Decision making in immunisation programs

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Declarations of interest

- Previous member and co-chair, ATAGI
- Previous chair, ACV
- Previous member, ACM/ACPM

What decisions need to be made?

- Is the vaccine high quality, safe and effective?
- In which groups should the vaccine be used?
- Is the vaccine worth the cost?

What decisions need to be made?

- Is the vaccine high quality, safe and effective?
  - Regulatory - does this tool work?
- In which groups should the vaccine be used?
  - Clinical/public health - what do we use this tool for?
- Is the vaccine worth the cost?
  - Health economics, public health, clinical - can we afford this tool?

What decisions need to be made?

- Is the vaccine high quality, safe and effective?
  - Regulatory
  - TGA (delegate of secretary) - supported by ACV
- In which groups should the vaccine be used?
  - Clinical/public health
  - ATAGI (via Australian Immunisation Handbook) supported by NCIRS
- Is the vaccine worth the cost?
  - Health economics, public health, clinical
  - Minister, on recommendation of PBAC

Regulatory assessment

- Preclinical data – why should this vaccine work?
- Quality, batch-to-batch variation (“Chemistry Manufacturing and Controls”),
- Non-clinical data - animal studies
- Clinical data - pivotal phase 3 studies, other studies, safety dataset
- Post registration - safety monitoring (“pharmacovigilance”), provider education, adverse events of special interest (“risk management plan”)

- Many regulatory guidelines – FDA, EMA

Balance of efficacy and safety

Benefits
- Prevention of mortality
- Prevention of severe disease
- Prevention of infection
- Indirect protection
- Special populations
- Other benefits (eg educational, economic productivity)



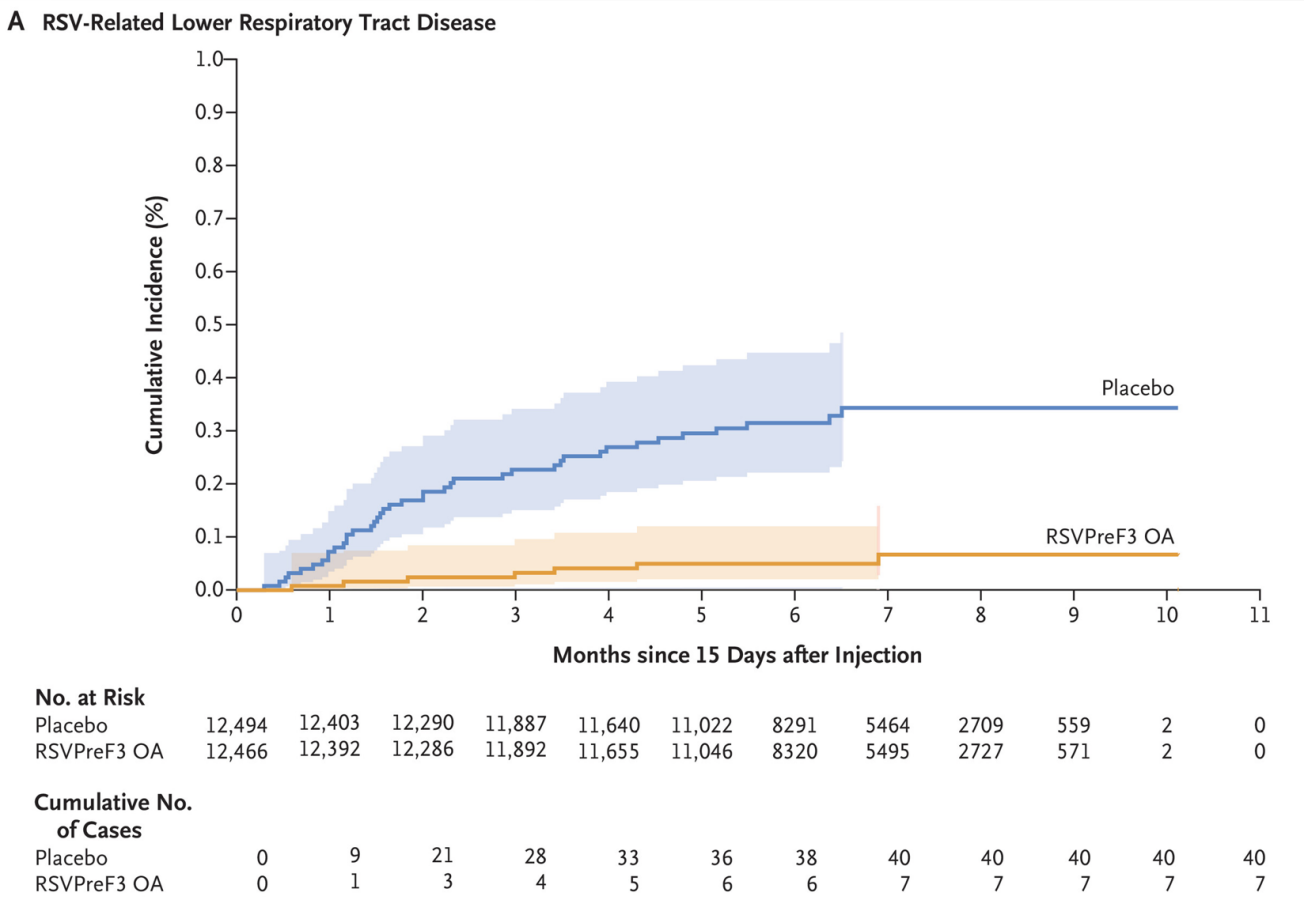
Uncertainty

Risks/harms
- Common adverse events – systemic/local
- Rare but serious adverse events
- Adverse events of special interest

