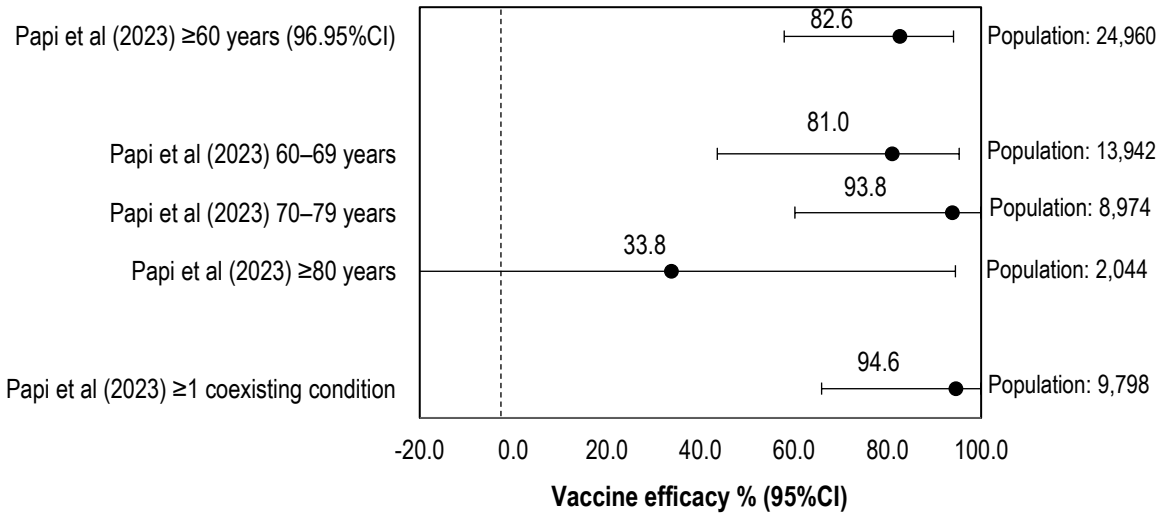
GRADE tables: Comparison of GSK AS01E adjuvanted RSVPreF3 vaccine (Arexvy) with placebo or no vaccine in adults aged ≥60 years

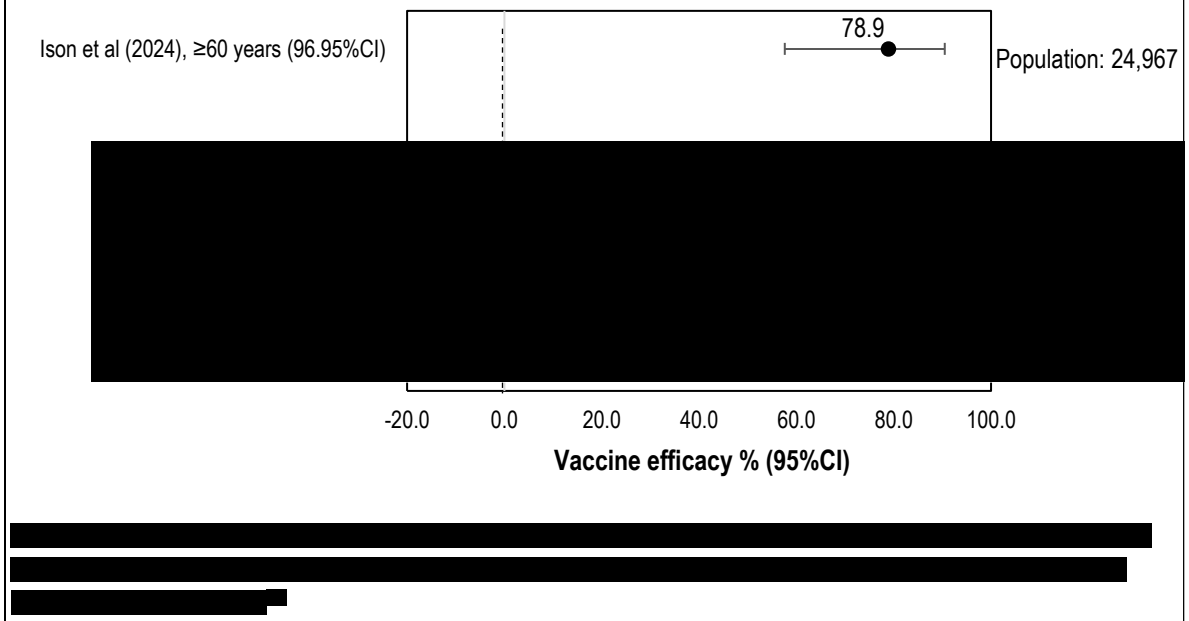
NCIRS is conducting GRADE assessments in support of the Australian Technical Advisory Group on Immunisation (ATAGI) and making pilot results available on the Centre's website. Please read this material as a supplement to the Australian Immunisation Handbook Respiratory Syncytial Virus (RSV) chapter.

Note: this GRADE includes published and unpublished data. Where unpublished data have been used, they have been redacted.

GSK AS01E adjuvanted RSVPreF3 vaccine (Arexvy) compared with placebo or no vaccine in adults aged 60 years and over

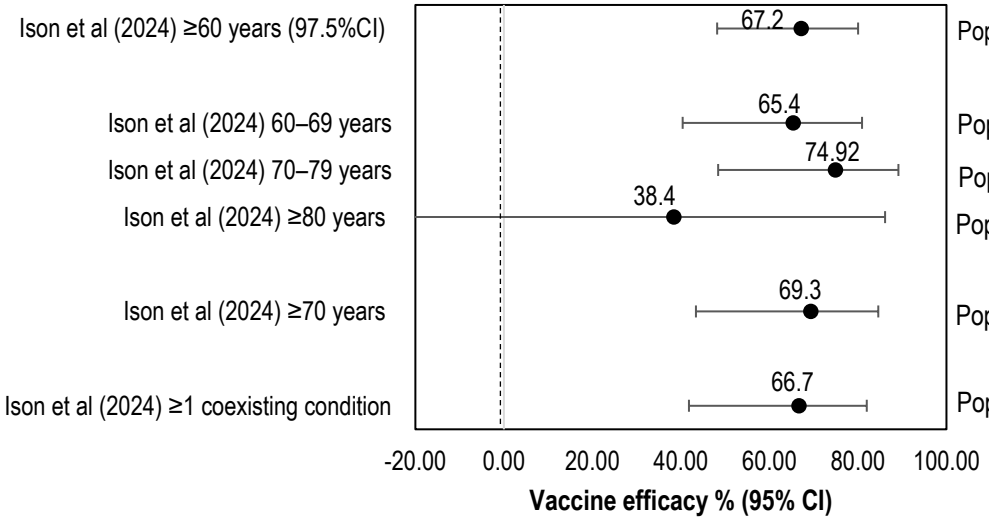
Patient or population: Adults aged ≥60 years
Intervention: GSK AS01E adjuvanted RSVPreF3 vaccine (Arexvy)
Comparison: Placebo or no vaccine

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
CRITICAL OUTCOMES				
RSV lower respiratory tract disease (LRTD) (≥2 lower respiratory signs/symptoms with at least 1 respiratory sign, or ≥3 respiratory signs lasting >24 hours) Assessed with: reverse-transcriptase polymerase chain reaction (RT-PCR) Total follow up: median 18 months	**RSVPreF3 vaccine efficacy against LRTD in older adults - Season 1 interim analysis (northern hemisphere, median follow up 6.7 months)**  	⊕⊕⊕◯ Moderate[a]	RSVPreF3 vaccine likely results in a moderate reduction in LRTD during the first season following single dose vaccination when compared with placebo. Note: Interpretation based on ≥60 years from final analysis.

