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RSV vaccines for subjects aged ≥75 years and subjects aged between ≥60 and <75 years at high risk of complications

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Title	RSV vaccines for subjects aged ≥75 years and subjects aged between ≥60 and <75 years at high risk of complications
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Technology	Respiratory syncytial virus (RSV) vaccines (Arexvy® (RSVpreF3), Abrysvo® (RSVPreF) and mRESVIA® (mRNA-1345))
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Authors report no conflict of interest.

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Cover image: Simplified representation of a fictional probabilistic sensitivity analysis on a cost-effectiveness plane with the diagonal willingness-to-pay line.

Executive Summary

Background

Respiratory syncytial virus (RSV) is a seasonable virus that generally causes mild cold-like symptoms. RSV infections in older adults can lead to acute respiratory infections (ARI) and lower respiratory tract infections (LRTI) with severe implications such as hospitalization or even death. RSVpreF (Abrysvo®), RSVPreF3 (Arexvy®), and mRNA-1345 (mRESVIA®) are 3 RSV prophylaxis vaccines that have been developed for subjects 60 years of age or older. Currently in Switzerland, approval has only been granted for RSVPreF3 and RSVpreF. To inform the reimbursement decision for RSV vaccines, the cost-effectiveness and budget impact of vaccination with either RSVpreF, RSVPreF3, or mRNA-1345 once every 2 years compared to no prophylaxis was estimated for Switzerland for 2 target populations: subjects aged ≥75 years, and subjects aged between ≥60 and <75 years at high risk of complications.

Methods

A clinical systematic review was conducted to search for RCTs evaluating RSVpreF, RSVPreF3 and mRNA-1345 compared to placebo, no prophylaxis or standard of care in older adults using RSV-related events as outcome. A systematic literature review was also performed for economic evaluations of the 3 vaccines in the target populations. The results of the systematic reviews served as input for the economic analyses. Additional targeted searches were performed for specific variables, such as RSV infection rate and quality of life to use as input for a newly developed health economic model for the Swiss setting.

Results clinical systematic review

Five publications were identified reporting data on 3 ongoing international RCTs, including European countries. The RCTs had a comparable study design and evaluated the vaccine efficacy (VE) of RSVpreF, RSVPreF3 and mRNA-1345 compared to placebo in healthy or medically stable subjects aged ≥60 years. Pre-specified interim analyses were planned. The overall risk of bias for the outcomes reported in the RCTs was “some concerns”. The RCTs showed the vaccine efficacy against RSV-related lower respiratory tract disease/illness (range VE 82.4%-85.7%) and RSV-related acute respiratory disease/illness (range VE 62.1%-71.7%) of a single dose of the RSV vaccines RSVpreF, RSVPreF3 or mRNA-1345 compared to placebo during one RSV season in subjects aged ≥60 years.

Results economic systematic review

In the economic systematic literature review 3 cost-utility analyses in subjects aged ≥60 years were identified. All studies assessed the cost-effectiveness of the vaccines RSVPreF3 and RSVpreF and none of mRNA-1345. The 2 studies conducted from a US societal perspective and from a Canadian societal perspective reported the maximum price-per-dose to be around $120 for the vaccines to be considered cost-effective given the relevant willing-to-pay (WTP) thresholds. The third study that was conducted from a Chinese healthcare perspective found the vaccines not to be cost-effective.

Economic evaluation and budget impact analysis

The results of the cost-effectiveness model built for the Swiss setting showed that administration of the RSV vaccines once every 2 years resulted in a gain in quality-adjusted life-years (QALYs) and higher costs compared to no prophylaxis in both target populations. For subjects aged ≥75 years, the incremental cost-effectiveness ratios (ICERs) were CHF 244’266, CHF 292’263 and CHF 258’699 per QALY gained for RSVPreF3, RSVpreF, and mRNA-1345, respectively. For subjects aged between ≥60 and <75 years at high risk of complications the ICERs were CHF 280’740, CHF 333’949 and CHF 296’879 per QALY gained, respectively. The reimbursement of RSV vaccines in the base case analysis is associated with a budget impact over 2 years of CHF 80.58 million, CHF 81.58 million, and CHF 80.91 million in the population of subjects aged ≥75 years, and CHF 12.83 million, CHF 13.0 million, and CHF 12.89 million for subjects aged between ≥60 and <75 years at high risk of complications for RSVPreF3, RSVpreF, and mRNA-1345, respectively.

One-way sensitivity analysis and scenario analyses showed that the cost-effectiveness results were most sensitive to the cost of the vaccine, the RSV infection rate and the decay of the vaccine efficacy in the second year. Assuming higher vaccination coverage and higher vaccine prices resulted in the largest budget impacts, while lower vaccine prices resulted in the lowest budget impact.

Conclusion

The present evaluation provided evidence for the vaccine efficacy for RSVPreF3, RSVpreF, and mRNA-1345 for one single dose and one RSV season based on interim analyses of ongoing clinical trials. Results of the economic evaluation showed that vaccination for prophylaxis of RSV is likely to generate additional QALYs and additional costs compared to no prophylaxis, which is current standard of care. For both the cost-effectiveness and budget impact analyses the main driver for the increased costs was the vaccine price.

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Abbreviations and acronyms

ARD	acute respiratory disease
ALRTI	acute lower respiratory track illness
ARI	acute respiratory illness
BIA	budget impact analysis
BAG	Bundesamt für Gesundheit
CDA-AMC	Canada’s Drug Agency l'Agence des médicaments du Canada
CDR	clinical data repository
CEA	cost-effectiveness Analysis
CEAC	cost-effectiveness acceptability curve
CE plane	cost-effectiveness plane
CHEC	consensus health economic criteria
CHF	Swiss franc
CHF	congestive heart failure
CI	confidence interval
CIRN	Canadian Immunization Research Network
COPD	chronic obstructive pulmonary disease
CPAP	continuous positive airway pressure
DARE	Database of Abstracts of Reviews of Effects
EKIF	Eidgenöossische Kommission für Impffragen
FDA	Food and Drug Administration
FOPH	Federal Office of Public health
GP	general practitioner
GSK	GlaxoSmithKline Biologicals S.A
GW	general ward

HAS	Haute Autorité de Santé
HARTI	hospitalised acute respiratory tract infection
HCP	healthcare provider
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
ICU	intensive care unit
IFA	indirect immunofluorescence assay
INAHTA	International Health Technology Assessment
LRTD	lower respiratory tract disease
LRTI	lower respiratory tract illness
NE	not estimated
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Care excellence
NR	not reported
OWSA	one-way sensitivity analysis
PICO (EO)	population, intervention, comparator, outcome, (economic outcomes)
PPD	price-per-dose
PRISMA	Preferred Reporting Items for Systematic Review and Meta- Analysis
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life year
RADT	rapid antigen detection test
RCT	randomised controlled trial
RESCEU	Respiratory Syncytial virus Consortium in Europe
RoB 2	Revised Cochrane Risk of Bias tool for randomised trials
RSV	respiratory syncytial virus
RT-PCR	reverse transcriptase-polymerase chain reaction

SD	standard deviation
SOS	Serious Outcomes Surveillance
STIKO	The German Standing Commission on Vaccination
USA	United States of America
WTP	willingness to pay

Objective of the health economic evaluation

The objective of a health economic evaluation is to generate a focused assessment in terms of costs and consequences of a health technology. The analytic methods applied to assess the value of using a health technology, their execution and the results are described. The analytical process is comparative and systematic. The domains covered in a health economic evaluation report include cost-effectiveness and budget impact. The purpose is to inform health policy and decision-making to promote an efficient, sustainable, equitable and high-quality health system.

1. Policy question and context

Respiratory syncytial virus (RSV) is a seasonable virus that is easily spread and generally causes mild cold-like symptoms. However, an RSV infection might lead to acute respiratory infections (ARI) and lower respiratory tract infections (LRTI), potentially resulting in severe symptoms, especially in older adults and young infants. [1] These severe cases require medical attendance in the form of self-managed, outpatient or inpatient care. Specifically for Switzerland, the RSV-related hospitalisation rates per 1'000 individuals aged ≥ 60 years were 0.4 in 2018/19 and 0.3 in 2019/20. [2] Besides its impact on morbidity, RSV is also associated with an increased mortality risk. A meta-analysis of Cong et al 2023 showed that RSV mortality risks in high-income countries have a U-shape association with age varying from 0.1/100'000 in the population in the age group 18-49 years to 80/100,000 in the population aged 75 years and older. [3]

The standard treatment of symptomatic RSV infections consists mainly of supportive care that includes hydration managements, oxygen supplementation and over-the-counter medications, such as antipyretic and anti-inflammatory drugs. [5] Recent developments focus on the prophylaxis of RSV by means of passive and active immunisation. Specifically for older adults, subunit, vector-based and nucleic acid vaccines have been developed. [5]

The following 3 vaccines have been approved by the Food and Drug Administration (FDA) in people 60 years of age or older: RSVPreF3, RSVpreF and mRNA1345. In Switzerland, approval has only been granted for RSVPreF3 and RSVpreF, while this is missing for mRNA1345. [6] Currently, none of these vaccines are covered by the mandatory health insurance in Switzerland.

To inform the reimbursement of these vaccines in Switzerland, the cost-effectiveness and budget impact of RSV vaccines in older adults and adults at high risk for complications were estimated.

2. Medical background

RSV is a common respiratory pathogen that affects people of all ages but poses particular risks for infants and older adults. [7,8] Particularly in adults aged 60 years or older, a 2021 European study reported that RSV illness had a prevalence of 5.7% across 2 RSV seasons. [9] In older adults, an RSV infection can lead to several serious complications affecting the respiratory system. RSV-related LRTI are common, with approximately 49% of older patients progressing to lower respiratory symptoms after RSV-positive ARI. [10] Moreover, in severe cases, RSV can lead to pneumonia, bronchiolitis, and exacerbation of existing conditions like chronic obstructive pulmonary disease (COPD) and congestive heart failure. [11]

RSV is transmitted primarily through respiratory droplets of an infected person and the incubation period lasts typically 4-6 days after exposure. The virus attaches to the epithelial cells of the upper

respiratory tract using surface proteins, allowing the viral genome to enter the host cell. [12,13] The infection of the respiratory epithelial cells triggers an immune response, leading to local inflammation and mucus production. The inflammation can obstruct airways, and the subsequent viral replication and the immune response leads to damage and death of the epithelial cells.[14] The virus has a seasonal pattern, with infections peaking during fall and winter months. In western Europe the RSV season lasts approximately from October to May and it peaks in the period between December and March, with a duration of 16 to 18 weeks. [15]

In general, RSV infections are not distinguishable from other respiratory viruses solely by means of clinical examination as they commonly manifest with mild, cold-like symptoms such as runny or congested nose, dry cough, low-grade fever, sore throat, sneezing, headache, fatigue. [9,16] As a result under detection is very common in RSV in older adults. [17] A combination of clinical evaluation and laboratory testing is necessary for an RSV diagnosis, although testing is not always needed for mild cases in otherwise healthy individuals. [16] The clinical evaluation typically involves assessing symptoms and risk factors (e.g. age and comorbidities), while there are several methods with varying sensitivities used for diagnostic testing including real-time reverse transcription-polymerase chain reaction (RT-PCR), rapid antigen detection tests (RADTs), indirect immunofluorescence assay (IFA), viral culture, and serology. [18–20]

The primary treatment for RSV in older adults remains supportive care, as there is no specific antiviral treatment approved for RSV in this population. Standard of care includes hydration agents, antipyretics, bronchodilators, and supplemental oxygen. [21,22] In severe cases requiring hospitalisation, treatment may include monitoring of respiratory status, mechanical ventilation in cases of respiratory failure, and treatment of complications, such as pneumonia or exacerbation of underlying conditions. [22] While not routinely used, some specific treatments include ribavirin and immunoglobulin for immunocompromised. [21,22]

RSV infections have a significant effect on disease and mortality in older and immunocompromised adults with approximately 1.5 million older adult cases in developed countries in 2015. [23–25] Specifically, there is increased risk of hospitalisation, need for intensive care, and even death, with case fatality proportions ranging from 8.18% to 9.88% in older and high-risk adults respectively. [26] In Switzerland, there were approximately 3’000-6’000 RSV hospitalisations each year for the years 2016 to 2021, and it has been estimated that in Europe 92% of RSV hospitalisations in adult patients (approximately 145’000 cases) occur in patients older than 65 years of age with the highest annual frequency of RSV hospitalisation being observed in adults aged 75-84 years. [21,27,28] The high rates of hospitalisation and significant health and socioeconomic burden emphasises the importance of prevention and management strategies for this population.

3. Technology

3.1 Technology description

RSV vaccines and monoclonal antibodies represent significant advancements in the prevention and prophylaxis of severe respiratory syncytial virus disease, particularly for vulnerable populations such as infants and older adults. Currently there are 3 RSV vaccines for older adults that have received marketing authorization from the European Commission:

1. RSVpreF (Abrysvo®) by Pfizer is a vaccine for pregnant women for the infant's protection and adults aged 60 years and over against lower respiratory tract disease (LRTD) caused by RSV. The vaccine is administered as an intramuscular injection in a single dose of 0.5 mL via an Act-O-Vial presentation, a vial and prefilled syringe presentation or vial and vial presentation. [29] RSVpreF consists of a recombinant, replication-incompetent, adenovirus serotype 26 vector encoding a conformation-stabilised RSV preF protein and recombinant RSV preF protein, with no adjuvant. [30]
2. RSVPreF3 (Arexvy®) by GlaxoSmithKline Biologicals S.A. (GSK) is a vaccine for adults over 60 years against LRTD caused by RSV, but recently received expanded approval for adults aged 50-59 years who are at increased risk of RSV disease. [31] Similar to RSVPreF, RSVPreF3 is administered as an intramuscular injection in a single dose of 0.5mL via a vial and vial presentation. [32] It utilises a combination of a recombinant subunit prefusion RSV F glycoprotein antigen (RSVPreF3) and the AS01E adjuvant. The vaccine stimulates the immune system in adults to produce a response specifically targeting RSVPreF3. [33]
3. mRNA-1345 (mRESVIA®) by Moderna is an RSV vaccine for active immunisation for the prevention of LRTD in adults aged 60 years or older. This vaccine is also administered in a single dose of 0.5mL through an intramuscular injection with a vial and prefilled syringe presentation. [34] It consists of an mRNA sequence encoding a stabilised prefusion F glycoprotein. The prefusion conformation of the F protein is a significant target of potent neutralising antibodies. This glycoprotein is expressed on the surface of the virus and is required for host cell invasion. [35]

3.2 Alternative technologies

In Switzerland, there are currently no approved alternative technologies for the prophylaxis of an RSV infection in adults. Standard of care in elderly people consists of supportive measurement and hydration agents, antipyretics, bronchodilators, and supplemental oxygen. [21]

3.3 Regulatory status / provider

In Switzerland, vaccines are mainly provided by general practitioners (GPs). [36] However, vaccines can also be administered in community pharmacies. To be authorised for vaccinating individuals, pharmacists need specific pre graduate or postgraduate training, and continuous education every

2 years. [37] Next to GPs and pharmacies, vaccines can also be provided by hospitals and vaccination centres. [38]

RSVpreF, RSVPreF3 and mRNA-1345 have been granted approval by the European commission, which is valid in all European Union member states plus Iceland, Liechtenstein and Norway. [39–41] Specifically in Switzerland, Swissmedic has authorised RSVpreF and RSVPreF3 since the beginning of November 2024, but for mRNA-1345 no information on the approval onto the Swiss healthcare market has been published up to now. [6]

RSVpreF and RSVPreF3 are currently available on the Dutch healthcare market and reviewed for reimbursement. [42] Likewise, The German Standing Commission on Vaccination (STIKO) made the announcement that everyone aged 75 years or older should receive RSVpreF or RSVPreF3, but no decisions on reimbursement have been made. [43] Furthermore, all brands are covered through Medicare in most states of the US. [44–46]

In France, Haute Autorité de Santé (HAS) recommends the seasonal vaccination of individuals aged ≥75 years and individuals aged ≥65 years with specific comorbidities. [47] To vaccinate these individuals, RSVpreF is reimbursed [48] while RSVPreF3 and mRNA-1345 are still under evaluation. Similarly in the United Kingdom, individuals over 75 years are eligible for the RSVpreF vaccine from 1 September 2024 while there is no decision for RSVPreF3 and mRNA-1345. [49]

4. Population, Intervention, Comparator, Outcome (PICO)

	PICO 1	PICO 2
P:	Subjects aged ≥75 years	Subjects aged between ≥60 and <75 years at high risk of complications[a]
I:	RSV vaccination: - Abrysvo® (RSVpreF) - Arexvy® (RSVPreF3) - mRESVIA® (mRNA-1345)	RSV vaccination: - Abrysvo® (RSVpreF) - Arexvy® (RSVPreF3) - mRESVIA® (mRNA-1345)
C:	- No prophylaxis - Standard of care	- No prophylaxis - Standard of care
O:	**Clinical outcomes** - RSV-related LRTI - RSV-related ARI - RSV-related LRTD - RSV-related severe LRTD - RSV-related emergency visits - RSV-related hospitalisations (with/without ICU) - RSV-related mortality - RSV-related general practitioner visits **Economic outcomes** - Quality adjusted life years (QALYs); incremental and total - Life years; incremental and total - Costs; incremental and total - Incremental cost-effectiveness ratio (ICER) - Budget-impact per year	**Clinical outcomes** - RSV-related LRTI - RSV-related ARI - RSV-related LRTD - RSV-related severe LRTD - RSV-related emergency visits - RSV-related hospitalisations (with/without ICU) - RSV-related mortality - RSV-related general practitioner visits **Economic outcomes** - Quality adjusted life years (QALYs); incremental and total - Life years; incremental and total - Costs; incremental and total - Incremental cost-effectiveness ratio (ICER) - Budget-impact per year

Abbreviations
ARI = acute respiratory illness, ICU = intensive care unit, LRTD = lower respiratory tract disease, LRTI = lower respiratory tract illness, RSV = respiratory syncytial virus.
Notes
a = High risk of complications was defined, based on the patient characteristics reported in the studies.

5. Research questions health economic evaluation

For the health economic evaluation of the technology the following research questions are addressed:

1. What is the cost-effectiveness of vaccination against RSV for subjects aged ≥75 years compared to no prophylaxis or standard of care?
2. What is the budget-impact of vaccination against RSV for subjects aged ≥75 years compared to no prophylaxis or standard of care?
3. What is the cost-effectiveness of vaccination against RSV for subjects aged between ≥60 and <75 years at high risk of complications compared to no prophylaxis or standard of care?
4. What is the budget-impact of vaccination against RSV for subjects aged between ≥60 and <75 years at high risk of complications compared to no prophylaxis or standard of care?

6. Methodology literature review

6.1 Systematic review of clinical evidence

The systematic review of clinical evidence was conducted following a concise internal review protocol. In general, a pragmatic approach was chosen, since the results from the clinical systematic review primarily served as input for the economic analyses.

6.1.1 Databases and search strategy

The focus of this health economic evaluation was to search for randomised controlled trials (RCTs). The systematic literature search was conducted in PubMed (MEDLINE), Embase.com and Cochrane Library on 3 September 2024. The search strategy was developed based on the PICO reported in ***Chapter 1.*** Search strings were compiled for the intervention RSV vaccines and limits were added for the study design RCTs, in the databases PubMed (MEDLINE) and Embase.com, and to exclude conference abstracts and preprints (***Appendix A***).

Electronic records of the articles retrieved by the searches were stored with Endnote reference manager software (Clarivate Analytics, United States of America [USA]) and uploaded in Rayyan software (Rayyan Systems Inc., USA). Duplicate records were deleted.

Reference lists of systematic reviews relevant to the research questions identified during the title and abstract screening were checked for potentially relevant additional references of primary studies. The identified systematic review was excluded after the reference check. Narrative reviews were excluded and not checked for references.

6.1.2 Study selection

Relevant articles were selected by a systematic approach with Rayyan software by one researcher in close collaboration with a second researcher. Any disagreements between the 2 researchers were resolved by discussion, if needed a third researcher was consulted. Firstly, the potential relevancy of the articles was assessed during the title/abstract screening. Potentially relevant articles were selected for full-text screening, all other articles were excluded without documenting the reason for exclusion. Secondly, the articles were assessed in full text based on the prespecified eligibility criteria, covering elements of the article, study design and PICO (see ***Table 1***). Articles were included in the systematic review if they fulfilled the inclusion criteria; the remaining articles were excluded and the primary reason for exclusion was listed.

To provide insight in the details of the selection process, the standardised Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) flow diagram with the results of the study selection and a table with the primary reasons for exclusion for each excluded article at full-text review were composed.

Table 1. Inclusion criteria for the clinical systematic literature search

Publication year	All
Language of publication	English
Country of study	Worldwide
Study design/publication type	- RCTs (published as full article in a peer-reviewed journal) - Systematic reviews (only used for a reference check)
Population	- Subjects aged ≥75 years - Subjects aged between ≥60 and <75 years at high risk of complications - Clear definition/selection of the study population
Intervention	- RSVpreF (Abrysvo®) - RSVPreF3 (Arexvy®) - mRNA-1345 (mRESVIA®)
Comparator	- Placebo - No prophylaxis - Standard of care
Outcome	RSV-related events: - RSV-related LRTI - RSV-related ARI - RSV-related LRTD - RSV-related emergency visits - RSV-related hospitalisations (with/without ICU) - RSV-related mortality - RSV-related general practitioner visits

Abbreviations
ARI = acute respiratory illness, ICU = intensive care unit, LRTD = lower respiratory tract disease, LRTI = lower respiratory tract illness, RSV = respiratory syncytial virus.

6.1.3 Data extraction, analysis and synthesis

The study characteristics, patient characteristics and results of the included RCTs were extracted in tables in Microsoft Word by one researcher in close collaboration with a second researcher. In addition, relevant figures presented in the articles or supplementary material were copy-pasted in this report. Data was stratified for each RSV vaccine: RSVpreF, RSVPreF3 and mRNA-1345. Since only one RCT was included for each RSV vaccine and the interim analyses of the RSVPreF3 trial

reported data over different RSV seasons or a specific subgroup, the data could not be pooled by meta-analysis and is presented narratively in summary tables. Data on the outcomes of interest is presented for the overall population aged ≥60 years, age groups, and high-risk conditions in subjects aged ≥60 years.

6.1.4 Quality appraisal of clinical studies

The included RCTs were critically appraised by one researcher in close collaboration with a second researcher with the revised Cochrane Risk of Bias tool for randomised trials (RoB 2) and visualised in a plot with the web application Robvis. [50–52] The risk of bias was not assessed on a per outcome basis, but for the outcomes class RSV-related events.

6.2 Systematic review of economic evidence

The systematic review of economic evidence was conducted following a concise internal review protocol and the general methodological approach is the same as for the clinical evaluation. The details of the systematic review methodology for the economic evaluation are described in the following sections.

6.2.1 Databases and search strategy

Database specific search strings were developed to identify scientific papers that describe the cost-effectiveness of RSVpreF, RSVPreF3 and mRNA-1345 in older adults (***Appendix D***). The search strings included terms specific to the intervention and outcomes of economic evaluations. Furthermore, limits were set to exclude conference abstracts and preprints. PubMed (MEDLINE), Embase.com, Cochrane library, Clinical Data Repository (CDR) databases (Database of Abstracts of Reviews of Effects (DARE), the Health Technology Assessment database (HTA), National Health Service Economic Evaluation Database (NHS EED), EconLit, and the Tufts Medical Centre Cost-Effectiveness Analysis [CEA] Registry were searched for peer-reviewed scientific literature. After entering the search strings into the pre-specified databases, electronic records of the articles were retrieved and uploaded in Rayyan software (Rayyan Systems Inc., USA) and duplicates were deleted. Additionally, in order to capture HTA reports published by government agencies, a pragmatic search was conducted for the international Health Technology Assessment database (INAHTA), National Institute for Health and Care Excellence (NICE) and Canada's Drug Agency l'Agence des médicaments du Canada (CDA-AMC) databases. The searches were conducted on 3 September and 19 September 2024 respectively.

6.2.2 Study selection

All articles retrieved from the databases were reviewed by one researcher in close collaboration with a second researcher. In the first step, the major topics of the articles were assessed based on relevancy and articles that seemed to contain relevant data for the objectives of the economic

evaluation were selected for the full-text screening. Subsequently, the articles screened in full text were assessed for inclusion based on pre-specified eligibility criteria (see ***Table 2***) and the remaining articles were excluded with the primary reason for exclusion listed.

To provide insight in the details of the selection process, a PRISMA flow diagram with the results of the study selection and a table with the primary reasons for exclusion at fulltext were composed.

Table 2. Inclusion criteria for the economic systematic literature search

	Inclusion criteria for economic studies
Publication year	All
Language of publication	English
Country of study	Worldwide
Study design/publication type	cost-utility analysis cost-effectiveness analysis cost-minimisation analysis cost-benefit analysis cost-consequence analysis costing studies
Population	- Subjects aged ≥75 years - Subjects aged between ≥60 and <75 years at high risk of complications - Clear definition/selection of the study population
Intervention	- RSVpreF (Abrysvo®) - RSVPreF3 (Arexvy®) - mRNA-1345 (mRESVIA®)
Comparator	- No prophylaxis - Standard of care
Outcome	- Quality adjusted life years (QALYs); incremental and total - Life years; incremental and total - Costs; incremental and total - Incremental cost-effectiveness ratio (ICER) - Budget-impact per year

6.2.3 Data extraction, analysis and synthesis

After finalising the screening phases, relevant data was extracted from the included studies by one researcher in close collaboration with a second researcher using a standardised data-extraction spreadsheet in Microsoft Excel. This spreadsheet included:

– first author, year

– country

– type of economic evaluation

– study population characteristics

– intervention

– comparator

– study perspective (healthcare (direct medical costs) /societal (direct medical costs+indirect costs, i.e. costs for productivity loss or informal care)

– methods of the economic evaluation (discount rates, time horizon)

– model used (yes/no, type of model, health states)

– outcomes (total/incremental costs, life-years, QALYs, ICER, max price-per-dose (PPD), willingness-to-pay (WTP), Budget impact)

6.2.4 Quality appraisal of economic studies

The identified studies from the economic systematic literature search were subjected to a critical appraisal using the Consensus Health Economic Criteria (CHEC) checklist. [53] This list consists of 19 items with clear questions about the economic evaluation that gives insight into the general quality of the study. Reviewing the scores on this CHEC checklist enables the assessment of each study's credibility, warning against the inclusion of low-quality papers in the analysis.

7. Results literature review

Summary statement literature review

Clinical evidence

In healthy or medically stable subjects aged ≥60 years, prespecified interim analyses of 3 ongoing international RCTs showed the vaccine efficacy against RSV-related lower respiratory tract disease/illness and RSV-related acute respiratory disease/illness of a single dose of the RSV vaccines RSVpreF, RSVPreF3 or mRNA-1345 compared to placebo during one RSV season. A second prespecified interim analysis of a single RSVPreF3 dose pre-season 1 also showed the vaccine efficacy against RSV-related lower respiratory tract disease and RSV-related acute respiratory illness of RSVPreF3 in subjects aged ≥60 years during 2 RSV seasons; re-vaccination with a single RSVPreF3 dose pre-season 2 did not seem to provide additional vaccine efficacy. For RSVpreF, RSVPreF3 and mRNA-1345 subgroup analyses were presented for different age and high-risk groups, however these results need to be interpreted with caution due to the low number of cases in the interim analyses.

Economic evidence

Three studies on the cost-effectiveness of RSVpreF and RSVPreF3 were included in the analysis. Of these, one CUA was conducted in the United States and one in Canada, both from a societal perspective using a discrete event simulation model. These studies calculated the price-per-dose for which RSVpreF and RSVPreF3 can potentially be cost-effective compared to no intervention given a willingness-to-pay threshold value. The third study was performed in China from a healthcare perspective using a decision tree model. In this study, the conclusion was that RSVpreF and RSVPreF3 were not cost-effective compared to no intervention. Differences between ICER estimates across all studies are related to cost estimates and differences in other input parameters used. This can be attributed to a multitude of factors including deviations in price per dose, analysis perspectives, time horizon and type and structure of the economic models.

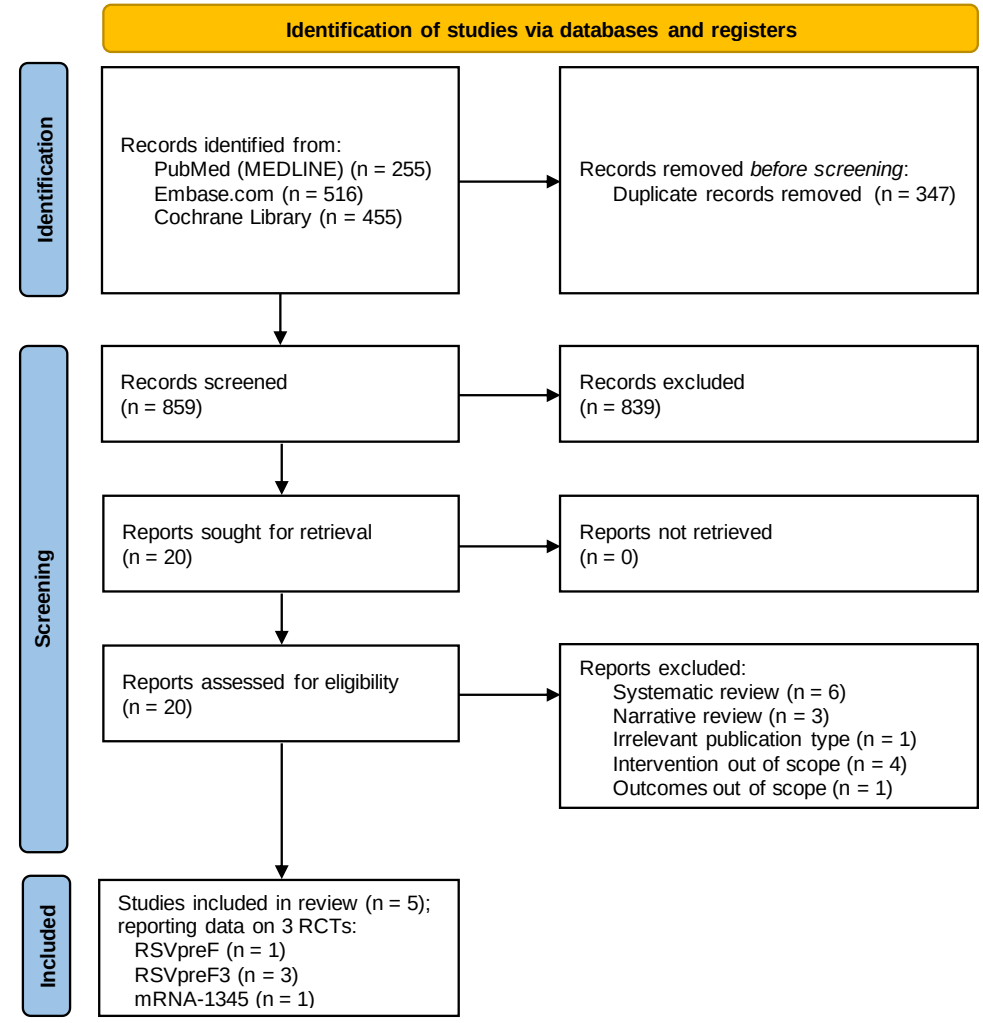
7.1 Review of clinical evidence

7.1.1 Search results

The results of the clinical systematic literature search are summarised in ***Figure 1***. In total, 859 unique records were identified in PubMed (MEDLINE), Embase.com and Cochrane Library with the search conducted on 3 September 2024. Of those, 839 records were excluded based on title and abstract. During the subsequent full-text selection 15 reports were excluded. Reasons for exclusion were as follows: systematic review excluded after the reference check (n=6), narrative

review (n=3), irrelevant publication type, i.e. abstract (n=1), intervention out of scope, i.e. other RSV vaccine (n=4), and outcomes out of scope (n=1). An overview of the reason for exclusion by each excluded article is enclosed in ***Appendix B***. Three ongoing RCTs were included in the clinical systematic review, covering the RSV vaccines of interest. [54–56] The RSVPreF3 trial published additional analyses. [57,58]

Figure 1. PRISMA flow diagram of the clinical systematic literature search



Notes
Search date 3 September 2024.

7.1.2 Study characteristics

Three ongoing RCTs on RSV vaccines in subjects aged ≥60 years form the clinical evidence base. In total, 5 articles reporting data on these RCTs were included. The RCTs were funded by the vaccine manufacturing companies. The study characteristics are summarised for each RSV vaccine: RSVpreF (***Table 3***), RSVPreF3 (***Table 4***), and mRNA-1345 (***Table 5***). Details of the outcome definitions are outlined in ***Table 6***.

RSVpreF

The phase 3 RCT “RENOIR” was designed to study the vaccine efficacy of RSVpreF (Abrysvo®) in older adults during 2 RSV seasons. [55] From August 2021 healthy or medically stable subjects aged ≥60 years were enrolled in 7 countries and randomised to a single dose of RSVpreF or placebo. At the data-cutoff in July 2022, a prespecified interim analysis was conducted in 17’215 subjects (mean age 68.3 years; 51% male) in the RSVpreF arm and 17’069 subjects (mean age 68.3 years; 50% male) in the placebo arm. At the data-cutoff 6 months of follow-up (mean 7 months) were completed during RSV season 1. In both study arms 52% of the subjects had ≥1 prespecified high-risk conditions (i.e. current tobacco use, diabetes, lung disease, heart disease, liver disease, renal disease) and 15% ≥1 chronic cardiopulmonary conditions (i.e. asthma, chronic obstructive pulmonary disease (COPD), congestive heart failure).

RSVPreF3

The objective of the phase 3 RCT “AReSVi-006” was to evaluate the efficacy of the RSVPreF3 OA vaccine (Arexvy®) in older adults during 3 consecutive RSV seasons in the Northern Hemisphere and for ≥2 consecutive seasons in the Southern Hemisphere. [54] From May 2021 healthy or medically stable subjects aged ≥60 years were enrolled in 17 countries and randomised to a single dose of RSVPreF3 or placebo. The first interim analysis published by Papi et al 2023 was conducted at the end of Northern Hemisphere RSV season 1 in July 2022, with a median follow-up of 6.7 months. [54] In total, 12’467 subjects (mean age 69.5 years; 48% male) were included in the RSVPreF3 arm and 12’499 subjects (mean age 69.6 years; 49% male) in the placebo arm.

A descriptive sub-group/post-hoc analysis of this interim analysis in subjects aged ≥60 years at high risk of complications was published by Feldman et al 2024. [57] At least one condition of interest (i.e. cardiorespiratory condition, COPD, asthma, CHF) or endocrine/metabolic condition [diabetes type1/2, advanced liver/renal disease]) was reported in 4,937 subjects in the RSVPreF3 arm and in 4’864 subjects in the placebo arm.

The second interim analysis published by Ison et al 2024 was conducted at the end of Northern Hemisphere RSV season 2 in March 2023. [58] The median follow-up was 17.8 months. Pre-season 2 subjects in the RSVPreF3 arm were re-randomised to receive a second RSVPreF3 OA dose or placebo, resulting in 3 study arms: RSVPreF3 pre-season 1, RSVPreF3 pre-season 1 & 2, and placebo. The subjects flow of the RCT is enclosed in ***Appendix C***. Vaccine efficacy in the study arms over 2 RSV seasons was analysed in the modified exposed population; baseline characteristics of the subjects were reported for the exposed population.

mRNA-1345

Wilson et al 2023 studied the vaccine efficacy of the mRNA-1345m vaccine (mRESVIA®) in the phase 2-3 RCT “ConquerRSV”, with a planned follow-up of 24 months. [56] From November 2021 healthy or medically stable subjects aged ≥60 years were enrolled in 22 countries and randomised to a single dose of mRNA-1345 or placebo. After up to 12 months follow-up (median 112 days) a prespecified interim analysis was conducted. The RSV season was not reported but based on the follow-up assumed RSV season 1. In total, 17’734 subjects were included in the mRNA-1345 arm and 17’679 subjects in the placebo arm. The mean age was 68.1 years, 51% were male, 29% had ≥1 coexisting conditions of interest (advanced liver/renal disease, asthma, chronic respiratory disease, CHF, COPD, diabetes), and 7% had a risk factor for lower respiratory tract disease (i.e. CHF, COPD).

Table 3. Study characteristics of the RSVpreF trial

Reference Study name Study id	Study design Status (planned follow-up) Funding	Country Study period Follow-up	Study population Study arm	Sample size	Age mean±SD (range); groups n (%)	Sex n (%) male	Ethnic-ity n (%) white	High-risk conditions n (%)	Frailty status n (%)
Walsh et al 2023 [55] RENOIR NCT05035212	Phase 3 RCT; interim analysis[a] Ongoing (2 RSV seasons) Industry funded	7 countries[b] August 2021-July 2022 RSV season 1; completed 6 m follow-up; mean 7 m (SD NR)	Subjects aged ≥60 years, healthy or with stable chronic medical conditions at baseline						
			RSVpreF (single dose 120 µg RSVpreF)	17'215	- 68.3±6.14 (59-95) y - 60-69 y: 10,757 (62.5%)[c] - 70-79 y: 5,488 (31.9%) - ≥80 y: 970 (5.6%)	8'800 (51.1%)	13'475 (78.3%)	≥1 prespecified high-risk conditions: 8'867 (51.5%) - current tobacco use: 2'642 (15.3%) - diabetes: 3'224 (18.7%) - lung disease[d]: 1'956 (11.4%) - heart disease[e]: 2'221 (12.9%) - liver disease: 335 (1.9%) - renal disease: 502 (2.9%) ≥1 chronic cardiopulmonary conditions: 2'595 (15.1%) - asthma: 1'541 (9.0%) - COPD: 1'012 (5.9%) - CHF: 293 (1.7%)	NR
			Placebo	17'069	- 68.3±6.18 (60-97) y - 60-69 y: 10,680 (62.6%) - 70-79 y: 5,431 (31.8%) - ≥80 y: 958 (5.6%)	8'601 (50.4%)	13'360 (78.3%)	≥1 prespecified high-risk conditions: 8'831 (51.7%) - current tobacco use: 2'571 (15.1%) - diabetes: 3'284 (19.2%) - lung disease[d]: 2'040 (12.0%) - heart disease[e]: 2'233 (13.1%) - liver disease: 329 (1.9%) - renal disease: 459 (2.7%) ≥1 chronic cardiopulmonary conditions: 2'640 (15.5%) - asthma: 1'508 (8.8%) - COPD: 1'080 (6.3%) - CHF: 307 (1.8%)	NR

Abbreviations
CHF = congestive heart failure, COPD = chronic obstructive pulmonary disease, m = months, n = number, NR = not reported, SD = standard deviation, y = years.
Notes
a = The prespecified interim analyses were planned when at least 29 cases had a first episode of RSV-related lower respiratory tract illness with ≥2 signs or symptoms and at least 15 cases had a first episode of RSV-related lower respiratory tract illness with ≥3 signs or symptoms. The interim analyses were conducted after the first RSV season ended or all subjects had been followed for 6 months post-injection (if there was no clear seasonality). This interim analysis was conducted when 44 subjects had ≥2 signs or symptoms.
b = Argentina, Canada, Finland, Japan, the Netherlands, South Africa, United States of America.
c = This age group included one 59-year-old participant.
d = This category includes COPD and other lung diseases.
e = This category includes congestive heart failure and other heart diseases.

