New Vaccines, or New to the NIP: Evidence and Policy

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Acknowledgment to:
Jean Li-Kim-Moy
Anny Huang
Amanda Van Eldik

and the rest of the NCIRS POSH team for the use of their slides

Overview

- New to the NIP:
  - Shingrix
  - Vaxelis

- New Vaccines – registered overseas but awaiting in Australia
  - RSV vaccine + monoclonal abs

Protect your patients from **shingles**

Changes to program advice

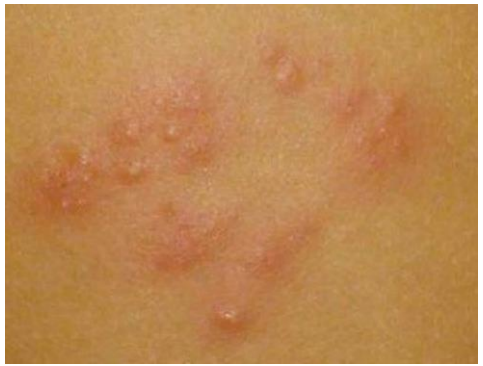
National **Immunisation** Program

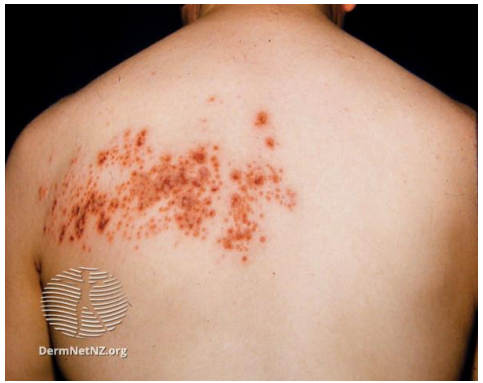
A joint Australian, State and Territory Government initiative

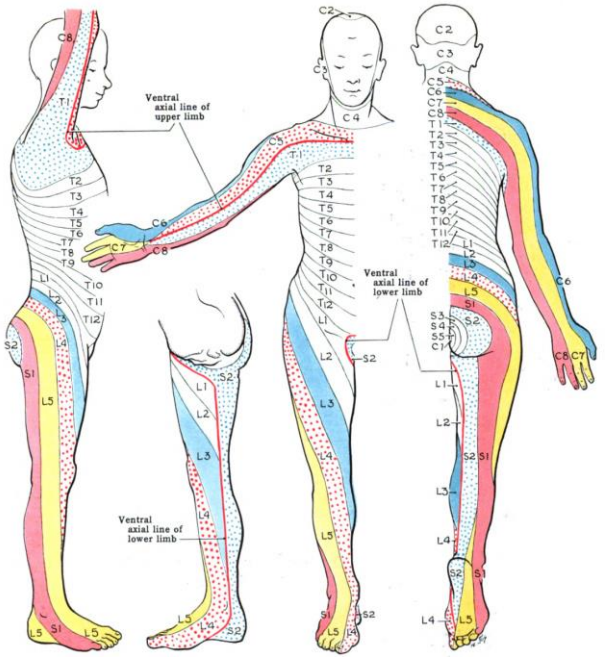
What is Shingles (Herpes Zoster HZ)

- A reactivation of latent Varicella Zoster Virus

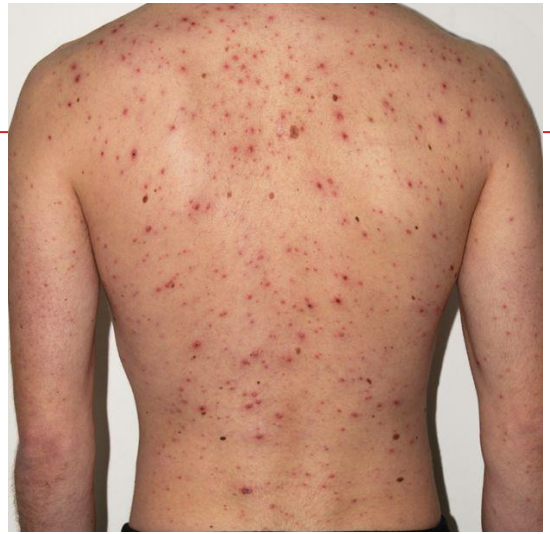
- Pain (prodrome)
- Starts as flat red rash.
- Develops vesicles (fluid filled blisters)
- Crusts over
- Dermatomal distribution
  - Typically one-sided
  - Stops in the midline
  - Rarely several adjacent dermatomes



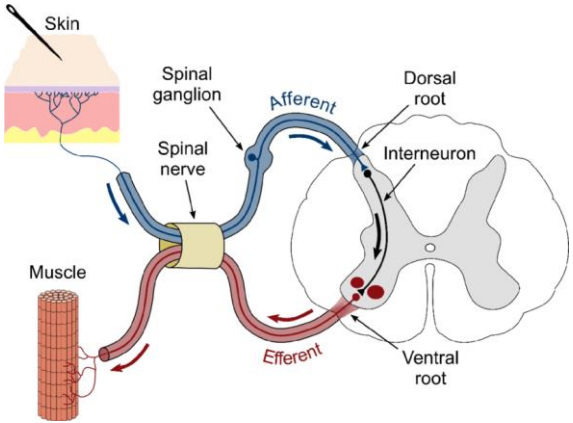




What causes Shingles?



