccine reduced RSV-associated lower respiratory tract infection in older adults.
RSV-associated acute respiratory illness No of participants: 94 339 (3 RCTs)	**VE 67%** (CI: 60% to 73%) **RR 0.33** (CI: 0.27 to 0.40)	0.9%	**0.3%** (0.2 to 0.4)	**6 fewer per 1 000** (7 fewer to 6 fewer)	⊕⊕⊕⊕ High	RSV prefusion vaccine reduced RSV-associated acute respiratory illness in older adults.
Mortality from illness caused by RSV No of participants: 50 437 (2 RCTs)	not estimable	0.0%	**0.0%** (0 to 0)	**0 fewer per 1 000** (0 fewer to 0 fewer)	⊕⊕◯◯ Low[a]	RSV prefusion vaccine may result in little to no difference in mortality from illness caused by RSV in older adults.
All-cause mortality No of participants: 50 437 (2 RCTs)	**RR 0.94** (CI: 0.71 to 1.24)	0.6%	**0.5%** (0.4 to 0.7)	**0 fewer per 1 000** (2 fewer to 1 more)	⊕⊕◯◯ Low[a]	RSV prefusion vaccine may result in little to no difference in all-cause mortality in older adults.
Serious adverse events related to vaccination No of participants: 90 503 (4 RCTs)	**RR 1.47** (CI: 0.51 to 4.20)	0.0%	**0.0%** (0 to 0.1)	**0 fewer per 1 000** (0 fewer to 0 fewer)	⊕⊕◯◯ Low[a]	RSV prefusion vaccine may result in little to no difference in serious adverse events related to vaccination.
Hospitalisation due to RSV disease	-	-	-	-	-	Not reported
Admission to an intensive care unit due to RSV disease	-	-	-	-	-	Not reported
Requirement for invasive ventilation due to RSV disease	-	-	-	-	-	Not reported
Duration of hospitalisation due to RSV disease	-	-	-	-	-	Not reported

CI: confidence interval
Explanations:
a. Imprecision: downgraded due to few or zero events (downgraded x 2 levels).

Table 2. Efficacy and safety of authorised (Arexvy by GSK, Abrysvo by Pfizer, and mResvia by Moderna) RSV prefusion (Respiratory Syncytial Virus prefusion F vaccine) vs placebo in older adults

Outcome No of participants (studies)	Vaccine efficacy (95% CI) Relative Risk (95% CI)	Anticipated absolute effects (95% CI)			Certainty	Comments
		With placebo	With RSV vaccination	Difference		
RSV-associated lower respiratory tract infection No of participants: 94 339 (3 RCTs)	VE 78% (CI: 69% to 84%) RR 0.22 (CI: 0.16 to 0.31)	0.5%	0.1% (0.1 to 0.1)	4 fewer per 1 000 (4 fewer to 3 fewer)	⊕⊕⊕⊕ High	Authorised RSV prefusion vaccine reduced RSV-associated lower respiratory tract infection in older adults.
RSV-associated acute respiratory illness No of participants: 94 339 (3 RCTs)	VE 67% (CI: 60% to 73%) RR 0.33 (CI: 0.27 to 0.40)	0.9%	0.3% (0.2 to 0.4)	6 fewer per 1 000 (7 fewer to 6 fewer)	⊕⊕⊕⊕ High	Authorised RSV prefusion vaccine reduced RSV-associated acute respiratory illness in older adults.
Mortality from illness caused by RSV No of participants: 50 437 (2 RCTs)	not estimable	0.0%	0.0% (0 to 0)	0 fewer per 1 000 (0 fewer to 0 fewer)	⊕⊕◯◯ Lowa	Authorised RSV prefusion vaccine may result in little to no difference in mortality from illness caused by RSV in older adults.
All-cause mortality No of participants: 50 437 (2 RCTs)	RR 0.94 (CI: 0.71 to 1.24)	0.6%	0.5% (0.4 to 0.7)	0 fewer per 1 000 (2 fewer to 1 more)	⊕⊕◯◯ Lowa	Authorised RSV prefusion vaccine may result in little to no difference in all-cause mortality in older adults.
Serious adverse events related to vaccination No of participants: 84 721 (3 RCTs)	RR 1.47 (CI: 0.51 to 4.20)	0.0%	0.0% (0 to 0.1)	0 fewer per 1 000 (0 fewer to 1 more)	⊕⊕◯◯ Lowa	Authorised RSV prefusion vaccine may result in little to no difference in serious adverse events related to vaccination.
Hospitalisation due to RSV disease	-	-	-	-	-	Not reported
Admission to an intensive care unit due to RSV disease	-	-	-	-	-	Not reported
Requirement for invasive ventilation due to RSV disease	-	-	-	-	-	Not reported
Duration of hospitalisation due to RSV disease	-	-	-	-	-	Not reported

CI: confidence interval
Explanations:
a. Imprecision: downgraded due to few or zero events (downgraded x 2 levels).

Table 3. Efficacy and safety of (unauthorised vaccine by MedImmune) RSV post-fusion F (Respiratory Syncytial Virus post-fusion F protein-based vaccine) vs placebo in older adults

Outcome No of participants (studies)	Vaccine efficacy (95% CI) Relative Risk (95% CI)	Anticipated absolute effects (95% CI)			Certainty	Comments
		With placebo	With RSV vaccination	Difference		
RSV-associated lower respiratory tract infection No of participants: 1 894 (1 RCT)	**VE – 0.37** **%** (CI: -196% to 37%) **RR 1.37** (CI: 0.63 to 2.96)	1.2%	**1.6%** (0.7 to 3.4)	**4 more per 1 000** (4 fewer to 23 more)	⊕⊕⊕◯ Moderate[a]	RSV post-fusion F protein-based vaccine probably resulted in little to no difference in RSV-associated lower respiratory tract infection in older adults.
RSV-associated acute respiratory illness No of participants: 1 894 (1 RCT)	**VE – 0.07%** (CI: - 115% to 47%) **RR 1.07** (CI: 0.53 to 2.15)	1.6%	**1.7%** (0.8 to 3.4)	**1 more per 1 000** (7 fewer to 18 more)	⊕⊕⊕◯ Moderate[a]	RSV post-fusion F protein-based vaccine probably resulted in little to no difference RSV-associated acute respiratory illness in older adults.
Mortality from illness caused by RSV No of participants: 1 894 (1 RCT)	not estimable	0.0%	**0.0%** (0 to 0)	**0 fewer per 1 000** (0 fewer to 0 fewer)	⊕⊕◯◯ Low[b]	RSV post-fusion F protein-based vaccine may result in little to no difference in mortality from illness caused by RSV in older adults.
All-cause mortality No of participants: 1 894 (1 RCT)	**RR 0.60** (CI: 0.14 to 2.51)	0.5%	**0.3%** (0.1 to 1.3)	**2 fewer per 1 000** (5 fewer to 8 more)	⊕⊕◯◯ Low[b]	RSV post-fusion F protein-based vaccine may result in little to no difference in all-cause mortality in older adults.
Serious adverse events related to vaccination No of participants: 1 894 (1 RCT)	not estimable	0.0%	**0.0%** (0 to 0)	**0 fewer per 1 000** (0 fewer to 0 fewer)	⊕⊕◯◯ Low[b]	RSV post-fusion F protein-based vaccine may result in little to no difference in serious adverse events related to vaccination.
Hospitalisation due to RSV disease	-	-	-	-	-	Not reported
Admission to an intensive care unit due to RSV disease	-	-	-	-	-	Not reported
Requirement for invasive ventilation due to RSV disease	-	-	-	-	-	Not reported
Duration of hospitalisation due to RSV disease	-	-	-	-	-	Not reported

