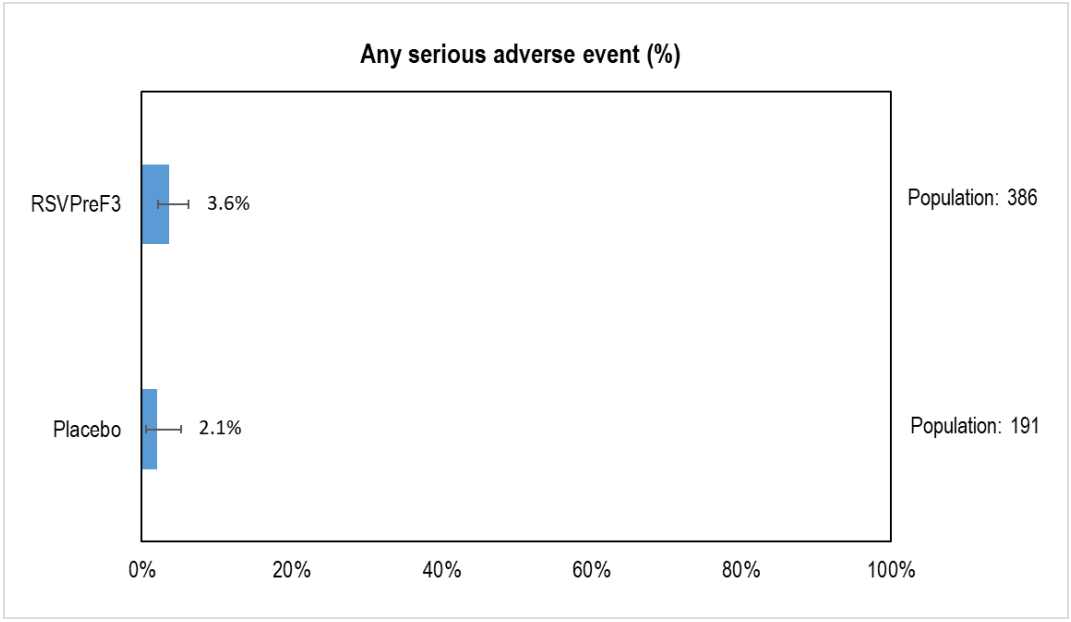
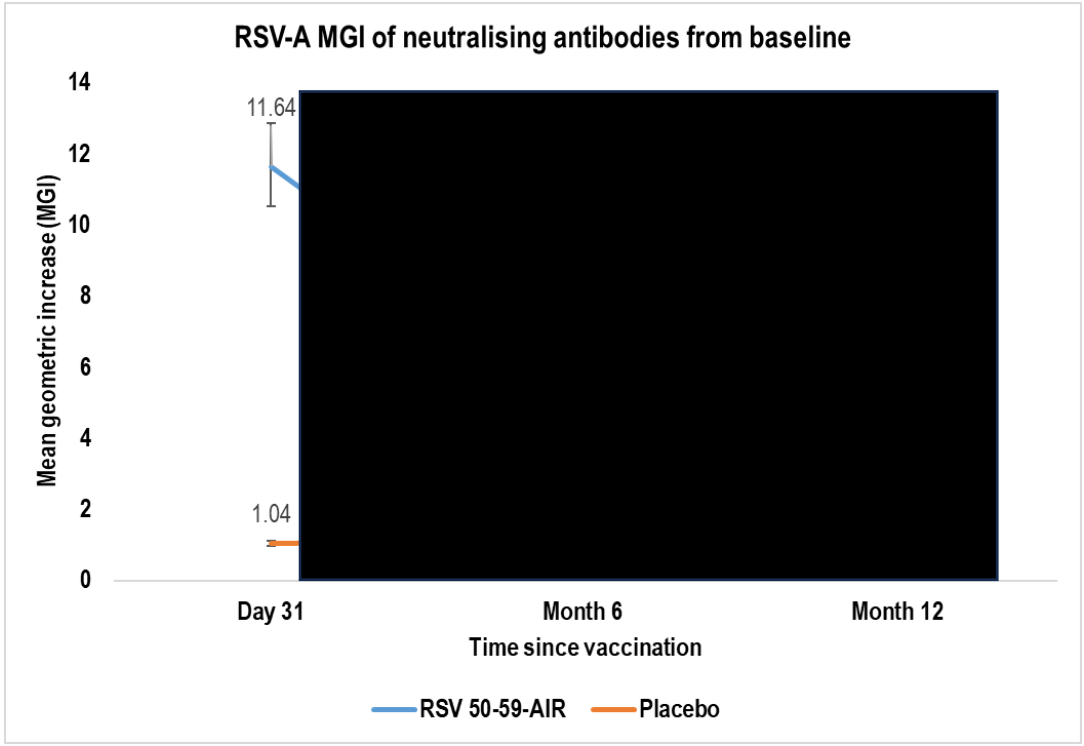
GRADE tables: Comparison of GSK RSVPreF3 (Arexvy) vaccine adjuvanted with AS01E with placebo or no vaccine in adults aged 50–59 years with medical risk factors for severe disease

