Coversheet on evidence assessment by ATAGI using the GRADE framework for Abrysvo (Pfizer) RSV vaccines in pregnant women

A summary of key methods and decisions on evidence assessment using the GRADE framework for developing ATAGI recommendations on the use of Abrysvo in pregnant women for the Australian Immunisation Handbook

Background

- Respiratory syncytial virus (RSV) infection is a well-known cause of significant hospitalisation, morbidity and mortality in infants and young children.
- RSV vaccines targeting the prefusion F protein are being investigated for their efficacy in preventing infection and severe disease.
- ATAGI undertook GRADE assessment in 2023 to make relevant recommendations on the use of RSV vaccine in pregnant women in anticipation of its availability in Australia.
- The Therapeutic Goods Administration (TGA) approved Abrysvo (Pfizer) vaccine in March 2024.

Research question

1. Should Abrysvo (Pfizer; Respiratory Syncytial Virus pre-fusion F protein vaccine [RSVPreF]) be recommended for pregnant womento prevent respiratory syncytial virus disease?

Table 1: Population, Intervention, Comparator, Outcomes (PICO) 2: RSV vaccine vs placebo, pregnant women for the protection of infants

Population	Pregnant women
Intervention	Abrysvo (Pfizer) non-adjuvanted RSV vaccine
Comparator	Placebo
Outcomes	*Critical* • Vaccine efficacy (VE) against RSV-confirmed severe medically attended lower respiratory tract illness (MA-LRTI) in infants (follow-up: 90 days, 180 days and 181 to 360 days) • VE against hospitalisation due to confirmed RSV in infants (follow up: 90 days, 180 days* and 181 to 360 days*) • Maternal serious adverse events (SAEs) • Infant SAEs • Infant adverse event of interest (AESI) – preterm birth *Important* • VE against RSV-confirmed MA-LRTI in infants (follow up: 90 days, 180 days and 181 to 360 days) • VE against RSV-A confirmed severe MA-LRTI in infants (follow up 180 days) • VE against RSV-B confirmed severe MA-LRTI in infants (follow up 180 days) • Systemic adverse events (AEs) in pregnant women • Local AEs in pregnant women * Outcomes not included were due to data that was not available or insufficient.

Literature search

PICO 1: Pfizer RSVPreF (Abrysvo) vaccine vs placebo

The literature search was undertaken on 7 June 2023 using the Medline, Embase and Cochrane CENTRAL databases to identify studies assessing efficacy and/or safety outcomes of the RSVPreF (Abrysvo) vaccine in pregnant women. Details of the search methods are presented in Appendix A. The citations were selected for review if they met the following criteria:

- *Study design:* Randomised controlled trial (RCT), observational study, meta-analysis
- *Population:* Pregnant women
- *Intervention:* Non-adjuvanted RSV vaccine
- *Comparator:* Placebo
- *Outcomes:* Effectiveness, efficacy, safety

The published literature search retrieved a total of two citations. Both were included for GRADE analysis. Additional company data (unpublished) based on the included study were also incorporated (see References).

Inclusion criteria and rationale

Table 2: Rationale for PICO and inclusion criteria

PICO	Rationale
Study type RCT, observational study, effectiveness studies	Vaccine efficacy and safety studies are available for the PICO question. The search criteria allow for future capture of relevant effectiveness and observational studies.
Population Pregnant women	Population of interest for this vaccine.
	Vaccine indicated for and studied in pregnant women, aged 18 to 49 years for the passive immunisation of infants for protection against severe RSV disease. It included pregnant women between 24- and 36-weeks' gestation who had an uncomplicated singleton pregnancy with no known risk for complications
Intervention Abrysvo (Pfizer) RSV vaccine	Current formulation in terms of dosage and included antigens and presence/absence of adjuvants.
Comparator Placebo /no vaccine	Placebo/no vaccine There are currently no studies comparing the vaccine of interest with other forms of passive immunisation to protect infants from severe RSV disease such as RSV-specific monoclonal antibodies.

Outcomes	Included outcome as stated above in Table 1. Included iteratively according to outcomes found in the studies.
	Ranking of importance discussed in many iterations with portfolio leads and ATAGI full panel.
	General framework (depending on outcomes measured in studies available): *Critical* • RSV (laboratory confirmed) LRTI/LRTD in infants • Severe RSV (laboratory confirmed) LRTI/LRTD in infants • RSV (laboratory confirmed) medically attended LRTI/LRTD in infants • Hospitalisation of infants for RSV respiratory illness • Death of intants due to RSV respiratory illness • SAEs and AESI *Important* • RSV A/B LRTD/LRTI • RSV (laboratory confirmed) acute respiratory infection in infants • Duration of protection • Systemic AEs in pregnant women • Local AEs in pregnant women Note: some outcomes may be missing in GRADE projects due to no data from available studies. Extra outcomes added due to relevance.