Outcome measures

- Effectiveness
  - Severe infection or mortality
  - Medical presentation (eg ED, GP attendance)
  - Any confirmed infection
- Surrogate outcomes
  - Carcinoma in situ (“pre-cancer”)
  - Immunogenicity
    - Seroconversion, change in Ab levels, seroprotection
    - Cellular assays
    - Immunobridging
- Safety
  - Systemic, local reactions
  - Severe
  - Discontinuation
  - Unexpected (“SUSAR”)
  - Adverse events of special interest eg Guillain Barre syndrome, ADEM
  - Mortality

RSV vaccine clinical trial



No. at Risk												
Placebo	12,494	12,403	12,290	11,887	11,640	11,022	8291	5464	2709	559	2	0
RSVPreF3 OA	12,466	12,392	12,286	11,892	11,655	11,046	8320	5495	2727	571	2	0

Cumulative No. of Cases												
Placebo	0	9	21	28	33	36	38	40	40	40	40	40
RSVPreF3 OA	0	1	3	4	5	6	6	7	7	7	7	7

RSV vaccine (Arexvy) trial

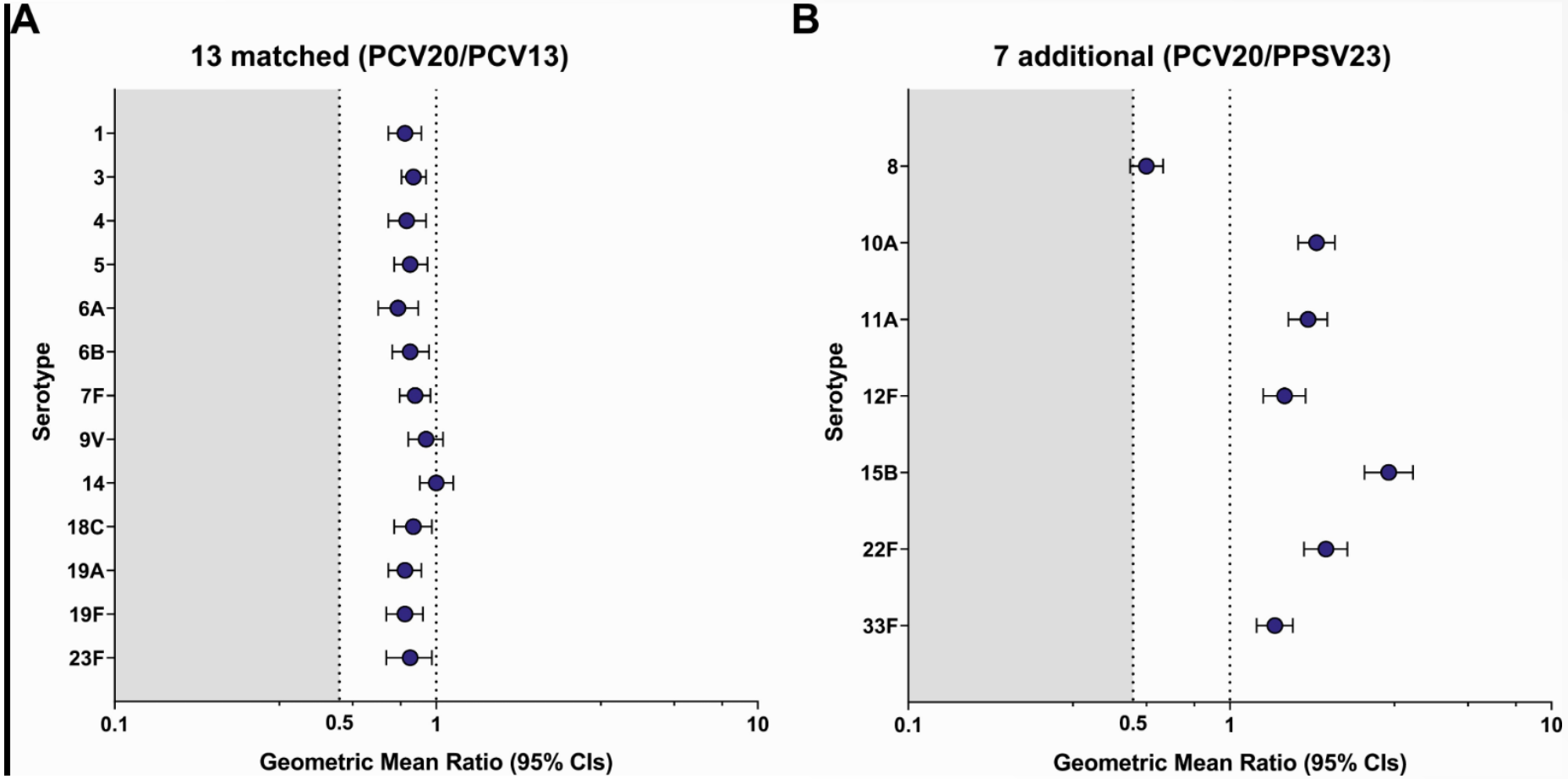
- Adults >60 years
- 17 countries
- RSVPreF3 (120µg + 25µg $AS01_E$ adjuvant) vs placebo

