5.09 RESPIRATORY SYNCYTIAL VIRUS VACCINE, Solution for injection 50 µg in 0.5 mL pre-filled syringe, mRESVIA®, MODERNA AUSTRALIA PTY LTD.

1 Purpose of submission

1.1 The Category 2 submission requested National Immunisation Program (NIP) listing of mRNA-1345 for the prevention of lower respiratory tract disease (LRTD) caused by respiratory syncytial virus (RSV) in individuals aged ≥ 75 years of age (YOA) and Aboriginal and Torres Strait Islander people aged 60-74 YOA.

1.2 Listing was requested on the basis of a cost-minimisation approach (CMA) compared with RSVPreF (Abrysvo®) (Table 1). The submission also presented a clinical comparison with RSVPreF3 OA (Arexvy®), which it described as a near market comparator. The submission presented a cost-utility analysis (CUA) comparing mRNA-1345 with no vaccine, noting that neither RSVPreF nor RSVPreF3 OA are currently listed on the NIP for the proposed indications.

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Adults aged ≥ 75 years; and Aboriginal and Torres Strait Islander people aged 60-74 years
Intervention	mRNA-1345 (mRESVIA)
Comparators	Main comparator: RSVPreF (Abrysvo) Near market comparator: RSVPreF3 OA (Arexvy) Supplementary comparator: No vaccination
Outcomes	Efficacy: • Primary endpoints: VE to prevent the first episode of RSV-LRTD with ≥ 2 or ≥ 3 symptoms (≥ 14 days postinjection to < 12 months postinjection) • Secondary endpoints: VE to prevent the first episode of RSV-ARD (≥ 14 days postinjection to < 12 months postinjection); VE to prevent first hospitalisation associated with RSV-ARD or RSV-LRTD (≥ 14 days postinjection to < 12 months post-injection) • Other secondary endpoints: VE to prevent all-cause hospitalisation (≥ 14 days postinjection to < 12 months postinjection); VE to prevent all-cause RSV-LRTD (≥ 14 days postinjection to < 12 months postinjection); VE to prevent first episode of RSV-LRTD ≥ 2 or ≥ 3 symptoms (≥ 14 days postinjection to < 24 months postinjection); VE to prevent the first episode of RSV-LRTD by RSV subtype A and RSV subtype B; VE to prevent first hospitalisation associated with RSV-ARD or RSV-LRTD[a] (≥ 14 days postinjection to < 24 months postinjection); Change in total frailty score (≥ 14 days postinjection to < 24 months postinjection) Immunogenicity: • Geometric mean titre (vaccine strain type) • Geometric mean concentration • Geometric mean fold-rise of postbaseline/baseline ab titres • Proportion of participants with ≥ 4-fold Increases in ab titres from baseline Safety: • Solicited local and systemic adverse reactions • Unsolicited AEs: MAAEs; AESI; SAE and AEs leading to withdrawal • Deaths
Clinical claim	Primary: For adults aged ≥ 75 years and Aboriginal and Torres Strait Islander people aged 60-74 years, compared to active vaccination with RSVPreF or RSVPreF3 OA, mRNA-1345 is associated with: • Non-inferior efficacy based on prevention of RSV-LRTD symptoms; and • Non-inferior safety, with a well-tolerated but different safety profile. Supplementary: For adults aged ≥ 75 years and Aboriginal and Torres Strait Islander people aged 60-74 years, compared to no RSV vaccination, mRNA-1345 is associated with: • Superior efficacy based on prevention of RSV-LRTD symptoms; and • Inferior safety.

Source: Table 1-1, p23 of the submission.

ab = antibody; AE = adverse event; AESI = adverse event of special interest; MAAE = medically attended adverse event; RSV = respiratory syncytial virus; RSV-ARD = respiratory syncytial virus related acute respiratory disease; RSV-LRTD = respiratory syncytial virus related lower respiratory tract disease; SAE = serious adverse event; VE = vaccine efficacy.

[a] Description corrected during evaluation from 'first episode' in the submission to 'first hospitalisation' reflecting the source document (p4, Attachment 2 (CSR) mRNA-1345 in the submission).

2 Background

Registration status

2.1 mRNA-1345 was approved on 28 March 2025 by the Therapeutic Goods Administration (TGA) for active immunisation for the prevention of LRTD caused by RSV in adults 60 years of age and older. The TGA dossier was accepted on 31 July 2023, however the TGA declined to approve the vaccine on 12 June 2024. The TGA Delegate was not satisfied that the evidence submitted by the sponsor had satisfactorily established the efficacy of the vaccine for the proposed indication. The sponsor subsequently applied to the TGA for reconsideration of the initial decision, and the final registration decision for approval was made on 28 March 2025. The TGA Delegate was satisfied that the additional evidence submitted by the sponsor satisfactorily established the efficacy of the vaccine (mRESVIA AusPAR, pp76-79).

2.2 mRNA-1345 received approval from the U.S. Food and Drug Administration (FDA) on 31 May 2024, the European Medicines Agency (EMA) in the European Union on 22 August 2024, and Health Canada on 6 November 2024. The approved TGA indication for mRNA-1345 is consistent with the approved FDA, EMA and Canada indications. Additionally, as of 12 June 2025, the FDA have approved mRNA-1345 for use in adults aged 18 to 59 years who are at increased risk of RSV-related LRTD, in addition to adults aged 60 years and older.

2.3 The submission requested NIP listing for a single dose of mRNA-1345 consistent with the TGA approved Product Information. Revaccination is being assessed in clinical trials at 12 months and 24 months from initial vaccination. It is a condition of TGA approval that the sponsor provides data from mRNA-1345 revaccination studies 301 and 302 when they become available (see paragraph 3.8 below). The Pre-Sub-Committee Response (PSCR) stated that there is currently no timeline for TGA registration for revaccination.

Previous PBAC consideration

2.4 Two alternative vaccines, RSVPreF and RSVPreF3 OA, have been considered by the Pharmaceutical Benefits Advisory Committee (PBAC) for the prevention of RSV-LRTD in adults ≥ 75 YOA and Aboriginal and Torres Strait Islander people aged 60 to 74 years. RSVPreF was recommended by the PBAC in November 2024, and again in July 2025[1]. RSVPreF3 OA was not recommended at the July 2024 PBAC meeting but was subsequently recommended at the July 2025 meeting[1]. A comparison of the RSVPreF, RSVPreF3 OA and current submissions is provided in the Committee-In-Confidence (CIC) section.

[1]https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/pbac-outcomes/2025-07/pbac-web-outcomes-07-2025.pdf

ATAGI Advice

2.5 The first request for Australian Technical Advisory Group on Immunisation (ATAGI) advice was submitted by the sponsor in March 2024, and ATAGI responded with pre-submission advice to the PBAC in September 2024. The second set of ATAGI pre-submission advice for the PBAC to consider was dated 26 June 2025. The evaluation noted that this submission to the PBAC (at the July 2025 cut-off for the November 2025 consideration) was partially in accordance with the ATAGI pre-submission advice to PBAC dated 26 June 2025.

2.6 The ATAGI provided post-submission advice to the PBAC dated 17 September 2025. The ESC noted that in its latest advice, the ATAGI maintained that there is insufficient evidence to support a non-inferiority claim of vaccine effectiveness between mRNA-1345 and RSVPreF and/or RSVPreF3 OA. ATAGI noted that longer term data are required to establish whether ongoing protection is comparable across the vaccine alternatives. The June 2025 ATAGI advice requested estimates of vaccine efficacy generated for interval periods (i.e., 12-18 months and 18-24 months). ATAGI advised that if alternative RSV vaccines become available on the NIP, and if non-inferiority of mRNA-1345 to alternative vaccines cannot be established, there will be no clear role for mRNA-1345 on the NIP.

2.7 Analyses reported in ATAGI's post-submission advice to the PBAC, showed that mRNA-1345 vaccine efficacy drops off in the 12-18 month period and further in the 18-24 month period. ATAGI stated this may suggest that more frequent revaccination is required for mRNA-1345 than its comparators, RSVPreF and RSVPreF3 OA. The ESC noted that ATAGI's analysis suggests a faster waning of protection than provided by the submission. The ESC noted ATAGI's advice that mRNA-1345 may require more-frequent revaccination than RSVPreF and RSVPreF3 OA.

For more detail on PBAC's view, see section 7 PBAC outcome.

3 Requested listing

MEDICINAL PRODUCT	Ex-Manufacturer Price	Number and timing of doses	Available brands
mRNA-1345, single-dose 50 µg /0.5mL, IM injection, prefilled syringe	$[redacted]	1 dose [a]	mRESVIA
National immunisation program • ≥ 75 years of age • Aboriginal and Torres Strait Islander people aged 60-74 Duration of listing: ongoing NIP cohort			

Source: Table 1-5, p40 of the submission.
IM = intramuscular; NIP = National Immunization Program
[a] The submission stated that booster frequency was "to be determined", however the submission requested NIP listing of a single injection for vaccination against RSV-disease caused by RSV in adults aged 75 years and older, or Aboriginal and Torres Strait Islander people aged 60-74 years (p40 of submission).

3.1 The price proposed in the submission for mRNA-1345 was $[redacted] per dose.

3.2 The submission proposed that mRNA-1345 could be given at any time of the year but, where possible, it should be offered from March onwards (before the start of the RSV season), where seasonality exists.

3.3 The submission stated that it is expected that mRNA-1345 will be able to be coadministered with COVID-19 vaccines and influenza vaccines. In general, ATAGI supports the coadministration of adult vaccines unless there is evidence to recommend separation (ATAGI Advice, June 2025), which may be the case for mRNA-1345. The evaluation noted that although coadministration may improve vaccine uptake, neutralising antibodies and the rate of seroconversion may be lower for mRNA-1345 when coadministered with an influenza vaccine than when administered alone. While the clinical significance of this on vaccine efficacy is unknown (ATAGI Advice, June 2025), ATAGI has suggested that mRNA-1345 should be delivered alone (ATAGI Advice, June 2025). The submission referred to 2 ongoing studies that are evaluating coadministration of mRNA-1345:

- RSVictory for coadministration with influenza [Afluria® Quadrivalent; SIIV4] and COVID-19 [mRNA-1273.222] vaccines;
- RSVibrant for coadministration with influenza vaccine [Fluzone HD]).

3.4 The evaluation noted that the requested NIP listing for adults aged ≥ 75 YOA and Aboriginal and Torres Strait Islander people aged 60-74 YOA is narrower than the approved TGA indication, which refers to adults 60 YOA and older. The analyses conducted in the economic and financial sections of the submission encompass the two populations for which listing is being sought; however, the submission used VE from the entire trial population (adults aged ≥ 60 YOA) in the CUA to determine cost effectiveness for adults aged ≥ 75 YOA and Aboriginal and Torres Strait Islander people aged 60-74 years (see paragraph 6.77 below). Subgroup analyses according to age were presented in the submission.

3.5 The 2024 ATAGI advice advised that ATAGI's preferred target population is for 1) otherwise healthy adults aged 75 years and older; 2) Aboriginal and Torres Strait Islander people aged ≥ 60 years; and 3) high-risk adults aged ≥ 60 years. The current submission did not request a listing for the third group.

Revaccination

3.6 The submission stated that the need for revaccination with mRNA-1345 has not been established. The submission did not specify when data to support revaccination with mRNA-1345 will become available and the PSCR confirmed there is no timeline available for a regulatory application (paragraph 2.3). The June 2025 ATAGI advice noted that the sponsor's request for ATAGI advice did not discuss the need for a booster dose. This was in contrast to the sponsor's March 2024 request for ATAGI advice, which stated that the dosing schedule was "Likely to be every other year", noting the vaccination schedule was yet to be confirmed, and was dependent on

ATAGI advice and continuing collection of mRNA-1345-P301 study data (ATAGI advice, September 2024).

3.7 The evaluation considered that given the observed waning of VE observed after administration with mRNA-1345 (see paragraph 6.21 below), the need for revaccination is likely. Revaccination will affect the long-term efficacy, cost-effectiveness, financial impact and safety profile of mRNA-1345. The submission did not consider revaccination in the economic evaluation or financial estimates. The PBAC has previously noted that if revaccination is requested in the future, this would require further PBAC consideration (paragraph 7.9, RSVPreF Public Summary Document [PSD], November 2024).

3.8 The submission provided limited data from mRNA-1345 studies 302 Part C and 301 Part B, describing the effect of revaccination on RSV neutralising antibody titres. These studies assessed revaccination at 12 months and 24 months, respectively. The PSCR indicated that while these studies are still ongoing, the results of current assessments will be submitted to the TGA at the end of October 2025 for P302 Part C (with Parts A and B which assess coadministration), and in March 2026 for P301 Part B (24 month follow-up), as part of the end of study CSR. The evaluator noted that it is a condition of TGA approval that the sponsor provide these data.

3.9 Immunogenicity results following revaccination at 12 months with mRNA-1345 post initial vaccination in Study 302 Part C (adults ≥ 50 Years) showed that mRNA-1345 elicited immunogenic responses similar to that following initial vaccination, and that revaccination met pre-specified non-inferiority success criteria, was well tolerated with no safety concerns[2]). Immunogenicity results from Study 301 Part B showed that at 1 month post revaccination (24 months after the initial vaccination) the level of antibody titres increased, although not to the levels seen after the initial vaccination.

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

4.1 The disease pathophysiology, clinical presentation in older adults, diagnosis and seasonality of RSV is known to the PBAC. In Australia, RSV became a notifiable disease in July 2021 and cases are monitored through the National Notifiable Diseases Surveillance System (NNDSS). RSV diagnosis is usually by reverse transcription polymerase chain reaction (RT-PCR) on nasal and/or throat swabs. RSV spreads via droplets and fomites, and can cause respiratory illness in individuals of all age groups, but poses a significant risk of severe respiratory illness for infants, older adults and individuals with specific underlying health conditions.

[2] https://www.cdc.gov/acip/downloads/slides-2024-06-26-28/04-RSV-Adult-Das-508.pdf

4.2 In Australia, RSV peaks in winter, though tropical regions experience greater year-round activity. The COVID-19 pandemic disrupted RSV patterns, but these returned to historic trends by 2023.

4.3 The requested NIP populations are consistent with the ATAGI Advice to the PBAC and are aligned with the recommendations provided in the Australian Immunisation Handbook for older adults, except the submission did not consider adults ≥ 60 YOA who are at a higher risk of developing severe RSV disease.

4.4 mRNA-1345 is supplied as a single-dose plastic pre-filled syringe containing 50 µg of RSV F protein mRNA. The mRNA sequence is encapsulated in lipid nanoparticles that encode the RSV fusion (F) glycoprotein stabilised in the prefusion conformation. The F glycoprotein is on the surface of the virus and is required for infection by helping the virus to enter host cells. It exists in two states, pre-fusion and post-fusion. The mRNA-1345 vaccine encodes for the RSV-A subtype, however, the submission stated that mRNA-1345 confers cross protection against both A and B strains of RSV. The impact of the selection of the encoding protein subtype A on the efficacy of mRNA-1345 against RSV subtype B is discussed further in paragraph 6.23 below.

4.5 The ESC noted that mRNA-1345 must be kept at temperatures between minus 40 and minus 15 degrees Celsius, while RSVPreF3 OA and RSVPreF should be stored in standard refrigerated conditions (2 to 8 degrees Celsius). This difference in cold chain requirements is important for rural and remote communities, particularly Aboriginal and Torres Strait Islander communities, where transport and reliable access to sufficient cold storage can be particularly challenging. In this regard, ATAGI stated that "cold chain management systems were introduced with COVID-19 vaccines. For facilities that do not have adequately cold storage and store mRESVIA between 2 degrees and 8 degrees, the shelf-life of mRESVIA is reduced to 30 days. This shorter shelf-life may result in expired stock" (ATAGI Advice, June 2025).

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

5.1 The submission nominated RSVPreF (Abrysvo) as the main comparator, which the evaluation considered to be appropriate. The main argument provided in support of this nomination was that at the November 2024 and July 2025 PBAC meetings, RSVPreF was recommended for NIP listing in the same populations requested in this submission (adults ≥ 75 YOA and for Aboriginal and Torres Strait Islander people aged 60-74 YOA; paragraph 7.1, RSVPreF PSD, November 2024).

5.2 The submission nominated RSVPreF3 OA (Arexvy) as a near market comparator. At the time the mRNA-1345 submission was prepared, RSVPreF3 OA had not been recommended for NIP listing by the PBAC from its consideration at the July 2024 meeting. RSVPreF3 OA was subsequently recommended for listing at the July 2025 PBAC meeting. The evaluation considered that RSVPreF3 OA is an appropriate alternative comparator.

5.3 Given that neither RSVPreF nor RSVPreF3 OA were listed on the NIP at the time of preparing the submission, no RSV vaccination was nominated as a supplementary comparator. The evaluation considered that no RSV vaccination is a relevant alternative comparator.

5.4 For the nominated comparators, the following analyses were presented in the submission:

- With respect to the clinical evidence, the submission provided an indirect treatment comparison (ITC) with RSVPreF and RSVPreF3 OA, and a direct comparison with placebo (no vaccine).
- With respect to the economic evaluation, the comparator 'no vaccine' was considered in a CUA and the comparator RSVPreF in a CMA. No CMA was presented for the comparator RSVPreF3 OA.
- With respect to the financial estimates, equal market share of mRNA-1345 and RSVPreF was assumed; the potential utilisation of RSVPreF3 OA was not considered.

At the time of the November 2025 PBAC meeting, neither RSVPreF nor RSVPreF3 OA were listed on the NIP.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer inputs

6.2 The PBAC noted and welcomed the input from three organisations via the Office of Health Technology Assessment Consultation Hub. The inputs were broadly supportive of RSV protection measures, including vaccination.

6.3 One medical organisation, the Australian College of Nurse Practitioners, discussed the importance of including RSV vaccines on the NIP, particularly for people aged 75 years and older. It noted that adults over 60 years are frequently hospitalised with RSV and those aged over 75 years face the highest risk. It stated that Aboriginal and Torres Strait Islander people are also disproportionately affected, underscoring health inequities within vulnerable populations.

6.4 Two consumer organisations, Asthma Australia and Lung Foundation Australia, described the advantages of vaccination against RSV. Asthma Australia stated that minimising asthma exacerbations is a key objective of asthma management and treatment, as exacerbations have a significant impact on quality of life and can extend beyond 4 weeks following RSV illness. It stated that current treatment with systemic corticosteroids is associated with substantial short-term and long-term side effects

and reducing the risk of LRTD and asthma exacerbations is likely to have a positive impact on the health and quality of life of people living with asthma. Lung Foundation Australia described how vaccination may avoid RSV infection that could lead to bronchiolitis, pneumonia and bronchitis. It highlighted the vulnerability of patients with lung cancer or lung disease who may require urgent medication attention if infected with RSV. It emphasised the prohibitive cost of vaccination to older Australians without listing on the NIP.

