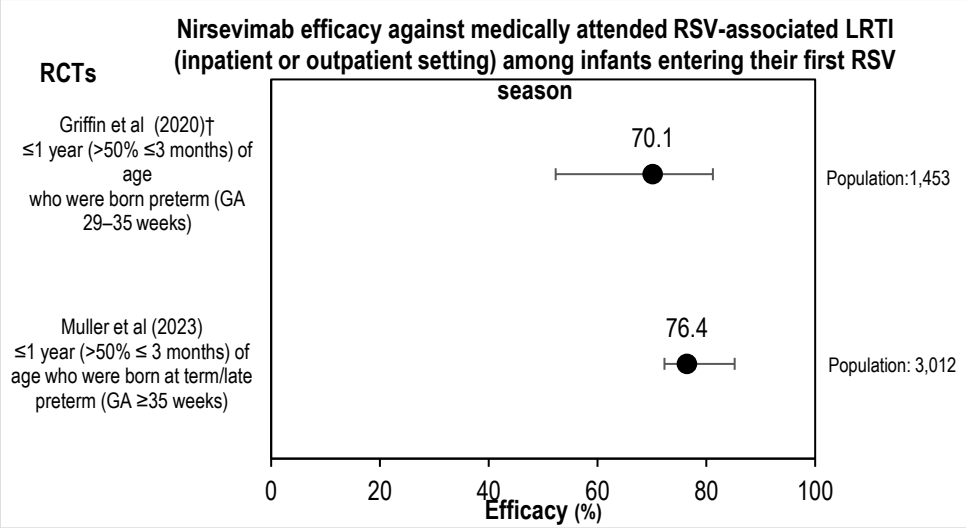
GRADE tables: Comparison of Sanofi nirsevimab (Beyfortus) with placebo or no nirsevimab in infants <8 months of age born during or entering their first RSV season

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

Sanofi nirsevimab (Beyfortus) compared with placebo/no nirsevimab for all infants <8 months of age born during or entering their first respiratory syncytial virus (RSV) season to prevent RSV disease

Patient or population: All infants <8 months of age born during or entering their first respiratory syncytial virus (RSV) season
Intervention: Nirsevimab (Beyfortus)
Comparison: Placebo or no nirsevimab

Outcomes (studies)	Impact	№ of participants	Certainty of the evidence (GRADE)	Interpretation statement
CRITICAL OUTCOMES				
Vaccine efficacy against RSV (laboratory confirmed) medically-attended lower respiratory tract infection [LRTI]/lower respiratory tract disease [LRTD]) Assessed with: Detection of RSV on a central test (PCR assay), the presence of signs of lower respiratory tract involvement on chest auscultation, and the presence of ≥1 clinical signs indicating severe respiratory disease. Follow-up: 150 days (2 RCTs)	 † Nirsevimab dosing was not adjusted by weight. All participants received one 50 mg dose (not final product dosing).		⊕⊕⊕⊕ High	Sanofi nirsevimab results in a **large reduction** in medically attended RSV-associated LRTI among infants entering their first RSV season when compared with placebo.

Sanofi nirsevimab (Beyfortus) compared with placebo/no nirsevimab for all infants <8 months of age born during or entering their first respiratory syncytial virus (RSV) season to prevent RSV disease