Results

- 26,664 participants
- LRTI in 7 of 12,466 in the vaccine group and 40 of 12,494 in the placebo group
- VE 82.6% (95% CI, 57.9 to 94.1)
- 2 patients hospitalised
- No deaths

Papi NEJM 2023
DOI: 10.1056/NEJMoa2209604

PCV20 - immunogenicity



Essink CID 2022
doi.org/10.1093/cid/ciab990

Assessing evidence – GRADE framework

Grading of Recommendations Assessment, Development and Evaluation

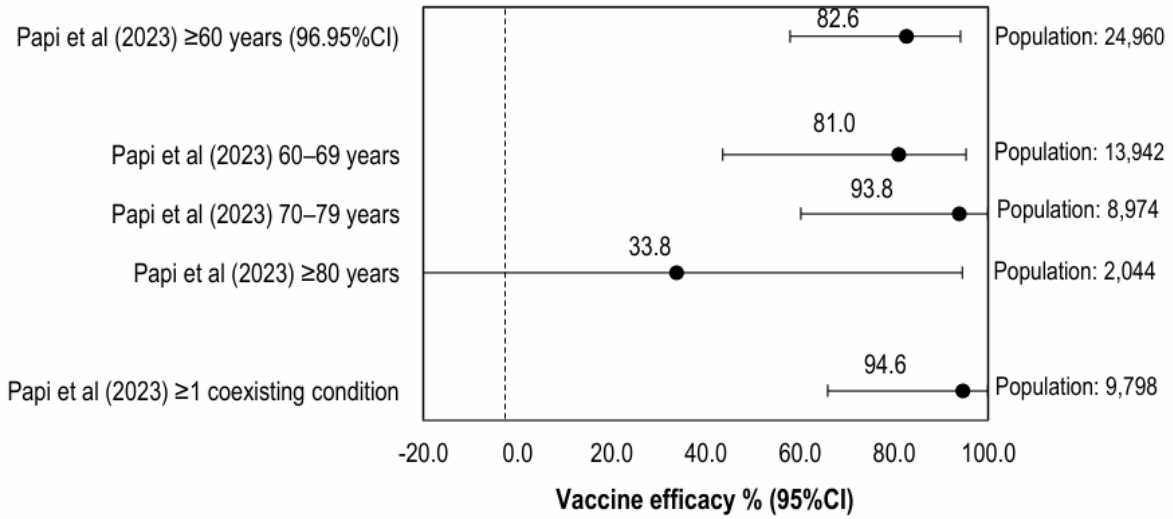
- Defining PICO questions
- Summary of evidence - study quality
- What outcomes are important?
- What does the body of evidence say?

PICO question

- In [population], does [intervention] when compared to [comparator] reduce [outcome]?

- In adults >60 years of age, does RSV vaccine, when compared to no RSV vaccine, reduce symptomatic RSV infection?