Table 4. Study characteristics of the RSVPreF3 trial

Reference Study name Study id	Study design Status (planned follow-up) Funding	Country Study period Follow-up	Study population Study arm	Sample size	Age mean±SD (range); groups n (%)	Sex n (%) male	Ethnicity n (%) white	High-risk conditions n (%)	Frailty status[a] n (%)
Papi et al 2023 [54] **AReSVi-006** **NCT04886596**	Phase 3 RCT; interim analysis Ongoing (36 m)[b] [c] Industry funded	17 countries[d] May 2021-April 2022 end Northern Hemisphere RSV season 1; median 6.7 m (max 10.1 m)	Subjects aged ≥60 years, healthy or with stable chronic medical conditions at baseline						
			RSVPreF3 pre-season 1 (single dose 120 µg RSVPreF3 OA)	12'467	- 69.5±6.5 (NR) y - 60-69 y: 6,963 (55.9%) - 70-79 y: 4,487 (36.0%) - ≥70 y: 5,504 (44.1%) - ≥80 y: 1,017 (8.2%)	5'979 (48.0%)	9'887 (79.3%)	- ≥1 conditions of interest: 4'937 (39.6%) - cardiorespiratory condition: 2'496 (20.0%) - endocrine/metabolic condition: 3'200 (25.7%)	- fit: 7'464 (59.9%) - pre-frail: 4'793 (38.4%) - frail: 189 (1.5%)
			Placebo	12'499	- 69.6±6.4 (NR) y - 60-69 y: 6,980 (55.8%) - 70-79 y: 4,491 (35.9%) - ≥70 y: 5,519 (44.2%) - ≥80 y: 1,028 (8.2%)	6'072 (48.6%)	9'932 (79.5%)	- ≥1 conditions of interest: 4,864 (38.9%) - cardiorespiratory condition: 2,422 (19.4%) - endocrine/metabolic condition: 3,236 (25.9%)	- fit: 7'521 (60.2%) - pre-frail: 4'781 (38.3%) - frail: 177 (1.4%)
Feldman et al 2023 [57] AReSVi-006 NCT04886596	Phase 3 RCT; descriptive sub-group/post-hoc analysis of the interim analysis Ongoing (36 m) Industry funded	17 countries[d] May 2021-April 2022 end Northern Hemisphere RSV season 1; median 6.7 m (range NR)	Subjects aged ≥60 years, with ≥1 stable chronic medical conditions at baseline (i.e. cardiorespiratory conditions [CHF; any chronic respiratory/pulmonary disease, incl. COPD, asthma, other conditions]; endocrine & metabolic conditions [diabetes mellitus type 1/2; advanced liver or renal disease])						
			RSVPreF3 pre-season 1 (single dose 120 µg RSVPreF3 OA)	4'937	NR	NR	NR	≥1 cardiorespiratory conditions: n=2,496 - COPD: n=1'131 - asthma: n=1'193 - chronic respiratory/pulm. disease: n=2'233 - CHF: n=398 ≥1 endocrine/metabolic conditions: n=3'200 - diabetes type 1/2: n=2'829 - advanced liver/renal disease: n=667 ≥2 conditions of interest: n=2'504	NR
			Placebo	4'864	NR	NR	NR	≥1 cardiorespiratory conditions: n=2'421 - COPD: n=1'113 - asthma: n=1'113 - chronic respiratory/pulm. disease: n=2'123 - CHF: n=403 ≥1 endocrine/metabolic conditions: n=3'236 - diabetes type 1/2: n=2'877 - advanced liver/renal disease: n=676 ≥2 conditions of interest: n=2'434	NR

Ison et al 2024 [58] AReSVi-006 NCT04886596	Phase 3 RCT; interim analysis Ongoing (36 m)[b] [e] Industry funded	17 countries[d] May 2021-March 2023 end Northern Hemisphere RSV season 2; median 17.8 m (range NR)	Subjects aged ≥60 years, healthy or with stable chronic medical conditions at baseline						
			RSVPreF3 pre-season 1 (single dose 120 µg RSVPreF3 OA)	6'228	- 69.5±6.4 (NR) y - 60-69 y: 3,480 (55.9%) - 70-79 y: 2,244 (36.0%) - ≥70 y: 2,748 (44.1%) - ≥80 y: 504 (8.1%)	2'945 (47.3%)	4'939 (79.3%)	- ≥1 condition of interest: 2,481 (39.8%) - cardiorespiratory condition: 1,261 (20.2%) - endocrine/metabolic condition: 1,611 (25.9%)	- fit: 3'758 (60.3%) - pre-frail: 2'358 (37.9%) - frail: 103 (1.7%)
			RSVPreF3 pre-season 1 & 2 (single dose 120 µg RSVPreF3 OA)	6'242	- 69.6±6.5 (NR) y - 60-69 y: 3,483 (55.8%) - 70-79 y: 2,245 (36.0%) - ≥70 y: 2,759 (44.2%) - ≥80 y: 514 (8.2%)	3'036 (48.6%)	4'951 (79.3%)	- ≥1 condition of interest: 2,502 (40.1%) - cardiorespiratory condition: 1,285 (20.6%) - endocrine/metabolic condition: 1,618 (25.9%)	- fit: 3'707 (59.4%) - pre-frail: 2'437 (39.0%) - frail: 86 (1.4%)
			Placebo	12'503	- 69.6±6.4 (NR) y - 60-69 y: 6,982 (55.8%) - 70-79 y: 4,493 (35.9%) - ≥70 y: 5,521 (44.2%) - ≥80 y: 1,028 (8.2%)	6'074 (48.6%)	9'936 (79.5%)	- ≥1 condition of interest: 4,922 (39.4%) - cardiorespiratory condition: 2,480 (19.8%) - endocrine/metabolic condition: 3,257 (26.0%)	- fit: 7'524 (60.2%) - pre-frail: 4'782 (38.2%) - frail: 177 (1.4%)

Abbreviations
CHF = congestive heart failure, COPD = chronic obstructive pulmonary disease, d = days, m = months, n = number, NR = not reported, SD = standard deviation, y = years.
Notes
a = Frailty status was assessed using a gait speed test: frail, subjects with a walking speed <0.4 m/s or not able to perform the test; pre-frail, subjects with a walking speed of 0.4-0.99 m/s; fit, subjects with a walking speed ≥1 m/s.
b = In this RCT, Northern-Hemisphere subjects (92%) will be monitored for 3 consecutive RSV seasons, Southern-Hemisphere subjects (8%) for at least 2 seasons.
c = Data included in this prespecified interim analysis was collected until the end of the first Northern Hemisphere RSV season and ≥35 cases of RSV-related lower respiratory tract disease had occurred, all in the Northern Hemisphere.
d = Australia, Belgium, Brazil, Canada, Estonia, Finland, France, Germany, Italy, Japan, Mexico, Russia, South Africa, South Korea, Spain, United Kingdom, United States of America.
e = Data included in this prespecified interim analysis was collected until the end of the second Northern Hemisphere RSV season and also included data for Southern Hemisphere subjects until the same data lock, covering ≥1 Southern Hemisphere seasons.

Table 5. Study characteristics of the mRNA-1345 trial

Reference Study name Study id	Study design Status (planned follow-up) Funding	Country Study period Follow-up	Study population Study arm	Sam-ple size	Age mean±SD (range); groups n (%)	Sex n (%) male	Ethnic-ity n (%) white	High-risk conditions n (%)	Frailty status[a] n (%)
Wilson et al 2023 [56] ConquerRSV NCT05127434	Phase 2-3 RCT; interim analysis Ongoing (24 m)[b] Industry funded	22 countries[c] Nov 2021-Nov 2022 RSV season NR (assume season 1, based on follow-up); up to 12 m follow-up; median 112 d (range 1-379)	Subjects aged ≥60 years, healthy or with stable chronic medical conditions at baseline						
			mRNA-1345 (single dose 50 µg mRNA-1345)	17,734	- 68.1±6.2 (60-95) y - 60-69 y: 11,281 (63.6%) - 70-79 y: 5,474 (30.9%) - ≥80 y: 979 (5.5%)	9,076 (51.2%)	11,240 (63.4%)	≥1 comorbidities of interest[d]: 5,238 (29.5%) risk factor for LRTD: 1,218 (6.9%) - CHF: 205 (1.2%) - COPD: 960 (5.4%) - CHF & COPD: 53 (0.3%)	- fit: 13,512 (76.2%) - vulnerable: 2,828 (15.9%) - frail: 997 (5.6%)
			Placebo	17,679	- 68.1±6.2 (60-96) y - 60-69 y: 11,222 (63.5%) - 70-79 y: 5,460 (30.9%) - ≥80 y: 997 (5.6%)	8,968 (50.7%)	11,216 (63.4%)	≥1 comorbidities of interest[d]: 5,128 (29.0%) risk factor for LRTD: 1,230 (7.0%) - CHF: 201 (1.1%) - COPD: 978 (5.5%) - CHF & COPD: 51 (0.3%)	- fit: 13,354 (75.5%) - vulnerable: 2,899 (16.4%) - frail: 1,017 (5.8%)

Abbreviations

CHF = congestive heart failure, COPD = chronic obstructive pulmonary disease, d = days, LRTD = lower respiratory tract disease, m = months, n = number, NR = not reported, SD = standard deviation, y = years.

Notes

a = Frailty status was based on the Edmonton Frailty scoring system and measured by means of the Edmonton Frail Scale across 9 domains: cognition, general health status, functional independence, social support, medication use, nutrition, mood, continence, and functional performance. Scores range from 0 to 17 points, with a score of 0 to 3 indicating fit, a score of 4 or 5 indicating vulnerable, and a score of 6 to 17 indicating frail.

b= The prespecified interim analyses were conducted when at least 50% of the anticipated cases of RSV-related LTRD had occurred: ≥43 cases of RSV-related LRTD with ≥2 signs or symptoms and ≥16 cases with ≥3 signs or symptoms.

c = 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 Kingdom, United States of America.

d = Comorbidities of interest include COPD, asthma, chronic respiratory disease, diabetes, CHF, advanced liver disease, or advanced renal disease.

Table 6. Outcome definitions

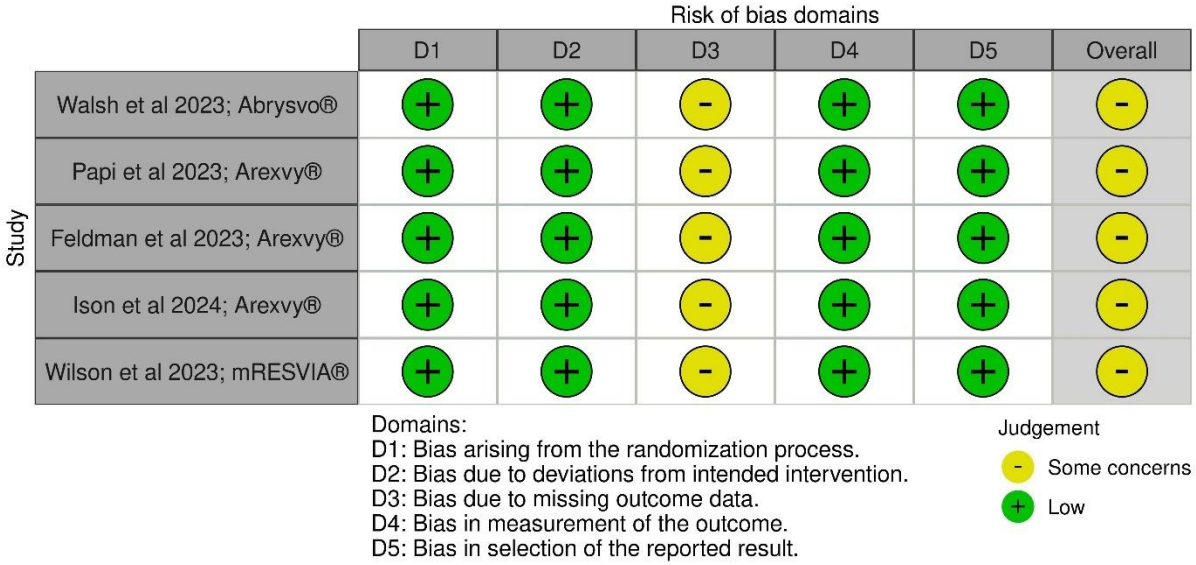
Reference	Outcome
Walsh et al 2023 [55] (RSVpreF)	**RSV-related[a] LRTI** - RSV-related LRTI with ≥2 signs/symptoms: first episode of RSV-related ARI with ≥2 of the 5 LRTI signs/symptoms lasting ≥1 day during the same illness within 15 days post-injection up to the end of the first RSV season or 6 months post-injection. - RSV-related LRTI with ≥3 signs/symptoms: first episode of RSV-related ARI with ≥3 of the 5 LRTI signs/symptoms lasting ≥1 day during the same illness within 15 days post-injection up to the end of the first RSV season or 6 months post-injection. → Symptoms: new/increased cough, new/increased wheezing, new/increased sputum production, new/increased shortness of breath, tachypnoea (≥25 breaths/minute or ≥15% increase from resting baseline). **RSV-related[a] ARI** - First episode of RSV-related ARI with new/increasing of ≥1 symptoms within 15 days post-injection up to the end of the first RSV season or 6 months post-injection. → Symptoms: sore throat, cough, nasal discharge, nasal congestion, wheezing, sputum production, shortness of breath.
Papi et al 2023 [54]; Feldman et al 2023 [57]; Ison et al 2024 [58] (RSVPreF3)	**RSV-related[b] LRTD** - First episode of RSV-related LRTD with ≥2 lower respiratory symptoms/signs for ≥24 hours including ≥1 lower respiratory sign or ≥3 lower respiratory symptoms for ≥24 hours. → Symptoms: new/increased sputum, new/increased cough, new/increased dyspnoea (shortness of breath). → Signs: new/increased wheezing, new/increased crackles/rhonchi based on chest auscultation, respiratory rate ≥20 respirations/minute, low/decreased oxygen saturation (i.e. oxygen saturation <95% or ≤90% if pre-season baseline was <95%), need for oxygen supplementation. **Severe RSV-related[b] LRTD** - "Clinical symptomology" definition. Presence of an LRTD with ≥1 of the following criteria: ≥2 lower respiratory signs or an LRTD episode assessed as 'severe' by the investigator; and with ≥1 RSV-positive swab detected by qRT-PCR. → Symptoms: new/increased wheezing, new/increased crackles/rhonchi based on chest auscultation, respiratory rate ≥20 respirations/minute, low/decreased oxygen saturation (=oxygen saturation <95% or ≤90% if preseason baseline is <95%), need for oxygen supplementation. - "Supportive therapy" definition. Presence of an LRTD with ≥1 of the following criteria: need for oxygen supplementation, need for positive airway pressure therapy (e.g. CPAP), need for other types of mechanical ventilation; and with ≥1 RSV-positive swab detected by qRT-PCR. **RSV-related[b] ARI** - First episode of RSV-related ARI with ≥2 respiratory symptoms/signs for ≥24 hours or ≥1 respiratory symptom/sign + 1 systemic symptom/sign for ≥24 hours. → Respiratory symptoms/signs: nasal congestion/rhinorrhoea, sore throat, new/increased sputum, new/increased cough, new/increased dyspnoea (shortness of breath), new/increased wheezing, new/increased crackles/rhonchi based on chest auscultation, respiratory rate ≥20 respirations/minute, low/decreased oxygen saturation (i.e. oxygen saturation <95% or ≤90% if pre-season baseline was <95%), need for oxygen supplementation. → Systematic symptoms/signs: fever (body temperature ≥38.0°C/100.4°F by any route) or feverishness (feeling of having fever without objective measurement), fatigue, body aches, headache, decreased appetite.
Wilson et al 2023 [56] (mRNA-1345)	**RSV-related[b] LRTD** - RSV-related LRTD with ≥2 symptoms: first episode of RSV-related LRTD with new/worsening of ≥2 symptoms for ≥24 hours within 14 days post-injection up to 12 months post-injection. - RSV-related LRTD with ≥3 symptoms: first episode of RSV-related LRTD with new/worsening of ≥3 symptoms for ≥24 hours within 14 days post-injection up to 12 months post-injection. → Symptoms: shortness of breath, cough and/or fever (≥37.8°C; 100.0°F), wheezing and/or rales and/or rhonchi, sputum production, tachypnoea (≥20 breaths/minute, or increase of ≥2 breaths/minute from baseline measurement in those with baseline tachypnoea), hypoxemia (new oxygen saturation ≤93% or new or increasing use of supplemental oxygen), pleuritic chest pain for ≥24 hours. In case of inability to fully assess other clinical parameters, radiologic evidence of pneumonia with RT-PCR-confirmed RSV infection can also be used to confirm RSV-related LRTD. **RSV-related[b] ARD** - First episode of RSV-related ARD with new/worsening of ≥1 symptoms for ≥24 hours within 14 days up post-injection to 12 months post-injection. → Symptoms: cough, stuffy nose, runny nose, sore throat, fever (≥37.8°C; 100.0°F), shortness of breath, observed tachypnoea (≥20 breaths/minute, or increase of ≥2 breaths/minute from baseline in those with baseline tachypnoea), hypoxemia (new oxygen saturation ≤93%, or new/increasing use of supplemental oxygen), wheezing, sputum production, hoarseness, sinus pain, chills, pleuritic chest pain for ≥24 hours. In case of inability to fully assess other clinical parameters, radiologic evidence of pneumonia with RT-PCR-confirmed RSV infection can also be used to confirm RSV-related ARD.

Abbreviations
ARI = acute respiratory illness, ARD = acute respiratory disease, CPAP = continuous positive airway pressure, LRTD = lower respiratory tract disease, LRTI = lower respiratory tract illness, RSV = respiratory syncytial virus, RT-PCR = reverse transcriptase-polymerase chain reaction.
Notes
a = RSV diagnosis by RT-PCR or nucleic acid amplification test.
b = RSV diagnosis by RT-PCR.

7.1.3 Study quality appraisal

The overall risk of bias for the outcomes class RSV-related events reported in the 3 ongoing RCTs was “some concerns” (***Table 7***). The RCTs were well-designed with extensive protocols. However, the published results were interim analyses based on prespecified thresholds for the minimum number of cases in the overall population aged ≥60 years and follow-up, resulting in lower number of cases. Subgroup analyses were descriptive and should be interpreted with caution since the RCTs were not powered to demonstrate significance of vaccine efficacy in the subgroups and there was no adjustment for multiplicity for the vaccine efficacy evaluations. Part of the outcomes were not included in the interim analyses, caused by a lack of cases to reliably assess vaccine efficacy.

Table 7. Risk of bias for the outcomes class RSV-related events



7.1.4 Clinical findings

RSVpreF

The results of the RSVpreF trial are presented in ***Table 8***, ***Figure 2*** and ***Figure 3***. [55] In subjects aged ≥60 years after a completed follow-up of 6 months during RSV season 1, the vaccine efficacy of a single RSVpreF dose against RSV-related lower respiratory tract illness (LRTI) with ≥2 signs or symptoms was 66.7% (96.7% CI 28.8 to 85.8), RSV-related LRTI with ≥3 signs or symptoms 85.7% (96.7% CI 32.0 to 98.7), and against RSV-related acute respiratory illness (ARI) 62.1% (95% CI 37.1 to 77.9). In addition, vaccine efficacy was reported for the subgroups 60-69 years, 70-79 years, ≥80 years, ≥60 years & ≥1 high-risk conditions, and ≥60 years & ≥1 chronic cardiopulmonary conditions.

In subjects aged ≥60 years at the end of RSV season 1, the vaccine efficacy of a single RSVpreF dose against RSV-related LRTI with ≥2 signs or symptoms was 65.1% (95% CI 35.9 to 82.0), against RSV-related LRTI with ≥3 signs or symptoms 88.9% (95% CI 53.6 to 98.7), and against RSV-related ARI 62.2% (95% CI 44.4 to 74.9). These results were not reported for subgroups.

Severe RSV-related LRTI (i.e. hospitalisation due to RSV-related LRTI or new/increased oxygen supplementation or mechanical ventilation) was not included in the analysis, because the number of cases of severe disease that had accrued at the data-cutoff date did not meet the prespecified minimum number of cases for the interim analysis.

RSVPreF3

The results of the RSVPreF3 trial are presented in ***Table 9***, ***Figure 4***, and ***Figure 5***. [54,57,58] In subjects aged ≥60 years after a median follow-up of 6.7 months up to the end of RSV season 1, the vaccine efficacy of a single RSVPreF3 dose against RSV-related LRTD with ≥2 or ≥3 signs or symptoms was 82.6% (96.95% CI 57.9 to 94.1), severe RSV-related LRTD 94.1% (95% CI 62.4 to 99.9), RSV-related LRTD medically attended visits 87.5% (95% CI 58.9 to 97.6), RSV-related ARI 71.7% (95% CI 56.2 to 82.3), and against RSV-related ARI medically attended visits 79.0% (95% CI 54.3 to 91.5). No RSV-related deaths occurred. For the outcome RSV-related LRTD with ≥2 or ≥3 signs or symptoms, vaccine efficacy was reported for the age groups 60-69 years, 70-79 years, ≥70 years, and ≥80 years. In addition, for RSV-related LRTD with ≥2 or ≥3 signs or symptoms and for RSV-related ARI subgroup data was presented for ≥60 years & ≥1 conditions of interest, ≥60 years & ≥1 cardiorespiratory conditions of interest, ≥60 years & ≥1 endocrine and metabolic conditions of interest, and ≥60 years & ≥2 conditions of interest.

In subjects aged ≥60 years after a median follow-up of 17.8 months up to the end of RSV season 2, the vaccine efficacy of a single RSVPreF3 dose against RSV-related LRTD with ≥2 or ≥3 signs or symptoms was 67.2% (97.5% CI 48.2 to 80.0), severe RSV-related LRTD 78.8% (95% CI 52.6 to 92.0), RSV-related LRTD medically attended visits 73.1% (95% CI 49.4 to 86.9), RSV-related ARI 52.7% (95% CI 40.0 to 63.0), and against RSV-related ARI medically attended visits 52.0% (95% CI 27.3 to 69.1). For the outcome RSV-related LRTD with ≥2 or ≥3 signs or symptoms, vaccine efficacy was reported for subgroups. Re-vaccination with a single RSVPreF3 dose pre-season 2 did not seem to provide additional vaccine efficacy (***Table 9***).

Vaccine efficacy could not be evaluated against RSV-related hospitalisations, because the number of events was too low.

mRNA-1345

The results of the mRNA-1345 trial are presented in ***Table 10*** and ***Figure 6***. [56] In subjects aged ≥60 years after a follow-up up to 12 months during RSV season 1, the vaccine efficacy of a single mRNA-1345 dose against RSV-related LRTD with ≥2 signs or symptoms was 83.7% (95.9% CI 66.0 to 92.2), RSV-related LRTD with ≥3 signs or symptoms 82.4% (96.4% CI 34.8 to 95.3), and against RSV-related acute respiratory disease (ARD) 68.4% (95% CI 50.9 to 79.7). In addition, vaccine efficacy was reported for the subgroups 60-69 years, 70-79 years, ≥80 years, ≥60 years & ≥1 comorbidities, and ≥60 years & COPD/CHF.

The outcome vaccine efficacy to prevent the first hospitalisation associated with RSV-related ARD or RSV-related LRTD was omitted, since a lack off enough cases to reliably assess vaccine efficacy.

Table 8. Results of the prespecified interim analysis of the RSVpreF trial in subjects aged ≥60 years

Reference	RSV vaccine (dose)	Follow-up	Outcome	Subgroup	Vaccine		Placebo		Vaccine efficacy (CI)
					Number of subjects	Number of events	Number of subjects	Number of events	
Walsh et al 2023 [55]	RSVpreF (single dose pre-season 1)	during RSV season 1; 6 m completed (mean 7 m)	RSV-related LRTI with ≥2 signs or symptoms[a]	≥60 y (overall)	16'306	11	16'308	33	66.7% (96.7% CI 28.8 to 85.8)
				60-69 y	NR	8	NR	19	57.9% (96.7% CI -7.4 to 85.3)
				70-79 y	NR	2	NR	9	77.8% (96.7% CI -18.7 to 98.1)
				≥80 y	NR	1	NR	5	80.0% (96.7% CI -104.3 to 99.7)
				≥60 y & ≥1 high-risk condition[b]	NR	6	NR	16	62.5% (96.7% CI -8.4 to 89.1)
				≥60 y & ≥1 chronic cardiopulmonary condition[c]	NR	4	NR	6	33.3% (96.7% CI -213.7 to 87.9)
			RSV-related LRTI with ≥3 signs or symptoms[a]	≥60 y (overall)	16'306	2	16'308	14	85.7% (96.7% CI 32.0 to 98.7)
				60-69 y	NR	2	NR	9	77.8% (96.7% CI -18.7 to 98.1)
				70-79 y	NR	0	NR	2	100% (96.7% CI -573.8 to 100)
				≥80 y	NR	0	NR	3	100% (96.7% CI -191.2 to 100)
				≥60 y & ≥1 high-risk condition[b]	NR	2	NR	8	75.0% (96.7% CI -39.1 to 97.9)
				≥60 y & ≥1 chronic cardiopulmonary condition[c]	NR	2	NR	4	50.0% (96.7% CI -302.1 to 96.4)
			RSV-related ARI	≥60 y (overall)	16'306	22	16'308	58	62.1% (95% CI 37.1 to 77.9)
				60-69 y	NR	14	NR	37	62.2% (95% CI 28.3 to 81.1)
				70-79 y	NR	5	NR	14	64.3% (95% CI -4.9 to 89.9)
				≥80 y	NR	3	NR	7	57.1% (95% CI -87.7 to 92.8)
				≥60 y & ≥1 high-risk condition[b]	NR	10	NR	27	63.0% (95% CI 21.0 to 84.0)
				≥60 y & ≥1 chronic cardiopulmonary condition[c]	NR	4	NR	8	50.0% (95% CI -86.6 to 89.0)
	RSVpreF (single dose pre-season 1)	end of RSV season 1	RSV-related LRTI with ≥2 signs or symptoms[a]	≥60 y (overall)	18'058	15	18'076	43	65.1% (95% CI 35.9 to 82.0)
			RSV-related LRTI with ≥3 signs or symptoms[a]	≥60 y (overall)	18'058	2	18'076	18	88.9% (95% CI 53.6 to 98.7)
			RSV-related ARI	≥60 y (overall)	18'058	37	18'076	98	62.2% (95% CI 44.4 to 74.9)

Abbreviations
ARI = acute respiratory illness, CI = confidence interval, CHF = congestive heart failure, COPD = chronic obstructive pulmonary disease, LRTI = lower respiratory tract illness, m = months, NR = not reported, RSV = respiratory syncytial virus, y = years.
Notes
a = Signs or symptoms included new/increased cough, new/increased wheezing, new/increased sputum production, new/increased shortness of breath, tachypnoea (≥25 breaths/minute or ≥15% increase from resting baseline).
b = High-risk conditions include current tobacco use, diabetes, lung disease (including COPD and other lung diseases), heart disease (including CHF and other heart diseases), liver disease, renal disease.
c = Chronic cardiopulmonary conditions include asthma, COPD, CHF.

Figure 2. Vaccine efficacy and cumulative number of cases of the RSVpreF trial in subjects aged ≥60 years from day 15 post-injection up to 6 months of follow-up completed during RSV season 1

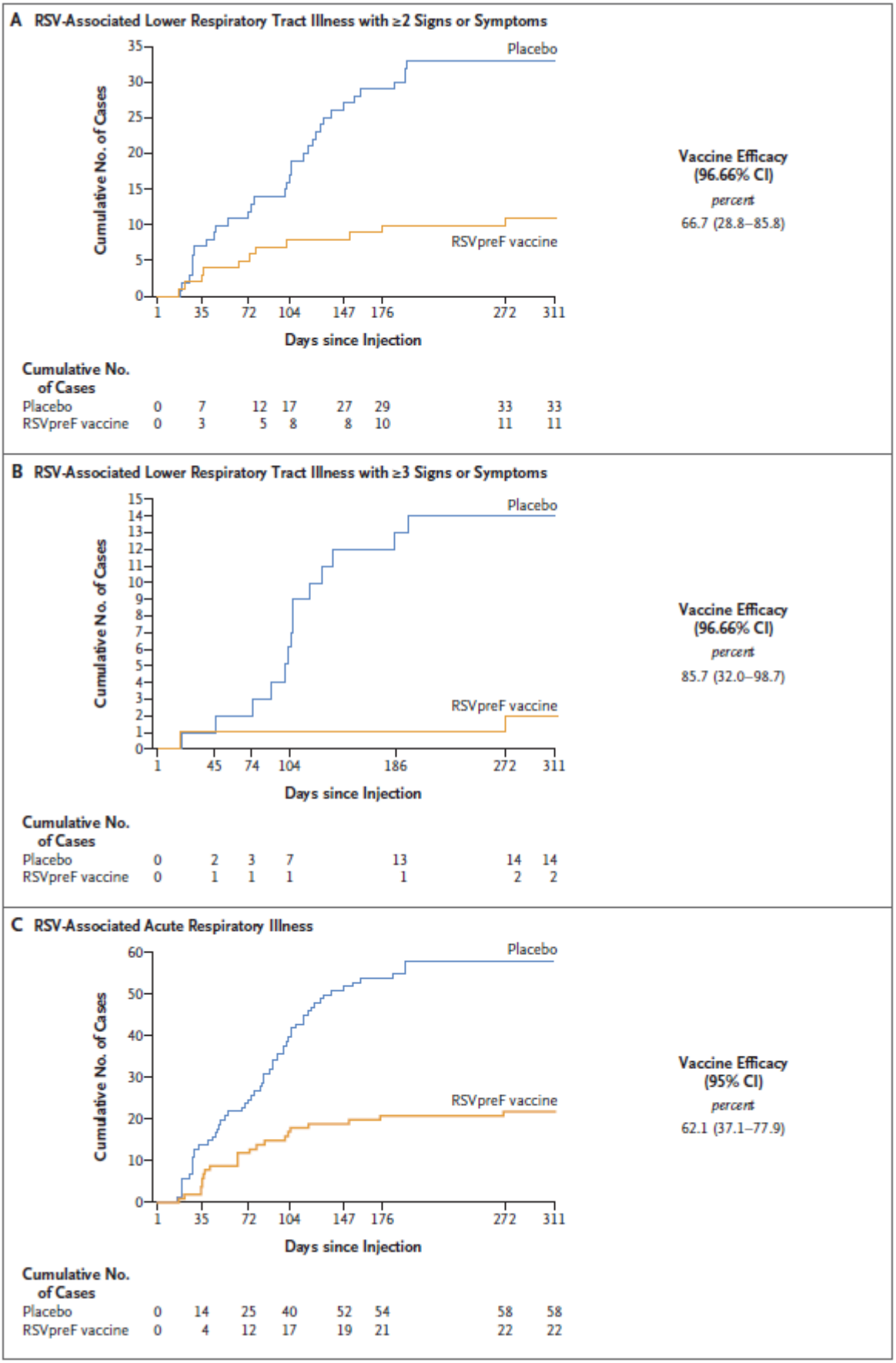


Figure 3. Vaccine efficacy and cumulative number of cases of the RSVpreF trial in subjects aged ≥60 years from day 15 post-injection up to the end of RSV season 1

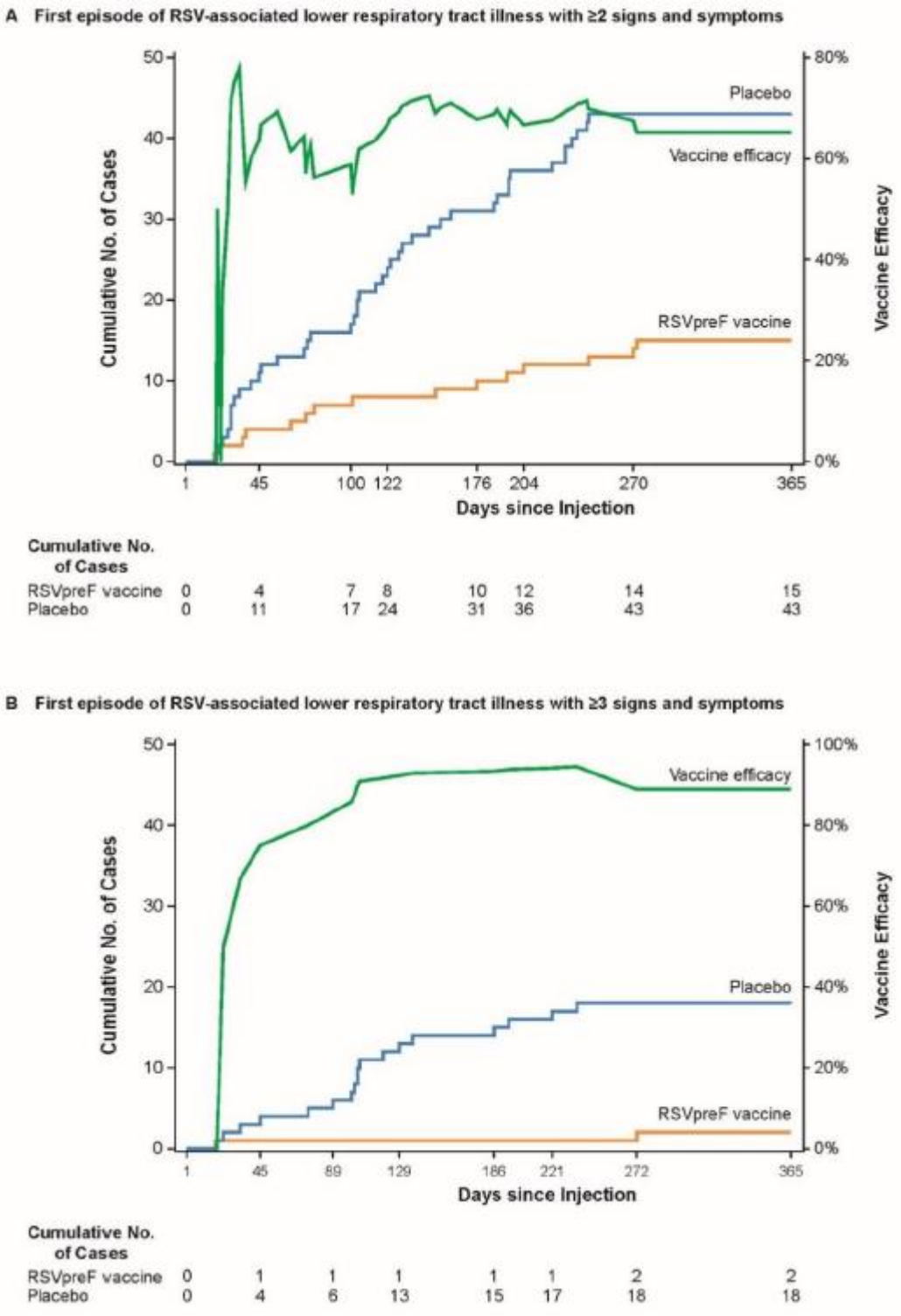


Table 9. Results of the prespecified interim analysis of the RSVPreF3 trial in subjects aged ≥60 years

Reference	RSV vaccine (dose)	Follow-up	Outcome	Subgroup	Vaccine		Placebo		Vaccine efficacy (CI)
					Number of subjects	Number of events	Number of subjects	Number of events	
Papi et al 2023 [54]; Feldman et al 2023 [57]	RSVPreF3 (single dose pre-season 1)	end RSV season 1 (median 6.7 m)	RSV-related LRTD with ≥2 or ≥3 signs or symptoms[a]	≥60 y (overall)	12'466	7	12'494	40	82.6% (96.95% CI 57.9 to 94.1)
				60-69 y	6'963	4	6'979	21	81.0% (95% CI 43.6 to 95.3)
				70-79 y	4'487	1	4'487	16	93.8% (95% CI 60.2 to 99.9)
				≥70 y	5'503	3	5'515	19	84.4% (95% CI 46.9 to 97.0)
				≥80 y	1'016	2	1'028	3	33.8% (95% CI -477.7 to 94.5)
				≥60 y & ≥1 condition of interest	4'937	1	4'861	18	94.6% (95% CI 65.9 to 99.9)
				≥60 y & ≥1 cardiorespiratory condition of interest[b]	2'496	1	2'421	12	92.1% (95% CI 46.7 to 99.8)
				≥60 y & ≥1 endocrine and metabolic condition of interest[c]	3'200	0	3'234	13	100% (95% CI 74.0 to 100)
				≥60 y & ≥2 conditions of interest	2'504	1	2'431	12	92.0% (95% CI 46.1 to 99.8)
			Severe RSV-related LRTD	≥60 y (overall)	12'466	1	12'494	17	94.1% (95% CI 62.4 to 99.9)
			RSV-related LRTD medically attended visits	≥60 y (overall)	12'466	3	12'494	24	87.5% (95% CI 58.9 to 97.6)
			RSV-related deaths	≥60 y (overall)	12'466	0	12'494	0	NE
			RSV-related ARI	≥60 y (overall)	12'466	27	12'494	95	71.7% (95% CI 56.2 to 82.3)
				≥60 y & ≥1 condition of interest	4'937	8	4'861	41	81.0% (95% CI 58.9 to 92.3)
				≥60 y & ≥1 cardiorespiratory condition of interest[b]	2'496	3	2'421	24	88.1% (95% CI 60.9 to 97.7)
				≥60 y & ≥1 endocrine and metabolic condition of interest[c]	3'200	6	3'234	29	79.4% (95% CI 49.4 to 93.0)
				≥60 y & ≥2 conditions of interest	2'504	3	2'431	24	88.0% (95% CI 60.5 to 97.7)
			RSV-related ARI medically attended visits	≥60 y (overall)	12'466	8	12'494	38	79.0% (95% CI 54.3 to 91.5)
Ison et al 2024 [58]	RSVPreF3 (single dose pre-season 1)	end RSV season 2 (median 17.8 m)	RSV-related LRTD with ≥2 or ≥3 signs or symptoms[a]	≥60 y (overall)	12'469	30	12'498	139	67.2% (97.5% CI 48.2 to 80.0)[d] 74.5% (97.5% CI 60.0 to 84.5)[e]
				60-69 y	6'963	17	6'981	74	65.4% (95% CI 40.4 to 80.9)[d] 72.9% (95% CI 53.7 to 85.0)[e]
				70-79 y	4'489	9	4'489	55	74.9% (95% CI 48.4 to 89.2)[d] 80.7% (95% CI 60.6 to 91.6)[e]
				≥70 y	5'506	13	5'517	65	69.3% (95% CI 43.4 to 84.6)[d] 76.4% (95% CI 56.7 to 88.1)[e]
				≥80 y	1'017	4	1'028	10	38.4% (95% CI -118.2 to 86.1)[d] 52.6% (95% CI -64.2 to 89.2)[e]
				≥60 y & ≥1 condition of interest	4'983	16	4'919	72	66.7% (95% CI 41.8 to 82.0)[d] 74.5% (95% CI 55.7 to 86.1)[e]
				≥60 y & ≥1 cardiorespiratory condition of interest[b]	2'546	10	2'479	56	73.8% (95% CI 47.9 to 88.2)[d] 80.1% (95% CI 60.6 to 91.0)[e]
				≥60 y & ≥1 endocrine and metabolic condition of interest[c]	3'229	8	3'255	32	63.1% (95% CI 17.4 to 85.4)[d] 70.6% (95% CI 34.8 to 88.3)[e]
			Severe RSV-	≥60 y (overall)	12'469	7	12'498	48	78.8% (95% CI 52.6 to 92.0)[d]

			related LRTD					82.7% (95% CI 61.6 to 93.4)[e]
			RSV-related LRTD medically attended visits	≥60 y (overall)	12'469	12	12'498	63	73.1% (95% CI 49.4 to 86.9)[d]
			RSV-related ARI	≥60 y (overall)	12'469	94	12'498	292	52.7% (95% CI 40.0 to 63.0)[d] 62.1% (95% CI 52.1 to 70.3)[e]
			RSV-related ARI medically attended visits	≥60 y (overall)	12'469	32	12'498	94	52.0% (95% CI 27.3 to 69.1)[d]
	RSVPreF3 (single dose pre-season 1&2)	end RSV season 2 (median 17.8 m)	RSV-related LRTD with ≥2 or ≥3 signs or symptoms[a]	≥60 y (overall)	12'469	30	12'498	139	67.1% (97.5% CI 48.1 to 80.0)[d]
				60-69 y	6'963	14	6'981	74	71.6% (95% CI 48.9 to 85.2)[d]
				70-79 y	4'489	12	4'489	55	66.2% (95% CI 35.7 to 83.6)[d]
				≥70 y	5'506	16	5'517	65	61.9% (95% CI 33.0 to 79.6)[d]
				≥80 y	1'017	4	1'028	10	38.6% (95% CI -117.2 to 86.2)[d]
				≥60 y & ≥1 condition of interest	4'983	12	4'919	72	75.1% (95% CI 53.6 to 87.8)[d]
				≥60 y & ≥1 cardiorespiratory condition of interest[b]	2'546	7	2'479	56	81.3% (95% CI 58.6 to 92.9)[d]
				≥60 y & ≥1 endocrine and metabolic condition of interest[c]	3'229	7	3'255	32	67.5% (95% CI 24.2 to 88.0)[d]
			Severe RSV-related LRTD	≥60 y (overall)	12'469	7	12'498	48	78.8% (95% CI 52.5 to 92.0)[d]
			RSV-related ARI	≥60 y (overall)	12'469	80	12'498	292	60.3% (95% CI 48.8 to 69.5)[d]

Abbreviations
ARD = acute respiratory disease, CI = confidence interval, LRTD = lower respiratory tract disease, m = months, NE = not estimated, RSV = respiratory syncytial virus, y = years.
Notes
a = Symptoms included new/increased sputum, new/increased cough, new/increased dyspnoea (shortness of breath); Signs included new/increased wheezing, new/increased crackles/rhonchi based on chest auscultation, respiratory rate ≥20 respirations/minute, low/decreased oxygen saturation (i.e. oxygen saturation <95% or ≤90% if pre-season baseline was <95%), need for oxygen supplementation.
b = Of the 13 RSV-LRTD and 27 RSV-ARI cases among subjects with cardiorespiratory conditions of interest, 13 RSV-LRTD and 24 RSV-ARI cases were among subjects with chronic respiratory or pulmonary disease; 2 RSV-LRTD and 5 RSV-ARI cases were among subjects with chronic heart failure.
c = Of the 13 RSV-LRTD and 35 RSV-ARI cases among subjects with endocrine and metabolic conditions of interest, 12 RSV-LRTD and 34 RSV-ARI cases were among subjects with diabetes mellitus.
d = Vaccine efficacy was estimated using a Poisson model adjusted for region and season ("with season as covariate").
e = Vaccine efficacy was estimated using a Poisson model adjusted for region ("without season as covariate"; post hoc analyses).