GSK AS01E adjuvanted RSVPreF3 vaccine (Arexvy) compared with placebo or no vaccine in adults aged 60 years and over				
Patient or population: Adults aged ≥60 years **Intervention:** GSK AS01E adjuvanted RSVPreF3 vaccine (Arexvy) **Comparison:** Placebo or no vaccine				
Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
continued **RSV lower respiratory tract disease (LRTD)** (≥2 lower respiratory signs/symptoms with at least 1 respiratory sign, or ≥3 respiratory signs lasting >24 hours) Assessed with: reverse-transcriptase polymerase chain reaction (RT-PCR) Total follow up: median 18 months	**RSVPreF3 vaccine efficacy against LRTD in older adults - Season 1 final analysis (northern and southern hemisphere, median follow up 11.5 months)**  		⊕⊕⊕◯ Moderate[a]	RSVPreF3 vaccine likely results in a moderate reduction in LRTD during the first season following single dose vaccination when compared with placebo. Note: Interpretation based on age ≥60 years from final analysis.

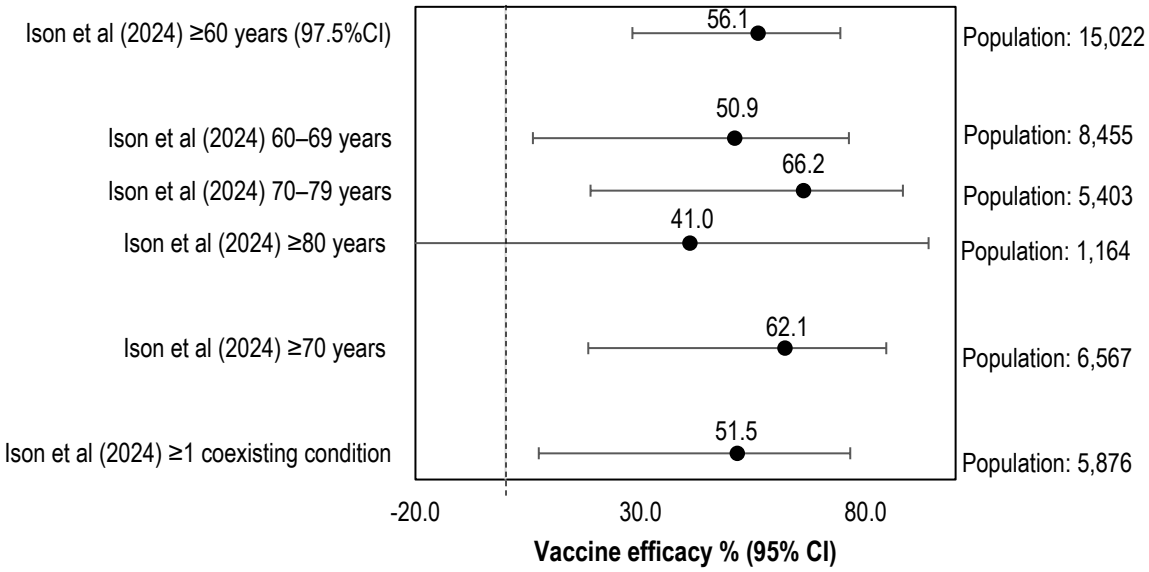
GSK AS01E adjuvanted RSVPreF3 vaccine (Arexvy) compared with placebo or no vaccine in adults aged 60 years and over

Patient or population: Adults aged ≥60 years
Intervention: GSK AS01E adjuvanted RSVPreF3 vaccine (Arexvy)
Comparison: Placebo or no vaccine

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
continued **RSV LRTD (season 2)** (≥2 lower respiratory signs/symptoms with at least 1 respiratory sign, or ≥3 respiratory signs lasting >24 hours) Assessed with: RT-PCR Total follow up: median 18 months	**RSVPreF3 vaccine efficacy of 1 dose (pre-season 1) against LRTD in older adults – Season 1 and 2 (median follow up 17.8 months)**  		⊕⊕⊕◯ Moderate[a]	RSVPreF3 vaccine likely results in a moderate reduction in LRTD **over two RSV seasons** following single dose vaccination prior to season 1 when compared with placebo.

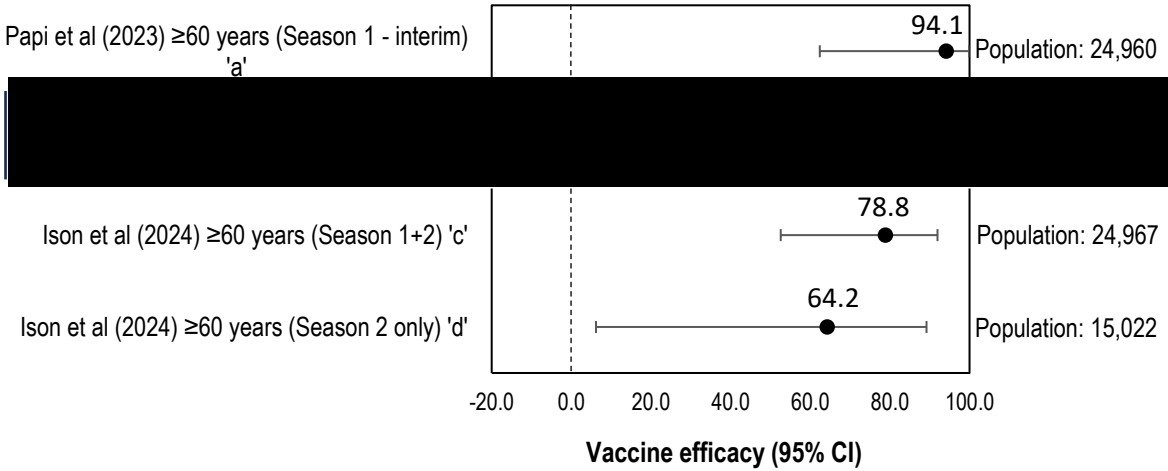
GSK AS01E adjuvanted RSVPreF3 vaccine (Arexvy) compared with placebo or no vaccine in adults aged 60 years and over