CI: confidence interval
Explanations:
a. Imprecision: A single study having 1894 sample size (downgraded x 1 level).
b. Imprecision: downgraded for very few or zero events (downgraded x 2 levels).

Table 4. Efficacy and safety of (both authorised and unauthorised) maternal RSV F (Respiratory Syncytial Virus F protein-based vaccine) vs placebo in infants

Outcome No of participants (studies)	Vaccine efficacy (95% CI) Relative Risk (95% CI)	Anticipated absolute effects (95% CI)			Certainty	Comments
		With placebo	With RSV vaccination	Difference		
Medically attended RSV-associated lower respiratory tract infection in infants No of participants: 12 010 (3 RCTs)	**VE 54%** (CI: 28% to 71%) **RR 0.46** (CI: 0.29 to 0.72)	2.4%	**1.1%** (0.7 to 1.7)	**13 fewer per 1 000** (17 fewer to 7 fewer)	⊕⊕⊕⊕ High	Maternal RSV F protein-based vaccine reduced medically attended RSV-associated lower respiratory tract infection in infants.
Medically attended severe RSV-associated lower respiratory tract infection in infants No of participants: 12 010 (3 RCTs)	**VE 74%** (CI: 44% to 88%) **RR 0.26** (CI: 0.12 to 0.56)	1.4%	**0.4%** (0.2 to 0.8)	**10 fewer per 1 000** (12 fewer to 6 fewer)	⊕⊕⊕⊕ High	Maternal RSV F protein-based vaccine reduced medically attended severe RSV-associated lower respiratory tract infection in infants.
Hospitalisation due to RSV disease No of participants: 11 502 (2 RCTs)	**VE 54%** (CI: 27% to 71%) **RR 0.46** (CI: 0.29 to 0.73)	1.9%	**0.9%** (0.5 to 1.4)	**10 fewer per 1 000** (13 fewer to 5 fewer)	⊕⊕⊕⊕ High	Maternal RSV F protein-based vaccine reduced hospitalisation due to RSV disease in infants.
Mortality from illness caused by RSV No of participants: 11 170 (2 RCTs)	**RR 0.72** (CI: 0.07 to 6.90)	0.0%	**0.0%** (0 to 0.1)	**0 fewer per 1 000** (0 fewer to 1 more)	⊕⊕◯◯ Low[a]	Maternal RSV F protein-based vaccine may result in little to no difference in mortality from illness caused by RSV in infants.
All-cause mortality No of participants: 11 170 (2 RCTs)	**RR 0.61** (CI: 0.33 to 1.11)	0.5%	**0.3%** (0.2 to 0.5)	**2 fewer per 1 000** (3 fewer to 1 more)	⊕⊕◯◯ Low[a]	Maternal RSV F protein-based vaccine may result in little to no difference in mortality from illness caused by RSV in infants.
Maternal serious adverse events related to vaccination No of participants: 12 389 (3 RCTs)	**RR 0.93** (CI: 0.06 to 13.76)	0.1%	**0.1%** (0 to 1.3)	**0 fewer per 1 000** (1 fewer to 12 more)	⊕⊕◯◯ Low[a]	Maternal RSV F protein-based vaccine may result in little to no difference in maternal serious adverse events related to vaccination.
Serious adverse events related to vaccination in infants No of participants: 12 098 (3 RCTs)	not estimable	0.0%	**0.0%** (0 to 0)	**0 fewer per 1 000** (0 fewer to 0 fewer)	⊕⊕◯◯ Low[a]	Maternal RSV F protein-based vaccine may result in little to no difference in serious adverse events related to vaccination in infants.
Admission to an intensive care unit due to RSV disease	-	-	-	-	-	Not reported
Requirement for invasive ventilation due to RSV disease	-	-	-	-	-	Not reported
Duration of hospitalisation due to RSV disease	-	-	-	-	-	Not reported

CI: confidence interval
Explanations:
a. Imprecision: downgraded for few or zero events (downgraded x 2 level).

Table 5. Efficacy and safety of authorised (Abrysvo by Pfizer) maternal RSV F (Respiratory Syncytial Virus F protein-based vaccine) vs placebo in infants