NCIRS is conducting GRADE in support of ATAGI and making results available on the NCIRS website. Please read this material as a supplement to the Australian Immunisation Handbook respiratory syncytial virus chapter.

Comparison of GSK RSVPreF3 (Arexvy) vaccine adjuvanted with AS01E with placebo or no vaccine in adults aged 50–59 years with medical risk factors for severe disease*

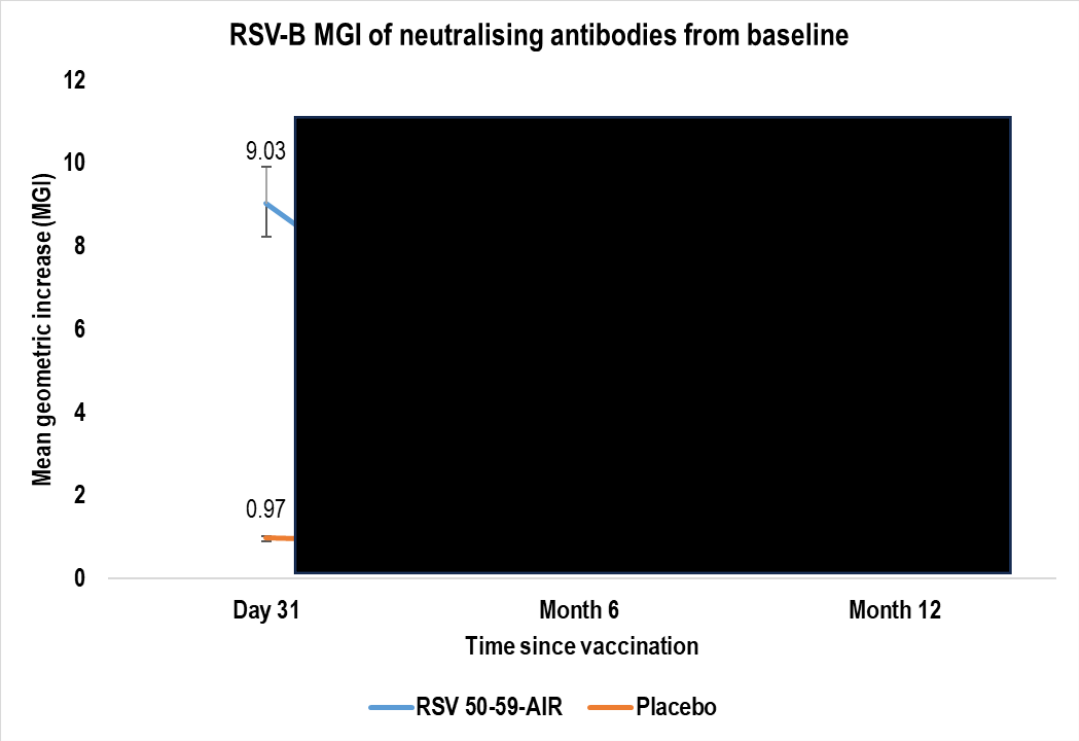
Patient or population: Adults aged 50-59 years medical risk factors for severe disease*
Intervention: GSK RSVPreF3 (Arexvy) vaccine adjuvanted with AS01E
Comparison: Placebo or no vaccine

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
Serious adverse events Follow up: 6 months		577 (1 randomised controlled trial [RCT])	⊕⊕⊕◯ Moderate[a,b]	RSVPreF3 likely results in little to no difference in serious adverse events. None of the serious adverse events were considered to be related to the vaccine.

Comparison of GSK RSVPreF3 (Arexvy) vaccine adjuvanted with AS01E with placebo or no vaccine in adults aged 50–59 years with medical risk factors for severe disease*				
Patient or population: Adults aged 50-59 years medical risk factors for severe disease* **Intervention:** GSK RSVPreF3 (Arexvy) vaccine adjuvanted with AS01E **Comparison:** Placebo or no vaccine				
Outcomes	**Impact**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Interpretation**
RSV-A mean geometric increase of neutralising antibodies from baseline Follow up: 30 days		517 (1 RCT)	⊕⊕⊕◯ Moderate[a,c]	RSVPreF3 likely results in a large increase in RSV-A neutralising antibodies at 30 days post vaccination.