Patient or population: Adults aged ≥60 years
Intervention: GSK AS01E adjuvanted RSVPreF3 vaccine (Arexvy)
Comparison: Placebo or no vaccine

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
continued **RSV LRTD (season 2)** (≥2 lower respiratory signs/symptoms with at least 1 respiratory sign, or ≥3 respiratory signs lasting >24 hours) Assessed with: RT-PCR Total follow up: median 18 months	**RSVPreF3 vaccine efficacy of 1 dose (pre-season 1) against LRTD in older adults during season 2 (median follow up 6.3 months)**  Data reviewed are from the aforementioned RCT (NCT04886596), study ongoing, estimates derived from the modified exposed population. Values shown for season 1 and 2 combined were adjusted with season as covariate; vaccine efficacy for both season 1 and 2 combined (n=24,967) and season 2 alone (n=15,022) were following 1 dose of Arexvy given pre-season 1.[2]		⊕⊕⊕◯ Moderate[a]	RSVPreF3 vaccine likely results in a moderate reduction in LRTD **during the 2nd RSV season** following single dose vaccination prior to season 1 when compared with placebo.

GSK AS01E adjuvanted RSVPreF3 vaccine (Arexvy) compared with placebo or no vaccine in adults aged 60 years and over

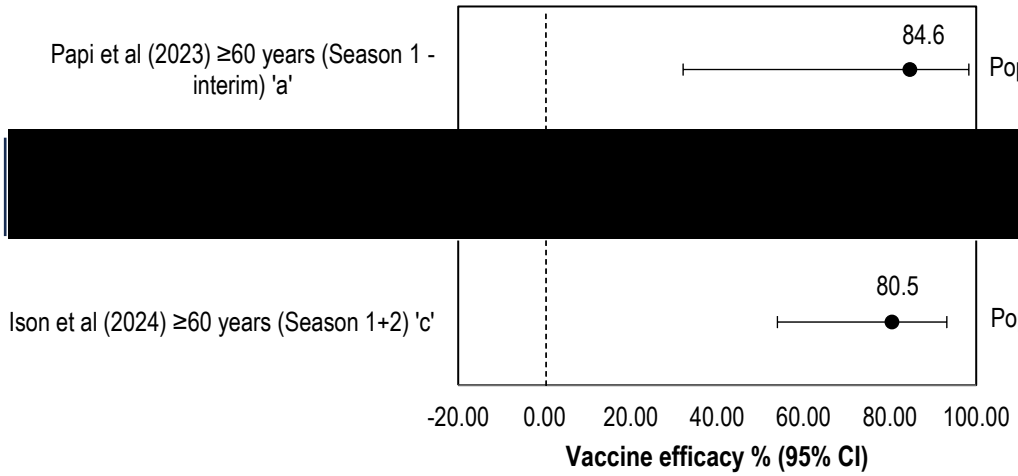
Patient or population: Adults aged ≥60 years
Intervention: GSK AS01E adjuvanted RSVPreF3 vaccine (Arexvy)
Comparison: Placebo or no vaccine

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
Severe LRTD (≥2 lower respiratory signs/symptoms with at least 1 respiratory sign, or ≥3 respiratory signs lasting >24 hours) Assessed with: RT-PCR **and based on 'clinical symptomology' and/or 'supportive therapy'**† Total follow up: median 18 months	**1 dose vaccine efficacy against severe LRTD**  Data reviewed are from the aforementioned RCT (NCT04886596), study ongoing, estimates derived from the modified exposed population. Values shown for season 1 and 2 combined were adjusted with season as covariate; all vaccine efficacy estimates shown were based on receipt of 1 dose of Arexvy given pre-season 1.[1-3] Median follow up times were: • 'a' Interim season 1 analysis, 6.7 months (complete northern hemisphere season) • 'b' Final season 1 analysis, 11.5 months (northern and southern hemisphere) • 'c' Season 1 and 2 median 11.5 months • 'd' Season 2 median 6.3 months (following time of revaccination season 2, placebo arm).		⊕⊕⊕◯ Moderate[a] ⊕⊕◯◯ Low[b]	RSVPreF3 vaccine likely results in a large reduction in severe LRTD **during the first season** following single dose vaccination compared with placebo. RSVPreF3 vaccine likely results in a moderate reduction in severe LRTD **over two RSV seasons** following single dose vaccination prior to season 1 when compared with placebo. RSVPreF3 vaccine may result in a moderate reduction in severe LRTD **during the 2nd RSV season** following single dose vaccination prior to season 1 when compared with placebo.

GSK AS01E adjuvanted RSVPreF3 vaccine (Arexvy) compared with placebo or no vaccine in adults aged 60 years and over				
Patient or population: Adults aged ≥60 years **Intervention:** GSK AS01E adjuvanted RSVPreF3 vaccine (Arexvy) **Comparison:** Placebo or no vaccine				
Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
Serious adverse events (SAEs) Assessed with: patient report of 'any' SAE Follow-up: 6 months post dose	There was no difference in proportion of **any SAEs** between vaccine or placebo groups among those 60 years and over. Papi 2023 (interim season 1 data): **n=522, 4.2% (95%CI: 3.8, 4.6) in vaccine group; n= 506, 4.0% (95%CI: 3.7, 4.4) in placebo group)** [redacted] Of note, there was no difference in proportion of **SAEs related to vaccine or placebo** between groups among those 60 years and over. Papi 2023 (interim season 1 data): **n=10, 0.1% (95%CI: 0, 0.1) in vaccine group; n= 7, 0.1% (95%CI: 0, 0.1) in placebo group** [redacted]	24,967 (1 RCT)[1,3]	⊕⊕⊕⊕ High	RSVPreF3 vaccine results in little to no difference in 'any' SAEs when compared with placebo. Note however, clinical trials are underpowered to detect rare SAEs.

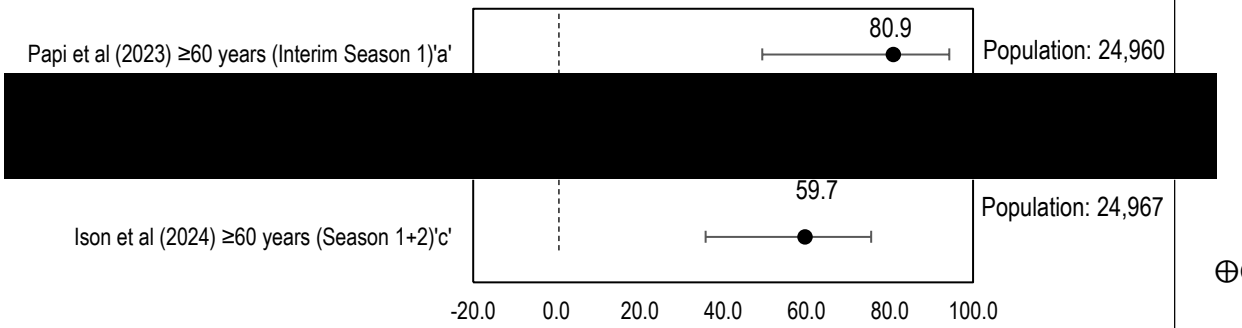
GSK AS01E adjuvanted RSVPreF3 vaccine (Arexvy) compared with placebo or no vaccine in adults aged 60 years and over