Clinical trials

6.5 Details of the studies presented in the submission are provided in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
ConquerRSV (NCT05127434)	A Phase 2/3, Randomized, Observer-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of mRNA-1345, an mRNA Vaccine Targeting Respiratory Syncytial Virus (RSV), in Adults ≥ 60 Years of Age. A Phase 2/3, Randomized, Observer-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of mRNA-1345, an mRNA Vaccine Targeting Respiratory Syncytial Virus (RSV), in Adults ≥ 60 Years of Age. A Phase 2/3, Randomized, Observer-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of mRNA-1345, an mRNA Vaccine Targeting Respiratory Syncytial Virus (RSV), in Adults ≥ 60 Years of Age A Phase 2/3, Randomized, Observer-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of mRNA-1345, an mRNA Vaccine Targeting Respiratory Syncytial Virus (RSV), in Adults ≥ 60 Years of Age J. Goswami, A. H. Baqui, P. A. Doreski, G. Perez Marc, G. Jimenez, S. Ahmed, et al. Humoral Immunogenicity of mRNA-1345 RSV Vaccine in Older Adults.	Clinical Study Report. Primary data analysis period – data cut off 30 Nov 2022 *Clinical Study Report.* Additional data analysis period – data cut off 30 Apr 2023 Clinical Study Report. Data memo-18.8 month analysis data cut off 30 Mar 2024 Clinical Study Protocol: Version 07 Oct 2021 Statistical Analysis Plan: Version 1.0. 29 Nov 2022 J Infect Dis 2024 Vol. 230 Issue 5 Pages e996-e1006. Accession Number: 38889247 PMCID: PMC11566230 DOI: 10.1093/infdis/jiae316.
	E. Wilson, J. Goswami, A. H. Baqui, P. A. Doreski, G. Perez-Marc, K. Zaman, et al. Efficacy and Safety of an mRNA-Based RSV PreF Vaccine in Older Adults.	NEJM 2023 Vol. 389 Issue 24 Pages 2233-2244. DOI: 10.1056/NEJMoa2307079.
RSVPreF (ABRYSVO)		
RENOIR (NCT05035212)	E. E. Walsh, G. Pérez Marc, A. M. Zareba, A. R. Falsey, Q. Jiang, M. Patton, et al. Efficacy and safety of a bivalent RSV prefusion F vaccine in older adults. A Phase 3 study to evaluate the efficacy, immunogenicity and Safety of Respiratory Syncytial Virus (RSV) Prefusion F Subunit Vaccine in Adults. E. E. Walsh, G. Pérez Marc, A. M. Zareba, A. R. Falsey, Q. Jiang, M. Patton, et al. Efficacy and safety of a bivalent RSV prefusion F vaccine in older adults.	NEJM 2023 Vol. 388 Issue 16 Pages 1465-1477 Clinical Study Protocol. Original protocol 07 Jul 2021 Supplementary Appendix. NEJM 2023;388:1465-77. DOI: 10.1056/NEJMoa2213836

Trial ID	Protocol title/ Publication title	Publication citation
	E. Walsh, G. P. Marc, A. R. Falsey, J. Qin, D. Eiras, M. Patton, et al. 2024; RENOIR Trial - RSVpreF Vaccine Efficacy over Two Seasons. J. F. M. Cardona, Tarek; Fukushima, Yasushi; Jiang, Q; Eiras, Daniel P; Anderson, Anneliesa P; Gurtman, A C. 2024. P-605. Bivalent RSV Prefusion F-Based Subunit Vaccine Generates High and Durable Neutralizing Titers Across an Entire RSV Season among Older Adults.	NEJM Vol. 391 Issue 15 Pages 1459-1461. DOI: 10.1086/421524. Paper No. S469 OFID 2024
RSVPreF3 OA (AREXVY)		
AReSVi-006 (NCT04886596)	Papi, A.; Ison, M.G., Langley, D.G. et al (for the AReSVi-006 Study Group). Respiratory Syncytial Virus Prefusion F Protein Vaccine in Older Adults. A Phase 3, randomized, placebo-controlled, observer-blind, multi-country study to demonstrate the efficacy of a single dose and annual revaccination doses of GSK's RSVPreF3 OA investigational vaccine in adults aged 60 years and above. A Phase 3, randomized, placebo-controlled, observer-blind, multi-country study to demonstrate the efficacy of a single dose and annual revaccination doses of GSK's RSVPreF3 OA investigational vaccine in adults aged 60 years and above. Ison, M., Papi, A., Athan, E., et al. 2024a. Efficacy, safety, and immunogenicity of the AS01E-adjuvanted respiratory syncytial virus prefusion F protein vaccine (RSVPreF3 OA) in older adults over three respiratory syncytial virus seasons (AReSVi-006): a multicentre, randomised, observer-blinded, placebo-controlled, phase 3 trial.	NEJM 2023;388:595-608 DOI: 10.1056/NEJMoa2209604 Clinical Study Protocol. Final amendment 24 Jan 2022 Statistical Analysis Plan: 20 Dec 2022 Lancet Respir Med. 2025 Jun;13(6):517-529. DOI: 10.1016/S2213-2600(25)00048-7.

Source: Table 2-3 and Table 2-4, p48-49 of the submission.

6.6 The submission was based on one head-to-head trial (ConquerRSV) comparing mRNA-1345 (N = 18,427) to placebo (N = 18,387) with a median time to follow-up of 18.8 months (data cut-off; 8 March 2024). The ConquerRSV trial was ongoing at the time of submission but has since been completed[3]. The patient population in the trial was adults ≥ 60 YOA.

6.7 For the ConquerRSV trial, the data cut-off (DCO) at 8 March 2024 reported VE analysis for the period up to 12, 18 and 24 months post vaccination, however few participants (9.6%) completed the final visit at 24 months after initial vaccination. The submission also presented results from two earlier DCOs, the first at 3.7 months (primary DCO) and the second at 8.6 months median time to follow-up. These DCOs reported VE analysis for the period up to 12 months. The evaluation considered that the primary DCO results were highly uncertain due to immaturity; this is further discussed in paragraph 6.17. A summary of the cumulative VE analyses conducted in ConquerRSV is presented in Table 3. The submission also presented subgroup analyses per age group to inform the target population for which NIP listing is being sought (see paragraph 6.24 below). Individuals in the subgroup of adults ≥ 75 YOA represented a small proportion of the study population (18%).

[3] https://clinicaltrials.gov/study/NCT05127434, accessed 2 Sep 2025.

Table 3: Summary of cumulative VE analysis time points of ConquerRSV

Data analysis DCO date	Number of participants randomised	Outcome	RSV season coverage	Median follow-up (months)	Used in the economic evaluation?
Primary data analysis DCO: 30 Nov 2022	35,541	VE at 12 months	< 50% had been followed up by 1 RSV season[a]	3.7	No
Additional data analysis DCO: 30 Apr 2023	36,557	VE at 12 months	One: 71.9% [b] Two: 28.1% [b]	8.6	No
Extended data analysis DCO: 08 Mar 2024[c]	36,814	VE at 12 months	NR	18.8	Yes
		VE at 18 months			
		VE at 24 months			

Source: compiled during the evaluation from p57 of the submission and p2 and p94 of the mRNA-1345 CSR for additional analysis of VE.
DCO = data cut-off; EMA = European Medicine Agency; NR = not reported; RSV = respiratory syncytial virus; VE = vaccine efficacy.
[a] p49/145 of the mRNA-1345 EMA report (EMA/329706/2024).
[b] Any participants vaccinated on or before 30 Apr 2023 (error in the CSR, likely to reflect 30 April 2022) in the northern hemisphere were considered to have 2 seasons and after 30 Apr 2023 (error in the CSR, likely to reflect the period 30 April 2022 – 30 April 2023) were considered to have 1 season. Any participants vaccinated on or before 30 Sep 2022 in the southern hemisphere were considered to have 2 seasons and after 30 Sep 2022 were considered to have 1 season.
[c] This DCO aligned with the end of the northern hemisphere RSV season when > 90% of participants had completed at least 12 months of follow-up.

6.8 No evidence for Aboriginal and Torres Strait Islander people was available from ConquerRSV. The submission addressed this lack of data by using multipliers to account for the anticipated higher incidence of RSV among Aboriginal and Torres Strait Islander people. ATAGI suggested that it may have been informative to provide efficacy for the high-risk subgroup aged 60-74 years and argue why those results would be applicable to the Aboriginal and Torres Strait Islander population (ATAGI Advice, June 2025), but this was not provided by the submission.

6.9 The submission presented immunogenicity results from a subgroup of participants of ConquerRSV to assess the immunogenic response 1 month post vaccination and at Day 181 post vaccination.

6.10 To support the non-inferiority claim, the submission conducted an anchored ITC of efficacy data comparing mRNA-1345 in the ConquerRSV trial to RSVPreF in the RENOIR trial and RSVPreF3 OA in the AReSVi-006 trial (Table 2). The PBAC have previously considered evidence from both RENOIR (RSVPreF PSDs, November 2024 and July 2025) and AReSVi-006 (RSVPreF3 OA PSDs, July 2024 and July 2025).

6.11 The key features of the direct randomised trials are summarised in Table 4**.**

Table 4: Key features of the included evidence – indirect comparisons

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
mRNA-1345 versus placebo						
ConquerRSV	36,814[a]	Phase 2/3 R, DB, PC, MC Single dose of mRNA-1345 Ongoing at time of submission (since completed)	Low	Adults ≥ 60 YOA	Primary outcome: reduction of the risk of first occurrence of RT-PCR confirmed RSV-LRTD (2 or 3 signs/symptoms) Key secondary outcomes: prevention of RSV-associated ARD, safety, PROs	Yes
RSVPreF versus placebo						
RENOIR (NCT05035212)	34,383[b]	Phase 3, R, DB, MC, PC Single dose of RSVPreF Ongoing [c]	Low	Adults ≥ 60 YOA	Primary outcome: VE for prevention of RSV-LRTI with ≥ 2 and ≥ 3 signs or symptoms. Secondary: VE for prevention of RSV-ARD, sRSV-LRTI, immunogenicity.	No
RSVPreF3 OA versus placebo						
AReSVi-006 (NCT04886596)	24,966	Phase 3 R, OB, PC, MC Single dose of RSVPreF3 OA Completed	Low	Adults ≥ 60 YOA	Primary outcome: reduction of the risk of first occurrence of RT-PCR confirmed RSV-LRTD Key secondary outcomes: safety, PROs	No

Source: compiled during the evaluation from Table 2-15, p58 and information provided in the submission (p60); mRNA-1345-P101 Clinical Study Report (p44); Table 3, p10 of the RSVPreF November 2024 PSD.

ARD = acute respiratory disease; DB = double blind; DCO = data cut-off; DE = dose escalation; MC = multi-centre; OB = observer blinded; PC = placebo-controlled; PRO = patient reported outcome; R = randomised; RSV = respiratory syncytial virus; RSV-LRTD = lower respiratory tract disease respiratory syncytial virus; RT-PCR = reverse transcription-polymerase chain reaction; sRSV-LRTI = severe lower respiratory tract illness; VE = vaccine efficacy; YOA = years of age.

[a] Number of participants randomised at the latest analysis (DCO 08 March 2024, 18.8 months median follow-up time).

[b] Number of participants randomised for primary analysis was 34,383; Number of participants randomised for EOS1 was 36,967. The sample size was increased from 30,000 to 45,000 with the implementation of Protocol Amendment 2 (dated 23 March 2022).

[c] Completion of RENOIR is expected by June 2026.

6.12 The RENOIR and AReSVi-006 trials were previously considered by the PBAC to have a low risk of bias (Table 3, RSVPreF PSD, November 2024; Table 4, RSVPreF3 OA PSD, July 2024).

6.13 The ConquerRSV, RENOIR and AReSVi-006 trials all used the predefined success criterion for meeting the primary objective if the lower bound of the confidence interval (CI) around the VE estimate was greater than 20%. All studies reported VE estimates excluding individuals who developed the outcome of interest before Day 15 post vaccination.

6.14 AReSVi-006 and RENOIR were designed to assess VE at the end of Season 1 and across multiple seasons (3 in AReSVi-006 and 2 in RENOIR), which allowed for season-specific analyses (paragraph 3.12, RSVPreF3 OA PSD, July 2024; Table 4, RSVPreF PSD,

November 2024). ConquerRSV recruited its participants throughout the year which, according to the submission, did not allow for season specific efficacy analyses. The evaluation considered that an interval-based analysis may have been informative in this context, potentially serving as a proxy for the length of an RSV season and providing additional insights into vaccine performance over time. ATAGI stated that landmark interval analyses are most informative for estimating longer-term efficacy (ATAGI Advice, June 2025), however the submission did not present such analyses.

6.15 The evaluation commented that the most notable differences between the ConquerRSV, RENOIR and AReSVi-006 trials in terms of their study design and patient characteristics that may affect the transitivity assumption between the trials are:

- Differences in censoring timepoints: In ConquerRSV, participants were censored at the earliest date of 12 months (or 18 months, or 24 months, depending on the specific analysis) and data cutoff date. In contrast, in RENOIR and AReSVi-006, participants without an RSV diagnosis were censored at the end of each RSV season. Broadly, VE at 12 months could be seen as a proxy for one RSV season if most participants have completed a 12-month follow-up since initial vaccination, however some participants may have been exposed to two RSV seasons (Table 3). Similarly, the 24-month follow-up could be a proxy for two seasons, noting that only 9.6% completed the last follow-up visit to inform this analysis.
- Differences in baseline comorbidities: ConquerRSV participants were healthier compared to RENOIR and AReSVi-006. In ConquerRSV, 29.6% of participants had ≥ 1 comorbidity compared to 51.7% in RENOIR and 39.9% in AReSVi-006. This difference might bias the ITC against mRNA-1345 (given trials with a higher proportion of participants with multiple comorbidities are likely to experience a higher incidence of RSV-related symptoms, and therefore greater potential for an incremental effect). The TGA noted that for ConquerRSV, there are some concerns regarding interpretation of VE due to potential skewing of the study population towards healthier older adults (TGA Delegate Overview report).
- Frailty: Although the studies did not use a common frailty scoring system to describe baseline characteristics, a greater proportion of participants in ConquerRSV (76%) were classified as "fit" compared to 60% in AReSVi-006. Baseline frailty data for the RENOIR study were not included in the submission. The direction of and magnitude of any bias is uncertain.
- Differences in definition of RSV-LRTD: ConquerRSV applied the broadest criteria for the definition of RSV-LRTD, incorporating a wider combination of possible signs and symptoms than AReSVi-006 and RENOIR. ConquerRSV was therefore more likely to capture a greater number of cases, including milder presentations, compared with the other trials. There is the possibility that this would bias the results of the ITC, noting that ATAGI stated ITCs performed on relative outcomes may not be affected by small differences in outcome definitions (ATAGI Advice, June 2025).

- The submission presented a number of scenarios based on different DCOs and follow-up periods across the 3 trials (see further discussion in paragraph 6.31). The submission's ITC base case analysis was based on the 3.7, 7.1, and 6.7 months median time to follow-up in ConquerRSV, RENOIR, and AReSVi-006, respectively. Given the shorter median time to follow-up in ConquerRSV compared with RENOIR and AReSVi-006, this comparison is prone to bias favouring mRNA-1345 as vaccine efficacy wanes over time.

Comparative effectiveness

mRNA-1345 versus placebo

6.16 Cumulative VE for the primary outcome, prevention of first episode of RSV-LRTD with ≥ 2 symptoms is presented in Table 5 for two DCO points (median follow-up of 3.7 months and 8.6 months), and the corresponding cumulative incidence curves are shown in Figure 1. To estimate VE at 12 months, participants without the event were censored at 12 months.

Table 5: Cumulative VE up to 12 months[a] in ConquerRSV for the prevention of RSV-LRTD with ≥ 2 symptoms in participants ≥ 60 YOA (single dose, PPE set, primary data analysis)

Primary endpoints	mRNA-1345				Placebo				VE[b] % CI[c]
	N	n (%)	T (person years)	n/T per 1000 (95% CI)	N	n (%)	T (year)	n/T (per 1000)	
Primary data analysis (VE up to 12 months[a]) - median follow-up time = 3.7 months									
RT-PCR-confirmed RSV-LRTD ≥ 2 symptoms	17,572[d]	9 (0.1)	6,271	1.4 (0.7, 2.7)	17,516	55 (0.3)	6,254	8.8 (6.6, 11.5)	**83.7 (66.0, 92.2)**
Additional analysis (VE up to 12 months[a]) - median follow-up time = 8.6 months									
RT-PCR-confirmed RSV-LRTD ≥ 2 symptoms	18,112[d]	47 (0.3)	13,121	3.6 (2.6, 4.8)	18,045	127 (0.7)	13,020	9.8 (8.1, 11.6)	**63.3 (48.7, 73.7)**
Extended analysis (VE up to 24 months[a]) - median follow-up time = 18.8 months									
RT-PCR-confirmed RSV-LRTD ≥ 2 symptoms	18,181[d]	132 (0.7)	NR	NR	18,132	248 (1.4)	NR	NR	**47.4 (35.0, 57.4)**
Pre-PBAC response (VE up to 24 months[a]) - median follow-up time = 24.1 months									
RT-PCR-confirmed RSV-LRTD ≥ 2 symptoms	18,164	161 (0.9)	NR	NR	18,120	286 (1.6)	NR	NR	**44.3 (32.4, 54.1)**

Source: Table 2-44 and Table 2-45, pp125-126 of the submission; p98 pf the ConquerRSV CSR (28 Sep 2023) presented in Attachment 3 of the submission; Pre-PBAC response Table 1.

CI = confidence interval; n = number of participants with event (RSV-LRTD with 2 or more symptoms); NR = not reported; PPE = per protocol efficacy; RSV-LRTD = respiratory syncytial virus-associated lower respiratory tract disease; RT-PCR = reverse transcriptase polymerase chain reaction; VE = vaccine efficacy; YOA = years of age.

[a] Participants without a case in the specified time period were censored at the earliest date of 12 months postinjection, date of early discontinuation, date of unrelated death, and data cutoff date.

[b] VE is estimated by 1 minus hazard ratio (mRNA-1345 versus placebo). The CI for VE was based on a stratified Cox proportional hazard model with Efron's method of tie handling and with the vaccination group as a fixed effect, adjusting for stratification factors at randomization.

[c] 95.88% CI for the primary endpoint for the primary analysis (3.7 months median time to follow-up). 95% CI for the additional analysis (8.6 months median time to follow-up).

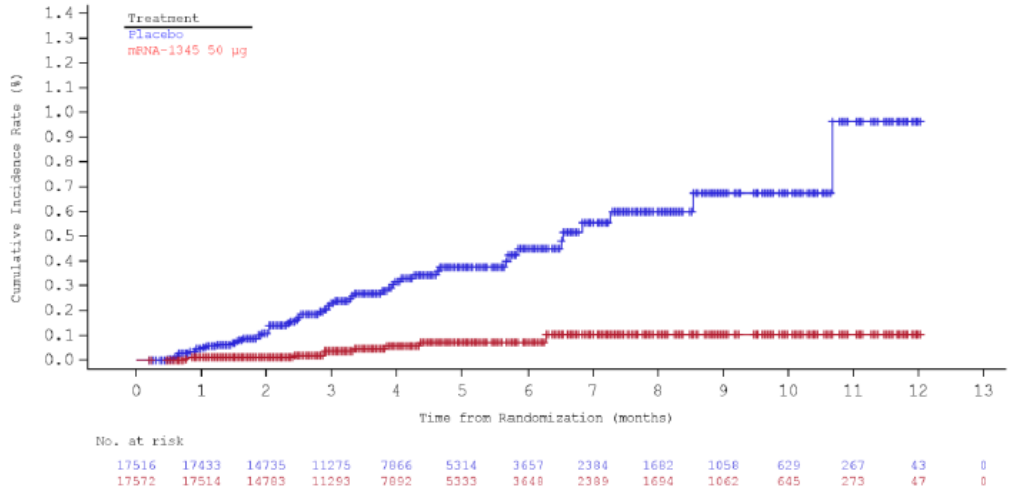
[d] The number of participants increases from one DCO to another as the trial continues the recruitment process.

Bold indicates that predefined lower bound of the CI around the vaccine efficacy was greater than 20%.

Notes: Number of participants with event was calculated as date of case−date of randomization+1. Participants without a case in the specified time period were censored at the earliest date of 12 months postinjection, date of early discontinuation, date of unrelated death, and data cutoff date.

Results in this table exclude individuals who develop the outcome within ≤ 14 days post vaccination.

Figure 1: Cumulative incidence curves in ConquerRSV for first episode of RSV-LRTD (≥ 2 symptoms) in participants ≥ 60 YOA, up to 12 months after injection, (single dose, PPE set, primary data analysis with 3.7 months median time to follow-up)



Source: Table 2-15, p127 of the submission.
PPE = per protocol efficacy; RSV-LRTD = respiratory syncytial virus-lower respiratory tract disease; YOA = years of age.
Note: Results exclude individuals who develop the outcome within ≤ 14 days post vaccination

6.17 The evaluation considered that the magnitude of these VE estimates from the planned primary data analysis (based on a prespecified number of RSV cases accrued) is highly uncertain given the extent of decline in the number of participants at risk in both the intervention and placebo arms from around 3 months of follow-up. Overall, the proportion of participants at risk at 12 months was 0.3%, 12.9% and 92.4% of the overall population in the VE analyses at 3.7, 8.6 and 18.8 months median follow-up, respectively. The EMA report stated that a substantial portion of participants (> 50%) in the primary analysis (3.7 months median follow-up) had no more than 3 months of follow-up, which is insufficient to capture the outcomes over a full RSV season (p49 of the EMA assessment report EMA/329706/2024[4]). Furthermore, there is a 66% reduction in antibody titres observed at approximately 6 months post vaccination (see Table 9) and therefore a longer duration of follow-up is required to capture the VE across the full 12 months.

6.18 A summary of the results for the prevention of first episode of RSV-LRTD with ≥ 2 or ≥ 3 symptoms at 3 different time points (12, 18 and 24 months) and first episode of RSV-acute respiratory distress (ARD) at the most recent efficacy DCO (08 March 2024; median time to follow-up of 18.8 months) is presented in Table 6 and the cumulative incidence curve for RSV-LRTD ≥ 2 symptoms is presented in Figure 2.

