Coversheet on evidence assessment by ATAGI using the GRADE framework for a further dose of COVID-19 vaccine during pregnancy in previously vaccinated pregnant women

A summary of the use of the GRADE approach in the development of ATAGI and Australian Immunisation Handbook recommendations comparing the use of a further dose of the COVID-19 vaccine during pregnancy in previously vaccinated pregnant women with no further dose of the COVID-19 vaccine during pregnancy in previously vaccinated pregnant women

Background

- In early 2021, the Australian Technical Advisory Group on Immunisation (ATAGI) approved the COVID-19 vaccine for pregnant women at any stage of pregnancy and since then, vaccine recommendations for pregnant women are the same as those for the general population.
- Global surveillance data from large numbers of pregnant women have not identified any significant safety concerns with mRNA COVID-19 vaccines given at any stage of pregnancy. Furthermore, there is evidence of antibody transfer in cord blood and breastmilk, which may offer protection to infants through passive immunity.
- Unlike ATAGI, other National Immunisation Technical Advisory Groups (NITAGs) such as the Advisory Committee on Immunization Practices (ACIP) and the National Advisory Committee on Immunization (NACI) are recommending a further dose in each pregnancy to prevent severe disease due to COVID-19 in both pregnant women and infants.
- The National Centre for Immunisation Research and Surveillance (NCIRS) is conducting this GRADE to evaluate the benefit of a further dose of COVID-19 vaccine during pregnancy against severe outcomes, such as COVID-19-related hospitalisation, in both pregnant women and their infants.

Research questions

1. Should previously vaccinated pregnant women receive a further dose of COVID-19 vaccine during pregnancy to prevent severe outcomes of in themselves (the pregnant women) and in infants aged ≤6 months?

Table 1: Population, Intervention, Comparator, Outcomes (PICO) – A further dose of the COVID-19 vaccine during pregnancy vs no further dose of the COVID-19 vaccine during pregnancy, previously vaccinated pregnant women and infants aged ≤6 months

Population	• Previously vaccinated pregnant women • Infants aged ≤6 months
Intervention	A further dose of the COVID-19 vaccine in previously vaccinated pregnant women
Comparator	No further dose of the COVID-19 vaccine in previously vaccinated pregnant women
Outcomes	*Critical* • Vaccine effectiveness (VE) against COVID-19-related hospitalisation in infants aged ≤6 months • VE against COVID-19 related hospitalisation in previously vaccinated pregnant women • VE against COVID-19-related death in infants aged ≤6 months • VE against COVID-19-related death in previously vaccinated pregnant women

Literature search

The literature search was undertaken between 27–28 August 2024 to identify publications assessing the use of a further dose of the COVID-19 vaccine during pregnancy in previously vaccinated pregnant women. The citations were included for review if they met the following criteria:

- *Study design:* Observational study
- *Publication date:* 1 January 2022–16 August 2024 (Omicron period)
- *Population:* Infants aged ≤6 months and previously vaccinated pregnant women
- *Intervention:* A further dose of COVID-19 vaccine in previously vaccinated pregnant women
- *Comparator:* No further dose of COVID-19 vaccine in previously vaccinated pregnant women
- *Outcomes:* Vaccine effectiveness (VE)

The published literature search retrieved a total of 5,711 unique citations, of which seven met the pre-defined inclusion criteria for the comparison of a further dose of the COVID-19 vaccine formulation to no dose of the COVID-19 vaccine formulation during pregnancy in previously vaccinated pregnant women. Seven observational studies reporting VE against COVID-19-related hospitalisation were identified.

Two studies reported VE against COVID-19-related hospitalisation in infants,[1,2] four studies reported VE against COVID-19-related hospitalisation in pregnant women[3-6] and one study reported this outcome in both infants and pregnant women.[7] These studies were from Canada, England, Israel and the United States of America (USA). One multi-country study included data from 18 countries including Argentina, Brazil, Egypt, France, Indonesia, Israel, Italy, Japan, Mexico, Nigeria, North Macedonia, Pakistan, Spain, Switzerland, Türkiye (Turkey), the UK, Uruguay and the USA.[5]

Two studies were test-negative case-control studies, five studies were cohort studies. The study characteristics and risk of bias (RoB) assessment for each individual study are presented in Appendix A. For detailed search strategy refer to Appendix B.