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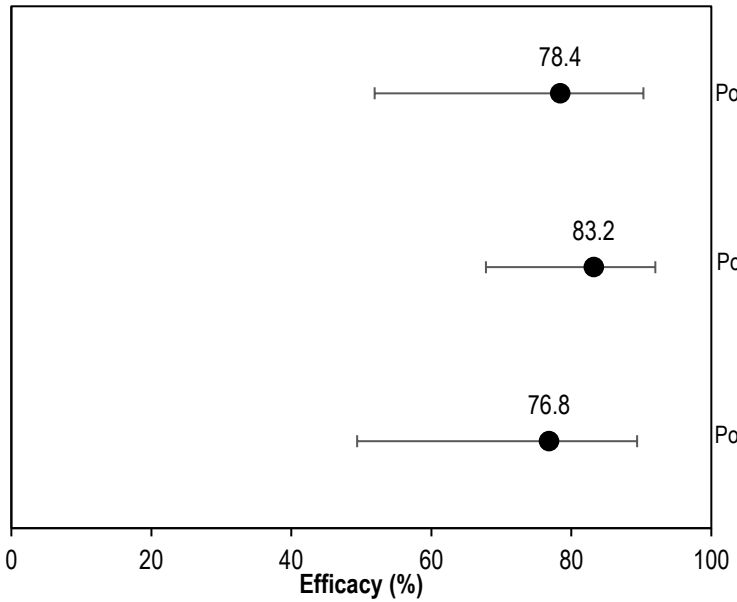
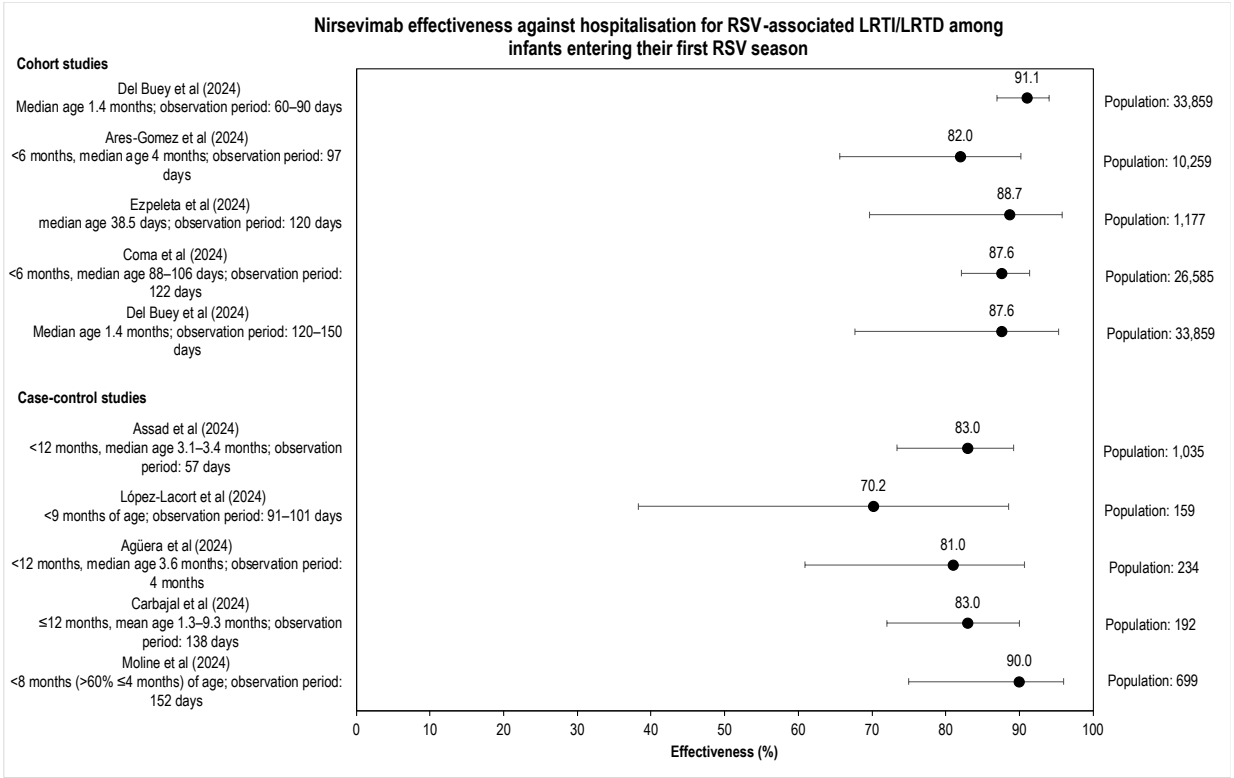
Outcomes (studies)	Impact	№ of participants	Certainty of the evidence (GRADE)	Interpretation statement
Vaccine efficacy against hospitalisation for RSV-associated LRTI/LRTD Follow-up: 150 days (3 RCTs)	**Nirsevimab efficacy against hospitalisation for RSV-associated LRTI among infants entering their first RSV season** **RCTs** Griffin et al (2020)† ≤1 year (>50% ≤3 months) of age who were born preterm (GA 29–35 weeks) Drysdale (2023)* ≤1 year of age (median age 4.5 months) who were born at term/preterm (GA ≥29 weeks) Muller et al (2023) ≤1 year (>50% ≤ 3 months) of age who were born at term/late preterm (GA ≥35 weeks)  † Nirsevimab dosing was not weight banded. All participants received one 50mg dose (not finalised product dosing). * The comparator group received standard care.		⊕⊕⊕◯ Moderate[a]	Sanofi nirsevimab likely results in a **large reduction** in hospitalisation for RSV-associated LRTI among infants entering their first RSV season when compared with placebo or standard care.