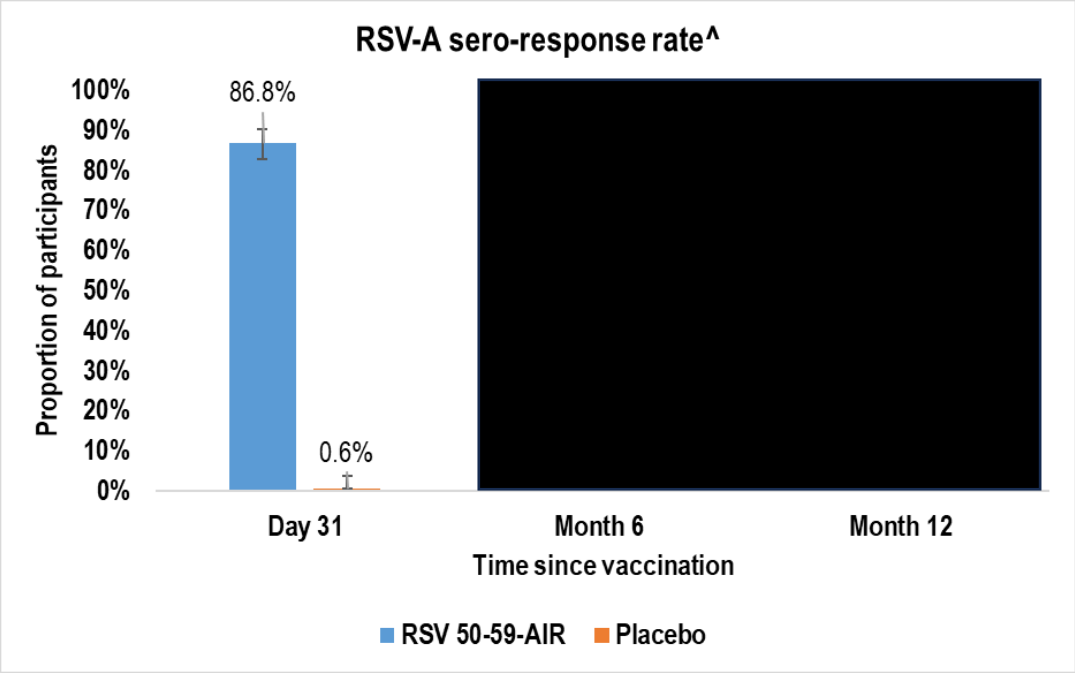
Comparison of GSK RSVPreF3 (Arexvy) vaccine adjuvanted with AS01E with placebo or no vaccine in adults aged 50–59 years with medical risk factors for severe disease*

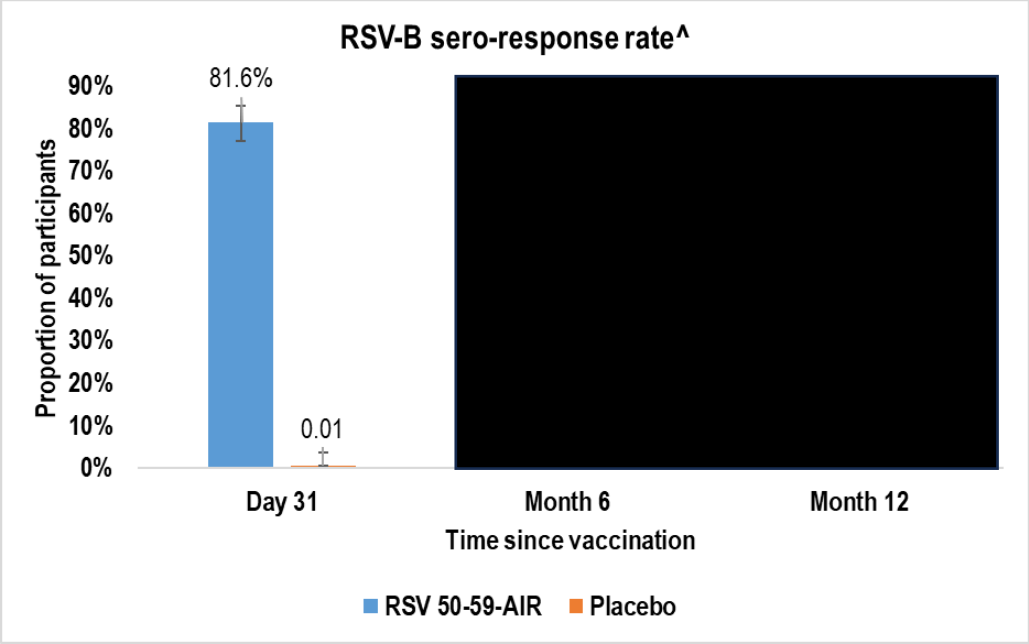
Patient or population: Adults aged 50-59 years medical risk factors for severe disease*
Intervention: GSK RSVPreF3 (Arexvy) vaccine adjuvanted with AS01E
Comparison: Placebo or no vaccine

