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 use of a further dose of the COVID-19 vaccine with no further dose of the COVID-19 vaccine during pregnancy in previously vaccinated pregnant women

Background

- In early 2021 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 also evidence of antibody transfer in cord blood and breastmilk, which may offer protection to infants through passive immunity.
- Unlike ATAGI, other NITAGs like 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 both pregnant women and infants from severe disease due to COVID-19.
- NCIRS is conducting this GRADE to evaluate the benefit of a further dose 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 COVID-19 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 completed on 27–28 August 2024 to identify all publications on 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:* Eligible primary studies were included according to the following hierarchy:
  - systematic reviews and meta-analyses of randomised controlled trials (RCTs)
  - randomised controlled trials and quasi-randomised trials
  - non-randomised comparative studies (e.g., prospective or retrospective cohort studies, case–control studies)
- *Publication date:* 1 January 2022 –16 August 2024 (Omicron period)
- *Population:* (i) infants ≤ 6 months and (ii) 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] 4 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, the United States of America (USA), and one multi country study[5] 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.

Two studies were test-negative case-control studies, 5 studies were cohort studies. The study characteristics and RoB of 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	Vaccine effectiveness studies were preferred, particularly nationwide studies with a large and diverse population included.
Population Infants aged ≤6 months Previously vaccinated pregnant women	Infants ≤6 months do not have a COVID-19 vaccine registered for use in this age group and 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, there was evidence that 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 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. Studies of unvaccinated pregnant women were included only when evidence comparing previously vaccinated women who did or did not receive a further dose was unavailable. These studies were considered indirect evidence, and the certainty of evidence was downgraded for indirectness in the GRADE assessment.
Outcomes	Included outcomes as stated above in Table 1 as these represent the severe outcomes that those at risk of severe disease from COVID-19 should be protected from by COVID-19 vaccination. Less severe outcomes, such as VE against COVID-19 infection, were excluded as the priority of recommendations is to protect people from severe outcomes of COVID-19 and also given 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* • 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
Effect size for VE	Effectiveness: <20=trivial, 20-49= small, 50-79= moderate, 80+= large effect

Abbreviations: ATAGI=Australian Technical Advisory Group on Immunisation; CI=confidence interval; TNCC=test-negative case-control; VE=vaccine effectiveness.

Risk of bias assessment

Risk of bias (RoB) assessment was carried out on all included studies by two assessors using ROBINS-I for comparative observational studies. Refer to appendix A for ROBINS-I rating of included studies. Risk of bias domains are assessed in relation to the effect of assignment to intervention (intention-to-treat effect), as required by the ROBINS-I tool.

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] Test negative case-control	VE against COVID-19-related hospitalisation in pregnant women who received further dose vs unvaccinated	Moderate	Low	Low	Low	Low	Low	Moderate	Moderate
	VE against COVID-19-related hospitalisation in infants when pregnant women who received further dose vs unvaccinated	Moderate	Low	Low	Low	Low	Low	Moderate	Moderate
Lipschuetz et al, 2023[2] Cohort study	VE against COVID-19-related hospitalisation in infants when pregnant women who received further dose vs no further dose	Moderate	Low	Low	Low	Low	Low	Moderate	Moderate
Jorgensen et al, 2023[1] Test negative case-control	VE against COVID-19-related hospitalisation in infants when pregnant women who received further dose vs no further dose	Moderate	Low	Low	Low	Low	Low	Moderate	Moderate
Zerbo et al, 2023[6] Retrospective cohort	VE against COVID-19-related hospitalisation in pregnant women who received further dose vs unvaccinated	Moderate	Low	Low	Low	Low	Low	Moderate	Moderate
Villar et al, 2023[5] Cohort study	VE against COVID-19-related hospitalisation (pregnant women) in pregnant women who received further dose vs no further dose	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Guedalia et al, 2022[3] Retrospective cohort	VE against COVID-19-related hospitalisation in pregnant women who received further dose vs no further dose	Moderate	Low	Low	Low	Low	Low	Moderate	Moderate

Schrag et al, 2022[4] Test negative case-control	VE against COVID-19-related hospitalisation in pregnant women who received further dose vs unvaccinated	Moderate	Low	Low	Low	Low	Low	Moderate	Moderate

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

Appendix B: Search Strategy

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

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)