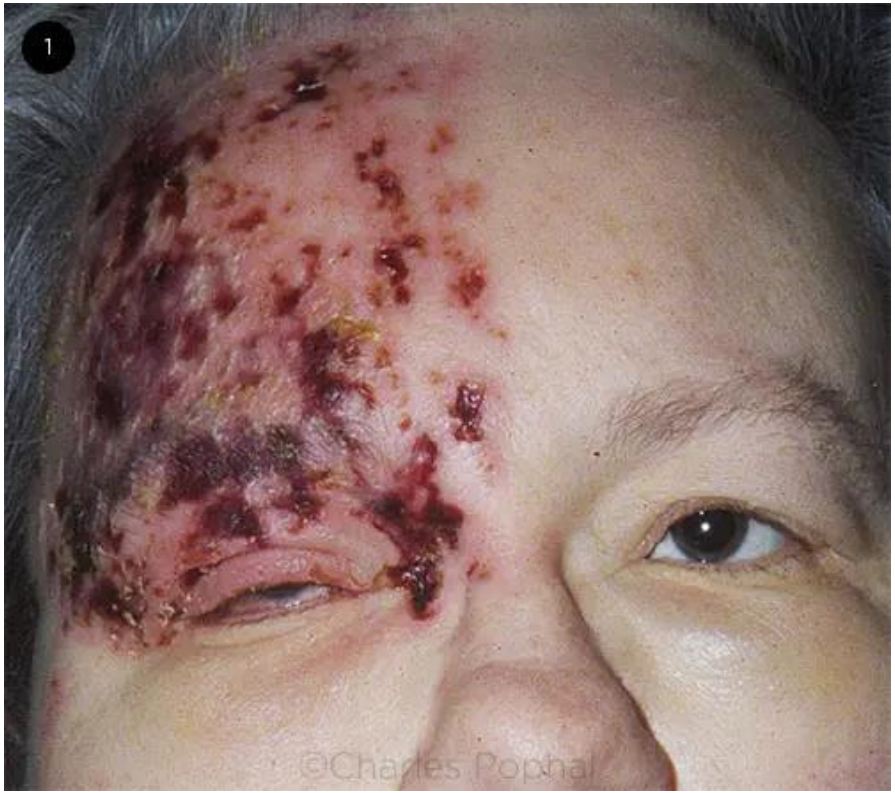
- Varicella zoster virus (VZV)
  - α-herpesviruses family. *Herpes infections for life!*
- Acquired earlier in life as “chickenpox” (varicella)
- Prior to varicella vaccine registration in 1999, **universal** exposure by adulthood (Ward 2007)
- Respiratory → Skin → Sensory nerves
- VZV dormant in dorsal root ganglia
- Reactivation:
  - Ganglionitis
  - Virus travels down nerve to skin
  - Causes characteristic vesicular rash



Why does shingles occur?

- T cell immunity: important to suppress virus throughout life. Antibodies / B cells not protective
- Immunosenescence: Weakening of immune function with age
- Risk factors:
  - Increasing age
  - Immunocompromising conditions especially impaired T cell function e.g. HIV, haematological malignancy, stem cell transplant
  - Immunosuppressive treatments: steroids, biologics, DMARDs
- Other triggers: Stress, intercurrent infection