Figure 4. Cumulative number of cases of the RSVPreF3 trial in subjects aged ≥60 years from day 15 post-injection up to the end of RSV season 1

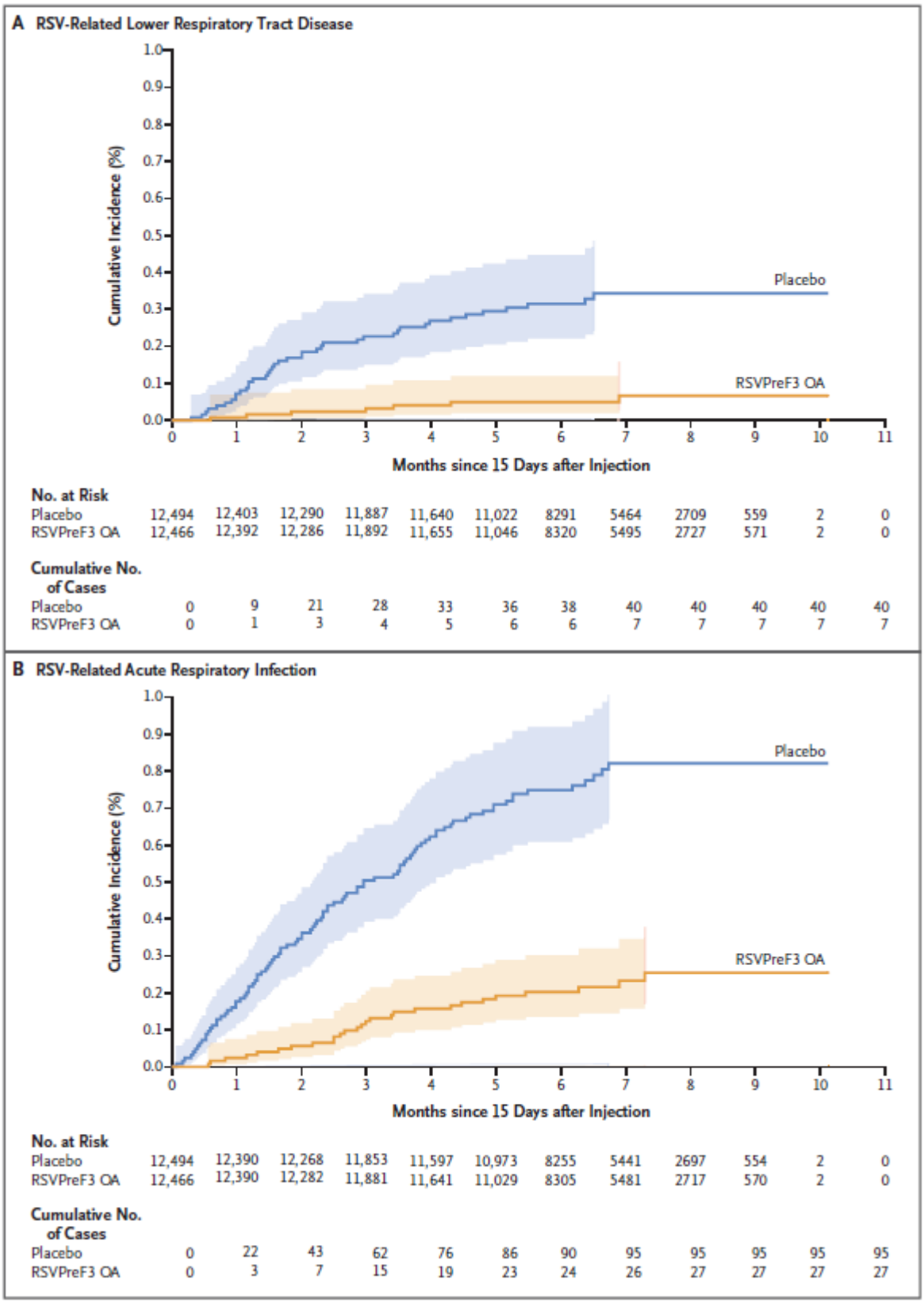
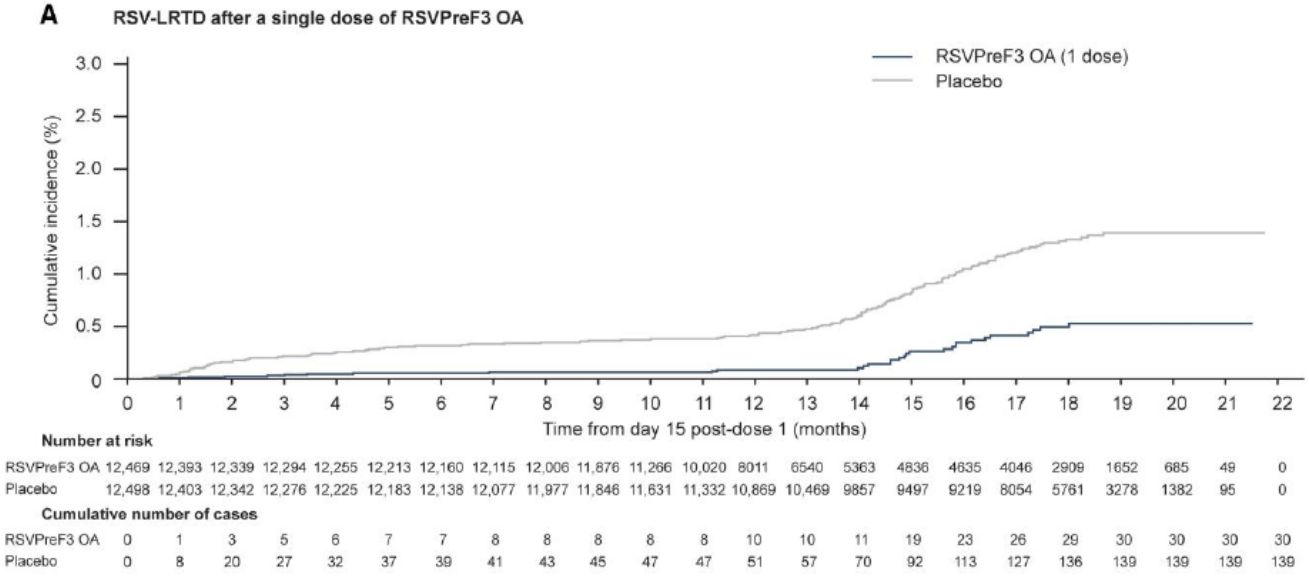


Figure 5. Cumulative number of cases of the RSVPreF3 trial in subjects aged ≥60 years from day 15 post-injection up to the end of RSV season 2



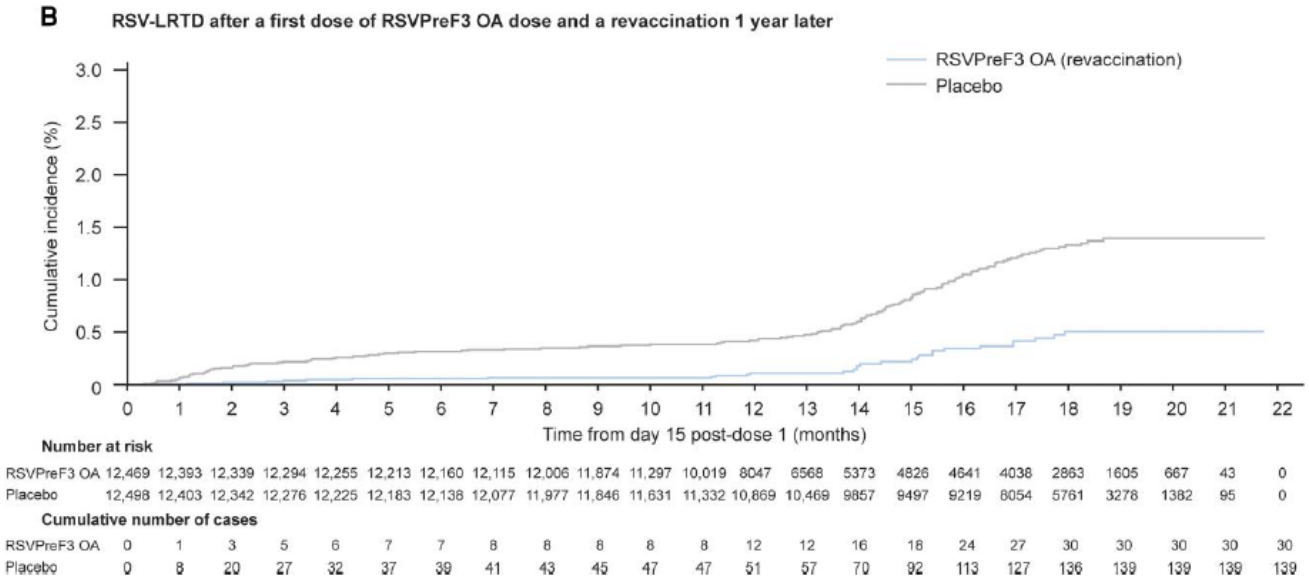


Table 10. Results of the prespecified interim analysis of the mRNA-1345 trial in subjects aged ≥60 years

Reference	RSV vaccine (dose)	Follow-up	Outcome	Subgroup	Vaccine		Placebo		Vaccine efficacy (CI)
					Number of subjects	Number of events	Number of subjects	Number of events	
Wilson et al 2023 [56]	mRNA-1345 (single dose pre-season 1)	RSV season NR (assume season 1, based on follow-up); up to 12 m (median 112 d)	RSV-related LRTD with ≥2 signs or symptoms[a]	≥60 y (overall)	17'572	9	17'516	55	83.7% (95.9% CI 66.0 to 92.2)
				60-69 y	11'168	8	11'118	33	76.0% (95% CI 48.0 to 88.9)
				70-79 y	5'440	1	5'416	22	95.4% (95% CI 65.9 to 99.4)
				≥80 y	964	0	982	0	NE (95% CI NE to NE)
				≥60 y & ≥1 comorbidity[b]	5'195	2	5'085	17	88.4% (95% CI 49.9 to 97.3)
				≥60 y & COPD/CHF	1'207	1	1'217	2	49.4% (95% CI -457.9 to 95.4)
			RSV-related LRTD with ≥3 signs or symptoms[a]	≥60 y (overall)	17'572	3	17'516	17	82.4% (96.4% CI 34.8 to 95.3)
				60-69 y	11'168	3	11'118	11	72.9% (95% CI 2.8 to 92.4)
				70-79 y	5'440	0	5'416	6	100% (95% CI NE to 100)
				≥80 y	964	0	982	0	NE (95% CI NE to NE)
				≥60 y & ≥1 comorbidity[b]	5'195	2	5'085	7	71.8% (95% CI -35.9 to 94.1)
				≥60 y & COPD/CHF	1'207	1	1'217	0	NE (95% CI NE to NE)
			RSV-related ARD	≥60 y (overall)	17'572	26	17'516	82	68.4% (95% CI 50.9 to 79.7)
				60-69 y	11'168	20	11'118	44	54.9% (95% CI 23.5 to 73.4)
				70-79 y	5'440	6	5'416	37	83.6% (95% CI 61.1 to 93.1)
				≥80 y	964	0	982	1	100% (95% CI NE to 100)
				≥60 y & ≥1 comorbidity[b]	5'195	7	5,085	20	65.7% (95% CI 18.9 to 85.5)
				≥60 y & COPD/CHF	1'207	1	1'217	3	66.1% (95% CI -225.7 to 96.5)

Abbreviations

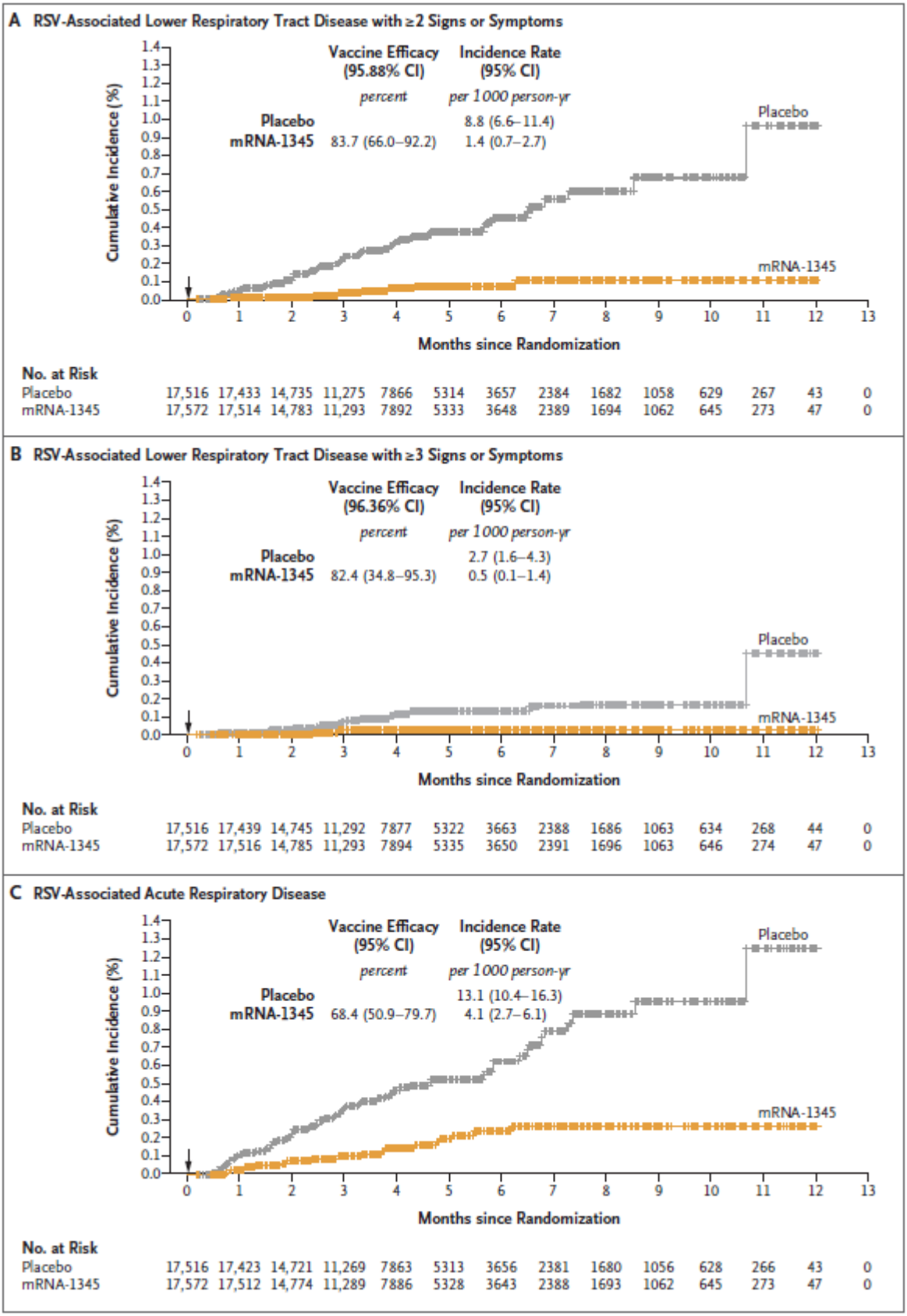
ARD = acute respiratory disease, CHF = congestive heart failure, CI = confidence interval, COPD = chronic obstructive pulmonary disease, d = days, LRTD = lower respiratory tract disease, m = months, NE = not estimated, RSV = respiratory syncytial virus, y = years.

Notes

a = Symptoms included shortness of breath, cough and/or fever (≥37.8°C; 100.0°F), wheezing and/or rales and/or rhonchi, sputum production, tachypnoea (≥20 breaths/minute, or increase of ≥2 breaths/minute from baseline measurement in those with baseline tachypnoea), hypoxemia (new oxygen saturation ≤93% or new or increasing use of supplemental oxygen), pleuritic chest pain for ≥24 hours. In case of inability to fully assess other clinical parameters, radiologic evidence of pneumonia with RT-PCR-confirmed RSV infection could also be used to confirm RSV-related LRTD.

b = Comorbidities of interest include COPD, asthma, chronic respiratory disease, diabetes, CHF, advanced liver disease, or advanced renal disease.

Figure 6. Vaccine efficacy and cumulative number of cases of the mRNA-1345 trial in subjects aged ≥60 years from day 14 post-injection up to 12 months follow-up (RSV season not reported)



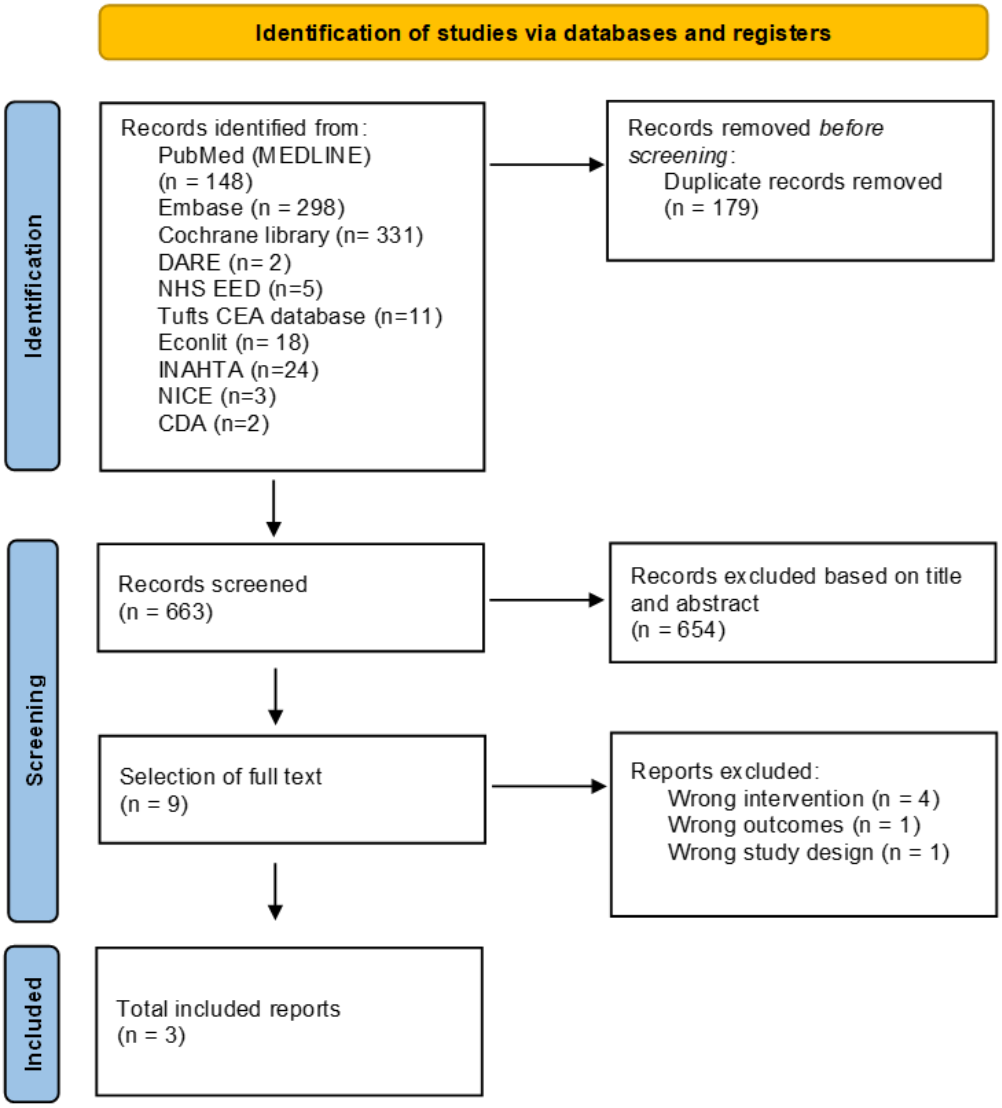
7.2 Review of economic evidence

7.2.1 Search results

The PRISMA diagram, shown in ***Figure 7*****,** summarises the literature search of the economic evidence on RSV vaccines. In total, 663 unique records were identified in the pre-specified databases and the HTA government agencies, on the RSVpreF, RSVPreF3 and mRNA-1345 vaccines in older adults for the cost-effectiveness search. Of those, 654 records were excluded based on their title and abstract, resulting in 9 studies to be screened in full- text. After applying the inclusion and exclusion criteria, 6 studies were excluded. Four articles were excluded for assessing the wrong intervention (hypothetical vaccine), one for not reporting economic outcomes, and one for wrong study design (review study) (see ***Appendix E***). The following 3 studies were included:

1. Moghadas, S. M., Shoukat, A., Bawden, C. E., Langley, J. M., Singer, B. H., Fitzpatrick, M. C., & Galvani, A. P. (2024). Cost-effectiveness of Prefusion F Protein-based Vaccines Against Respiratory Syncytial Virus Disease for Older Adults in the United States. *Clinical Infectious Diseases*, *78*(5), 1328–1335.
2. Shoukat, A., Bawden, C. E., Röst, G., LeBlanc, J. J., Galvani, A. P., Langley, J. M., & Moghadas, S. M. (2024). Impact and cost-effectiveness analyses of vaccination for prevention of respiratory syncytial virus disease among older adults in Ontario: A Canadian Immunization Research Network (CIRN) study. *Vaccine*, *42*(7), 1768–1776.
3. Wang, Y., Fekadu, G., & You, J. H. S. (2023). Comparative Cost-Effectiveness Analysis of Respiratory Syncytial Virus Vaccines for Older Adults in Hong Kong. *Vaccines*, *11*(10), 1605.

Figure 7. PRISMA flow diagram of the economic systematic literature search



Abbreviations
DARE = Database of Abstracts of Reviews of Effects, HTA = Health Technology Assessment, NHS EED = NHS Economic Evaluation Database, CEA = Cost-effectiveness Analysis, INAHTA = International Health Technology Assessment, NICE = National Institute for Health and Care excellence, CDA-AMC = Canada's Drug Agency l'Agence des médicaments du Canada

7.2.2 Study characteristics

The 3 included reports outline cost-utility analyses on RSV vaccines in subjects aged ≥60 years, and ***Table 11*** summarises their study characteristics. All studies include both RSVpreF and RSVPreF3, and none assess the cost-effectiveness of mRNA-1345. The studies are model-based, and they refer to the same data on vaccine efficacy, namely the placebo-controlled trials conducted by Papi et al 2023 and Walsh et al 2023. [54,55] The application of a Discrete Event Simulation model and a societal perspective was both described by the studies of Moghadas et al 2024 and Shoukat et al 2024. [59,60] These were conducted in the United States and Canada, respectively. Wang et al 2023 applied a Decision Tree model and used a healthcare perspective to estimate the cost-effectiveness of RSV vaccination in China. [61] The time horizon varied among studies ranging from 1

RSV season to 2 years. Regarding the reported results, all studies documented QALYs, costs and ICER estimates and none of the studies reported on life-years. Additionally, Moghadas et al 2024 and Shoukat et al 2024 recorded the maximum price-per-dose (PPD) for which the vaccines could potentially be considered cost-effective given a fixed willingness-to-pay threshold. [59,60] All articles describe the execution of a sensitivity analysis. In Moghadas et al 2024, structural uncertainty was explored by varying vaccine efficacy profiles, and joint parameter uncertainty was investigated through a probabilistic sensitivity analysis. [59] Shoukat et al 2024 and Wang et al 2023 also describe a probabilistic sensitivity analysis, and an additional one-way sensitivity analysis was performed by Wang et al 2023, varying all model parameters. [60,61]

Table 11. Study characteristic of the included cost-effectiveness studies

Reference	Country	Type of economic evaluation	Patient population	Intervention	Comparator	Effectiveness data	Type of Economic model	Perspective	Time Horizon	Discount rates	Outcomes
Moghadas et al 2024 [62]	United States	Cost-utility analysis	Older adults, ≥60	RSVPreF3 and RSVpreF	No vaccine	Papi et al 2023[54] and Walsh et al 2023	Discrete Event Simulation	Societal	1 RSV season	3%	· Max PPD · QALY · Costs · ICER (Costs/QALY)
Shoukat et al 2024 [60]	Canada	Cost-utility analysis	Older adults, ≥60	RSVPreF3and RSVpreF	No vaccine	Papi et al 2023[54] and Walsh et al 2023[55]	Discrete Event Simulation	Societal	2 RSV seasons	1.5%	· Max PPD · QALY · Costs · ICER (Costs/QALY)
Wang et al 2023 [61]	China	Cost-utility analysis	Older adults, ≥60	RSVPreF3and RSVpreF	No vaccine	Papi et al 2023[54] and Walsh et al 2023[55]	Decision Tree	Healthcare	2 years	3%	· QALY · Costs · ICER (Costs/QALY)

Abbreviations
ICER = incremental cost-effectiveness ratio, PPD = price-per-dose, QALY = quality-adjusted life year

7.2.3 Study quality appraisal

The completed CHEC checklists for these 3 studies are presented in ***Table 12.*** All 3 studies performed well on the checklist as they included all relevant items for cost-effectiveness studies. In all 3 studies, the comparator strategy was not described extensively since it consists of the absence of an intervention and not a different intervention or a standard of care. However, while all studies included the most relevant inputs and outcomes, the study by Shoukat et al 2024 did not include adverse events in their analysis contrary to the other two. [60] The studies by Moghadas et al 2024 and by Shoukat et al 2024 declare potential conflicts of interest of the authors of the manuscript while the authors of the study by Wang et all 2023 declared none. [59,60] Additionally, Shoukat et al 2024 provided a paragraph in their study about the ethics and guidelines related to the hospitalization data that were used from the Canadian Immunization Research Network (CIRN) Serious Outcomes Surveillance (SOS) Network and the guidelines followed for the health economic reporting. [60] Moghadas et al 2024 included a similar paragraph however no ethics approval was required since they used publicly available data sources, while Wang et al 2023 did not dedicate a paragraph on ethical issues, they also used published data. [59,61]

Table 12. Critical appraisal of cost-effectiveness studies using the CHEC checklist [53]

			Moghadas et al 2024 [59]	Shoukat et al 2024 [60]	Wang et al 2023 [61]
Study design	**1**	Is the study population clearly described?	✓	✓	✓
	2	Are competing alternatives clearly described?	✓	✓	✓
	3	Is a well-defined research question posed in answerable form?	✓	✓	✓
	4	Is the economic study design appropriate to the stated objective?	✓	✓	✓
	5	Is the chosen time horizon appropriate in order to include relevant costs and consequences?	✓	✓	✓
	6	Is the actual perspective chosen appropriate?	✓	✓	✓
Costs	**7**	Are all important and relevant costs for each alternative identified?	✓	✓	✓
	8	Are all costs measured appropriately in physical units?	✓	✓	✓
	9	Are costs valued appropriately?	✓	✓	✓
Outcomes	**10**	Are all important and relevant outcomes for each alternative identified?	✓	X	✓
	11	Are all outcomes measured appropriately?	✓	✓	✓
	12	Are outcomes valued appropriately?	✓	✓	✓
Interpretation and results	**13**	Is an incremental analysis of costs and outcomes of alternatives performed?	✓	✓	✓
	14	Are all future costs and outcomes discounted appropriately?	✓	✓	✓
	15	Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	✓	✓	✓
	16	Do the conclusions follow from the data reported?	✓	✓	✓
	17	Does the study discuss the generalisability of the results to other settings and patient/client groups?	✓	✓	✓
	18	Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	X	X	✓
	19	Are ethical and distributional issues discussed appropriately?	✓	✓	X

7.2.4 Economic findings

The outcomes of all cost-utility analyses are described in ***Table 13***. Despite some comparability across studies in statements on cost-effectiveness, there are large differences in the ICER estimates presented. An ICER of $93'981 per QALY gained for RSVPreF3 and $94'651 per QALY gained for RSVpreF was calculated in Moghadas et al 2024.This was based on a maximum price-per-dose of $127 and $118, respectively and a willingness-to-pay threshold of $95,000/QALY. [59] In the study performed by Shoukat et al 2024 the ICERs was $49'478 per QALY gained for RSVPreF3 and $49'711 per QALY gained for RSVpreF using a willingness-to-pay threshold of $50,000/QALY and a maximum price-per-dose of $119 and $114, respectively, and the study by Wang et al 2023 reported $219'299 per QALY gained and $137'907 per QALY gained for RSVPreF3 and RSVpreF, respectively. [60,61] These differences in ICER values are mainly driven by costs of the vaccines. The studies by Moghadas et al 2024 and Shoukat et al 2024 were both conducted from a societal perspective while the study by Wang et al 2023 followed a healthcare provider's perspective. [59–61] The effectiveness estimates are based on the same RCTs. The minor differences in incremental QALYs across studies arise from variations in utility inputs used and the inclusion of adverse events. It should be noted here that the study by Wang et al 2023 reported outcomes per person, whereas the 2 other studies used a population size of 100'000. [61] The differences in costs across studies can be attributed to a multitude of factors including deviations in price per dose, analysis perspectives, time horizon and economic models. None of the studies reported life years gained in their results. Regarding the economic impact of RSVPreF3 and RSVpreF on a national level, the budget impact was estimated at approximately $8-9 billion during the first RSV season in Moghadas et al 2024 and $7-7.5 billion over 2 RSV seasons in Shoukat et al 2024. [59,60] These estimates are calculated for a population of 100'000 in both analyses.

Table 13. Outcomes of cost-effectiveness studies

Reference		Costs			QALYs			ICER (per QALY)	WTP	Max PPD	Budget impact
	Vaccine		No Vaccine	Incremental	Vaccine	No vaccine	Incremental				
Moghadas et al 2024 [59]	RSVPreF3	NR	NR	$ 5'562'363[a]	NR	NR	59.19[a]	$ 93'981	$ 95'000	$ 127	$ 8'699'485[a]
	RSVpreF	NR	NR	$ 5'368'121[a]	NR	NR	56.71[a]	$ 94'651		$ 118	$ 8'209'939[a]
Shoukat et al 2024 [60]	RSVPreF3	NR	NR	$ 3'744'784[a]	NR	NR	52.52[a]	$ 49'478	$ 50'000	$ 119	$ 7'499'833[a]
	RSVpreF	NR	NR	$ 3'744'784[a]	NR	NR	49.46[a]	$ 49'711		$ 114	$ 7'153'181[a]
Wang et al 2023 [61]	RSVPreF3	$ 149	$ 26	$ 123	0.001559	0.002127	0.000568	$ 219'299	$ 49'594	$ 70	NR
	RSVpreF	$ 113	$ 26	$ 87	0.00148	0.002127	0.000647	$ 137'907		$ 81	NR

Abbreviations

ICER = incremental cost-effectiveness ratio, NR = not reported, QALY = quality-adjusted life year, PPD = price-per-dose, WTP = willingness to pay

Notes

a = estimates are calculated for a population of 100.000

8. Methodology economic evaluation and budget impact analysis

8.1 Economic evaluation

8.1.1 Patient population, intervention and comparator

8.1.1.1 Target population

Two target populations were defined for the current analysis: 1) subjects aged ≥75 years, and 2) subjects aged between ≥60 and <75 years at high risk of complications. In line with the definitions used in the trials, being at high risk of complications is defined as the occurrence of ≥1 comorbidities. Relevant comorbidities include congestive heart failure, COPD, diabetes, asthma, chronic heart failure, liver disease or renal disease. [63–65] The sizes of the target population were informed by Federal Statistical Office that contains population data on Switzerland. [66] From this data, the population of ≥75-year-old subjects was estimated to be 916'603 individuals, whereas the population of subjects aged between ≥60 and <75 years at high risk of complications is approximately 10% of the overall age group, resulting in 146'563 subjects. [67,68]

8.1.1.2 Intervention

The interventions are the following 3 RSV vaccines: RSVpreF, RSVPreF3 and mRNA-1345.

8.1.1.3 Comparator

The comparator is no prophylaxis.

8.1.2 Type of economic evaluation

The current evaluation is a cost-utility analysis.

8.1.3 Perspective

The analysis was performed from the healthcare payers' perspective. Costs of healthcare services covered by the Swiss mandatory health insurance were analysed, irrespective of the actual payer (mandatory health insurer, other social insurer, government (federal government, cantons, communities) out-of-pocket). The analysis did not include indirect costs due to informal care or productivity losses and additional non-medical costs for patients, such as travel costs. Since the study was performed from the Swiss healthcare payers' perspective relevant cost input parameters were based on data from Switzerland as much as possible.

8.1.4 Time horizon

The model horizon should be sufficiently long to reflect all meaningful differences in costs or outcomes between interventions compared. [69] For the current analysis, this implies a model horizon that aligns with the duration of the vaccine's protection and frequency of administration. [70] The Bundesamt für Gesundheit (BAG) and Eidgenössische Kommission für Impffragen (EKIF) recommend an RSV vaccination every 2 years since one vaccination is estimated to provide at least 2 years of protection against RSV disease. [6] While studies on long-termduration of vaccine protection are ongoing, the second season estimates of vaccine efficacy in the AReSVi-006 trial indicated a durable protection over the time horizon and no additional vaccine efficacy after re-vaccination with a second dose. For these reasons, a model time horizon of 2 years was considered most suitable for the base case analysis. An alternative horizon of 1 year was incorporated in the scenario analysis.

8.1.5 Discount rate

In the base case analysis, costs and effects were discounted at 3.0% per annum. Alternative discount rates of 0% and 5% per annum were explored in scenario analyses.

8.1.6 Modelling

8.1.6.1 Model structure

Most cost-utility analyses on RSV vaccines make use of a decision tree model or a discrete event simulation. [62,71–76] A decision tree is considered the most suitable model design for the current analysis based on its simplicity, suitability for short time horizons and compatibility with only aggregated patient data being available.