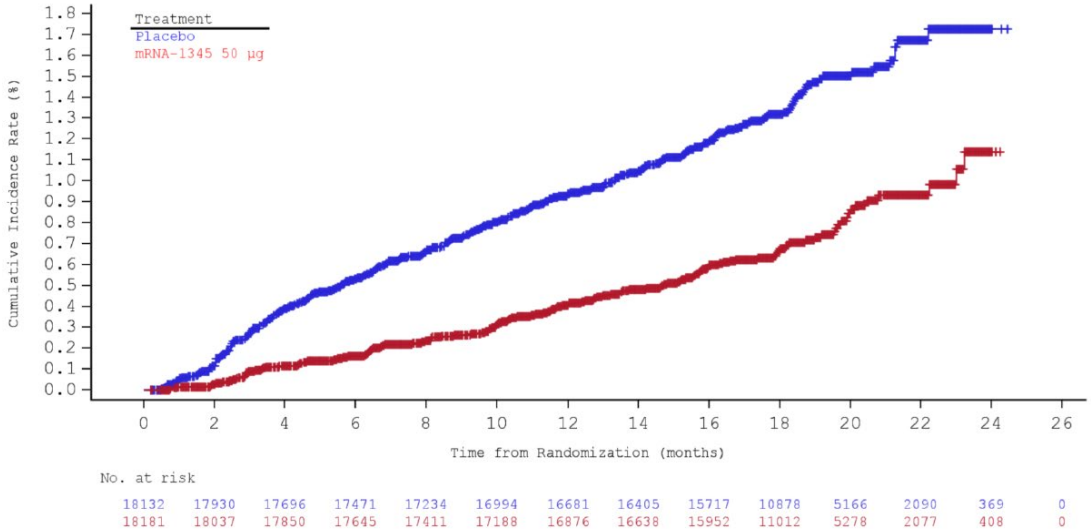
[4] European Medicina Agency. 2024. EMA/329706/2024 Assessment report

Table 6: Cumulative VE in ConquerRSV for the prevention of RSV-LRTD with ≥ 2 or ≥ 3 symptoms and RSV-ARD in participants ≥ 60 YOA (single dose, PPE set, 18.8-months median time to follow-up)

Primary endpoints	mRNA-1345 (N= 18,181)			Placebo (N = 18,132)			VE % 95% CI
	n (%)	T (person years)	n/T per 1000 (95% CI)	n (%)	T (person years)	n/T per 1000 (95% CI)	
VE for the prevention of RSV-LRTD ≥ 2 symptoms							
12 months	73 (0.4)	17,650	4.1 (3.2, 5.2)	165 (0.9)	17,491	9.4 (8.0, 11.0)	**56.2 (42.2, 66.7)[a]**
18 months	113 (0.6)	24,764	4.6 (3.8, 5.5)	225 (1.2)	24,493	9.2 (8.0, 10.5)	**50.3 (37.5, 60.7)[b]**
24 months	132 (0.7)	27,564	4.8 (4.0, 5.7)	248 (1.4)	27,257	9.1 (8.0, 10.3)	**47.4 (35.0, 57.4)[a]**
VE for the prevention of RSV-LRTD ≥ 3 symptoms							
12 months	30 (0.2)	17,668	1.7 (1.1, 2.4)	66 (0.4)	17,545	3.8 (2.9, 4.8)	**54.9 (30.5, 70.7)[a]**
18 months	46 (0.3)	24,808	1.9 (1.4, 2.5)	91 (0.5)	24,602	3.7 (3.0, 4.5)	**49.9 (27.8, 65.6)[b]**
24 months	52 (0.3)	27,617	1.9 (1.4, 2.5)	100 (0.6)	27,383	3.7 (3.0, 4.4)	**48.4 (27.9, 63.1)[a]**
VE for the prevention of RSV-ARD							
12 months	140 (0.8)	17,621	7.9 (6.7, 9.4)	282 (1.6)	17,442	16.2 (14.3, 18.2)	**50.9 (39.8, 59.9)[a]**
18 months	214 (1.2)	24,697	8.7 (7.5, 9.9)	398 (2.2)	24,377	16.3 (14.8, 18.0)	**46.9 (37.2, 55.3)[b]**
24 months	249 (1.4)	27,488	9.1 (8.0, 10.3)	434 (2.4)	27,130	16.0 (14.5, 17.6)	**43.4 (33.8, 51.6)[a]**

Source: Table 2-39, p117 of the submission.
CI = confidence interval; PPE = per-protocol efficacy; RSV-ARD = respiratory syncytial virus-associated acute respiratory disease; RSV-LRTD = respiratory syncytial virus-associated lower respiratory tract disease; VE = vaccine efficacy; YOA = years of age.
Note: Number of participants with event was calculated as date of case−date of randomisation+1. Participants without a case in the specified time period were censored at the earliest date of 12 months postinjection, date of early discontinuation, date of unrelated death, and data cutoff date.
Results in this table exclude individuals who develop the outcome within ≤ 14 days post vaccination.
[a] VE is estimated by 1 minus hazard ratio (mRNA-1345 versus placebo). The CI for VE was based on a stratified Cox proportional hazard model with Efron's method of tie handling and with the vaccination group as a fixed effect, adjusting for stratification factors at randomisation.
[b] VE is estimated by 1 minus the ratio of incidence rates (mRNA-1345 versus placebo) as reported in the Clinical Study protocol mRNA-1345-P301, p27.
Bold indicates that predefined lower bound of the CI around VE was greater than 20%.

Figure 2: Cumulative incidence curves in Conquer RSV for first episode of RSV-LRTD (≥ 2 symptoms) in participants ≥ 60 YOA, up to 24 months after injection, (single dose, PPE set, 18.8-months median time to follow-up)



Source: Figure 2-14, p119 of the submission.
PPE = per protocol efficacy; RSV-LRTD = respiratory syncytial virus-lower respiratory tract disease; YOA = years of age.
Note: Results in this Figure exclude individuals who develop the outcome within ≤ 14 days post vaccination.

6.19 The submission stated that the results show ongoing VE, with the lower bound of the 95% CI ≥ 20% across all endpoints and for the different time points. Cumulative VE drops from 56.2% (95% CI 41.9, 67.2) at 12 months to 47.4% (95% CI 34.7, 57.7) at 24 months (Table 6).

6.20 Results in Figure 2 for the cumulative incidence of first episode of RSV-LRTD (≥ 2 symptoms) show that at around 16-18 months there is a substantial drop in number of participants at risk with the proportion decreasing from 60% at Month 16, to 2.1% by Month 24 (ATAGI Advice, June 2025). The evaluation considered this to mean that the longer-term estimate (i.e., 24 months) remains highly uncertain (ATAGI Advice, June 2025). ATAGI concluded that based on the available evidence, durability of vaccine effectiveness in adults ≥ 60 YOA appears to be established for up to 16 months (ATAGI Advice, June 2025). The evaluation commented that longer-term follow-up data are necessary to inform VE beyond 16-18 months.

6.21 In Figure 2, after 12 months, the arms of the cumulative incidence plot remain separated, yet parallel, suggesting a loss of immunity (ATAGI Advice, June 2025). The evaluation considered that results with estimates of VE based around time interval cases of RSV (e.g. 0–12 months, 12–24, 24+) would have been informative to aid the interpretation of the long-term efficacy of mRNA-1345. ATAGI recommended that the Sponsor provide results with estimates of VE based around interval cases of RSV (e.g. 0–12 months, 12–24, 24+) (ATAGI Advice, June 2025); this was not provided by the submission.

6.22 The VE results by RSV subtype (A and B) are summarised in Table 7.

Table 7: Cumulative VE for the prevention of RSV-LRTD with ≥ 2 symptoms and ARD in participants ≥ 60 YOA by RSV subtype (single dose, PPE set, 18.8-months median time to follow-up)

Primary endpoints	mRNA-1345		Placebo		VE[a] % 95% CI
	N	n (%)	N	n (%)	
VE for the prevention of RSV A					
RSV-LRTD ≥ 2 symptoms					
12 months	18,181	36 (0.20)	18,132	102 (0.56)	**65.0 (48.8, 76.0)**
24 months	18,181	54 (0.30)	18,132	128 (0.71)	**58.2 (42.5, 69.6)**
RSV-ARD					
12 months	18,181	60 (0.33)	18,132	150 (0.83)	**60.3 (46.5, 70.6)**
24 months	18,181	91 (0.50)	18,132	195 (1.08)	**53.8 (40.7, 64.0)**
VE for the prevention of RSV B					
RSV-LRTD ≥ 2 symptoms					
12 months	18,181	37 (0.20)	18,132	64 (0.35)	42.6 (14.0, 61.7)
24 months	18,181	77 (0.42)	18,132	122 (0.67)	37.4 (16.8, 53.0)
RSV-ARD					
12 months	18,181	80 (0.44)	18,132	133 (0.73)	**40.3 (21.3, 54.8)**
24 months	18,181	157(0.86)	18,132	241 (1.33)	**35.5 (21.1, 47.2)**

Source: Table 2-41, p121 of the submission.

ARD = acute respiratory disease; CI = confidence interval; n = number of participants with event; PPE = per-protocol efficacy; RSV = respiratory syncytial virus; RSV-LRTD = respiratory syncytial virus-associated lower respiratory tract disease; VE = vaccine efficacy; YOA = years of age.

Note: RSV-LRTD with 2 or more symptoms and RSV-ARD was calculated as date of case−date of randomization+1. Participants without a case in the specified time period were censored at the earliest date of 12 months postinjection, date of early discontinuation, date of unrelated death, and data cutoff date.

Results in this table exclude individuals who develop the outcome within ≤ 14 days post vaccination.

[a] VE based on HR was defined as 100% × (1−hazard ratio [mRNA-1345 vs placebo]). The CI for VE was based on a stratified Cox proportional hazard model with Efron's method of tie handling and with the vaccination group as a fixed effect, adjusting for stratification factors at randomisation.

Bold indicates that predefined lower bound of the CI around VE was greater than 20%.

6.23 VE against RSV disease endpoints caused by RSV subtype B was numerically lower than that measured against disease caused by RSV subtype A, although the CIs for the point estimates overlapped. ConquerRSV was not powered to compare VE by RSV subtypes. Noting this limitation, the lower bound 95% CI for the VE for the prevention of RSV-LRTD ≥ 2 symptoms for RSV B was lower than 20%, therefore it did not meet the pre-defined efficacy criteria. The PSCR stated that this is not a meaningful threshold from which to draw conclusions regarding effectiveness against RSV B strains, given the statistical power limitation acknowledged by the evaluation. The ATAGI Advice noted that for RSV seasons that contain higher rates of RSV B cases, the VE may not confer the benefit as reported in ConquerRSV (ATAGI Advice, June 2025). A numeric difference favouring subtype RSV A was also reported in RENOIR (RSVPreF) and AReSVi-006 (RSVPreF3 OA), noting that only AReSVi-006 resulted in a lower bound 95% CI ≥ 20% for prevention of RSV-LRTD caused by RSV subtype B (p12, RSVPreF PSD, November 2024).

6.24 The submission presented an assessment of VE for age subgroups relevant to inform the NIP listing. The VE for the prevention of RSV-LRTD (≥ 2 symptoms), RSV-ARD and severe RSV (median time to follow-up 18.8 months) is summarised in Table 8.

Table 8: Cumulative VE for the prevention of RSV-LRTD in subgroups of adults based on age, over 12 and 24 months (single dose, PPE set, 8.6 and 18.8-month follow-up)

Age Group	RSV-LRTD ≥ 2 symptoms			RSV-ARD			Severe RSV[b]		
	mRNA-1345 cases, n/N	Placebo cases, n/N	VE, % (95% CI)	mRNA-1345 cases, n/N	Placebo cases, n/N	VE, % (95% CI)	mRNA-1345 cases, n/N	Placebo cases, n/N	VE, % (95% CI)
12 months (8.6 months median follow-up)[a]									
Overall	47/18,112	127/18,045	**63.3 (48.7,73.7)**	86/18,112	185/18,045	**53.9 (40.5,64.3)**	11/18,112	43/18,045	**74.6 (50.7, 86.9)**
60 to 74 YOA	36/14,830	110/14,765	**67.6 (52.8,77.7)**	71/14,830	157/14,765	**55.2 (40.7,66.1)**	9/18,830	39/14,765	**77.1 (52.8, 88.9)**
≥ 75 YOA	11/3,282	17/3,280	35.3 (-38.1, 69.7)	15/3,282	28/3,280	46.7 (0.1, 71.5)	2/3,282	4/3,280	49.6 (-175.4, 90.8)
60-74 YOA ≥ 1 comorbidity	10/4,317	43/4,198	**77.4 (55.1, 88.7)**	20/4,317	47/4,198	**58.7 (30.3, 75.5)**	5/4,317	20/4,198	**75.7 (35.2, 90.9)**
60 to 69 YOA	31/11219	77/11170	**60.1 (39.5, 73.7)**	56/11219	109/11170	**49.1 (29.8, 63.1)**	NR	NR	NR
70 to 79 YOA	10/5464	45/5439	**78.0 (56.3, 88.9)**	23/5464	69/5439	**67.0 (47.0, 79.4)**	NR	NR	NR
≥ 80 YOA	5/1436	6/1429	-20.3 (-294.2, 63.3)	7/1429	7/1436	-0.2 (-185.6, 64.9)	NR	NR	NR
24 months (18.8 months median follow-up)									
Overall	132/18,181	248/18,132	**47.4 (35.0, 57.4)**	249/18,181	434/18,132	**43.4 (33.8, 51.6)**	36/18,181	80/18,132	**55.4 (33.8, 69.9)**
60 to 74 YOA	104/14,899	201/14,849	**48.9 (35.2, 59.7)**	200/14,899	353/14,849	**44.1 (33.6, 53.0)**	27/14,899	65/14,849	**58.9 (35.6, 73.8)**
≥ 75 YOA	28/3,282	47/3,283	40.8 (5.4, 62.9)	49/3,282	81/3,283	40.1 (14.5, 58.0)	9/3,282	15/3,283	39.8 (-37.5, 73.7)
60-74 YOA ≥ 1 comorbidity	23/4,343	68/4,219	**67.4 (47.8, 79.7)**	42/4,343	95/4,219	**57.4 (38.8, 70.4)**	9/4,343	34/4,219	**74.4 (46.6, 87.7)**
60 to 69 YOA	83/11,269	147/11,238	**44.3 (27.1, 57.4)**	36/11,269	62/11,238	**42.5 (13.3, 61.9)**	156/11,269	252/11,238	**39.0 (25.5, 50.1)**
70 to 79 YOA	36/5,487	81/5,459	**56.0 (34.9, 70.3)**	11/5,487	29/5,459	**62.3 (24.6, 81.2)**	69/5,487	145/5,459	**53.1 (37.5, 64.8)**
≥ 80 YOA	13/1,425	20/1,435	35.3 (-30.1, 67.8)	5/1,425	9/1,435	44.7 (-65.1, 81.5)	24/1,425	37/1,435	35.4 (-7.9, 61.4)

Source: Table presented in Section 2.6.2.1, p146 of the submission and Table 2-65, p147 of the submission; Table 32 and Table 38, pp129-139 of the mRNA-1345-P301 CSR for additional analysis (DCO 23 April 2023).

CI = confidence interval; CSR = clinical study report; DCO = data cut-off; NR = not reported; PPE = per protocol efficacy; RSV-ARD = respiratory syncytial virus–associated acute respiratory disease; RSV-LRTD = respiratory syncytial virus–associated lower respiratory tract disease; VE = vaccine efficacy; YOA = years of age.

[a] Relevant subgroup analyses were not provided for the period up to 12 months at the latest DCO with 18.8 months follow-up.

[b] The CSR defined severe RSV-LRTD as disease presenting with shortness of breath or cases requiring emergency room/urgent care visit.

Bold indicates that predefined lower bound of the CI around the vaccine efficacy was greater than 20%.

6.25 The results show that VE is lower in the ≥ 75 and ≥ 80 YOA subgroups compared with the overall population (≥ 60 YOA), with the lower 95% CI being below the 20% threshold for all outcomes for both ≥ 75 and ≥ 80 YOA subgroups at 12 and 24 months. This is likely driven by the ≥ 80 YOA subgroup, as the lower 95% CI is > 20% in the 70-79 YOA subgroup. ConquerRSV was not powered to assess VE in adults ≥ 75 YOA.

6.26 In its review of these data ATAGI noted there was an:

> "overall lack of evidence presented in the current Request for Advice specific to the target population. Although the VE may be lower for some outcomes in the ≥ 75-year age group (the main target population), the numbers of RSV cases are small, and it is likely that VE has been established for the target population. The durability of vaccine effectiveness appears to be established for up to 16 months in the intention-to-treat (ITT) population." (ATAGI Advice, June 2025).

Immunogenicity

6.27 The submission presented immunogenicity outcomes from a subgroup of participants in ConquerRSV (n=1,893). Results of neutralising antibody (nAb) levels from serum collected at baseline (pre-immunisation), study Day 29 and Day 181 (6 months post vaccination) from the per protocol immunogenicity set are presented in Table 9. No immunogenicity data were presented for timepoints beyond 181 days.

Table 9: Summary of nAb Levels (IU/mL) responses at Day 29 and Day 181 against RSV-A and RSV-B subtypes in a subgroup of ConquerRSV (single dose, PPI set, 18.8-months median time to follow-up)

	RSV A		RSV B	
	mRNA-1345 (n=1,532)	Placebo (n=341)	mRNA-1345 (n=1,532)	Placebo (n=341)
Baseline (Day 1)				
n[a]	1,531	341	1,531	340
GMT (95% CI[b])	2,554.4 (2416.9, 2699.8)	2,399.6 (2134.0, 2698.3)	1,423.3 (1351.6, 1498.9)	1,367.0 (1,218.6, 1,533.5)
Day 29				
n[a]	1,512	333	1,510	333
GMT (95% CI[b])	21,275.6 (20,098.6, 22,521.6)	2,414.4 (2,154.2, 2,706.0)	7,227.7 (6,848.5, 7,627.9)	1,305.0 (1,160.6, 1,467.4)
GMFR (95% CI[b])	8.34 (7.89, 8.81)	1.00 (0.95, 1.05)	5.10 (4.86, 5.36)	0.96 (0.91, 1.03)
SRR%[bc] (95% CI[e])	74.0% (71.7, 76.2)	0.6% (0.1, 2.2)	56.5% (54.0, 59.0)	1.5% (0.5, 3.5)
≥ 2-fold increase from baseline, %[f,d] (95% CI[e])	91.2% (89.7, 92.6)	4.5% (2.5, 7.3)	84.2% (82.2, 86.0)	5.4% (3.2, 8.4)
Day 181				
n[a]	1,421	318	1,421	318
GMT (95% CI[b])	7,083.8 (6,678.5, 7,513.7)	2,113.2 (1,874.8, 2,381.9)	2,795.3 (2,651.3, 2,947.1)	1,124.4 (1,003.6, 1,259.7)
GMFR (95% CI[b])	2.80 (2.66, 2.96)	0.88 (0.82, 0.95)	1.99 (1.89, 2.08)	0.83 (0.77, 0.90)
SRR%[bc] (95% CI[e])	32.8% (30.4, 35.3)	3.5% (1.7, 6.1)	19.9% (17.8, 22.0)	3.2% (1.5, 5.7)
≥ 2-fold increase from baseline, %[f,d] (95% CI[e])	61.0% (58.4, 63.5)	8.2% (5.4, 11.8)	46.7% (44.1, 49.3)	9.1% (6.2, 12.9)

Source: Table 2-42, p122 of the submission; Table 8, pp20-21 of the Extended Analysis CSR (median follow-up 18.8 months).
CI = confidence interval; GM = geometric mean; GMFR = geometric mean fold-rise; GMT = geometric mean titre; LLOQ = lower limit of quantification; max = maximum; min = minimum; nAb = neutralizing antibody; PPI = per-protocol immunogenicity; RSV-A = respiratory syncytial virus subtype A; RSV-B = respiratory syncytial virus subtype B; SRR = seroresponse rate; ULOQ = upper limit of quantification.
Note: One participant had missing data for GMFR and SRR and were therefore excluded from analyses.
[a] Number of participants with non-missing data at the visit (baseline or post-baseline).
[b] 95% CI was calculated based on the t-distribution of the log-transformed values or the difference in the log-transformed values for GM value and GM fold-rise, respectively, then back transformed to the original scale for presentation.
[c] Seroresponse at a participant level was defined as a change from below the LLOQ to equal or above 4 x LLOQ, or at least a 4-fold increase if baseline was equal to or above the LLOQ. For RSV-A, LLOQ: 13 IU/mL, ULOQ: 259,061 UL/mL; for RSV-B, LLOQ: 10 IU/mL, ULOQ: 112,476 IU/mL.
[d] Number of participants meeting the criterion at the timepoint.
[e] 95% CI was calculated using the Clopper-Pearson method.
[f] ≥ z-fold increase from baseline at participant level was defined as a change from below the LLOQ to equal or above z x LLOQ, or at least

6.28 The submission stated that all parameters of immunogenicity measured at Day 181 postinjection remain elevated relative to baseline. At Day 29 the GMT demonstrated an 8.3-fold increase above baseline, which then reduced to a 2.8-fold increase by Day 181 (66% reduction).

6.29 The evaluation considered that the decline from Day 29 to Day 181 should be interpreted with caution, as higher titres do not necessarily equate to greater efficacy. While higher titres may prolong protection, the key is maintaining levels above a protective threshold, noting that an immunological correlate of protection for RSV has not yet been established. Therefore, it is unknown whether, or at what point, immunity conferred by mRNA-1345 is likely to decline to a point below a protective threshold.