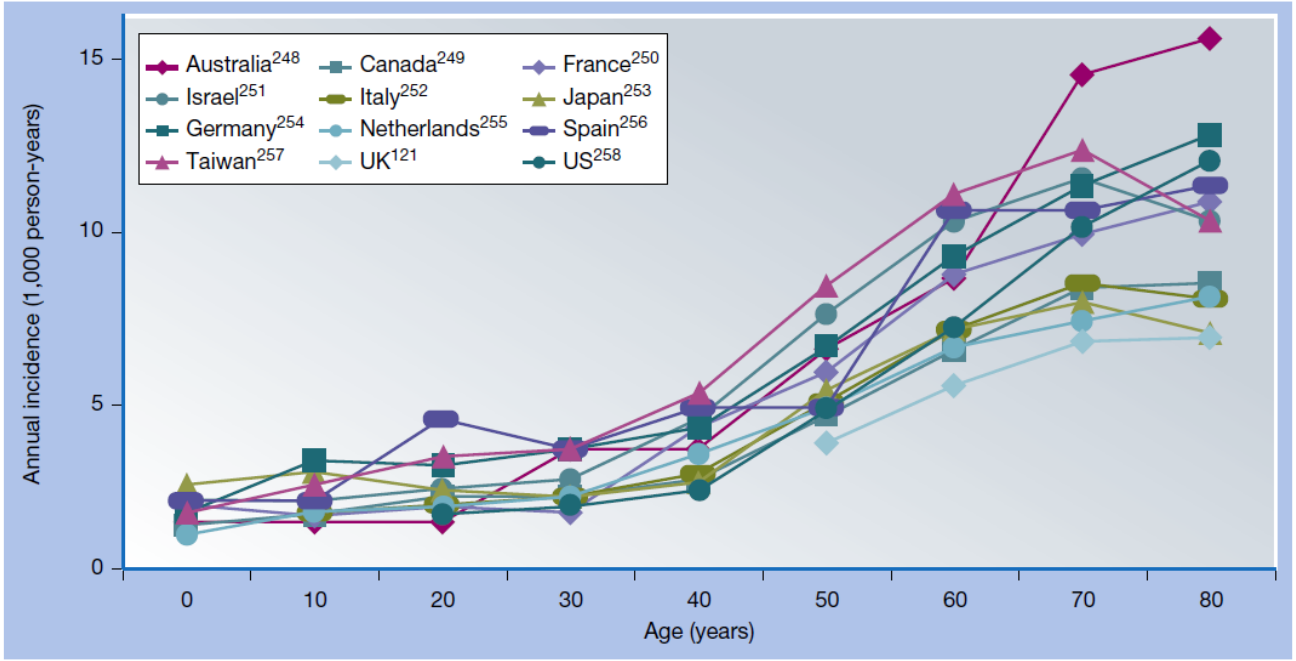
Complications



- Herpes zoster ophthalmicus
  - Cranial nerve II, III or Ophthalmic branch of V
  - Inflammation of multiple structures of eye
  - Risk of blindness

How commonly does shingles occur?

- Lifetime risk is 20-30%
- 50% of 85 year olds will have had shingles (Cohen 2013)
- **Annual** incidence in Australia (MacIntyre 2015)
  - **50–59 years**: 6.3 per 1,000 population
  - **>70 years**: 15-20 per 1,000 population



Incidence of HZ by age (Zoster Vaccine Chapter Plotkin's Vaccines 8th Ed 2022. Fig 66.2)

Risk increases from ~50 years old

Recombinant zoster vaccine – Shingrix (GSK)

- Subunit **glycoprotein E** vaccine with **AS01B adjuvant system**

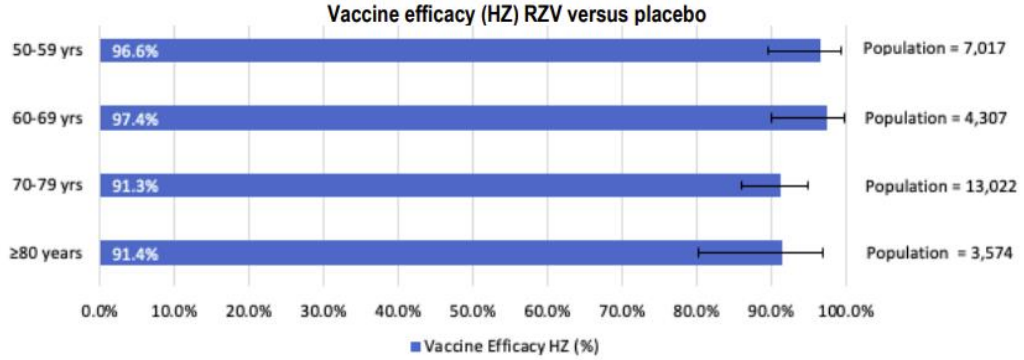
- Registered from 50 years in immunocompetent; from 18 years in immunocompromised
- 2 dose schedule. 2-6 month interval. (1-2 months in immunocompromised)

- NIP funded from 1 Nov 2023: A 2-dose course of Shingrix® will be available for free for:
  - people aged 65 years and older
  - First Nations people aged 50 years and older
  - immunocompromised people aged 18 years and older with the following medical conditions:
    - haemopoietic stem cell transplant
    - solid organ transplant
    - haematological malignancy
    - advanced or untreated HIV