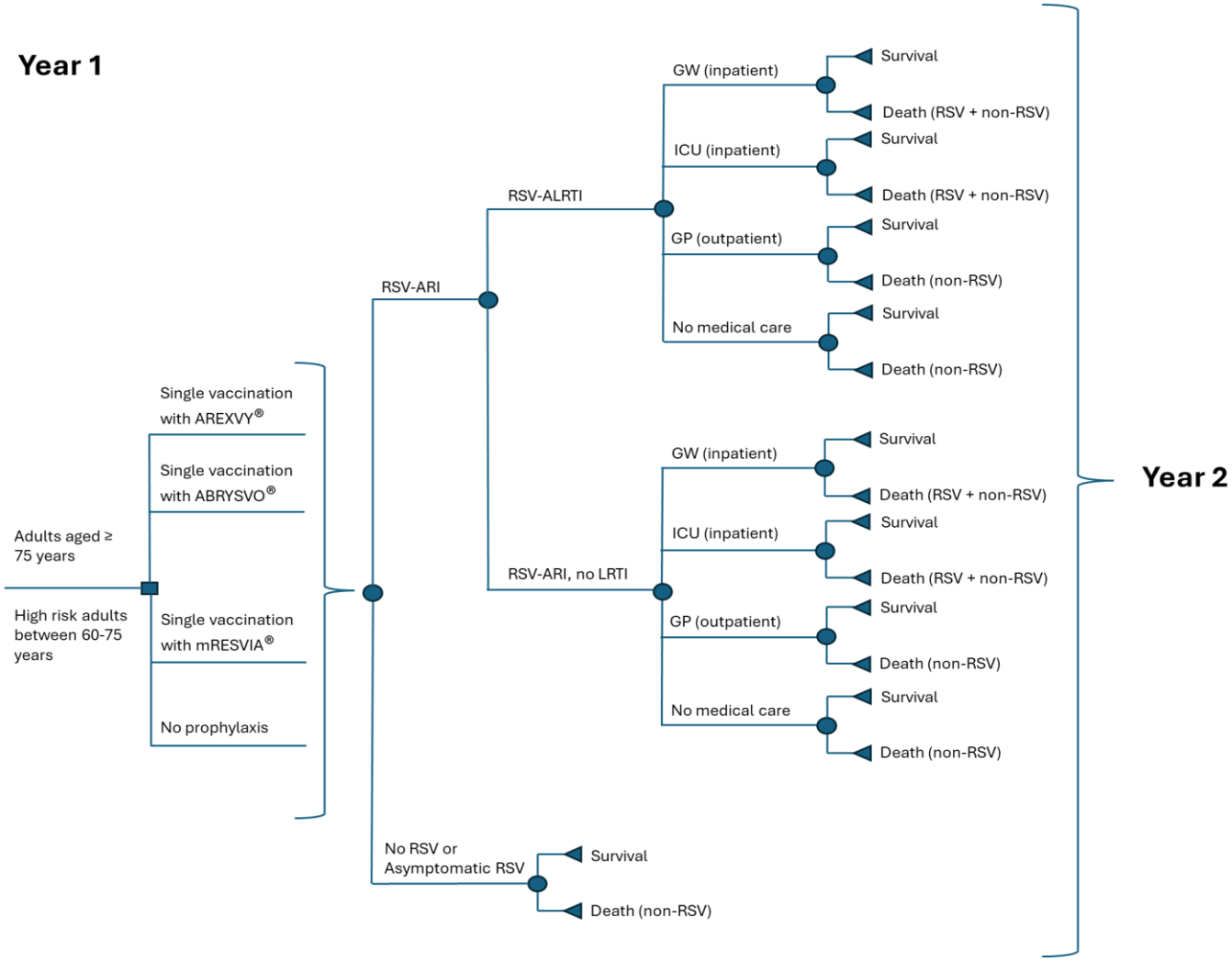
Figure 8 illustrates the structure of the decision analytic model. The model starts with a decision node representing the choice between the interventions (i.e. RSVpreF, RSVPreF3 or mRNA-1345) and the comparator (no prophylaxis). Subsequently, the first chance node indicates the probabilities of the following outcomes: 1) contracting an RSV-related acute respiratory illness (ARI), and 2) not contracting an RSV infection or displaying an asymptomatic RSV infection.

To understand these chance nodes, the outline of the RSV progression is presented. The second chance node represents the probabilities related to the type of infection that an RSV-ARI can further evolve into. These consist of 1) an ALRTI, which is associated with more severe symptoms, or 2) an infection that does not progress to an ALRTI (RSV-ARI, no LRTI), which often leads to milder symptoms (e.g. URTI). The subsequent steps in the tree are the same for these 2 groups and defined based on healthcare use required.

Depending on the severity of the symptoms, patients might seek medical treatment in the form of inpatient or outpatient care. These possibilities are captured in the third set of decision nodes consisting of 4 branches that represent a general ward (GW) hospitalisation, an intensive care unit (ICU) admission, GP visits and no medical care. The fourth chance nodes divide patients into those that survive or succumb to death. In case of hospitalisations, patients may survive or die due to either RSV or non-RSV related causes. For patients who do not seek medical care, or only receive outpatient care the probability to die is only informed by background mortality. In the case that adults do not get infected or contract an asymptomatic RSV infection their probability of death is also informed by background mortality.

All adults that survive year 1 transition to year 2, in which they might contract an RSV infection, possibly for a first or second time. In the second year, individuals re-enter the model at the first chance node. In this year, the vaccine efficacy is assumed to drop by a small percentage in all vaccine types, based on the second season results in the AReSVi-006 trial showing a slight decay in vaccine efficacy in the second year after vaccination. Additionally, the model contains different mortality rates due to the population having aged one year. Other probabilities were assigned the same value in year 2 as in year 1 due to redundance or insufficient data.

Figure 8. Schematic overview of the decision tree.



8.1.6.2 Model software and validity of the model

The model was programmed in Microsoft Excel. The economic model structure was based on examples used in previous HTAs on RSV vaccines and the economic model was validated by a clinical expert for its accuracy in representing the disease and its progression through an evaluation of its conceptual framework and alignment with clinical expertise. The expert's input ensured that the model's design, assumptions, and outcomes were consistent with real-world clinical observations and the natural history of the disease. Furthermore, a technical validation was conducted guided by the TECH-VER checklist. [77] White box testing (i.e. detailed inspection of code and calculations) of the input data transformations, pre-calculations, and event calculations were done by a second modeler who was not involved in the initial model construction. A number of minor errors were identified, which were resolved using parallel programming by the initial model builder and the model reviewer. Black box testing (i.e. testing if model outcomes are in line with expectations) was performed using extreme value testing of mortality, utility, vaccine efficacy, vaccine costs and healthcare costs parameters. Lastly, cross model validation was based on CUAs that were

identified in the systematic search on economic evidence. Since cost estimates are country specific and should not be cross-checked, QALY gains were compared.

8.1.7 Input parameters

The model input parameters on clinical outcomes and utilities were informed by the results of the data extraction of the systematic literature search of efficacy, effectiveness, and safety and additional pragmatic literature searches. Costs were based on databases available at the Federal Office of Public Health (FOPH) or pragmatic literature searches. A clinical expert was consulted when data could not be identified in the literature and if certain input parameters required validation. During a one-hour interview, the expert was questioned on topics regarding vaccine efficacy (decay), ALRTI among RSV-ARI and specifics of inpatient and outpatient care. The detailed questionnaire can be found in ***Appendix F***. An overview of the input parameters used for the base case is provided in ***Table 14.***

Table 14. Input parameters

Input parameter	Base case value		Source
	Subjects ≥75 years	Subjects aged ≥60 and <75 years with high risk for complications	
Epidemiological data			
Population size	916'603	146'563	Bundesamt für Statistik [67,68]
Infection rate	6.7 per 1'000 people		Shi et al 2019 [25]
Vaccine coverage	37.5		Chen et al 2022[78]
Trial data			
Vaccine efficacy for RSV-ARI			
For RSVPreF3 arm	0.717		Papi et al 2023 [54]
For RSVpreF arm	0.621		Walsh et al 2023 [55]
For mRNA-1345 arm	0.684		Wilson et al 2023 [56]
Probability that RSV-ARI evolves in RSV-ALRTI			
For RSVPreF3 arm	0.259		Papi et al 2023 [54]
For RSVpreF arm	0.500		Walsh et al 2023 [55]
For mRNA-1345 arm	0.346		Wilson et al 2023 [56]
For no prophylaxis arm	0.545		Trial data of placebo arms [54–56]
Medical attendance probabilities			
RSV-ARI (no LRTI)			
GW hospitalization	0.08288		Falsey et al 2014 [79], Stucki et al 2024 [2]
ICU hospitalization	0.01463		Falsey et al 2014 [79], Stucki et al 2024 [2]
GP (outpatient)	0.60250		Expert opinion
No medical care	0.30000		Expert opinion
RSV-ALRTI			
GW hospitalization	0.14625		Falsey et al 2014 [79], Stucki et al 2024 [2]

ICU hospitalization		0.04875	Falsey et al 2014 [79], Stucki et al 2024 [2]
GP (outpatient)		0.70500	Expert opinion
No medical care		0.10000	Expert opinion
Utilities			
GW hospitalization (mean value during stay)		0.576[a]	Falsey et al 2022 [80]
ICU hospitalization (mean value during stay)		0.402[a]	Marti et al 2016 [81]
GP (outpatient) Pre-season		0.890	Mao et al 2022 [82]
GP (outpatient) Week 0		0.530	Mao et al 2022 [82]
GP (outpatient) Week 1		0.750	Mao et al 2022 [82]
GP (outpatient) Week 2		0.730	Mao et al 2022 [82]
GP (outpatient) Week 3		0.830	Mao et al 2022 [82]
GP (outpatient) Week 4		0.860	Mao et al 2022 [82]
No medical care Pre-season		0.900	Mao et al 2022 [82]
No medical care Week 0		0.650	Mao et al 2022 [82]
No medical care Week 1		0.820	Mao et al 2022 [82]
No medical care Week 2		0.870	Mao et al 2022 [82]
No medical care Week 3		0.880	Mao et al 2022 [82]
No medical care Week 4		0.930	Mao et al 2022 [82]
Resource use for GP (outpatient)			
GP visit duration		30 minutes	Expert opinion
Number of GP visits		2	Expert opinion
Medication prescription probabilities			
Antipyretic	0.457	0.571	Falsey et al 2005 [23]
Cough suppressant	0.413	0.804	Falsey et al 2005 [23]
Systemic corticosteroid	0.100	0.375	Falsey et al 2005 [23]
Bronchodilator	0.043	0.518	Falsey et al 2005 [23]
Costs			

GW hospitalization	CHF 10’729	CHF 9’054	SwissDRG [83]
ICU hospitalization	CHF 18’554	CHF 17’615	SwissDRG [83]
GP (outpatient)			
GP visit		CHF 101	TARMED [84]
Medications	CHF 15	CHF 43	Spezialitätenliste [85]
Vaccination			
Vaccine price (RSVPreF3, RSVpreF, mRNA-1345)		CHF 203	German market prices [86–88]
Vaccine administration costs		CHF 50	TARMED [84]
Mortality			
RSV-related mortality			
RSV-ARI (no LRTI) hospitalization	0.056	0.043	Havers et al 2024 [89], Bundesamt für Statistik [90]
RSV-ALRTI	0.200	0.103	Tseng et al 2020 [91]
Background mortality			
First year	0.044	0.009	Bundesamt für Statistik [90]
Second year	0.050	0.010	Bundesamt für Statistik [90]

Abbreviations

ALRTI = acute lower respiratory tract illness, ARI = acute respiratory illness, GP = general practitioner, GW = general ward, ICU = intensive care unit, LRTI = lower respiratory illness, RSV = respiratory syncytial virus

Notes

a = Utilities during the days of hospitalisation

Expert opinion was gathered through discussions with a Swiss clinical expert, who has expertise in the disease trajectory

8.1.7.1 Vaccine efficacy

Three RCTs were detected in the systematic review for each of the 3 vaccines (i.e. RENOIR, AReSVi-006 and ConquerRSV). In these trials, vaccine efficacy was expressed as the reduced probability of a symptomatic RSV-ALRTI or RSV-ARI due to vaccination (i.e. intervention) compared to placebo (i.e. comparator). To calculate this estimate, each of the 3 trials provide data on the number of RSV-ALRTI and RSV-ARI cases among individuals in both treatment groups. Using these event counts, the probability of contracting RSV-ARI and division of RSV-ALRTI among all RSV-ARI cases were determined for each vaccine. Because of the low number of events occurring in the subgroups by age and low/high risk within all RSV trials, the efficacy estimates for subgroups was considered very uncertain. Therefore, the decision was made to use the estimates of the total trial population, i.e. all participants aged ≥ 60 as input for both target populations. Hence, estimates of vaccine efficacy against RSV-ARI in subjects aged ≥60 years, as reported in the RSV clinical trials, were used in the economic model. This implies a vaccine efficacy of a single RSVpreF dose of 62.1% (95% CI 37.1 to 77.9), a vaccine efficacy of a single RSVPreF3 dose of 71.7% (95% CI 56.2 to 82.3) and a vaccine efficacy of 68.4% (95% CI 50.9 to 79.7) for a single dose of mRNA-1345. The clinical expert confirmed that the vaccine efficacy will most likely be comparable across age groups and low/high risk groups but indicated that the consequences of an RSV infection will be more severe for people with comorbidities.

In the AReSVi-006 trial, after a median follow-up of 17.8 months up to the end of RSV season 2, the vaccine efficacy of a single RSVPreF3 dose against RSV-related ARI was estimated at 52.7% (95% CI 40.0 to 63.0), implying a 19% decay in vaccine efficacy in the second season. Based on this observation a 19% decay in vaccine efficacy in the second year was used for all types of RSV vaccines. According to the clinical expert, a vaccine efficacy decay in the second year is not to be expected and for that reason a scenario without decay was incorporated in the scenario analysis.

8.1.7.2 Vaccine coverage

The uptake of RSV vaccines in Switzerland was assumed to be similar to the uptake of influenza vaccination in Switzerland, on average 37.5%. [92] Based on input from the clinical expert a scenario was included using a higher uptake of 50%, which was considered the highest realistic uptake to be expected.

8.1.7.3 RSV infection rates and associated health care use

Since the trials were conducted when COVID restrictions were in effect, it is expected that the incidence estimates for RSV events in the trials are an underestimation from real-world practice. To account for the impact of these restrictions on the probabilities of contracting RSV-ARI, incidence data of RSV to inform the first chance node (i.e. the probability to contract RSV-ARI) in the

decision tree were retrieved from the meta-analysis by Shi et al 2019. [25] The pooled estimate in this study was based on 9 community-based studies that reported the RSV-ARI incidence in industrialised countries and was approximately 6.7 per 1000 people, resulting in an infection rate of 0.7% in the base case. An alternative scenario was explored in which the RSV infection rate was based on the weighted average of RSV-ARIs cases among participants in the 3 RSV trials.

Regarding the proportion of ALRTI among all RSV-ARI cases, calculations based on the trial outcomes resulted in 25.9%, 50% and 34.6%, respectively for RSVPreF3, RSVpreF and mRNA-1345. The pooled estimate of these trials, which was used to inform the proportion of ALRTI among RSV-ARI in the “no prophylaxis” branch of the economic model, is 54.5%.

Probabilities that infections resulted in hospitalization, outpatient care or no medical care were estimated as much as possible on published literature separately for RSV-ALRTI and RSV-ARI that does not result in ALRTI. The probability to be hospitalized for an RSV-ALRTI was 19.5% according to a study published by Falsey et al 2014. [79] No source has been found on the hospitalization risk for patients with RSV-ARI that does not develop into ALRTI. In the cost-effectiveness study by Herring et al 2022, an assumption was made that the probability of hospitalisation for an RSV-ALRTI was twice as likely as for and RSV-ARI(no LRTI). [79] The clinical expert agreed with this assumption resulting in a hospitalization risk of 9.75 % for the RSV-ARI (no LRTI) patients. Based on the findings of Stucki et al 2024 on Swiss hospitalisation data between 2003 and 2021, it was estimated that 75% of people that require hospitalisation for RSV are hospitalised in the GW and 25% in the ICU.[2] According to the clinical expert these estimates reflect the clinical practice for the patients with an RSV-ALRTI, however it is expected that for the patients with and RVS-ARI (no LRTI) the percentage that would be admitted to the ICU would be lower, around 15%.

Due to the lack of published data on the proportion of patients in each type of infection that would not require medical care, the clinical expert estimated that 10% of the RSV-ALRTIs would require no medical care, and that for the RSV-ARIs (no LRTI) this percentage would be 30%. The uncertainty over these probabilities is addressed in the OWSA and the PSA. The percentage of people receiving outpatient care was calculated as the remaining percentage.

8.1.7.4 Adverse events

Adverse events as a consequence of vaccination were incorporated in 2 CUAs that were identified in the systematic review on economic evidence. In the analysis conducted by Wang et al 2023 and Moghadas et al 2024, the negligible effect of these AE on the ICER estimate were emphasised, partly due to insufficient data. In Moghadas et al 2024, the assumption was made that disutility scores were similar to non-medically attended RSV infections with an effect that only lasts 1.5 days. In Wang et al 2023, adverse events with grades beyond 3 were considered. This means that calculations were based on probabilities of 3.8% and 1.0% to experience an AE due to RSVpreF and

RSVPreF3, respectively. In this model, a disutility of 0.000677 and costs of 1 GP visit were used to estimate the impact of these severe adverse events, which was very limited.

Given these reasons, along with the clinical expert's opinion on the low probability of experiencing an adverse event and the likelihood that these patients will only receive a dose of paracetamol, the adverse events were not considered in the current economic model.

8.1.7.5 Utilities

Swiss specific data on the health-related-quality of life of adult RSV patients could not be identified in the pragmatic literature search for input parameters. Therefore, estimates from the Respiratory Syncytial virus Consortium in Europe (RESCEU) observational study were used to inform QALYs for RSV patients in the outpatient setting and for those who do not require medical care in the economic model. [93] In Mao et al 2022, the RESCEU study was reported, and it contains health-related quality of life estimates for 34 RSV patients who originated from Belgium, the Netherlands and the United Kingdom. [94] They reported their health status on the EQ-5D-5L questionnaire at different timepoints: previously to the RSV season, during the RSV episode, and after the season over a total of 5 weeks. The scores on this questionnaire were converted to utilities using country-specific value sets that correspond to the participants' country of origin. Since an RSV infection does not last an entire year, the QALY estimates were calculated using pre-season utility estimates for the part of the year in which patients are not infected. Additionally, these pre-season utility estimates were used for individuals who experience an asymptomatic infection or are uninfected.

The RESCEU study was deemed an appropriate source to inform the economic model due to the reasonable degree of resemblance in healthcare systems, socioeconomic context and cultural factors across Switzerland, Belgium, the Netherlands and United Kingdom. Furthermore, it is an up-to-date source as it was published in 2022, and it was used in a CUA on RSV vaccines published by Wang et al in 2023. [72]

For the inpatient setting, Swiss specific utility estimates could not be obtained. Therefore, the study by Falsey et al 2022 was consulted as it assessed the quality of life in hospitalised patients based on data of the hospitalised acute respiratory tract infection (HARTI) study. [80] To account for the utility estimates related to an ICU admittance, the study by Marti et al 2016 was used. [81] This publication describes the OSCAR trial, which focuses on the quality of life and resource use of individuals that were admitted to the ICU due acute respiratory conditions. [95] The utilities corresponding to an ICU visit and hospital stay were applied over a period of 2 week based on the study by Falsey et al 2005. [23] The assumption was made that after a hospitalisation the subjects experience utilities equal to the outpatient estimates reported by Mao et al in 2022 for the following 5 weeks.

A variety of reasons led to the selection of Falsey et al 2022 and Marti et al 2016 to inform the input parameters of the economic model. [80,81] Due to a large sample size of 238 RSV patients in the HARTI study and 795 patients in the OSCAR trial, the robustness of the utility estimates is emphasised. [80,95] Furthermore, the HARTI study was referred to in a CUA on RSV vaccines published by Wang et al in 2023 and the OSCAR trial included patients from England, Wales and Scotland which resemble Switzerland in terms of healthcare systems, socioeconomic context and cultural factors. [61,80,95]

All utilities presented above were considered valid by the clinical expert.

8.1.7.6 Costs

8.1.7.6.1 Vaccine costs

Currently, there are no Swiss prices for any of the 3 vaccines, therefore their price in Germany was used. For all vaccines the same price has been used of approximately €213.6 or CHF 203.4 using the average annual euro to CHF exchange rate of the Swiss National Bank. [96] The uncertainty around vaccine price in Switzerland is assessed in the scenario analyses where it is varied between CHF 103 and CHF 303. Apart from the vaccine price, additional costs of CHF 50 that were calculated using the TARMED tariff codes: 00.0010, 00.0015, 00.0020, 00.0030 were added for the vaccine administration. [84] The vaccine and vaccine administration costs are applied in the model in the first year for all subjects that receive the vaccination.

8.1.7.6.2 Healthcare costs

For the individuals receiving only outpatient care for the RSV infection, an average of 2 visits to the GP was included. In addition, costs for different medication were included (antipyretics, cough suppressants, bronchodilators, and oral corticosteroids), based on input from the clinical expert. The probabilities of medication use varied between the 2 populations of interest and were based on the study by Falsey et al 2005. [23] The costs per 30 minute GP visit were calculated to be approximately CHF 101 based on tariff codes: 00.0010, 00.0015, 00.0020, 00.0030 of TARMED using the taxpoint value of 0.89 and Analysenliste codes: 4700.00, 1371.00, 3157.00, 1245.00/1245.01 using the taxpoint value of 1.[97,98] The medication costs were calculated to be CHF 15 and CHF 43 for the population aged ≥ 75 years and the population aged between ≥60 and <75 years at high risk of complications, respectively, using prices from the publicly available price on Spezialitätenliste. [85,99]

For the patients that required a hospitalisation, the average duration of a hospitalisation was estimated to be 10 days for the population over 75 year and 7 days for the population aged 60 to 75 years based on MedStat Data. [100] Using the corresponding Swiss DRG codes E77C and E70B this resulted in an average of CHF 10’729 and CHF 9’054 for a GW admission for the 2 target populations respectively using a base rate of CHF 9’467. [99,101] For an average hospitalisation in the ICU

the corresponding costs were CHF 18’554 and CHF 17’615 using the Swiss DRG codes E87B, E87A, E36D, and E36C, for an average length of stay of 14 days for the population aged ≥75 years and 12 days for the population aged between ≥60 and <75 years at high risk of complications using the same base rate of CHF 9’467. [99,101]

8.1.7.7 Mortality

8.1.7.7.1 RSV-related mortality

For the patients that are admitted to the hospital (either GW or ICU) RSV-related mortality was applied. RSV-ARI (no LRTI) mortality for the duration of the hospitalisation was informed by the findings of the study by Havers et al 2024, where data on the in-hospital mortality over 7 RSV seasons were provided. These probabilities of death are 4.3% and 5.6% for patients between 60 and 75 and older than 75, respectively. [89] Following the conclusion of the hospitalisation period, background mortality was applied for the respective age groups based on data from Swiss lifetables from the Bundesamt für Statistik. [90] In case of RSV-ALRTI hospitalisation, annual mortality data were used from the 2020 study by Tseng et al in which they assessed the short- and long- term mortality of RSV hospitalised older adults, more than 90% of which experience a moderate to severe LRTI. The probabilities of death that were estimated in this study are 10.3% and 20% for patients between 60 and 75 and older than 75, respectively. [91] Swiss specific mortality estimates could not be identified and due to a lack of data, no differentiation in RSV-related mortality was made between the ICU and GW setting.

8.1.7.7.2 Background mortality

The background mortality was based on the most recent Swiss lifetables derived from the Bundesamt für Statistik. [90] Where background mortality was used, for the high risk population a 25% increased mortality risk was applied due to the presence of comorbidities based on findings by Caughey et a 2010. [102]

8.1.8 Uncertainty analysis

8.1.8.1 Scenario analyses

Structural uncertainty was explored in several scenario analyses.

Table 15 shows the different scenario analyses, compared with the base case analysis.

Table 15. Scenario analyses

	Base case		Scenario
Population			
Infection rate	6.7 per 1'000 people		5 per 1'000 people
Costs			
Vaccine price (RSVPreF3, RSVpreF, mRNA-1345)	CHF 203		CHF 103 CHF 303
Hospitalization costs	Subjects ≥75 years	GW: CHF 10'729 ICU: CHF 18'554	GW: CHF 12'426 ICU: CHF 30'171
	Subjects aged ≥60 and <75 years with high risk for complications	GW: CHF 9'054 ICU: CHF 17'615	
Efficacy			
Second year vaccine efficacy decay	19% decay		No decay
Time horizon	2 years		1 year
Discounting rate	3%		No discounting 5%

Abbreviations

CHF = Swiss franc, GW = general ward, ICU = intensive care unit, LRTI = lower respiratory illness

8.1.8.2 One-way sensitivity analyses (OWSA)

Parameter uncertainty was first tested in the OWSA, where model parameters were systematically and independently varied. All model parameters were varied along their 95% confidence interval. If the 95% confidence interval or standard errors around model parameters were not reported a standard error of 20% of the mean value of the parameter was assumed. For the vaccine price a standard error of 50% was used. The incremental cost-effectiveness ratio (ICER) was recorded at the upper and lower limits to produce a tornado diagram. The OWSA was run for both target populations for each of the 3 vaccines. ***Appendix G*** provides the values used in one-way sensitivity analyses (OWSA).

8.1.8.3 Probabilistic sensitivity analysis (PSA)

Joint parameter uncertainty was explored through a PSA. In this analysis, all parameters were assigned distributions and standard errors, after which they were varied simultaneously. Standard errors were calculated if the confidence interval was reported. If such estimates were not available, a default value of 20% was applied. Because of the high uncertainty around the cost of the vaccine a standard error of 50% was used for this parameter. Distributions, mean values and the standard error that were applied in the PSA are provided in ***Appendix H***. Monte Carlo simulations were performed (with 1'000 iterations), and the results were recorded. Results were plotted on the cost-effectiveness plane (CE plane). From these results, a cost-effectiveness acceptability curve (CEAC) was produced. The PSA was run for both target populations for the 3 vaccines.

8.2 Budget impact analysis

8.2.1 Objective

The budget impact analysis (BIA) is performed over 2 years in order to evaluate the monetary impact of - vaccination against RSV for subjects aged ≥75 years and subjects aged between ≥60 and <75 years at high risk of complications compared to no prophylaxis or standard of care in Switzerland.

8.2.2 Patient population

Two target populations were defined for the BIA: 1) subjects aged ≥75 years, and 2) subjects aged between ≥60 and <75 years at high risk of complications. The population size based on data from the Federal Statistical Office are 916'603 for subjects aged ≥75 years and 1'465'632 for subjects aged between ≥60 and <75 years. [68] However only 10% of the population between ≥60 and <75 years are estimated to be of high risk of complications therefore the size of the second target population was estimated to be 146'563. [67] A coverage rate of 37.5% was used for the base case assuming that it is equal to the influenza vaccination coverage found in published literature which was confirmed plausible during the clinical expert interview. [92] An alternative vaccination coverage rate of 50% was explored in the scenario analysis. As a result, the sizes of the 2 target populations are multiplied with the coverage rate resulting in sizes of the populations of the vaccinated subjects in year one of approximately 343'726 and 54'961 respectively. [68] Additionally, population growth is considered to occur in following years. In order to account for this, the future population sizes were calculated using epidemiological data of the Federal Statistical Office in order to calculate the average annual budget impact over a 4-year and a 6-year time horizon for both target populations. [68] Therefore, the population sizes of vaccinated subjects are 357'235 and 58'143 in year 3, as well as 366'092 and 61'138 in year 5 for the population of subjects aged ≥75 years and the population of subjects aged between ≥60 and <75 years at high risk of complications respectively.

8.2.3 Technology

The interventions are the following 3 RSV vaccines RSVpreF, RSVPreF3 and mRNA-1345. Budget impact was calculated for each vaccine separately, assuming that the full target population received one type of vaccine. Different market share combinations of the 3 vaccines were not explored in this analysis due to a lack of data.

8.2.4 Time horizon

The time horizon of the BI model was restricted to 2 years. The average annual budget impact over 4 and 6 years was also assessed.

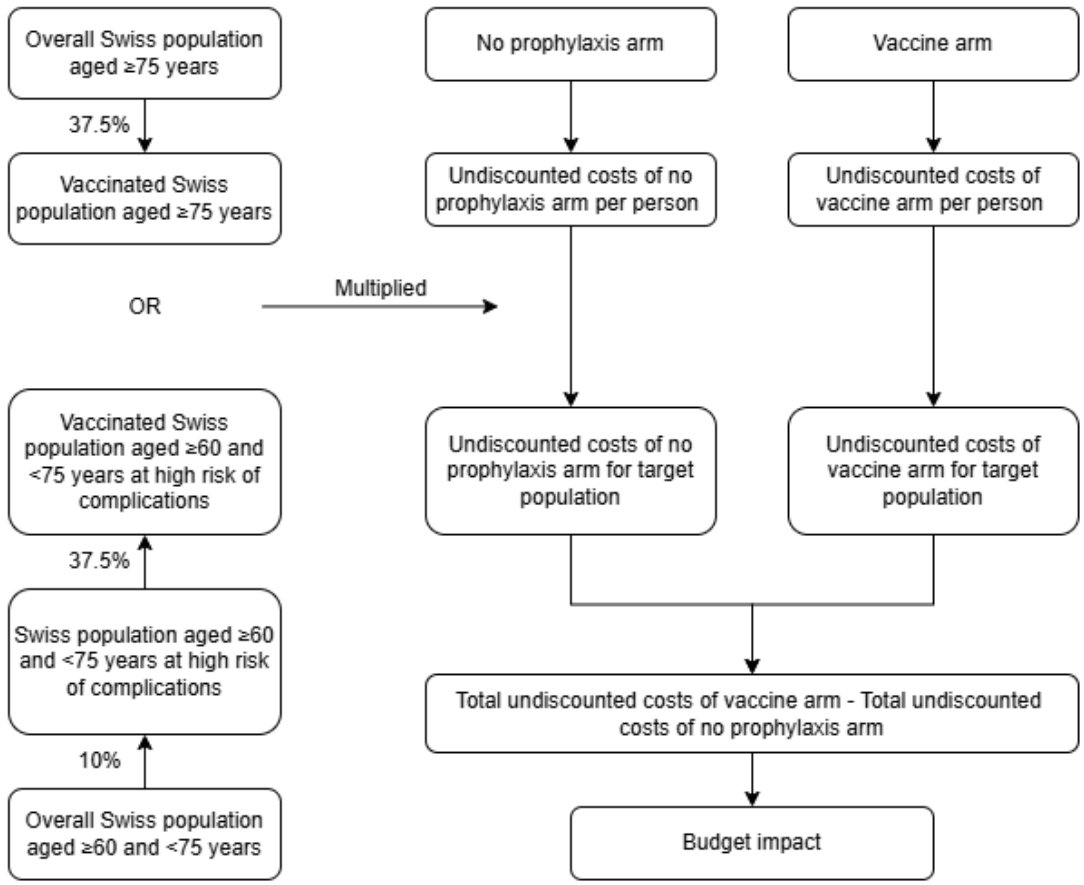
8.2.5 Perspective

The BIA was performed from the Swiss healthcare payer perspective. Costs of healthcare services covered by the Swiss mandatory health insurance were analysed, irrespective of the actual payer (mandatory health insurer, other social insurer, government (federal government, cantons, communities) out-of-pocket). The analysis did not include indirect costs due to informal care or productivity losses and additional non-medical costs for patients, such as travel costs.

8.2.6 Model description

The model used for the BIA is described extensively in ***Section 8.1.6***. The undiscounted vaccination costs and healthcare costs (as described for the cost-effectiveness model ***Section 8.1.7.6***) were multiplied by the number of subjects of the 2 target populations in Switzerland. The vaccine and vaccine administration costs are applied in the first year for all subjects that will receive a vaccination. ***Figure 9*** provides a visual representation of the budget impact calculations.

Figure 9. Schematic representation of budget impact calculation



8.2.7 Input data

The input data for the budget impact analysis is described in ***Section 8.1.7***.

8.2.8 Base case and scenario analyses

The scenario analyses explored for the BIA are described in ***Table 16.***

Table 16. Budget impact scenario analyses

	Base case		Scenario
Costs			
Vaccine price (RSVPreF3, RSVpreF, mRNA-1345)	CHF 203		CHF 103 CHF 303
Hospitalization costs	Subjects ≥75 years	GW: CHF 10'729 ICU: CHF 18'554	GW: CHF 12'426 ICU: CHF 30'171
	Subjects aged ≥60 and <75 years with high risk for complications	GW: CHF 9'054 ICU: CHF 17'615	
Vaccine coverage			
	37.5%		50%
Time horizon	2 years	One year	

Abbreviations

CHF = Swiss franc

8.2.9 Model software and validation of the model

The model software and validation of the model are described in ***Section 8.1.6.2***.

9. Results economic evaluation and budget impact analysis

9.1 Economic Evaluation

9.1.1 Base case results

The base case analysis was conducted using inputs and assumptions as described in previous sections. In ***Table 17,*** total costs and QALYs are presented for each vaccine per target population. Furthermore, the incremental results and ICER per QALY compared to no prophylaxis are shown. In both target populations, all interventions resulted in incremental QALYs at additional costs. For subjects aged ≥75 years, the ICERs for RSVPreF3, RSVpreF and mRNA-1345 were estimated at CHF 244'266, CHF 292'263 and CHF 258'699 per QALY gained, respectively. In the second target population, consisting of subjects aged between ≥60 and <75 years at high risk of complications, the ICERs were CHF 280'740, CHF 333'949 and CHF 296'879 per QALY gained, for RSVPreF3, RSVpreF and mRNA-1345, respectively. In both populations, the RSVPreF3 vaccine resulted in the lowest ICERs.

Across the populations, all RSV vaccines result in higher ICER estimates in the subjects aged between ≥60 and <75 years at high risk of complications compared to the subjects aged ≥75 years. This effect is mainly caused by the higher gain in incremental QALYs for the subjects aged ≥75 years.

Table 17. Costs, QALYs, and corresponding incremental costs and QALYs (discounted, per person)

Target Population	Intervention	Costs (CHF)	QALYs	Incremental Costs (CHF)	Incremental QALYs	ICER (CHF per QALY gained)
Subjects aged ≥75	RSVPreF3	260	1.68096	235	0.00096	244'266
	RSVpreF	263	1.68082	238	0.00081	292'263
	mRNA-1345	261	1.68091	236	0.00091	258'699
	No prophylaxis	25	1.68000	N/A	N/A	N/A
Subjects aged between ≥60 and <75 years at high risk of complications	RSVPreF3	260	1.74595	234	0.00083	280'740
	RSVpreF	263	1.74583	237	0.00071	333'949
	mRNA-1345	261	1.74591	235	0.00079	296'879
	No prophylaxis	26	1.74512	N/A	N/A	N/A

Abbreviations

CHF = Swiss franc, ICER = incremental cost-effectiveness ratio, QALY = quality-adjusted life year

9.1.2 Scenario analyses

Deterministic results of the cost-utility analysis were explored in 7 different scenarios, which are detailed in the previous ***Section 8.1.8.1***. ***Table 18*** presents the results of the scenario analyses. In all scenarios similar trends in the deterministic ICERs were observed for both target populations.

The results indicate that an alternative estimate of 0.63% for the infection rate, based on a pooled estimate of the placebo arms in the clinical trials, had a negative impact on the incremental QALYs. Therefore, the ICERs that correspond to this scenario were higher than the base case.

Varying vaccine prices with minus or plus CHF 100 in the second and third scenario had a substantial impact on the incremental costs, while the gain in QALYs remained the same. Higher vaccine prices lead to an increase in incremental costs and higher ICERs, while lower vaccines prices resulted in lower ICERs.

The scenario where vaccine efficacy was equal in the second and first year, resulted in lower ICERS due to an increase in incremental QALYs. This increase is caused by higher efficacy estimates as compared to the base case, in which the vaccine efficacy decreases by 19% in the second year.

Furthermore, an alternative source of hospitalization costs, i.e., Stucki et al 2024, is related to lower ICERs due to a higher cost estimate of a hospitalization.[2] The hospitalizations averted due to vaccination therefore caused lower incremental costs.

A time horizon of 1 year caused higher ICERs since vaccination occurs in the first year of the model. Therefore, the costs are highest in this year, and these are offset against QALYs gained in only one year. Considering a two-year time horizon, the mean total costs are substantially lower while the mean total QALYs are only slightly lower.

Lastly, the 2 scenarios in which discounting rates were not considered or set to 5%, had the least effect on deterministic ICERs among all scenarios. Logically, applying no discounting rates in the analysis led to lower ICERs while a discounting rate of 5% was related to higher ICERs.

Table 18. Outcomes of scenario analyses cost-effectiveness

Scenario	Intervention	Incremental costs (CHF)	Incremental QALYs	ICER (costs per QALY gained)
Subjects aged ≥75 years				
Base case	RSVPreF3	235	0.0009606	244'266
	RSVpreF	238	0.0008127	292'263
	mRNA-1345	236	0.0009107	258'699
Infection rate	RSVPreF3	236	0.0008976	262'772
	RSVpreF	239	0.0007595	314'137
	mRNA-1345	237	0.0008510	278'220
Vaccine price (CHF 103)	RSVPreF3	135	0.0009606	140'163
	RSVpreF	138	0.0008127	169'221
	mRNA-1345	136	0.0009107	148'892
Vaccine price (CHF 303)	RSVPreF3	335	0.0009606	348'368
	RSVpreF	338	0.0008127	415'305
	mRNA-1345	336	0.0009107	368'507
Equal vaccine efficacy in year 1 and 2	RSVPreF3	233	0.0010672	218'737
	RSVpreF	236	0.0009090	259'980
	mRNA-1345	234	0.0010140	231'154
Hospitalisation costs	RSVPreF3	226	0.0009606	235'132
	RSVpreF	230	0.0008127	282'610
	mRNA-1345	227	0.0009107	249'399
Time horizon one year	RSVPreF3	235	0.0004662	503'283
	RSVpreF	238	0.0003958	600'201
	mRNA-1345	236	0.0004426	532'311
No discounting	RSVPreF3	234	0.0009754	240'342
	RSVpreF	237	0.0008252	287'636
	mRNA-1345	235	0.0009247	254'565
Discounting 5%	RSVPreF3	235	0.0009512	246'820
	RSVpreF	238	0.0008048	295'276
	mRNA-1345	236	0.0009018	261'391
Subjects aged between ≥60 and <75 years at high risk of complications				
Base case	RSVPreF3	234	0.0008417	277'767
	RSVpreF	237	0.0007163	330'556
	mRNA-1345	235	0.0007992	293'772
Source of infection rate	RSVPreF3	235	0.0007865	298'885
	RSVpreF	238	0.0006694	355'371
	mRNA-1345	236	0.0007468	316'013
Vaccine price (CHF 103)	RSVPreF3	134	0.0008417	158'958
	RSVpreF	137	0.0007163	190'950
	mRNA-1345	135	0.0007992	168'644
Vaccine price (CHF 303)	RSVPreF3	334	0.0008417	396'576
	RSVpreF	337	0.0007163	470'162

	mRNA-1345	335	0.0007992	418’900
Equal vaccine efficacy in year 1 and 2	RSVPreF3	233	0.0009276	250’739
	RSVpreF	236	0.0007934	296’872
	mRNA-1345	234	0.0008822	264’732
Hospitalisation costs	RSVPreF3	222	0.0008417	264’166
	RSVpreF	227	0.0007163	316’571
	mRNA-1345	224	0.0007992	280’034
Time horizon one year	RSVPreF3	234	0.0004479	521’996
	RSVpreF	237	0.0003829	618’304
	mRNA-1345	235	0.0004259	551’213
No discounting	RSVPreF3	234	0.0008535	273’676
	RSVpreF	237	0.0007263	325’776
	mRNA-1345	235	0.0008104	289’471
Discounting 5%	RSVPreF3	234	0.0008342	280’425
	RSVpreF	237	0.0007100	333’661
	mRNA-1345	235	0.0007921	296’566

Abbreviations

CHF = Swiss franc, ICER = incremental cost-effectiveness ratio, QALY = quality-adjusted life year

To further analyse the relation between prices of the RSV vaccines and cost-effectiveness results, ***Figure 10*** and ***Figure 11*** describe the linear relation. These plots highlight the increasing trend between high vaccine prices and high ICER values.