Abbreviations: AE=adverse event; AESI=adverse event of special interest; LRTI/LRTD=lower respiratory tract illness/disease; SAE= serious adverse event; RCT=randomised controlled trial; RSV=respiratory syncytial virus

Risk of bias assessment

Risk of bias (RoB) was assessed for all selected studies using the standard GRADE criteria. Two assessors independently undertook this using the RoB 2.0 tool for randomised controlled trials (Appendix B).

Appendix A: Literature Search Strategy

Table A1: PICO 1 – Pfizer RSVPreF (Abrysvo) vaccine vs placebo

Cochrane Library Central Register of Controlled Trials (CENTRAL), Issue 6 of 12, June 2023: RSV vaccines – Maternal – FINAL (as at 07.06.23)

Notes: No age, language or date limits applied.

ID	Search Hits
#1	MeSH descriptor: [Respiratory Syncytial Virus, Human] explode all trees 104
#2	MeSH descriptor: [Respiratory Syncytial Virus Infections] explode all trees 449
#3	("respiratory syncytial"):ti,ab,kw 1177
#4	rsv:ti,ab,kw 1054
#5	#1 OR #2 OR #3 OR #4 1415
#6	MeSH descriptor: [Immunization] explode all trees 6890
#7	MeSH descriptor: [Immunization Programs] explode all trees 304
#8	MeSH descriptor: [Vaccines] explode all trees 15898
#9	(immuni* OR vaccin*):ti,ab,kw 39485
#10	#6 OR #7 OR #8 OR #9 39660
#11	#5 AND #10 440
#12	MeSH descriptor: [Respiratory Syncytial Virus Vaccines] explode all trees 65
#13	#11 OR #12 440
#14	Pfizer*:ti,ab,kw 2742
#15	Abrysvo*:ti,ab,kw 0
#16	("PF 06928316*" OR "PF-06928316*" OR PF06928316*):ti,ab,kw 3
#17	("RSV pre F*" OR "RSV-pre-F*" OR RSVpreF*):ti,ab,kw 91
#18	(bivalen* NEAR/3 ("prefusion F" OR "prefusion-F" OR prefusionF)):ti,ab,kw 7
#19	(bivalen* NEAR/3 recombinant):ti,ab,kw 29
#20	(bivalen* NEAR/3 (protein* OR subunit*)):ti,ab,kw 15
#21	"MATernal Immunization Study for Safety":ti,ab,kw 0
#22	MATISSE*:ti,ab,kw 35
#23	NCT04424316*:ti,ab,kw 1
#24	#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 2902
#25	#13 AND #24 90
#26	MeSH descriptor: [Pregnancy] explode all trees 31117
#27	(pregnan* OR matern* OR antenatal*):ti,ab,kw 92565
#28	#26 OR #27 92931
#29	#25 AND #28 26
#30	MeSH descriptor: [Immunogenicity, Vaccine] explode all trees 646
#31	immunogen*:ti,ab,kw 16408
#32	MeSH descriptor: [Antibody Formation] explode all trees 1104
#33	(antibod* NEAR/3 (respons* OR form*)):ti,ab,kw 5927
#34	(immun* NEAR/3 (respon* OR protect*)):ti,ab,kw 18396
#35	MeSH descriptor: [Antibodies, Viral] explode all trees 4405
#36	MeSH descriptor: [Antibodies, Neutralizing] explode all trees 753
#37	MeSH descriptor: [Treatment Outcome] explode all trees 180744
#38	MeSH descriptor: [Vaccine Efficacy] explode all trees 44
#39	efficac*:ti,ab,kw 430841
#40	effective*:ti,ab,kw 408362
#41	MeSH descriptor: [Safety] explode all trees 18462
#42	MeSH descriptor: [Safety-Based Drug Withdrawals] explode all trees 11
#43	MeSH descriptor: [Product Surveillance, Postmarketing] explode all trees 434
#44	MeSH descriptor: [Drug Evaluation] explode all trees 5966
#45	MeSH descriptor: [Population Surveillance] explode all trees 779
#46	MeSH descriptor: [Adverse Drug Reaction Reporting Systems] explode all trees 157
#47	(adverse NEAR/3 (effect*OR event*)):ti,ab,kw 147272
#48	(safe OR safety OR aefi OR aesi):ti,ab,kw 328132
#49	MeSH descriptor: [Mortality] explode all trees 21868
#50	MeSH descriptor: [Death] explode all trees 8019
#51	(mortalit* OR death* OR fatal* OR case-fatal* OR lethal* OR died):ti,ab,kw 179776
#52	MeSH descriptor: [Pregnancy Complications] explode all trees 15942
#53	MeSH descriptor: [Infant, Premature] explode all trees 4885
#54	MeSH descriptor: [Infant, Low Birth Weight] explode all trees 2637
#55	#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 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 986315
#56	#29 AND #55 26