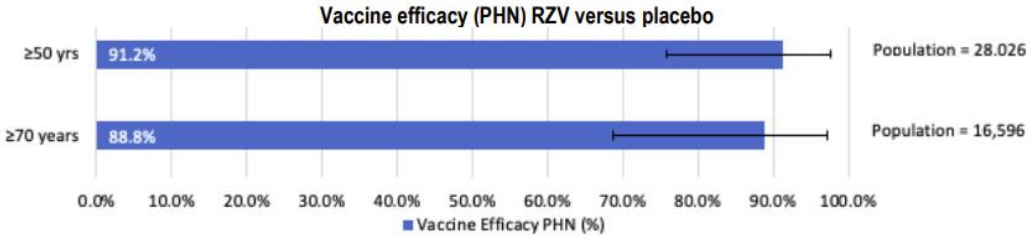
Shingrix – vaccine efficacy

Shingrix has high efficacy against both HZ (91-97%) and post-herpetic neuralgia (89-91%); Works equally well in the elderly

Vaccine efficacy against confirmed herpes zoster (HZ)
Assessed with: PCR/blinded ascertainment committee confirmed
[VE = (1-RR)x100]
follow up: range 3.2 years to 3.7 patient years
№ of participants: 27922 (2 RCTs)



Vaccine efficacy against post-herpetic neuralgia (PHN)
Assessed with: Worst pain score ≥3 on ZBPI for pain developing / persisting >90 days post rash onset
[VE = (1-RR)x100]
follow up: mean 3.8 years
№ of participants: 27,916 (2 RCTs)



https://ncirs.org.au/sites/default/files/2021-07/Shingrix%20vs%20Placebo%20Immunocompetent%20Adults%20GRADE_FINAL.pdf

Shingrix duration of protection

- **At 10 years**: Immunogenicity studies show that antibody levels, and cell mediated immunity remain 6x and 3.5x higher than baseline respectively.(Hastie 2020)
- Modelling to **20 years** predicts immunogenicity still higher than baseline. (Hastie 2020)
- But **no established correlate of protection**.
- Booster dose at 10 years leads to good immune response but ? if required.
- Vaccine efficacy remaining 84-85% for years 6, 7, and 8 after vaccination. (Boutry 2022)

Shingrix has higher rates of post-vax reactions

- **Zostavax**: Similar to other vaccines in older adults (Oxman 2005)
  - 48.3% have a reaction at the injection site
    - Pain: 36%
    - Redness: 35%
  - Systemic side effects in 25% (e.g. muscle aches, fatigue)

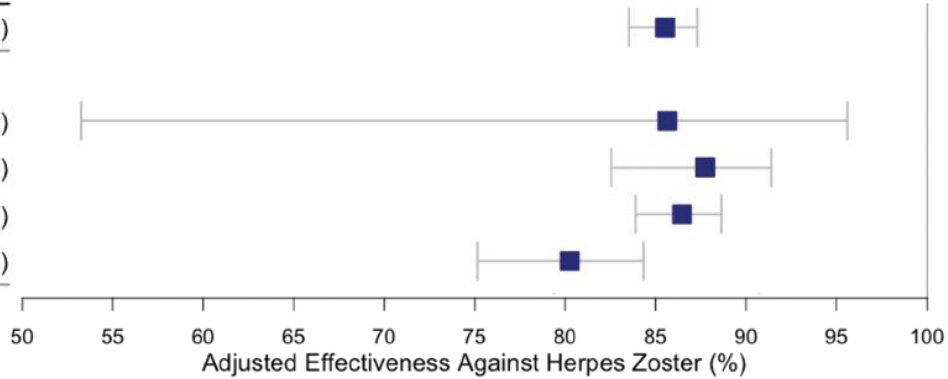
- **Shingrix**: Generally more reactogenic than other adult vaccines (Lal 2015, Cunningham 2016)
  - 74-82% had a reaction at the injection site
    - Pain: 69-79%
    - Redness: 38%
  - Systemic side effects in 53-66%

Summary of main differences between Zostavax and Shingrix

- Shingrix remains efficacious in very elderly
- **Waning of protection is less with Shingrix**
- Shingrix can be given to severely immunocompromised individuals (It is preferred for all immunocompromised)
- Shingrix requires 2 doses
- Local adverse reactions are prominent with Shingrix and may affect completion of the 2-dose schedule

Real world effectiveness of Shingrix

Subgroup[a]	Unadjusted Vaccine Effectiveness (95% CI)	Adjusted Vaccine Effectiveness[b] (95% CI)
Overall	68.3 (64.4, 71.7)	85.5 (83.5, 87.3)
Age		
Ages 50-59	74.3 (20.3, 91.7)	85.6 (53.3, 95.6)
Ages 60-69	75.5 (66.8, 81.9)	87.7 (82.5, 91.4)
Ages 70-79	69.4 (64.3, 73.8)	86.5 (83.9, 88.6)
Ages 80+	60.2 (51.1, 67.6)	80.3 (75.1, 84.3)