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
RSV-B mean geometric increase of neutralising antibodies from baseline Follow up: 30 days		517 (1 RCT)	⊕⊕⊕◯ Moderate[a,c]	RSVPreF3 likely results in a large increase in RSV-B neutralising antibodies at 30 days post vaccination.

Comparison of GSK RSVPreF3 (Arexvy) vaccine adjuvanted with AS01E with placebo or no vaccine in adults aged 50–59 years with medical risk factors for severe disease*

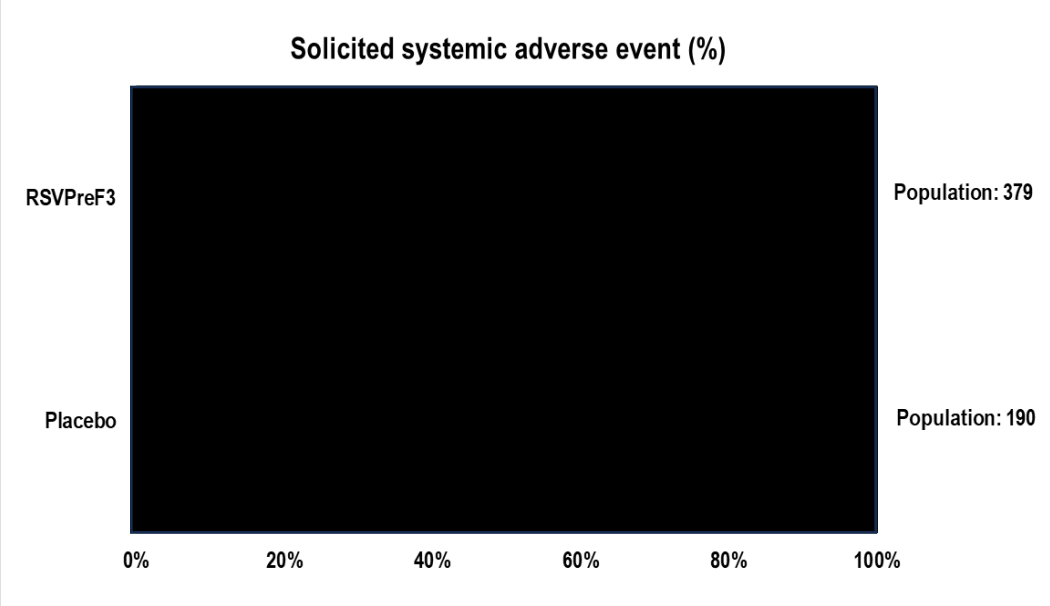
Patient or population: Adults aged 50-59 years medical risk factors for severe disease*
Intervention: GSK RSVPreF3 (Arexvy) vaccine adjuvanted with AS01E
Comparison: Placebo or no vaccine

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
RSV-A sero-response rate (SRR)^ Follow up: 30 days		519 (1 RCT)	⊕⊕⊕◯ Moderate[a,c]	RSVPreF3 likely results in a large increase in SRR for RSV-A at 30 days post vaccination.

Comparison of GSK RSVPreF3 (Arexvy) vaccine adjuvanted with AS01E with placebo or no vaccine in adults aged 50–59 years with medical risk factors for severe disease*				
Patient or population: Adults aged 50-59 years medical risk factors for severe disease* **Intervention:** GSK RSVPreF3 (Arexvy) vaccine adjuvanted with AS01E **Comparison:** Placebo or no vaccine				
Outcomes	**Impact**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Interpretation**
RSV-B SRR^ Follow up: 30 days		519 (1 RCT)	⊕⊕⊕◯ Moderate[a,c]	RSVPreF3 likely results in a large increase in SRR for RSV-B at 30 days post vaccination.