DSR – 0
CENTRAL - 26

EMBASE: RSV vaccines – Maternal – FINAL (as at 07.06.23)

Notes: No age, language or date limits applied.

Database: Embase <1974 to 2023 June 05>
Search Strategy:

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1 exp Human respiratory syncytial virus/ (8807)
2 exp respiratory syncytial virus infection/ (7770)
3 (respiratory adj2 syncytial).tw. (20465)
4 rsv.tw. (20038)
5 1 or 2 or 3 or 4 (31747)
6 exp Immunization/ (370857)
7 exp vaccine/ (412968)
8 (immuni$ or vaccin$).tw. (797713)
9 6 or 7 or 8 (943768)
10 5 and 9 (7618)
11 exp respiratory syncytial virus vaccine/ (1932)
12 10 or 11 (7915)
13 Pfizer$.tw. (44771)
14 Abrysvo$.tw. (0)
15 ("PF 06928316$" or PF-06928316$ or PF06928316$).tw. (0)
16 ("RSV pre F$" or RSV-pre-F$ or RSVpreF$).tw. (44)
17 (bivalen$ adj3 ("prefusion F" or prefusion-F or prefusionF)).tw. (8)
18 (bivalen$ adj3 recombinant).tw. (132)
19 (bivalen$ adj3 (protein$ or subunit$)).tw. (271)
20 "MATernal Immunization Study for Safety".tw. (0)
21 MATISSE$.tw. (76)
22 NCT04424316$.tw. (1)
23 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 (45267)
24 12 and 23 (114)
25 exp pregnancy/ (773475)
26 (pregnan$ or matern$ or antenatal$).tw. (1007226)
27 25 or 26 (1253500)
28 24 and 27 (29)
29 exp vaccine immunogenicity/ (6662)
30 immunogen$.tw. (122034)
31 exp antibody production/ (62467)
32 exp antibody response/ (63881)
33 (antibod$ adj3 (respons$ or form$)).tw. (81998)
34 (immun$ adj3 (respon$ or protect$)).tw. (506303)
35 exp virus antibody/ (107816)
36 exp neutralizing antibody/ (52511)
37 exp drug efficacy/ (1020839)
38 efficac$.tw. (1611664)
39 effective$.tw. (3304332)
40 exp safety/ (564040)
41 exp postmarketing surveillance/ (39224)
42 exp drug surveillance program/ (26704)
43 exp adverse drug reaction/ (637013)
44 (adverse adj3 (effect$ or event$)).tw. (739465)
45 (safe or safety or aefi or aesi).tw. (1567053)
46 exp mortality/ (1376971)
47 exp death/ (817498)
48 (mortalit$ or death$ or fatal$ or case-fatal$ or lethal$ or died).tw. (3127234)
49 exp pregnancy complication/ (159189)
50 exp prematurity/ (127400)
51 exp low birth weight/ (74948)
52 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 or 49 or 50 or 51 (9975382)
53 28 and 52 (28)

MEDLINE: RSV vaccines – Maternal – FINAL (as at 07.06.23)

Notes: No age, language or date limits applied.