- Healthcare claims database study confirmed **VE 80-88% across all ages**. (Sun 2021)

- **2 doses needed for good protection.** (Izurieta 2021)
  - VE 70.1% for 2 doses
  - VE 56.9% for 1 dose

Median follow-up 7 months

Practice Points

- **Shingrix can be given in patients who have previously had shingles.** Recurrent shingles can occur, especially in immunocompromised.
  - Aim for 12m interval for immunocompetent and 3m interval for immunocompromised.
- **Shingrix can be given in patients in patients who have previously had Zostavax.**
  - Aim for 12m separation from Zostavax.
- **Knowledge of / serology for previous chickenpox is not required prior to Shingrix**. >97% of ≥30 y.o. will have had VZV exposure.

Practice Points

- **Coadministration with influenza or COVID-19 vaccines is acceptable**, but if possible, separate vaccines to avoid confusion regarding adverse events

- **Patients who present >6 months since their first Shingrix dose do not need to restart the schedule**.
  - Discuss with GP if concerned about prolonged period between doses

When should people be vaccinated?

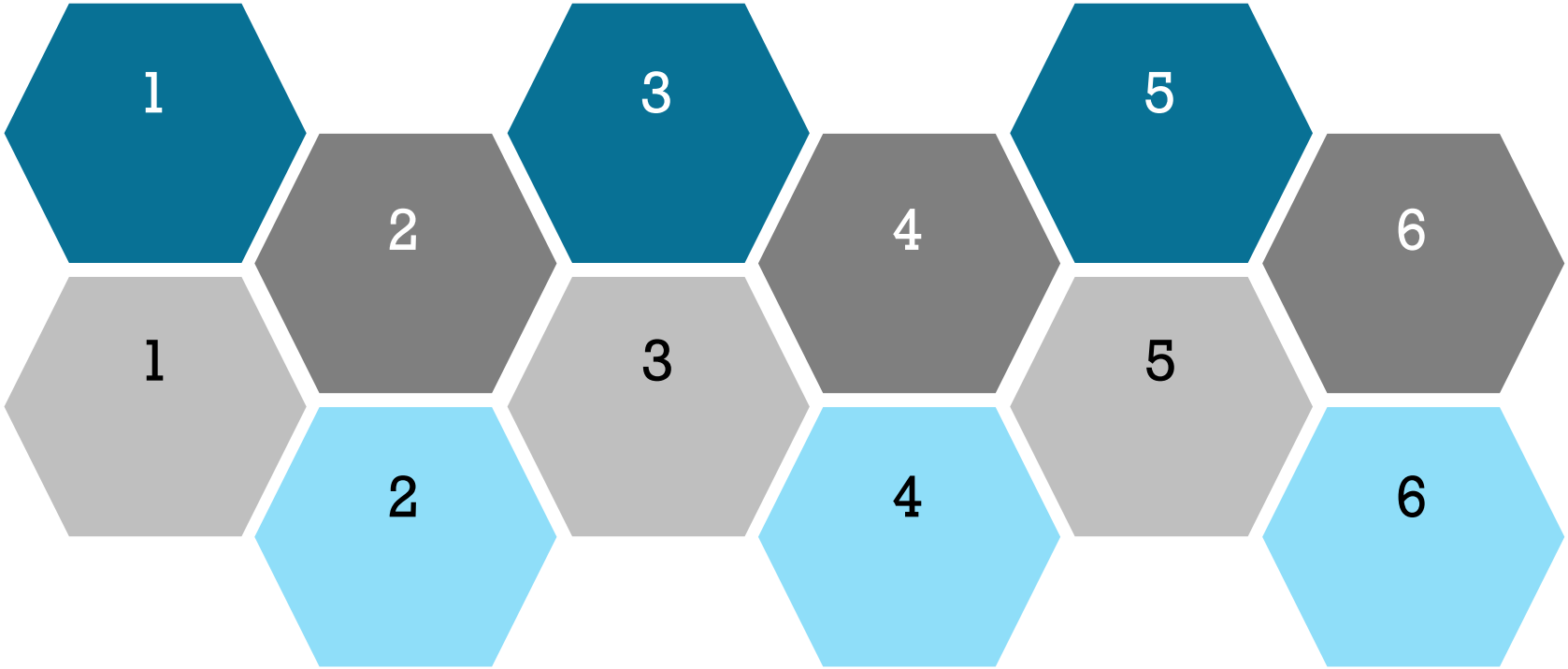
- Immunocompetent adults eligible from 50y (but free from 65yrs + in non-Indigenous patients)
- Immunocompromised adults eligible from 18y
- Balance the increasing risk of shingles with increasing age vs waning of protection
  - Earlier vaccination at a younger age when Shingles risk is lower, may mean protection has waned when patient is older and at increased risk of Shingles.
- In immunocompromised, GP discussion advised
- Consider patient preference