Indirect treatment comparison: mRNA-1345 versus RSVPreF and RSVPreF3 OA

6.30 The submission provided an anchored (placebo) ITC for mRNA-1345 (ConquerRSV) against RSVPreF (RENOIR) and RSVPreF3 OA (AReSVi-006) for VE assessed as RSV-LRTD ≥ 2 symptoms, RSV-LRTD with ≥ 3 symptoms and ARD in the ≥ 75 YOA population. No comparative results were presented in the submission for the ≥ 60 YOA population, however, an ITC for this population was included in the request for advice submitted to ATAGI (ATAGI advice, June 2025).

6.31 Results of the anchored ITC presented in the submission for the ≥ 75 YOA population included:

- Base case: Used the primary analysis with the first available data point from each trial. Given the short follow-up periods (3.7, 7.1, and 6.7 months median time to follow-up in ConquerRSV, RENOIR and AReSVi-006, respectively), the evaluation considered that this comparison is vulnerable to confounding due to the differences in the timing of vaccination relative to the incidence of RSV. Furthermore, the shorter follow-up duration for mRNA-1345 likely captures vaccine efficacy closer to its peak, before waning effects become more pronounced compared to RENOIR and AReSVi-006. VE against RSV-LRTD with ≥ 2 symptoms in ConquerRSV was substantially higher at 3.7 months follow-up (83.7%) than at 8.6 months follow-up (63.3%), which is more closely aligned with the follow-up periods in RENOIR and AReSVi-006.
- Scenario 1: Matched the 8.6-month median time to follow-up data from mRNA-1345 with combined Season 1 and 2 data from RSVPreF (16.4 months, Walsh et al. 2024) and RSVPreF3 OA (17.8 months, Ison et al. 2024). The submission stated that ConquerRSV was initiated at the tail-end of the 2021-2022 RSV season, and the additional analysis completed at a median follow-up of 8.6 months included a large number of subjects who were exposed to two RSV seasons. The evaluation considered that this claim was not supported by the data in the submission, given that only 28.1% of participants were exposed to 2 RSV seasons in ConquerRSV at this timepoint. The timing of recruitment was unclear, making it difficult to determine the level of exposure to RSV among participants. Additionally, waning VE of RSVPreF and RSVPreF3 OA with longer follow-up could result in relatively higher apparent effectiveness of mRNA-1345.
- Scenario 2: Applied 8.6-month data for mRNA-1345, 7.6-month data for RSVPreF (Season 2 only), and 6.7-month data for RSVPreF3 OA. The evaluation was not able to verify the ITC presented comparing mRNA-1345 with RSVPreF for this scenario as source data was not presented by the submission. The evaluation extracted the relevant source data from the PSD (Table 9, RSVPreF PSD, November 2024) and the ITC results based on these data are reported in Figure 3. ATAGI noted that the comparison of ConquerRSV at 8.6 months of follow up versus Season 2 of RENOIR was inappropriate as participants in the RENOIR cohort were followed up for 7.6

months for their second season, which does not represent 7.6 months from injection (ATAGI advice, June 2025).

- Scenario 3: Applied 18.8 months data for mRNA-1345 (reporting VE up to 24 months) and the combined Season 1 and 2 data for RSVPreF and RSVPreF3 OA (16.4 months follow-up and 17.8 months follow-up, respectively). The evaluation noted that this scenario provided the longest-term follow-up evidence and considered it is the most relevant to inform long-term comparative efficacy, noting that very few participants (2.1%) in ConquerRSV remain at risk at 24 months (paragraph 6.20). ATAGI recommended that a comparison of results at longer follow-up be provided as they are likely to be the most informative (ATAGI Advice, June 2025).

6.32 Differences between ConquerRSV, RENOIR and AReSVi-006 in terms of their study design and patient characteristics that are likely to affect the transitivity of the ITC have been described in paragraph 6.15. The evaluation noted that other issues that may limit the interpretation of the results include:

- The results presented in the submission and relied upon for the clinical claim were based on sub-group analyses of those ≥ 75 YOA from all 3 trials. These subgroups represented a small proportion of the relevant trials; 18% in ConquerRSV, 16% in RENOIR, and 21% in AReSVi-006. The small sample sizes and limited number of cases observed resulted in wide confidence intervals, precluding robust conclusions and raising concerns about statistical reliability of the ITCs.
- The outcomes reported and used in the ITC for the ≥ 75 YOA population in RENOIR were based on the subset of outcomes that were medically attended (medically attended events in RENOIR included: telephone consultation with a medical practitioner, doctors visit, emergency room visit, or hospitalisation). These outcome definitions were narrower than the corresponding outcomes reported in ConquerRSV which were not restricted to those that were medically attended. The reason for the inclusion of data relating to medically attended cases in RENOIR in the ITC was not addressed by the submission. The direction and magnitude of any bias is uncertain.

6.33 Data extracted from the 3 trials and used to inform the ITC for participants who were ≥ 75 YOA are shown in Table 10. A summary of the ITC results for the base case and scenarios in participants aged ≥ 75 YOA is provided in Figure 3 and Table 11. ITC results relating to RSV-LRTD ≥ 3 symptoms for all scenarios could not be replicated during the evaluation and it was not clear from the submission which outcomes were used to derive these results. A range of errors in the results of the ITC were identified by the evaluation. The results presented in Table 11 and Figure 3 were corrected during the evaluation using the data consistent with the scenarios proposed in the submission.

Table 10: Trial observations used as part of the ≥ 75 YOA ITC

	ConquerRSV			RENOIR			AreSVi-006		
	Placebo cases, n/N	mRNA-1345 cases, n/N	VE, % (95% CI)	Placebo cases, n/N	RSVPreF cases, n/N	VE, % (95% CI)	Placebo cases, n/N	RSVPreF3 OA cases, n/N	VE, % (95% CI)
Outcome: RSV-ARD									
Primary analysis	11/2,815	1/2,809	90.9 (29.3, 98.8)	8/2,904	1/2,892	87.5 (6.8, 99.7)	NR	NR	NR
Additional Analysis	28/3,280	15/3,282	46.7 (0.1, 71.5)	12/2,477 [a]	6/2,486 [a]	50.0 (-43.9,84.6) [a]	NR	NR	NR
Extended Analysis / Season 1&2	81/3,283	49/3,282	40.1 (15.5, 58.0)	20/2,904	7/2,892	65.0 (13.8, 87.5)	NR	NR	NR
Outcome: RSV-LRTD ≥ 2 symptoms									
Primary analysis	6/2,815	1/2,809	83.3 (-38.9, 98.0)	7/2,904	1/2,892	85.7 (-11.2, 99.7)	6/2,646	3/2,671	52.5 (-122.5, 92.3)
Additional Analysis	17/3,280	11/3,282	35.3 (-38.1, 69.7)	5/2,477 [a]	3/2,486 [a]	40.0 (-208.4,90.7) [a]	NR	NR	NR
Extended Analysis / Season 1&2	47/3,283	28/3,282	40.8 (5.4, 62.9)	12/2,904	4/2,892	66.7 (-10.0, 92.2)	24/2,647	8/2,672	49.3 (-18.2, 80.6)
RSV-LRTD ≥ 3 symptoms									
Primary analysis	1/2,815	0/2,809	100 (NE, 100)	3/2904	0/2892	100 (-142,100)	NR	NR	NR
Additional Analysis	5/3,280	3/3,282	40.1 (-150.8, 85.7)	3/2477	2/2486	33.3 (-482.0-94.4)	NR	NR	NR
Extended Analysis / Season 1&2	16/3,283	9/3,282	43.8 (-27.1, 75.2)	6/2904	2/2892	66.7 (-86.4,96.7)	NR	NR	NR

Source: Table 2-124, p204 of the submission. Table 9, p19 of RSVPreF PSD, November 2024 PBAC meeting.

CI = confidence interval; ITC = indirect treatment comparison; RSV-ARD = respiratory syncytial virus acute respiratory disease; RSV-LRTD = respiratory syncytial virus related lower respiratory track disease; NE = not estimable; NR = not reported; VE = vaccine efficacy; YOA = years of age. Several errors were noted in the submission Table 2-124 and have been corrected in this table.

[a] Sourced during the evaluation from Table 9, RSVPreF PSD, November 2024.

Table 11: Bucher ITC results in participants ≥ 75 YOA (after correction during evaluation)

Outcome	Comparison	RR (incidence rate)	95% CI	p-value
Base case				
RSV-ARD	mRNA-1345 vs RSVPreF	0.73	0.04, 13.41	0.830
RSV-LRTD ≥ 2 symptoms	mRNA-1345 vs RSVPreF3 OA	0.34	0.03, 4.23	0.400
	mRNA-1345 vs RSVPreF	1.16	0.06, 22.87	0.920
RSV-LRTD ≥ 3 symptoms	mRNA-1345 vs RSVPreF	2.33[c]	0.03, 182.43[c]	0.704[c]
Scenario 1[b]				
RSV-ARD	mRNA-1345 vs RSVPreF (corrected)	1.52	0.53, 4.41	0.438
RSV-LRTD ≥ 2 symptoms	mRNA-1345 vs RSVPreF3 OA (corrected)	1.96	0.65, 5.88	0.231
	mRNA-1345 vs RSVPreF (corrected)	1.93	0.5, 7.53	0.342
RSV-LRTD ≥ 3 symptoms[a]	mRNA-1345 vs RSVPreF (corrected)	1.79[e]	0.21, 15.32[e]	0.594[e]
Scenario 2[b]				
RSV-ARD	mRNA-1345 vs RSVPreF (corrected)	1.08[d]	0.34, 3.44[d]	0.902[d]
RSV-LRTD ≥ 2 symptoms	mRNA-1345 vs RSVPreF3 OA (corrected)	1.31	0.27, 6.33	0.740
	mRNA-1345 vs RSVPreF (corrected)	1.08[d]	0.21, 5.46[d]	0.923[d]
RSV-LRTD ≥ 3 symptoms[a]	mRNA-1345 vs RSVPreF (corrected)	0.90[e]	0.09, 8.92[e]	0.931[e]
Scenario 3				
RSV-ARD	mRNA-1345 vs RSVPreF	1.72	0.68, 4.36	0.251
RSV-LRTD ≥ 2 symptoms	mRNA-1345 vs RSVPreF3 OA	1.80	0.72, 4.55	0.211
	mRNA-1345 vs RSVPreF	1.78	0.52, 6.05	0.355
RSV-LRTD ≥ 3 symptoms[a]	mRNA-1345 vs RSVPreF (corrected)	1.68[e]	0.28, 10.12[e]	0.570[e]

Source: Table 2-125, p205 of the submission.

CI = confidence interval; ITC = indirect treatment comparison; RSV-ARD = respiratory syncytial virus related acute respiratory disease; RSV-LRTD = respiratory syncytial virus related lower respiratory tract disease; RR = risk ratio; YOA = years of age.

RR < 1 favours mRNA-1345.

Outcomes for participants aged ≥ 75 years for RSVPreF include RSV-LRTI with ≥ 2 symptoms, RSV-LRTI with ≥ 3 symptoms, and RSV-ARD defined as medically attended RSV requiring any healthcare visit. These results are not directly comparable with the outcomes reported for mRNA-1345 and RSVPreF3 OA.

Several errors were noted in the submission and were corrected during the evaluation.

[a] ITC conducted during the evaluation used RSV-LRTD ≥ 3 symptoms reported in ConquerRSV and RENOIR and RSV-LRTD ≥ 3 symptoms as reported in AreSVi-006

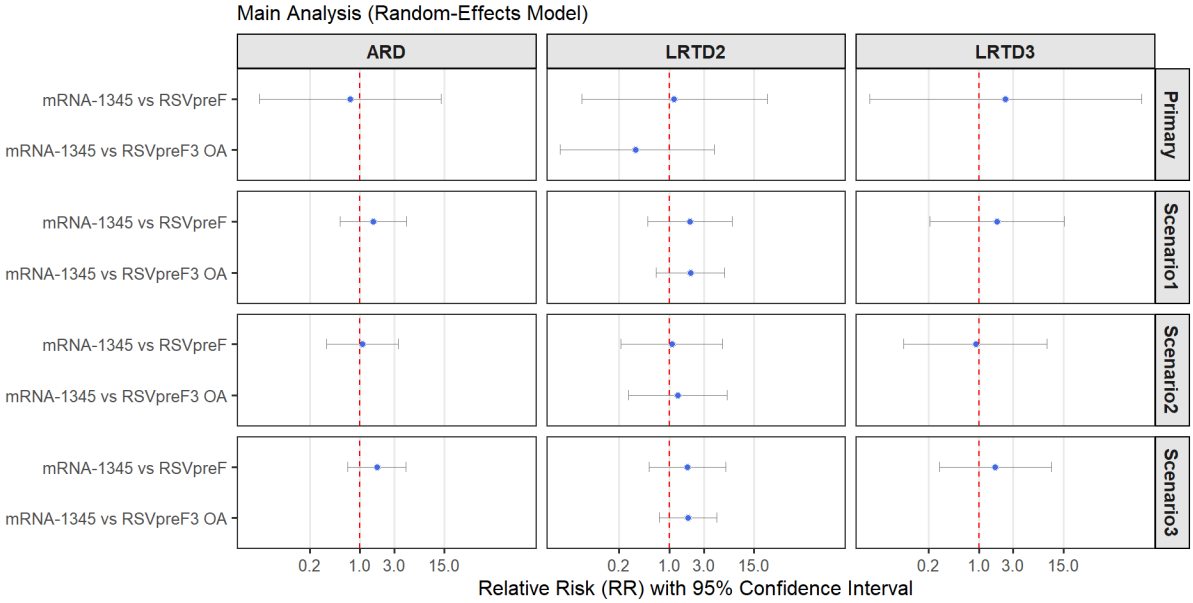
[b] Results in the Table 2-125 of the submission incorrectly reported Scenario 2 results as Scenario 1, and Scenario 1 results as Scenario 2.

[c] Could not be verified as there were 0 cases in both mRNA-1345 and RSVPreF.

[d] The submission did not provide the source data for RSVPreF for these comparisons in Table 2-124. During the evaluation, the results reported in the submission could not be replicated.

[e] The source data for RSVPreF were incorrectly reported in Table 2-124 of the submission. During the evaluation, the results reported in the submission could not be replicated.

Figure 3: Forest plot of the anchored ITC for ≥ 75 YOA in ConquerRSV, RENOIR and AreSVi-006



Source: Produced during the evaluation using the amended results from Table 11.
ARD = acute respiratory diseases; ITC = indirect treatment comparison; LRTD= lower respiratory track diseases; LRTD2 = lower respiratory track diseases with ≥ 2 symptoms; LRTD3 = lower respiratory track diseases with ≥ 3 symptoms; RR= relative risk; YOA = years of age.
RR < 1 favours mRNA-1345.
Note: Outcomes for participants aged ≥ 75 years for RSVPreF include RSV-LRTI with ≥ 2 symptoms, RSV-LRTI with ≥ 3 symptoms, and RSV-ARD defined as medically attended RSV requiring any healthcare visit. These results are not directly comparable with the outcomes reported for mRNA-1345 and RSVPreF3 OA.

6.34 Across all scenarios for all outcomes for the ≥ 75 YOA group, no statistically significant differences were observed between the mRNA-1345, RSVPreF3 OA, or RSVPreF vaccines. The submission did not establish a formal non-inferiority margin. While no statistically significant differences were observed, the relative risk estimates consistently indicated a trend favouring RSVPreF and RSVPreF3 OA over mRNA-1345, particularly for Scenario 3. As such, the evaluation considered that the possibility that mRNA-1345 provides less protection against the presented outcomes cannot be ruled out, noting that the ITC lacks sufficient power to demonstrate statistical superiority of any vaccine.

6.35 The submission presented evidence of a waning effect for mRNA-1345 (Das 2024) and RSVPreF3 OA (Papi 2023) conducted in the overall population ≥ 60 YOA (data not shown). Both vaccines exhibit waning over time; the rate of waning for mRNA-1345 was calculated at approximately 2.4% per month and 2.1% per month for RSVPreF3 OA. The submission stated that the sponsor was not able to identify a similar calculation of waning for RSVPreF. These findings suggest that mRNA-1345 wanes at a faster rate than RSVPreF3 OA. The evaluation considered that this comparison should be viewed with caution, as both estimates of waning are unvalidated projections and are therefore uncertain.

6.36 The ATAGI advised that evidence on "waning of vaccine efficacy in the target population (aged 75 years and above) would be most informative. The evaluation noted that where data are insufficient for subgroup analyses, evidence to support the

generalisability of vaccine waning from the whole trial population to the target population would be required. Where waning of vaccine efficacy for mRNA-1345 is different to that for RSVPreF, the Sponsor should clearly describe how non-inferiority is maintained" (ATAGI Advice, June 2025). The submission did not discuss the waning profile in participants ≥ 75 YOA.

Comparative harms

mRNA-1345 versus placebo

6.37 The Clinical Study Report for the latest follow-up did not report solicited adverse reactions (ARs), therefore the solicited ARs reported at the 8.6 months median time to follow-up are shown in Table 12.

Table 12: Summary of participants with solicited ARs within 7 days after injection in ConquerRSV (single dose, solicited safety set, 8.6 months median time to follow-up)

AR category	mRNA-1345 (N=18,174) n (%)	Placebo (N=18,102) n (%)
Solicited adverse reactions[a]		
Any ARs (local or systemic)	12,119 (68.6)	6,782 (38.5)
Grade 3	1,069 (6.1)	685 (3.9)
Grade 4	35 (0.2)	29 (0.2)
Grade 3 or 4	1,104 (6.2)	714 (4.1)
Local ARs		
Administration site (local)	10,367 (58.7)	2,845 (16.2)
Pain, any grade	9,942 (56.3)	2,407 (13.7)
Any local AR, Grade 3 or 4	558 (3.2)	305 (1.7)
Systemic ARs		
Any systemic AR	8,432 (47.7)	5,798 (32.9)
Fatigue, any grade	5,470 (31.0)	3,518 (20.0)
Headache, any grade	4,764 (27.0)	3,332 (18.9)
Myalgia, any grade	4,574 (25.9)	2,542 (14.4)
Arthralgia, any grade	3,867 (21.9)	2,477 (14.1)
Grade 3	77 (0.4)	41 (0.2)
Grade 4	35 (0.2)	29 (0.2)
Any systemic AR, Grade 3/4	710 (4.0)	508 (2.9)

Source: Table 2-57, Table 2-58 and Table 2-59 pp137-139 of the submission.
AR = adverse reaction.
[a] solicited events collected were solicited administration site events (pain, erythema, and swelling, axillary swelling or tenderness) and solicited systemic events (fever, headache, fatigue, myalgia, arthralgia nausea/vomiting and chills).

6.38 Whilst a higher incidence of ARs was generally observed in the mRNA-1345 arm compared to placebo, the solicited events were transient and generally mild to moderate in reactogenicity (Grade 1 and Grade 2).

6.39 A summary of unsolicited treatment-emergent adverse events (TEAEs) up to 28 days and up to the latest DCO after injection is presented in Table 13.

Table 13: Summary of unsolicited TEAEs in ConquerRSV (cumulative from study start) (safety set, 28-day post vaccination, 18.8 median follow-up)

AE Category	mRNA-1345 (N=18,369) n (%)	Placebo (N=18,31A6) n (%)
Unsolicited TEAEs up to 28 days after injection, regardless of relationship to study injection		
All	3,823 (20.8)	3,467 (18.9)
Serious	126 (0.7)	114 (0.6)
Fatal	2 (< 0.1)	6 (< 0.1)
Medically attended	1,664 (9.1)	1,587 (8.7)
Leading to study discontinuation	2 (< 0.1)	11 (< 0.1)
Severe ≥ Grade 3	138 (0.8)	138 (0.8)
Any AESI	3 (< 0.1)	9 (< 0.1)
Unsolicited TEAEs up to 28 days after injection, related to study injection		
All	1,050 (5.7)	807 (4.4)
Serious	4 (< 0.1)	2 (< 0.1)
Fatal	0	0
Medically attended[a]	67 (0.4)	51 (0.3)
Leading to study discontinuation	0	0
Severe ≥ Grade 3	54 (0.3)	53 (0.3)
Any AESI	1 (< 0.1)	2 (< 0.1)
Unsolicited TEAEs up to data cutoff date (08 Mar 2024), regardless of relationship to study injection		
Serious	2,296 (12.5)	2,298 (12.5)
Fatal	211 (1.1)	223 (1.2)
Medically attended	10,476 (57.0)	10,227 (55.8)
Leading to study discontinuation	233 (1.3)	256 (1.4)
Any AESI	102 (0.6)	115 (0.6)

Source: Table 2-43, p123 of the submission.
AESI = adverse event of special interest; TEAE = treatment-emergent adverse event.
[a] medically attended TEAEs included emergency room/urgent care, outpatient physician visits and per-protocol illness visits.

6.40 Overall, the incidence of unsolicited TEAEs, serious adverse events, fatal events, medically attended adverse events, severe TEAEs, adverse events of special interest (AESIs) and TEAEs leading to study discontinuation, including those considered to be related to study injection per investigator, was balanced between the groups. Most events occurred between 28 days and 6 months after injection and no fatal events were considered related to study injection by the investigator.