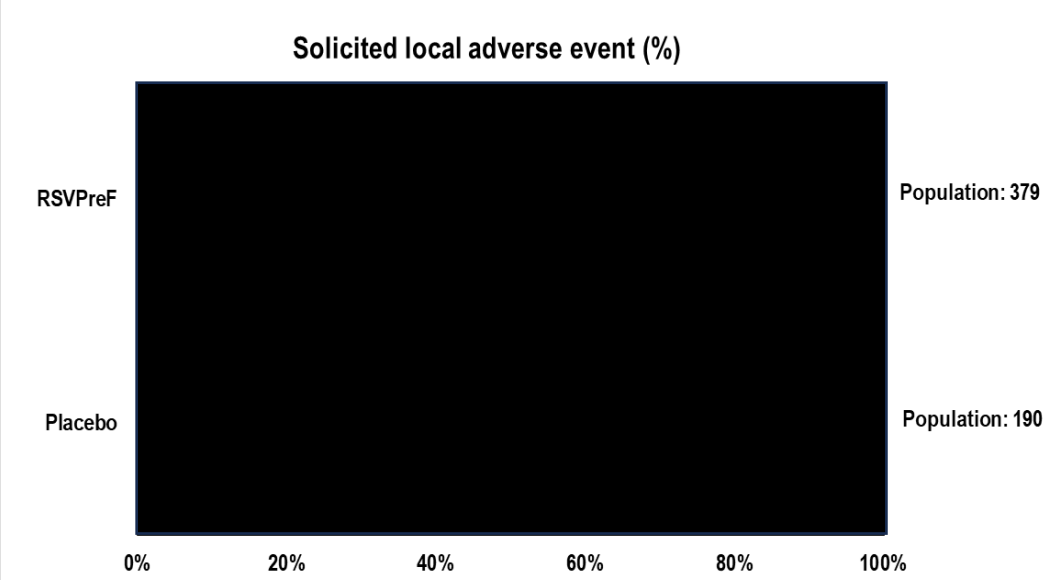
Comparison of GSK RSVPreF3 (Arexvy) vaccine adjuvanted with AS01E with placebo or no vaccine in adults aged 50–59 years with medical risk factors for severe disease*

Patient or population: Adults aged 50-59 years medical risk factors for severe disease*
Intervention: GSK RSVPreF3 (Arexvy) vaccine adjuvanted with AS01E
Comparison: Placebo or no vaccine

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
Any solicited systemic adverse events Follow up: 4 days	 The most frequently reported systemic events were fatigue, myalgia and headache. Grade 3 solicited systemic adverse events were reported in [redacted] participants in the RSVPreF group and in [redacted] participants in the placebo group.	569 (1 RCT)	⊕⊕⊕⊕ High[a]	RSVPreF3 results in an increase in systemic adverse events.

Comparison of GSK RSVPreF3 (Arexvy) vaccine adjuvanted with AS01E with placebo or no vaccine in adults aged 50–59 years with medical risk factors for severe disease*

Patient or population: Adults aged 50-59 years medical risk factors for severe disease*
Intervention: GSK RSVPreF3 (Arexvy) vaccine adjuvanted with AS01E
Comparison: Placebo or no vaccine

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
Any solicited local adverse events Follow up: 4 days	 The most frequently reported local adverse event was pain at the injection site. Grade 3 solicited local adverse events were reported in [redacted] participants in the RSVPreF group and [redacted] in the placebo group.	569 (1 RCT)	⨁⨁⨁⨁ High[a]	RSVPreF3 results in a large increase in solicited local adverse events.

Comparison of GSK RSVPreF3 (Arexvy) vaccine adjuvanted with AS01E with placebo or no vaccine in adults aged 50–59 years with medical risk factors for severe disease*

Patient or population: Adults aged 50-59 years medical risk factors for severe disease*
Intervention: GSK RSVPreF3 (Arexvy) vaccine adjuvanted with AS01E
Comparison: Placebo or no vaccine

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

Explanations

a. Inconsistency not assessed as only one study included
b. Imprecision assessed as serious due to small sample size with low event numbers. It is noted that the study was not powered to detect a difference between treatment arms for this outcome
c. Indirectness assessed as serious due to no efficacy outcomes available in this population. Immunogenicity outcomes are available however, there is not a defined correlate of protection for neutralising antibodies and RSV disease.

Footnotes

*Medical risk factors include: cardiac disease; chronic respiratory conditions; immunocompromising conditions; chronic metabolic disorders, including diabetes; chronic kidney disease (stage 4 or 5); chronic neurological conditions; obesity

^ Sero-response rate defined as the percentage of participants with a 4-fold or greater increase in neutralization titres from pre- to 1 month post-vaccination/12 months post vaccination.