Figure 10. Deterministic ICERs at varying vaccine prices, with ICER values on the Y axis and vaccine prices on the X axis, for subjects aged ≥75 years

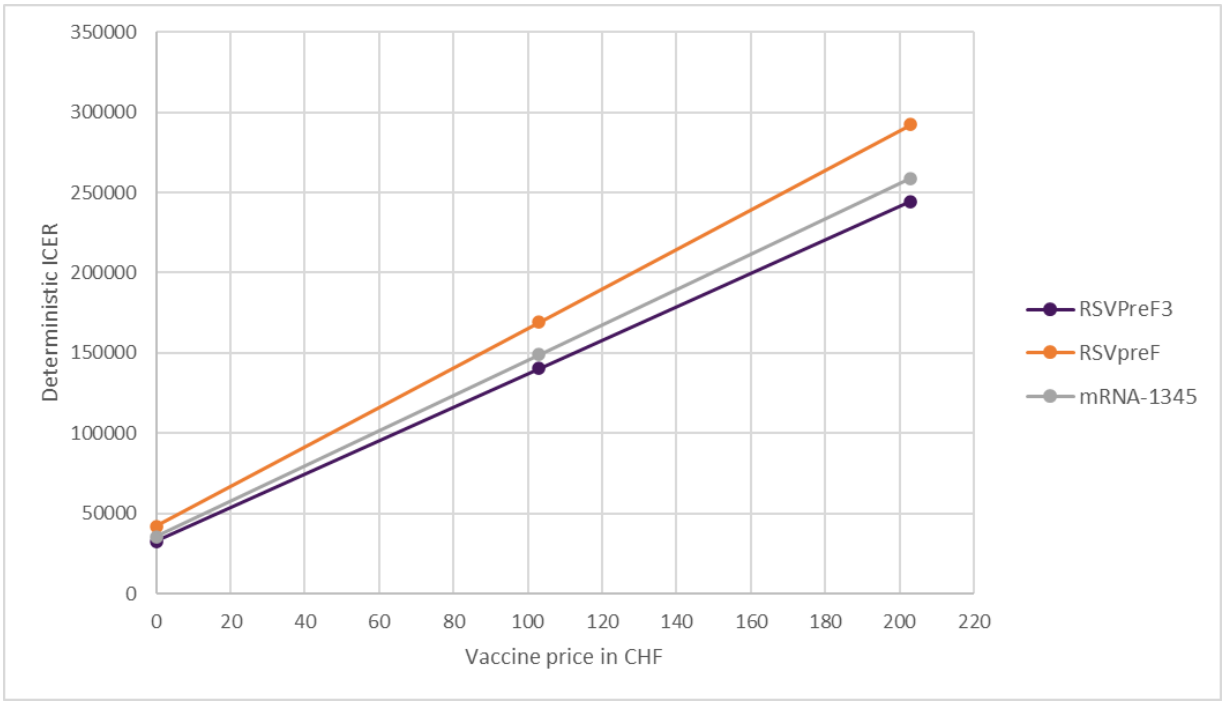
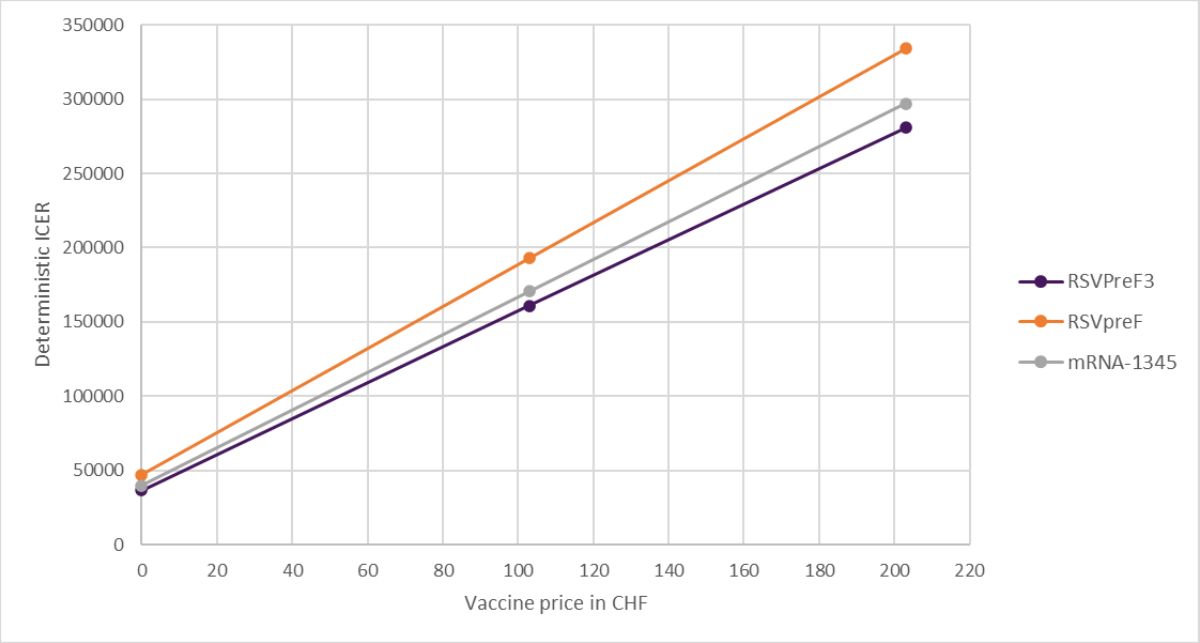


Figure 11. Deterministic ICERs at varying vaccine prices, with ICER values on the Y axis and vaccine prices on the X axis, for subjects ≥60 and <75 years at high risk of complications



9.1.3 Probabilistic sensitivity analysis

The probabilistic results in the population ≥75 years of age are depicted in the ***Figure 12*** to ***Figure 17***. The incremental cost-effectiveness planes in ***Figure 12***, ***Figure 13***, and ***Figure 14*** point to comparable trends across the vaccines. In these plots, the purple dots represent an ICER that is calculated in one of 1'000 Monte Carlo simulations (i.e., iterations) while the orange dot indicates the deterministic ICER. The ICERs of all PSA iterations were located in the north-east quadrant of the cost-effectiveness plane, meaning that if parameter uncertainty is considered, the vaccines will provide more QALYs at higher costs compared to no prophylaxis. Only the ranges in which the PSA iterations fall differ slightly among vaccine types.

Furthermore, similar conclusions can be drawn from the cost-effectiveness acceptability curves in ***Figure 15***, ***Figure 16***, and ***Figure 17***. For RSVPreF3, there was a 50% probability that the vaccine was cost-effective at a willingness to pay threshold of CHF 235'000, and 90% probability at a threshold of CHF 425'000. The thresholds that correspond to a 50% and 90% probability to be cost-effective were CHF 285'000 and CHF 525'000 for RSVpreF and CHF 245'000 and CHF 455'000 for mRNA-1345, respectively.

Figure 12. Incremental cost-effectiveness plane RSVPreF3 (Subjects aged ≥75 years)

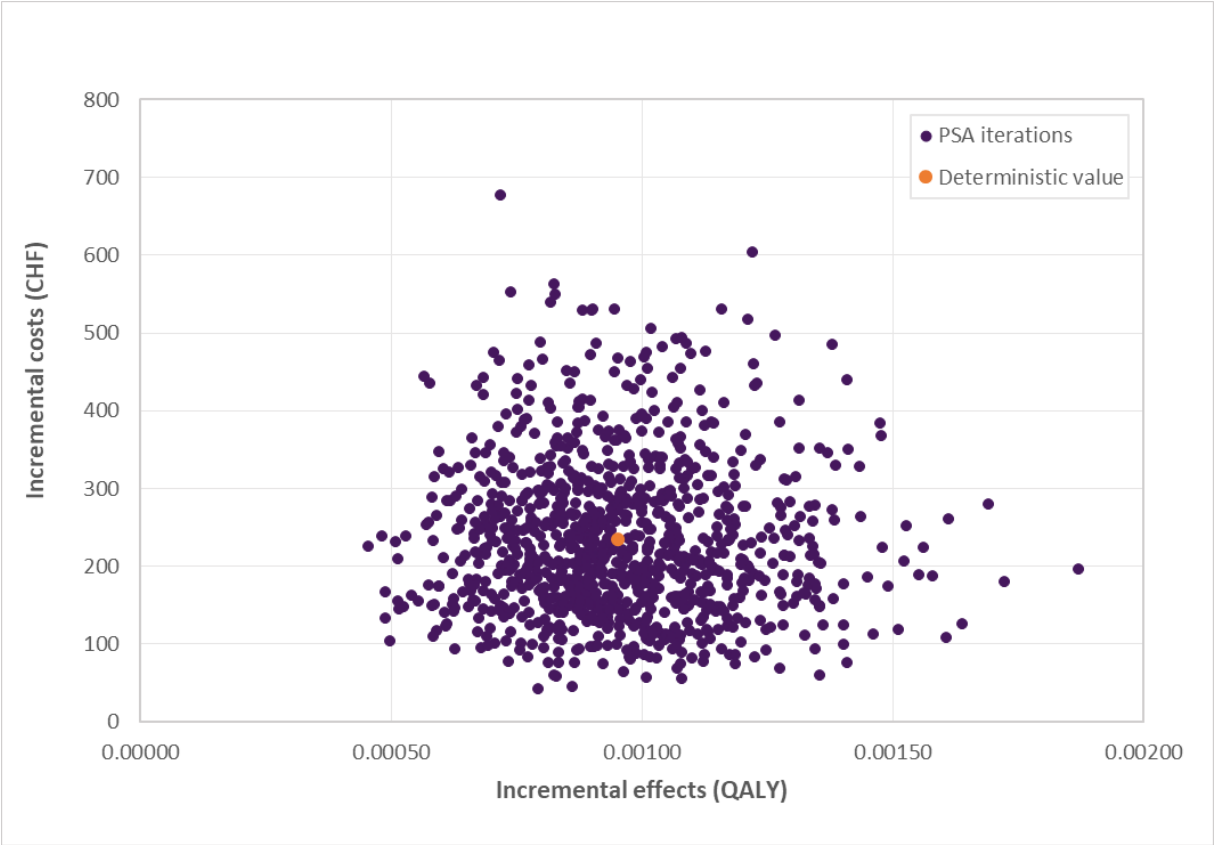


Figure 13. Incremental cost-effectiveness plane RSVpreF (Subjects aged ≥75 years)

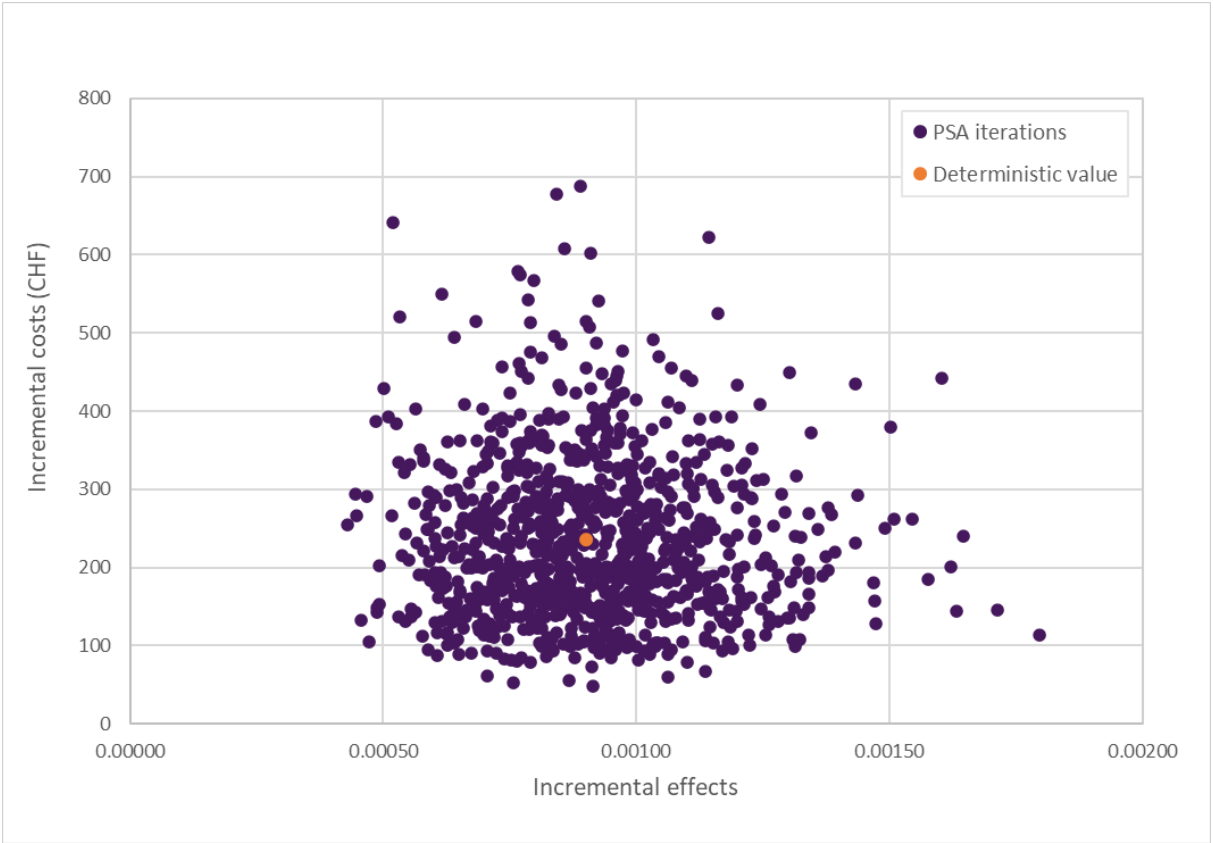


Figure 14. Incremental cost-effectiveness plane mRNA-1345 (Subjects aged ≥75 years)

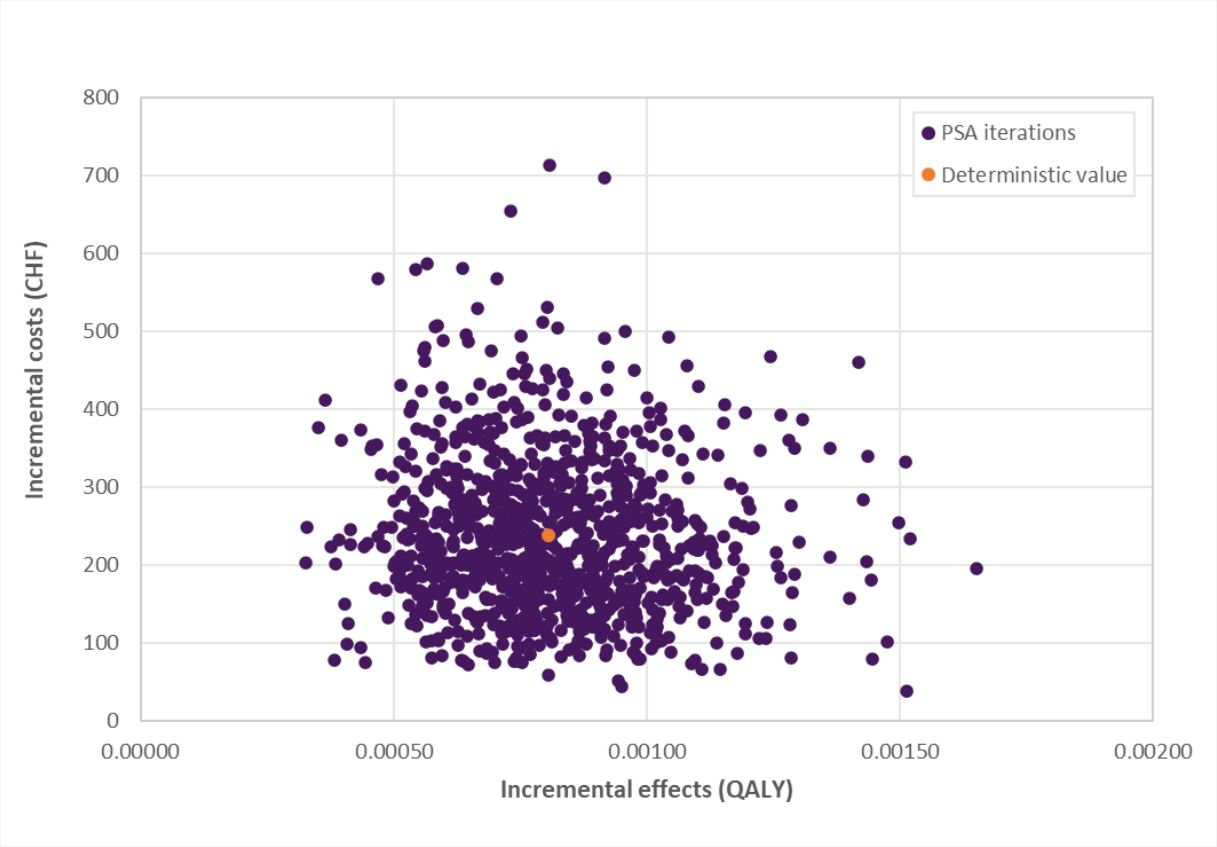


Figure 15. Cost-effectiveness acceptability curve RSVPreF3 (Subjects aged ≥75 years)

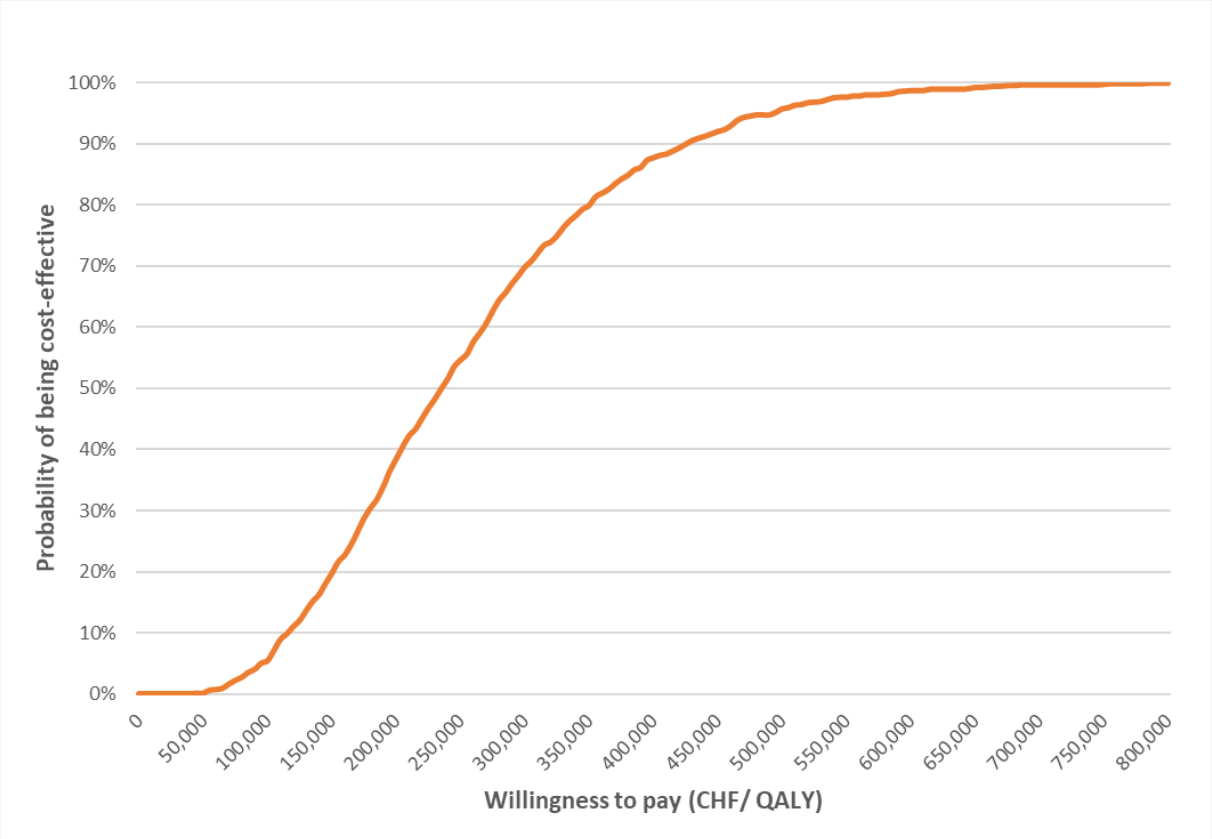


Figure 16. Cost-effectiveness acceptability curve RSVpreF (Subjects aged ≥75 years)

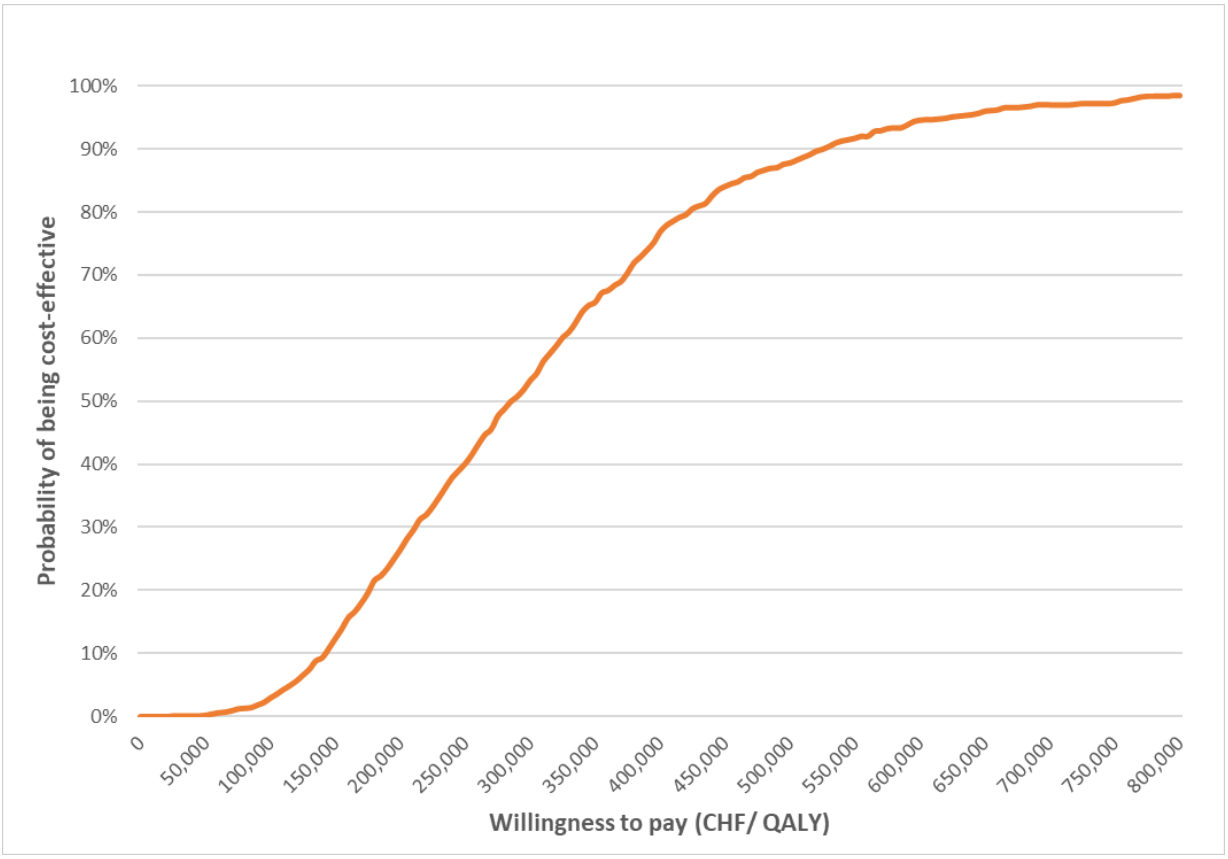
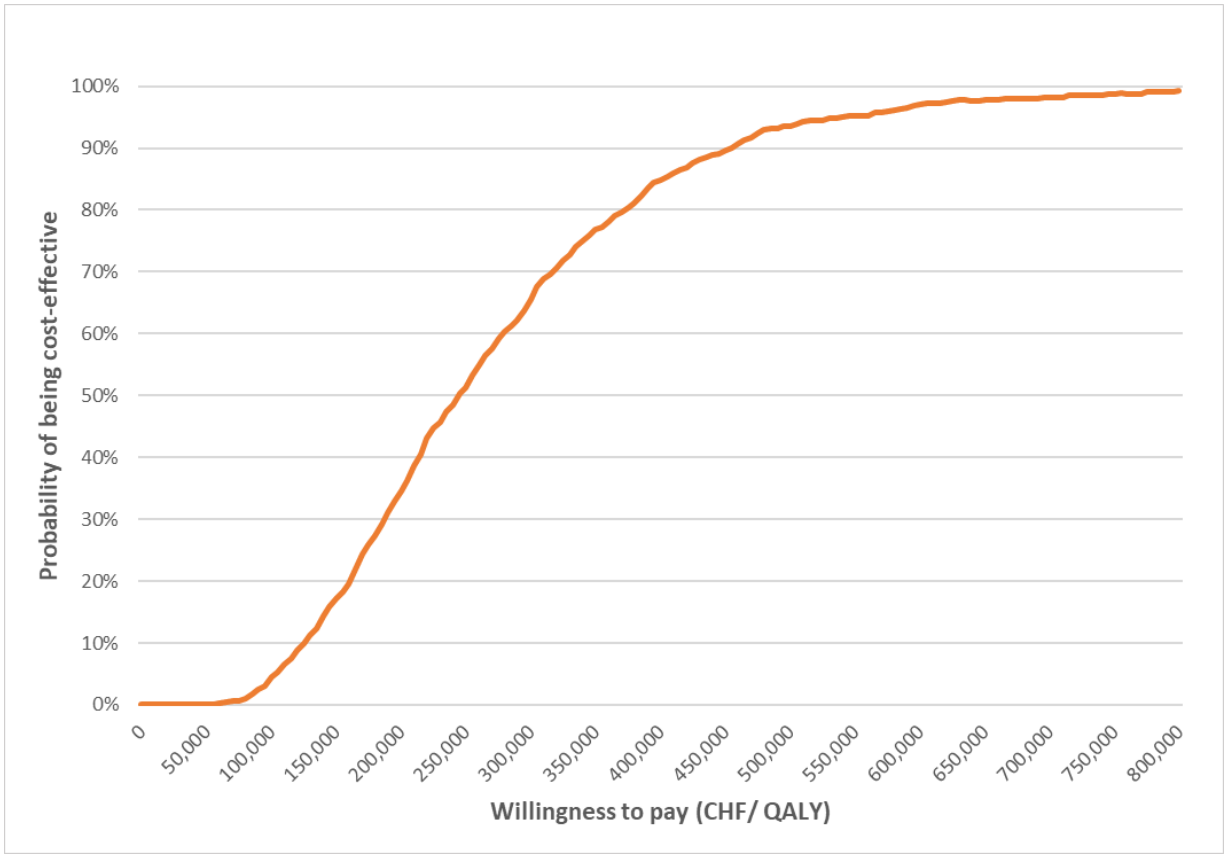


Figure 17. Cost-effectiveness acceptability curve mRNA-1345 (Subjects aged ≥75 years)



The results of the PSA for the high-risk population aged ≥60 and <75 years at high risk for complications are depicted in ***Figure 18*** to ***Figure 23***. Similar to the results of the first population, all PSA iterations were located in the north-east quadrant of the cost-effectiveness plane, meaning that the vaccines provide more QALYs at higher costs compared to no prophylaxis.

Furthermore, the cost-effectiveness acceptability curves in ***Figure 21***, ***Figure 22***, and ***Figure 23*** point to similar trends across the 3 vaccine types. For RSVPreF3, there was a 50% probability that the vaccine is cost-effective at a willingness to pay threshold of CHF 265'000, and 90% probability at a threshold of CHF 500'000. The thresholds that corresponded to a 50% and 90% probability that the vaccine is cost-effective were CHF 320'000 and CHF 595'000 for RSVpreF and CHF 285'000 and CHF 515'000 for mRNA-1345, respectively.

Figure 18. Cost-effectiveness plane RSVPreF3 (Subjects aged between ≥60 and <75 years at high risk of complications)

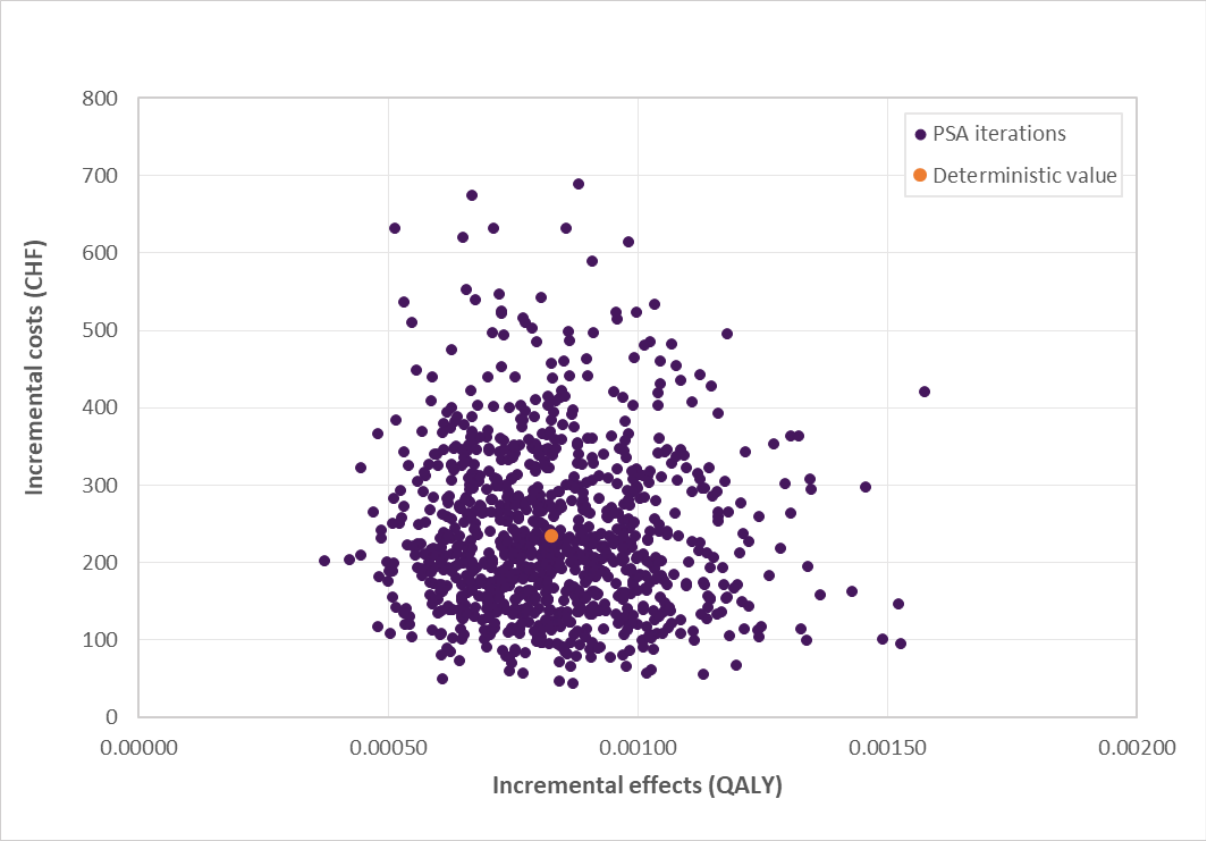


Figure 19. Cost-effectiveness plane RSVpreF (Subjects aged between ≥60 and <75 years at high risk of complications)

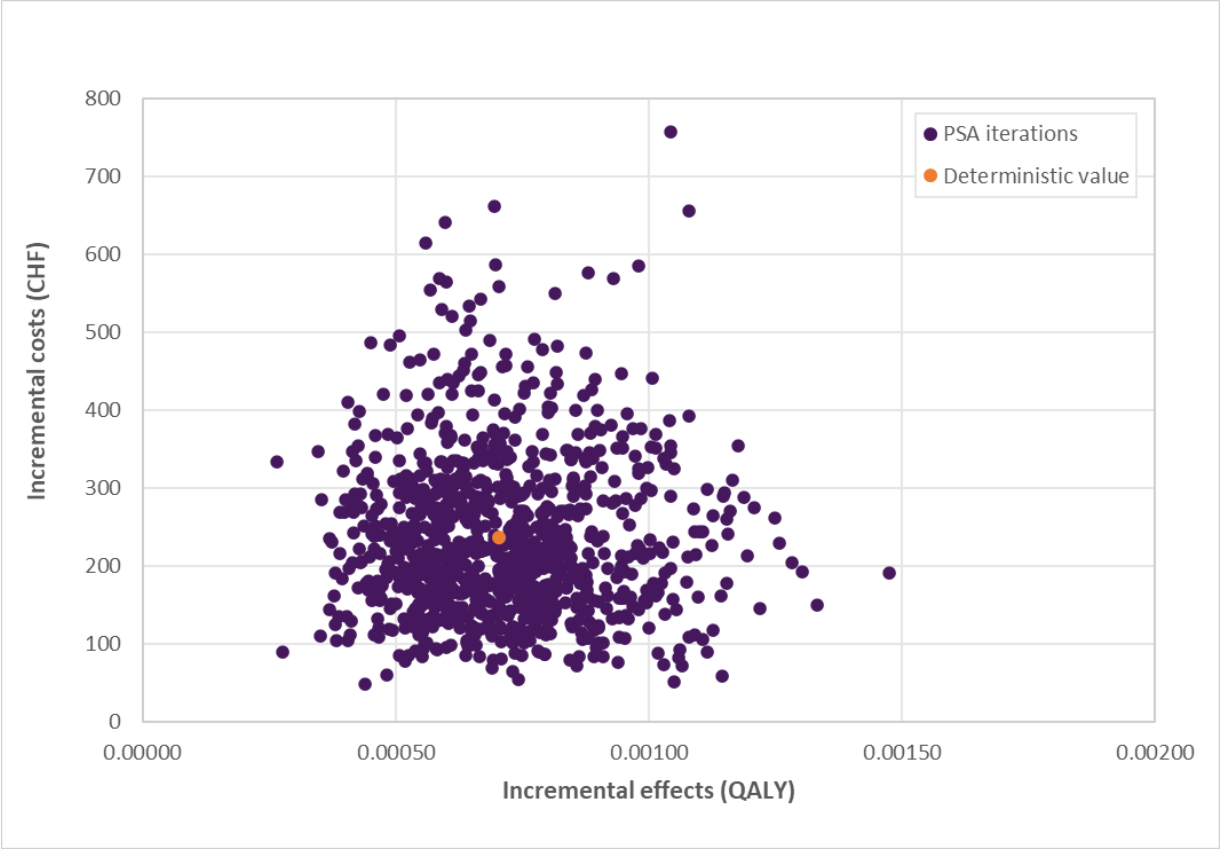


Figure 20. Cost-effectiveness plane mRNA-1345 (Subjects aged between ≥60 and <75 years at high risk of complications)

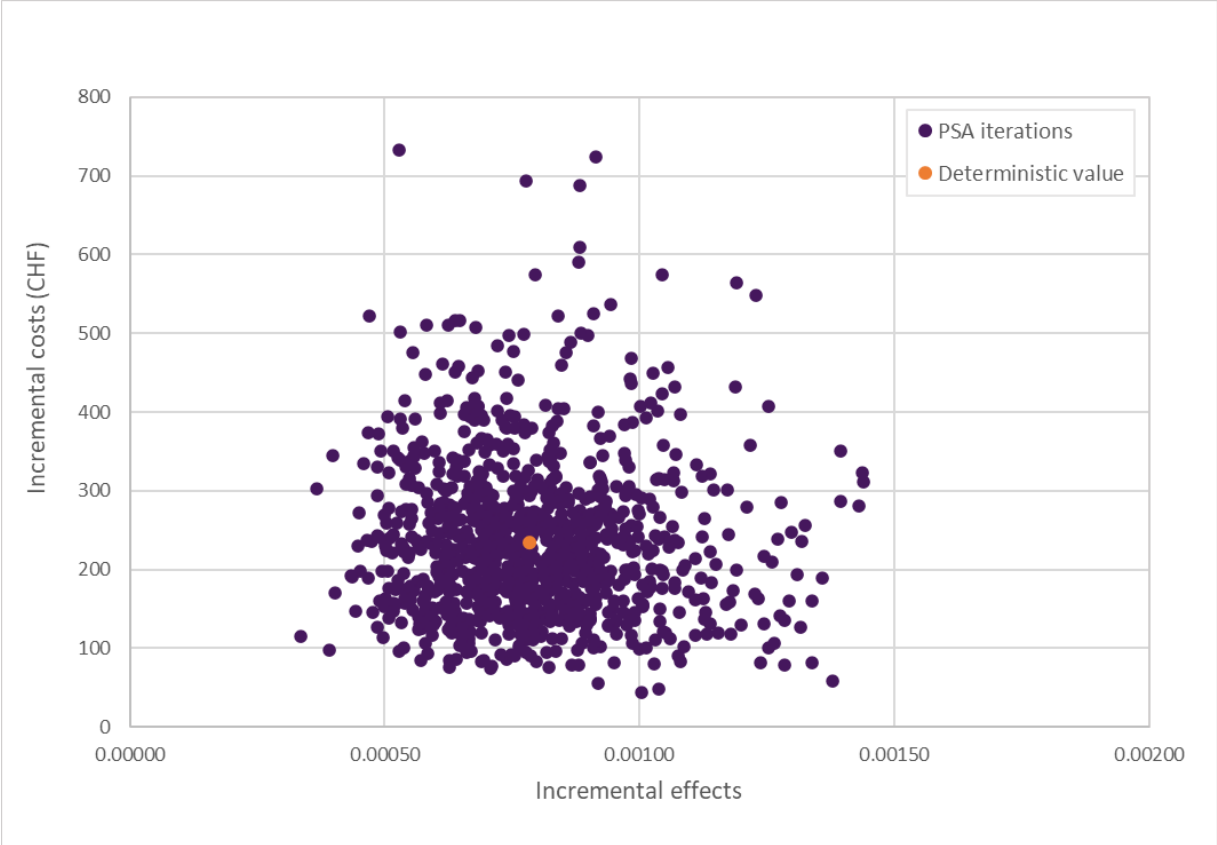


Figure 21. Cost-effectiveness acceptability curve RSVPreF3 (Subjects aged between ≥60 and <75 years at high risk of complications)