6.41 The submission presented additional data on AESIs for which ATAGI had raised concerns, in particular acute pericarditis. Investigator-reported events of myocarditis or pericarditis were reviewed by a Cardiac Event Adjudication Committee (CEAC). Review of cumulative safety data showed that no CEAC adjudicated events of acute myocarditis or acute pericarditis were reported within a 42-day risk window. For the period beyond 42 days postinjection, there were 3 participants in the mRNA-1345 group and 2 participants in the placebo group with CEAC adjudicated events of acute pericarditis. None were assessed by the investigator to be related to study injection. No CEAC adjudicated cases of acute myocarditis were reported in either group.

mRNA-1345 versus RSVPreF and RSVPreF3 OA

6.42 Due to the difference in safety outcome definitions and time to follow-up across trials, the submission did not provide an anchored ITC for safety outcomes. The evaluation considered that this was reasonable and consistent with ATAGI's view (ATAGI Advice, June 2025).

6.43 The submission presented a comparison of safety data for mRNA-1345 with RSVPreF and RSVPreF3 OA by calculating a crude incidence ratio between the vaccine and placebo arms of the individual trials and then comparing the ratio between the trials (see Table 14; differences in the types of events presented across comparisons reflect variations in how outcomes were defined and reported in the pivotal trials, rather than the analytical approach applied). While unsolicited AEs were reported at a higher rate in ConquerRSV than RENOIR, the incidence ratio between the trials is comparable. The submission claimed that based on the data presented, RSVPreF3 OA appears to be more reactogenic than mRNA-1345, noting that most events in both trials were mild in severity.

6.44 ATAGI considered that a claim of non-inferiority in safety is unlikely to be sufficiently supported by the naïve (unanchored, unadjusted) comparison as there were no data regarding the type of event symptoms (ATAGI Advice, June 2025). While the data presented by the submission did not preclude a difference in the type of event symptoms between vaccines, the evaluation considered that there do not appear to be substantial differences in the overall adverse event profiles between mRNA-1345 and RSVPreF and RSVPref3 OA.

Table 14: Crude comparison of solicited local and systemic ARs with RSVPreF, RSVPreF3 OA and mRNA-1345 (adults ≥ 60 years of age)

Comparison of RENOIR vs ConquerRSV						
Outcome	**RENOIR**			**ConquerRSV[d]**		
	RSVPreF incidence N=17,215	**Placebo incidence N=17,069**	**Crude ratio[h]**	**mRNA-1345 incidence N=17,734**	**Placebo incidence N=17,679**	**Crude ratio[h]**
	AR, to 1 month post injection			**Unsolicited TEAE, up to 28 days**		
Any	9.0%	8.5%	1.0	20.4%	18.8%	1.0
Severe	2.3%	2.3%	NA	0.7%	0.7%	NA
	AR, average follow-up 6.78 months			**Unsolicited TEAE, median of 3.7 months follow-up**		
Any serious adverse event[g]	2.3%	2.3%	NA	2.8%	2.8%	NA
AR leading to discontinuation	< 0.1%	< 0.1%	NA	< 0.1 %	< 0.1 %	NA
Related	0.0%	0.0%	NA	0.0%	0.0%	NA
Death[f]	0.3%	0.3%	1	0.1%	0.1%	1
Deaths, related	0.0%	0.0%	NA	0.0%	0.0%	NA
Comparison of AreSVi-006 vs ConquerRSV						
Outcome	**AreSVi-006[c]**			**ConquerRSV[d]**		
	RSVPreF3 OA Incidence N=879	**Placebo Incidence N=878**	**Crude ratio**	**mRNA-1345 Incidence N=17,665**	**Placebo Incidence N=17,679**	**Crude ratio**
Solicited local and systemic ARs[a,b]						
Any solicited reaction	71.9%	27.9%	2.6	68.6%	38.5%	1.8
Any Grade 3 or 4 solicited reaction	4.1%	0.9%	4.6	6.2%	4.1%	1.5
Unsolicited ARs						
Any/All unsolicited TEAE	33.0%	17.8%	1.9	20.4%	18.8%	1.1
Grade 3 unsolicited TEAE	2.0%	1.3%	1.5	0.7%	0.7%	1
Any/All unsolicited TEAE related to vaccine	24.9%	5.8%	4.3	5.8%	4.5%	1.3
Grade 3 unsolicited TEAE related to vaccine	0.9%	0.2%	4.5	0.3%	0.3%	1
Any SAE[e]	4.2%	4.0%	1.0	2.8%	2.8%	1
Fatal SAE regardless of relationship to study vaccination	0.4%	0.5%	0.8	0.1%	0.1%	1

Source: Table 2-122, p201; Table 2-123, p201 of the submission. Table 36, p60 of ATAGI Advice, June 2025.
AR = adverse reaction; NA = not applicable; SAE = serious adverse event; TEAE = treatment-emergent adverse events.
[a] AreSVi-006 followed Up to 4 days after injection, ARs were measured from mild (grade 1) to severe (grade 3)
[b] ConquerRSV followed up to 7 days after injection
[c] AreSVi-006 followed Up to 30 days after injection
[d] ConquerRSV followed up to 28 days after injection
[e] Up to 6 months follow-up for RSVPreF3 OA and up to November 2022 database lock (median follow-up 6.7 months) for mRNA-1345. RSVPreF3 OA events calculated using the exposed population data set as reported in Papi 2023 and Attachment 23. mRNA-1345 events calculated using the safety set per protocol.
[f] Corresponds to adverse event leading to death in RENOIR and deaths due to any cause in ConquerRSV.
[g] There were 3 events assessed as related to study intervention by the investigator in 3 participants receiving RSVPreF group and none receiving placebo. The 3 cases reported were: Hypersensitivity (allergic reaction; moderate severity, Guillain-Barre syndrome (GBS; life-threatening), and Miller Fisher syndrome (MFS; severe) (a rare form of GBS).
[h] Calculated incidence treatment / incidence placebo if greater than 0.1% difference in arms.

Benefits/harms

6.45 A benefits and harms table is not presented for the comparison against RSVPreF and RSVPreF3 OA as the submission made a claim of non-inferiority. A summary of the comparative benefits and harms for mRNA-1345 versus placebo in participants aged ≥ 60 years is presented in Table 15. The benefits and harms are not presented for participants ≥ 75 YOA because the number of events was low in this subgroup, and ConquerRSV was not powered to detect statistically significant differences between arms for outcomes in this subgroup.

Table 15: Summary of comparative benefits and harms for mRNA-1345 and placebo

Benefits						
RT-PCR confirmed RSV-LRTD						
Event	**mRNA-1345**	**Placebo**	**Absolute Difference n (%)**	**Cumulative VE% (CI [a])**		
≥ 60 YOA, cumulative estimates over consecutive seasons (18.8-months median time to follow-up)						
14 days to 12 months	73/18,181 (0.4%)	165/18,132 (0.9%)	40 (0.5%)	56.2 (41.9, 67.2)		
14 days to 18 months	113/18,181 (0.6%)	225/18,132 (1.2%)	112 (0.6%)	50.3 (37.5, 60.7)		
14 days to 24 months	132/18,181(0.7%)	248/18,132 (1.4%)	116 (0.7%)	47.4 (34.7, 57.7)		
Harms ≥ 60 YOA						
ConquerRSV	**mRNA-1345 n/N**	**Placebo n/N**	**RR (95% CI)**	**Event rate/100 patients**		**RD (95% CI)**
				mRNA-1345	**Placebo**	
Solicited Grade 3 events within 7 days following vaccination						
Any AR	1069/17665	685/17598	**1.56 (1.42, 1.71),** p< 0.00001	6.1	3.9	**0.02 (0.02, 0.03),** p< 0.00001
Admin-site AR	558/17665	305/17598	**1.82 (1.59, 2.09),** p< 0.00001	3.2	1.7	**0.01 (0.01, 0.02),** p< 0.00001
Systemic AR	77/17665	41/17598	**1.87 (1.28, 2.73),** p=0.001	0.4	0.2	**0.002 (0.00, 0.00),** p=0.0010
Unsolicited ARs within 28 days post vaccination						
Any Grade 3	124/17734	119/17679	1.04 (0.81, 1.33), p=0.77	0.7	0.7	0.00 (-0.00, 0.00), p=0.77
Any Grade 3 related to the intervention	52/17734	48/17679	1.08 (0.73, 1.60), p=0.70	0.3	0.3	0.00 (-0.00, 0.00), p=0.70
Any medically attended	1842/17734	1739/17679	1.06 (0.99, 1.12), p=0.09	10.4	9.8	0.005(-0.00, 0.01), p=0.09

Source: Table 2-19, p100; Table 22-20, p101; Table 2-21, p103; Table 2-31, pp118-119 of the submission. Compiled during the evaluation from evaluation from Table 12.4, p296 of 'RSV OA = Adj-006 Study Report (Blinded End of Season 2) Published 28 Jun 2023' of the Submission.

AR = adverse reaction; CI = confidence interval; N = number of participants; n = number of participants with at least one RT-PCR confirmed RSV-LRTD; n/T (per 1000) = incidence rate of participants reporting at least one event; RD = risk difference; RR = relative risk; RSV-LRTD = respiratory syncytial virus related lower respiratory tract disease; RSV = respiratory syncytial virus; RT-PCR = reverse transcription-polymerase chain reaction; T (year) = sum of follow-up time (from Day 15 post-vaccination till first occurrence of the event or till the efficacy data lock point or till drop-out date) expressed in years; VE = vaccine efficacy; YOA = years of age.

RR and RD were calculated by the submission and should be considered as indicative as the study was not powered for comparisons of safety.

Bold indicates statistically significant results.

6.46 On the basis of direct evidence presented by the submission, for every 1,000 individuals ≥ 60 YOA vaccinated with mRNA-1345, in comparison with placebo (no vaccine):

- Approximately 7 fewer adults will have RT-PCR confirmed RSV-LRTD over a period of 24 months.
- Approximately 20 additional adults would experience any Grade 3 solicited events within 7 days of vaccination.
- Approximately 2 additional adults would experience grade 3 systemic solicited events within 7 days of vaccination.

Clinical claim

mRNA-1345 versus placebo

6.47 The submission claimed that for adults aged ≥ 75 years and Aboriginal and Torres Strait Islander people ≥ 60 years of age, mRNA-1345 is superior in terms of effectiveness compared to placebo.

6.48 The ESC agreed with the evaluation that this claim was adequately supported for adults ≥ 60 YOA for up to 16 months. Beyond 16 months, the proportion of participants remaining at risk is too small (2% at 24 months) to allow for meaningful conclusions about long-term effectiveness (paragraph 6.20).

6.49 It was noted that there was a reduction in cumulative VE from 56.2% (42.2, 66.7) at 12 months, to 50.3% (37.5, 60.7) at 18 months and 47.4% (35.0, 57.4) at 24 months. It was also noted that immunogenicity data in ConquerRSV showed a substantial decline (66%) in antibody levels post vaccination, between Month 2 and Month 6 (Day 181). The ESC considered that the longevity of the immune response is a key consideration. The approximate interval-specific VE estimated during the evaluation revealed notably lower VE after 12 months than was evident from the cumulative VE estimates (interval efficacy of 28.3% for 12–24 months for RSV-LRTD ≥ 2 symptoms estimated by the evaluation, compared with cumulative efficacy of 47.4% for 0-24 months in ConquerRSV.)

6.50 The evaluation considered that the clinical claim was not adequately supported for adults ≥ 75 YOA. VE in the ≥ 75 YOA subgroup is lower compared to the VE in the overall population and the lower 95% CI was below the 20% threshold for success for RSV-LRTD ≥ 2 symptoms, RSV-ARD, and severe RSV. However, the evaluation acknowledged that although the VE was lower in adults ≥ 75 YOA compared with those ≥ 60 YOA, the extent of the age effect on VE may be considered uncertain given the low number of observed RSV cases and the small sample size in the ≥ 75 YOA subgroup, comprising only 18% of the overall population. The ESC agreed with the evaluation that this is an area of uncertainty and may present an applicability issue of the ConquerRSV trial efficacy to the proposed target population, given the low proportion of trial participants ≥ 75 YOA and no Aboriginal and Torres Strait Islander

participants (see paragraph 6.54). The PSCR and Pre-PBAC response stated that the ConquerRSV trial was not powered to compare VE by population subgroups and therefore wider confidence intervals are expected due to reduced sample size and event accrual.

6.51 The PBAC has noted a similar issue in previous considerations of RSV vaccines where the clinical trial (i.e. RENOIR) was not powered to detect statistically significant differences between the arms for the subgroup of participants for which listing is being sought (paragraph 7.15, RSVPreF PSD, November 2024).

6.52 The PSCR provided the results of a real-world evidence study published after the sponsor's submission to the PBAC, evaluating the effectiveness of a single dose of RSVPreF3 OA, RSVPreF and mRNA-1345 against RSV-hospitalisation among 6,958 adults ≥ 60 years across 26 US hospitals during two RSV seasons (2023–2025) (Surie 2025). The study provided results for the subgroups of patients 60-74 years and ≥ 75 years for RSVPreF3 OA and RSVPreF but was unable to assess mRNA-1345 effectiveness due to low uptake (n=3). VE was lower in ConquerRSV than as reported in Surie (2025) for RSVPreF3 OA and RSVPreF, particularly in the ≥ 75 YOA subgroup.

6.53 The Pre-PBAC response provided 24 month follow-up data summarising VE for the period from 14 days to 24 months post-injection. The Pre-PBAC response stated that efficacy of mRNA-1345 was sustained through the extended follow-up period (an interval that includes at least two RSV seasons) and demonstrated a plateau with comparable estimates at 18.8 months (VE 47.4; 95% CI 35.0, 57.4) and 24.1 months (VE 44.3; 95% CI 32.4, 54.1) median follow-up (Table 5).

6.54 Although no data were presented to support the requested listing for Aboriginal and Torres Strait Islander people 60-74 YOA, the ESC and the evaluation considered that it may be reasonable to accept the claim given that it is unlikely that direct evidence in this population will ever become available. The PSCR stated that the reliability of any morbidity data in this patient population would be further limited by small patient numbers.

6.55 Overall, with respect to the efficacy of the mRNA-1345 vaccine compared to no vaccine observed in the ConquerRSV trial, the PBAC agreed with the arguments presented by the evaluation, the ESC and the ATAGI. It considered that the claim of superior efficacy:

- Was adequately supported for adults ≥ 60 YOA for up to 16 months;
- Was uncertain for adults ≥ 75 YOA because VE for this age group is lower than VE in the overall population (≥ 60 YOA) and the lower 95% CI is below the 20% threshold for VE success, notwithstanding the low number of observed RSV cases and the small sample size in the ≥ 75 YOA subgroup.

The PBAC also noted that:

- The longevity of the immune response is a key consideration given that immunogenicity data in ConquerRSV showed a substantial decline (66%) in antibody levels between Month 2 and Month 6 post vaccination;
- The findings of the overall ConquerRSV trial population may not be applicable to the proposed target population (≥ 75 YOA) given the low proportion of trial participants ≥ 75 YOA (18%).

6.56 The submission described mRNA-1345 as inferior, but with a well-tolerated safety profile compared to placebo. The PBAC agreed with the evaluation that this claim was adequately supported by the available evidence.

Indirect treatment comparison: mRNA-1345 versus RSVPreF and RSVPreF3 OA

6.57 The submission claimed that for adults ≥ 75 YOA and Aboriginal and Torres Strait Islander people ≥ 60 YOA, mRNA-1345 is non-inferior in terms of efficacy compared to RSVPreF and RSVPreF3 OA. The sponsor's revision of the non-inferiority clinical claim, as described in the PSCR and Pre-PBAC response, is noted in paragraph 6.62.

6.58 The ESC agreed with the evaluation that this claim was not adequately supported, because:

- The ITCs relied on sub-group analyses from the ConquerRSV (mRNA-1345), RENOIR (RSVPreF), and AReSVi-006 (RSVPreF3 OA) trials. These subgroups had small sample sizes (relative to the overall trial samples: 18% in ConquerRSV, 16% in RENOIR, and 21% in AReSVi-006) and a limited number of RSV cases that resulted in wide confidence intervals, precluding robust conclusions and raising concerns about statistical reliability of the ITCs (paragraph 6.32).
- The long-term analyses (Scenario 3: median follow-up of 18.8 months for mRNA-1345, 16.4 months for RSVPreF, and 17.8 months for RSVPreF3 OA), which are the most informative for the long-term comparative assessment of efficacy, consistently yielded point estimates favouring RSVPreF and RSVPreF3 OA over mRNA-1345across all outcomes evaluated for the ≥ 75 YOA population (Table 11). Given the lack of a formal non-inferiority margin, the possibility that mRNA-1345 provides less protection than RSVPreF and RSVPreF3 OA against the presented outcomes cannot be ruled out.
- The outcomes reported and used in the ITC for ≥ 75 YOA population in the RENOIR trial were based on the subset of outcomes that were medically attended, whereas the corresponding outcomes reported in the ConquerRSV trial were not restricted to those medically attended (paragraph 6.32). This is likely to bias the ITC of mRNA-1345 with RSVPreF, however the direction and magnitude of bias remains unclear.
- There are further limitations related to the transitivity of the included population, with differences in the number of baseline comorbidities and differences in exposure to circulating RSV across trials.

6.59 While the PSCR maintained that the ITC for the NIP population ≥ 75 YOA demonstrates that there is no statistically significant difference between the vaccines for comparable outcome variables at each of the timepoints (Table 11), it also acknowledged that demonstrating non-inferiority of mRNA-1345 versus RSVPreF and RSVPreF3 OA is challenging (see paragraph 6.61 below).

6.60 The submission described mRNA-1345 as non-inferior in terms of safety compared to RSVPreF and RSVPreF3 OA. The evaluation and the ESC considered that this claim was adequately supported by the evidence, however the evidence provided does not allow for a comparison of how the adverse event profile may differ between the vaccines. The ESC noted the ATAGI's view, that there is no clear reason to favour mRNA or protein vaccines based on safety profile.

6.61 The ESC agreed with the evaluation that the claim of non-inferior efficacy of mRNA-1345 compared to RSVPreF and RSVPreF3 OA was not supported by the evidence. Long-term results for cumulative VE of RSV-LRTD ≥ 2 symptoms consistently favoured RSVPreF and RSVPreF3 OA over mRNA-1345 in patients ≥ 75 YOA, with a relative risk of 1.80 (95%CI: 0.72, 4.55) when comparing mRNA-1345 with RSVPreF3 OA and 1.78 (95%CI: 0.52, 6.05) when comparing mRNA-1345 with RSVPreF3.

6.62 The ESC noted that in September 2025, the ATAGI advised that contingent upon the availability of alternative RSV vaccines on the NIP, if non-inferiority of mRESVIA to alternative vaccines cannot be established, there is no clear role for mRESVIA on the NIP (see paragraph 2.6). With respect to the ITC, the PSCR acknowledged that "it is likely that the PBAC will be challenged to infer non-inferiority based on the data coming directly from the clinical studies". Further, the Pre-PBAC response stated that the clinical trials across the three vaccines were not designed for comparison across study outcomes or timepoints, and highlighted that ATAGI considered the transitivity assumption is likely violated in its pre-PBAC advice (26 June 2025). With reference to this ATAGI advice, the Pre-PBAC response stated that given the transitivity assumptions have been demonstrated not to hold, it is not feasible to draw a comparative conclusion from the ITC.

6.63 The PBAC noted that the pre-PBAC response conceded that clinical non-inferiority between mRNA-1345 and RSVPreF and/or RSVPreF3 OA could not be established based on the trial data presented. The PBAC agreed with this assessment, based on the results for cumulative VE of RSV-LRTD ≥ 2 symptoms consistently favouring RSVPreF and RSVPreF3 OA over mRNA-1345 in patients ≥ 75 YOA, as presented in the ITC. While the PBAC noted that the pre-PBAC response proposed that the CUA provided in the submission could be used to determine an appropriate cost-effective price for mRNA-1345 against placebo, "whereby the price would not exceed the price for RSVPreF or RSVPreF3 OA", it also noted the difficulty of finding a clinical place for mRNA-1345 if an alternative RSV vaccine (i.e. RSVPreF and/or RSVPreF3 OA) becomes available on the NIP, given that non-inferior efficacy for mRNA-1345 compared with RSVPreF or RSVPreF3 OA was not supported.

6.64 The PBAC considered that the claim of non-inferior comparative safety was not adequately supported by the data based on the crude incidence ratios calculated by the submission; however, the PBAC noted the evaluation's comment that there do not appear to be substantial differences in the overall adverse event profiles between the mRNA-1345, RSVPreF and RSVPref3 OA vaccines.

Economic analysis

Cost-minimisation approach

6.65 As summarised in Table 16, the submission presented a CMA comparing mRNA-1345 with RSVPreF as the primary economic evaluation, based on the ITC of mRNA-1345 against RSVPreF. The submission analysis included only the acquisition cost of a single dose of the respective vaccines (based on the publicly available price in the private market for RSVPreF) and assumed the same costs of administration and management of adverse events. The submission proposed a price for mRNA-1345 that is [redacted]% lower than the private market price for RSVPreF based on public information.