Inclusion criteria and rationale

Table 2: Rationale for PICO and inclusion criteria

PICO	Rationale
Study type Observational study, meta-analysis	Vaccine effectiveness (VE) studies were preferred, particularly nationwide studies with a large and diverse population included.
Population Infants aged ≤6 months Previously vaccinated pregnant women	There is no COVID-19 vaccine registered for use in infants aged ≤6 months, therefore, it is important to evaluate if a further dose during pregnancy can **prevent severe outcomes of COVID-19 in infants.** Early in the COVID-19 pandemic, pregnancy was considered a risk factor for severe disease. Since the Omicron period, this risk has decreased; however, maternal complications of severe COVID-19 may still be an issue. Therefore, it is important to evaluate if a further vaccine dose during pregnancy can **prevent severe outcomes of COVID-19 during pregnancy.**
Intervention A further dose of the COVID-19 vaccine in previously vaccinated pregnant women	Previously vaccinated pregnant women are not routinely recommended to receive a further COVID-19 vaccine. Therefore, the aim was to evaluate if the intervention of a further dose during pregnancy can **prevent severe outcomes of COVID-19 during pregnancy** to inform future recommendations.
Comparator No further dose of the COVID-19 vaccine in previously vaccinated pregnant women	This comparator was used as it was most relevant to the most recent ATAGI recommendations regarding vaccinated pregnant women who are not routinely recommended further dose during pregnancy.

Outcomes	The outcomes stated in Table 1 (above) represent the severe COVID-19 disease outcomes which COVID-19 vaccination should protect at-risk individuals from. Less severe outcomes, such as VE against COVID-19 infection, were excluded, as the recommendations prioritise protecting people from severe outcomes of COVID-19 and because most of the population has had exposure to COVID-19 through previous vaccination, natural infection or hybrid immunity.
	Ranking of importance discussed in many iterations with portfolio leads and the full ATAGI panel.
	General framework (depending on outcomes measured in studies available): *Critical* • VE against COVID-19-related hospitalisation in infants aged ≤6 months • VE against COVID-19 related hospitalisation in previously vaccinated pregnant women • VE against COVID-19-related death in infants aged ≤6 months • VE against COVID-19-related death in previously vaccinated pregnant women

Abbreviations: ATAGI=Australian Technical Advisory Group on Immunisation; VE=vaccine effectiveness

Risk of bias assessment

Risk of bias (RoB) assessment was carried out on all included studies by two assessors using Risk of Bias In Non-randomised Studies - of Interventions (ROBINS-I) for comparative observational studies. Refer to Appendix A for ROBINS-I rating of included studies.

Appendix A

Table A1: Risk of Bias assessment for comparative, observational studies using ROBINS-I

Study	Outcome	Confounding	Selection	Intervention classification	Deviations from intervention	Missing data	Measurement of outcomes	Selection of the reported results	Overall bias
Kirsebom et al, 2023[7]	VE against COVID-19-related hospitalisation (pregnant women)	Moderate	Low	Low	Low	Low	Low	Moderate	Moderate
	VE against COVID-19-related hospitalisation (infants)	Moderate	Low	Low	Low	Low	Low	Moderate	Moderate
Lipschuetz et al, 2023[2]	VE against COVID-19-related hospitalisation (infants)	Moderate	Low	Low	Low	Low	Low	Moderate	Moderate
Jorgensen et al, 2022[1]	VE against COVID-19-related hospitalisation (infants)	Moderate	Low	Low	Low	Low	Low	Moderate	Moderate
Zerbo et al, 2023[6]	VE against COVID-19-related hospitalisation (pregnant women)	Moderate	Low	Low	Low	Low	Low	Moderate	Moderate
Villar et al, 2023[5]	VE against COVID-19-related hospitalisation (pregnant women)	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Guedalia et al, 2022[3]	VE against COVID-19-related hospitalisation (pregnant women)	Moderate	Low	Low	Low	Low	Low	Moderate	Moderate
Schrage et al, 2022[4]	VE against COVID-19-related hospitalisation (pregnant women)	Moderate	Low	Low	Low	Low	Low	Moderate	Moderate

Abbreviations: ROBINS-I=Risk of Bias In Non-randomised Studies - of Interventions; VE=vaccine effectiveness