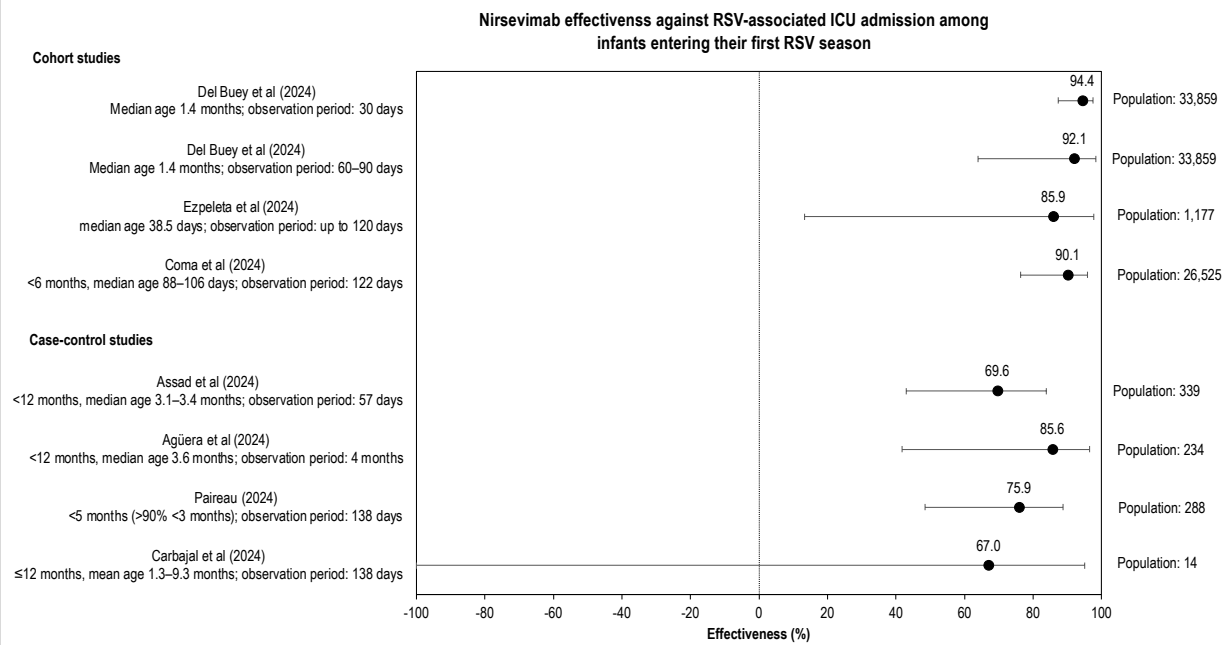
Sanofi nirsevimab (Beyfortus) compared with placebo/no nirsevimab for all infants <8 months of age born during or entering their first respiratory syncytial virus (RSV) season to prevent RSV disease

Patient or population: All infants <8 months of age born during or entering their first respiratory syncytial virus (RSV) season
Intervention: Nirsevimab (Beyfortus)
Comparison: Placebo or no nirsevimab

Outcomes (studies)	Impact	№ of participants	Certainty of the evidence (GRADE)	Interpretation statement
Vaccine effectiveness: Hospitalisation for RSV-associated LRTI/LRTD Follow-up: range 57–152 days (9 non-randomised studies)			⊕⊕⊕◯ Moderate[b]	Sanofi nirsevimab likely results in a **large reduction** in hospitalisation for RSV-associated LRTI among infants entering their first RSV season when compared with no nirsevimab.

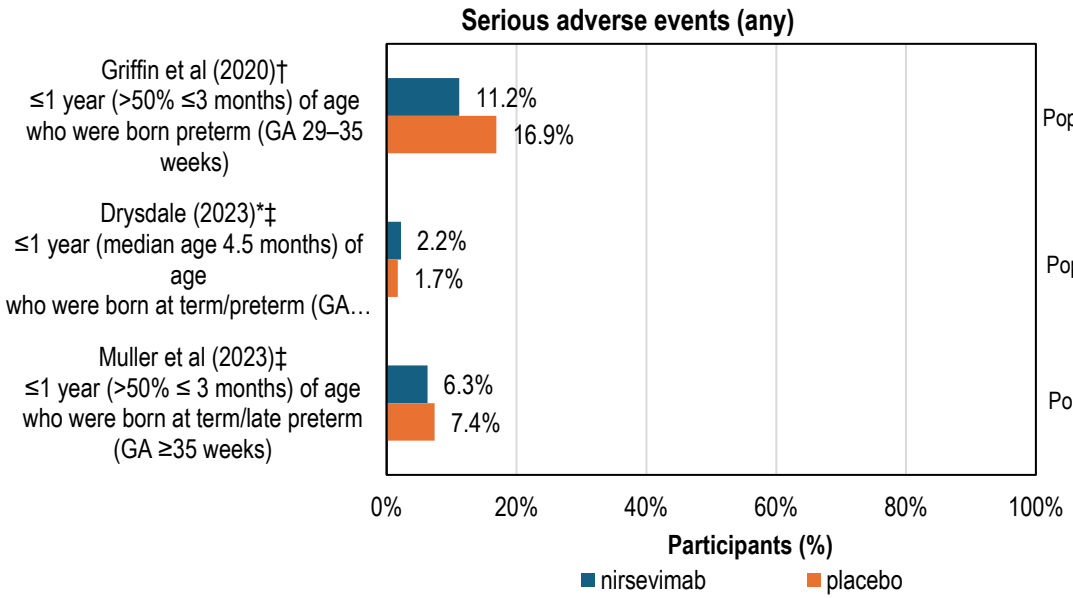
Sanofi nirsevimab (Beyfortus) compared with placebo/no nirsevimab for all infants <8 months of age born during or entering their first respiratory syncytial virus (RSV) season to prevent RSV disease

Patient or population: All infants <8 months of age born during or entering their first respiratory syncytial virus (RSV) season
Intervention: Nirsevimab (Beyfortus)
Comparison: Placebo or no nirsevimab

Outcomes (studies)	Impact	№ of participants	Certainty of the evidence (GRADE)	Interpretation statement
Vaccine effectiveness: intensive care unit (ICU) admissions for RSV-associated LRTI/LRTD Follow-up: range 57–138 days (7 non-randomised studies)			⊕⊕⊕◯ Moderate[b]	Sanofi nirsevimab likely results in a **large reduction** in RSV-associated ICU admission among infants entering their first RSV season when compared with no nirsevimab.