Database: MEDLINE(R) 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 Respiratory Syncytial Virus, Human/ (3864)
2 exp Respiratory Syncytial Virus Infections/ (8621)
3 (respiratory adj syncytial).tw. (16281)
4 rsv.tw. (14651)
5 1 or 2 or 3 or 4 (22018)
6 exp Immunization/ (208361)
7 exp Immunization Programs/ (16022)
8 exp Vaccines/ (276119)
9 (immuni$ or vaccin$).tw. (662941)
10 6 or 7 or 8 or 9 (763664)
11 5 and 10 (4804)
12 exp Respiratory Syncytial Virus Vaccines/ (895)
13 11 or 12 (4834)
14 Pfizer$.tw. (6303)
15 Abrysvo$.tw. (0)
16 ("PF 06928316$" or PF-06928316$ or PF06928316$).tw. (0)
17 ("RSV pre F$" or RSV-pre-F$ or RSVpreF$).tw. (28)
18 (bivalen$ adj3 ("prefusion-F" or prefusion-F or prefusionF)).tw. (7)
19 (bivalen$ adj3 recombinant).tw. (118)
20 (bivalen$ adj3 (protein$ or subunit$)).tw. (238)
21 "MATernal Immunization Study for Safety".tw. (0)
22 MATISSE$.tw. (64)
23 NCT04424316$.tw. (1)
24 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 (6728)
25 13 and 24 (37)
26 exp Pregnancy/ (1002945)
27 (pregnan$ or matern$ or antenatal$).tw. (785343)
28 26 or 27 (1252554)
29 25 and 28 (14)
30 exp Immunogenicity, Vaccine/ (3296)
31 immunogen$.tw. (91057)
32 exp Antibody Formation/ (63612)
33 (antibod$ adj3 (respons$ or form$)).tw. (69376)
34 (immun$ adj3 (respon$ or protect$)).tw. (382389)
35 exp Antibodies, Viral/ (122422)36 exp Antibodies, Neutralizing/ (18235)
37 exp Treatment Outcome/ (1240909)
38 exp Vaccine Efficacy/ (748)
39 efficac$.tw. (1082976)
40 effective$.tw. (2501669)
41 exp Safety/ (88681)
42 exp Safety-Based Drug Withdrawals/ (416)
43 exp Product Surveillance, Postmarketing/ (18178)
44 exp Drug Evaluation/ (42056)
45 exp Population Surveillance/ (74452)
46 exp Adverse Drug Reaction Reporting Systems/ (8806)
47 (adverse adj3 (effect$ or event$)).tw. (459341)
48 (safe or safety or aefi or aesi).tw. (1016829)
49 exp Mortality/ (423113)
50 exp Death/ (164019)
51 (mortalit$ or death$ or fatal$ or case-fatal$ or lethal$ or died).tw. (2148520)
52 exp Pregnancy Complications/ (473206)
53 exp Infant, Premature/ (64659)
54 exp Infant, Low Birth Weight/ (38801)
55 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 or 49 or 50 or 51 or 52 or 53 or 54 (7506287)
56 29 and 55 (14)

Appendix B

Table B1: Risk of bias assessment using ROB 2.0

Study	Outcome	Randomisation process	Deviations from intervention	Missing data	Measurement of outcomes	Selection of the reported results	Overall bias
PICO 1							
Kampmann 2023	Efficacy	Low	Low	Low	Low	Low	Low
	Safety	Low	Low	Low	Low	Low	Low
Simões 2022	Efficacy	Low	Low	Low	Low	Low	Low
	Safety	Low	Low	Low	Low	Low	Low

References

1. Kampmann B, Madhi SA, Munjal I, et al. Bivalent Prefusion F Vaccine in Pregnancy to Prevent RSV Illness in Infants. *New England Journal of Medicine* 2023. Available from: https://www.nejm.org/doi/full/10.1056/NEJMoa2216480
2. Simões EAF, Center KJ, Tita ATN, et al. Prefusion F Protein-Based Respiratory Syncytial Virus Immunization in Pregnancy. *New England Journal of Medicine* 2022;386:1615-26. Available from: https://www.nejm.org/doi/pdf/10.1056/NEJMoa2106062?articleTools=true
3. Pfizer. Unpublished CSR c3671008 report body. 2022.
4. FDA. 2023. FDA Briefing Document Respiratory Syncytial Virus Vaccine (Proposed Trade Name: Abrysvo) FDA. Available from: https://www.fda.gov/media/168185/download.
5. Pfizer. Unpublished CSR c3671003 report body. 2022.
6. Pfizer. A PHASE 2B PLACEBO-CONTROLLED, RANDOMIZED STUDY OF A RESPIRATORY SYNCYTIAL VIRUS (RSV) VACCINE IN PREGNANT WOMEN. U.S National Library of Medicine: 2022. Available from: https://classic.clinicaltrials.gov/ct2/show/results/NCT04032093.