Table 16: Summary and results of the cost-minimisation approach

Parameter	mRNA-1345	RSVPreF
Dose form	Injectable	Injectable
Presentation and pack	Pre-filled syringe, single	Syringe and diluent, single, requiring reconstitution
Therapeutic dose	50 micrograms/0.5 mL	120 microgram/0.5 mL
Dose, mL	0.5	0.5
Doses required, n	1	1
Packs required	1.00	1.00
Vaccine acquisition cost	**$[redacted]**	**$331.99**
Administration cost: MBS item 3 (June 2025)	$19.60	$19.60
Cost of vaccine	**$[redacted]**	**$351.59**

Source: Table 3-2, pp217-218 of the submission.
mL = millilitre; MBS = Medicare Benefits Schedule; n = number.

6.66 The submission proposed equi-effective doses of mRNA-1345 50 mcg/0.5 mL and RSVPreF 120 mcg/0.5 mL for the basis of the CMA. The submission noted that marginally different adverse event profiles were observed in the two pivotal trials for mRNA-1345 and RSVPreF, which is not expected to significantly impact their therapeutic comparability.

6.67 Since the non-inferiority between mRNA-1345 and RSVPreF has not been established, the cost-minimisation approach comparing mRNA-1345 with RSVPreF as the primary economic evaluation was not supported by the clinical evidence. The supplementary modelled cost-utility analysis comparing a single dose of mRNA-1345 with no vaccine may be informative for decision making, however the evaluation and the ESC noted several concerns with the model for the ≥ 75 YOA population. Analogous issues also applied to the assessment of cost effectiveness in Aboriginal and Torres Strait Islander people 60-74 YOA.

Cost-utility analysis

6.68 The submission presented a CUA comparing a single dose of the mRNA-1345 vaccine with no vaccine based on ConquerRSV and implementing a modelled evaluation for the following populations:

- Adults ≥ 75 YOA
- Aboriginal and Torres Strait Islander people 60-74 YOA.

6.69 A summary of the model structure, key inputs and rationale for the CUA is presented in Table 17. The ESC considered the model structure to be reasonable. However, the ESC noted that the submission's CUA used a range of parameters which differed from those previously accepted by the PBAC for RSV vaccines (see paragraph 6.89). These differences are discussed in Table 17 and the paragraphs below. The ESC considered that most of these parameters should align with the PBAC's previous advice.

Table 17: Summary of model structure, key inputs and rationale

Component	Description
Population	Adults ≥ 75 YOA, Aboriginal and Torres Strait Islander people 60-74 YOA.
Intervention	mRNA-1345
Comparator	No vaccine
Type of analysis	Cost-effectiveness analysis (cost-utility analysis)
Outcomes	Cost/QALY; Cost/LYs, cost/hospitalisation avoided
Time horizon	5-year duration of protection, lifetime for LYs and QALYs. The ESC considered the time horizon to be optimistic given the ConquerRSV trial provides only 18.8 months of data. The pre-PBAC response accepted a 4-year time horizon.
Discounting	3.5% for both costs and outcomes. The ESC considered the discount rate should be 5% in the base case consistent with PBAC guidelines. The pre-PBAC response accepted a discount rate of 5% for costs and outcomes.
Methods used to generate results	Static cohort decision tree
Health states	MA-RSV-ARD, RSV-LRTD, RSV-No LRTD. RSV-LRTD and RSV-No LRTD are subdivided based on setting of care (hospitalisation, emergency department (ED), and outpatient treatments [a])
Cycle length	1 year
Epidemiological inputs	
Seasonality	October: 8.0%; November: 12.0%; December: 14.0%; January: 20.0%; February: 17.0%; March: 10.0%; April: 6.0%; May: 3.0%; June–August: 2.0%; September: 4.0% (Nazareno et al. 2022, Saiyed et al. 2024).
Medically attended respiratory syncytial virus-acute respiratory disease (MA-RSV-ARD) incidence	**≥ 75 YOA:** 6.5% (pooled unadjusted incidence of 3.3% from Foley et al. 2024, Price et al. 2019, Varghese et al. 2018) x 2.0 (under-ascertainment multiplier) - see paragraph 6.71. The ESC noted that a rate of 4.12% was used for RSVPreF and should also be used for mRNA-1345. The pre-PBAC response retained the unadjusted incidence of 3.3% and applied a 2.0 under-ascertainment multiplier. **Aboriginal and Torres Strait Islander people 60-74 YOA:** 12.4% (assumption based on approximately 2 times ≥ 75 YOA incidence) - see paragraph 6.72. The ESC considered that this figure is also potentially over-estimated due to the under-ascertainment assumption. The ESC considered the assumption should be consistent with that applied to RSVPreF (6.18%). The pre-PBAC response retained the incidence of 6.18% with a 2.0 under-ascertainment multiplier .

Component	Description	
Hospitalisation rates (per 100,000 person-year)	**≥ 75 YOA**: 360 (Nazareno et al 2022 AIHW NHMD 2009-2017 Australia). The ESC considered this was reasonable and similar to the rate accepted for RSVPreF (384). The pre-PBAC response retained a rate of 360/100,000. **Aboriginal and Torres Strait Islander people 60-74 YOA**: 96; those ≥ 65 YOA: 188 (estimated based on Nazareno et al. 2022). The ESC noted these rates are lower than the 576/100,000 accepted by PBAC in 60-74 group for RSVPreF. The pre-PBAC response accepted a hospitalisation rate of 576/100,000.	
RSV-related mortality (30-day mortality following hospitalisation)	**≥ 75 YOA**: 75-79 YOA: 10.3%; 80-84 YOA: 10.3%; 85+ YOA: 14.9% (Hamilton et al. 2022). **Aboriginal and Torres Strait Islander people 60-74 YOA:** 60-64 YOA: 7.2%; 65-69 YOA: 8.0%; 70-74 YOA: 8.0% (relative risk of 1.18 from Hamilton et al. 2022 applied to the general population mortality). The ESC noted that this was higher than PBAC's accepted rate for RSVPreF (4.22%).	
Background mortality	ABS lifetables (general population). The ESC considered this source to be appropriate, although acknowledging that it underestimates Aboriginal and Torres Strait Islander mortality.	
Vaccine efficacy		
Vaccination month	Year round	
VE data	18.8-month VE data[b] of ITT population (≥ 60 YOA; 8 March 2024 data cutoff) from ConquerRSV were extrapolated over 5 years using a non-linear model. Averaged annual VE was estimated using modelled monthly VE and seasonality (see Table 19). The ESC noted that VE data was based on limited duration of follow up and appears to over-estimate the incident protection. The ESC noted that the protection is the cumulative figure, which is not appropriate.	
Adverse events	The difference between the AE rates for mRNA-1345 and placebo (1.43% and 1.13% for grade 3 local and systemic AEs, respectively) from ConquerRSV	
HRQoL (utility values)	Population norm (Redwood et al. 2024): 60-64 YOA: 0.86 65-74 YOA: 0.88 ≥ 75 YOA: 0.86	Utility decrement (one-off) (Hutton 2024): Inpatient treatment: 0.0193 (0.0095 – 0.0316) Outpatient/ED treatment: 0.0185 (0.0053 – 0.0347). The ESC noted that the figure of 0.0185 was unverifiable and higher than used in the previous RSVPreF submission (0.0054). The pre-PBAC response retained the values of 0.0193 for hospitalised RSV and 0.0185 for medically attended outpatient RSV. AE utility decrement (one-off) (estimate based on Prosser et al. 2019) Grade 3 Local: 0.1 quality adjusted days Grade 3 Systemic: 0.4 quality adjusted days
Costs		
RSV management costs (per case)	**RSV-LRTD** Outpatient: $231 ED: $2,044 (≥ 75 YOA), $2,239 (Aboriginal and Torres Strait Islander 60–74 YOA) Hospitalisation: $14,403 (≥ 75 YOA), $15,686 (Aboriginal and Torres Strait Islander 60–74 YOA). The ESC noted that this cost should be consistent with lower costs used previously for RSVPreF. The pre-PBAC response revised the hospitalisation cost to apply ED costs to ED-only episodes and subtracted ED costs from the hospitalisation unit cost, reducing it from $14,403 to $12,359 (≥ 75 YOA) and from $15,686 to $13,447	**RSV-No LRTD** Outpatient: $215 ED: $1,134 (≥ 75 YOA); $1,246 (Aboriginal and Torres Strait Islander 60–74 YOA)

Component	Description
	(Aboriginal and Torres Strait Islander 60–74 YOA).
Administration cost	$17.57/case (weighted across GP visits 71%, $42.85 via MBS item 23; pharmacies 18%, $20.05 via National Immunisation Program Vaccine Incentive Program 2025; and community settings 11%, assumed $0.00). The ESC considered this calculated cost to be unclear, as it does not reflect the weighted mean cost across GP, pharmacy, and community settings. The pre-PBAC response revised the administration cost from $17.57 to $7 per dose to align with the RSVpreF PSD.
Software	Microsoft Excel

Source: Compiled during evaluation based on Table 3-3, pp219-220 of the submission.
ABS = Australian Bureau of Statistics; AE = adverse event; AIHW = Australian Institute of Health and Welfare; ED = emergency department; HRQoL = health-related quality of life; ITT = intention-to-treat; LY = life year; MA-RSV-ARD = medically attended respiratory syncytial virus-acute respiratory disease; NHMD = National Hospital Morbidity Database; PBAC = Pharmaceutical Benefits Advisory Committee; PSD = Public Summary Document; QALY = quality-adjusted life year; RSV = respiratory syncytial virus; RSV-ARD = respiratory syncytial virus-acute respiratory disease; RSV-LRTD = respiratory syncytial virus-lower respiratory tract disease; RSV-No LRTD = respiratory syncytial virus-no lower respiratory tract disease; VE = vaccine efficacy; YOA = years of age.
[a] The outpatient cost presented appears to reflect GP visits in the community rather than care provided in outpatient specialist settings.
[b] Noted in ATAGI Advice June 2025 (p5) as monthly interval-specific data, but no source was provided to confirm this.

6.70 The submission applied a 3.5% discount rate for both costs and health outcomes, which the evaluation noted is inconsistent with the 5% rate used in other RSV vaccine submissions to the PBAC (Table 25, RSVPreF3 OA PSD, July 2024; Table 16, RSVPreF PSD, November 2024), and with the Guidelines for preparing submissions to the PBAC. The pre-PBAC response accepted a discount rate of 5% for costs and outcomes.

6.71 The evaluation considered that the pooled unadjusted estimated incidence (3.3%) for medically attended RSV-ARD (MA-RSV-ARD) of the ≥ 75 YOA population was based on inapplicable data and was likely overestimated. Specifically, the submission relied on test positivity rates from the included studies (Foley et al. 2024, Price et al. 2019, Varghese et al. 2018). The submission further applied a 2.0 x multiplier to adjust for under-ascertainment of test performance; however, this was inconsistent with ATAGI's recommended multiplier of 1.5 (ATAGI Advice, September 2024). This resulted in an estimated incidence of MA-RSV-ARD of 6.5%. An MA-RSV-ARD of 4.12[5]% was used for this population in a previous RSV vaccine submission (estimated based on Table 13, RSVPreF PSD, November 2024). Both the PSCR and pre-BAC response maintained that the submission incidence of 3.3% with a 2.0 x multiplier correctly adjusts for under-ascertainment. However, the ESC considered that a rate of 4.12% should be used for mRNA-1345.

6.72 The submission applied two multipliers to the estimated incidence rate of 3.1% for Aboriginal and Torres Strait Islander people aged 60-74 YOA. This estimated incidence rate was based on the incidence rate of RSV in non-Indigenous people obtained from the studies per paragraph 6.71. The applied multipliers include:

[5] 398/100,000 (hospitalised) + 299/100,000 (emergency) + 3,423/100,000 (outpatient) (Table 13, RSVPreF PSD, November 2024).

- An incident rate ratio (IRR) of 2.0 (mid-point of the range 1.8–2.2), based on ATAGI Advice (ATAGI Advice, June 2025), to indicate the higher incidence among Aboriginal and Torres Strait Islander people.
- An under-ascertainment multiplier of 2.0 to account for adjustment of test performance. As noted in paragraph 6.71, 1.5 has been recommended as a more appropriate multiplier.

The PSCR and pre-PBAC response maintained that the appropriate rate and under-ascertainment multiplier for Aboriginal and Torres Strait Islander people aged 60-74 YOA were used in the submission.

6.73 These adjustments resulted in an applied incidence rate for Aboriginal and Torres Strait Islander people of 12.4%. The ESC agreed with the evaluation that this is likely overestimated for the same reasons as described in paragraph 6.71. An MA-RSV-ARD rate of 6.18%[6] was used for this population in the RSVPreF submission (estimated based on Table 13, RSVPreF PSD, November 2024).

6.74 The hospitalisation rate was estimated at 360 per 100,000 person-years for the ≥ 75 YOA population (Nazareno et al. 2022; paragraph 6.51, RSVPreF PSD, November 2024). This is slightly lower than the estimate of 384 per 100,000 person-years previously accepted by the PBAC (paragraph 7.16, RSVPreF PSD, November 2024). The ESC considered this to be reasonable and similar to that accepted for RSVPreF (384 per 100,000 person-years). The pre-PBAC response maintained a rate of 360/100,000 .

6.75 The submission used a calibration approach to align the modelled RSV-related hospitalisation rate with the target hospitalisation rate (based on Nazareno et al. 2022). To match the target hospitalisation rate, the model back-calculated the proportion of RSV cases progressing to LRTD (%RSV-LRTD), while keeping the RSV incidence and hospitalisation proportion among RSV-LRTD cases unchanged (hospitalisation rate = (RSV incidence; MA-RSV-ARD) × (%RSV-LRTD) × (%RSV-LRTD hospitalised)). While this calibration introduces some uncertainty it is acceptable given the limitations of the available data. However, to better reflect inputs previously accepted by PBAC for the ≥ 75 YOA population, including hospitalisation rates (384 per 100,000 person-year; paragraph 7.16, RSVPreF PSD, November 2024) and MA-RSV-ARD (4.12%; Table 13, RSVPreF PSD, November 2024), revised calibration inputs are provided in scenario 2 (see Table 18). This scenario indicates that the model was slightly sensitive to these alternative inputs.

[6] 597/100,000 (hospitalised) + 448/100,000 (emergency) + 5,134/100,000 (outpatient) (Table 13, RSVPreF PSD, November 2024).

Table 18: Calibration approach presented by the submission and alternative scenario analyses conducted during the evaluation: adults ≥ 75 YOA model

Scenario	Incidence MA-RSV-ARD	Proportion of RSV that is RSV-LRTD	RSV-LRTD hospitalisation proportion	Hospitalisation rate	ICER
Submission base case	6.5% (paragraph 6.71)	16.8% (back calculated)	32.8% Nguyen-Van-Tam et al. (2022)	0.00360 (paragraph 6.74)	$ [redacted][1] (base case)
#1	6.5%	17.95% (back calculated)	32.8%	0.00384 (para 7.16, RSVPreF PSD, November 2024)	$ [redacted][1] (- [redacted]%)
#2	4.12% (Table 13, RSVPreF PSD, November 2024)	28.5% (back calculated)	32.8%	0.00384 (para 7.16, RSVPreF PSD, November 2024)	$ [redacted][2] (+ [redacted]%)
#3	4.12% (Table 13, RSVPreF PSD, November 2024)	16.8%	55.5% (back calculated) [a]	0.00384 (para 7.16, RSVPreF PSD, November 2024)	$ [redacted][2] (+ [redacted]%)
#4	4.12% (Table 13, RSVPreF PSD, November 2024)	30.0% [b]	31.0 % (back calculated) [a]	0.00384 (para 7.16, RSVPreF PSD, November 2024)	$ [redacted][2] (+ [redacted]%)

Source: Compiled during evaluation using Attachment 17B - Moderna RSV Model_v11.14_20250613_AUS_July 2025.
ICER = incremental cost-effectiveness ratio; MA-RSV-ARD = medically attended respiratory syncytial virus–acute respiratory disease; para = paragraph; PSD = Public Summary Document; RSV = respiratory syncytial virus; RSV-LRTD = respiratory syncytial virus–lower respiratory tract disease; YOA = years of age.
[a] Assume ED = 0% (from 1.4%) for simplicity.
[b] Assumption based on a midpoint of 26%-33.3% in Table 2.1-2 p15, ATAGI Advice, September 2024.
The redacted values correspond to the following ranges:
[1] *$25,000 to < $35,000*
[2] *$35,000 to < $45,000*

6.76 The submission used age-specific RSV mortality for in-hospital deaths from Hamilton et al. 2022, which retrospectively analysed 30-day mortality following hospitalisation with RSV in Ontario, Canada. The submission stated that the study was considered the most applicable to the Australian population that reported age-specific RSV-mortality in the adult population. The study is likely to overestimate RSV-related mortality, as it appears to examine all-cause mortality rather than RSV-specific outcomes and focuses on individuals at high risk with multiple comorbidities. The ESC noted that the mortality rates ranging from 10.3% to 14.9% for the ≥ 75 YOA population (see Table 17) are higher than the 4.22% previously accepted by the PBAC for both ≥ 75 YOA and Aboriginal and Torres Strait Islander people 60–74 YOA populations (paragraph 7.16, RSVPreF PSD, November 2024). The PSCR disagreed with the use of 4.22% for all age groups, stating it is insufficient to capture age-related differences in mortality risk in RSV infection. However, the PSCR did not address the concerns that Hamilton (2022) might overestimate RSV-related mortality given they report all-cause mortality, not RSV-attributable mortality, and they include high-risk populations with multiple comorbidities, which may not reflect the general population.

6.77 The submission model relied on efficacy data from all participants ≥ 60 YOA in ConquerRSV, which differs from the proposed target population of ≥ 75 YOA. While VE was lower in the ≥ 75 YOA population than the ≥ 60 YOA population, the use of ≥ 60 YOA VE data for the ≥ 75 YOA population might be acceptable for modelling

purposes, noting that the limitations of the evidence (paragraph 6.32) and that the PBAC has accepted economic models applying ≥ 60 YOA VE data for those ≥ 75 YOA populations in previous considerations of RSV vaccines (paragraph 7.14, RSVPreF3 OA PSD, July 2024; paragraph 6.45, RSVPreF PSD, November 2024). Similarly, while the PBAC noted that a lower VE may be observed in Aboriginal and Torres Strait Islander people due to higher rates of medical risk factors and comorbidities, it accepted the use of VE estimates from the intention to treat population of RSVPreF's pivotal trial for this group in the RSVPreF submission (paragraph 6.45, RSVPreF PSD, November 2024).

6.78 The estimates of VE used in the economic model are based on the waning and extrapolation model presented to ATAGI (ATAGI Advice, June 2025). The submission further incorporated seasonality and converted the estimates to annual average VE to align with the 1-year cycle length. A summary of extrapolated annual VE used in the economic model is presented in Table 19.

Table 19: Extrapolated VE used in the economic model

Averaged annual VE	mRNA-1345				
	Year 1	Year 2	Year 3	Year 4	Year 5
Base case VE values applied in the model (including seasonality)					
RSV-ARD	57.0%	40.5%	32.4%	26.6%	22.0%
RSV-LRTD ≥ 2 symptoms [a]	64.2%	45.6%	35.7%	28.4%	22.5%
Excluding seasonality (applied in the model) [b]					
RSV-ARD	53.9%	39.2%	31.5%	25.9%	21.4%
RSV-LRTD ≥ 2 symptoms [a]	60.7%	43.9%	34.5%	27.5%	21.7%
ConquerRSV					
RSV-ARD	50.9%	No interval efficacy presented			
RSV-LRTD ≥ 2 symptoms	56.2%	No interval efficacy presented			

Source: Figure 3-2, Figure 3-3 p241; Table 2-39, p117; Table 3-21, p242 of the submission.
RSV-ARD = respiratory syncytial virus-acute respiratory disease; RSV-LRTD = respiratory syncytial virus-lower respiratory tract disease; VE = vaccine efficacy.
[a] Due to the model structure, direct VE for RSV-LRTD is not applied independently. Instead, it is treated as incremental benefits over RSV-ARD VE.
[b] Replacing the submission's value by 100%/12 in 'Seasonality' worksheet of the economic model.