Sanofi nirsevimab (Beyfortus) compared with placebo/no nirsevimab for all infants <8 months of age born during or entering their first respiratory syncytial virus (RSV) season to prevent RSV disease

Patient or population: All infants <8 months of age born during or entering their first respiratory syncytial virus (RSV) season
Intervention: Nirsevimab (Beyfortus)
Comparison: Placebo or no nirsevimab

Outcomes (studies)	Impact	№ of participants	Certainty of the evidence (GRADE)	Interpretation statement
Serious adverse events (SAE)^ Follow-up: 360 days (3 RCTs)		Population: 1,447 Population: 8,035 Population: 2,994	⨁⨁⨁◯[c] Moderate	Sanofi nirsevimab likely results in **little to no difference** in any SAE when compared with placebo or standard care. Note, however, clinical trials are not powered to detect rare SAE.

Sanofi nirsevimab (Beyfortus) compared with placebo/no nirsevimab for all infants <8 months of age born during or entering their first respiratory syncytial virus (RSV) season to prevent RSV disease

Patient or population: All infants <8 months of age born during or entering their first respiratory syncytial virus (RSV) season
Intervention: Nirsevimab (Beyfortus)
Comparison: Placebo or no nirsevimab

Outcomes (studies)	Impact	№ of participants	Certainty of the evidence (GRADE)	Interpretation statement
Serious adverse events (SAE)^ Follow-up: 360 days (3 RCTs)	*continued* † Nirsevimab dosing was not adjusted by weight. All participants received one 50mg dose (not finalised product dosing). * The comparator group received standard care. ‡ Nirsevimab was given as a single 50mg dose if weighing <5kg or a single 100mg dose if weighing ≥5kg (finalised product dosing). **Serious adverse events (SAE): related** In one phase 3 RCT (Drysdale et al), there was one serious adverse event (<0.1%; n=1/4015) (infantile spasms [West syndrome]) 23 days after receipt of nirsevimab that was considered related to the intervention because the relationship to nirsevimab could not be ruled out. The occurrence of this event was within expected background rates for the trial size. There were no related SAEs reported in the standard care group (n=0/4020).[1] ^ SAE were defined as any AE that results in death; is immediately life-threatening; requires inpatient hospitalisation or prolongation of existing hospitalisation; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect in offspring of the subject; is an important medical event that may jeopardise the subject; or may require medical intervention to prevent one of the outcomes listed above		⨁⨁⨁◯[c] Moderate	Sanofi nirsevimab likely results in **little to no difference** in any SAE when compared with placebo or standard care. Note, however, clinical trials are not powered to detect rare SAE

Sanofi nirsevimab (Beyfortus) compared with placebo/no nirsevimab for all infants <8 months of age born during or entering their first respiratory syncytial virus (RSV) season to prevent RSV disease

Patient or population: All infants <8 months of age born during or entering their first respiratory syncytial virus (RSV) season
Intervention: Nirsevimab (Beyfortus)
Comparison: Placebo or no nirsevimab

Outcomes (studies)	Impact	№ of participants	Certainty of the evidence (GRADE)	Interpretation statement
Adverse events of special interest (AESI) – hypersensitivity, immune complex disease, and thrombo-cytopenia Follow-up: range 204 days to 360 days (3 RCTs)	Griffin et al (2020) n=1447 † • 0.5% (no CIs provided) (n=5/968) of participants in the intervention group and • 0.6% (no CIs provided) (n=3/479) of participants in the placebo group reported AESI. Drysdale et al (2023) n=8035‡ • 0.1% (no CIs provided) (n=3/4015) of participants in the intervention group and • <0.1% (no CIs provided) (n=1/4020) of participants who received standard care reported AESI. Muller et al (2023) n=2984^ • 0.2% (no CIs provided) (n=4/1988) of participants in the intervention group and • 0% (no CIs provided) (n=0/996) of participants in the placebo group reported AESI. † All AESI were grade 1 in severity and considered by the investigator to be related to nirsevimab or placebo; these events were rash (4 participants) and petechiae (1 participant) in the nirsevimab group; and rash (3 participants) in the placebo group. The case of petechiae was of 1 day in duration, occurred approximately 4 months after receipt of nirsevimab, and was considered related to the trial drug by the investigator. However, this participant was not seen by a health care provider for the petechiae, no laboratory assessments for petechiae were performed, and the adverse event was reported based on parental description. ‡ All AESI were assessed to be grade 1 or grade 2 in severity. These events were drug reaction (reported as fever and rash) (1 participant), maculopapular rash (1 participant), allergic dermatitis (1 participant) in the nirsevimab group; and food allergy (1 participant) in the standard care group. ^ All four AESI were assessed by the study investigator as related hypersensitivity events and were limited to cutaneous findings. No other anaphylaxis or other serious hypersensitivity was reported.		⊕⊕⊕⊕ High	Sanofi nirsevimab results in l**ittle to no difference** in AESI when compared with placebo or standard care Note however, clinical trials are not powered to detect rare adverse events