Appendix B: Search strategy

MEDLINE: COVID-19 vaccines – VE and safety in pregnancy and infants (as at 27.08.24)

Notes: Date limited from 2022–2024

Database: Ovid MEDLINE® All including Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946-current>

Search strategy:

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1 exp COVID-19/ (273019)

2 ('2019 nCoV$' or 2019-nCoV$ or 2019nCoV$ or 'n CoV$' or n-CoV$ or nCoV$).tw. (3424)

3 ('covid 19' or covid-19 or covid19).tw. (369643)

4 exp SARS-CoV-2/ (177240)

5 ("Severe Acute Respiratory Syndrome Coronavirus 2" or "Severe Acute Respiratory Syndrome Coronavirus-2" or "SARS coronavirus 2" or "SARS coronavirus-2").tw. (37157)

6 ('SARS CoV2' or SARS-CoV2 or SARSCoV2 or SARS-CoV-2).tw. (127322)

7 1 or 2 or 3 or 4 or 5 or 6 (427440)

8 exp Immunization/ (218206)

9 exp Immunization Programs/ (16542)

10 exp Vaccines/ (290562)

11 (vaccin$ or immunis$ or immuniz$).tw. (525207)

12 8 or 9 or 10 or 11 (635056)

13 7 and 12 (71633)

14 exp COVID-19 Vaccines/ (27691)

15 13 or 14 (71940)

EMBASE: COVID-19 vaccines – VE and safety in pregnancy and infants (as at 28.08.24)

Notes: Date limited from 2022–2024

Database: Embase <1974 to 2024 August 26>

Search strategy:

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1 exp coronavirus disease 2019/ (420868)

2 ('2019 nCoV$' or 2019-nCoV$ or 2019nCoV$ or 'n CoV$' or n-CoV$ or nCoV$).tw. (4470)

3 ('covid 19' or covid-19 or covid19).tw. (427754)

4 exp Severe acute respiratory syndrome coronavirus 2/ (120841)

5 ("Severe Acute Respiratory Syndrome Coronavirus 2" or "Severe Acute Respiratory Syndrome Coronavirus-2" or "SARS coronavirus 2" or "SARS coronavirus-2").tw. (38948)

6 ('SARS CoV2' or SARS-CoV2 or SARSCoV2 or SARS-CoV-2).tw. (152318)

7 1 or 2 or 3 or 4 or 5 or 6 (530772)

8 exp immunization/ (402406)

9 exp vaccine/ (441353)

10 (immuni$ or vaccin$).tw. (851969)

11 8 or 9 or 10 (1011474)

12 7 and 11 (104876)

13 exp SARS-CoV-2 vaccine/ (50178)

14 12 or 13 (106064)

15 exp RNA vaccine/ (21096)

16 ((rna or mrna or (messenger adj1 rna)) adj3 vaccin$).tw. (14324)