Abbreviations: AE=adverse event; MGI=mean geometric increase; RSV=respiratory syncytial virus; SRR=sero-response rate

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: Comparison of GSK RSVPreF3 (Arexvy) vaccine adjuvanted with AS01E with placebo or no vaccine in adults aged 50–59 years with medical risk factors for severe disease*

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Serious adverse events (follow up: 6 months)									
1	Randomised trials	Not serious	NA[a]	Not serious	Serious[b]	NA	There was a higher proportion of serious adverse events amongst vaccine recipients (3.6%) compared to placebo recipients (2.1%). None of the serious adverse events were considered to be related to the vaccine	⊕⊕⊕◯ Moderate	Critical
RSV-A mean geometric increase (MGI) of neutralising antibodies from baseline (follow up: 30 days)									
1	Randomised trials	Not serious	NA[a]	Serious[c]	Not serious	NA	The MGI of RSV-A neutralising antibodies from baseline to 30 days post vaccination was higher for vaccine recipients (11.64; 95% CI: 10.53, 12.87) compared to placebo recipients (1.04; 95% CI: 0.98, 1.11).	⊕⊕⊕◯ Moderate	Important
RSV-B mean geometric increase of neutralising antibodies from baseline (follow up: 30 days)									
1	Randomised trials	Not serious	NA[a]	Serious[c]	Not serious	NA	The MGI of RSV-B neutralising antibodies from baseline to 30 days post vaccination was higher for vaccine recipients (9.03; 95% CI: 8.22, 9.92) compared to placebo recipients (0.97; 95% CI: 0.9, 1.03).	⊕⊕⊕◯ Moderate	Important

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
RSV-A sero-response rate (SRR)^ (follow up: 30 days)									
1	Randomised trials	Not serious	NA[a]	Serious[c]	Not serious	NA	The proportion of participants who had a SRR for RSV-A at 30 days post vaccination was higher for vaccine recipients (86.8%; 95% CI: 82.8, 90.2) compared to placebo recipients (0.6%; 95% CI: 0, 3.1)	⊕⊕⊕◯ Moderate	Important
RSV-B sero-response rate (SRR)^ (follow up: 30 days)									
1	Randomised trials	Not serious	NA[a]	Serious[c]	Not serious	NA	The proportion of participants who had a SRR for RSV-B at 30 days post vaccination was higher for vaccine recipients (81.6%; 95% CI: 77.1, 85.5) compared to placebo recipients (0.6%; 95% CI: 0, 3.1)	⊕⊕⊕◯ Moderate	Important
Solicited systemic adverse events (follow up: 4 days)									
1	Randomised trials	Not serious	NA[a]	Not serious	Not serious	NA	There was a higher proportion of solicited systemic adverse events amongst vaccine recipients [redacted] compared to placebo recipients [redacted]. The most frequently reported systemic events were fatigue, myalgia and headache. Grade 3 solicited systemic adverse events were reported in [redacted] vaccine recipients and in [redacted] placebo recipients.	⊕⊕⊕⊕ High	Important

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Solicited administration site events (follow up: 4 days)									
1	Randomised trials	Not serious	NA[a]	Not serious	Not serious	NA	There was a higher proportion of solicited administration site events amongst vaccine recipients [redacted] compared to placebo recipients [redacted]. The most frequently reported local adverse event was pain at the injection site. Grade 3 solicited local adverse events were reported in [redacted] vaccine recipients and [redacted] placebo recipients.	⊕⊕⊕⊕ High	Important

Explanations

a. Inconsistency not assessed as only one study included.
b. Imprecision assessed as serious due to small sample size with low event numbers. It is noted that the study was not powered to detect a difference between treatment arms for this outcome.
c. Indirectness assessed as serious due to no efficacy outcomes available in this population. Immunogenicity outcomes are available however, there is not a defined correlate of protection for neutralising antibodies and RSV disease.