Outcome No of participants (studies)	Vaccine efficacy (95% CI) Relative Risk (95% CI)	Anticipated absolute effects (95% CI)			Certainty	Comments
		With placebo	With RSV vaccination	Difference		
Medically attended RSV-associated lower respiratory tract infection in infants No of participants: 7 483 (2 RCTs)	**VE 68%** (CI: 21% to 87%) **RR 0.32** (CI: 0.13 to 0.79)	1.7%	**0.5%** (0.2 to 1.3)	**12 fewer per 1 000** (15 fewer to 4 fewer)	⊕⊕⊕⊕ High	Authorised maternal RSV F protein-based vaccine reduced medically attended RSV-associated lower respiratory tract infection in infants.
Medically attended severe RSV-associated lower respiratory tract infection in infants No of participants: 7 483 (2 RCTs)	**VE 84%** (CI: 63% to 93%) **RR 0.16** (CI: 0.07 to 0.37)	1.0%	**0.2%** (0.1 to 0.4)	**8 fewer per 1 000** (9 fewer to 6 fewer)	⊕⊕⊕⊕ High	Authorised maternal RSV F protein-based vaccine reduced medically attended severe RSV-associated lower respiratory tract infection in infants.
Hospitalisation due to RSV disease No of participants: 6 975 (1 RCTs)	**VE 68%** (CI: 35% to 84%) **RR 0.32** (CI: 0.16 to 0.65)	0.9%	**0.3%** (0.1 to 0.6)	**6 fewer per 1 000** (7 fewer to 3 fewer)	⊕⊕⊕⊕ High	Authorised maternal RSV F protein-based vaccine reduced hospitalisation due to RSV disease in infants.
Mortality from illness caused by RSV No of participants: 6 975 (1 RCTs)	**RR 0.33** (CI: 0.01 to 8.14)	0.0%	**0.0%** (0 to 0.2)	**0 fewer per 1 000** (0 fewer to 2 more)	⊕⊕◯◯ Low[a]	Authorised maternal RSV F protein-based vaccine may result in little to no difference in mortality from illness caused by RSV in infants.
All-cause mortality No of participants: 6 975 (1 RCTs)	**RR 0.42** (CI: 0.15 to 1.18)	0.3%	**0.1%** (0.1 to 0.4)	**2 fewer per 1 000** (3 fewer to 1 more)	⊕⊕◯◯ Low[a]	Authorised maternal RSV F protein-based vaccine may result in little to no difference in mortality from illness caused by RSV in infants.
Maternal serious adverse events related to vaccination No of participants: 7 763 (2 RCTs)	**RR 3.99** (CI: 0.45 to 35.70)	0.0%	**0.1%** (0 to 1)	**1 more per 1 000** (0 fewer to 9 more)	⊕⊕◯◯ Low[a]	Authorised maternal RSV F protein-based vaccine may result in little to no difference in maternal serious adverse events related to vaccination.
Serious adverse events related to vaccination in infants No of participants: 7 529 (2 RCTs)	not estimable	0.0%	**0.0%** (0 to 0)	**0 fewer per 1 000** (0 fewer to 0 fewer)	⊕⊕◯◯ Low[a]	Authorised maternal RSV F protein-based vaccine may result in little to no difference in serious adverse events related to vaccination in infants.
Admission to an intensive care unit due to RSV disease	-	-	-	-	-	Not reported
Requirement for invasive ventilation due to RSV disease	-	-	-	-	-	Not reported
Duration of hospitalisation due to RSV disease	-	-	-	-	-	Not reported

CI: confidence interval
a. Imprecision: downgraded for few or zero events (downgraded x 2 level).

Table 6. Efficacy and safety of live attenuated (unauthorised, RSV/ΔNS2/Δ1313/I1314L, RSV/276, etc.) RSV (Respiratory Syncytial Virus) vaccine vs placebo in infants and children

Outcome No of participants (studies)	Vaccine efficacy (95% CI) Relative Risk (95% CI)	Anticipated absolute effects (95% CI)			Certainty	Comments
		With placebo	With RSV vaccination	Difference		
All-cause medically attended acute respiratory illnesses (MAARI) No of participants: 171 (5 RCTs)	**VE 26%** (CI: - 1% to 46%) **RR 0.74** (CI: 0.54 to 1.01)	53.6%	**39.6%** (28.9 to 54.1)	**139 fewer per 1 000** (246 fewer to 5 more)	⨁◯◯◯ Very low[a,b]	The evidence is very uncertain about the effect of live attenuated RSV vaccine on all-cause medically attended acute respiratory illnesses (MAARI) in infants and children.
RSV-associated MAARI No of participants: 192 (5 RCTs)	**VE 38%** (CI: - 24% to 69%) **RR 0.62** (CI: 0.31 to 1.24)	19.6%	**12.2%** (6.1 to 24.4)	**75 fewer per 1 000** (136 fewer to 47 more)	⨁◯◯◯ Very low[a,b]	The evidence is very uncertain about the effect of live attenuated RSV vaccine on RSV-associated medically attended acute respiratory illnesses (MAARI) in infants and children.
Otitis Media in infants/ children No of participants: 204 (5 RCTs)	**RR 0.97** (CI: 0.28 to 3.37)	3.4%	**3.3%** (0.9 to 11.4)	**1 fewer per 1 000** (24 fewer to 80 more)	⨁⨁◯◯ Low[b]	Live attenuated RSV vaccine may result in little to no difference in otitis Media in infants/ children.
Serious adverse events related to vaccination No of participants: 204 (5 RCTs)	not estimable	0.0%	**0.0%** (0 to 0)	**0 fewer per 1 000** (0 fewer to 0 fewer)	⨁⨁◯◯ Low[b]	Live attenuated RSV vaccine may result in little to no difference in serious adverse events related to vaccination.
Mortality from illness caused by RSV	-	-	-	-	-	Not reported
All-cause mortality	-	-	-	-	-	Not reported
Hospitalisation due to RSV disease	-	-	-	-	-	Not reported
Admission to an intensive care unit due to RSV disease	-	-	-	-	-	Not reported
Requirement for invasive ventilation due to RSV disease	-	-	-	-	-	Not reported
Duration of hospitalisation due to RSV disease	-	-	-	-	-	Not reported

CI: confidence interval
Explanations
a. Indirectness: The evidence, sourced solely from Phase 1 trials, primarily targeted safety assessments, not vaccine efficacy. Outcomes related to efficacy were reported via post-vaccination surveillance. Due to this, the evidence has been downgraded by one level for indirectness.
b. Imprecision: All trials are phase 1 trials and sample size is very low and/or no or few events (downgraded x 2 level).

Table 7. Efficacy and safety of (unauthorised vaccine by Novavax) RSV recombinant F nanoparticle vaccine vs placebo in women of childbearing age