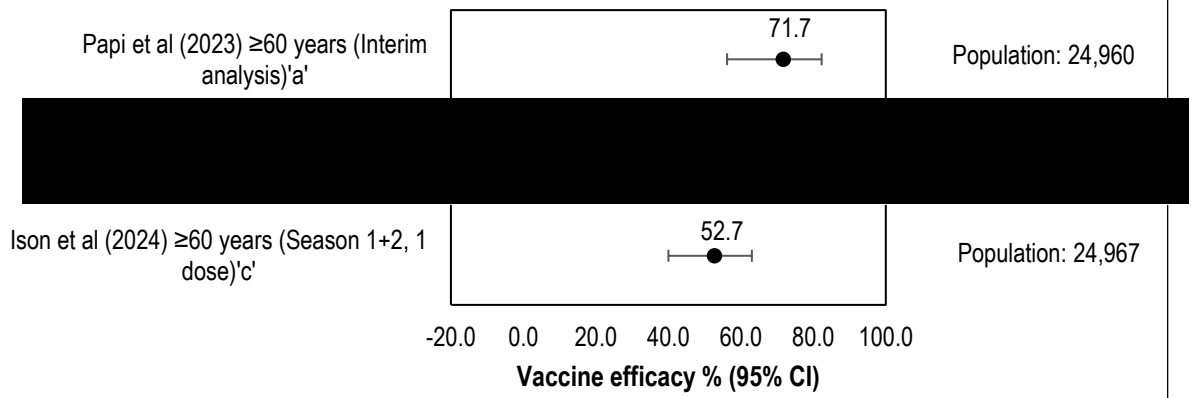
Patient or population: Adults aged ≥60 years
Intervention: GSK AS01E adjuvanted RSVPreF3 vaccine (Arexvy)
Comparison: Placebo or no vaccine

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
RSV LRTD – Subtype A (≥2 lower respiratory signs/symptoms with at least 1 respiratory sign, or ≥3 respiratory signs lasting >24 hours) Assessed with: reverse-transcriptase polymerase chain reaction (RT-PCR) Total follow up: median 18 months	**1 dose vaccine efficacy against RSV-A LRTD**  Data reviewed are from the aforementioned RCT (NCT04886596), study ongoing, estimates derived from the modified exposed population. Values shown for season 1 and 2 combined were adjusted with season as covariate; all vaccine efficacy estimates shown were based on receipt of 1 dose of Arexvy given pre-season 1.[1-3] Median follow up times were: • 'a' Interim season 1 analysis, 6.7 months (complete northern hemisphere season) • 'c' Season 1 and 2 median 11.5 months.		⨁⨁◯◯ Low[b]	RSVPreF3 vaccine may result in a large reduction in LRTD subtype A **during the first season** following single dose vaccination when compared with placebo. RSVPreF3 vaccine may result in a large reduction in LRTD subtype A **over two RSV seasons** following single dose vaccination prior to season 1 when compared with placebo.

GSK AS01E adjuvanted RSVPreF3 vaccine (Arexvy) compared with placebo or no vaccine in adults aged 60 years and over

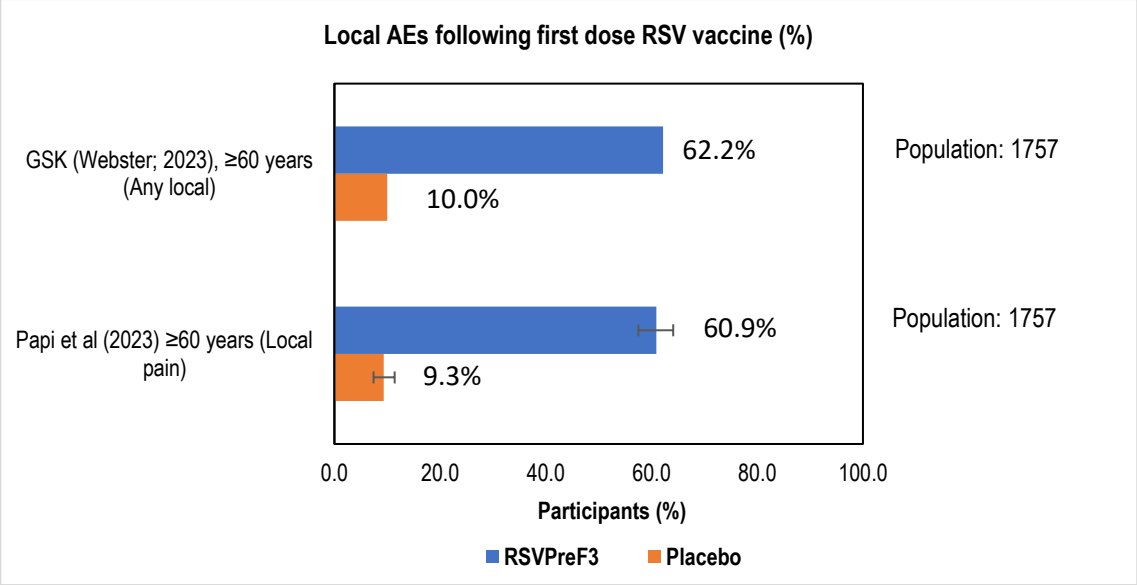
Patient or population: Adults aged ≥60 years
Intervention: GSK AS01E adjuvanted RSVPreF3 vaccine (Arexvy)
Comparison: Placebo or no vaccine

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
RSV LRTD – Subtype B (≥2 lower respiratory signs/symptoms with at least 1 respiratory sign, or ≥3 respiratory signs lasting >24 hours) Assessed with: RT-PCR Total follow up: median 18 months	**1 dose vaccine efficacy against RSV-B LRTD**  Data reviewed are from the aforementioned RCT (NCT04886596), study ongoing, estimates derived from the modified exposed population. Values shown for season 1 and 2 combined were adjusted with season as covariate; all vaccine efficacy estimates shown were based on receipt of 1 dose of Arexvy given pre-season 1.[1-3] Median follow up times were: • 'a' Interim season 1 analysis, 6.7 months (complete northern hemisphere season) • 'c' Season 1 and 2 median 11.5 months.		⨁⨁◯◯ Low[b]	RSVPreF3 vaccine may result in a moderate reduction in LRTD subtype B **during the first season** following single dose vaccination when compared with placebo. Note: Interpretation based on final season 1 analysis. RSVPreF3 vaccine may result in a moderate reduction in LRTD subtype B **over two RSV seasons** following single dose vaccination prior to season 1 when compared with placebo.