GRADE assessment - Arexvy

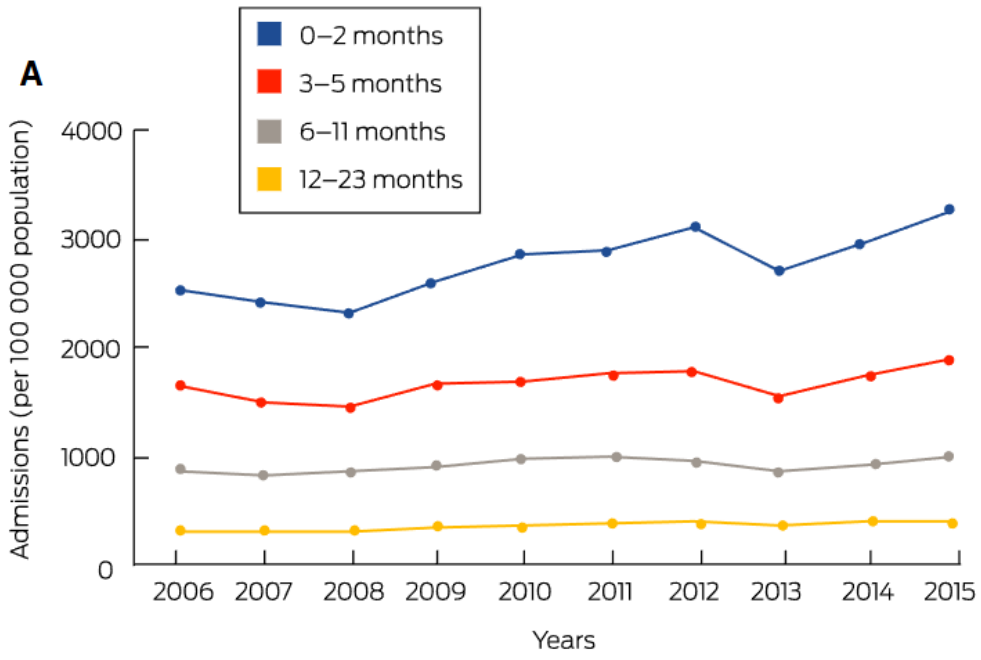
Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
CRITICAL OUTCOMES				
RSV lower respiratory tract disease (LRTD) (≥2 lower respiratory signs/symptoms with at least 1 respiratory sign, or ≥3 respiratory signs lasting >24 hours) Assessed with: reverse-transcriptase polymerase chain reaction (RT-PCR) Total follow up: median 18 months	**RSVPreF3 vaccine efficacy against LRTD in older adults - Season 1 interim analysis (northern hemisphere, median follow up 6.7 months)**  	⊕⊕⊕◯ Moderate[a]	RSVPreF3 vaccine likely results in a moderate reduction in LRTD during the first season following single dose vaccination when compared with placebo. Note: Interpretation based on ≥60 years from final analysis.

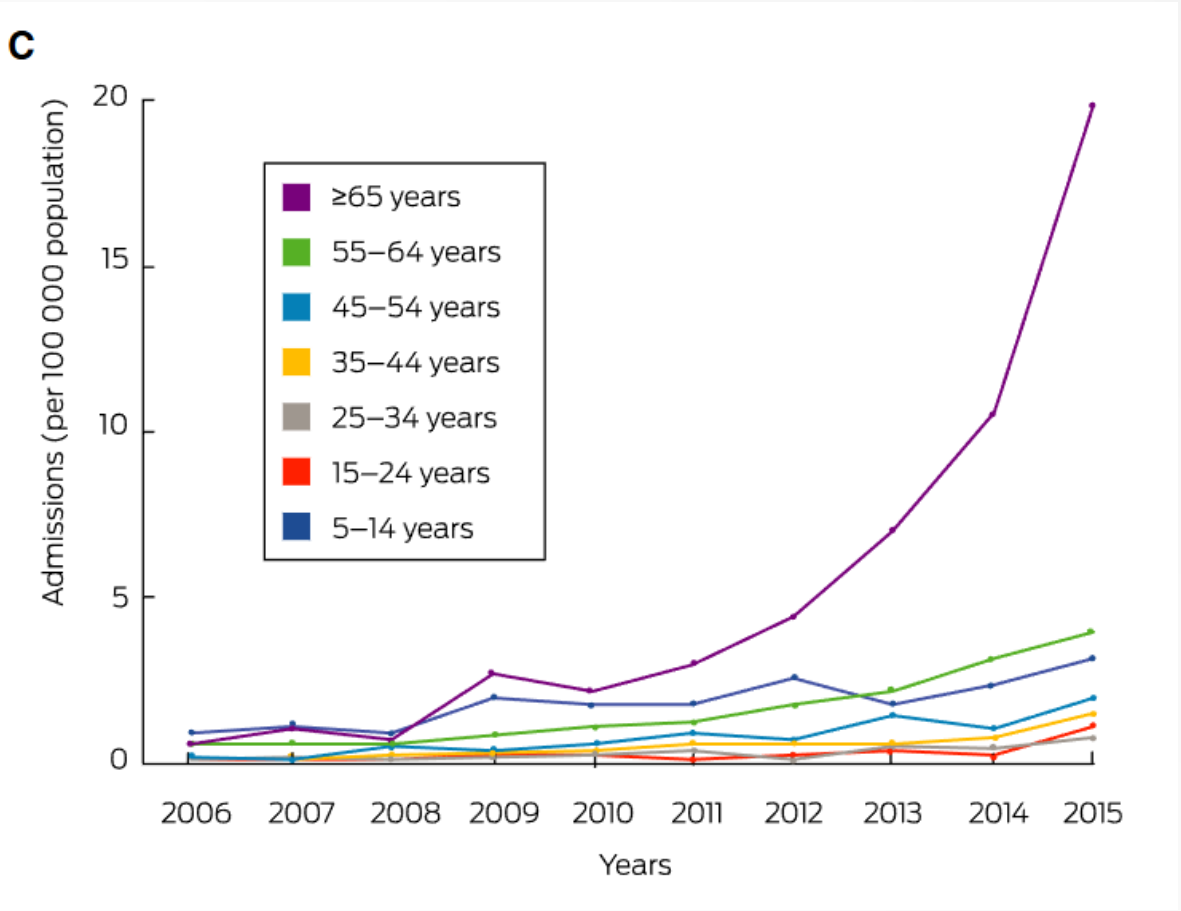
Assessing burden of disease

- Notification, primary care, ED, hospital, mortality
- Other - cancer, cirrhosis,
- Indirect - social burden, education,
- Equity and special populations - medical risk factors, Indigenous people