Sanofi nirsevimab (Beyfortus) compared with placebo/no nirsevimab for all infants <8 months of age born during or entering their first respiratory syncytial virus (RSV) season to prevent RSV disease

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

Explanations

a. Downgraded for imprecision due to wide confidence intervals (≥20 percentage points)
b. Downgraded for risk of bias. The observation period of some vaccine effectiveness studies did not span a full RSV season, did not account for seasonality (i.e. time of receiving nirsevimab within the RSV season, or local RSV activity and intensity), and had immortal time bias (i.e. did not account for time since immunisation).
c. Downgraded for inconsistency across studies. NCIRS calculated chi squared test for Griffin et al (2020) shows a significant difference in SAE (any) between nirsevimab (16.9%) vs placebo (11.2%) p=0.002.

Abbreviations: AE=adverse event; AESI=adverse events of special interest; CI=confidence interval; ICU=intensive care unit; LRTD=lower respiratory tract disease; LRTI=lower respiratory tract infection; SAE=serious adverse events

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: Sanofi nirsevimab (Beyfortus) compared to placebo/no nirsevimab for all infants aged <8 months born during or entering their first respiratory syncytial virus (RSV) season to prevent RSV disease

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Vaccine efficacy against RSV (laboratory confirmed) medically attended lower respiratory tract infection (LRTI)/lower respiratory tract disease (LRTD) (follow-up: 150 days; assessed with: Detection of RSV on a central test [PCR assay], the presence of signs of lower respiratory tract involvement on chest auscultation, and the presence of ≥1 clinical sign indicating severe respiratory disease)									
2	Randomised trials	Not serious	Not serious	Not serious	Not serious	None	In the phase 2 RCT among infants ≤1 year (50% ≤3 months) of age who were born preterm (GA [gestational age] 29–35 weeks),[2] the efficacy against medically attended RSV-associated lower respiratory tract infection through 150 days after injection was **70.1% (95% CI: 52.3–81.2%).**	⨁⨁⨁⨁ High	CRITICAL

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
							continued In the phase 3 RCT among infants ≤1 year (>50% ≤3 months) of age who were born at term or late preterm (GA ≥35 weeks),[3] the efficacy against medically attended RSV-associated lower respiratory tract infection through 150 days after injection was **76.4% (95% CI: 62.3–85.2%)**.		

Vaccine efficacy against hospitalisation for RSV-associated LRTI/LRTD (follow-up: 150 days)

3	Randomised trials	Not serious	Not serious	Not serious	Serious[a]	None	In the phase 2 RCT among infants ≤1 year (>50% ≤3 months) of age who were born preterm (GA 29–35 weeks),[2] the efficacy against hospitalisation for RSV-associated LRTI through 150 days after injection was **78.4% (95% CI: 51.9–90.3%).**	⊕⊕⊕◯ Moderate	CRITICAL

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
							continued In the phase 3 RCT among infants ≤1 year of age (median age 4.5 months) who were born at term or preterm (GA ≥29 weeks),[1] the efficacy against hospitalisation for RSV-associated LRTI through 150 days after injection was **83.2% (95% CI: 67.8–92.0%).** In the phase 3 RCT among infants ≤1 year (>50% ≤3 months) of age who were born at term or late preterm (GA ≥35 weeks),[3] the efficacy against hospitalisation for RSV-associated LRTI through 150 days after injection was **76.8% (95% CI: 49.4–89.4%).**		

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Vaccine effectiveness (VE): Hospitalisation for RSV-associated LRTI/LRTD (follow-up: range 57 days to 152 days)									
9	Non-randomised studies	Serious[b]	Not serious	Not serious	Not serious	None	<u>Cohort studies</u> Del Buey et al (2024):[4] VE among infants with a median age of 1.4 months at 60–90 days: **91.1% (95% CI: 86.9–94.0%)**, at 120–150 days: **87.6% (95% CI: 67.7–95.3%)** Ares-Gomez et al (2024):[5] VE among infants <6 months (median age 4 months) at 97 days**: 82.0% (95% CI: 65.6–90.2%)** Ezpeleta et al (2024):[6] VE among infants with a median age of 38.5 days at 120 days: **88.7% (95% CI: 69.6–95.8%)** Coma et al (2024):[7] VE among infants <6 months (median age 88–106 days) at 122 days: **87.6% (95% CI: 82.1–91.4%)**	⨁⨁⨁◯ Moderate	CRITICAL