GSK AS01E adjuvanted RSVPreF3 vaccine (Arexvy) compared with placebo or no vaccine in adults aged 60 years and over				
Patient or population: Adults aged ≥60 years **Intervention:** GSK AS01E adjuvanted RSVPreF3 vaccine (Arexvy) **Comparison:** Placebo or no vaccine				
Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
RSV acute respiratory illness (ARI) ≥2 symptoms (at least 1 respiratory) lasting >24 hours Assessed with: RT-PCR Total follow up: median 18 months	**1 dose vaccine efficacy against RSV-ARI**  Data reviewed are from the aforementioned RCT (NCT04886596), study ongoing, estimates derived from the modified exposed population. Values shown for season 1 and 2 combined were adjusted with season as covariate; all vaccine efficacy estimates shown were based on receipt of 1 dose of Arexvy given pre-season 1.[1-3] Median follow up times were: • 'a' Interim season 1 analysis, 6.7 months (complete northern hemisphere season) • 'c' Season 1 and 2 median 11.5 months.	Population: 24,960 Population: 24,967	⊕⊕⊕◯ Moderate[a]	RSVPreF3 vaccine likely results in a moderate reduction in RSV-associated ARI **during the first season** following single dose vaccination when compared with placebo. RSVPreF3 vaccine likely results in a moderate reduction in RSV-associated ARI **over two RSV seasons** following single dose vaccination prior to season 1 when compared with placebo.

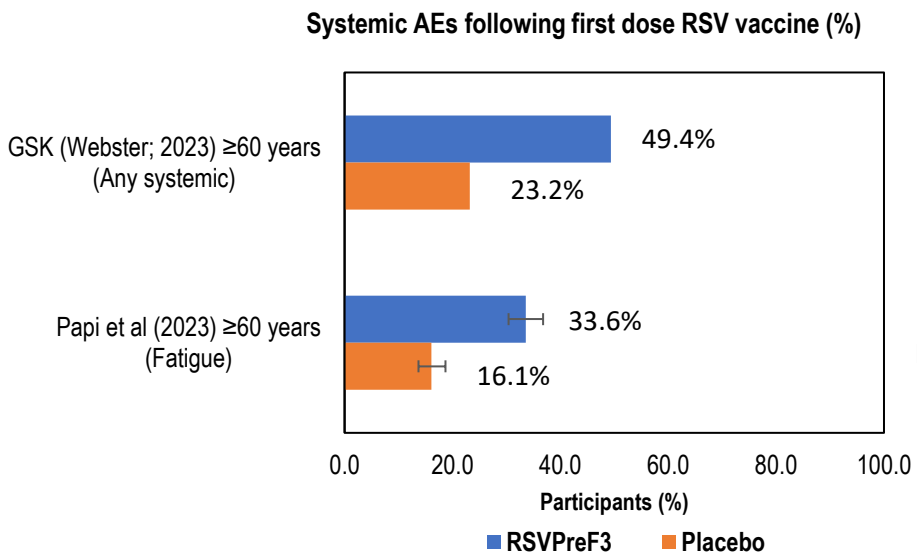
GSK AS01E adjuvanted RSVPreF3 vaccine (Arexvy) compared with placebo or no vaccine in adults aged 60 years and over

Patient or population: Adults aged ≥60 years
Intervention: GSK AS01E adjuvanted RSVPreF3 vaccine (Arexvy)
Comparison: Placebo or no vaccine

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
Solicited local AEs Assessed with: Patient diary record Follow-up: 4 days	 *Note: confidence intervals not available for 'Any local AE' Data reviewed are from the aforementioned RCT (NCT04886596). Estimates derived from the solicited safety set population.[1,4]		⊕⊕⊕⊕ High	RSVPreF3 vaccine results in a large increase in local AEs when compared with placebo.

GSK AS01E adjuvanted RSVPreF3 vaccine (Arexvy) compared with placebo or no vaccine in adults aged 60 years and over

Patient or population: Adults aged ≥60 years
Intervention: GSK AS01E adjuvanted RSVPreF3 vaccine (Arexvy)
Comparison: Placebo or no vaccine

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
Solicited systemic AEs Assessed with: patient diary record Follow-up: 4 days	 Population: 1757 Population: 1757 *Note: confidence intervals not available for 'Any systemic AE' Data reviewed are from the aforementioned RCT (NCT04886596). Estimates derived from the solicited safety set population.[1,4]		⊕⊕⊕⊕ High	RSVPreF3 vaccine results in a moderate increase in systemic AEs when compared with placebo.

GSK AS01E adjuvanted RSVPreF3 vaccine (Arexvy) compared with placebo or no vaccine in adults aged 60 years and over

Patient or population: Adults aged ≥60 years
Intervention: GSK AS01E adjuvanted RSVPreF3 vaccine (Arexvy)
Comparison: Placebo or no vaccine

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation

Explanations

a. Downgraded for wide confidence intervals
b. Downgraded for very wide confidence intervals

Footnotes

† Severe RSV-LRTD Definition 1 – 'Clinical symptomology': An event meeting the case definition of LRTD with at least one RSV-positive swab detected by qRT-PCR. Presence of an LRTD with at least one of the following criteria: • at least two lower respiratory signs; • an LRTD episode assessed as 'severe' by the investigator; AND • with at least one RSV-positive swab detected by qRT-PCR. Lower respiratory signs: new or increased wheezing; new or increased crackles/ronchi based on chest auscultation; respiratory rate ≥20 respirations/min; low or decreased oxygen saturation (<95% or ≤90% if preseason baseline is <95%); need for oxygen supplementation. Severe RSV-LRTD Definition 2 – 'Supportive therapy': Presence of an LRTD with at least one of the following criteria: • need for oxygen supplementation; • need for positive airway pressure therapy (e.g. cpap); • need for other types of mechanical ventilation; AND • with at least one RSV-positive swab detected by qRT-PCR.

Abbreviations: ARI=acute respiratory illness; CI=confidence interval; CSR=clinical study report; LRTD=lower respiratory tract disease; RCT=randomised controlled trial; RSV=respiratory syncytial virus; RT-PCR=reverse-transcriptase polymerase chain reaction; SAE=serious adverse event

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

GRADE evidence profile

Evidence profile: A single dose of GSK AS01E adjuvanted RSVPreF3 vaccine (Arexvy) compared with placebo or no vaccine in adults aged ≥60 years

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
RSV-LRTD (≥2 lower respiratory signs/symptoms with at least 1 respiratory sign, or ≥3 respiratory signs lasting >24 hours) (follow-up: median 18 months; assessed with: reverse-transcriptase polymerase chain reaction [RT-PCR])									
1	Randomised trials	Not serious	N/A	Not serious	Serious[a]	None	**Vaccine efficacy % (95% CI)** Season 1 – interim analysis • Papi, et al (2023) ≥60 years: 82.60% (96.95% CI: 57.90–94.10) • Papi, et al (2023) ≥70 years: 84.40% (46.90–97.00) • Papi, et al (2023) ≥80 years: 33.80% (−477.70–94.50) • Papi, et al (2023) 60–69 years: 81.00% (43.60–95.30) • Papi, et al (2023) 70–79 years: 93.80% (60.20–99.90) • Papi, et al (2023) ≥1 coexisting condition of interest: 94.60% (65.90–99.90) Season 1 – final analysis • Ison, et al (2024) ≥60 years: 78.86% (96.95% CI: 57.61–90.48) [redacted]	⨁⨁⨁◯ Moderate	CRITICAL