Evidence to Decision Framework

PICO Question	
Population	Age 50–59 years old with medical risk factors for severe disease
Intervention	Arexvy (GSK) adjuvanted RSV vaccine
Comparison	Placebo
Main outcomes	*Efficacy* • RSV subtype A neutralising antibodies – Important • RSV subtype B neutralising antibodies – Important *Safety* • Serious adverse events (SAEs) – Critical • Systemic adverse events – Important • Local adverse events – 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 ≥50 years with risk factors for severe disease. RSV hospitalisation rates increase with age in older adults.[1,2] Analysis of Australian Institute of Health and Welfare National Hospital Morbidity Database during 2016–2019 indicates that the rate of RSV-coded hospitalisations for adults aged 50–64 years is 26 per 100,000 (AIHW, unpublished NCIRS analysis) This is likely underestimated due to testing and administrative coding limitations. This compares to 78.9 per 100,000 for Australian adults aged 50–64 years for influenza.[3]
- Further analysis of 2016–2019 data indicates that 69% of hospitalisations in adults aged 20–64 years were in people with at least 1 comorbidity (AIHW, unpublished NCIRS analysis).
- Priority groups such as those with comorbidities, have an increased risk of severe RSV disease in comparison to the general population.[1,4-7] In a US study conducted across three RSV seasons (2017–19, 2018–19, 2019–20), the incidence of RSV associated hospitalisation among adults aged 50–64 years with chronic obstructive pulmonary disease (COPD) (204.8–210.3 per 100,000 population), coronary artery disease (154.0–168.2 per 100,000 population) and diabetes mellitus (113.5–116.8 per 100,000 population) was up to 6.3, 5.0 and 3.4 times higher, respectively, than the RSV incidence rate among all hospitalised adults aged 50–64 years (Site 1: 40.91–63.0 and Site 2: 33.46–57.1, per 100,000 population).[4]
- In the same study, the incidence of RSV associated hospitalisation among adults aged 40–59 years with congestive heart failure (231.6–485.8 per 100,000 population), was 4.1–11.9 times higher than the RSV incidence rate among all hospitalised adults aged 50–64 years.[4]

Desirable effects

How substantial are the desirable anticipated effects?

Don't know	Varies	Large	Moderate	Small	Trivial

- Arexvy RSV vaccine results in a large increase in RSV-A and RSV-B neutralising antibodies at 30 days post vaccination in adults aged 50-59 years with medical risk factors for severe RSV disease. Arexvy was found to have non-inferior immunogenicity in adults aged 50–59 years compared with adults ≥60 years. The RSV-A and RSV-B mean geometric increase in neutralising antibodies 30 days after RSV vaccination in adults aged 50–59 years with increased risk for severe disease was 11.63 and 9.05, respectively. In adults aged ≥60 years, the RSV-A and RSV-B mean geometric increase in neutralising antibodies 30 days after RSV vaccination was 9.58 and 7.22, respectively. The adjusted geometric mean ratio of RSV vaccine recipients ≥60 years versus 50–59 years for RSV-A and RSV-B neutralisation titres was 0.83 (95% CI: 0.72, 0.95) and 0.80 (95% CI: 0.71, 0.91), respectively. This met the non-inferiority criterion as the upper limits of the confidence intervals were below 1.5.
- There are no efficacy outcomes for the Arexvy RSV vaccine in adults 50-59 years with medical risk factors. However, Arexvy has been found to be efficacious at preventing RSV disease in adults aged ≥60 years, with high levels of efficacy for more serious outcomes (severe lower respiratory tract disease), and moderate levels of efficacy against milder disease (acute respiratory infection).[8] Similar or higher neutralising antibody levels in those aged 50-59 years are expected to confer similar protection.
- Additionally, there is data on immune response of the Arexvy vaccine in adults aged 18 years and over who received a lung or kidney transplant. The phase 2 randomised controlled trial found that one dose of Arexvy resulted in an increase in RSV-A and RSV-B neutralising antibody at on month post vaccination.[9]
- Overall, there is moderate certainty evidence of increasing neutralising antibodies against RSV-A and RSV-B following vaccination with Arexvy RSV vaccine.

Undesirable effects

How substantial are the undesirable anticipated effects?

Don't know	Varies	Large	Moderate	Small	Trivial

- There is a moderate increase in any systemic adverse events and a large increase in any local adverse events with Arexvy RSV vaccine compared with placebo.
- There is little to no difference in serious adverse events with Arexvy compared with placebo. Serious adverse events were reported in 15 (3.9%) vaccine recipients and 4 (2.1%) placebo recipients. None were considered to be related to vaccine.
- Most solicited adverse events were mild to moderate in severity and resolved within 4 to 8 days. The rates of severe Grade 3 adverse events were similar with Arexvy compared with placebo.
- Overall, any local and systemic adverse events were reported more frequently in adults aged 50–59 years (local: 76%, systemic: 54%) compared to adults aged ≥60 years (local: 63%, systemic 41%). Grade 3 adverse events were similar between adults 50–59 years (local: 5%, systemic: 4%) and adults ≥60 years (local: 3%, systemic: 3%).