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
							continued <u>Case-control studies</u> Assad et al (2024):[8] VE among infants (median age 3.1–3.4 months) at 57 days: **83.0% (95% CI: 73.4–89.2%)** Lopez-Lacort et al (2024):[9] VE among infants <9 months at 91–101 days: **70.2% (95% CI: 38.3–88.5%)** Agüera et al (2024):[10] VE among infants <12 months (median age 3.6 months) at 4 months: **81.0% (95% CI: 60.9– 90.7%)** Carbajal et al (2024):[11] VE among infants ≤12 months (mean age 1.3–9.3 months) at 138 days: **83.0% (95% CI: 72.0–90.0%)** Moline et al (2024):[12] VE among infants aged <8 months (>60% ≤4 months) at 152 days: **90.0% (95% CI: 75.0–96.0%)**		

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Vaccine effectiveness: ICU admissions for RSV-associated LRTI/LRTD (follow-up: range 57 days to 138 days)									
7	Non-randomised studies	Serious[b]	Not serious	Not serious	Not serious	None	<u>Cohort studies</u> Del Buey et al (2024):[4] VE among infants with a median age of 1.4 months at 30 days: **94.4% (95% CI: 87.3–97.5%)** and at 60–90 days: **92.1% (95% CI: 64–98.3%)**. Ezpeleta et al (2024):[6] VE among infants with a median age of 38.5 days at 120 days: **85.9% (95% CI: 13.2–97.7%)**. Coma et al (2024):[7] VE among infants <6 months (median age 88–106 days) at 122 days: **90.1% (95% CI: 76.3–95.9%)**. <u>Case-control studies</u> Assad et al (2024):[8] VE among infants (median age 3.1–3.4 months) at 57 days: **69.6% (95% CI: 42.9–83.8%)**	⨁⨁⨁◯ Moderate	CRITICAL

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
							<u>Case-control studies</u> ***(continued)*** Agüera et al (2024):[10] VE among infants <12 months (median age 3.6 months) at 4 months: **85.6% (95% CI: 41.7–96.4%)** Paireau et al (2024):[13] VE among infants <5 months (>90% <3 months) at 138 days: **75.9% (95% CI: 48.5– 88.7%)** Carbajal et al (2024):[11] VE among infants ≤12 months (mean age 1.3–9.3 months) at 138 days: **67.0% (95% CI: -100.0–95.0%)**		

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Serious adverse events (SAE) (follow-up: 360 days; assessed with any AE that: results in death; is immediately life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect in offspring of the subject; is an important medical event that may jeopardize the subject; or may require medical intervention to prevent one of the outcomes listed above)									
3	Randomised trials	Not serious	Not serious	Not serious	Serious[c]	None	Throughout the phase 2 RCT among infants ≤1 year (>50% ≤3 months) of age who were born preterm (GA 29–35 weeks),[2] in the intervention arm there were 108/968 **(11.2%)** SAE compared to 81/479 **(16.9%)** in the placebo arm. No SAE assessed as related to the intervention. Throughout the phase 3 RCT among infants ≤1 year of age (median age 4.5 months) who were born at term or preterm (GA ≥29 weeks),[1] in the intervention arm there were 89/4015 **(2.2%)** SAE compared to 67/4020 **(1.7%)** in the comparator arm, who received standard care.	⨁⨁⨁◯ Moderate	CRITICAL

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
							continued There was one SAE (infantile spasms [West syndrome]) that was considered related to the intervention because the relationship to nirsevimab could not be ruled out. In the phase 3 RCT among infants ≤1 year (>50% ≤3 months) of age who were born at term or late preterm (GA ≥35 weeks),[3] in the intervention arm there were 125/1998 **(6.3%)** SAE compared to 74/996 **(7.4%)** in the placebo arm. No SAE assessed as related to the intervention.		

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Adverse events of special interest (AESI) - hypersensitivity, immune complex disease, and thrombocytopenia (follow-up: range 204 days to 360 days)									
3	Randomised trials	Not serious	Not serious	Not serious	Not serious	None	In the phase 2 RCT among infants ≤1 year (>50% ≤3 months) of age who were born preterm (GA 29–35 weeks),[2] in the intervention group there were 5/968 **(0.5%)** AESI compared to 3/479 **(0.6%)** in the placebo group. In the phase 3 RCT among infants ≤1 year of age (median age 4.5 months) who were born at term or preterm (GA ≥29 weeks),[1] in the intervention group there were 3/4015 **(0.1%)** AESI compared to 1/4020 **(<0.1%)** in the comparator group, who received standard care.	⨁⨁⨁⨁ High	CRITICAL

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
							continued In the phase 3 RCT among infants ≤1 year (>50% ≤3 months) of age who were born at term or late preterm (GA ≥35 weeks),[3] in the intervention group there were 4/1998 **(0.2%)** AESI compared to 0/996 **(0%)** in the placebo group.		

Explanations

a. Downgraded for imprecision due to wide confidence intervals (≥20 percentage points)
b. Downgraded for risk of bias. The observation period of some vaccine effectiveness studies did not span a full RSV season, did not account for seasonality (i.e. time of receiving nirsevimab within the RSV season, or local RSV activity and intensity), and had immortal time bias (i.e. did not account for time since immunisation).
c. Downgraded for inconsistency across studies. NCIRS calculated chi squared test for Griffin et al (2020) shows a significant difference in SAE (any) between nirsevimab (16.9%) vs placebo (11.2%) p=0.002.