6.79 The ESC agreed with the evaluation that extrapolation of VE in the submission presents several issues. In particular,

- Duration of follow-up: Extrapolation of the duration of protection to 5 years is based on limited follow-up data from ConquerRSV (median follow-up of 18.8 months). The pre-PBAC response accepted a 4-year time horizon.
- Data limitations: As source data were not provided, the non-linear model fit could not be verified by the evaluation. The estimated VE in the model is higher than observed in ConquerRSV in Year 1 for both RSV-ARD (57.0% vs 50.9%) and RSV-LRTD ≥ 2 symptoms (64.2% vs 56.2%). The PSCR stated that the source data used for extrapolations cannot be provided and that the processes undertaken have been described in the submission. However, the ESC considered that without the provision of the underlying source data, the use

of these data in the submission cannot be supported. The PSCR stated that the non-linear waning model presented in the submission is the same that has been presented to the Advisory Committee on Immunization Practices (ACIP) of the United States Centers for Disease Control and Prevention (CDC) (see also next dot point). The clarification sought regarding the differences in waning shapes between the submission (non-linear) and the analysis presented to ACIP (linear) remains unaddressed.

- Magnitude and pattern of waning: The waning estimates, which showed a slower and more stable plateau pattern over time compared to earlier time points, are highly uncertain as they are not supported by clinical data. Uncertainties raised by ATAGI remain. In particular, ATAGI requested clarification on whether the waning model used a cumulative or interval analysis (ATAGI Advice, June 2025). The sponsor responded that the estimates were based on monthly interval-specific data; however, no source data were provided to verify this. The submission did not explicitly state whether the estimates were cumulative or interval based. If cumulative, the ESC noted that it may overstate protection at later time points, as early effects inflate the average. An external waning analysis for ConquerRSV presented to the U.S. CDC assuming a linear waning pattern, suggested a more rapid decline in VE, approximately 2.4% per month[7]. An approximate interval efficacy estimate conducted during the evaluation (for information purposes only) also showed a sharper decline, with VE for RSV-LRTD dropping to 28.3% at 12–24 months, compared to 45.6% in the submission's model. The PSCR stated that this analysis was inappropriate as it lacks statistical rigour, however the PSCR did not provide alternative estimates of interval-specific VE. The submission indicated that follow-up in ConquerRSV was ongoing at time of submission, with 24-month follow-up data expected, which would allow for greater precision in the presented model. Additional analyses, including alternative waning assumptions were to be conducted and incorporated into the PBAC submission (ATAGI Advice, June 2025). No additional analyses were presented in the submission to the PBAC.
- Seasonality: The use of seasonality for RSV vaccines was not previously supported by ATAGI (ATAGI Advice, September 2024) or PBAC (paragraph 6.51, RSVPreF3 OA PSD, July 2024). The PSCR disagreed with removing the seasonality from the economic model, stating that while the optimal timing for a roll-out of a national program vaccination against RSV in older adults may vary between the states, national data on seasonality ought to be applied.

[7] p17 in Update on Moderna's RSV Vaccine, mRESVIA (mRNA-1345), in Adults ≥ 60 Years of Age, presented to the Advisory Committee on Immunization Practices (ACIP) of the United States Centers for Disease Control and Prevention (CDC). This is presented in the submission as 'Das 2024 June ACIP'.

These issues suggest that the VE used in the model is likely overestimated compared with the trial data. Additionally, the waning of VE over time suggests a potential need for revaccination sooner than the extrapolated period of 5 years. The ESC noted that revaccination was not considered in the current model.

6.80 The submission used unpublished utility decrement values for RSV-related QALY loss, sourced from ACIP presentations and based on the JIVE COVID/RSV utilities study (Hutton et al. 2023, 2024). These values were derived from a time trade-off survey but the material provided with the submission lacked methodological details and could not be verified during the evaluation. The disutility values likely reflect a U.S. outpatient setting which may include more severe cases, compared to typical Australian GP visits and may overstate the RSV impact on disutility. The outpatient disutility (0.0185) used in the model was higher than previously considered by the PBAC in the RSVPreF model (0.0054; paragraph 6.40, RSVPreF PSD, November 2024). A sensitivity analysis using the lower RSVPreF value is presented in Table 22 (≥ 75 YOA) and Table 23 (Aboriginal and Torres Strait Islander people 60-74 YOA). The PSCR maintained that the disutility for outpatients applied in the submission (0.0185) represents the most applicable data. The PSCR stated that the disutility applied in the RSVPreF model (0.0054) is based on a conference abstract and therefore the submission's estimate (from Hutton 2023, 2024) represents a more applicable and more contemporary estimate for disutility in patients with medically attended RSV. However, the ESC stated that the required detail of the utility derivation is not available in Hutton et al. 2024, and therefore the smaller utility decrement applied in the RSVPreF model remains relevant to the mRNA-1345 model. The pre-PBAC response stated that the outpatient decrement (0.0054) from Mao et al. does not report a single per-episode decrement, and includes a relatively healthy, community-dwelling cohort with only a minority of medically attended episodes, which likely understates disutility. The response retained the value of 0.0185 for medically attended outpatient RSV.

6.81 The submission used a similar approach to previous RSV vaccine evaluations in estimating hospitalisation costs (e.g., based on AR-DRGs (E62A, E62B, E65), IHACPA 2025-2026 national efficient price determination, National Hospital Cost Data Collection 2022-23 public hospital report; Table 14, RSVPreF PSD, November 2024). However, the evaluation noted that the submission adjusted population weights based on the risk of comorbidities, accounting for potential differences in healthcare utilisation. The PBAC did not support a severity-related adjustment when it was applied in a previous RSV submission (paragraph 6.68, RSVPreF3 OA PSD, July 2024). The pre-PBAC response did not adjust the comorbidity-prevalence weighting of hospitalisation costs; it stated that the populations in question have a higher prevalence of high-risk conditions (e.g., COPD, heart failure) and therefore a costlier case-mix than the all-episode average should be reflected.

6.82 The submission further assumed that all hospitalisation cases would involve an emergency department (ED) visit, and ED treatment cost ($2,044 for ≥ 75 YOA

population). This double counts ED costs since the AR-DRGs already include an allowance for ED. The pre-PBAC response revised the hospitalisation cost to apply ED costs to ED-only episodes and subtracted ED costs from the hospitalisation unit cost, reducing it from $14,403 to $12,359 (≥ 75 YOA) and from $15,686 to $13,447 (Aboriginal and Torres Strait Islander 60–74 YOA).

6.83 The evaluation noted that excluding the adjustments based on both comorbidity prevalence (paragraph 6.81) and the ED costs (paragraph 6.82), the hospitalisation cost would have been $9,983 compared to $14,403 in the base case (≥ 75 YOA population).

6.84 The model for the Aboriginal and Torres Strait Islander people 60-74 YOA population presents various issues including:

- Underestimating hospitalisation rates including 96 per 100,000 person-year in 60–64 YOA to 188 per 100,000 in 65–74 YOA. The ESC noted that the PBAC previously accepted a rate of 576 per 100,000 person-year in this population (7.18, RSVPreF PSD, November 2024). The pre-PBAC response accepted a hospitalisation rate of 576/100,000 .
- Applying background mortality from the general population (ABS lifetables) rather than population-specific mortality. Due to the structure of the model, this was not able to be varied in sensitivity analyses.
- Similar issues as per the ≥ 75 YOA population (such as overestimating RSV-mortality rates, overestimating hospitalisation costs, overestimating incidence).

The modelled outcomes for Aboriginal and Torres Strait Islander people aged 60–74 years may not be informative without substantial revision of the model.

6.85 A summary of the key drivers of the models is presented in Table 20.

Table 20: Key drivers of the models

Description	Method/Value	Impact
≥ 75 YOA population	**Base case: $[redacted][1]/QALY gained**	
VE duration	18.8-month VE data of ITT population (≥ 60 YOA; 8 March 2024 data cutoff) from ConquerRSV were extrapolated over 5 years using non-linear model.	High, favours mRNA-1345 Use of 2-year duration increased the ICER to $[redacted][2]/QALY gained.
RSV-related mortality	High value for all-cause mortality rather than RSV-specific outcomes and focuses on individuals at high risk with multiple comorbidities (Hamilton et al. 2022).	High, favours mRNA-1345 Use of 4.22% (para 7.16, RSVPreF PSD, November 2024) increased the ICER to $ [redacted][2]/QALY gained.
Disutility (outpatient)	High value for disutility (0.0185) applied to outpatients obtained from unpublished literature.	Moderate, favours mRNA-1345 Use of 0.0054 (para 6.40, RSVPreF PSD, November 2024) increased the ICER to $ [redacted][3]/QALY gained.
Hospitalisation cost	High value of hospitalisation cost ($12,281.71) driven by comorbidity adjustment and additional from 100% ED assumption ($2,044).	Moderate, favours mRNA-1345 Use of $9,983 (without comorbidity adjustment and 0% ED) increased the ICER to $[redacted][3]/QALY gained.
Aboriginal and Torres Strait Islander people 60-74 YOA population	**Base case: $[redacted][1]/QALY gained**	
Hospitalisation rate	Applying low values (96 per 100,000 person-year in 60–64 YOA to 188 per 100,000 in 65–74 YOA) estimated based on Nazareno et al 2022.	High, favours no vaccine Use of 567 per 100,000 person-year decreased the ICER to $[redacted][4]/QALY gained[a].
VE duration	18.8-month VE data of ITT population (≥ 60 YOA; 8 March 2024 data cutoff) from ConquerRSV were extrapolated over 5 years using non-linear model.	High, favours mRNA-1345 Use of 2-year duration increased the ICER to $[redacted][2]/QALY gained.
RSV-related mortality	High value for all-cause mortality rather than RSV-specific outcomes and focuses on individuals at high risk with multiple comorbidities (Hamilton et al. 2022).	High, favours mRNA-1345 Use of 4.22% (para 7.16, RSVPreF PSD, November 2024) increased the ICER to $ &&&&[3]/QALY gained.

Source: Compiled during evaluation using Attachment 17B - Moderna RSV Model_v11.14_20250613_AUS_July 2025.
ED = emergency department; ICER = incremental cost-effectiveness ratio; para = paragraph; PSD = Public Summary Document; QALYs = quality-adjusted life years; RSV-ARD = respiratory syncytial virus; VE = vaccine efficacy; YOA = years of age.
[a] This estimate has been done as part of the calibration approach.
The redacted values correspond to the following ranges:
[1] *$25,000 to < $35,000*
[2] *$55,000 to < $75,000*
[3] *$35,000 to < $45,000*
[4] *$5,000 to < $15,000*

6.86 The submission did not present a stepped analysis. A summary of the stepped economic evaluation results estimated during the evaluation is presented in Table 21.

Table 21: Stepped economic evaluation results

	mRNA-1345	No vaccine	Incremental difference
≥ 75 YOA population			
Eligible population	**2,166,835**	**2,166,835**	
Step 1: Cost-effectiveness analysis (trial follow-up: 18 months [a])			
Costs	$[redacted]	$275,501,759	$[redacted]
RSV-LRTD cases avoided	29,814	46,188	16,374
Incremental cost per case avoided			**$[redacted][1]**
Step 2: Data transformed into LY (18 months [a])			
Costs	$[redacted]	$275,501,759	$[redacted]
LY lost	1,496,154	1,500,398	4,245
Incremental cost per life year gained			**$[redacted][2]**
Step 3: Applied utility values (18 months [a])			
Costs	$[redacted]	$275,501,759	$[redacted]
QALYs lost	1,289,934	1,295,047	5,113
Incremental cost per QALY gained			**$[redacted][3]**
Step 4: Extrapolate VE to 5-year duration of protection			
Costs	$[redacted]	$868,403,441	$[redacted]
LYs lost	3,389,979	3,396,545	6,566
QALYs lost	2,923,293	2,931,394	8,102
Cost per LY gained			**$[redacted][4]**
Incremental cost per QALY gained			**$[redacted][5]**
Aboriginal and Torres Strait Islander people 60-74 YOA population [b]			
	mRNA-1345	**No vaccine**	**Incremental difference**
Eligible population	**80,954**	**80,954**	
Step 1: Cost-effectiveness analysis (trial-follow up: 18 months [a])			
Costs	$[redacted]	$9,629,210	$[redacted]
RSV-LRTD cases avoided	467	720	254
Incremental cost case avoided			**$[redacted][6]**
Step 2: Data transformed into LY (18 months [a])			
Costs	$[redacted]	$9,629,210	$[redacted]
LY lost	20,039	20,128	89
Incremental cost per life year gained			**$[redacted][7]**
Step 3: Applied utility values (18 months [a])			
Costs	$[redacted]	$9,629,210	$[redacted]
QALYs lost	20,039	20,128	89
Incremental cost per QALY gained			**$[redacted][3]**
Step 4: Extrapolate VE to 5-year time horizon			
Costs	$[redacted]	$22,582,484	$[redacted]
LYs lost	49,435	49,589	155
QALYs lost	43,555	43,886	331
Cost per LY gained			**$[redacted][3]**
Incremental cost per QALY gained			**$[redacted][5]**

Source: Compiled during evaluation using Attachment 17B - Moderna RSV Model_v11.14_20250613_AUS_July 2025.

LY = life years; QALYs = quality-adjusted life years; RSV-LRTD = respiratory syncytial virus-lower respiratory tract disease; YOA = years of age.

[a] Based on 24 months per the model's structure.

[b] In the Excel model, choosing high-risk only, then minimum age at 60 YOA and maximum age 74 YOA.

The redacted values correspond to the following ranges:

[1] *$15,000 to < $25,000*

[2] *$75,000 to < $95,000*

[3] *$55,000 to < $75,000*

[4] *$35,000 to < $45,000*

[5] *$25,000 to < $35,000*

[6] *$45,000 to < $55,000*

[7] *$135,000 to < $155,000*

6.87 The results of key univariate / multivariate sensitivity analyses for the ≥ 75 YOA population are summarised in Table 22.

Table 22: Sensitivity analyses: ≥ 75 YOA population

Analysis		Incremental Costs (discounted)	Incremental QALYs (discounted)	ICER	ICER changed (%)
	Base-case	$[redacted]	8,102	$[redacted][1]	
A	Discount rate: 5% (base case: 3.5%)	$[redacted]	7,644	$[redacted][1]	+[redacted]%
	Discount rate: 0% (base case: 3.5%)	$[redacted]	9,470	$[redacted][1]	[redacted]%
	Seasonality (base case: seasonality applied)				
B	Seasonality removed	$[redacted]	7,778	$[redacted][1]	+[redacted]%
	Hospitalisation rate, incidence rate and calibration scenario (base case: hospitalisation rate: 0.00360, MA-RSV-ARD incidence: 6.5%, proportion of RSV that is RSV-LRTD: 16.8%, RSV-LRTD hospitalisation proportion: 32.8%)				
C	Hospitalisation rate: 0.00384 (para 7.16, RSVPreF PSD, November 2024), MA-RSV-ARD incidence: 4.12% (Table 13, RSVPreF PSD, November 2024), Proportion of RSV that is RSV-LRTD: 28.5% (back calculate), RSV-LRTD hospitalisation proportion; 32.8%; i.e. scenario #2 from Table 18.	$[redacted]	7,582	$[redacted][2]	+[redacted]%
	RSV-related death (base case: 10.3% for 75-84 YOA, 14.9% for ≥ 85 YOA)				
D	4.22% (para 7.16, RSVPreF PSD, November 2024)	$[redacted]	4,667	$[redacted][3]	+[redacted]%
	8.00% (ATAGI's advised upper bound for a sensitivity analysis)	$[redacted]	6,628	$[redacted][2]	+[redacted]%
	Hospitalisation cost (base case: $14,403 per case with comorbidity prevalence adjustment and 100% ED)				
E	$9,983 (without comorbidity adjustment and 0% ED)	$[redacted]	8,102	$[redacted][2]	+[redacted]%
	Vaccine administration cost (base case: $17.57)				
F	$7.00 (para 6.40, RSVPreF PSD, November 2024)	$[redacted]	8,102	$[redacted][1]	-[redacted]%
	Disutility (base case; 0.0185 for outpatients)				
G	0.0054 (para 6.40, RSVPreF PSD, November 2024)	$[redacted]	6,481	$[redacted][2]	+[redacted]%
	VE duration (base case: 5-year duration of protection)				
H	1-year	$[redacted]	3,124	$[redacted][4]	+[redacted]%
I	2-year	$[redacted]	5,113	$[redacted][3]	+[redacted]%
J	3-year	$[redacted]	6,492	$[redacted][5]	+[redacted]%
	Multivariate				
K	(A B C D E F G)	$[redacted]	2,630	$[redacted][6]	+[redacted]%
L	(A B C D E F G) + H	$[redacted]	990	$[redacted][7]	+[redacted]%
M	(A B C D E F G) + I	$[redacted]	1,645	$[redacted][8]	+[redacted]%
N	(A B C D E F G) + J	$[redacted]	2,101	$[redacted][6]	+[redacted]%

Source: Compiled during evaluation using Attachment 17B - Moderna RSV Model_v11.14_20250613_AUS_July 2025.
ATAGI = Australian Technical Advisory Group on Immunisation; ED = emergency department; ICER = incremental cost-effectiveness ratio; MA-RSV-ARD = medically attended respiratory syncytial virus–acute respiratory disease; MBS = Medicare Benefits Schedule; para =

paragraph; PSD = Public Summary Document; QALY = quality adjusted life year; RSV-LRTD = respiratory syncytial virus–lower respiratory tract disease; VE = vaccine efficacy; YOA = years of age.
The redacted values correspond to the following ranges:
[1] *$25,000 to < $35,000*
[2] *$35,000 to < $45,000*
[3] *$55,000 to < $75,000*
[4] *$115,000 to < $135,000*
[5] *$45,000 to < $55,000*
[6] *$95,000 to < $115,000*
[7] *$355,000 to < $455,000*
[8] *$155,000 to < $255,000*

6.88 The results of key univariate / multivariate sensitivity analyses for Aboriginal and Torres Strait Islander people 60-74 YOA are summarised in Table 23.

Table 23: Sensitivity analyses: the Aboriginal and Torres Strait Islander people 60-74 YOA model

Analysis		Incremental Costs (discounted)	Incremental QALYs (discounted)	ICER	ICER changed (%)
	Base-case	$[redacted]	331	$[redacted][1]	
A	Discount rate: 5% (base case: 3.5%)	$[redacted]	311	$[redacted][1]	+[redacted]%
	Discount rate: 0% (base case: 3.5%)	$[redacted]	398	$[redacted][2]	-[redacted]%
	Seasonality (base case: seasonality applied)				
B	Seasonality removed	$[redacted]	318	$[redacted][1]	+[redacted]%
	Hospitalisation rate and calibration scenario (base case: hospitalisation rate: 0.00096 (60-64 YOA) 0.00188 (65-74 YOA), MA-RSV-ARD incidence: 12.4%, proportion of RSV that is RSV-LRTD: 2.4% (60-64 YOA) 4.6% (65-74 YOA), RSV-LRTD hospitalisation proportion; 32.8%)				
C	Hospitalisation rate: 0.00567 (para 7.18, RSVPreF PSD, November 2024), MA-RSV-ARD incidence: 6.18% (Table 13, RSVPreF PSD, November 2024) Proportion of RSV that is RSV-LRTD: 28% (back-calculate) RSV-LRTD hospitalisation proportion; 32.8%	$[redacted]	626	$[redacted][3]	-[redacted]%
	RSV-related death probability (base case: 10.3% for75-84 YOA, 14.9% for ≥ 85 YOA)				
D	4.22% (para 7.16, RSVPreF PSD, November 2024).	$[redacted]	270	$[redacted][4]	+[redacted]%
	8.00% (ATAGI's advised upper bound for a sensitivity analysis)	$[redacted]	336	$[redacted][1]	-[redacted]%
	Hospitalisation cost (base case: $15,686 per case with comorbidity prevalence adjustment and 100% ED)				
E	$9,983 (without comorbidity prevalence adjustment and 0% ED)	$[redacted]	331	$[redacted][1]	+[redacted]%
	Vaccine administration cost (base case: $17.57)				
F	$7.00 (para 6.40, RSVPreF PSD, November 2024)	$[redacted]	331	$[redacted][1]	-[redacted]%
	Disutility (base case; 0.0185 for outpatients)				
G	0.0054 (para 6.40, RSVPreF PSD, November 2024)	$[redacted]	319	$[redacted][1]	+[redacted]%
	VE duration (base case: 5-year duration of protection)				
H	1-year	$[redacted]	112	$[redacted][5]	+[redacted]%
I	2-year	$[redacted]	189	$[redacted][6]	+[redacted]%
J	3-year	$[redacted]	249	$[redacted][7]	+[redacted]%
	Multivariate				
K	(A B C D E F G)	$[redacted]	285	$[redacted][1]	-[redacted]%
L	(A B C D E F G) + H	$[redacted]	95	$[redacted][5]	+[redacted]%
M	(A B C D E F G) + I	$[redacted]	163	$[redacted][6]	+[redacted]%
N	(A B C D E F G) + J	$[redacted]	214	$[redacted][7]	+[redacted]%

Source: Compiled during evaluation using Attachment 17B - Moderna RSV Model_v11.14_20250613_AUS_July 2025.

ATAGI = Australian Technical Advisory Group on Immunisation; ED = emergency department; ICER = incremental cost-effectiveness ratio; MA-RSV-ARD = medically attended respiratory syncytial virus–acute respiratory disease; MBS = Medicare Benefits Schedule; para = paragraph; PSD = Public Summary Document; RSV-LRTD = respiratory syncytial virus–lower respiratory tract disease; VE = vaccine efficacy; YOA = years of age.