RSV hospitalisations

2 Respiratory syncytial virus-coded hospitalisation rates (principal diagnosis only), Australia, 2006–2015, by age group and year: A. children under 2 years of age; B. children from 2 years to under 5 years of age; C. children aged 5 years or more and adults





Saravanos MJA 2019

Evidence to decision framework

- Is this a priority problem?
- Benefits and harms of the options
- Resource use
- Equity
- Acceptability
- Feasibility

Other considerations

- Coverage - age vs Indigenous vs comorbidities;
- Models of delivery eg school vs primary care
- Other vaccines - needle burden, schedule points
- Indirect protection eg LAIV in school age children
- Surrogate outcomes eg meningococcal vaccines
- Long term outcomes eg HPV and cervical cancer
- Platform technologies eg mRNA and pandemic preparedness

Outcomes

- Recommend eg COVID vaccines in >75 years
- Conditional recommendation: "consider" in >65, medical at risk
- Recommend against
- No recommendation

- (Recommended but not funded)

Different economic tools answer different questions

What are the costs associated with disease?	• No intervention • Costs only ✓**"The cost of disease is estimated at $1.3 billion."**	Cost of illness study ***Economic burden***
What is the cost of an intervention?	• One intervention • Costs only ✓**"The cost of the vaccine program is $15 per vaccinated girl."**	Costing study/analysis ***Cost composition***
What are the monetary consequences of the intervention?	• Intervention versus comparator • Costs only, including costs associated with outcomes ✓**"Vaccination costs $2 million a year but will save the health system $500,000 a year."**	Budget impact analysis ***Affordability*** ***Sustainability***
Is the intervention cost-effective? Are the additional costs worth the outcomes?	• Intervention versus comparator • Costs and outcomes ✓**"Vaccination costs $10,000 per death prevented."**	Full economic evaluation ***Value for money*** ***Efficiency***

Economic assessment

- Intervention vs comparator
- Who is paying? Perspective
- Cost effectiveness
  - Cost per outcome eg $ per death avoided
- Cost utility
  - Type of cost effectiveness
  - Cost of health adjusted years of life
  - Common comparator



No intervention
Health burden
Cost of illness

Intervention
Intervention cost
Health burden
Cost of illness

Turner H Front Public Health 2021
doi.org/10.3389/fpubh.2021.722927

ICER

- Incremental cost effectiveness ratio
- Cost effectiveness only one consideration
  - Economic
    - Budget impact
    - Sustainability
    - Affordability
  - Non-economic
    - acceptability,
    - availability,
    - political aspects
    - Supply chain robustness
    - Technology premium