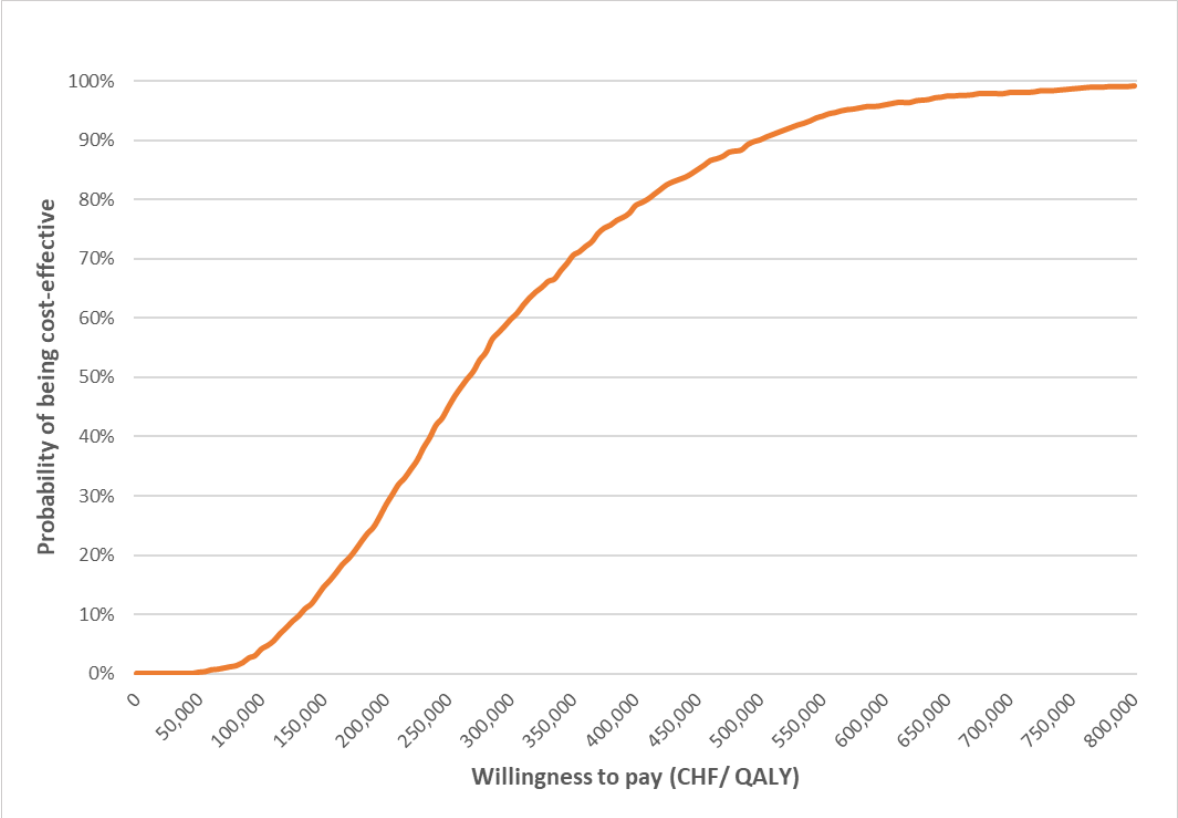


Figure 22. Cost-effectiveness acceptability curve RSVpreF (Subjects aged between ≥60 and <75 years at high risk of complications)

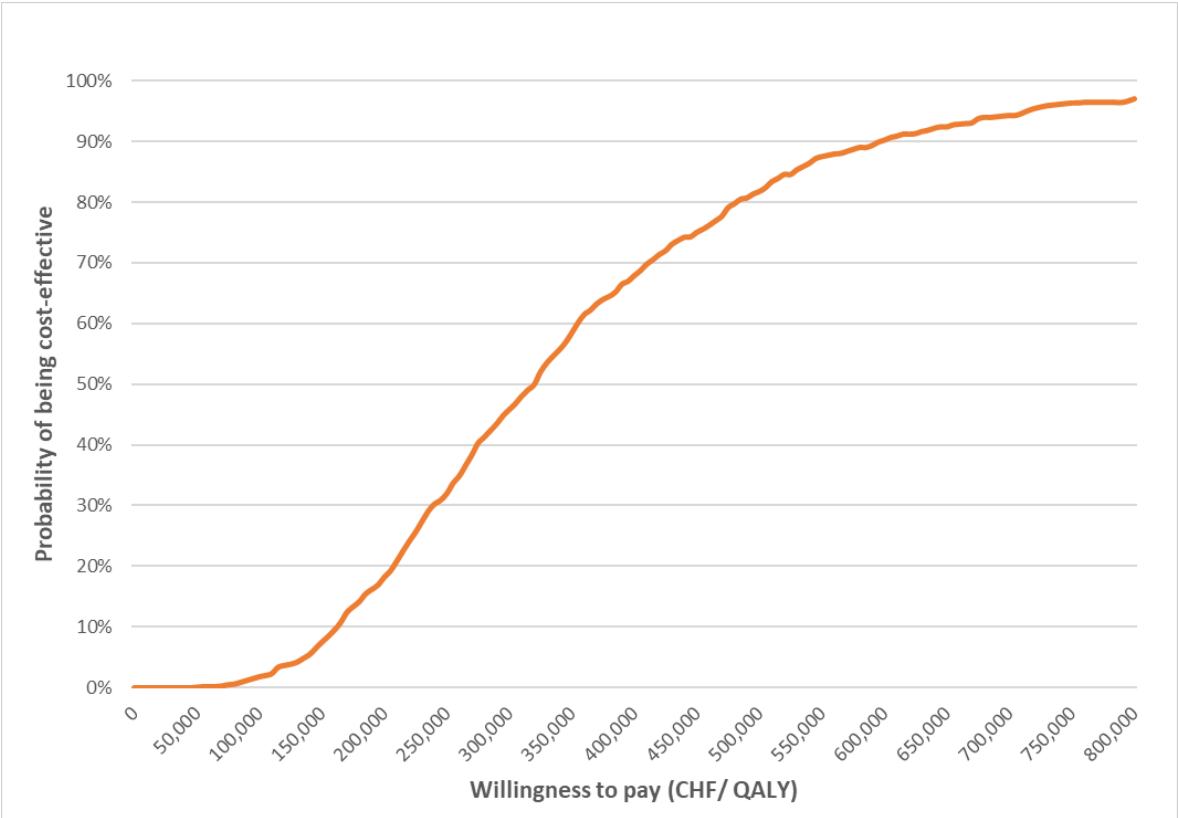
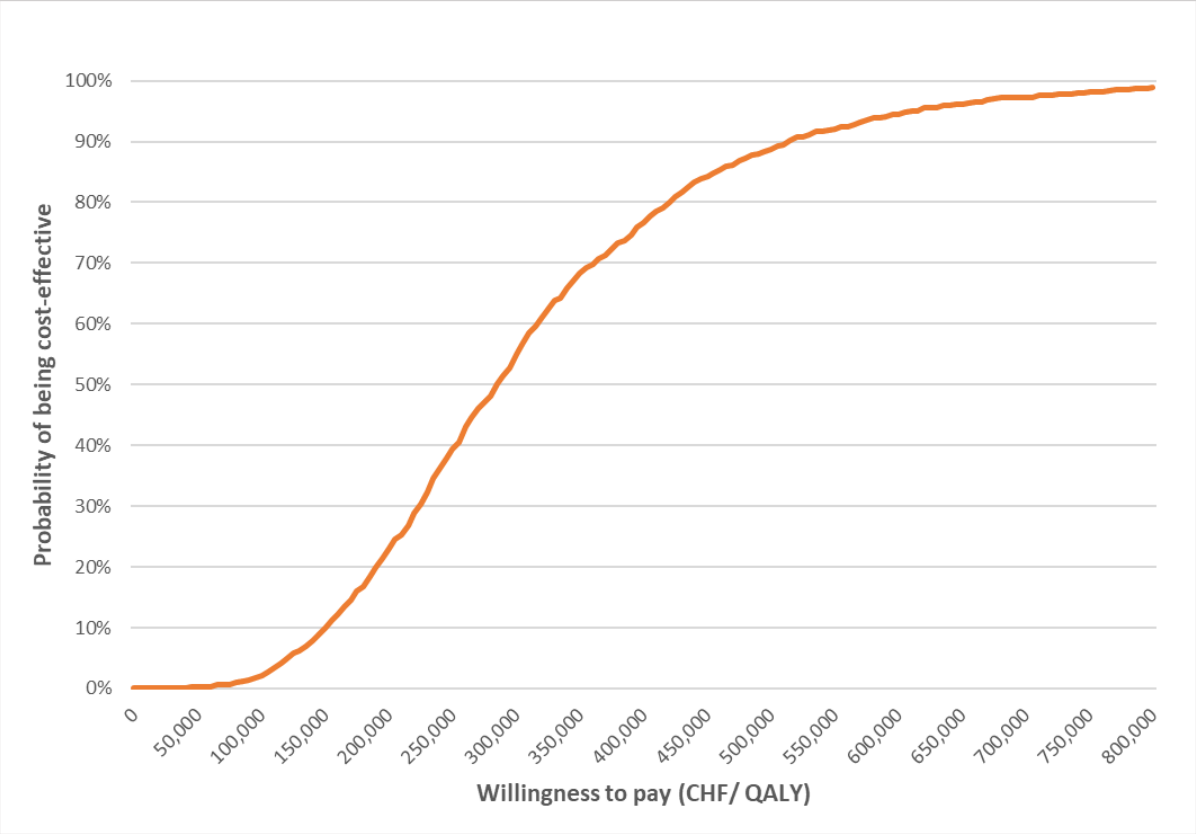
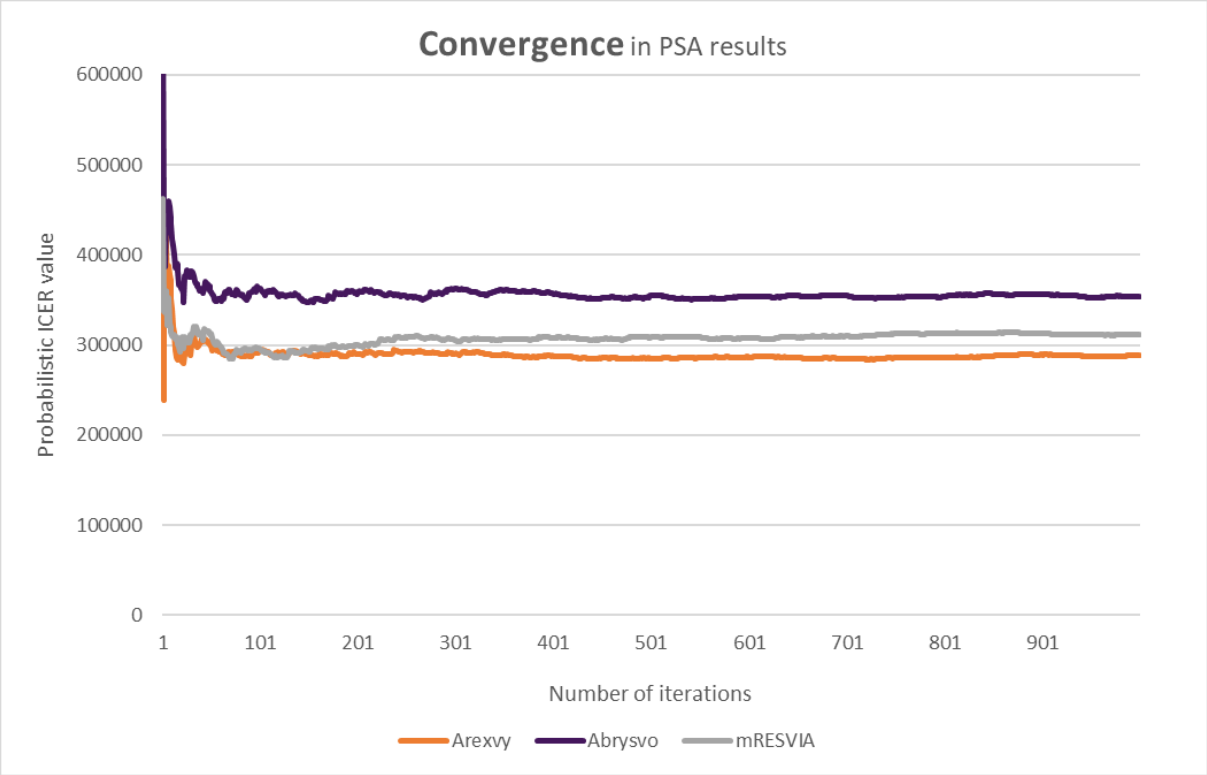


Figure 23. Cost-effectiveness acceptability curve mRNA-1345 (Subjects aged between ≥60 and <75 years at high risk of complications)



To test the convergence of probabilistic results, a visual inspection of ***Figure 24*** was conducted. In this figure, the number of Monte Carlo simulations in the PSA (i.e., iterations) is mentioned on the x-axis while the probabilistic ICER values are placed on the y-axis. Stability can be recognised in probabilistic ICER values of approximately CHF 290'000-350'000 from around 500 iterations onwards as depicted by the flat horizontal lines. Therefore, 1'000 iterations were deemed sufficient to obtain stable PSA results.

Figure 24. Convergence test PSA results



9.1.4 One-way sensitivity analysis

Figure 25 to ***Figure 27*** present the OWSA tornado diagrams of the 3 RSV vaccines in the population subjects aged ≥75 years. The spread of each bar reflects the possible ICER range at upper and lower values of one specific parameter, holding all other parameters constant. The costs of the vaccine had the highest impact on the ICER. Secondly, the infection rate (i.e. probability of RSV-ARI in adults) had substantial impact on the ICERs of RSVPreF3, RSVpreF and mRNA-1345. When infection rates increase, the effects of the vaccines will be larger in absolute terms leading to higher incremental QALYs and lower ICERs for RSVPreF3, RSVpreF and mRNA-1345. Furthermore, decay of vaccine efficacy in the second year, vaccine efficacy, GP tariff for vaccine administration, probability of a hospitalization due to RSV-ALTRI and the pre-season utility estimate of medically attended subjects were in the third, fourth, fifth, sixth and seventh ranks of parameters with the highest impact on the results.

Figure 25. Tornado diagram of One-Way Sensitivity analysis RSVPreF3 (Subjects aged ≥75 years)

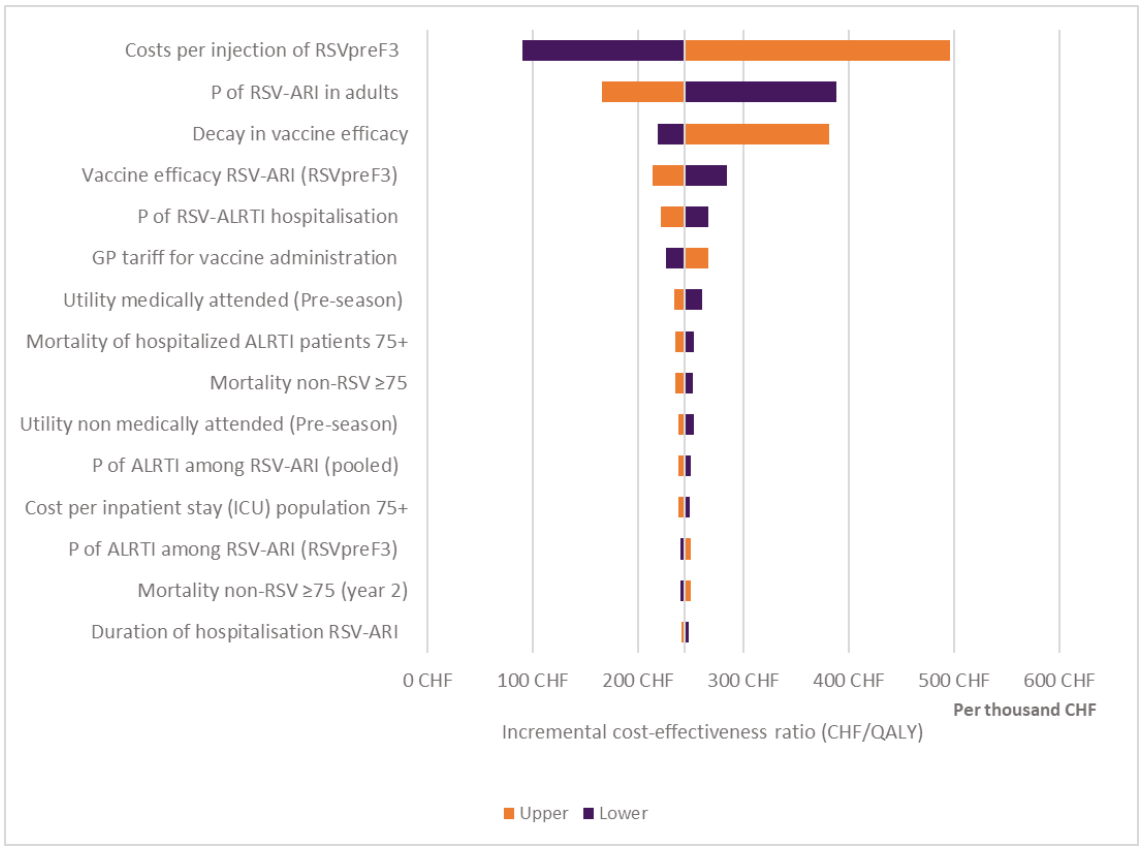


Figure 26. Tornado diagram of One-Way Sensitivity analysis RSVpreF (Subjects aged ≥75 years)

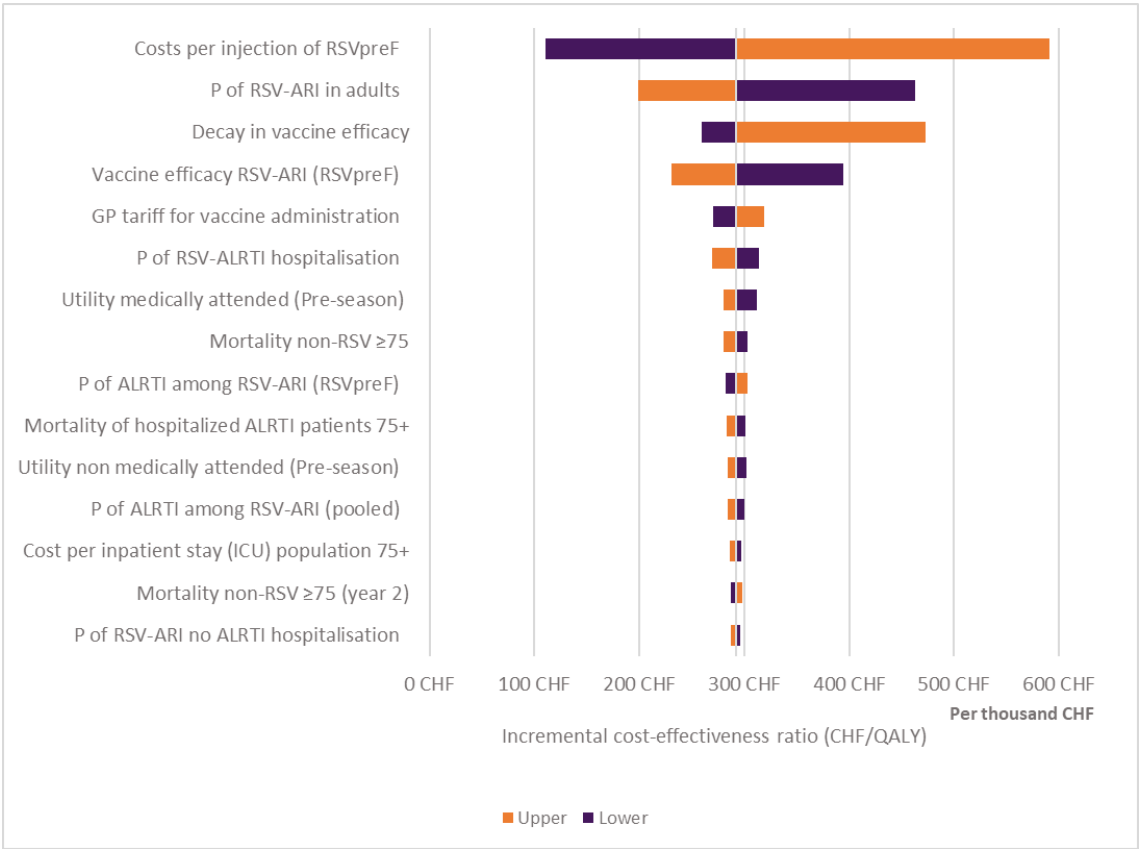
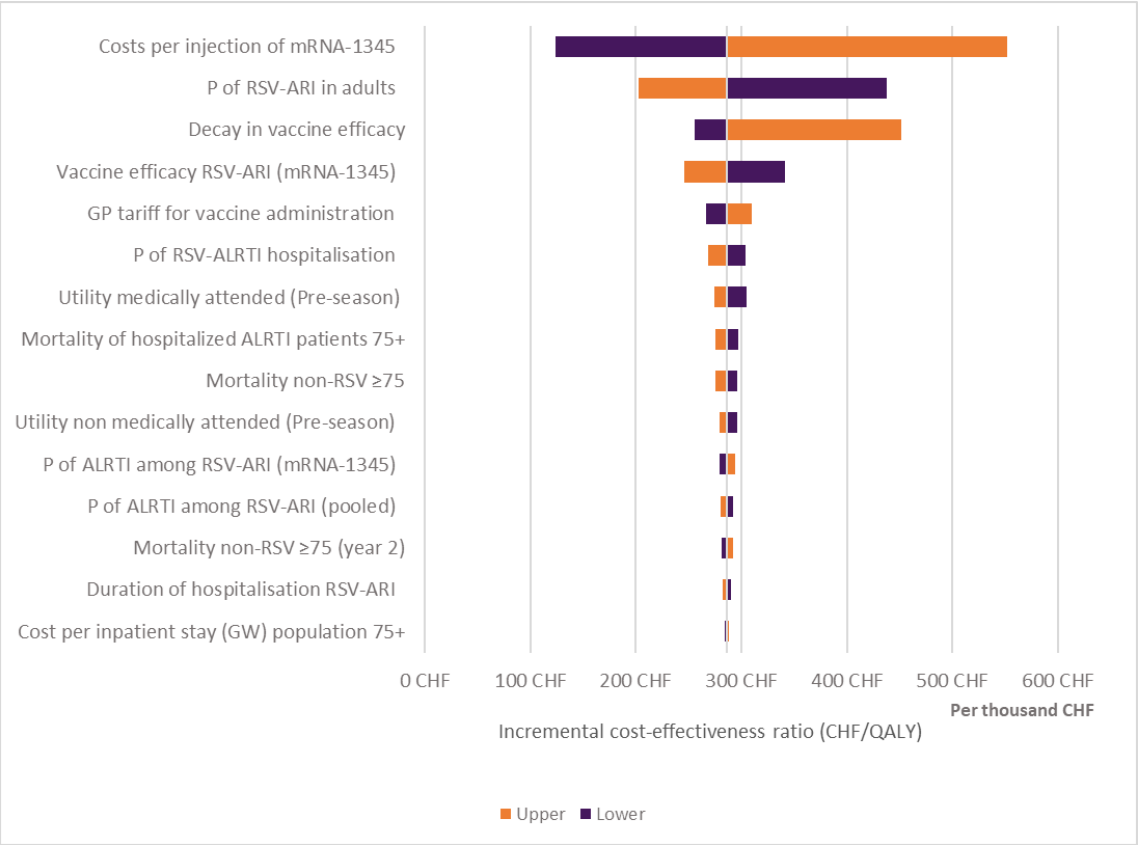


Figure 27. Tornado diagram of One-Way Sensitivity analysis mRNA-1345 (Subjects aged ≥75 years)



The OWSA tornado diagrams for subjects aged between ≥60 and <75 years at high risk of complications are depicted in ***Figure 28*** to ***Figure 30***. Analogous to the diagrams in the first target population, the costs of the vaccine and the infection rate were the input parameters with the highest impact on the ICER. Furthermore, parameters appearing in the third, fourth, fifth and sixth rank were similar to the first target population.

Figure 28. Tornado diagram of One-Way Sensitivity analysis RSVPreF3 (Subjects aged between ≥60 and <75 years at high risk of complications)

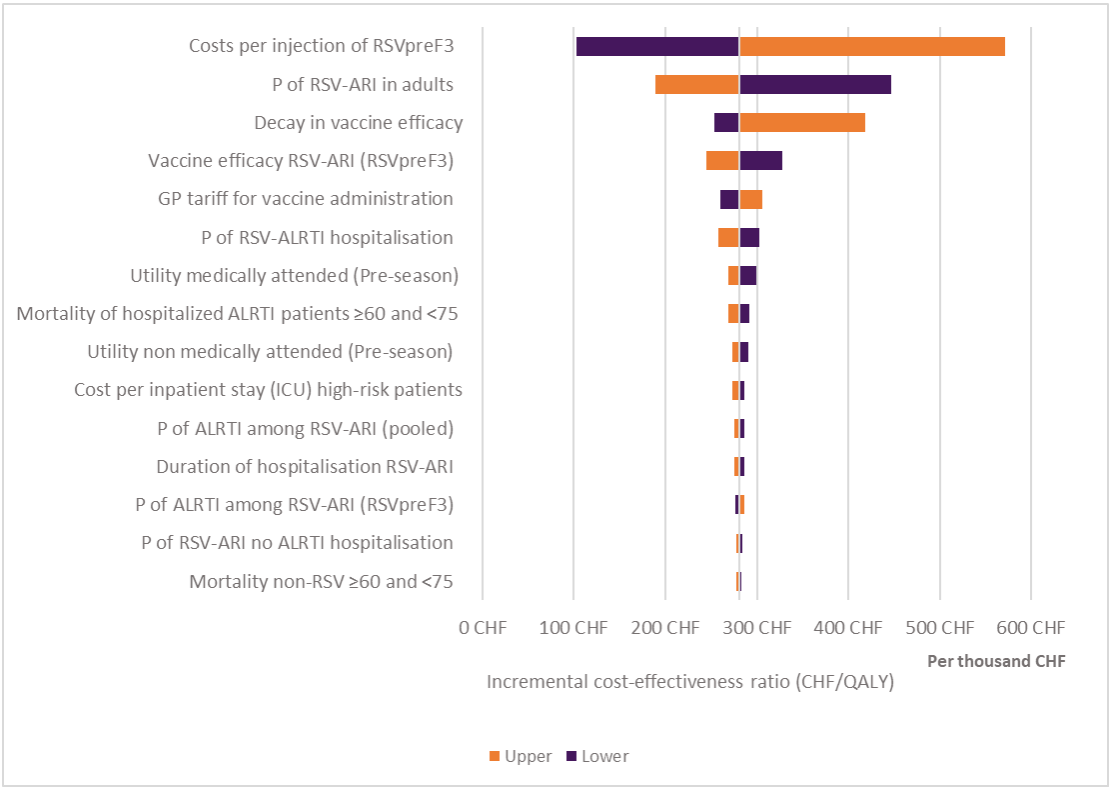


Figure 29. Tornado diagram of One-Way Sensitivity analysis RSVpreF (Subjects aged between ≥60 and <75 years at high risk of complications)

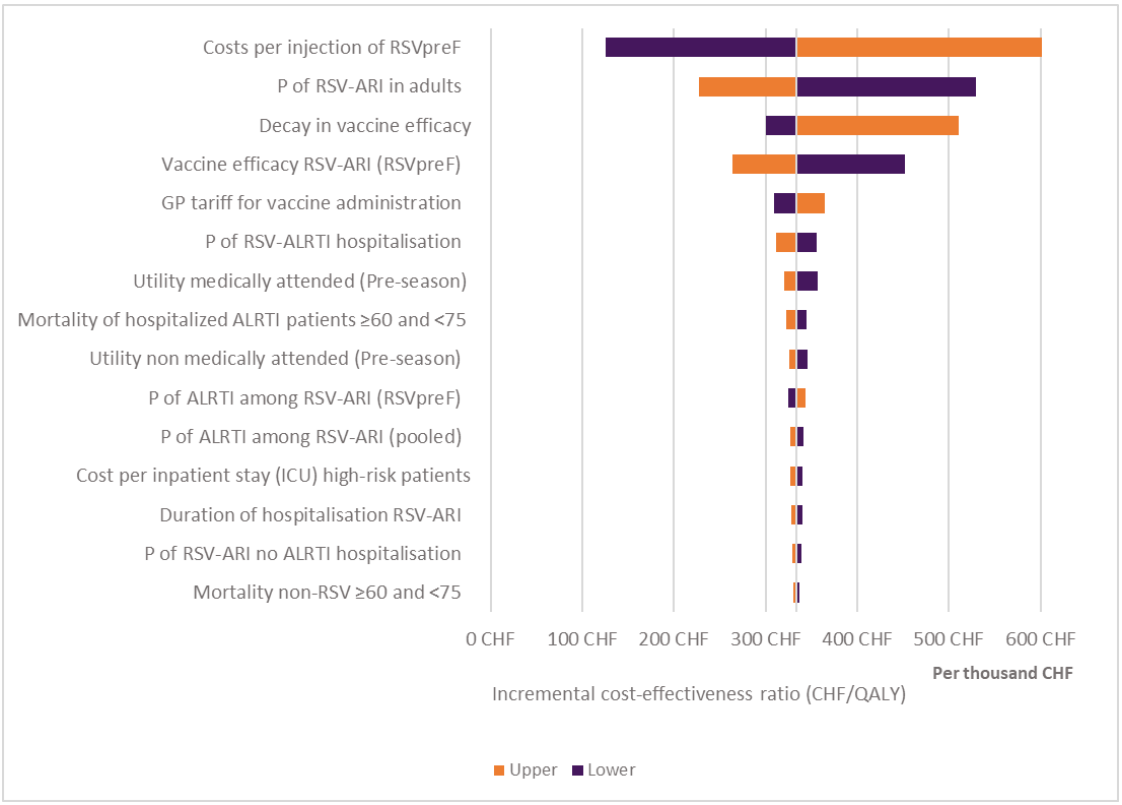
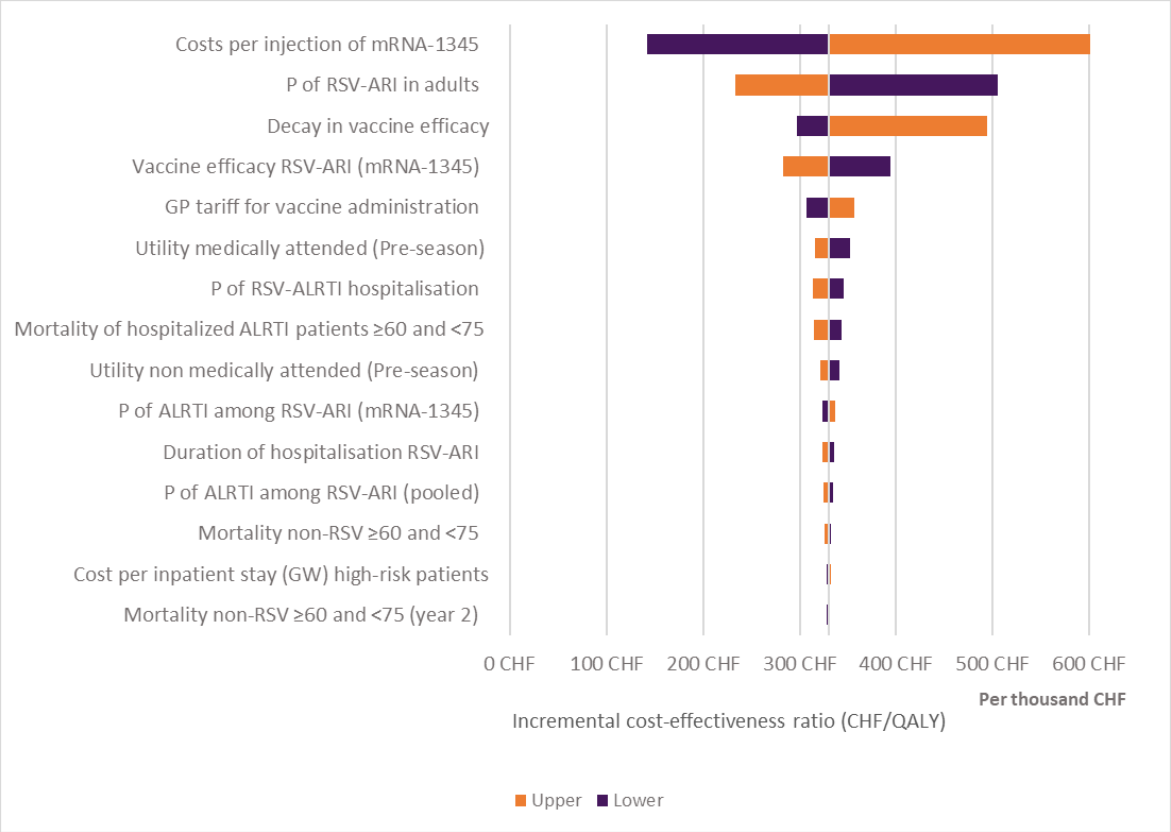


Figure 30. Tornado diagram of One-Way Sensitivity analysis mRNA-1345 (Subjects aged between ≥60 and <75 years at high risk of complications)



9.1.5 Budget impact analysis

The budget impact for the 2 target populations over a period of 2 years with a vaccination coverage of 37.5% is presented in

Table 19. The reimbursement of RSV vaccines is associated with a budget impact of CHF 80.58 million, CHF 81.58 million, and CHF 80.91 million over a period of 2 years in the population of subjects aged ≥75 years, and CHF 12.83 million, CHF 13.0 million, and CHF 12.89 million for the population of subjects aged between ≥60 and <75 years at high risk of complications for RSVPreF3, RSVpreF, and mRNA-1345 respectively. RSVpreF has the highest budget impact while RSVPreF3 has the lowest in both populations. The budget impact is mainly associated to the vaccination costs.

Table 19. Outcomes of budget impact analysis base case

Treatment	RSVPreF3	RSVpreF	mRNA-1345	No prophylaxis
Subjects aged ≥75 years				
Total costs 2025-2026	CHF 89'344'693	CHF 90'352'784	CHF 89'677'656	CHF 8'763'201
Costs of Vaccination	CHF 87'111'419	CHF 87'111'419	CHF 87'111'419	-
Healthcare costs	CHF 2'233'274	CHF 3'241'365	CHF 2'566'236	CHF 8'763'201
Budget impact	CHF 80'581'491	CHF 81'589'582	CHF 80'914'454	-
Annual average budget impact	CHF 40'290'746	CHF 40'794'791	CHF 40'457'227	-
Subjects aged between ≥60 and <75 years at high risk of complications				
Total costs 2025-2026	CHF 14'280'301	CHF 14'446'765	CHF 14'335'153	CHF 1'441'959
Costs of Vaccination	CHF 13'928'962	CHF 13'928'962	CHF 13'928'962	-
Healthcare costs	CHF 351'339	CHF 517'803	CHF 406'191	CHF 1'441'959
Budget impact	CHF 12'838'341	CHF 13'004'806	CHF 12'893'194	-
Annual average budget impact	CHF 6'419'171	CHF 6'502'403	CHF 6'446'597	-

Abbreviations
CHF = Swiss franc
Notes
The vaccination costs include the costs of the vaccine and the vaccine administration costs. The vaccine coverage rate is assumed 37.5% for the base case.

Results of the scenario analyses for the budget impact are presented in ***Table 20***. The scenarios in which the vaccination coverage of 37.5% was increased to 50% and the vaccine price was increased to CHF 303 resulted in the largest budget impacts, while a vaccine price of CHF 103 resulted in the lowest budget impact.

Table 20. Outcomes of scenario analyses on budget impact

Treatment	RSVPreF3	RSVpreF	mRNA-1345
Subjects aged ≥75 years			

Base case	CHF 80’581’491	CHF 81’589’582	CHF 80’914’454
Vaccine price CHF 103	CHF 46’208’879	CHF 47’216’970	CHF 46’541’842
Vaccine price CHF 303	CHF 114’954’104	CHF 115’962’195	CHF 115’287’067
Other hospitalization costs	CHF 77’545’027	CHF 78’876’782	CHF 77’983’962
Vaccine coverage 50%	CHF 107’441’988	CHF 108’786’110	CHF 107’885’939
Time horizon one year	CHF 82’993’756	CHF 83’507’806	CHF 83’161’881
Subjects aged between ≥60 and <75 years at high risk of complications			
Base case	CHF 12’838’341	CHF 13’004’806	CHF 12’893’194
Vaccine price CHF 103	CHF 7’342’221	CHF 7’508’686	CHF 7’397’074
Vaccine price CHF 303	CHF 18’334’461	CHF 18’500’926	CHF 18’389’314
Other hospitalization costs	CHF 12’203’864	CHF 12’450’131	CHF 12’284’875
Vaccine coverage 50%	CHF 17’117’788	CHF 17’339’741	CHF 17’190’925
Time horizon one year	CHF 13’234’775	CHF 13’317’623	CHF13’261’775

Abbreviations
CHF = Swiss franc
Notes
The vaccine coverage rate is assumed 37.5% for the base case.

The annual average budget impact was calculated over 4 and 6 years to reflect on the increase in size of the target populations. Since it is expected that the sizes of the target populations are going to increase in the coming years the number of vaccinations and therefore the costs are going to increase. In

Table 21 the results shown are calculated by estimating the budget impact for each round of vaccination (i.e. year one, year 3 and year 5) by calculating the undiscounted costs per person and then multiplied by the number of subjects that will receive the vaccine using the vaccination coverage rate of 37.5% as in the base case as presented in ***Section 8.2.2***. Consequently, the annual average over 4 years is calculated by summing the costs generated in the first 2 vaccination rounds and then dividing by 4, while for the annual budget impact over 6 years the costs generated in the first 3 vaccination rounds are summed and then are divided by 6. The results show that with the increase in the number of subjects receiving the vaccine, the annual average also shows an increase. For the population aged ≥75 years the annual average budget impact for the 3 vaccines in the base case is calculated at CHF 40.29 million for RSVPreF3, CHF 40.79 million for RSVpreF, and CHF 40.45 million for mRNA-1345, while over 4 years the annual average budget impact is CHF 41.08 million, CHF 41.59 million, and CHF 41.25 million, and for 6 years the annual average budget impact is CHF 41.69 million, CHF 42.21 million, and CHF 41.88 million for each for the 3 vaccines respectively. Accordingly, for the population aged between ≥60 and <75 years at high risk

of complications the annual average budget impact for the 3 vaccines in the base case is estimated at CHF 4.41 million for RSVPreF3, CHF 6.50 million for RSVpreF, and CHF 6.44 million for mRNA-1345, while over 4 years the annual average budget impact is CHF 6.60 million, CHF 6.69 million, and CHF 6.63 million, and for 6 years the annual average budget impact is CHF 6.78 million, CHF 6.87 million, and CHF 6.81 million for each for the 3 vaccines respectively.

Table 21. Average annual budget impact for 4 and 6 years

Treatment	RSVPreF3	RSVpreF	mRNA-1345
Subjects aged ≥75 years			
Over 4 years	CHF 41’082’465	CHF 41’596’415	CHF 41’252’217
Over 6 years	CHF 41’692’443	CHF 42’214’024	CHF 41’864’716
Subjects aged between ≥60 and <75 years at high risk of complications			
Over 4 years	CHF 6’604’977	CHF 6’690’618	CHF 6’633’197
Over 6 years	CHF 6’783’533	CHF 6’871’489	CHF 6’812’516

10. Discussion

The present health economic evaluation estimated the cost-effectiveness and budget impact of vaccination against RSV compared to no prophylaxis or standard of care for the population of subjects aged ≥75 years and for subjects aged between ≥60 and <75 years at high risk of complications. In this section, the main strengths, limitations and evidence gaps of this health economic evaluation are discussed.