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
							Vaccine efficacy % (95% CI) *continued* Season 1 and 2, following 1 dose vaccine (given pre-season 1) • Ison, et al (2024) ≥60 years: 67.18% (97.5% CI: 48.19–80.04) • Ison, et al (2024) 60–69 years: 65.36% (40.40–80.93) • Ison, et al (2024) 70–79 years: 74.89% (48.42–89.15) • Ison, et al (2024) ≥80 years: 38.37% (−118.17–86.14) • Ison, et al (2024) ≥70 years: 69.30% (43.40–84.60) • Ison, et al (2024) ≥1 coexisting condition of interest: 66.68% (41.82–82.00) Season 2, 1 dose vaccine (given pre-season 1) • Ison, et al (2024) ≥60 years: 56.10% (97.5% CI: 28.20–74.40) • Ison, et al (2024) 60–69 years: 50.90% (6.10–76.30) • Ison, et al (2024) 70–79 years: 66.20% (18.90–88.30) • Ison, et al (2024) ≥80 years: 41.00% (−209.90–94.00) • Ison, et al (2024) ≥70 years: 62.10% (18.40–84.60) • Ison, et al (2024) ≥1 coexisting condition of interest: 51.50% (7.40–76.60) 1-3		

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Severe LRTD (≥2 lower respiratory signs/symptoms with at least 1 respiratory sign, or ≥3 respiratory signs lasting >24 hours) (follow-up: median 18 months; assessed with: RT-PCR and based on 'clinical symptomology' and/or 'supportive therapy')									
1	Randomised trials	Not serious	N/A	Not serious	Serious[a]	None	**Vaccine efficacy (95% CI)** Season 1 • Papi, et al (2023) ≥60 years (interim analysis) 94.10% (62.40–99.90) [redacted] Seasons 1 and 2 (following 1 dose vaccine given pre-season 1) • Ison, et al (2024) ≥60 years: 78.83% (52.59–91.96) 1-3	⨁⨁⨁◯ Moderate	CRITICAL
1	Randomised trials	Not serious	N/A	Not serious	Very serious[b]	None	Season 2 (following 1 dose vaccine given pre-season 1) • Ison, et al (2024) ≥60 years: 64.20% (6.20–89.20) 2	⨁⨁◯◯ Low	CRITICAL

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Serious adverse events (SAEs) (follow-up: 6 months; assessed with: patient report of 'any' SAE)									
1	Randomised trials	Not serious	N/A	Not serious	Not serious	None	There was no difference in proportion of any SAEs between vaccine or placebo groups among those 60 years and over: Papi, et al (2023) (interim season 1 data) **n=522, 4.2% (95% CI: 3.8–4.6) in vaccine group; n= 506, 4.0% (95% CI: 3.7–4.4) in placebo group)** [redacted] Of note, there was no difference in proportion of SAEs related to vaccine or placebo between groups among those 60 years and over: Papi, et al (2023): **n=10, 0.1% (95% CI: 0, 0.1) in vaccine group; n= 7, 0.1% (95% CI: 0–0.1) in placebo group)** [redacted] [1,3]	⊕⊕⊕⊕ High	CRITICAL

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
RSV-LRTD – Subtype A (≥2 lower respiratory signs/symptoms with at least 1 respiratory sign, or ≥3 resp signs lasting >24 hours) (follow-up: 10 months; assessed with: RT-PCR)									
1	Randomised trials	Not serious	N/A	Not serious	Very serious[b]	None	**Vaccine efficacy (95% CI)** Season 1 • Papi, et al (2023) ≥60 years: 84.60% (32.10–98.30) [redacted] Seasons 1 and 2 (following 1 dose vaccine given pre-season 1) • Ison, et al (2024) ≥60 years: 80.46% (53.95–93.20) 1-3	⨁⨁◯◯ Low	IMPORTANT
RSV-LRTD – Subtype B (≥2 lower respiratory signs/symptoms with at least 1 respiratory sign, or ≥3 respiratory signs lasting >24 hours) (follow-up: 10 months; assessed with: RT-PCR)									
1	Randomised trials	Not serious	N/A	Not serious	Very serious[b]	None	**Vaccine efficacy (95% CI)** Season 1 • Papi, et al (2023) ≥60 years: 80.90% (49.40–94.30) [redacted] Seasons 1 and 2 (following 1 dose vaccine given pre-season 1) • Ison et, al (2024) ≥60 years: 59.66% (35.80–75.54) 1-3	⨁⨁◯◯ Low	IMPORTANT

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
RSV-acute respiratory illness (ARI) ≥2 symptoms (at least 1 respiratory) lasting >24 hours (follow-up: 10 months; assessed with: RT-PCR and 2 symptoms [at least 1 respiratory] lasting >24 hours)									
1	Randomised trials	Not serious	N/A	Not serious	Serious[a]	None	**Vaccine efficacy (95%CI)** Season 1 • Papi, et al (2023) ≥60 years 71.70% (56.20–82.30) [redacted] Seasons 1 and 2 (following 1 dose vaccine given pre-season 1) • Ison, et al (2024) ≥60 years (Season 1+2, 1 dose) 52.74% (40.01–63.04) 1-3	⨁⨁⨁◯ Moderate	IMPORTANT
Solicited local AEs (follow-up: 4 days; assessed with: patient diary record)									
1	Randomised trials	Not serious	N/A	Not serious	Not serious	None	There was a higher proportion of any local or pain reported amongst vaccine recipients compared with placebo recipients in adults aged ≥60 years. • GSK (Webster; 2023) ≥60 years, any local: RSVPreF3 62.2% vs placebo 10.0% • Papi, et al (2023) ≥60 years, local pain: RSVPreF3 60.9% vs placebo 9.3% 1,4	⨁⨁⨁⨁ High	IMPORTANT

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Solicited systemic AEs (follow-up: 4 days; assessed with: patient diary record)									
1	Randomised trials	Not serious	N/A	Not serious	Not serious	None	There was a higher proportion of any systemic AE or fatigue reported amongst vaccine recipients compared with placebo recipients in adults aged ≥60 years. • GSK (Webster; 2023) ≥60 years, any systemic: RSVPreF3 49.4% vs placebo 23.2% • Papi, et al (2023) ≥60 years, fatigue: RSVPreF3 33.6% vs placebo 16.1% [1,4]	⨁⨁⨁⨁ High	IMPORTANT