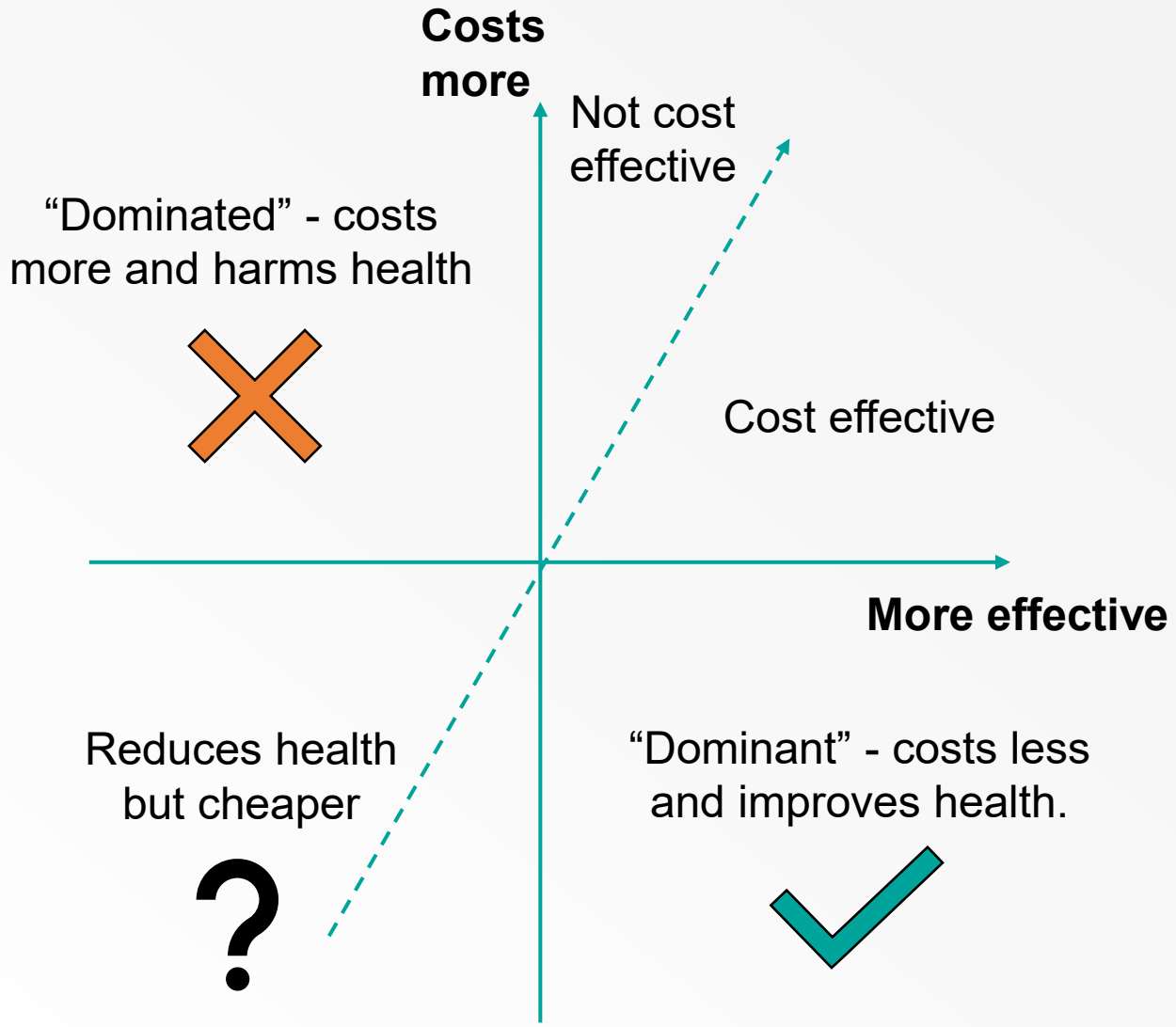


Table 27: Economic evaluation results of RSVPreF3 OA vs no vaccine per age group in five-year categories (submission base case settings)

Age group (YOA)	Population	RSV-LRTD hospitalisations	30-day mortality within hospital admission	Possibility of death given RSV-LRTD[a]	Incremental costs ($)	Incremental QALYs	ICER
60-64	[redacted]1	4%	4.67%	0.20%	[redacted]	3,095	$95-115k
65-69	[redacted]1	9%		0.43%		4,064	$55-75k
70-74	[redacted]1					3,146	[redacted]3
75-79	[redacted]1	18%	10.87%	2.00%		7,297	$5-15k
80-84	[redacted]5					3,785	[redacted]4
≥85	[redacted]5	34%		3.66%		4,099	Dominant

Source: Table 3-24 & 3-43of the submission; attachment 'RSV OA static model_v16_PBAC_FINAL' of the submission.
ICER = incremental cost-effectiveness ratio; LRTD = lower respiratory tract disease; QALY = quality-adjusted life years; RSV = respiratory syncytial virus; RSVPreF3 OA= RSV Pre-fusion protein 3 older adult; YOA = years of age.
a calculated as 30-day mortality within hospital admission multiplied by the proportion of hospitalised RSV-LRTD cases.

PBAC summary, July 2024:
rsvpref3-arexvy-psd-july-2024.pdf

Table 30: Estimated use and financial implications for ≥60 YOA population

	2025	2026	2027	2028	2029	2030	Total
Estimated extent of use							
Predicted number of people vaccinated with RSVPreF3 OA	2-3 M	400-500K	500-600K	500-600K	500-600K	3	4
Estimated financial implications of listing RSVPreF3 OA in the NIP							
Federal	$500-600M	$100-200M	$100-200M	$100-200M	$100-200M	6	7
NIP	4	6	6	6	6	6	7
PBS	8	8	8	8	8	8	8
MBS	8	8	8	8	8	8	8
Other Federal Budgets	8	8	8	8	8	8	8
State and Territory Governments	Cost saving					8	8
All budgets combined	8	8	10	11	12	12	5

Source: Table 4-7, compiled from Section 4.5 of the submission.

; MBS = Medicare Benefits Schedule; NIP = National Immunisation Program; PBS = Pharmaceutical Benefits Schedule; RSVPreF3 OA = RSV prefusion protein 3 older adult; YOA = years of age; Yr = year.

The PBAC recommended that respiratory syncytial virus vaccine (Arexvy, RSVPreF3 OA) be a designated vaccine for the purposes of the *National Health Act 1953* for the prevention of lower respiratory tract disease (LRTD) caused by RSV in the two populations requested by the resubmission, which included adults 75 years of age and above, and Aboriginal and Torres Strait Islander peoples aged 60 to 74 years.

The PBAC considered that Arexvy helped protect against LRTD caused by RSV more than not getting the vaccine and considered it was generally safe and well tolerated although there were some uncertainties around how long Arexvy's protection would last. The PBAC noted the clinical evidence for Arexvy over three seasons, and advised that it would be reasonable to accept vaccine efficacy (VE) over a period of three years for the purposes of the economic evaluation.