A systematic review of clinical evidence for RSV vaccination was performed using a pragmatic approach (e.g. the title/abstract and full-text selection were done by one researcher in close collaboration with a second researcher instead of in duplicate), since results mainly served as input for the health economic model. The search focused on RCTs evaluating RSVpreF, RSVPreF3 and mRNA-1345 compared to placebo, no prophylaxis or standard of care in older adults using RSV-related events as outcome. The systematic literature search conducted in PubMed (MEDLINE), Embase.com and Cochrane Library resulted in 5 publications presenting interim analyses of 3 ongoing RCTs evaluating the vaccine efficacy of RSVpreF, RSVPreF3 or mRNA-1345. The systematic review for this economic evaluation was aimed at the vaccine efficacy of the individual RSV vaccines. RCT evidence was found for the 3 RSV vaccines of interest. Three recently published systematic reviews reported pooled vaccine efficacy for RSV vaccines. [103–105] The 3 ongoing RCTs were international trials, including European countries, with a comparable study design and the overall risk of bias for the outcomes reported in the RCTs was “some concerns”. All 3 trials included adults aged ≥60 years. Proportions of patients with at least one high-risk condition varied between trials from 30 to 50%. Three publications reported on the vaccine efficacy against RSV-related acute respiratory illness/disease after 1 RSV season, which varied between 62.1% and 71.7%. [54–56] For RSVPreF3 a second prespecified interim analysis was published reporting on the vaccine efficacy of RSVPreF3 over 2 RSV seasons. In addition, a post-hoc analysis for RSVPreF3 was identified presenting the vaccine efficacy in subjects aged ≥60 years at high risk of complications defined as at least one condition of interest (i.e. cardiorespiratory condition (COPD, asthma, chronic respiratory/pulmonary disease, CHF) or endocrine/metabolic condition (diabetes type1/2, advanced liver/renal disease). None of the trial populations were representative for the populations defined for the current health economic evaluation in terms of age and risk of complications (i.e. subjects aged ≥75 years and subjects aged between ≥60 and <75 years at high risk of complications), since the age of the overall study population was ≥60 years and the stratification in age groups was not exactly in line with the defined age groups of the populations of interest (i.e. no age threshold of 75 years was reported). In addition, the vaccine efficacy estimates for subgroups were presented for different age and high-risk groups, were too uncertain to use as input for the model due to the low number of events and number of subjects within the different subgroups. Therefore, the vaccine efficacy for acute respiratory illness/disease for the overall population aged ≥60 years for the 3 RSV vaccines (62.1% for RSVpreF, 71.7% for RSVPreF3 and 68.4% for mRNA-1345) was assumed to be equal and representative for all age and risk groups. [54–56] This assumption was

discussed with a clinical expert, who indicated that vaccine efficacy was expected not to differ by age and number of co-morbidities.

A systematic literature search for the costs, cost-effectiveness and budget impact was conducted to identify studies with relevant information on inputs and outcomes. Of the 9 studies that were identified for the full-text review, only 3 studies were found in line with the predefined criteria and reporting on the cost-effectiveness of RSVpreF, RSVPreF3 and mRNA-1345. None of the studies were conducted for the Swiss setting. Two studies reported cost-effectiveness analyses conducted in the US and Canada that aimed to determine the range of price-per-dose (PPD) for RSVpreF and RSVPreF3 to be considered cost-effective given a certain willingness-to-pay threshold. In the US study the vaccines were found to be cost-effective for PPD of around $120 using a willingness to pay (WTP) of $95,000/QALY. [59] For Canada the PPD was reported to be maximum $140 to $160 for a WTP of $50,000/QALY. [60] The third study reported on the cost-effectiveness of RSVpreF and RSVPreF3 from the Hong-Kong perspective. [61] For the base-case analysis the vaccine price was benchmarked to the US RSV vaccine prices at 4 levels (25%, 50%, 75%, 100%). The cost-effectiveness estimates strongly depended on the vaccine price and RSV attack rate. Comparison of the present study results with the published studies showed that the gain in QALYs in the published studies ranged between 0.00049 and 0.00065 per person, while in the current study the QALY gains were higher, between 0.00071 to 0.00096 per person, but in the same order of magnitude. Differences can be explained by the use of different input parameters. In the study of Wang et al, 2023 for example, which is most comparable to the current study because this study also used a decision-tree model, the percentage of RSV-ALRTI among all RSV infections was assumed lower (16%) than in the current study (26 to 50%). This implies that by preventing RSV infections, more RSV-ALRTI are avoided resulting in larger gains in QALYs. Because of higher vaccine prices the current study resulted in higher ICERs than the US and Canadian study.

The cost-effectiveness model structure for the present health economic evaluation was informed based on previously published models. Decision tree models and discrete event simulation were the most commonly used type of models to evaluate RSV vaccination. Because discrete event simulation models would require patient-level data and are more complex and time-consuming to build, a decision tree model was chosen for the present study. Because the current model had to be based on published input data only and the time horizon for the analyses was short (2 years), a decision tree model was considered an appropriate model structure for the current analysis. A Markov model could have been an alternative option but was considered less relevant because of the short time horizon. The simplicity of the decision-tree model was an advantage, but also had some limitations. First, the economic model was static, which implied that there was a constant rate at which susceptible older adults became infected, and herd protection was not incorporated in the model. Secondly, immunisation among patients was not included, implying that individuals that had been previously infected did not face a lower probability of being infected in the second year. Lower RSV infection rates in the second year among previously infected subjects would have resulted in a lower effect of the vaccine in the second year and higher ICERs.

One of the main strengths of the present health economic evaluation is that the vaccine efficacy was based on a systematic review for RCTs reporting on the efficacy of RSV vaccination. In addition, the model structure and inputs were informed by a systematic review for costs, cost-effectiveness and budget impact of RSV vaccination. A second strength of the model is that the model makes a distinction between RSV-ARIs resulting in ALRTI and RSV-ARIs, not evolving in LRTI. Because the impact of LRTI is more severe, the model also captures the effect of the vaccines on different types of infections. Finally, all model assumptions and inputs are validated by a clinical expert.

The vaccine prices for Switzerland are currently not yet available. Therefore, the price of the vaccines was assumed equal for all vaccines and based on a German source, CHF 203. Using this price, the ICERS for the different vaccine types varied between CHF 244'266/QALY and CHF 292'263/QALY for the population aged ≥75 years and CHF 277'767/QALY and CHF 330'556/QALY for the population aged between ≥60 and <75 years at high risk of complications. Scenario analyses showed that increasing the vaccine prices with minus and plus CHF 100 would decrease or increase the ICERS with about CHF 100'000 per QALY gained, respectively, showing that the cost-effectiveness results were strongly dependent on the vaccine price. This was also confirmed by the one-way sensitivity analyses that showed that vaccine price was the parameter with the highest impact on the results. The budget impact analysis resulted in estimates of around CHF 80 million for all 3 vaccines over 2 years (about CHF 40 million/year) for the population aged ≥75 years. Results for the population aged between ≥60 and <75 years at high risk of complications were lower around CHF 13 million over 2 years (about 6.5 million per year). Results didn't differ much between the different types of vaccines, but overall estimates were strongly dependent on the vaccine costs as shown by scenario analyses.

The model analyses required making several other assumptions. For 2 out of 3 vaccine types, vaccine efficacy data was only available for one season/year, while based on the recommendation of one RSV vaccination per 2 years, the model would require vaccine efficacy data for the first and second year. In the base-case analysis a decay of about 19% was used based on the study of Ison et al 2024 reporting the vaccine efficacy in the first and second season. [58] A scenario analysis was performed using no decay in the second year. The ICERs reported for this scenario resulted in a decrease of the ICERs with about 10-12%.

The RSV infection risk for the comparator group was based on a meta-analysis of Shi et al 2019 reporting a pooled estimate based on 9 community-based studies that reported the RSV-ARI incidence. [25] This was preferred over using the infection risk observed in the trials, because the trials ran during the COVID pandemic and associated restrictions could have influenced the RSV infection risk. The impact of using the infection rate observed in the trials was explored in a scenario analysis. Under detection is very common in RSV in older adults. If RSV infection rates are higher in reality, the ICERs for the vaccines might be overestimated in the current analysis.

The analyses included 2 populations, the population of subjects aged ≥75 years and subjects aged between ≥60 and <75 years at high risk of complications. Due to a lack of specific data for adults with high risk of complications it was not possible to specify all parameters separately for this second target population. Therefore, the majority of parameters were assumed equal to the first population except for the RSV-related mortality and background mortality (due to the lower age of the second population) and medication use. The expert expected the vaccine efficacy and infection risk to be the same for subjects aged between ≥60 and <75 years at high risk of complications. According to the expert, differences between the target population are centered around the consequences of an RSV infection, which could be more severe in high-risk patients aged between ≥60 and <75 years compared to subjects aged ≥75 years. As a result of a lack of data specific for the second target population (i.e. probability to develop RSV-ALRTI, risk for hospitalization, division GW/ICU and risk for RSV-mortality) the results for this population should be interpreted with caution.

11. Conclusion

The present health economic evaluation provided evidence for the vaccine efficacy for RSVPreF3, RSVpreF, and mRNA-1345 for one single dose and one RSV season based on interim analyses of ongoing clinical trials. The reported vaccine efficacy estimates were used as input in the newly developed health economic model to estimate the cost-effectiveness of vaccination against RSV versus no prophylaxis over a two-year time horizon in accordance with the current recommendations for RSV vaccination in Switzerland. Results showed that vaccination for prophylaxis of RSV is likely to generate additional QALYs and additional costs compared to no prophylaxis, which is current standard of care. Out of the vaccines under evaluation, RSVPreF3, RSVpreF, and mRNA-1345, RSVPreF3 resulted in the lowest ICERs, while RSVpreF was the one with the highest ICERs, but the differences across the vaccine types were small. ICERs for subjects aged ≥ 60 and <75 years at high risk for complications were somewhat higher than for subjects aged ≥ 75 years. Vaccine prices and the RSV infection rates were the parameters with the highest impact on the ICERs. The budget impact analyses that were conducted for each vaccine separately showed that RSVPreF3 had the lowest budget impact and RSVpreF the highest, but the differences were small. Also, for the budget impact analysis the main driver for the increased costs was the vaccine price. Because the current analyses are based on interim estimates for vaccine efficacy, cost-effectiveness results might change when the final vaccine efficacy estimates become available. Results for the subjects aged ≥ 60 and <75 years at high risk for complications should be interpreted with caution, because due to a lack of data it was not possible to specify all parameters separately for this second target population, although the clinical expert indicated that consequences of an RSV infection are more severe in this group.

12. References

1. Shi T, Denouel A, Tietjen AK, et al. Global Disease Burden Estimates of Respiratory Syncytial Virus-Associated Acute Respiratory Infection in Older Adults in 2015: A Systematic Review and Meta-Analysis. *J Infect Dis* 2020; 222: S577–S583.

2. Stucki M, Lenzin G, Agyeman PK, et al. Inpatient burden of respiratory syncytial virus (RSV) in Switzerland, 2003 to 2021: an analysis of administrative data. *Eurosurveillance* 2024; 29: 2400119.

3. Cong B, Dighero I, Zhang T, et al. Understanding the age spectrum of respiratory syncytial virus associated hospitalisation and mortality burden based on statistical modelling methods: a systematic analysis. *BMC Med* 2023; 21: 224.

4. Swissmedic 2019 © Copyright. Public Summary SwissPAR – Arexvy®, https://www.swissmedic.ch/swissmedic/en/home/ueber-uns/publikationen/public-summary-swiss-par/public-summary-swiss-par-arexvy.html (accessed 24 October 2024).

5. Alfano F, Bigoni T, Caggiano FP, et al. Respiratory Syncytial Virus Infection in Older Adults: An Update. *Drugs Aging* 2024; 41: 487–505.

6. Impfempfehlungen gegen Erkrankungen mit dem Respiratorischen Synzytial-Virus (RSV). BAG-Bulletin 47.

7. World Health Organization. Guidelines on the quality, safety and efficacy of respiratory syncytial virus vaccines. 2019, (https://www .who .int/ docs/ default -source/ biologicals/ ecbs/ rsv -guidelines -post -ecbs .pdf?sfvrsn= e9176411_2).

8. Nam HH, Ison MG. Respiratory syncytial virus infection in adults. *BMJ* 2019; l5021.

9. Korsten K, Adriaenssens N, Coenen S, et al. Burden of respiratory syncytial virus infection in community-dwelling older adults in Europe (RESCEU): an international prospective cohort study. *Eur Respir J* 2021; 57: 2002688.

10. Bosch W, Speiser LJ, Wi C-I, et al. Incidence of Respiratory Syncytial Virus in Community-Dwelling Adults Aged 18–64 Years Over 2 Seasons, 2022–2024, in a North American Community. *Open Forum Infectious Diseases* 2024; 11: ofae597.

11. Branche AR, Saiman L, Walsh EE, et al. Incidence of Respiratory Syncytial Virus Infection Among Hospitalized Adults, 2017–2020. *Clinical Infectious Diseases* 2022; 74: 1004–1011.

12. Hall CB. Nosocomial Respiratory Syncytial Virus Infections: The ‘Cold War’ Has Not Ended. *Clinical Infectious Diseases* 2000; 31: 590–596.

13. Hall CB, Douglas RG. Modes of transmission of respiratory syncytial virus. *The Journal of Pediatrics* 1981; 99: 100–103.

14. Belperio JA, Weigt SS, Fishbein MC, et al. Chronic Lung Allograft Rejection: Mechanisms and Therapy. *Proceedings of the American Thoracic Society* 2009; 6: 108–121.

15. Broberg EK, Waris M, Johansen K, Snacken R, Penttinen P. Seasonality and geographical spread of respiratory syncytial virus epidemics in 15 European countries, 2010 to 2016. Euro Surveill. 2018;23(5):pii=17-00284, https://www.eurosurveillance.org/content/10.2807/1560- 7917.ES.2018.23.5.17-00284.

16. Wald TG, Miller BA, Shult P, et al. Can Respiratory Syncytial Virus and Influenza A be Distinguished Clinically in Institutionalized Older Persons? *J American Geriatrics Society* 1995; 43: 170–174.

17. Scholz S, Dobrindt K, Tufts J, et al. The Burden of Respiratory Syncytial Virus (RSV) in Germany: A Comprehensive Data Analysis Suggests Underdetection of Hospitalisations and Deaths in Adults 60 Years and Older. *Infect Dis Ther* 2024; 13: 1759–1770.

18. Falsey AR, Walsh EE. Respiratory Syncytial Virus Infection in Elderly Adults: *Drugs & Aging* 2005; 22: 577–587.

19. Falsey AR, McCann RM, Hall WJ, et al. Evaluation of Four Methods for the Diagnosis of Respiratory Syncytial Virus Infection in Older Adults. *J American Geriatrics Society* 1996; 44: 71–73.

20. Englund JA, Cohen RA, Bianco V, et al. Evaluation of Clinical Case Definitions for Respiratory Syncytial Virus Lower Respiratory Tract Infection in Young Children. *Journal of the Pediatric Infectious Diseases Society* 2023; 12: 273–281.

21. Alfano F, Bigoni T, Caggiano FP, et al. Respiratory Syncytial Virus Infection in Older Adults: An Update. *Drugs Aging* 2024; 41: 487–505.

22. Villanueva D-DH, Arcega V, Rao M. Review of respiratory syncytial virus infection among older adults and transplant recipients. *Therapeutic Advances in Infection* 2022; 9: 20499361221091413.

23. Falsey AR, Hennessey PA, Formica MA, et al. Respiratory Syncytial Virus Infection in Elderly and High-Risk Adults. *N Engl J Med* 2005; 352: 1749–1759.

24. Jansen AGSC, Sanders EAM, Hoes AW, et al. Influenza- and respiratory syncytial virus-associated mortality and hospitalisations. *Eur Respir J* 2007; 30: 1158–1166.

25. Shi T, Denouel A, Tietjen AK, et al. Global Disease Burden Estimates of Respiratory Syncytial Virus–Associated Acute Respiratory Infection in Older Adults in 2015: A Systematic Review and Meta-Analysis. *The Journal of Infectious Diseases* 2020; 222: S577–S583.

26. Nguyen-Van-Tam JS, O'Leary M, Martin ET, et al. Burden of respiratory syncytial virus infection in older and high-risk adults: a systematic review and meta-analysis of the evidence from developed countries. *Eur Respir Rev* 2022; 31: 220105.

27. Bundesamt für Gesundheit (BAG). Respiratorisches-Synzytial-Virus (RSV), https://www.bag.ad-min.ch/bag/de/home/krankheiten/krankheiten-im-ueberblick/rsv.html (accessed 14 June 2024).

28. Osei-Yeboah R, Spreeuwenberg P, Del Riccio M, et al. Estimation of the Number of Respiratory Syncytial Virus–Associated Hospitalizations in Adults in the European Union. *The Journal of Infectious Diseases* 2023; 228: 1539–1548.

29. Pfizer Laboratories Div Pfizer Inc. ABRYSVO® (Respiratory Syncytial Virus Vaccine) for injection, for intramuscular use Initial U.S. Approval: 2023, https://labeling.pfizer.com/ShowLabeling.aspx?id=19589#section-2 (accessed 2 January 2025).

30. Falsey AR, Williams K, Gymnopoulou E, et al. Efficacy and Safety of an Ad26.RSV.preF–RSV preF Protein Vaccine in Older Adults. *N Engl J Med* 2023; 388: 609–620.

31. European Commission approves expanded age indication for GSK's Arexvy, the first respiratory syncytial virus (RSV) vaccine for adults aged 50-59 at increased risk | GSK, https://www.gsk.com/en-gb/media/press-releases/european-commission-approves-

expanded-age-indication-for-gsk-s-arexvy-the-first-respiratory-syncytial-virus-rsv-vaccine-for-adults-aged-50-59-at-increased-risk/ (2024, accessed 28 October 2024).

32. GlaxoSmithKline. AREXVY (Respiratory Syncytial Virus Vaccine, Adjuvanted) for injectable suspension, for intramuscular use, https://gskpro.com/content/dam/global/hcpportal/en_US/Prescribing_Information/Arexvy/pdf/AREXVY.PDF (2023).

33. Swathi M. Arexvy: A Comprehensive Review of the Respiratory Syncytial Virus Vaccine for Revolutionary Protection. *Viral Immunology* 2024; 37: 12–15.

34. ModernaTX. MRESVIATM (Respiratory Syncytial Virus Vaccine) Injectable suspension, for intramuscular use, https://www.fda.gov/media/179005/download (2024).

35. Moderna Receives U.S. FDA Approval for RSV Vaccine mRESVIA(R), https://investors.modernatx.com/news/news-details/2024/Moderna-Receives-U.S.-FDA-Approval-for-RSV-Vaccine-mRESVIAR/default.aspx (accessed 28 October 2024).

36. Vaccinations in Switzerland. *Expatica Switzerland*, https://www.expatica.com/ch/healthcare/healthcare-basics/vaccinations-in-switzerland-134305/ (accessed 23 October 2024).

37. Zimmermann C, Jusufoska M, Tolic J, et al. Pharmacists' approaches to vaccination consultations in Switzerland: a qualitative study comparing the roles of complementary and alternative medicine (CAM) and biomedicine. *BMJ Open* 2023; 13: e074883.

38. Which types of vaccines against Covid-19 are currently relevant for Switzerland?, https://naturalsciences.ch/id/vdxEH (accessed 23 October 2024).

39. Arexvy | European Medicines Agency (EMA), https://www.ema.europa.eu/en/medicines/human/EPAR/arexvy (2023, accessed 24 October 2024).

40. Abrysvo | European Medicines Agency (EMA), https://www.ema.europa.eu/en/medicines/human/EPAR/abrysvo (2023, accessed 24 October 2024).

41. mResvia | European Medicines Agency (EMA), https://www.ema.europa.eu/en/medicines/human/EPAR/mresvia (2024, accessed 24 October 2024).

42. Ministerie van Volksgezondheid W en S. Advies - wel of niet vergoeden RSVPreF3-vaccin (Arexvy®) voor bepaalde patiënten met verhoogd risico op ziekte door RS-virus - Werkagenda - Zorginstituut Nederland, https://www.zorginstituutnederland.nl/werkagenda/infectieziekten/gvs-advies-rsvpref3-vaccin-arexvy-voor-bepaalde-patienten-met-hoog-risico-op-ziekte-door-rs-virus (2024, accessed 24 October 2024).

43. Addo M, Cornely O, Denkinger M, et al. RSV vaccination strategies for high-risk patients 2023: a collaborative position paper by leading German medical societies and organizations. *Infection* 2024; 52: 285–288.

44. AREXVY Coverage | AREXVY (Respiratory Syncytial Virus Vaccine, Adjuvanted), https://arexvyhcp.com/practice-education/coverage/ (accessed 24 October 2024).

45. Savings & Support | ABRYSVO® (Respiratory Syncytial Virus Vaccine), https://www.abrysvo.com/savings-and-support (accessed 24 October 2024).

46. 2024 Reimbursement Codes, https://reimbursement.modernatx.com/2024-reimbursement-codes/ (accessed 24 October 2024).

47. AREXVY (Vaccin du Virus Respiratoire Syncytial (VRS) (recombinant, avec adjuvant)) - Virus Respiratoire Syncytial (VRS). *Haute Autorité de Santé*, https://www.has-

sante.fr/jcms/p_3538266/fr/arexvy-vaccin-du-virus-respiratoire-syncytial-vrs-recombinant-avec-adjuvant-virus-respiratoire-syncytial-vrs (accessed 24 October 2024).

48. France Adds Pfizer's Abrysvo to Reimbursed Medicines List, https://www.navlin-daily.com/article/22786/france-adds-pfizer-s-abrysvo-to-reimbursed-medicines-list (accessed 24 October 2024).

49. RSV vaccination of older adults: information for healthcare practitioners. *GOV.UK*, https://www.gov.uk/government/publications/respiratory-syncytial-virus-rsv-programme-information-for-healthcare-professionals/rsv-vaccination-of-older-adults-information-for-healthcare-practioners (accessed 24 October 2024).

50. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023), www.training.cochrane.org/handbook (2023).

51. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019; l4898.

52. Risk of bias tools - robvis (visualization tool), https://www.riskofbias.info/welcome/robvis-visualization-tool.

53. Evers S, Goossens M, de Vet H, et al. Criteria list for assessment of methodological quality of economic evaluations: Consensus on Health Economic Criteria. *Int J Technol Assess Health Care* 2005; 21: 240–245.

54. Papi A, Ison MG, Langley JM, et al. Respiratory Syncytial Virus Prefusion F Protein Vaccine in Older Adults. *N Engl J Med* 2023; 388: 595–608.

55. Walsh EE, Pérez Marc G, Zareba AM, et al. Efficacy and Safety of a Bivalent RSV Prefusion F Vaccine in Older Adults. *N Engl J Med* 2023; 388: 1465–1477.

56. Wilson E, Goswami J, Baqui AH, et al. Efficacy and Safety of an mRNA-Based RSV PreF Vaccine in Older Adults. *N Engl J Med* 2023; 389: 2233–2244.

57. Feldman RG, Antonelli-Incalzi R, Steenackers K, et al. Respiratory Syncytial Virus Prefusion F Protein Vaccine Is Efficacious in Older Adults With Underlying Medical Conditions. *Clinical Infectious Diseases* 2024; 78: 202–209.

58. Ison MG, Papi A, Athan E, et al. Efficacy and Safety of Respiratory Syncytial Virus (RSV) Prefusion F Protein Vaccine (RSVPreF3 OA) in Older Adults Over 2 RSV Seasons. *Clinical Infectious Diseases* 2024; 78: 1732–1744.

59. Moghadas SM, Shoukat A, Bawden CE, et al. Cost-effectiveness of Prefusion F Protein-based Vaccines Against Respiratory Syncytial Virus Disease for Older Adults in the United States. *Clinical Infectious Diseases* 2024; 78: 1328–1335.

60. Shoukat A, Bawden CE, Röst G, et al. Impact and cost-effectiveness analyses of vaccination for prevention of respiratory syncytial virus disease among older adults in Ontario: A Canadian Immunization Research Network (CIRN) study. *Vaccine* 2024; 42: 1768–1776.

61. Wang Y, Fekadu G, You JHS. Comparative Cost-Effectiveness Analysis of Respiratory Syncytial Virus Vaccines for Older Adults in Hong Kong. *Vaccines* 2023; 11: 1605.

62. Moghadas SM, Shoukat A, Bawden CE, et al. Cost-effectiveness of Prefusion F Protein-based Vaccines Against Respiratory Syncytial Virus Disease for Older Adults in the United States. *Clin Infect Dis* 2023; 78: 1328–1335.

63. Wilson E, Goswami J, Baqui AH, et al. Efficacy and Safety of an mRNA-Based RSV PreF Vaccine in Older Adults. *New England Journal of Medicine* 2023; 389: 2233–2244.

64. Papi A, Ison MG, Langley JM, et al. Respiratory Syncytial Virus Prefusion F Protein Vaccine in Older Adults. *New England Journal of Medicine* 2023; 388: 595–608.

65. Walsh EE, Perez-Marc G, Zereba A, et al. Efficacy and Safety of a Bivalent RSV Prefusion F Vaccine in Older Adults | New England Journal of Medicine, https://www.nejm.org/doi/10.1056/NEJMoa2213836?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed (2023, accessed 26 November 2024).

66. Switzerland. *datadot*, http://data.who.int/countries/756 (accessed 22 November 2024).

67. MonAM Swiss Monitoring System of Addiction and Noncommunicable Diseases, https://ind.obsan.admin.ch/en/monam (accessed 12 May 2024).

68. Bundesamt für Statistik. Demografische Bilanz nach Alter. STAT-TAB – interaktive Tabellen (BFS), https://www.pxweb.bfs.admin.ch/pxweb/de/px-x-0102020000_103/px-x-0102020000_103/px-x-0102020000_103.px/ (accessed 5 December 2024).

69. O'Mahony JF, Newall AT, Rosmalen J van. Dealing with Time in Health Economic Evaluation: Methodological Issues and Recommendations for Practice. *Pharmacoeconomics* 2015; 33: 1255.

70. CDC. Vaccines for Older Adults. *Respiratory Syncytial Virus Infection (RSV)*, https://www.cdc.gov/rsv/vaccines/older-adults.html (2024, accessed 17 October 2024).

71. Shoukat A, Bawden CE, Röst G, et al. Impact and cost-effectiveness analyses of vaccination for prevention of respiratory syncytial virus disease among older adults in Ontario: A Canadian Immunization Research Network (CIRN) study. *Vaccine* 2024; 42: 1768–1776.

72. Wang Y, Fekadu G, You JHS. Comparative Cost-Effectiveness Analysis of Respiratory Syncytial Virus Vaccines for Older Adults in Hong Kong. *Vaccines (Basel)* 2023; 11: 1605.

73. Postma MJ, Cheng C-Y, Buyukkaramikli NC, et al. Predicted Public Health and Economic Impact of Respiratory Syncytial Virus Vaccination with Variable Duration of Protection for Adults ≥60 Years in Belgium. *Vaccines (Basel)* 2023; 11: 990.

74. Herring WL, Zhang Y, Shinde V, et al. Clinical and economic outcomes associated with respiratory syncytial virus vaccination in older adults in the United States. *Vaccine* 2022; 40: 483–493.

75. Gessner BD. The cost-effectiveness of a hypothetical respiratory syncytial virus vaccine in the elderly. *Vaccine* 2000; 18: 1485–1494.

76. Zeevat F, Luttjeboer J, Paulissen JHJ, et al. Exploratory Analysis of the Economically Justifiable Price of a Hypothetical RSV Vaccine for Older Adults in the Netherlands and the United Kingdom. *J Infect Dis* 2022; 226: S102–S109.

77. Büyükkaramikli NC, Rutten-van Mölken MPMH, Severens JL, et al. TECH-VER: A Verification Checklist to Reduce Errors in Models and Improve Their Credibility. *Pharmacoeconomics* 2019; 37: 1391–1408.

78. Chen C, Liu X, Yan D, et al. Global influenza vaccination rates and factors associated with influenza vaccination. *Int J Infect Dis* 2022; 125: 153–163.

79. Falsey AR, McElhaney JE, Beran J, et al. Respiratory Syncytial Virus and Other Respiratory Viral Infections in Older Adults With Moderate to Severe Influenza-like Illness. *The Journal of Infectious Diseases* 2014; 209: 1873–1881.

80. Falsey AR, Walsh EE, Osborne RH, et al. Comparative assessment of reported symptoms of influenza, respiratory syncytial virus, and human metapneumovirus infection during hospitalization and post-discharge assessed by Respiratory Intensity and Impact Questionnaire. *Influenza Resp Viruses* 2022; 16: 79–89.

81. Marti J, Hall P, Hamilton P, et al. One-year resource utilisation, costs and quality of life in patients with acute respiratory distress syndrome (ARDS): secondary analysis of a randomised controlled trial. *j intensive care* 2016; 4: 56.

82. Mao Z, Li X, Korsten K, et al. Economic Burden and Health-Related Quality of Life of Respiratory Syncytial Virus and Influenza Infection in European Community-Dwelling Older Adults. *The Journal of Infectious Diseases* 2022; 226: S87–S94.

83. SwissDRG - Vergütung von Spitalleistungen nach leistungsorientierten Pauschalen, https://www.swissdrg.org/de (accessed 15 August 2023).

84. TARMED. Swiss National Tariff Catalogue, https://www.bag.admin.ch/bag/de/home/versicherungen/krankenversicherung/krankenversicherung-leistungen-tarife.html (accessed 12 May 2024).

85. Spezialitätenliste (SL) und Geburtsgebrechen-Spezialitätenliste (GGSL), https://www.spezialitätenliste.ch (accessed 12 May 2024).

86. Vonberg I. RSV-Schutzimpfung bei besonders gefährdeten Patientinnen und Patienten. *Deutsche Gesellschaft für Infektiologie*, https://www.dgi-net.de/rsv-schutzimpfung-bei-besonders-gefaehrdeten-patientinnen-und-patienten/ (2023, accessed 12 December 2024).

87. Vonberg I. RSV-Schutzimpfung bei besonders gefährdeten Patientinnen und Patienten. *Deutsche Gesellschaft für Infektiologie*, https://www.dgi-net.de/rsv-schutzimpfung-bei-besonders-gefaehrdeten-patientinnen-und-patienten/ (2023, accessed 12 December 2024).

88. Preisapo.de :: MRESVIA Injektionsdispersion i.e.Fertigspritze :: Ihre persönliche Versandapotheke. *Preisapo*, https://www.preisapo.de/mresvia-injektionsdispersion-i-e-fertigspritze-ml--19373637 (accessed 12 December 2024).

89. Havers FP, Whitaker M, Melgar M, et al. Burden of Respiratory Syncytial Virus–Associated Hospitalizations in US Adults, October 2016 to September 2023. *JAMA Netw Open* 2024; 7: e2444756.

90. Bundesamt für Statistik. Lebenserwartung, https://www.bfs.admin.ch/bfs/de/home/statistiken/bevoelkerung/geburten-todesfaelle/lebenserwartung.html (accessed 12 May 2024).

91. Tseng HF, Sy LS, Ackerson B, et al. Severe Morbidity and Short- and Mid- to Long-term Mortality in Older Adults Hospitalized with Respiratory Syncytial Virus Infection. *The Journal of Infectious Diseases* 2020; 222: 1298–1310.

92. Thomas RE, Lorenzetti DL. Interventions to increase influenza vaccination rates of those 60 years and older in the community. *Cochrane Database Syst Rev* 2018; 5: CD005188.

93. RESCEU – REspiratory Syncytial virus Consortium in EUrope, https://resc-eu.org/ (accessed 3 January 2025).

94. Mao Z, Li X, Korsten K, et al. Economic Burden and Health-Related Quality of Life of Respiratory Syncytial Virus and Influenza Infection in European Community-Dwelling Older Adults. *The Journal of Infectious Diseases* 2022; 226: S87–S94.

95. Conventional positive pressure ventilation or High Frequency Oscillatory Ventilation (HFOV) for adults with acute respiratory distress syndrome. *ISRCTN Registry*. DOI: 10.1186/ISRCTN10416500.

96. SNB data portal. *SNB data portal*, https://data.snb.ch/en/topics/ziredev/cube/devkua (accessed 10 January 2025).

97. Tarmed 01.09_BR (KVG) Online Browser, https://browser.tartools.ch/de/tarmed_kvg (accessed 10 January 2025).

98. BAG B für G. Analysenliste (AL), https://www.bag.admin.ch/bag/de/home/versicherungen/krankenversicherung/krankenversicherung-leistungen-tarife/Analysenliste.html (accessed 10 January 2025).

99. SwissDRG, https://www.swissdrg.org/de (accessed 12 May 2024).

100. Medstat-Regionen, https://www.bfs.admin.ch/bfs/de/home/statistiken/gesundheit/nomenklaturen/medsreg.html (accessed 10 January 2025).

101. tarifsuisse ag, https://tarifsuisse.ch (accessed 10 January 2025).

102. Caughey GE, Ramsay EN, Vitry AI, et al. Comorbid chronic diseases, discordant impact on mortality in older people: a 14-year longitudinal population study. *Journal of Epidemiology & Community Health* 2010; 64: 1036–1042.

103. Riccò M, Cascio A, Corrado S, et al. Efficacy of Respiratory Syncytial Virus Vaccination to Prevent Lower Respiratory Tract Illness in Older Adults: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Vaccines* 2024; 12: 500.

104. Wu Y, Lu Y, Bai Y, et al. Efficacy, Safety, and Immunogenicity of Subunit Respiratory Syncytial Virus Vaccines: Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Vaccines* 2024; 12: 879.

105. Zeng B, Liu X, Yang Q, et al. Efficacy and safety of vaccines to prevent respiratory syncytial virus infection in infants and older adults: A systematic review and meta-analysis. *International Journal of Infectious Diseases* 2024; 146: 107118.

13. Appendices

A. Search strategy clinical systematic literature search

Table 22. PubMed (Medline)

Population	No search string
Intervention	"Respiratory Syncytial Virus Vaccines"[Mesh] OR RSV vaccin*[tiab] OR respiratory syncytial virus vaccin*[tiab] OR abrysvo[tiab] OR RSVpreF[tiab] OR pf-06928316[tiab] OR arexvy[tiab] OR RSVPreF3[tiab] OR gsk3844766a[tiab] OR mRESVIA[tiab] OR mRNA-1345[tiab] OR (("Respiratory Syncytial Virus Infections"[Mesh] OR respiratory syncytial virus infection*[tiab] OR RSV[tiab]) AND ("Vaccination"[Mesh] OR vaccin*[tiab]))
Comparator	No search string
Outcomes	No search string
Limits	*RCTs*[a] ((("randomized controlled trial"[pt] OR "controlled clinical trial"[pt] OR "randomized"[tiab] OR "placebo"[tiab]) OR ("clinical trials as topic"[mesh:noexp]) OR (randomly[tiab] OR trial[ti])) NOT (animals[mh] NOT humans[mh]))
	No conference abstracts and preprints NOT (congress[pt] OR preprint[pt])

Notes
a = Cochrane RCT sensitivity and precision maximising filter (2023 revision).

Table 23. Embase.com

Population	No search string	
Intervention	'respiratory syncytial virus vaccine'/exp OR (RSV NEXT vaccin*):ti,ab OR ('respiratory syncytial virus' NEXT vaccin*):ti,ab OR 'pf 06928316'/exp OR 'pf 06928316':ti,ab OR abrysvo:ti,ab OR RSVpreF:ti,ab OR 'gsk 3844766a'/exp OR 'gsk 3844766a':ti,ab OR arexvy:ti,ab OR RSVPreF3:ti,ab OR mRESVIA:ti,ab OR mRNA-1345:ti,ab OR (('respiratory syncytial virus infection'/exp OR ('respiratory syncytial virus' NEXT infection*):ti,ab OR RSV:ti,ab) AND ('Vaccination'/exp OR vaccin*:ti,ab))	
Comparator	No search string	
Outcomes	No search string	
Limits	*RCTs*[a]	
	1	'randomized controlled trial'/exp
	2	'controlled clinical trial'/de
	3	random*:ti,ab,tt
	4	'randomization'/de
	5	'intermethod comparison'/de
	6	placebo:ti,ab,tt
	7	(compare:ti,tt OR compared:ti,tt OR comparison:ti,tt)
	8	((evaluated:ab OR evaluate:ab OR evaluating:ab OR assessed:ab OR assess:ab) AND (compare:ab OR compared:ab OR comparing:ab OR comparison:ab))
	9	(open NEXT/1 label):ti,ab,tt
	10	((double OR single OR doubly OR singly) NEXT/1 (blind OR blinded OR blindly)):ti,ab,tt
	11	'double blind procedure'/de
	12	(parallel NEXT/1 group*):ti,ab,tt
	13	(crossover:ti,ab,tt OR 'cross over':ti,ab,tt)
	14	((assign* OR match OR matched OR allocation) NEAR/6 (alternate OR group OR groups OR intervention OR interventions OR patient OR patients OR subject OR subjects OR participant OR participants)):ti,ab,tt

	15	(assigned:ti,ab,tt OR allocated:ti,ab,tt)
	16	(controlled NEAR/8 (study OR design OR trial)):ti,ab,tt
	17	(volunteer:ti,ab,tt OR volunteers:ti,ab,tt)
	18	'human experiment'/de
	19	trial:ti,tt
	20	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19
	21	(((random* NEXT/1 sampl* NEAR/8 ('cross section*' OR questionnaire* OR survey OR surveys OR database or databases)):ti,ab,tt) NOT ('comparative study'/de OR 'controlled study'/de OR 'randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt OR 'randomly assigned':ti,ab,tt))
	22	('cross-sectional study'/de NOT ('randomized controlled trial'/exp OR 'controlled clinical study'/de OR 'controlled study'/de OR 'randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt OR 'control group':ti,ab,tt OR 'control groups':ti,ab,tt))
	23	('case control*':ti,ab,tt AND random*:ti,ab,tt NOT ('randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt))
	24	('systematic review':ti,tt NOT (trial:ti,tt OR study:ti,tt))
	25	(nonrandom*:ti,ab,tt NOT random*:ti,ab,tt)
	26	'random field*':ti,ab,tt
	27	('random cluster' NEAR/4 sampl*):ti,ab,tt
	28	(review:ab AND review:it) NOT trial:ti,tt
	29	('we searched':ab AND (review:ti,tt OR review:it))
	30	'update review':ab
	31	(databases NEAR/5 searched):ab
	32	((rat:ti,tt OR rats:ti,tt OR mouse:ti,tt OR mice:ti,tt OR swine:ti,tt OR porcine:ti,tt OR murine:ti,tt OR sheep:ti,tt OR lambs:ti,tt OR pigs:ti,tt OR piglets:ti,tt OR rabbit:ti,tt OR rabbits:ti,tt OR cat:ti,tt OR cats:ti,tt OR dog:ti,tt OR dogs:ti,tt OR cattle:ti,tt OR bovine:ti,tt OR monkey:ti,tt OR monkeys:ti,tt OR trout:ti,tt OR marmoset*:ti,tt) AND 'animal experiment'/de)
	33	('animal experiment'/de NOT ('human experiment'/de OR 'human'/de))
	34	#21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33
	35	#20 NOT #34
		No conference abstracts and preprints/select other publication types AND ([article]/lim OR [article in press]/lim OR [conference paper]/lim OR [conference review]/lim OR [data papers]/lim OR [editorial]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR [review]/lim OR [short survey]/lim)

Notes
a = Cochrane Highly Sensitive Search Strategy for identifying randomised trials in Embase (2023 revision); Embase.com format (adapted from Glanville 2019).