Vaxelis- the alternate to Infanrix Hexa

Reminder: Vaxelis / DT5aP-HBV-IPV-Hib(PRP-OMP)

- TGA approval 22 March 2022
- Added to NIP from 1 July 2023: "alternative vaccine" (Infanrix hexa)
- Dosage and administration:
  - 0.5mL IM
  - Pre-filled syringe: Liquid suspension ---> No reconstitution required
  - Can be given from 6 weeks of age
  - Minimum interval between primary doses: 1 month
- Contraindication:
  - History of anaphylaxis to vaccine component

6 general facts and 6 disease-specific facts



General fact 1: 12 antigens in Vaxelis

1. Diphtheria toxoid
2. Tetanus toxoid
3. Pertussis toxoid (PT)
4. Pertussis filamentous haemagglutinin (FHA)
5. Pertussis pertactin (PRN)
6. Pertussis fimbriae type 2 (FIM2)
7. Pertussis fimbriae type 3 (FIM3)
8. Hepatitis B
9. Polio type 1
10. Polio type 2
11. Polio type 3
12. Hib polyribosyl ribitol phosphate (PRP)

Compared to Infanrix hexa: 10 antigens – the basis of head-to-head comparisons between the 2 vaccines.

General fact 2: Widespread use in other countries

- European Union
  - Longest history of use, approved by EMA in Feb 2016
- USA
  - Licenced in 2018
  - Commercially available since June 2021
- UK
  - Registered in January 2021

Table 2.3-2 Countries using Vaxelis and number of doses supplied from May 2017 to 31 Dec 2020

	2017	2018	2019	2020	Cumulative
Germany	73,703	318,284	410,931	391,792	1,194,710
Spain	138,896	488,017	493,439	679,928	1,800,280
Italy	9,630	108,827	202,722	228,062	549,241
France	0	54,687	159,546	237,301	451,534
Netherlands	0	388,820	712,304	523,077	1,624,201
Greece	0	0	9,882	31,820	41,702
Switzerland	0	0	5,553	57,944	63,497
DOSES TOTAL (million)	**222,229**	**1,358,635**	**1,994,377**	**2,149,924**	**5,725,165**

- Considered to have a good safety profile overall
  - No specific safety concerns
  - Millions of doses co-administered with other vaccines – including influenza

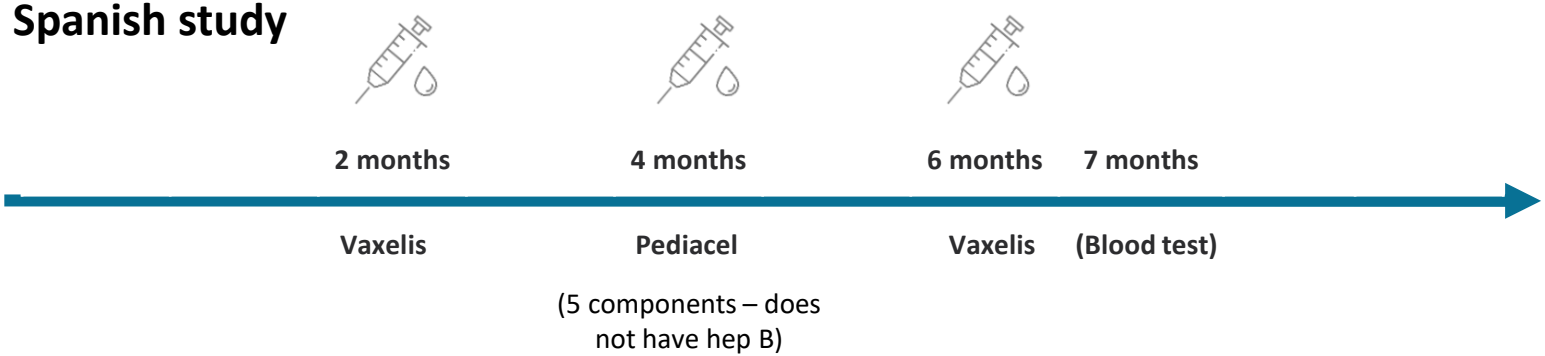
- General fact 3: Co-administration with NIP vaccines (Recommendation: Vaxelis can be co-administered with NIP vaccines at each schedule point)

- General fact 4: Co-administration with Bexsero (Recommendation: Vaxelis can be co-administered with Bexsero)
  - Does the Hib component of **Vaxelis** interfere with immune response to Bexsero?
    - Vaxelis: Hib PRP protein conjugated to outer membrane protein of meningococcal B (PRP-OMP)
    - After dose 1 Bexsero: **Vaxelis** group had slightly higher immunogenicity to all 3 men B antigens
    - After dose 2 Bexsero: **Infanrix hexa** group had slightly higher immunogenicity to 2 out of 3 men B antigens
    - Sample sizes too small to know if statistically significant