Consistent with its previous advice, the PBAC considered there is a high clinical need for an effective vaccine for this population. The PBAC noted that this population would be addressed in a future resubmission.

- Both RSV vaccines (Arexvy, Abrysvo) endorsed by PBAC in older adults >75 years and Aboriginal and Torres Strait Islander people >60 years
- Flagged future submission for 60-74 year olds with medical risk factors

PBAC July 2025 minutes (published 22 Aug 2025)

Monitoring and evaluation

- Process evaluation
  - Program delivery providers
  - Primary care
  - Consumers
- Vaccination coverage
- Effectiveness and impact
- Vaccine safety

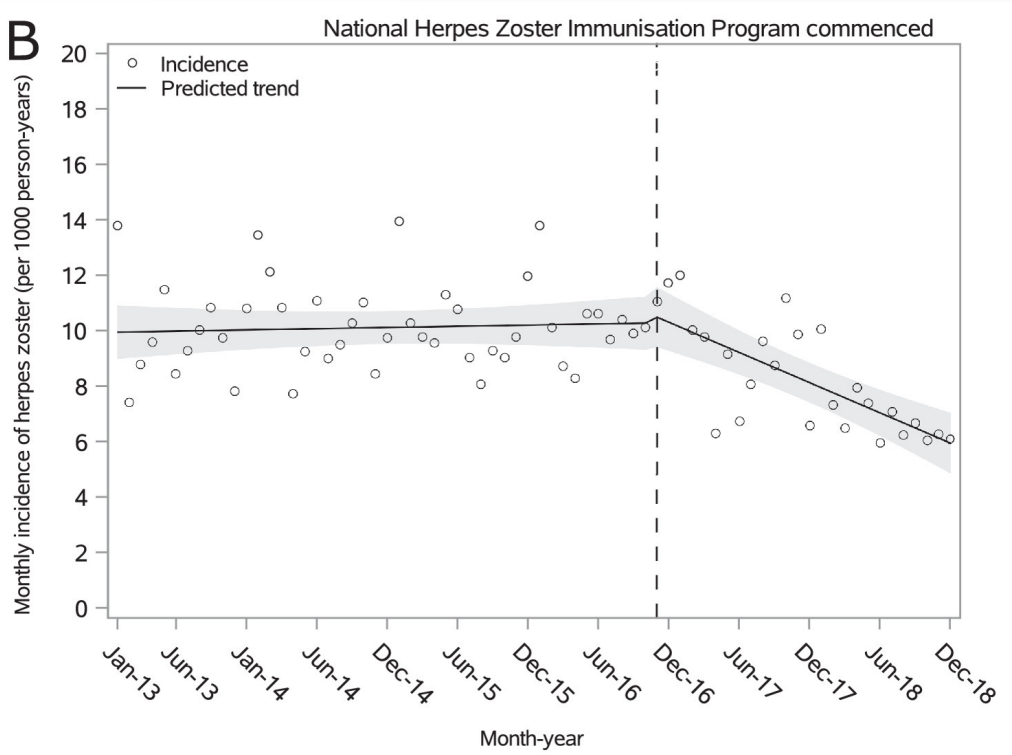
Zostavax evaluation

- Process
  - Procurement and supply could be improved
  - Need for education of clinicians esp immunosuppression
  - Need for better consumer resources
- Coverage (18 months after introduction)
  - 34% in 70 year olds
  - 26% in 71-80 year olds
  - Higher in Indigenous people
  - Higher coverage than US (28%), lower than UK (55%)