Table 24. Cochrane Library

Population	No search string
Intervention	[mh "Respiratory Syncytial Virus Vaccines"] OR (("RSV" NEXT vaccin*) OR ("respiratory syncytial virus" NEXT vaccin*) OR abrysvo OR RSVpreF OR pf-06928316 OR arexvy OR RSVPreF3 OR gsk3844766a OR mRESVIA OR mRNA-1345):ti,ab OR (([mh "Respiratory Syncytial Virus Infections"] OR ("respiratory syncytial virus" NEXT infection*):ti,ab OR RSV:ti,ab) AND ([mh Vaccination] OR vaccin*:ti,ab))
Comparator	No search string
Outcomes	No search string
Limits	*No conference abstracts and preprints* NOT (congress:pt OR preprint:pt)

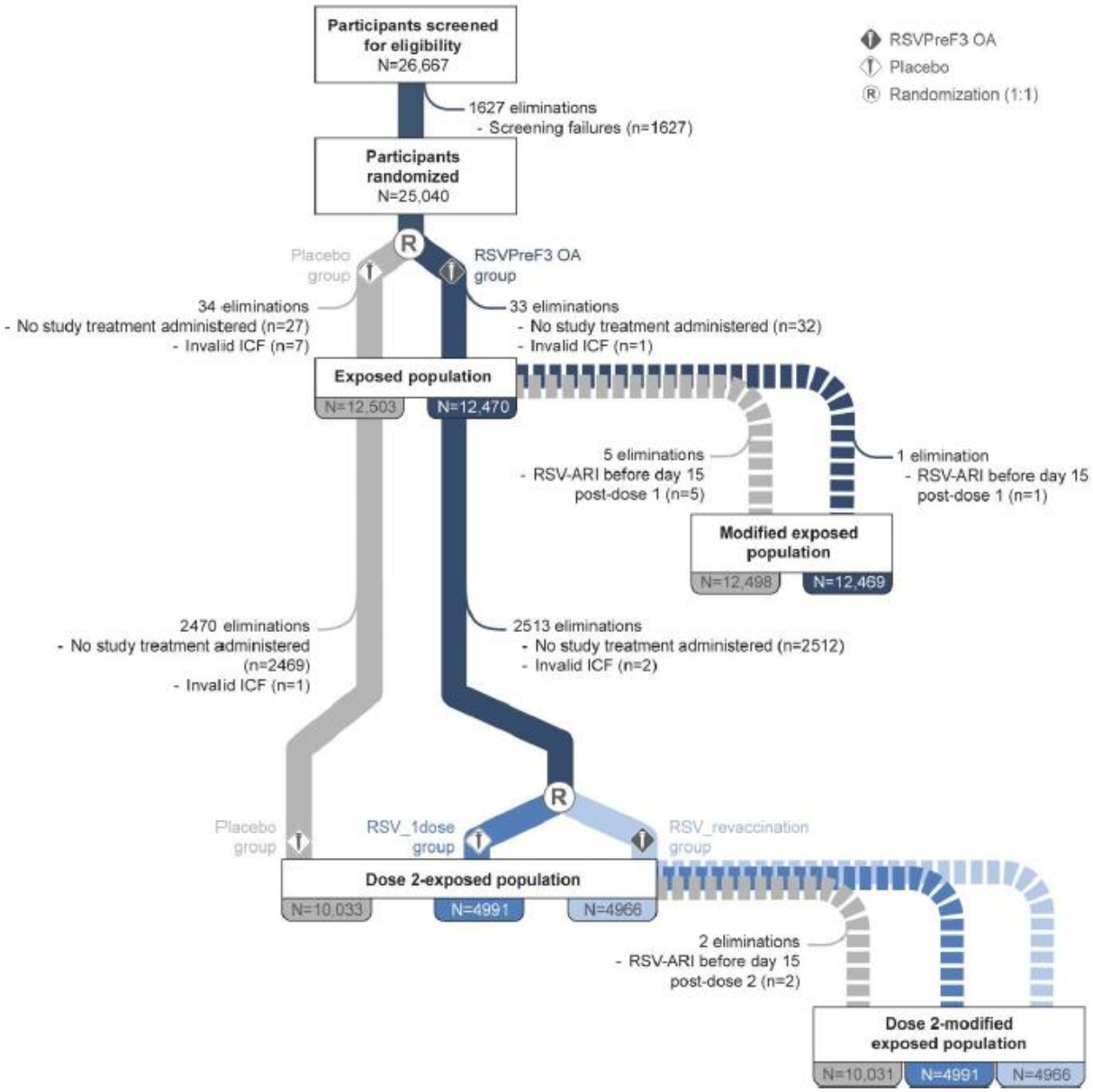
B. Excluded studies during full-text selection clinical systematic review

Table 25. Excluded studies found with the clinical systematic literature search

Reference	Reason for exclusion
Abbasi HQ, Oduoye MO. Revitalizing hope for older adults: The use of the novel Arexvy for immunization against respiratory syncytial virus. Health Sci Rep. 2023;6(10):e1648.	Narrative review
Awar M, Mylonakis E. In older adults, an AS01E-adjuvanted RSVPreF3 OA vaccine reduced RSV-related lower respiratory tract disease. Annals of Internal Medicine. 2023;176(6):JC62-JC3.	Irrelevant publication type (abstract)
Bouzid D, Visseaux B, Ferré VM, Peiffer-Smadja N, Le Hingrat Q, Loubet P. Respiratory syncytial virus in adults with comorbidities: an update on epidemiology, vaccines, and treatments. Clin Microbiol Infect. 2023;29(12):1538-50.	Narrative review
Curran D, Matthews S, Cabrera ES, Pérez SN, Breva LP, Rämet M, Helman L, Park DW, Schwarz TF, Melendez IMG, Schaefer A, Roy N, Stephan B, Molnar D, Kostanyan L, Powers JH 3rd, Hulstrøm V; Members of the AReSVi-006 Study Group. The respiratory syncytial virus prefusion F protein vaccine attenuates the severity of respiratory syncytial virus-associated disease in breakthrough infections in adults ≥60 years of age. Influenza Other Respir Viruses. 2024 Feb 3;18(2):e13236.	Outcomes out of scope
Falloon J, Yu J, Esser MT, Villafana T, Yu L, Dubovsky F, et al. An Adjuvanted, Postfusion F Protein-Based Vaccine Did Not Prevent Respiratory Syncytial Virus Illness in Older Adults. Journal of infectious diseases. 2017;216(11):1362-70.	Intervention out of scope (MEDI7510 vaccine)
Falsey AR, Walsh EE. Safety and immunogenicity of a respiratory syncytial virus subunit vaccine (PFP-2) in ambulatory adults over age 60. Vaccine. 1996 Sep;14(13):1214-8.	Intervention out of scope (PFP-2 vaccine)
Falsey AR, Hosman T, Bastian AR, Vandenberghe S, Chan EKH, Douoguih M, et al. Long-term efficacy and immunogenicity of Ad26.RSV.preF–RSV preF protein vaccine (CYPRESS): a randomised, double-blind, placebo-controlled, phase 2b study. Lancet infectious diseases. 2024.	Intervention out of scope (Ad26.RSV.preF-RSV vaccine)
Falsey AR, Williams K, Gymnopoulou E, Bart S, Ervin J, Bastian AR, et al. Efficacy and Safety of an Ad26.RSV.preF-RSV preF Protein Vaccine in Older Adults. New England journal of medicine. 2023;388(7):609-20.	Intervention out of scope (Ad26.RSV.preF-RSV vaccine)
Pang Y, Lu H, Cao D, Zhu X, Long Q, Tian F, et al. Efficacy, immunogenicity and safety of respiratory syncytial virus prefusion F vaccine: systematic review and meta-analysis. BMC Public Health. 2024;24(1):1244.	Systematic review
Riccò M, Cascio A, Corrado S, Bottazzoli M, Marchesi F, Gili R, et al. Efficacy of Respiratory Syncytial Virus Vaccination to Prevent Lower Respiratory Tract Illness in Older Adults: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Vaccines (Basel). 2024;12(5).	Systematic review
Simoes EA, Tan DH, Ohlsson A, Sales V, Wang EE. Respiratory syncytial virus vaccine: a systematic overview with emphasis on respiratory syncytial virus subunit vaccines. Vaccine. 2001;20(5):954-60.	Systematic review
Tenenbaum T, Liese J, Welte T, Rademacher J. Respiratory Syncytial Virus-Associated Respiratory Diseases in Children and Adults. Dtsch Arztebl Int. 2024;121(9):303-12.	Narrative review
Wu Y, Lu Y, Bai Y, Zhu B, Chang F, Lu Y. Efficacy, Safety, and Immunogenicity of Subunit Respiratory Syncytial Virus Vaccines: Systematic Review and Meta-Analysis of Randomized Controlled Trials. Vaccines (Basel). 2024;12(8).	Systematic review
Zeng B, Liu X, Yang Q, Wang J, Ren Q, Sun F. Efficacy and safety of vaccines to prevent respiratory syncytial virus infection in infants and older adults: A systematic review and meta-analysis. Int J Infect Dis. 2024;146:107118.	Systematic review
Zhu T, Zhang C, Yu L, Chen J, Qiu H, Lyu W, et al. The preventive effect of vaccine prophylaxis on severe respiratory syncytial virus infection: A meta-analysis. Virol Sin. 2015;30(5):371-8.	Systematic review

C. Supplement information Ison et al 2024

Figure 31. Flow of participants in the RCT of Ison et al 2024[58]



Abbreviations
ICF = informed consent form, N = number of participants, n = number of participants eliminated, placebo = group of participants randomised to receive placebo pre-season 1 and 2, R = randomisation (1:1), RSV = respiratory syncytial virus, RSV-ARI = RSV-related acute respiratory illness, RSV_1dose = group of participants who received a dose of RSV prefusion F protein-based vaccine (RSVPreF3 OA) pre-season 1 and were randomised to receive a placebo dose pre-season 2, RSVPreF3 OA = group of participants randomised to receive a dose of RSVPreF3 OA pre-RSV season 1, RSV_revaccination = group of participants who received a first dose of RSVPreF3 OA pre-season 1 and were randomised to receive a second RSVPreF3 OA dose (revaccination) pre-season 2.

D. Search strategy economic systematic literature search

Table 26. PubMed (Medline)

Population	No search string
Intervention	"Respiratory Syncytial Virus Vaccines"[Mesh] OR RSV vaccin*[tiab] OR respiratory syncytial virus vaccin*[tiab] OR abrysvo[tiab] OR RSVpreF[tiab] OR pf-06928316[tiab] OR arexvy[tiab] OR RSVPreF3[tiab] OR gsk3844766a[tiab] OR mRESVIA[tiab] OR mRNA-1345[tiab] OR (("Respiratory Syncytial Virus Infections"[Mesh] OR respiratory syncytial virus infection*[tiab] OR RSV[tiab]) AND ("Vaccination"[Mesh] OR vaccin*[tiab]))
Comparator	No search string
Outcomes	"Technology Assessment, Biomedical"[Mesh] OR "Cost-Benefit Analysis"[Mesh] OR "Quality-Adjusted Life Years"[Mesh] OR technology assessment*[tiab] OR economic evaluat*[tiab] OR economic value[tiab] OR cost-benefit*[tiab] OR cost-effectiv*[tiab] OR cost-efficien*[tiab] OR cost-efficac*[tiab] OR cost-minim*[tiab] OR cost-utilit*[tiab] OR cost-consequen*[tiab] OR budget impact analys*[tiab] OR quality-adjusted life-year*[tiab] OR quality-adjusted lifeyear*[tiab] OR qaly*[tiab] [a]
Limits	*No conference abstracts and preprints* NOT (congress[pt] OR preprint[pt])

Notes
a = The economic search filter is a customised search filter for economic outcomes, which has been developed together with an information specialist. Existing economic search filters were used as input.

Table 27. Embase.com

Population	No search string
Intervention	'respiratory syncytial virus vaccine'/exp OR (RSV NEXT vaccin*):ti,ab OR ('respiratory syncytial virus' NEXT vaccin*):ti,ab OR 'pf 06928316'/exp OR 'pf 06928316':ti,ab OR abrysvo:ti,ab OR RSVpreF:ti,ab OR 'gsk 3844766a'/exp OR 'gsk 3844766a':ti,ab OR arexvy:ti,ab OR RSVPreF3:ti,ab OR mRESVIA:ti,ab OR mRNA-1345:ti,ab OR (('respiratory syncytial virus infection'/exp OR ('respiratory syncytial virus' NEXT infection*):ti,ab OR RSV:ti,ab) AND ('Vaccination'/exp OR vaccin*:ti,ab))
Comparator	No search string
Outcomes	'biomedical technology assessment'/exp OR 'economic evaluation'/exp OR 'quality adjusted life year'/exp OR 'program cost effectiveness'/de OR ((technology NEAR/3 assessment*) OR (economic* NEAR/3 (evaluat* OR value)) OR ((cost OR costs) NEAR/3 (benefit* OR effectiv* OR efficien* OR efficac* OR minim* OR utilit* OR consequen*)) OR 'budget impact analys*':ti,ab OR (qualit* NEAR/3 adjust* NEAR/3 (life-year* OR lifeyear*)) OR qaly*):ab,ti [a]
Limits	*No conference abstracts and preprints/select other publication types* AND ([article]/lim OR [article in press]/lim OR [conference paper]/lim OR [conference review]/lim OR [data papers]/lim OR [editorial]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR [review]/lim OR [short survey]/lim)

Notes
a = The economic search filter is a customised search filter for economic outcomes, which has been developed together with an information specialist. Existing economic search filters were used as input.

Table 28. Cochrane Library

Population	No search string
Intervention	[mh "Respiratory Syncytial Virus Vaccines"] OR (("RSV" NEXT vaccin*) OR ("respiratory syncytial virus" NEXT vaccin*) OR abrysvo OR RSVpreF OR pf-06928316 OR arexvy OR RSVPreF3 OR gsk3844766a OR mRESVIA OR mRNA-1345):ti,ab OR (([mh "Respiratory Syncytial Virus Infections"] OR ("respiratory syncytial virus" NEXT infection*):ti,ab OR RSV:ti,ab) AND ([mh Vaccination] OR vaccin*:ti,ab))
Comparator	No search string
Outcomes	[mh "Technology Assessment, Biomedical"] OR [mh "Cost-Benefit Analysis"] OR [mh "Quality-Adjusted Life Years"] OR technology assessment*:ti,ab OR economic evaluat*:ti,ab OR economic value:ti,ab OR cost-benefit*:ti,ab OR cost-effectiv*:ti,ab OR cost-efficien*:ti,ab OR cost-efficac*:ti,ab OR cost-minim*:ti,ab OR cost-utilit*:ti,ab OR cost-consequen*:ti,ab OR budget impact analys*:ti,ab OR quality-adjusted life-year*:ti,ab OR quality-adjusted lifeyear*:ti,ab OR qaly*:ti,ab [a]

Limits	*No conference abstracts and preprints* NOT (congress:pt OR preprint:pt)

Notes
a = The economic search filter is a customised search filter for economic outcomes, which has been developed together with an information specialist. Existing economic search filters were used as input.

Table 29. Tufts Medical Centre Cost-Effectiveness Analysis Registry

Population	No search string
Intervention	keyword:("Respiratory Syncytial Virus" OR "RSV") AND keyword:("Vaccination" OR "vaccine")
Comparator	No search string
Outcomes	No search string
Limits	No search string

Table 30. CRD databases

Population	No search string
Intervention	(((RSV) OR (respiratory syncytial virus*)) AND (vaccin*))
Comparator	No search string
Outcomes	No search string
Limits	No search string

E. Excluded studies during full-text selection economic systematic review

Table 31. Excluded studies found in the economic systematic literature search

Title	Reason for exclusion
Crawford, R., Bailey, S., & Cornelissen, T. (2024). Cost-effectiveness of respiratory syncytial virus vaccines for adults. Canadian Journal of Health Technologies, 4(2).	Wrong study design
Gessner, B. D. (2000). The cost-effectiveness of a hypothetical respiratory syncytial virus vaccine in the elderly.	Wrong intervention
Herring, W. L., Zhang, Y., Shinde, V., Stoddard, J., Talbird, S. E., & Rosen, B. (2022). Clinical and economic outcomes associated with respiratory syncytial virus vaccination in older adults in the United States. Vaccine, 40(3), 483–493.	Wrong intervention
Kurai, D., Mizukami, A., Preckler, V., Verelst, F., Molnar, D., Matsuki, T., Ho, Y., & Igarashi, A. (2024). The potential public health impact of the respiratory syncytial virus prefusion F protein vaccine in people aged ≥60 years in Japan: Results of a Markov model analysis. Expert Review of Vaccines, 23(1), 303–311.	Wrong outcomes
Meijboom, M. J., Pouwels, K. B., Luytjes, W., Postma, M. J., & Hak, E. (2013). RSV vaccine in development: Assessing the potential cost-effectiveness in the Dutch elderly population. Vaccine, 31(52), 6254–6260.	Wrong intervention
Postma, M., Cheng, C.-Y., Buyukkaramikli, N., Hernandez Pastor, L., Vandersmissen, I., Van Effelterre, T., Openshaw, P., & Simoens, S. (2023). Predicted Public Health and Economic Impact of Respiratory Syncytial Virus Vaccination with Variable Duration of Protection for Adults ≥60 Years in Belgium. Vaccines, 11(5), 990.	Wrong intervention

F. Clinical expert interview

Interview economic analysis of RSV vaccines for older adults

Brief introduction

The project aims to estimate the cost-effectiveness of RSV vaccines in 2 different target populations:

1) Older adults aged ≥75 years

2) Adults between ≥60 and <75 years of age at high risk of complications.

The analysis will use a time horizon of 2 years, because an RSV vaccination is recommended every 2 years since one vaccination is estimated to provide at least 2 years of protection.

A literature review was performed to inform the vaccine efficacy for 3 different types of RSV vaccines: RSVpreF (Abrysvo®), RSVpreF3 (Arexvy®), mRNA-1345 (mRESVIA). For all RSV types, randomised controlled trials were found: the RENOIR, AReSVi-006 and ConquerRSV trial, respectively. All trials included adults aged ≥60 years. Proportions of patients with at least one high-risk condition varied between trials from 30 to 50%.

Vaccine efficacy

Because the populations in the vaccine efficacy trials are not completely in line with our target population for the economic analysis we need to make some assumptions. The vaccine efficacy

trials included adults aged ≥60 years of which 30-50% had more than one high-risk condition. The first target population for our analysis is defined as adults aged ≥75 years, the second target population as adults aged ≥60 years and <75 years of age at high risk of complications. Although the trials report vaccine efficacy estimates by subgroups, the number of cases per subgroup are very low and less reliable. In addition, 2 trials only report vaccine efficacy over one year/RSV season. One trial had a follow-up of 2 years/seasons.

Questions regarding vaccine efficacy:

- Would it be valid to assume that an RSV vaccine is equally effective for subjects aged ≥60 years, as for subjects aged ≥75 years?

- Would it be valid to assume that an RSV vaccine is equally effective for subjects aged ≥60 years with and without high risk of complications?

- Based on the one study for which data over 2 seasons were available, the vaccine efficacy seems to decrease with about 15-20% for the second season. Is this a realistic value or do you expect this to be lower/higher in daily practice?

- Vaccine coverage is still unknown for RSV. Would it be valid to assume that vaccine coverage for RSV will be the same as for influenza, 35-40%?

Economic analysis

To estimate all effects and costs for the different RSV vaccines compared to no prophylaxis a health economic model is developed. This model requires a lot of input data that are obtained from published literature, databases and registries. Inputs will as much as possible be based on the Swiss setting.

The figure below shows the structure of the model. As depicted in the figure below, elderly adults might get infected with RSV and contract an Acute Respiratory Syncytial Virus (RSV-ARI), or they might not get infected. Subsequently, the RSV infection can develop further into an Acute Lower Respiratory Tract Infection (ALRTI) or, the RSV cann9ot progress into an ALRTI (e.g., only an Upper Respiratory Tract Infection). For both options adults can be hospitalized and admitted to the General Ward or Intensive Care Unit. They can also receive outpatient care which consists of a visit to the General Practitioner, or they might not seek medical care. In case of a hospitalization, they might die from RSV. For all options adults might die due to non-RSV related causes

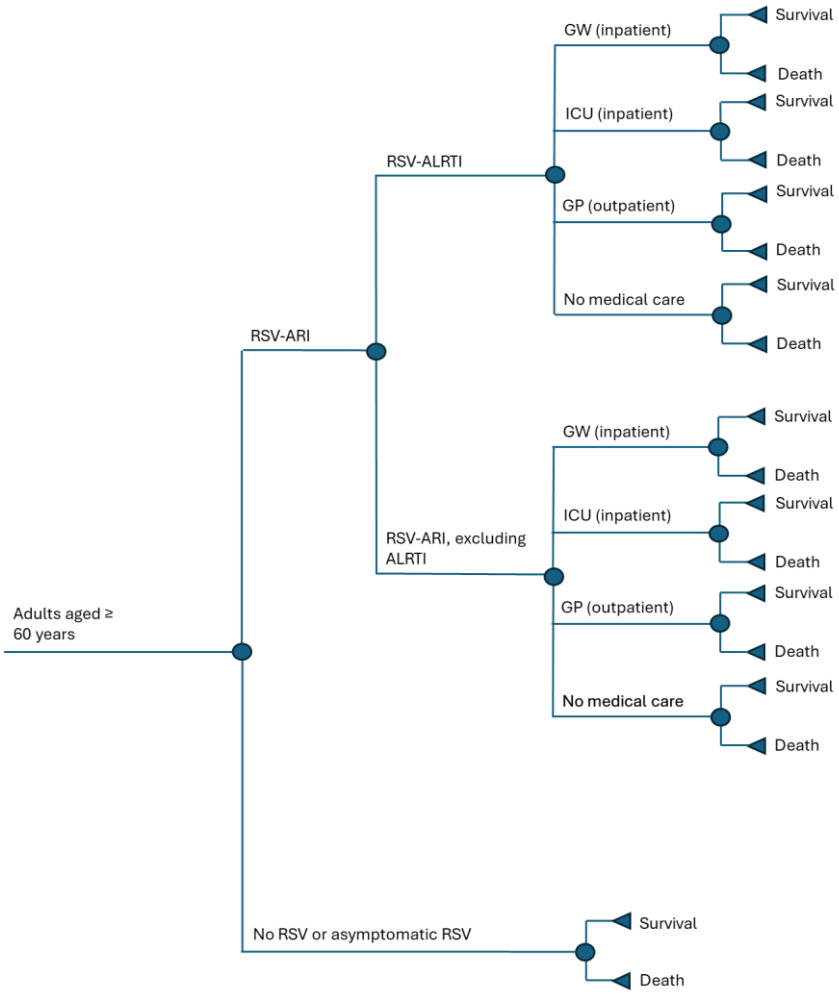


Figure 32. Health economic model for RSV vaccines

Questions regarding RSV occurrence

- Do you know any data source that reports annual RSV infection rates specifically for the Swiss setting?

- In the placebo-arms of the trials about 45% of the RSV-ARIs developed into RSV-ALRTI. Is this percentage representative for daily practice in adults aged ≥60 years?

- Is it more likely for adults at high risk for complications that RSV-ARIs develop into RSV-ALRTI (compared to healthy individuals ≥60 years)?

Resource use associated with RSV

Based on a target literature search the following table was composed regarding inputs for the different options in the health economic model.

Table 32. Resource use table

Type of infection	Probability	Type of care	Probability	Type of care	Proportion of patients	Resource use	Regime (suggestion from literature)
RSV-ALRTI	45%	Hospitalization	19.5%	GW (inpatient)	75%	-	-
				ICU (inpatient)	25%	-	-
		Outpatient	28%	GP (outpatient)		GP visit	One 25-minute consultation
						Antipyretic	Paracetamol 4000mg/day
						Cough suppressant	Dextromethorphan 20mg 4 times/ day
						Decongestant	Phenylephrine nasal 1% spray, 2 to 3 sprays in each nostril 4 times / day
						Systemic corticosteroid	prednisone (40 mg/day for 7 days)
						Bronchodilator	albuterol sulfate HFA (1 package with 60 puffs with 0.09 mg/puff)
						Antibiotic	amoxicillin (2,000 mg/day for 7 days) and cefuroxime (1,000 mg/day for 7 days)
		No medical care		-	-	-	-
RSV-ARI (no LRTI)	55%	Hospitalization		GW (inpatient)	75%	-	-
				ICU (inpatient)	25%	-	-
		Outpatient	28%	GP (outpatient)		GP visit	One 25-minute consultation
						Antipyretic	Paracetamol 4000mg/day
						Cough suppressant	Dextromethorphan 20mg 4 times/ day
						Decongestant	Phenylephrine nasal 1% spray, 2 to 3 sprays in each nostril 4 times / day
						Systemic corticosteroid (sometimes) (10%)	prednisone (40 mg/day for 7 days)
						Bronchodilator	albuterol sulfate HFA (1 package with 60 puffs with 0.09 mg/puff)
						Antibiotic	amoxicillin (2,000 mg/day for 7 days) and cefuroxime (1,000 mg/day for 7 days)
		No medical care		-	-	-	-

Questions regarding patients who receive inpatient care (ICU or GW)

- In a previously published study, the probability to be hospitalized for an RSV-ALRTI was assumed to be 19.5%. No source has been found for a hospitalization risk for RSV-ARI(noLRTI). Do you expect this risk to be equal, lower or higher than 19.5% for RSV-ARI(noLRTI)? And for adults at high risk of complications?

- 25% of RSV hospitalizations in Switzerland include ICU admittance. Is there a higher chance that RSV-ALRTI leads to an ICU admittance? If yes, how much higher? And for adults at high risk of complications?

- The probability to require outpatient care was reported to be 28% for RSV-ARIs. No source has been found for RSV-ALRTI. Do you expect this risk to be equal, lower or higher?

Questions regarding patients receiving outpatient care only (GP)

- How many GP visits do patients have on average if they receive outpatient care only? Min 2 times to 3 times (30 minutes) Please, specify for RSV-ARI(no LRTI) and RSV-ALRTI and for adults at high risk for complications.

- Is it valid to assume that patients that receive only outpatient care do not require any emergency department visits?

- During the GP visit(s), what medication (i.e., antipyretic, cough suppressant, decongestant, systemic corticosteroid, bronchodilator, antibiotic), is usually prescribed by the practitioner and along which regimens?
    - Does this regimen differ for adults with RSV-ARI(no LRTI) compared to RSV-ALRTI?
    - Does this regimen differ for adults at high risk for complications?

Question regarding RSV vaccine-related adverse events

- If patients experience (serious) adverse events from the vaccines (i.e., erythema, swelling, headache, fatigue, myalgia), would they receive additional care and what would that entail?

Question regarding the quality-of-life inputs for RSV patients

- In economic analyses the health-related quality of life is often expressed on a scale from 1 (perfect health) to 0 (death). Are the following average health-related quality of life values obtained from published literature plausible?
    - 0.58 for RSV hospitalized on the general ward
    - 0.40 for RSV hospitalized with an ICU visit
    - 0.74 for RSV requiring an outpatient visit
    - 0.83 for RSV not requiring care

G. Parameter values in the OWSA

Parameter	Base Value	Lower Value	Upper Value
P of RSV-ARI in adults	0.0067	0.004334	0.009569
VE RSV-ARI (RSVPreF3)	0.717	0.611002	0.822998
VE RSV-ARI (RSVpreF)	0.621	0.463003	0.778997
VE RSV-ARI (mRNA-1345)	0.684	0.571002	0.796998
P of ALRTI among RSV-ARI (pooled)	0.544681	0.480706	0.607932
P of ALRTI among RSV-ARI (RSVPreF3)	0.259259	0.113512	0.439985
P of ALRTI among RSV-ARI (RSVpreF)	0.5	0.293376	0.706624
P of ALRTI among RSV-ARI (mRNA-1345)	0.346154	0.176858	0.538754
RSV-ALRTI hospitalisation	0.195	0.12452	0.276772
P of hospitalisations leading to GW (ALRTI)	0.75	0.406763	0.967889
P of hospitalisations leading to GW (no ALRTI)	0.85	0.387847	0.99978
RSV-ARI no ALRTI hospitalisation	0.0975	0.102832	0.100288
P of Antipyretic in high-risk RSV patients	0.571429	0.439887	0.698047
P of Cough suppressant in high-risk RSV patients	0.803571	0.68987	0.896414
P of Systemic corticosteroid in high-risk RSV patients	0.375	0.253066	0.505548
P of Bronchodilator in high-risk RSV patients	0.517857	0.386892	0.647592
P of Antipyretic in older RSV patients	0.456522	0.315125	0.601582
P of Cough suppressant in older RSV patients	0.413043	0.275149	0.558264
P of Systemic corticosteroid in older RSV patients	0.1	0.031469	0.201802
P of Bronchodilator in older RSV patients	0.043478	0.005244	0.118654
In hospital mortality of RSV-ARI patients ≥60 and <75	0.043196	0.042296	0.044105
In hospital mortality of RSV-ARI patients 75+	0.056478	0.055739	0.057223
Mortality of hospitalized ALRTI patients ≥60 and <75	0.102679	0.06644	0.145653
Mortality of hospitalized ALRTI patients 75+	0.2	0.160571	0.24255

Mortality non-RSV ≥75	0.04371	0.028216	0.062362
Mortality non-RSV ≥75 (year 2)	0.049892	0.032195	0.07117
Mortality non-RSV ≥60 and <75	0.009445	0.006109	0.013488
Mortality non-RSV ≥60 and <75 (year 2)	0.010475	0.006775	0.014959
Duration of hospitalisation RSV-ARI	2	1.216014	2.783986
Number of GP visits (outpatient)	2	1.216014	2.783986
Time per GP visit (outpatient)	30	18.24022	41.75978
Medically attended (=outpatient) Pre-season	0.89	0.785341	0.962469
Medically attended (=outpatient) W0	0.53	0.349447	0.706567
Medically attended (=outpatient) W1	0.75	0.586383	0.883154
Medically attended (=outpatient) W2	0.73	0.544876	0.880635
Medically attended (=outpatient) W3	0.83	0.629745	0.960924
Medically attended (=outpatient) W4	0.86	0.7205	0.956138
Non medically attended Pre-season	0.9	0.844801	0.9442
Non medically attended W0	0.65	0.599221	0.699149
Non medically attended W1	0.82	0.685687	0.922876
Non medically attended W2	0.87	0.780319	0.938827
Non medically attended W3	0.88	0.789397	0.947668
Non medically attended W4	0.93	0.845586	0.982444
Utility score of hospitalization	0.576	0.571998	0.579997
Utility score of ICU admittance	0.402	0.362339	0.442306
GP visit - Costs of first 5 min	18.61	12.04341	26.5826
GP visit - Costs of further 5 min	18.61	12.04341	26.5826
GP visit - Costs of last 5 min	9.31	6.024941	13.29844
GP visit - Study of patient dossier	18.61	12.04341	26.5826
Costs for antipyretic in high-risk RSV patients	4.58	2.963935	6.54209
Costs for cough suppressant in high-risk RSV patients	25.6	16.56697	36.56714

Costs for systemic corticosteroid in high-risk RSV patients	14.4	9.318921	20.56902
Costs for bronchodilator in high-risk RSV patients	27.05	17.50533	38.63833
Cost per inpatient stay (GW) 60 to 75 population with comorbidities	9054	5859.271	12932.77
Cost per inpatient stay (ICU) 60 to 75 population with comorbidities	17615	11399.5	25161.33
Cost per inpatient stay (GW) population over 75	10729	6943.243	15325.35
Cost per inpatient stay (ICU) population over 75	18554	12007.17	26502.61
Cost per inpatient stay (GW) Stucki 2024	12426.07	8041.499	17749.45
Cost per inpatient stay (ICU) Stucki 2024	30171.46	19525.38	43097.03
Costs per injection of RSVPreF3	198.05	53.96196	434.0896
Costs per injection of RSVpreF	198.05	53.96196	434.0896
Costs per injection of mRNA-1345	198.05	53.96196	434.0896
GP tariff for vaccine administration	50	32.35736	71.4202

H. Parameter values in the PSA

Parameter	Mean value	SE	Distributor
Infection rates			
P of RSV-ARI in adults	0.0067	0.00134	Beta
P of RSV-ARI (scenario with trial data)	0.005074	0.001015	Beta
Trial data			
VE RSV-ARI (Arexvy)	0.717	0.054082	Normal
VE RSV-ARI (Abrysvo)	0.621	0.080612	Normal
VE RSV-ARI (mRESVIA)	0.684	0.057653	Normal
P of ALRTI among RSV-ARI (pooled)	0.544681	0.032486	Beta
P of ALRTI among RSV-ARI (Arexvy)	0.259259	0.084337	Beta
P of ALRTI among RSV-ARI (Abrysvo)	0.5	0.1066	Beta
P of ALRTI among RSV-ARI (mRES-VIA)	0.346154	0.093301	Beta
Medical attendance			
RSV-ALRTI hospitalisation	0.195	0.039	Dirichlet
RSV-ALRTI hospitalisation leading to GW	0.14625	0.02925	Dirichlet
RSV-ALRTI hospitalisation leading to ICU	0.04875	0.00975	Dirichlet
RSV-ALRTI GP visit	0.705	0.141	Dirichlet
RSV-ALRTI no visit	0.1	0.02	Dirichlet
P of hospitalisations leading to GW (ALRTI)	0.75	0.15	Beta
P of hospitalisations leading to GW (no ALRTI)	0.85	0.17	Beta
RSV-ARI no ALRTI hospitalisation	0.0975	0.0195	Dirichlet

RSV-ALRTI no ALRTI hospitalisation leading to GW	0.082875	0.016575	Dirichlet
RSV-ALRTI no ALRTI hospitalisation leading to ICU	0.014625	0.002925	Dirichlet
RSV-ALRTI no ALRTI GP visit	0.6025	0.1205	Dirichlet
RSV-ALRTI no ALRTI no visit	0.3	0.06	Dirichlet
Patients aged ≥60 and <75 at high risk			
Antipyretic in high-risk RSV patients	0.571429	0.06613	Beta
Cough suppressant in high-risk RSV patients	0.803571	0.053091	Beta
Decongestant in high-risk RSV patients	0.214286	0.054832	Beta
Systemic corticosteroid in high-risk RSV patients	0.375	0.064694	Beta
Bronchodilator in high-risk RSV patients	0.517857	0.066773	Beta
Patients aged ≥75			
Antipyretic in older RSV patients	0.456522	0.073442	Beta
Cough suppressant in older RSV patients	0.413043	0.072598	Beta
Decongestant in older RSV patients	0.326087	0.069118	Beta
Systemic corticosteroid in older RSV patients	0.1	0.044233	Beta
Bronchodilator in older RSV patients	0.043478	0.030068	Beta
Mortality			
In hospital mortality of RSV-ARI patients ≥60 and <75	0.043196	0.000462	Beta
In hospital mortality of RSV-ARI patients 75+	0.056478	0.000378	Beta
Mortality of hospitalized ALRTI patients ≥60 and <75	0.102679	0.020281	Beta

Mortality of hospitalized ALRTI patients 75+	0.2	0.020937	Beta
Background mortality			
Mortality non-RSV ≥75	0.04371	0.008742	Beta
Mortality non-RSV ≥75 (year 2)	0.049892	0.009978	Beta
Mortality non-RSV ≥60 and <75	0.009445	0.001889	Beta
Mortality non-RSV ≥60 and <75 (year 2)	0.010475	0.002095	Beta
Resource use			
Inpatient			
Duration of hospitalisation RSV-ARI	2	0.4	Normal
Outpatient			
Number of GP visits (outpatient)	2	0.4	Normal
Time per GP visit (outpatient)	30	6	Normal
Utility			
Medically attended (=outpatient) Pre-season	0.89	0.045918	Beta
Medically attended (=outpatient) W0	0.53	0.091837	Beta
Medically attended (=outpatient) W1	0.75	0.076531	Beta
Medically attended (=outpatient) W2	0.73	0.086735	Beta
Medically attended (=outpatient) W3	0.83	0.086735	Beta
Medically attended (=outpatient) W4	0.86	0.061224	Beta
Non medically attended Pre-season	0.9	0.02551	Beta
Non medically attended W0	0.65	0.02551	Beta
Non medically attended W1	0.82	0.061224	Beta
Non medically attended W2	0.87	0.040816	Beta
Non medically attended W3	0.88	0.040816	Beta
Non medically attended W4	0.93	0.035714	Beta

Utility score of hospitalization	0.576	0.002041	Beta
Utility score of ICU admittance	0.402	0.020408	Beta
		Healthcare costs	
Outpatient			
GP visit - Costs of first 5 min	18.61	3.722	Gamma
GP visit - Costs of further 5 min	18.61	3.722	Gamma
GP visit - Costs of last 5 min	9.31	1.862	Gamma
GP visit - Study of patient dossier	18.61	3.722	Gamma
Costs of medication - Antipyretic	4.58	0.916	Gamma
Costs of medication - Cough suppressant	25.6	5.12	Gamma
Costs of medication - Decongestant	Fixed		
Costs of medication - Systemic corticosteroid	14.4	2.88	Gamma
Costs of medication - Bronchodilator	27.05	5.41	Gamma
Inpatient			
Cost per inpatient stay (GW) 60 to 75 population with comorbidities	9054	1810.8	Gamma
Cost per inpatient stay (ICU) 60 to 75 population with comorbidities	17615	3523	Gamma
Cost per inpatient stay (GW) population over 75	10729	2145.8	Gamma
Cost per inpatient stay (ICU) population over 75	18554	3710.8	Gamma
Cost per inpatient stay (GW) Stucki 2024	12426.07	2485.214	Gamma
Cost per inpatient stay (ICU) Stucki 2024	30171.46	6034.291	Gamma
Vaccines			
Costs per injection of Arexvy	198.05	99.025	Gamma

Costs per injection of Abrysvo	198.05	99.025	Gamma
Costs per injection of mRESVIA	198.05	99.025	Gamma
GP tariff for vaccine administration	50	10	Gamma
General	General		
Population size subjects aged between ≥60 and <75 years at high risk for complications	128817		Fixed
Population size subjects aged ≥75 years	916603		Fixed
P of high-risk among Swiss population aged ≥60 and <75	0.1		Fixed
Vaccine coverage	0.375		Fixed
Discount rate	0.03		Fixed