Explanations

a. Downgraded for wide confidence intervals

b. Downgraded for very wide confidence intervals

Evidence to Decision Framework: **A single dose of GSK AS01E adjuvanted RSVPreF3 vaccine (Arexvy) compared with placebo or no vaccine in adults aged ≥60 years**

Should Arexvy (GSK; Recombinant Respiratory Syncytial Virus pre-fusion F protein vaccine [RSVPreF3] adjuvanted with AS01E) be recommended for adults aged ≥60 years to prevent respiratory syncytial (RSV) disease? PICO Question	
Population	Adults aged ≥60 years
Intervention	Arexvy (GSK) adjuvanted RSV vaccine
Comparison	Placebo
Main outcomes	*Efficacy* • RSV (laboratory confirmed) lower respiratory tract illness/disease (LRTI/LRTD) – Critical • RSV (laboratory confirmed) severe LRTI/LRTD – Critical • RSV – Subtype A (laboratory confirmed) LRTI/LRTD – Important • RSV – Subtype B (laboratory confirmed) LRTI/LRTD – Important • RSV (laboratory confirmed) acute respiratory infection – Important *Safety* • Serious adverse events (SAEs) – Critical • Systemic adverse events (AEs) – Important • Local AEs – Important
Setting	Global middle- to high-income settings (e.g. Europe, Canada, the US, Australia)

ASSESSMENT

Problem

Is the problem a priority?

Don't know	Varies	No	Probably no	Probably yes	Yes

- RSV is increasingly recognised as a significant respiratory viral illness which causes morbidity and mortality in older adults, including those aged ≥60 years. RSV hospitalisation rates increase with age in older adults.[5,6] Analysis of the Australian Institute of Health and Welfare National Hospital Morbidity Database (AIHW, unpublished NCIRS analysis) indicates that between 2016 and 2019 the rate of RSV-coded hospitalisations for adults aged ≥60 years was 101 per 100,000 and increased to 194 per 100,000 for those aged ≥75 years. These numbers are likely underestimated due to testing and administrative coding limitations. By comparison, the hospitalisation rate in Australian adults aged ≥65 years for influenza was 287.5 per 100,000.[7]
- There is also an increasing trend in in-hospital death rates with age, with the highest in-hospital death rate (2016–2019) seen in older adults aged ≥80 years (7.2 [95% CI: 2.8–11.4] per 100,000 population).
- Priority groups, such as First Nations people and those with comorbidities, have an increased risk of severe RSV disease than the non-Indigenous and general population.[5,8-11]

Desirable effects

How substantial are the desirable anticipated effects?

Don't know	Varies	Large	Moderate	Small	Trivial

- Arexvy (GSK) adjuvanted RSV vaccine results in significant reductions in RSV LRTD in adults aged ≥60 years, including those aged 70–79 years and those with ≥1 medical comorbidity.
- Relatively larger reductions are seen against more severe LRTD. Benefits persist into the second RSV season, but total duration of protection is unknown.
- There is low certainty evidence of protection against both RSV A and B subtypes and variability over time which may be related to dominant strains in the season studied. Effectiveness against RSV subtypes will require ongoing monitoring for strain changes over time.

Undesirable effects

How substantial are the undesirable anticipated effects?

Don't know	Varies	Large	Moderate	Small	Trivial

- There is a large increase in local AEs, and a moderate increase in systemic AEs with Arexvy (GSK) adjuvanted RSV vaccine compared with placebo.
- Most post-vaccination AEs are mild to moderate in severity and resolve within 4 days. Solicited local and systemic AEs occur at similar frequencies to adjuvanted zoster vaccine,[12] which is recommended and funded on the National Immunisation Program (NIP).
- There are no differences in total serious adverse events between vaccine and placebo groups.
- There were a very small number of rare adverse events of special interest (AESI). The study assessed in this GRADE showed an imbalance of atrial fibrillation occurring within 30 days of vaccination (vaccine: 7, placebo: 1).[13] At 6 months, this imbalance did not persist, with atrial fibrillation being reported in 0.1% of Arexvy and 0.1% of placebo recipients with none of the events of atrial fibrillation being considered related to the vaccine.[13] In other studies of Arexvy, which were not eligible for inclusion in this GRADE assessment because they involved co-administration of Arexvy with other vaccines or there was no placebo comparator, three cases of autoimmune inflammatory neurologic conditions (Guillain Barré syndrome [GBS] n=1, acute disseminated encephalomyelitis [ADEM] n=2)[14] were reported in the Arexvy RSV vaccine group. Low event numbers do not allow determination if rates of these adverse events are significantly raised compared with control groups. As clinical trials are not powered to detect rare SAEs, clarification of whether these are true safety signals will require large post-marketing surveillance studies.

Balance of effects

Does the balance between desirable and undesirable effects favour the intervention or the comparison?

Don't know	Varies	Favours comparison	Probably favours comparison	Does not favour either comparison or intervention	Probably favours intervention	Favours intervention

- The balance of effects probably favours vaccination with Arexvy (GSK) adjuvanted RSV vaccine.
- The vaccine is efficacious and there is a high burden of disease, particularly as age increases.
- The undesirable effects from vaccination are typical common post-vaccination local and systemic AEs and relatively brief in duration. Rare AESI require further investigation to determine whether there is a risk associated with vaccination.

Certainty of evidence

What is the overall certainty of the evidence of effects?

No included studies	Very low	Low	Moderate	High

- The overall certainty of evidence is moderate.
- 3 outcomes had high certainty evidence (all were safety outcomes).
- 3 outcomes with moderate certainty of evidence: vaccine efficacy against LRTD (non-severe and severe) and against acute respiratory infection.
- 2 outcomes had low certainty evidence due to imprecision around efficacy estimates by RSV A and B subtypes.
- Most of these outcomes were downgraded due to imprecision around estimates.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

Important uncertainty	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability

- There is a possibility of important uncertainty. While some people will value protection against RSV disease, other people and providers may be less familiar with RSV infection than other vaccine-preventable respiratory viral infections such as influenza.[15]
- Uncertainty is likely to reduce with increased public and provider awareness of RSV over time.

Acceptability

Is the intervention acceptable to key stakeholders?

Don't know	Varies	No	Probably no	Probably yes	Yes

RSV vaccination for adults aged ≥60 years is likely to be acceptable to key stakeholders based on good uptake of influenza vaccine (which provides protection against a similar respiratory viral illness), with an estimated 62.5% of adults aged 65–74 years and 68.5% aged ≥75 years vaccinated in 2021.[16]

Equity

What would be the impact on health inequities?