The redacted values correspond to the following ranges:

[1] *$25,000 to < $35,000*
[2] *$15,000 to < $25,000*
[3] *$5,000 to < $15,000*
[4] *$35,000 to < $45,000*
[5] *$115,000 to < $135,000*
[6] *$55,000 to < $75,000*
[7] *$45,000 to < $55,000*
[8] *$155,000 to < $255,000*

6.89 The ESC noted numerous concerns regarding the economic model, as discussed above. The ESC considered that to determine an appropriate cost-effective price for mRNA-1345 against placebo, several model inputs would require revision to address the identified concerns. The ESC considered the modelled VE estimates to be unreliable, noting that the duration of protection from the vaccine was uncertain but data suggested more rapid waning of effect with mRNA-1345 than RSVPreF and RSVPreF3 OA (paragraph 2.7). Other key concerns were: hospitalisation rate, RSV-related mortality, utility values, RSV management costs, and discount rate. The ESC considered that key model parameters such as discount rate, baseline risks and management costs should be consistent with the models of other RSV vaccines considered by the PBAC. The ESC noted the multivariate sensitivity analyses prepared during the evaluation and considered these were informative.

mRNA-1345 cost per person

6.90 The intervention costs per patient are presented in Table 24.

Table 24: Vaccine cost per person

	Trial dose and duration	Cost-minimisation approach	Cost utility analysis	Financial estimates
Mean dose	1 dose	1 dose	1 dose	1 dose
Mean duration	One-off	One-off	One-off	One-off
Vaccine acquisition	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Administration fee [a]	$19.60	$19.60	$17.57	$19.60
Cost/person/course	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Source: Table 3-26, p245; p268 of the submission; 'Costs.Direct' in Attachment 17B - Moderna RSV Model_v11.14_20250613_AUS_July 2025.

[a] Administration fee for the cost-minimisation approach, financial estimates (and trial dose and duration) is based MBS item 3 (100%; no coadministration assumption) while for the cost-utility analysis, an alternate approach is used (weighted across GP visits 71%, $42.85 via MBS item 23; pharmacies 18%, $20.05 via National Immunisation Program Vaccine Incentive Program 2025; and community settings 11%, assumed $0.00). This cost was revised in the pre-PBAC response from $17.57 to $7 per dose to align with the RSVpreF PSD.

Estimated PBS usage & financial implications

6.91 This submission was not considered by DUSC.

6.92 The submission presented the financial impact of introducing a single dose of mRNA-1345 onto the NIP for adults: ≥ 75 YOA; and Aboriginal and Torres Strait Islander people 60-74 YOA. This was consistent with the economic model and the requested NIP listing. The financial estimates incorporated a hypothetical listing of RSVPreF on the NIP based on the PBAC's positive recommendation at the time the mRNA-1345 submission was prepared and consistent with the submission's nomination of RSVPreF as the primary comparator, although RSVPreF3 OA has also been subsequently recommended by the PBAC for listing on the NIP.

6.93 The submission used an epidemiological approach to estimate the eligible population and accounted for the market share attributed to RSVPreF. Key inputs used by the submission are presented in Table 25.

Table 25: Key inputs of the financial estimates

Data	Value and source		Evaluation comment
Eligible population			
Incident population (eligible population)	≥ 75 YOA Yr 1: 2,372,508 to Yr 6: 265,314 ABS population projections	Aboriginal and Torres Strait Islander people 60-74 YOA Yr 1: 86,887 to Yr 6: 3,762 ABS population projections	Appropriate
Uptake rate (any RSV vaccine)	≥ 75 YOA [redacted]% ([redacted]% in 1st year of the incident population and [redacted]% in 2nd year onward applied to those not vaccinated in 1st year) Annual uptake rates of influenza vaccine in > 65 year per NCIRS	Aboriginal and Torres Strait Islander people 60-74 YOA [redacted]% - [redacted]% ([redacted]% - [redacted]% in 1st year of the incident population, and [redacted]% - [redacted]% in 2nd year onward applied to those not vaccinated in 1st year) Annual uptake rates of influenza vaccine in > 65 years age group, indigenous adults per NCIRS	Total 6-year uptake rate might be reasonable. However, the first-year uptake is likely overestimated (e.g., might be less than [redacted]% in ≥ 75 YOA). Additionally, the model seems to incorrectly apply the later-year uptake resulting in a total vaccinated population that exceeds the proposed uptake.
Market share	Status quo: RSVPreF: 100% Predicted market: mRNA-1345: [redacted]% RSVPreF: [redacted]% Assumption (ATAGI Advice, June 2025)		ATAGI considered that a [redacted]% market share is reasonable as a base case for the estimate of utilisation of mRNA-1345, contingent upon the claim of non-inferiority vs RSVpreF being accepted, and noting mRNA-1345 may be impacted if there is public hesitancy for mRNA technology. Uptake may also be overestimated given immunogenicity against RSV may be compromised when mRNA-1345 is coadministered with an influenza vaccine.
Administration fee	$19.60 MBS item 3 assumed to both mRNA-1345 and RSVPreF.		The MBS item is reasonable. However, mRNA-1345 and RSVPreF may have different administration costs, especially due to potential differences in coadministration with other vaccines.

Source: Compiled during the evaluation using Attachment 18 (Section 4 financial estimates July 2025) of the submission.
ABS = Australian Bureau of Statistics; ATAGI = Australian Technical Advisory Group on Immunisation; MBS = Medicare Benefits Schedule; NCIRS = National Centre for Immunisation Research and Surveillance; RSV = respiratory syncytial virus; YOA = years of age.

6.94 A summary of the estimated use and financial implications for listing mRNA-1345 is presented in Table 26.

Table 26: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
≥ 75 YOA						
Estimated extent of use						
Number vaccinated (vials)	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][3]
Estimated financial implications of mRNA-1345						
NIP	$[redacted][4]	$[redacted][5]	$[redacted][5]	$[redacted][6]	$[redacted][6]	$[redacted][7]
Estimated financial implications for RSVPreF						
Cost to NIP	-$[redacted][4]	-$[redacted][6]	-$[redacted][7]	-$[redacted][7]	-$[redacted][8]	-$[redacted][8]
Net financial implications						
Net cost to NIP	-$[redacted][9]	-$[redacted][10]	-$[redacted][10]	-$[redacted][10]	-$[redacted][10]	-$[redacted][10]
Net cost to MBS	$0	$0	$0	$0	$0	$0
Net cost to NIP/MBS	-$[redacted][9]	-$[redacted][10]	-$[redacted][10]	-$[redacted][10]	-$[redacted][10]	-$[redacted][10]
	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Year 6**
Aboriginal and Torres Strait Islander people 60-74 YOA						
Estimated extent of use						
Number vaccinated (vials)	[redacted][11]	[redacted][12]	[redacted][13]	[redacted][13]	[redacted][13]	[redacted][13]
Estimated financial implications of mRNA-1345						
NIP	$[redacted][14]	$[redacted][14]	$[redacted][14]	$[redacted][14]	$[redacted][14]	$[redacted][14]
Estimated financial implications for RSVPreF						
Cost to NIP	-$[redacted][14]	-$[redacted][14]	-$[redacted][14]	-$[redacted][14]	-$[redacted][14]	-$[redacted][14]
Net financial implications						
Net cost to NIP	-$[redacted][14]	-$[redacted][14]	-$[redacted][14]	-$[redacted][14]	-$[redacted][14]	-$[redacted][14]
Net cost to MBS	$0	$0	$0	$0	$0	$0
Net cost to NIP/MBS	-$[redacted][14]	-$[redacted][14]	-$[redacted][14]	-$[redacted][14]	-$[redacted][14]	-$[redacted][14]

Source: Compiled during the evaluation using Attachment 18 (Section 4 financial estimates July 2025) of the submission.
MBS = Medicare Benefits Schedule; NIP = National Immunisation Program; YOA = years of age.
The redacted values correspond to the following ranges:
[1] *500,000 to < 600,000*
[2] *200,000 to < 300,000*
[3] *300,000 to < 400,000*
[4] *$100 million to < $200 million*
[5] *$60 million to < $70 million*
[6] *$70 million to < $80 million*
[7] *$80 million to < $90 million*
[8] *$90 million to < $100 million*
[9] *$20 million to < $30 million*
[10] *$10 million to < $20 million*
[11] *10,000 to < 20,000*
[12] *500 to < 5,000*
[13] *5,000 to < 10,000*
[14] *$0 to < $10 million*

6.95 The total cost to the NIP of listing mRNA-1345 for the ≥ 75 YOA population was estimated to be $80 million to < $90 million in Year 6, and a total of $500 million to < $600 million in the first 6 years of listing. The total cost to the NIP of listing mRNA-1345 for the Aboriginal and Torres Strait Islander people 60-74 YOA population was estimated to be $0 to < $10 million in Year 6, and a total of $10 million to < $20 million in the first 6 years of listing. The submission estimated a net saving to the NIP due to

the lower price of mRNA-1345 used in the financial estimates compared to that of RSVPreF. There was no change in the number of vaccinated individuals.

6.96 The financial estimates were based on the same model presented to ATAGI in June 2025. ATAGI raised several concerns about the estimates presented at that time (ATAGI Advice, June 2025). The following issues were not addressed in the submission to the PBAC:

- The total vaccinated population exceeds the proposed uptake ([redacted]% vs [redacted]% in the ≥ 75 YOA population, and [redacted]% vs [redacted]% in the Aboriginal and Torres Strait Islander people 60-74 YOA population). The ESC noted that the model seems to incorrectly apply the later-year uptake (e.g., [redacted]% for the ≥ 75 YOA population) to the incident population after the second year of each annual incident cohort (rather than only in the second year), which inflates the total uptake. The PSCR stated that the financial estimates calculate annual eligible prevalent cohorts, which estimates uptake amongst annual cohorts comprising individuals newly entering the eligible age group, adjusted by reductions due to deaths and those who are no longer eligible due to being previously vaccinated.
- The uptake rates should only be applied those who have not received an RSV vaccine (by removing individuals who have received a vaccine from the 'at-risk' population).
- The impact of background mortality on the size of the eligible population should be accounted for.

6.97 The ATAGI noted that if revaccination of mRNA-1345 is required within six years, revaccination uptake should be explicitly modelled (ATAGI Advice, June 2025). This was not included in the financial estimates, noting that this was consistent with the submission's proposed listing of a single dose only. The ESC noted the absence of estimates for revaccination with mRNA-1345 and that the sponsor does not currently have a timeline for regulatory filings for revaccination.

6.98 The submission assumed that mRNA-1345 would account for [redacted]% of the 100% market share currently attributed to RSVPreF (status quo assumption). ATAGI considered that the [redacted]% market share assumption was uncertain, noting possible public hesitancy toward mRNA technology, potential differences in vaccine efficacy waning between RSVPreF and mRNA-1345, and logistical challenges that may affect market share (ATAGI Advice, June 2025). Additionally, PBAC's recent recommendation of another RSV vaccine (RSVPreF3 OA) is expected to impact the market share assumption. The ESC also considered the market share assumptions to be uncertain.

6.99 There may be higher administration costs for mRNA-1345, particularly if RSVPreF can be coadministered with other vaccines. ATAGI noted potential implementation issues including that lower immunogenicity when coadministered with other vaccines (e.g., influenza) suggested that mRNA-1345 should be delivered alone (ATAGI Advice, June

2025). The ESC considered that assuming the same administration cost between the vaccines in the submission might not be reasonable.

6.100 Overall, the evaluation considered that the model overestimated the financial impact of listing mRNA-1345 on the NIP, as the anticipated use of mRNA-1345 was overestimated. The consequent reduction in total spend on RSV vaccines is unlikely to be realised.

Quality Use of Medicines

6.101 The submission presented information on a quality use of medicines approach, including:

- Use of a prefilled syringe (PFS) presentation for mRNA-1345, which is preferred by healthcare providers, and simplifies preparation as reconstitution is not required. Reduced risk of needle contamination, needle stick injuries, and dosage errors may be reduced by use of PFS;
- Ongoing post-marketing safety surveillance through AusVaxSafety for mRNA-1345.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

7.1 The PBAC deferred its consideration of respiratory syncytial virus (RSV) vaccine mRNA-1345 (mRESVIA) for the prevention of lower respiratory tract disease (LRTD) caused by RSV in individuals aged 75 years of age (YOA) and above, and for Aboriginal and Torres Strait Islander peoples aged 60 to 74 YOA. The PBAC considered that the clinical place of mRNA-1345 is uncertain and deferred its decision pending further advice on the potential NIP listing of previously recommended RSV vaccines, RSVPreF (Abrysvo) and RSVPreF3 OA (Arexvy). While the PBAC acknowledged that the superiority of mRNA-1345 over no vaccination was adequately supported for adults $\geq$ 60 YOA for up to 16 months, it considered that superior efficacy over no vaccination in the ≥ 75 years population was uncertain, and non-inferior efficacy for mRNA-1345 compared with RSVPreF and/or RSVPreF3 OA was not supported.

7.2 At the time of the November 2025 PBAC meeting, neither RSVPreF nor RSVPreF3 OA were listed on the NIP, although both vaccines received a positive recommendation at the July 2025 PBAC meeting for adults ≥ 75 YOA and for Aboriginal and Torres Strait Islander peoples aged 60 to 74 years. Given that non-inferior efficacy for mRNA-1345 compared with RSVPreF and/or RSVPreF3 OA was not supported in these populations, the PBAC advised that it would only be appropriate to recommend mRNA-1345 for NIP listing at a cost-effective price if there remains a clinical need for a vaccine against RSV on the vaccination schedule. This is consistent with the post-submission ATAGI advice (17 September 2025), which did not support non-inferiority and stated that a clinical place for mRNA-1345 could not be identified if an alternative RSV vaccine (i.e. RSVPreF and/or RSVPreF3 OA) becomes available on the NIP.

7.3 The PBAC further noted that there is not a clinical need for multiple RSV vaccines in terms of rapid mutation of RSV, and there is not a requirement for a different RSV vaccine modality in terms of a messenger RNA vaccine (mRNA-1345) versus a protein vaccine (RSVPreF and RSVPreF3 OA). In addition to the PBAC's clinical and economic conclusions regarding the data presented in the submission (described below), these issues collectively formed the reasoning that the PBAC's decision for mRNA-1345 should be deferred in order to clarify the potential listing of the RSV vaccines already recommended by the PBAC and the potential clinical place of mRNA-1345 on the vaccination schedule.

7.4 Consistent with its previous advice, the PBAC considered there is a high clinical need for vaccines against RSV to reduce the risk of infection in older adults, especially for those aged over 75 years, for Aboriginal and Torres Strait Islander peoples aged 60 to 74 YOA, and for those vulnerable due to existing medical conditions (paragraph 7.4, RSVPreF3 OA Public Summary PSD, July 2024). The PBAC noted the proposed NIP listing of a vaccine against RSV was supported by the consumer input received from the Australian College of Nurse Practitioners, Asthma Australia, and Lung Foundation Australia. The organisations did not preference a particular RSV vaccine in their input.

7.5 The PBAC accepted the wording of the proposed listing on the NIP as a single dose of mRNA-1345 as described in Section 3 (Requested listing). The PBAC noted that populations specified for vaccination (individuals aged ≥ 75 YOA and Aboriginal and Torres Strait Islander peoples aged 60 to 74 YOA) are included in the identified groups of older adults who are at risk of LRTD due to RSV (paragraph 7.4). However, the PBAC considered that the efficacy of mRNA-1345 in the ≥ 75 age group is uncertain (see paragraph 7.10 below), as is the magnitude of the longer term VE conferred by a single dose (see paragraph 7.11 below).

7.6 The PBAC accepted the following nominated comparators:

- RSVPreF as the main comparator, which was the only RSV vaccine to have been recommended for listing on the NIP at the time of preparing the submission; and
- RSVPreF3 OA as a near market comparator, which was considered at the July 2024 meeting and was subsequently recommended for listing on the NIP at the July 2025 meeting.

7.7 In the context of the deferral, the PBAC did not accept 'no vaccine' as a comparator noting this would only be relevant if neither RSVPreF nor RSVPreF3 OA were listed on the NIP.

7.8 The submission claimed that for adults ≥ 75 YOA and Aboriginal and Torres Strait Islander people ≥ 60 YOA, mRNA-1345 is non-inferior in terms of efficacy compared to RSVPreF and RSVPreF3 OA. The submission provided an ITC for mRNA-1345 (ConquerRSV trial) against RSVPreF (RENOIR trial) and RSVPreF3 OA (AReSVi-006 trial) for VE assessed as RSV-LRTD ≥ 2 symptoms, RSV-LRTD with ≥ 3 symptoms and ARD in the ≥ 75 YOA population, using placebo as the common reference.

7.9 The ConquerRSV trial compared the efficacy and safety of mRNA-1345 to placebo in adults ≥ 60 years, and was ongoing at the time the submission was prepared although has since been completed. The evaluation considered that the results for the primary analysis were highly uncertain due to immaturity and the PBAC noted that a substantial portion of participants (> 50%) in the primary analysis had no more than 3 months of follow-up, which is insufficient to capture the outcomes over a full 12-month RSV season. The PBAC noted the additional data provided in the pre-PBAC response as described in 6.53.

7.10 Based on evidence from the ConquerRSV trial, the PBAC considered that mRNA-1345 vaccine was an effective vaccine for RSV in adults ≥ 60 years for up to 16 months and this effect could be assumed to be extended to Aboriginal and Torres Strait Islander people 60-74 YOA. However, regarding the target population of adults ≥ 75 years, the PBAC considered that the claim of superior efficacy was uncertain because VE for this age group is lower than in the overall population (≥ 60 YOA), although noted the low number of observed RSV cases in the ≥ 75 YOA subgroup.

7.11 The PBAC observed that the cumulative estimate of VE in ConquerRSV for the primary outcome (RSV-LRTD ≥ 2 symptoms) declined over time from 56.2% at 12 months, to 50.3% at 18 months, and then to 47.4% at 24 months post vaccination, and furthermore there was a substantial decline of > 66% in antibody levels between Month 2 and Month 6 post vaccination. The PBAC indicated that the longevity of the immune response and comparison of the durations of response between mRNA-1345 and the other recommended vaccines is a key consideration.

7.12 The PBAC considered that non-inferior efficacy between mRNA-1345 and RSVPreF and/or RSVPreF3 OA could not be established based on the results for cumulative VE of RSV-LRTD ≥ 2 symptoms consistently favouring RSVPreF and RSVPreF3 OA over mRNA-1345 in patients ≥ 75 YOA (Table 11).

7.13 The PBAC considered that the claim of non-inferior comparative safety was not adequately supported by the data but noted the evaluation's comment that there do not appear to be substantial differences in the overall adverse event profiles between the mRNA-1345, RSVPreF and RSVPref3 OA vaccines.

7.14 The PBAC acknowledged the Sponsor's revision of the initial clinical claim in the pre-PBAC response to state that it is not feasible to draw a clinical conclusion from the ITC, given that the clinical trials across the three vaccines were not designed for comparison across study outcomes/timepoints and therefore the transitivity assumption has been demonstrated not to hold. However, the PBAC considered that it may be reasonable to conclude that the mRESVIA vaccine is inferior to the RSVPreF and/or RSVPreF3 OA vaccines in terms of VE, and that it may have a shorter duration of effect and more frequent revaccination may be required. While the PBAC noted that the pre-PBAC response proposed that the CUA provided in the submission could be used to determine an appropriate cost-effective price for mRNA-1345 against placebo, "whereby the price would not exceed the price for RSVPreF or RSVPreF3 OA",

it agreed with ATAGI (paragraph 7.2) regarding the difficulty of finding a clinical place for mRNA-1345 if an alternative RSV vaccine (i.e. RSVPreF and/or RSVPreF3 OA) becomes available on the NIP.

7.15 The submission presented a CMA comparing mRNA-1345 with RSVPreF as the primary economic evaluation, based on the ITC of mRNA-1345 against RSVPreF. The PBAC considered that since the non-inferiority between mRNA-1345 and RSVPreF has not been established and that mRNA-1345 may be clinically inferior to RSVPreF, the cost-minimisation approach comparing mRNA-1345 with RSVPreF as the primary economic evaluation was not supported by the clinical evidence.

7.16 In the context of the deferral, the PBAC did not accept 'no vaccine' as a comparator (as described in paragraph 7.7), and therefore the CUA was not considered relevant.

7.17 The PBAC noted that the submission requested listing on the NIP for a single dose of vaccine and that if the sponsor wishes to request listing for revaccination in the future, PBAC consideration of a new submission would be required.

7.18 The PBAC will make a decision regarding listing a single dose of mRNA-1345 on the NIP based on the supply of the additional information from the Department. No additional information from the sponsor is required at this time.

Outcome:
Deferred

Committee-In-Confidence information

7.19 [redacted]

[redacted]

[redacted]

End Committee-In-Confidence information

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor's Comment

The sponsor had no comment.