General fact 5: Interchangeability

(Recommendation: Vaxelis interchangeable with Infanrix hexa if required)

- **1 Spanish study**



  - At 7 months: adequate levels of antibodies to **all 6 components** of Vaxelis (including hep B)

- **1 paper from Sicily**
  - Describes a gradual changeover process from using Infanrix hexa to Vaxelis for the entire island using a mixed-schedule approach: took 4 years to complete

General fact 6: Aluminium

- **Aluminium adjuvants:**
  - Same chemical composition in Vaxelis and Infanrix hexa but different quantities
  - Aluminium phosphate
    - Vaxelis: Al^{3+} content **0.17mg**
    - Infanrix hexa: Al^{3+} content **0.50mg**
  - Aluminium hydroxyphosphate sulfate
    - Vaxelis: Al^{3+} content **0.15mg**
    - Infanrix hexa: Al^{3+} content **0.32mg**

Disease facts:

- Disease-specific fact 1: Diphtheria: no difference between Infanrix-hexa and Vaxelis
- Disease-specific fact 2: Tetanus: excellent immunogenicity
- Disease-specific fact 3: Hepatitis B: long lasting protection
- Disease-specific fact 4: Polio: **Both Vaxelis and Infanrix hexa offer excellent protection against all 3 poliovirus subtypes**
- Disease-specific fact 5: *Haemophilus influenzae* type b: **Vaxelis performs well in children with additional risk factors for severe Hib disease**

Disease-specific fact 6: Pertussis

- **5 pertussis antigens** in Vaxelis vs **3 pertussis antigens** in Infanrix hexa
  - Is this better? ("Broader protection") ==> We don't know!
  - Lower quantities of each antigen in Vaxelis compared to Infanrix hexa
    - Is this worse? ==> We don't know!

Take home message: 5 antigens aren't necessarily better than 3

Antigen	Quantity in Vaxelis	Quantity in Infanrix hexa	Higher antibody titre 1 month after 3 doses	Higher antibody titre at 13 months of age	Higher antibody titre at 4-5 years of age
Pertussis toxoid (PT)	20 µcg	**25 µcg**	**Vaxelis**	No significant difference	**Vaxelis**
Filamentous haemagglutinin (FHA)	20 µcg	**25 µcg**	**Infanrix hexa**	**Infanrix hexa**	**Infanrix hexa**
Pertactin (PRN)	3 µcg	**8 µcg**	**Infanrix hexa**	No significant difference	**Infanrix hexa**
Fimbriae type 2 (FIM2)	**5 µcg**	Nil	n/a	n/a	n/a
Fimbriae type 3 (FIM3)	**5 µcg**	Nil	n/a	n/a	n/a

Allergy & Asthma NETWORK

What is RSV?

RSV is a common respiratory virus. By the time children are 2 or 3 years old, most have been infected by RSV at least once, with few problems. However, for some, the virus can be life-threatening – and the infection sends more babies to the hospital than any other condition.

Who are high-risk people for RSV?

For some, the virus can be life-threatening. High-risk groups include:

- Premature babies in first year of life
- Infants under 6 months
- Children with asthma
- Patients of any age with a weakened immune system or underlying lung or heart problems

Infants are most severely affected by RSV. Signs and symptoms of severe RSV infection in infants include:

- Short, shallow, and rapid breathing
- Struggling to breathe — chest muscles and skin pull inward with each breath
- Cough
- Poor feeding
- Unusual tiredness
- Irritability
- Fever – (temperature above 100 degrees Fahrenheit). Fever may not always be present

Adults/Older Children:

- Congested or runny nose
- Dry cough
- Low-grade fever
- Sore throat
- Sneezing
- Headache

RSV infection can spread to the lower respiratory tract, causing inflammation of the small airway passages entering the lungs. These signs include

- Fever
- Severe cough
- Wheezing
- Rapid breathing or difficulty breathing
- Bluish color of the skin due to lack of oxygen (cyanosis)

www.allergyasthmanetwork.org

Surveillance

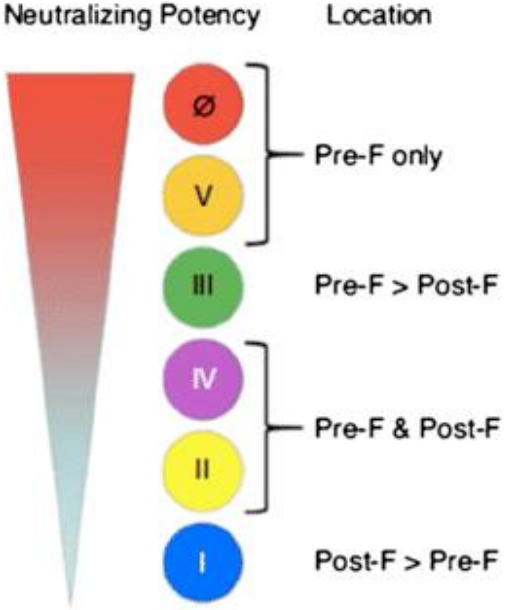
Respiratory syncytial virus (RSV) is the most common cause of respiratory and breathing infections in children. RSV is a common cause of bronchiolitis and pneumonia in children under one year old, and may trigger symptoms in children with asthma.