Don't know	Varies	Increased	Probably increased	Probably no impact	Probably reduced	Reduced

- The potential impact on health inequities is likely to vary dependent on program design and uptake.
- As the burden of RSV infection and severe outcomes is higher in Aboriginal and Torres Strait Islanders,[5] RSV vaccination could reduce health inequities if there was adequate uptake of the vaccine within this population. This population often has higher rates of comorbid conditions who would be expected to benefit more from vaccination.
- Similarly, RSV vaccination could address the increased burden of disease in those with medical comorbidities who have increased risk of RSV hospitalisation.[8-11]

  A lower age-based recommendation in these priority populations than the general population would be one way to address these health inequities. A universal vaccination program in which standard and higher risk individuals were eligible from the same age may have no impact on (or worsen) health inequities.

Feasibility

Is the intervention feasible to implement?

Don't know	Varies	No	Probably no	Probably yes	Yes

- RSV vaccine should be feasible to implement using the vaccine delivery system already in use including through primary care and pharmacist vaccination.
- Potential challenges include training requirements for a new vaccine on the NIP, adequate resourcing for distribution to a large number of individuals, the need to ensure there is no detrimental impact on other older adult vaccination programs such as influenza, zoster and pneumococcal vaccines, and potential for further doses of RSV vaccine if required in the future.

ATAGI RECOMMENDATION

- A single dose Arexvy (GSK) adjuvanted RSV vaccine is recommended for all adults aged ≥75 years, First Nations people aged ≥60 years, and people aged ≥60 years with medical conditions that put them at increased risk of severe RSV disease.

JUSTIFICATION AND CONSIDERATIONS

Additional considerations

- The increased burden of RSV with age suggests that among the general population, the benefit of vaccination is likely to be greater in those who are older i.e. adults aged ≥75 years.
- First Nations individuals and those with medical risk factors for severe RSV disease have increased RSV disease burden and are recommended for vaccination from 60 years of age, which is at an earlier age than the general population.
- Due to a lower burden of disease among adults aged 60–74 years in the general population, protective efficacy from vaccination may be lower in non-First Nations individuals and those without comorbidities aged between 60–74 years compared with adults aged ≥75 years.
- Post-marketing safety surveillance is recommended after introduction of RSV vaccine onto the NIP to monitor for safety signals and AESI including autoimmune inflammatory neurologic conditions and atrial fibrillation.

Justification

- Arexvy (GSK) adjuvanted RSV vaccine is efficacious at preventing RSV disease in adults aged ≥60 years, with high levels of efficacy for more serious outcomes (severe LRTD), and moderate levels of efficacy against milder disease (acute respiratory infection).
- The vaccine appears efficacious for at least 2 years with duration of protection beyond that unclear.
- Due to the high burden of disease, which increases with age,[5,6] and the lack of a current vaccine, introduction of a national vaccination program in older adults is likely to have substantial clinical benefit.
- First nations people and individuals with comorbid conditions including cardiovascular conditions, chronic respiratory conditions, immunocompromising conditions, chronic kidney disease, and diabetes mellitus are at increased risk of severe RSV disease.[8-11]
- Post-vaccination adverse events are common but occur at similar frequencies to other adjuvanted older adult vaccines on the NIP.
- Rare adverse events of special interest in clinical trials are noted but require post-marketing surveillance studies to establish if any links exist to vaccination.

  The body of evidence suggests that in comparison to no vaccine, the benefits of Arexvy (GSK) adjuvanted RSV vaccine are likely to outweigh the higher frequency of non-serious adverse events following immunisation.

References

1. Papi A, Ison MG, Langley JM, et al. Respiratory syncytial virus prefusion F protein vaccine in older adults. *New England Journal of Medicine* 2023;388(7):595-608.
2. Ison MG, Papi A, Athan E, et al. Efficacy and safety of respiratory syncytial virus prefusion F protein vaccine (RSVPreF3 OA) in older adults over 2 RSV seasons. *Clinical Infectious Diseases* 2024:1-13.
3. GSK. CSR(2). OA=ADJ-006 Study Report (VE Analysis 2) 30 Mar 2023 Synopsis - CONFIDENTIAL.
4. GSK. RSVPreF3 Vaccine for Respiratory Syncytial Virus (RSV) in Older Adults: Vaccines and Related Biological Products Advisory Committee Meeting March 1, 2023; 2023 [Available from: https://www.fda.gov/media/165649/download.
5. Saravanos GL, Sheel M, Homaira N, et al. Respiratory syncytial virus-associated hospitalisations in Australia, 2006-2015. *Medical Journal of Australia* 2019;210(10):447-53.
6. Nazareno AL, Muscatello DJ, Turner RM, et al. Modelled estimates of hospitalisations attributable to respiratory syncytial virus and influenza in Australia, 2009-2017. I*nfluenza and Other Respiratory Viruses* 2022;16(6):1082-90.
7. Moa AM, Menzies RI, Yin JK, et al. Modelling the influenza disease burden in people aged 50-64 and >/=65 years in Australia. *Influenza and Other Respiratory Viruses* 2022;16(1):132-41.
8. Branche AR, Saiman L, Walsh EE, et al. Incidence of Respiratory syncytial virus infection among hospitalized adults, 2017-2020. *Clinical Infectious Diseases* 2022;74(6):1004-11.
9. Prasad N, Walker TA, Waite B, et al. Respiratory syncytial virus-associated hospitalizations among adults with chronic medical conditions. *Clinical Infectious Diseases* 2021;73(1):e158-e63.
10. Loubet P, Lenzi N, Valette M, et al. Clinical characteristics and outcome of respiratory syncytial virus infection among adults hospitalized with influenza-like illness in France. *Clinical Microbiology and Infection* 2017;23(4):253-9.
11. Wyffels V, Kariburyo F, Gavart S, et al. A real-world analysis of patient characteristics and predictors of hospitalization among US Medicare beneficiaries with respiratory syncytial virus infection. *Advances in Therapy* 2020;37(3):1203-17.
12. National Centre for Immunisation Research and Surveillance. Shingrix vs Placebo Immunocompetent Older Adults - GRADE 2021 [updated June 2021. Available from: https://ncirs.org.au/sites/default/files/2021-07/Shingrix%20vs%20Placebo%20Immunocompetent%20Adults%20GRADE_FINAL.pdf.
13. GSK. RSVPreF3 OA -Vaccine and Related Biological Products Advisory Committee - Sponsor Briefing Document 2023.
14. Melgar M, Britton A, Roper LE, et al. Use of respiratory syncytial virus vaccines in older adults: recommendations of the Advisory Committee on Immunization Practices — United States, 2023. *Morbidity and Mortality Weekly Report* 2023;72(29).
15. Hurley LP, Allison MA, Kim L, et al. Primary care physicians' perspectives on respiratory syncytial virus (RSV) disease in adults and a potential RSV vaccine for adults. *Vaccine* 2019;37(4):565-70.
16. Hull B, Hendry A, Dey A, et al. Annual Immunisation Coverage Report [Internet]. National Centre for Immunisation Research and Surveillance; 2022 [cited September 2023]. Available from: https://ncirs.org.au/sites/default/files/2022-12/NCIRS%20Annual%20Immunisation%20Coverage%20Report%202021_FINAL.pdf.