16 exp RNA, Messenger/ (453691)	17 (protein adj4 subunit).tw. (23591)
17 (rna or mrna or (messenger adj1 rna)).tw. (1130663)	18 (Pfizer$ or BioNTech$ or Moderna$ or Novavax$).tw. (53738)
18 (protein adj4 subunit).tw. (21140)	19 15 or 16 or 17 or 18 (94965)
19 (Pfizer$ or BioNTech$ or Moderna$ or Novavax$).tw. (7978)	20 7 and 19 (25493)
20 16 or 17 or 18 or 19 (1295683)	21 exp bnt 162 vaccine/ (388)
21 7 and 20 (26145)	22 (BNT162b2$ or tozinameran$ or comirnaty$ or "Bivalent Original Omicron BA.1" or "Bivalent Original Omicron BA.4/BA.5" or "WT/OMI BA.4/BA.5").tw. (8724)
22 exp BNT162 Vaccine/ (4016)	23 exp elasomeran/ (7752)
23 (BNT162b2$ or tozinameran$ or comirnaty$ or "Bivalent Original Omicron BA.1" or "Bivalent Original Omicron BA.4/BA.5" or "WT/OMI BA.4/BA.5").tw. (5482)	24 (mRNA-1273$ or elasomeran$ or spikevax$ or "Bivalent Original Omicron BA.1" or "Bivalent Original Omicron BA.4/BA.5").tw. (4944)
24 exp 2019-nCoV Vaccine mRNA-1273/ (962)	25 exp nvx-cov2373 vaccine/ (918)
25 (mRNA-1273$ or elasomeran$ or spikevax$ or "Bivalent Original Omicron BA.1" or "Bivalent Original Omicron BA.4/BA.5").tw. (2103)	26 (NVX-CoV2373$ or TAK-019$ or "SARS-CoV-2 rS with Matrix-M1 adjuvant" or Covovax$ or Nuvaxovid$).tw. (346)
26 (NVX-CoV2373$ or TAK-019$ or "SARS-CoV-2 rS with Matrix-M1 adjuvant" or Covovax$ or Nuvaxovid$).tw. (148)	27 21 or 22 or 23 or 24 or 25 or 26 (14471)
27 22 or 23 or 24 or 25 or 26 (6936)	28 14 or 20 or 27 (106851)
28 15 or 21 or 27 (83902)	29 exp Treatment Outcome/ (2711619)
29 exp Treatment Outcome/ (1299212)	30 exp Vaccine Efficacy/ (441353)
30 exp Vaccine Efficacy/ (1117)	31 efficac$.tw. (1750988)
31 efficac$.tw. (1201177)	32 effective$.tw. (3596631)
32 effective$.tw. (2779935)	33 exp Safety/ (594931)
33 exp Safety/ (90436)	34 exp Safety-Based Drug Withdrawals/ (830)
34 exp Safety-Based Drug Withdrawals/ (420)	35 exp "Drug-Related Side Effects and Adverse Reactions"/ (672327)
35 exp "Drug-Related Side Effects and Adverse Reactions"/ (136915)	36 exp Product Surveillance, Postmarketing/ (40132)
36 exp Product Surveillance, Postmarketing/ (19053)	37 exp Drug Evaluation/ (210104)

37 exp Drug Evaluation/ (42084)	38 exp Adverse Drug Reaction Reporting Systems/ (40939)
38 exp Adverse Drug Reaction Reporting Systems/ (9308)	39 (adverse adj2 (effect$ or event$)).tw. (795787)
39 (adverse adj2 (effect$ or event$)).tw. (504448)	40 (safe or safety or aefi or aesi).tw. (1696889)
40 (safe or safety or aefi or aesi).tw. (1124894)	41 ((post marketing or post-marketing or postmarketing or post licensure or post-licensure or postlicensure) adj2 (surveillance or monitor$)).tw. (5968)
41 ((post marketing or post-marketing or postmarketing or post licensure or post-licensure or postlicensure) adj2 (surveillance or monitor$)).tw. (3858)	42 outcome$.tw. (3791599)
42 outcome$.tw. (2559409)	43 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 (10463932)
43 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 (6929053)	44 28 and 43 (83015)
44 28 and 43 (37021)	45 limit 44 to infant <to one year> (512)
45 limit 44 to "all infant (birth to 23 months)" (732)	46 exp pregnancy/ (810361)
46 exp Pregnancy/ (1038924)	47 (pregnan$ or matern$ or antenatal$).tw. (1061434)
47 (pregnan$ or matern$ or antenatal$).tw. (832304)	48 exp infant/ (1184148)
48 exp Infant/ (1284485)	49 (newborn$ or neonat$ or baby or babies or infant$ or offspring).tw. (1123337)
49 (newborn$ or neonat$ or baby or babies or infant$ or offspring).tw. (921436)	50 46 or 47 or 48 or 49 (2576647)
50 46 or 47 or 48 or 49 (2603330)	51 44 and 50 (4832)
51 44 and 50 (1973)	52 45 or 51 (4832)
52 45 or 51 (1973)	53 animal experiment/ not (human experiment/ or human/) (2664478)
53 exp animals/ not humans.sh. (5251605)	54 52 not 53 (4781)
54 52 not 53 (1963)	55 limit 54 to yr="2022 - 2024" (3694)
55 limit 54 to yr="2022 - 2024" (1476)	