Outcome No of participants (studies)	Vaccine efficacy (95% CI) Relative Risk (95% CI)	Anticipated absolute effects (95% CI)			Certainty	Comments
		With placebo	With RSV vaccination	Difference		
New RSV infection No of participants: 300 (1 RCT)	**VE 50%** (CI: 8% to 73%) **RR 0.50** (CI: 0.27 to 0.92)	21.4%	**10.7%** (5.8 to 19.7)	**107 fewer per 1 000** (156 fewer to 17 fewer)	⨁◯◯◯ Very low[a, b]	The evidence is very uncertain about the effect of RSV recombinant F nanoparticle vaccine on new RSV infection in women of childbearing age.
Mortality from illness caused by RSV No of participants: 300 (1 RCT)	not estimable	0.0%	**0.0%** (0 to 0)	**0 fewer per 1 000** (0 fewer to 0 fewer)	⨁⨁◯◯ Low[b]	RSV recombinant F nanoparticle vaccine may result in little to no difference on mortality caused by RSV disease in women of childbearing age.
All-cause mortality No of participants: 300 (1 RCT)	not estimable	0.0%	**0.0%** (0 to 0)	**0 fewer per 1 000** (0 fewer to 0 fewer)	⨁⨁◯◯ Low[b]	RSV recombinant F nanoparticle vaccine may result in little to no difference on all-cause mortality in women of childbearing age.
Serious adverse events related to vaccination No of participants: 300 (1 RCT)	not estimable	0.0%	**0.0%** (0 to 0)	**0 fewer per 1 000** (0 fewer to 0 fewer)	⨁⨁◯◯ Low[b]	RSV recombinant F nanoparticle vaccine may result in little to no difference on serious adverse events related to vaccination in women of childbearing age.
Hospitalisation due to RSV disease	-	-	-	-	-	Not reported
Admission to an intensive care unit due to RSV disease	-	-	-	-	-	Not reported
Requirement for invasive ventilation due to RSV disease	-	-	-	-	-	Not reported
Duration of hospitalisation due to RSV disease	-	-	-	-	-	Not reported

CI: confidence interval
Explanations
a. Indirectness: The evidence was obtained from a single Phase 2 trial, primarily designed to evaluate safety rather than vaccine efficacy. The outcomes relevant to efficacy were reported through post-vaccination surveillance rather than as primary endpoints of the trial. Given this deviation from the direct assessment of vaccine efficacy, we have downgraded the evidence by one level for indirectness.
b. Imprecision: Single, phase 2 trial and sample size is very low and/or no or few events (downgraded x 2 levels).

Annex 2. Updated information retrieved in the first update of the living systematic review

Figure 1. **Flow diagram of the first update of the living systematic review**

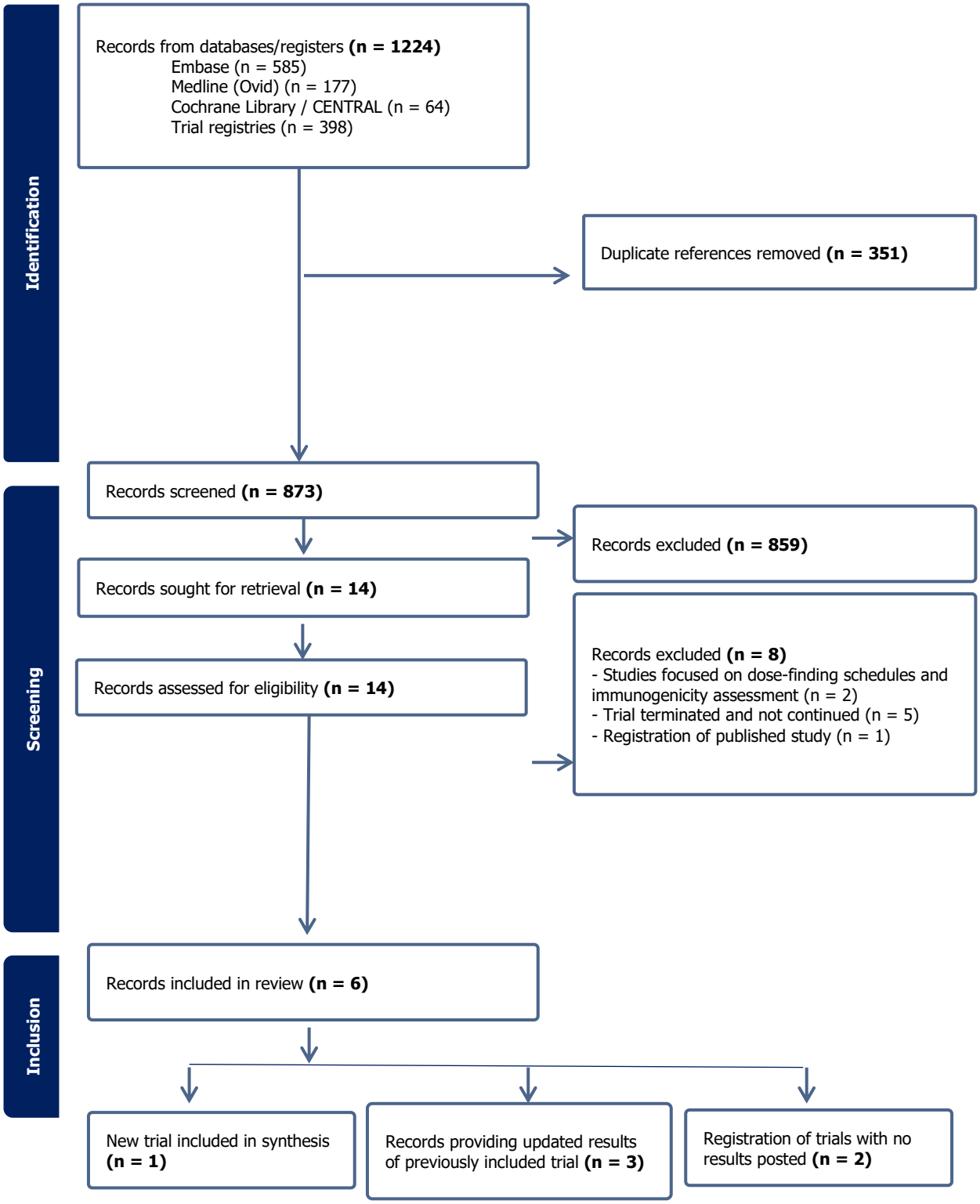

Figure 2. Efficacy of both authorised and unauthorised RSV prefusion vaccine vs placebo in older adults for RSV-associated lower respiratory tract infection (subgroup authorised vaccine vs unauthorised vaccine)