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

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 13 or 14 (71940)	15 exp RNA vaccine/ (21096)
16 exp RNA, Messenger/ (453691)	16 ((rna or mrna or (messenger adj1 rna)) adj3 vaccin$).tw. (14324)
17 (rna or mrna or (messenger adj1 rna)).tw. (1130663)	17 (protein adj4 subunit).tw. (23591)
18 (protein adj4 subunit).tw. (21140)	18 (Pfizer$ or BioNTech$ or Moderna$ or Novavax$).tw. (53738)
19 (Pfizer$ or BioNTech$ or Moderna$ or Novavax$).tw. (7978)	19 15 or 16 or 17 or 18 (94965)
20 16 or 17 or 18 or 19 (1295683)	20 7 and 19 (25493)
21 7 and 20 (26145)	21 exp bnt 162 vaccine/ (388)
22 exp BNT162 Vaccine/ (4016)	22 (BNT162b2$ 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)
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)	23 exp elasomeran/ (7752)
24 exp 2019-nCoV Vaccine mRNA-1273/ (962)	24 (mRNA-1273$ or elasomeran$ or spikevax$ or "Bivalent Original Omicron BA.1" or "Bivalent Original Omicron BA.4/BA.5").tw. (4944)
25 (mRNA-1273$ or elasomeran$ or spikevax$ or "Bivalent Original Omicron BA.1" or "Bivalent Original Omicron BA.4/BA.5").tw. (2103)	25 exp nvx-cov2373 vaccine/ (918)
26 (NVX-CoV2373$ or TAK-019$ or "SARS-CoV-2 rS with Matrix-M1 adjuvant" or Covovax$ or Nuvaxovid$).tw. (148)	26 (NVX-CoV2373$ or TAK-019$ or "SARS-CoV-2 rS with Matrix-M1 adjuvant" or Covovax$ or Nuvaxovid$).tw. (346)
27 22 or 23 or 24 or 25 or 26 (6936)	27 21 or 22 or 23 or 24 or 25 or 26 (14471)
28 15 or 21 or 27 (83902)	28 14 or 20 or 27 (106851)
29 exp Treatment Outcome/ (1299212)	29 exp Treatment Outcome/ (2711619)
30 exp Vaccine Efficacy/ (1117)	30 exp Vaccine Efficacy/ (441353)
31 efficac$.tw. (1201177)	31 efficac$.tw. (1750988)
32 effective$.tw. (2779935)	32 effective$.tw. (3596631)
33 exp Safety/ (90436)	33 exp Safety/ (594931)
34 exp Safety-Based Drug Withdrawals/ (420)	34 exp Safety-Based Drug Withdrawals/ (830)
35 exp "Drug-Related Side Effects and Adverse Reactions"/ (136915)	35 exp "Drug-Related Side Effects and Adverse Reactions"/ (672327)
36 exp Product Surveillance, Postmarketing/ (19053)	36 exp Product Surveillance, Postmarketing/ (40132)
37 exp Drug Evaluation/ (42084)	37 exp Drug Evaluation/ (210104)
38 exp Adverse Drug Reaction Reporting Systems/ (9308)	38 exp Adverse Drug Reaction Reporting Systems/ (40939)

39 (adverse adj2 (effect$ or event$)).tw. (504448) 40 (safe or safety or aefi or aesi).tw. (1124894) 41 ((post marketing or post-marketing or postmarketing or post licensure or post-licensure or postlicensure) adj2 (surveillance or monitor$)).tw. (3858) 42 outcome$.tw. (2559409) 43 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 (6929053) 44 28 and 43 (37021) 45 limit 44 to "all infant (birth to 23 months)" (732) 46 exp Pregnancy/ (1038924) 47 (pregnan$ or matern$ or antenatal$).tw. (832304) 48 exp Infant/ (1284485) 49 (newborn$ or neonat$ or baby or babies or infant$ or offspring).tw. (921436) 50 46 or 47 or 48 or 49 (2603330) 51 44 and 50 (1973) 52 45 or 51 (1973) 53 exp animals/ not humans.sh. (5251605) 54 52 not 53 (1963) 55 limit 54 to yr="2022 - 2024" (1476)	39 (adverse adj2 (effect$ or event$)).tw. (795787) 40 (safe or safety or aefi or aesi).tw. (1696889) 41 ((post marketing or post-marketing or postmarketing or post licensure or post-licensure or postlicensure) adj2 (surveillance or monitor$)).tw. (5968) 42 outcome$.tw. (3791599) 43 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 (10463932) 44 28 and 43 (83015) 45 limit 44 to infant <to one year> (512) 46 exp pregnancy/ (810361) 47 (pregnan$ or matern$ or antenatal$).tw. (1061434) 48 exp infant/ (1184148) 49 (newborn$ or neonat$ or baby or babies or infant$ or offspring).tw. (1123337) 50 46 or 47 or 48 or 49 (2576647) 51 44 and 50 (4832) 52 45 or 51 (4832) 53 animal experiment/ not (human experiment/ or human/) (2664478) 54 52 not 53 (4781) 55 limit 54 to yr="2022 - 2024" (3694)
Cochrane Library Central Register of Controlled Trials (CENTRAL), Issue 7 of 12, August 2024 (via Wiley): **COVID-19 vaccines – VE and safety in pregnancy and infants (as at 28.08.24)** #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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