Abbreviations: AE=adverse event; AESI=adverse events of special interest; CI=confidence interval; GA=gestational age; ICU=intensive care unit; LRTD=lower respiratory tract disease; LRTI=lower respiratory tract infection; SAE=serious adverse events; VE=vaccine effectiveness

Evidence to Decision Framework: Nirsevimab (Beyfortus) compared with placebo or no nirsevimab in infants aged <8 months born during or entering their first RSV season

Should one dose of nirsevimab (Beyfortus, by Sanofi) be recommended for all infants aged <8 months born during or entering their first RSV season to prevent RSV disease?	
Population	All infants aged <8 months born during or entering their first respiratory syncytial virus (RSV) season
Intervention	Nirsevimab
Comparison	Placebo or no nirsevimab
Main outcomes	*Efficacy* • RSV (laboratory confirmed) medically attended lower respiratory tract illness/disease LRTI/LRTD – Critical • Hospitalisation for RSV-associated LRTI/LRTD – Critical *Effectiveness* • Hospitalisation for RSV-associated LRTI/LRTD – Critical • Intensive care Unit (ICU) admissions for RSV-associated LRTI/LRTD – Critical *Safety* • Serious adverse events (SAEs) – Critical • Adverse events of special interest (AESI) – Critical
Setting	Global middle- to high-income settings (e.g. Europe, North America, South America, Africa, Asia, Australia)

ASSESSMENT

Problem
Is the problem a priority?

Don't know	Varies	No	Probably no	Probably yes	Yes

- RSV disease is a respiratory infection that affects nearly all children in their first few years of life.[14]
- Infants often develop bronchiolitis, a lower respiratory tract infection, which may require hospitalisation and supplementary oxygen and/or respiratory ventilatory support.
- RSV-associated hospitalisation rates are highest among infants aged <6 months , preterm infants (<37 weeks gestational age), and infants with comorbidities.[14,15]
- Between 2016–2019, data on hospitalisations among infants aged <6 months from the Australian Institute of Health and Welfare (AIHW) National Hospitalisation and Morbidity database showed a hospitalisation rate of 3,100 per 100,000 (RSV-specific coded principal and additional diagnoses; AIHW, unpublished NCIRS analysis). As this is a conservative estimate based only on RSV-specific coded hospitalisation, it is likely to underestimate the true disease burden due to not accounting for some diagnoses with unspecified causes where a substantial proportion are likely to be RSV-attributable, such as acute unspecified bronchiolitis. Nonetheless, the relative disease burden remains particularly significant in this age group.

Desirable effects

How substantial are the desirable anticipated effects?

Don't know	Varies	Large	Moderate	Small	Trivial

- Across three clinical trials among preterm or preterm and term infants entering their first RSV season, nirsevimab resulted in a large reduction in RSV medically-attended lower respiratory tract infection (LRTI) and hospitalisation for RSV-associated LRTI (through 150 days following immunisation).
- Consistent efficacy has been demonstrated across infant subgroups, including gestational age (≥37 weeks: 84.4% [95% CI, 64.9–94.1]; <37 weeks: 78.3% [95% CI, 33.5–94.7]) and infant weight at randomisation (<5kg: 82.1% [95% CI, 59.1–93.3] or ≥5kg: 85.2 [95% CI, 57.0–96.2]).[1]
- Across non-randomised studies, nirsevimab demonstrated consistently high effectiveness with a large reduction in hospitalisation for RSV-associated LRTI and RSV-associated ICU admission (observation period up to 152 days and 138 days, respectively), among infants entering their first RSV season.
- Although nirsevimab efficacy/effectiveness beyond 150 days is uncertain, immunogenicity data from nirsevimab RCT participants, including preterm and term infants, shows persistent neutralising antibodies above baseline up to 1 year post dose, although the level of clinical protection is uncertain.[16,17]

Undesirable effects

How substantial are the undesirable anticipated effects?

Don't know	Varies	Large	Moderate	Small	Trivial

- There was little to no difference in total SAEs when nirsevimab was compared to placebo or standard care. Two clinical trials reported any SAEs that were comparable between nirsevimab and placebo arms.[1,3] One clinical trial reported a significantly higher incidence of any SAE among placebo recipients (16.9%) compared to nirsevimab recipients (11.2%) (NCIRS calculated chi squared test p=0.002).
- Adverse events of special interest (AESI) among participants who received nirsevimab were rare and comparable to those who received placebo or standard care.
- AESI consisted of mild hypersensitivity events that predominantly involved cutaneous reactions.
- Post marketing safety surveillance conducted in Western Australia reported one or more adverse events within 3 days after nirsevimab administration occurred in 11.4% (47/410) of infants. The frequency of a local reaction (2.3%; 9/410), fatigue (7.1%; 29/410), fever (1.7%; 14/410) and rash (1.7%; 7/410) were low.[18]

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 favours infant immunisation with nirsevimab compared to placebo/no nirsevimab.
- Among infants entering their first RSV season, Phase 2 and 3 clinical trials demonstrated a large reduction in RSV medically-attended LRTI and hospitalisation for RSV-associated LRTI, and non-randomised studies demonstrated a large reduction in hospitalisation for RSV-associated LRTI and RSV-associated ICU admission.
- SAEs were comparable, or occurred less frequently, with nirsevimab than placebo/standard care.
- AESI were rare and comparable between nirsevimab and placebo/standard care arms.