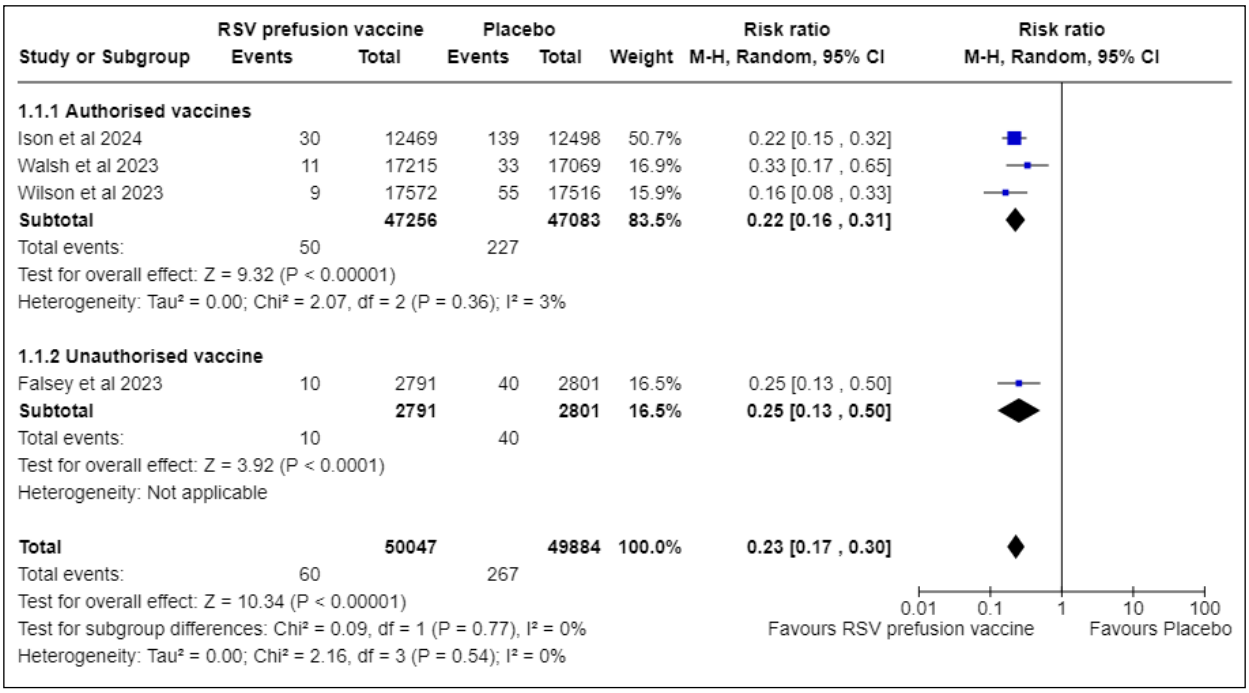

Figure 3. Efficacy of authorised RSV prefusion vaccine vs placebo in older adults for RSV-associated acute respiratory illness

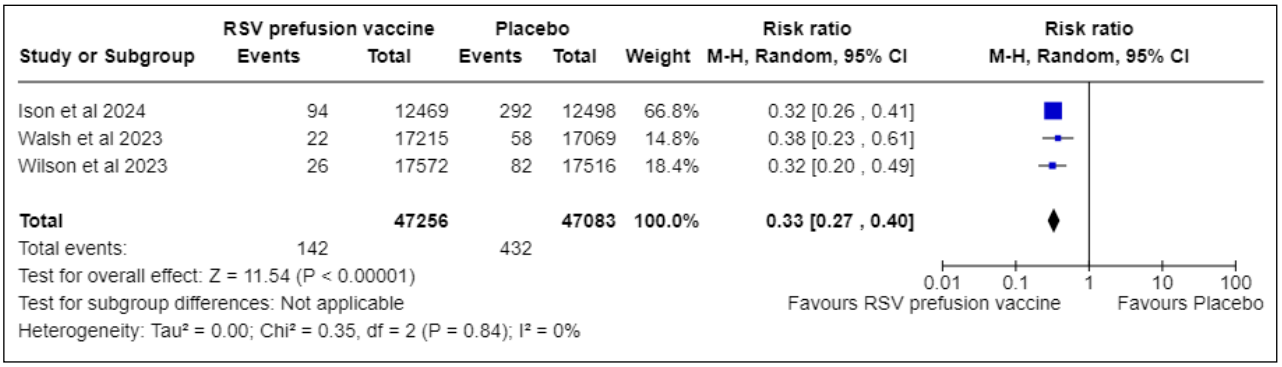

Figure 4. Serious adverse events related to vaccination in (both authorised and unauthorised) RSV prefusion vs placebo in older adults (subgroup authorised vaccine vs unauthorised vaccine)

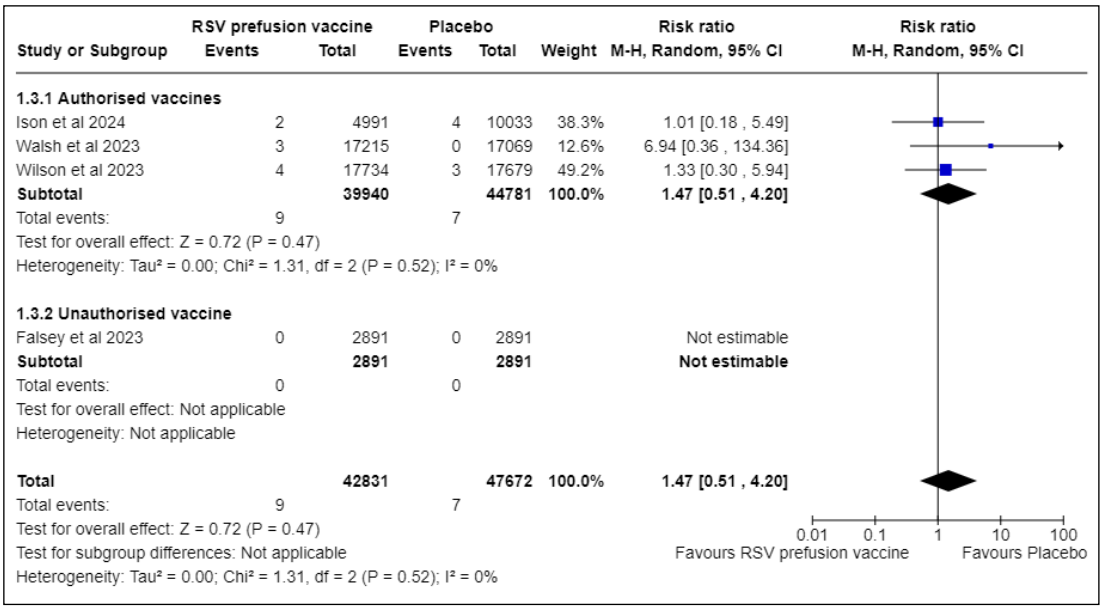

Figure 5. Risk of bias assessment of the newly included trial (authorised vaccine mResvia by Moderna)