Cochrane Library Central Register of Controlled Trials (CENTRAL), Issue 7 of 12, August 2024: **COVID-19 vaccines – VE and safety in pregnancy and infants (as at 28.08.24)** **Notes: Date limited from 2022-2024** #1 MeSH descriptor: [COVID-19] explode all trees 7987 #2 (2019 NEXT nCoV OR 2019nCoV OR "n CoV" OR nCoV):ti,ab,kw 397 #3 ("covid 19" OR "covid-19" OR covid19):ti,ab,kw 20589 #4 MeSH descriptor: [SARS-CoV-2] explode all trees 3334 #5 ("Severe Acute Respiratory Syndrome Coronavirus 2" OR "Severe Acute Respiratory Syndrome Coronavirus-2" OR "SARS coronavirus 2" OR "SARS coronavirus-2"):ti,ab,kw 2335 #6 ("SARS CoV2" OR "SARS-CoV2" OR SARSCoV2 OR "SARS-CoV-2"):ti,ab,kw 869 #7 #1 OR #2 OR #3 OR #4 OR #5 OR #6 20848 #8 MeSH descriptor: [Immunization] explode all trees 7380 #9 MeSH descriptor: [Immunization Programs] explode all trees 346 #10 MeSH descriptor: [Vaccines] explode all trees 17482 #11 (vaccin* OR immunis* OR immuniz*):ti,ab,kw 35587 #12 #8 OR #9 OR #10 OR #11 35808 #13 #7 AND #12 3391 #14 MeSH descriptor: [COVID-19 Vaccines] explode all trees 730 #15 #13 OR #14 3391 #16 MeSH descriptor: [RNA, Messenger] explode all trees 1863 #17 (rna or mrna or (messenger NEAR/1 rna)):ti,ab,kw 22449 #18 (protein NEAR/4 subunit):ti,ab,kw 380 #19 (Pfizer* OR BioNTech* OR Moderna* OR Novavax*):ti,ab,kw 3685	

#20 #16 OR #17 OR #18 OR #19 26326 #21 #7 AND #20 1372 #22 MeSH descriptor: [BNT162 Vaccine] explode all trees 116 #23 (BNT162b2* OR tozinameran* OR comirnaty*):ti,ab,kw 361 #24 MeSH descriptor: [2019-nCoV Vaccine mRNA-1273] explode all trees 61 #25 (mRNA-1273* OR elasomeran* OR spikevax*):ti,ab,kw 201 #26 (NVX-CoV2373* OR TAK-019* OR "SARS-CoV-2 rS with Matrix-M1 adjuvant" OR Covovax* OR Nuvaxovid*):ti,ab,kw 13 #27 #22 OR #23 OR #24 OR #25 OR #26 483 #28 #15 OR #21 OR #27 3962 #29 MeSH descriptor: [Pregnancy] explode all trees 34266 #30 (pregnan* OR matern* OR antenatal*):ti,ab,kw 101362 #31 MeSH descriptor: [Infant] explode all trees 46409 #32 (newborn* OR neonat* OR baby OR babies OR infant* OR offspring):ti,ab,kw 97731 #33 #29 OR #30 OR #31 OR #32 168275 #34 #28 AND #33 341 #35 MeSH descriptor: [Treatment Outcome] explode all trees 203814 #36 MeSH descriptor: [Vaccine Efficacy] explode all trees 78 #37 efficac*:ti,ab,kw 469161 #38 effective*:ti,ab,kw 448926 #39 MeSH descriptor: [Safety] explode all trees 5150 #40 MeSH descriptor: [Safety-Based Drug Withdrawals] explode all trees 11	

#41 MeSH descriptor: [Drug-Related Side Effects and Adverse Reactions] explode all trees 5231 #42 MeSH descriptor: [Product Surveillance, Postmarketing] explode all trees 565 #43 MeSH descriptor: [Drug Evaluation] explode all trees 6560 #44 MeSH descriptor: [Adverse Drug Reaction Reporting Systems] explode all trees 185 #45 (adverse NEAR/2 (effect* OR event*)):ti,ab,kw 347564 #46 (safe OR safety OR aefi OR aesi):ti,ab,kw 360606 #47 (("post marketing" OR "post-marketing" OR postmarketing OR "post licensure" OR "post-licensure" OR postlicensure) NEAR/2 (surveillance OR monitor*)):ti,ab,kw 857 #48 outcome*:ti,ab,kw 852623 #49 #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 1436802 #50 #34 AND #49 341 #51 #50 with Cochrane Library publication date Between Jan 2022 and Aug 2024 166	

References

Should previously vaccinated pregnant women receive a further dose of COVID-19 vaccine during pregnancy to prevent severe outcomes of COVID-19 in themselves (the pregnant women) and in infants aged ≤6 months?

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