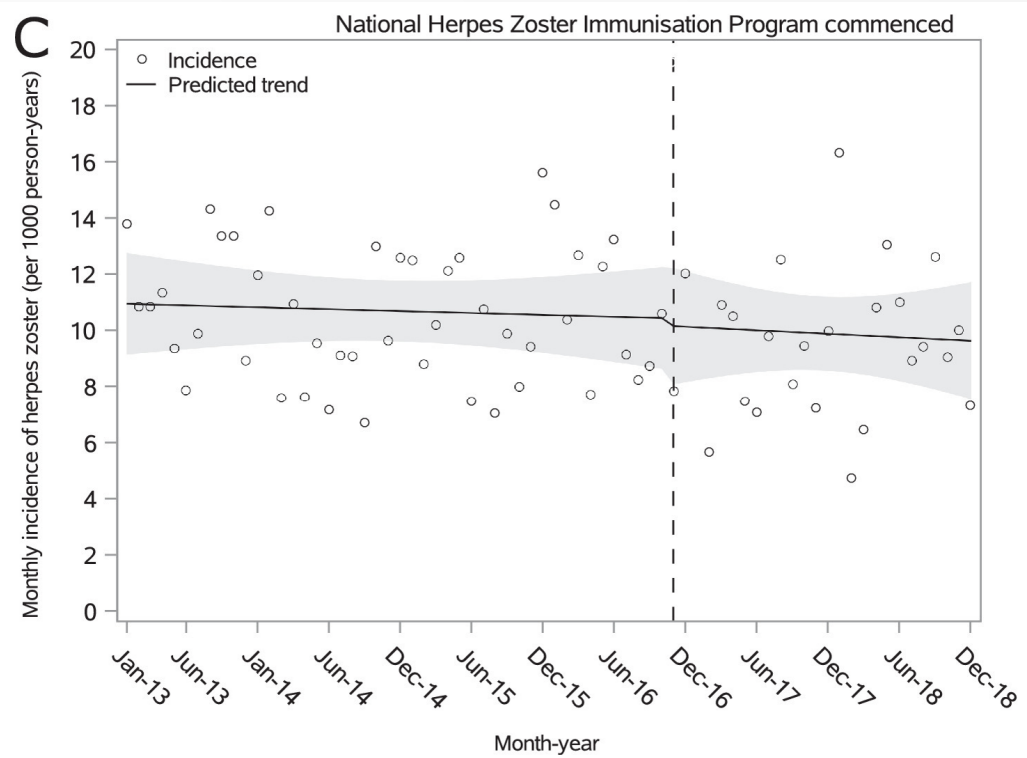
Zostavax evaluation

- Safety
  - TGA Adverse Events Management System
  - AusVaxSafety (active participant-based surveillance system)
  - Mostly well tolerated
  - Serious errors – immunocompromised
  - One death from disseminated VZV.

Impact



70-79 year olds



80-89 year olds

Lin, J Infect 2022
DOI: 10.1016/j.jinf.2022.01.011

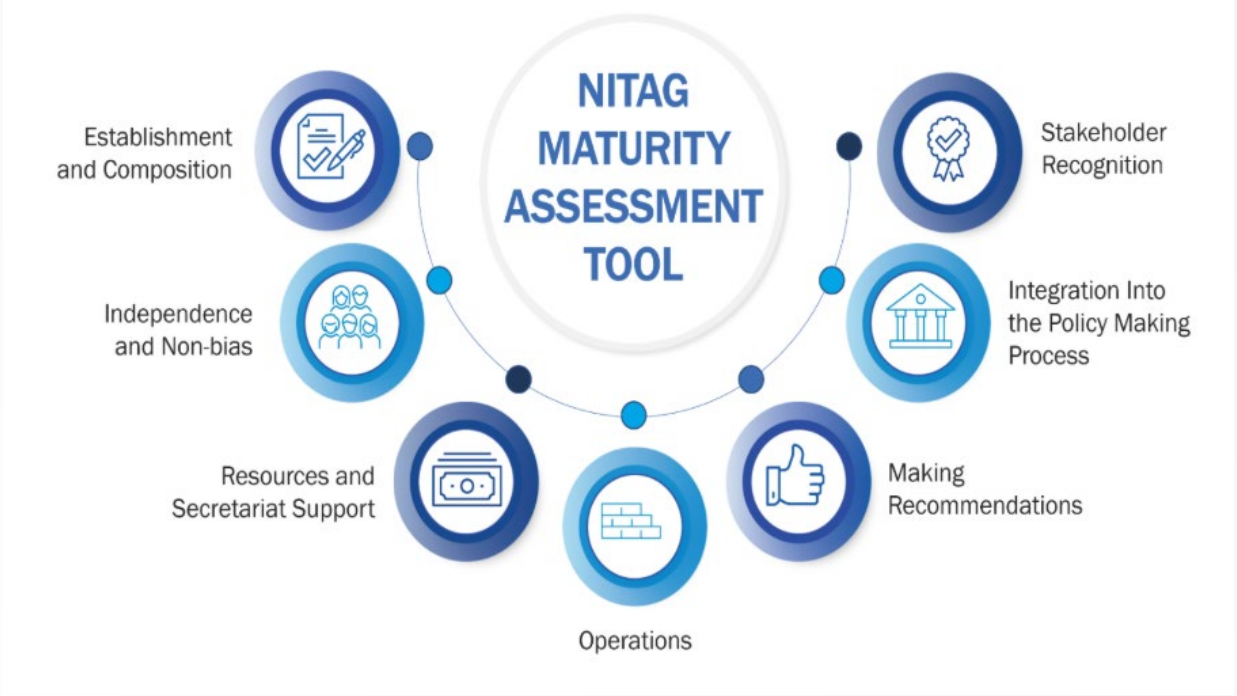
Emergency programs

- Vaccines may/may not be registered
- Timeliness important – public health response
- Epidemiology uncertain and changing

- Often funded by states/territories
  - Examples – COVID, Japanese Encephalitis, Mpox

International processes

- Regulatory agencies
  - WHO ‘Stringent regulators’ – mostly EU, US, Health Canada, UK, Switzerland
- National Immunisation Technical Advisory Groups (NITAGs)
  - NITAG maturity assessment tool – link
- Vaccine funding
  - National programs
  - GAVI (Global Alliance for Vaccines and Immunization)



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