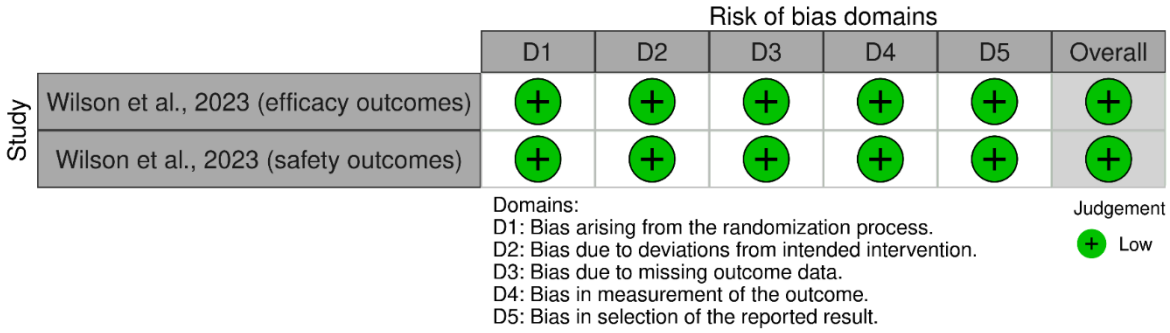

Table 8. Characteristics of the included trials

Author, year of publication Design	Population	Funding	Timing of study	Type of vaccine	Control/ Placebo	Sample size	Recruitment method	Geographical setting	Pre-specified review outcomes reported in study
Older adults (RSV perfusion vaccines)									
Wilson et al., 2023 (1) Phase 2/3 RCT	Adults aged 60 years or older	Industry funded	Start date: November 17, 2021 End date: August 25, 2025 (estimated)	mRNA-1 345 vaccine – Lipid nanoparticle-encapsulated mRNA based vaccine encoding mRSVPreF glycoprotein	Placebo (sterile normal saline solution for injection)	Total: 35 541 (17 793 intervention, 17748 control) Safety: (17 734 intervention, 17 679 control) Per-protocol efficacy (17 572 intervention, 17 516 control)	Randomisation (randomly assigned in a 1:1 ratio).	22 countries (Argentina, Australia, Bangladesh, Belgium, Canada, Chile, Columbia, Costa Rica, Finland, Germany, Japan, Mexico, New Zealand, Panama, Poland, Singapore, South Africa, South Korea, Spain, Taiwan, United Kington, United States)	**Vaccine efficacy:** - RSV-associated lower respiratory tract disease with ≥2 signs or symptoms - RSV-associated lower respiratory tract disease with ≥3 signs or symptom - RSV-Associated Acute Respiratory Disease - Efficacy According to RSV subtype **All-cause mortality;** **Serious adverse events related to vaccination;** **Unsolicited adverse events;** **Adverse events of particular interest (AESI);** **Local reactions;** **Systemic reactions**

Table 9. Characteristics of the participants

Author, year of publication	Age	Sex	Ethnicity	Comorbidities	Education	Socioeconomic status
Older adults (RSV perfusion vaccines)						
Wilson et al., 2023 (1)	**Intervention:** Mean 68.1 (SD=6.2), Median 67 (60-95) ≥80 year: 979 (5.5%) **Control:** Mean 68.1 (SD=6.2), Median 67 (60-96) ≥80 year: 997 (5.6%)	Both male and female	**Intervention:** White 11 240 (63.4%) Black 2 203 (12.4%) Asian 1 540 (8.7%) Other 2 682 (15.1%) Unknown/not reported 69 (0.4%) **Control:** White 11 216 (63.4%) Black 2 158 (12.2%) Asian 1 529 (8.6%) Other 2 671 (15.1%) Unknown/not reported 105 (0.6%)	**Intervention:** Frailty status (Edmonton Frail Scale across nine domains): Fit 13 512 (76.2%); Vulnerable 2 828 (15.9%), Frail 997 (5.6%), Missing data 397 (2.2%) No. of existing conditions of interest: none 12 496 (70.5%), ≥1 existing condition 5 238 (29.5%) Risk factors for lower respiratory tract disease: Present: 1 218 (6.9%) [Congestive heart failure 205 (1.2%), COPD 960 (5.4%), both 53 (0.3%)] Absent: 16 516 (93.1%) **Intervention:** Frailty status (Edmonton Frail Scale across nine domains): Fit 13 354 (75.5%); Vulnerable 2 899 (16.4%), Frail 1 017 (5.8%), Missing data 409 (2.3%) No. of existing conditions of interest: none 12 551 (71%), ≥1 existing condition 5 128 (29.0%) Risk factors for lower respiratory tract disease: Present: 1 230 (7.0%) [Congestive heart failure 201 (1.1%), COPD 978 (5.5%), both 51 (0.3%)] Absent: 16 449 (93.0%)	Not reported	Not reported

Table 10. Characteristics of intervention and comparator

Author, year of publication	Type of vaccine	Number of doses	Number of RSV seasons reported	Placebo (e.g., no intervention, vaccine not directed against RSV, one RSV vaccine with another RSV vaccine, same vaccine at same/different doses at same/ different dosing schedule, monoclonal antibodies, etc.)
Older adults (RSV perfusion vaccines)				
Wilson et al., 2023 (1)	mRNA-Based RSVPreF vaccine: lipid nanoparticle–encapsulated mRNA-based vaccine encoding the membrane-anchored RSV-F glycoprotein (mRNA-1345 vaccine)	1 (50 µg of mRNA-1345)	1	Placebo (0.9% sodium chloride - normal saline injection)

Table 11. Efficacy and effectiveness measures (primary outcomes)