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 RSV vaccine.
- The vaccine increases neutralising antibodies and there is a high burden of disease, particularly as age increases and in those with comorbid conditions.
- The undesirable effects from vaccination are typical common post-vaccination local and systemic adverse events and relatively brief in duration. While no rare adverse events of special interest were detected in this study, it was not powered to detect rare events. Post-marketing surveillance is being conducted to monitor for AESI in adults receiving Arexvy.

Certainty of evidence
What is the overall certainty of the evidence of effects?

No included studies	Very low	Low	Moderate	High

- Overall, the certainty of evidence is moderate.
- Inconsistency was not assessed as only one study in the population of interest was identified
- Imprecision was downgraded to serious for serious adverse events due to small sample size with low event numbers. It is noted that the study was not powered to detect a difference between treatment arms for safety outcomes.
- Indirectness assessed as serious due to no efficacy outcomes available in this population. Immunogenicity outcomes are available however, there is not a defined correlate of protection for neutralising antibodies and RSV disease.

Values
I*s 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.
- 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 in those aged 50-59 years with increased risk of RSV disease is likely to be acceptable to key stakeholders based on good uptake of influenza vaccination, a vaccine against a similar respiratory viral illness, which is estimated in 2021 at 38.2% in all adults aged 59–<65 years.[10] Vaccine uptake in individuals with increased risk of severe disease is likely to be higher than the general population within the same age group.

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 will vary dependent on program design, funding and vaccine uptake but will probably be reduced
- RSV vaccination could address the increased burden of disease in those with medical comorbidities who have increased risk of RSV hospitalisation.

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.

ATAGI recommendation
• A single dose Arexvy RSV vaccine can be considered in adults aged 50-59 years old with medical risk factors for severe disease.
Justification and considerations
• Arexvy RSV vaccine increases RSV-A and RSV-B neutralising antibodies in adults aged 50–59 years with medical risk factors for severe disease. Arexvy was found to be non-inferior in terms of immunogenicity in adults aged 50–59 years compared with adults ≥60 years. Arexvy has been found to be efficacious at preventing RSV disease in adults aged ≥60 years, with high levels of efficacy for more serious outcomes (severe lower respiratory tract disease) and moderate levels of efficacy against milder disease (acute respiratory infection).[11] RSV vaccination in individuals 50–59 years induces similar neutralising antibody levels to adults aged ≥60 years and is likely to provide similar levels of protection. • 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.[4-7] Adults aged 50–59 years with comorbid conditions are at increased risk of RSV disease however this risk is unlikely to exceed the risk in older adults aged ≥75 years. • Post-vaccination adverse events are more common in adults aged 50–59 years compared to adults aged ≥60 years but most of these are mild. Severe adverse events in adults aged 50–59 years receiving Arexvy RSV vaccine are rare and occur at similar frequencies to people aged ≥60 years. • The body of evidence suggests that in comparison to no vaccine, the benefits of Arexvy RSV vaccine are likely to outweigh the higher frequency of non-serious adverse events following immunisation in this population.

References

1. 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.
2. Nazareno AL, Muscatello DJ, Turner RM, et al. Modelled estimates of hospitalisations attributable to respiratory syncytial virus and influenza in Australia, 2009-2017. *Influenza and Other Respiratory Viruses* 2022;16(6):1082-90.
3. 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.
4. 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.
5. Prasad N, Walker TA, Waite B, et al. Respiratory syncytial virus-associated hospitalizations among adults with chronic medical conditions. *Clinical and Infectious Diseases* 2021;73(1):e158-e63.
6. 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):253-59.
7. 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. *Advance Therapies* 2020;37(3):1203-17.
8. 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.
9. Gerber S. RSV-OA=ADJ-023: Immune response and safety among adult lung and kidney transplant recipients ≥ 18 years of age, preliminary results. *Meeting of the Advisory Committee on Immunization Practices (ACIP)*. October 24, 2024. Available from: https://www.cdc.gov/acip/downloads/slides-2024-10-23-24/04-RSV-Adult-Gerber-508.pdf
10. Hull B, Hendry A, Dey A, et al. Annual Immunisation Coverage Report [Internet]. National Centre for Immunisation Research and Surveillance; 2022. Available from: https://ncirs.org.au/sites/default/files/2022-12/NCIRS%20Annual%20Immunisation%20Coverage%20Report%202021_FINAL.pdf (accessed September 2023).