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 was moderate.
- 2 outcomes were assessed as a high certainty of evidence.
- 4 outcomes were assessed as a moderate certainty of evidence.
- Evidence was downgraded due to imprecision around estimates, inconsistency, and risk of bias.
- Across clinical trials, there was inconsistency in the proportion of participants reporting any SAE with one trial reporting a significantly higher incidence among placebo recipients (16.9%) compared to nirsevimab recipients (11.2%) (NCIRS calculated chi squared test p=0.002).
- Many observational studies had a relatively short observation period, falling within the first half of the RSV season and did not account for time from immunisation to outcome (immortal time bias), timing of nirsevimab administration within the RSV season, or local RSV activity and intensity, potentially over- or underestimating vaccine effectiveness.

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 unlikely to be important uncertainty in how people value protection against RSV disease in infants.
- 80%–90% of current and future parents are aware of RSV and around 50–60% are aware that it causes pneumonia and bronchiolitis.[19]

Acceptability

Is the intervention acceptable to key stakeholders?

Don't know	Varies	No	Probably no	Probably yes	Yes

- Infant immunisation with nirsevimab will probably be acceptable to key stakeholders (parents/guardians and immunisation providers). Countries offering a universal nirsevimab immunisation program, such as Spain, have had high uptake with coverage ranging between 79%–99%.[5,9]
- Stakeholder acceptance will likely depend on factors such as perceived benefits, safety profile, national or jurisdictional funding, and integration into existing infant immunisation and injection schedules.
- Although nirsevimab is administered as a single intramuscular dose (50 mg in 0.5 mL if weight is <5 kg; 100mg in 1 mL if weight is ≥5kg), and studies show a favourable safety profile, the addition of a needle-based intervention to the existing infant schedule may affect acceptability among some parents/guardians.

Equity

What would be the impact on health inequities?

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

- Aboriginal and Torres Strait Islander infants have increased burden of RSV hospitalisation with an incidence rate ratio of 2.0 from 0 to <12 months and 1.5 from 12 months to <5 years of age compared to non-indigenous children (2016–2019 AIHW, unpublished NCIRS analysis).
- Health inequity could be decreased if high immunisation uptake is achieved through a universal program. Conversely, a universal program with lower immunisation uptake, particularly among high-risk populations, such as Aboriginal and Torres Strait Islander infants or those with risk conditions, could increase health inequities.
- It should be noted that at the time of writing, nirsevimab was being used alongside maternal RSV vaccination aiming to ensure comprehensive coverage and reduce health inequity. This multi-product program is likely to have the greatest impact on reducing health inequity compared to either a nirsevimab-only or maternal vaccination only program.
- Strategies to achieve high uptake, regardless of program design, may include communications, resources and initiatives targeted to and co-designed with high-risk populations such as Aboriginal and Torres Strait Islander parents and communities, as well as ensuring ease of access and availability to free immunisation.

Feasibility

Is the intervention feasible to implement?

Don't know	Varies	No	Probably no	Probably yes	Yes

- Nirsevimab should be feasible to implement as there is already a delivery system for infant immunisation in Australia through hospital, General Practice, Community Health Services, and Aboriginal Health Services.
- Suitability for nirsevimab to be co-administered with other childhood immunisations is likely to aid feasibility.[20]
- Potential challenges include assessing eligibility i.e. for infants born to mothers who received maternal RSV vaccine; the need to administer nirsevimab in post-natal settings by midwives including training requirements for administering a new immunisation product; administrative demands on clinical staff including accurate recording of immunisation on the Australian Immunisation Register; and the need for legislative reform for funding under the National Immunisation Program.

ATAGI recommendation

Nirsevimab is recommended in all infants aged <8 months born during or entering their first respiratory syncytial virus (RSV) season, to prevent severe RSV disease.

Justification and considerations

- A national infant RSV immunisation program is likely to have substantial clinical benefit due to infants aged 0 to <6 months having the highest burden of RSV disease.
- Nirsevimab given to infants aged <8 months born during or entering their first RSV season had high levels of efficacy and effectiveness against severe RSV disease.
- Serious adverse events were comparable, or occurred less frequently, with nirsevimab than placebo/standard care.
- AESI were rare and comparable between nirsevimab and placebo/standard care arms.
- Coordination of a comprehensive maternal RSV vaccination program during pregnancy with a complementary program for nirsevimab administered to infants who remain at risk of RSV after birth prior to their first RSV season, is likely to further increase the proportion of children with protection against RSV during their first 6 months of life.
- The body of evidence suggests that in comparison to no nirsevimab, the benefits of nirsevimab outweigh the potential undesirable effects following immunisation.

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