Author, year of publication	Type of vaccine	Frequency of RSV infection	Hospitalisation due to RSV disease	Mortality from illness caused by RSV	All-cause mortality	Requirement for invasive ventilation	Vaccine efficacy (VE) with CI (Confidence interval) (as reported in the included studies)
Older adults (RSV perfusion vaccines)							
Wilson et al., 2023 (1)	mRNA-Based RSVPreF vaccine: lipid nanoparticle–encapsulated mRNA-based vaccine encoding the membrane-anchored RSV-F glycoprotein (mRNA-1345 vaccine)	**Intervention group:** RSV-Associated Lower Respiratory Tract Disease with ≥2 Signs or Symptoms: 9/17 572 RSV-associated lower respiratory tract disease with ≥3 signs or symptoms: 3/17 572 RSV-Associated Acute Respiratory Disease: 26/17 572 **Control group:** RSV-Associated Lower Respiratory Tract Disease with ≥2 Signs or Symptoms: 55/17 516 (36 RSV A, 19 RSV B) RSV-associated lower respiratory tract disease with ≥3 signs or symptoms: 17/17 516 RSV-Associated Acute Respiratory Disease: 82/17 516	Not reported	Up to 28 days: **Intervention:** 0/17 734 **Control:** 0/17 679 12 months and 24 months: Not reported (data not yet available)	Up to 28 days: **Intervention:** 2/17 734 **Control:** 4/17 679 12 months and 24 months: Not reported (data not yet available)	None reported	RSV-Associated Lower Respiratory Tract Disease with ≥2 Signs or Symptoms: 83.7% (66.0 to 92.2) According to RSV subtype RSV A = 91.7% (73.0 to 97.4), RSV B = 68.5% (21.1 to 87.4) RSV-associated lower respiratory tract disease with ≥3 signs or symptoms: 82.4% (34.8 to 95.3) According to RSV subtype RSV A = 90.0% (22.0 to 98.7) RSV B = 71.5% (-37.0 to 94.1) RSV-Associated Acute Respiratory Disease: 68.4% (50.9 to 79.7) RSV A = 78.5% (58.8 to 88.8) RSV B = 51.7% (10.6 to 73.9)

Table 12. Efficacy and effectiveness measures (secondary outcomes)

Author, year of publication	Type of vaccine	Measures of symptomatology (i.e., symptom scores, duration of symptoms)	Reported as prescription rate, clinician or self-reported antibiotic use, antibiotic purchases, or the number of antibiotic days/courses	Acute otitis media (AOM) [children only]	Duration of stay in an intensive care unit	Duration of protection	Development of asthma [children]	Reduced functional capacity [adults-all]	Requirement for rehabilitation stay due to potential adverse events
Older adults (RSV perfusion vaccines)									
Wilson et al., 2023 (1)	RSVPreF glycoprotein encoding mRNA encapsulated in lipid nanoparticle capsule (mRNA-145 vaccine)	Not reported	Not reported	Not applicable	Not reported	Not reported	Not applicable	Not reported	Not reported

Table 13. Safety measurements

Author, year of publication	Type of vaccine	All serious adverse events related to vaccination, including neurological disorders such as Guillain-Barre Syndrome	Unsolicited adverse events (spontaneously reported/ other adverse events)	Adverse events of particular interest (AESI): breakthrough infections/VAERS	Solicited adverse events Local reactions (redness, swelling, pain/tenderness)	Solicited adverse events Systemic reactions (fever, fatigue etc.)
Older adults (RSV perfusion vaccines)						
Wilson et al., 2023 (1)	RSVPreF glycoprotein encoding mRNA encapsulated in lipid nanoparticle capsule (mRNA-145 vaccine)	**Vaccine group**: Serious adverse event related to vaccine or placebo: 4/17 734 **Control group**: Serious adverse event related to vaccine or placebo: 3/17 679	**Intervention:** Any unsolicited adverse event: 3 624/17 734 (20.4%) Grade 3 unsolicited adverse event: 124/ 17 734 (0.7%) **Control:** Any unsolicited adverse event: 3 331/17 679 (18.8%) Grade 3 unsolicited adverse event: 119/ 17 679 (0.7%)	AESIs defined as thrombocytopenia, neurologic disease (including GBS), anaphylaxis and myocarditis/pericarditis. **Intervention group:** Any AESI: 3/17 734 (<0.1%) Any AESI related to vaccination: 1/17 734 (<0.1%) **Control group:** Any AESI: 8/17 679 (<0.1%) Any AESI related to vaccination: 1/17 679 (<0.1%) No cases of acute disseminated encephalomyelitis or Guillain–Barré syndrome.	**Intervention:** Any solicited local reaction: 10 367/17 662 (58.7%) Grade 3 or 4: 558/17 662 (3.2%) Redness: 357/17 659 (2%) Swelling: 662/17 660 (3.7%) Pain/tenderness: 9 942/17 661 (56.3%) **Control:** Any solicited local reaction: 2 845/17 598 (16.2%) Grade 3 or 4: 305/17 593 (1.7%) Redness: 101/17 659 (0.6%) Swelling: 59/17 592 (0.3%) Pain/tenderness: 2 407/17 593 (13.7%)	**Intervention:** All systemic solicited events: 8 432/17 662 (47.7%) Grade 3 or 4: 710/17 662 (4.0%) Fever: 501/17 651 (2.8%) Headache: 4 764/17 658 (27%) Fatigue: 5 470/17 658 (31.0%) Myalgia: 4 574/17 658 (25.9%) Arthralgia: 3 867/17 658 (21.9%) Nausea, vomiting: 1 248/17 658 (7.1%) Chills: 2 045/17 658 (11.6%) **Control:** All systemic solicited events: 5 798/17 597 (32.9%) Grade 3 or 4: 510/17 597 (2.9%) Fever: 234/17 593 (1.3%) Headache: 3 332 /17 592 (18.9%) Fatigue: 3 518/17 592 (20.0%) Myalgia: 2 542/17 592 (14.4%) Arthralgia: 2 477/17 591 (14.1%) Nausea, vomiting: 933/17 591 (5.3%) Chills: 1 181/17 591 (6.7%)

Table 14. Updated information on RSV perfusion vaccine for older adults - Arexvy by GSK

Author, year of publication Design	Type of vaccine	Measures of symptomatology (i.e., symptom scores, duration of symptoms)	Vaccine efficacy (VE) with CI (Confidence interval) (as reported in the included studies)	Unsolicited adverse events Local reactions (redness, swelling, pain/tenderness)	Solicited adverse events Systemic reactions (fever, fatigue etc.) and related serious adverse events
Older adults (RSV perfusion vaccine - Arexvy by GSK)					
Ison et al., 2024 (2)	RSVPreF3 OA vaccine - RSVPreF3 antigen and liposome-based AS01E adjuvant system	-	**Efficacy over two seasons of 1 RSVPreF3 OA dose** RSV related lower respiratory tract disease: 67.2% (48.2 to 80.0) According to RSV subtype RSV A 80.5% (54.0 to 93.2) RSV B 59.7%, (35.8 to 75.5) RSV related severe lower respiratory tract disease: 78.8% (52.6 to 92.0) RSV related acute respiratory infection: 52.7% (40.0 to 63.0) **Efficacy over two seasons of a first dose followed by revaccination** RSV related lower respiratory tract disease: 67.1% (48.1 to 80.0) According to RSV subtype RSV A 55.9% (16.8 to 78.2) RSV B 72.1%, (52.5 to 84.5) RSV related severe lower respiratory tract disease: 78.8% (52.5 to 92.0) RSV related acute respiratory infection: 60.3% (48.8 to 69.5)	**Vaccine group (Dose 2–exposed population)**: Any unsolicited reaction 791/4 991 (15.8%); any grade 3 unsolicited reaction 54/4 991 (1.1%); **Control group**: Any unsolicited reaction 1496/10 033 (14.9%); any grade 3 unsolicited reaction 120/10 033 (1.2%)	**Vaccine group (Dose 2–solicited safety population)**: Any solicited reaction 91/345 (26.4%); any grade 3 solicited reaction 3/345 (0.9%); **Control group**: Any solicited reaction 147/667 (22.0%); any grade 3 solicited reaction 10/667 (1.5%); **Any related serious AE**: **Vaccine group (Dose 2–exposed population)**: 2/4 991 (o.1%) **Control group**: 4/10 033 (0.0%)
Feldman et al., 2023 (4)	RSVPreF3 OA vaccine - RSVPreF3 antigen and liposome-based AS01E adjuvant system	-	RSV-Associated Lower Respiratory Tract Disease by coexisting condition of interest: No condition of interest: 72.5% (30.0 to 90.9) ≥1 condition of interest: 94.6% (65.9 to 99.9) ≥2 conditions of interest: 92.0% (46.1 to 99.8) RSV-Associated Acute Respiratory Disease by coexisting condition of interest : No condition of interest: 64.4% (39.0 to 80.1) ≥1 condition of interest: 81.0% (58.9 to 92.3) ≥2 conditions of interest: 88.0% (60.5 to 97.7)	-	-
Curran et al. 2023 (3)	RSVPreF3 OA vaccine - RSVPreF3 antigen and liposome-based	1. Median peak FLU-PRO Chest/Respiratory scores D1-D7 from onset of RSV-ARI episode Vaccine group = 24/27. Median: 1.07 (0.29, 2.21) Mean:	-	-	-

Author, year of publication Design	Type of vaccine	Measures of symptomatology (i.e., symptom scores, duration of symptoms)	Vaccine efficacy (VE) with CI (Confidence interval) (as reported in the included studies)	Unsolicited adverse events Local reactions (redness, swelling, pain/tenderness)	Solicited adverse events Systemic reactions (fever, fatigue etc.) and related serious adverse events
	AS01E adjuvant system	1.32 (1.02) Placebo group = 76/95. Median = 1.86 (1.43, 2.50) Mean: 1.90 (0.93) P value = 0.0258 2. Median peak FLU-PRO upper respiratory score (nose, throat and eyes) D1-D7 from onset of RSV-ARI episode Vaccine group = 24/27. Median: 1.59 (0.80, 2.20) Mean: 1.56 (0.88) Placebo group = 76/95. Median = 1.40 (1.10, 1.94) Mean: 1.49 (0.73) P value = 0.7199 3. Median peak FLU-PRO gastrointestinal score D1-D7 from onset of RSV-ARI episode Vaccine group = 24/27 had data. Median: 0.00 (0.00, 0.38) Mean: 0.25 (0.42) Placebo group = 76/95 had data. Median = 0.00 (0.00, 0.50) Mean: 0.26 (0.39) 4. Median peak FLU-PRO body/systemic score D1-D7 from onset of RSV-ARI episode Vaccine group = 24/27 had data. Median: 0.86 (0.27, 1.53) Mean: 1.01 (0.83) Placebo group = 76/95 had data. Median = 1.00 (0.55, 1.64) Mean: 1.14 (0.80) 5. Median peak FLU-PRO total score D1-D7 from onset of RSV-ARI episode Vaccine group = 24/27 had data. Median: 1.00 (0.50, 1.65) Mean: 1.09 (0.70) Placebo group = 76/95 had data. Median = 1.10 (0.74, 1.71) Mean: 1.22 (0.62) 6. Overall estimated least squares mean (standard error) of the FLU-PRO total score during first 7 days of the RSV-ARI episode Vaccine group (24/27 had data) = 0.76 (0.15) Placebo group (24/27 had data) = 0.81 (0.15) Estimated difference = -0.05 (-0.3, 0.2, p=0.6956) 7. Overall estimated least squares mean (standard error) of the SF-12 physical functioning scale during the RSV-ARI episode Vaccine group (20/27 had data) = 72.16 (9.99) Placebo group (69/95 had data) = 65.16 (9.80) Estimated difference = 7.00 (-9.86, 23.85, p=0.4125) 8. Observed estimated least squares mean (standard error) for the EQ-5D utility score Vaccine group (19/27 had data) = 0.8896 (0.0719) Placebo group (69/95 had data) = 0.8109 (0.0736) Estimated difference = 0.0786 (-0.0340 0.1913, p=0.1695) 9. Duration of the RSV-ARI episode – median (mean) Vaccine group = 11.0 days (12.8 days)			

Author, year of publication Design	Type of vaccine	Measures of symptomatology (i.e., symptom scores, duration of symptoms)	Vaccine efficacy (VE) with CI (Confidence interval) (as reported in the included studies)	Unsolicited adverse events Local reactions (redness, swelling, pain/tenderness)	Solicited adverse events Systemic reactions (fever, fatigue etc.) and related serious adverse events
		Placebo group = 14.0 days (19.0 days) 10. Medical visit rate during the RSV-ARI episode Vaccine = 8/27 (29.6%) Placebo = 38/95 (40.0%) Efficacy against RSV- confirmed ARI with medically attended visits = 79.0% (54.3 – 91.5%) 11. Medical visit rate during the RSV-LRTD episode Vaccine = 3/7 (42.7%) Placebo = 24/40 (60.0%) Efficacy against RSV-confirmed ARI with medically attended visits = 87.5% (58.9 – 97.6%)			

Table 15. List of excluded records during full-text screening

Author, Year	Reasons for exclusion
Dieussaert et al, 2024 [52]	Trial terminated and not continued.
NCT04605159, Phase 3 trial [53]	Trial terminated and not continued.
NCT05327816, Phase 1/2 trial [54]	Trial terminated and not continued.
NCT04908683, Phase 3 trial [55]	Trial terminated and not continued.
NCT05242432, Phase 3 trial [56]	Trial terminated and not continued.
NCT05045144, Phase 3 trial [57]	Focused on safety and immunogenicity
NCT05127434, Phase 3 trial [58]	Trial registry of included study.
NCT05059301, Phase 3 trial [59]	Focused on safety and immunogenicity

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