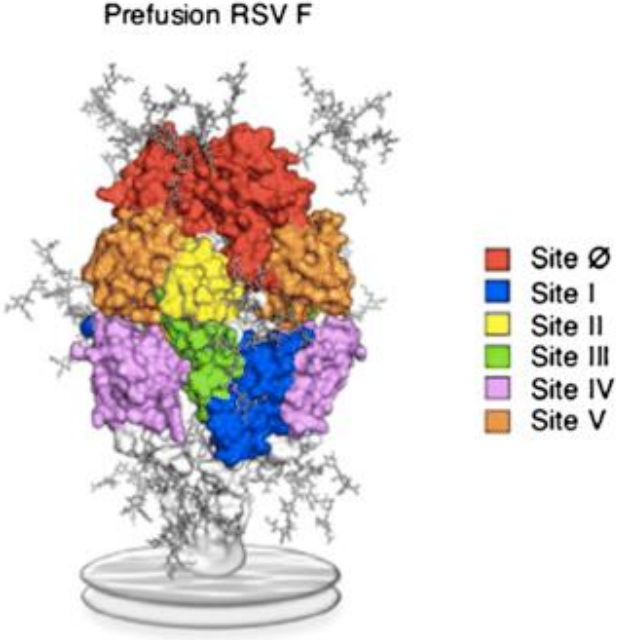
RSV

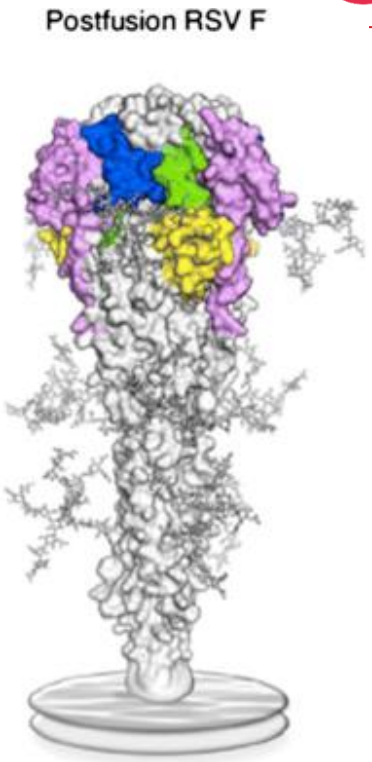
- Current therapeutics
- Vaccination in older adults
- Vaccination of pregnant women
- Long acting monoclonal antibodies in infants

Background

- RSV vaccine development began in the 1960's
  - Formalin inactivated RSV (FI-RSV) vaccine: induced a severe lung inflammatory response [vaccine-associated enhanced response] during the 1st natural RSV infection after vaccination in RSV-naïve infants.
    - 2 deaths
- Discovered that the RSV surface protein "F" rearranges its structure when the virus infects and fuses with a cell.
- Today, vaccines only contain the pre-fusion RSV surface protein; NAID developed a strategy to "lock" the F into its original "pre-fusion" configuration
  - Elicited a higher immune response
  - Protected against a vaccine-associated enhanced response







Current Opinion in Virology

What do we currently use for RSV prevention in Australia?

- Palivizumab
  - Injectable monoclonal antibody
  - Licensed in 1999 for use in high risk infants
  - Requires monthly intramuscular injections ; 5 monthly-doses of palivizumab are recommended during an RSV season
  - Costs ~ $ 8750 per patient

- Who would qualify for Palivizumab?
  - Ex-preterm:
    - History of chronic lung disease
    - Born ≤26 weeks gestation;
  - Infants with comorbidities:
    - **Cardiac**: Infants with haemodynamically significant congenital heart disease between 0 to <6 months age;
    - **Pulmonary**: on respiratory and/or oxygen support.
    - **Neuromuscular:** impaired ability to clear secretions from the upper airways
    - Low immunity: Children <24 months who will be profoundly immunocompromised *may be considered*
  - *Insufficient data are available to recommend palivizumab prophylaxis for children with cystic fibrosis or Down syndrome.*

Upcoming prevention strategies

Vaccination

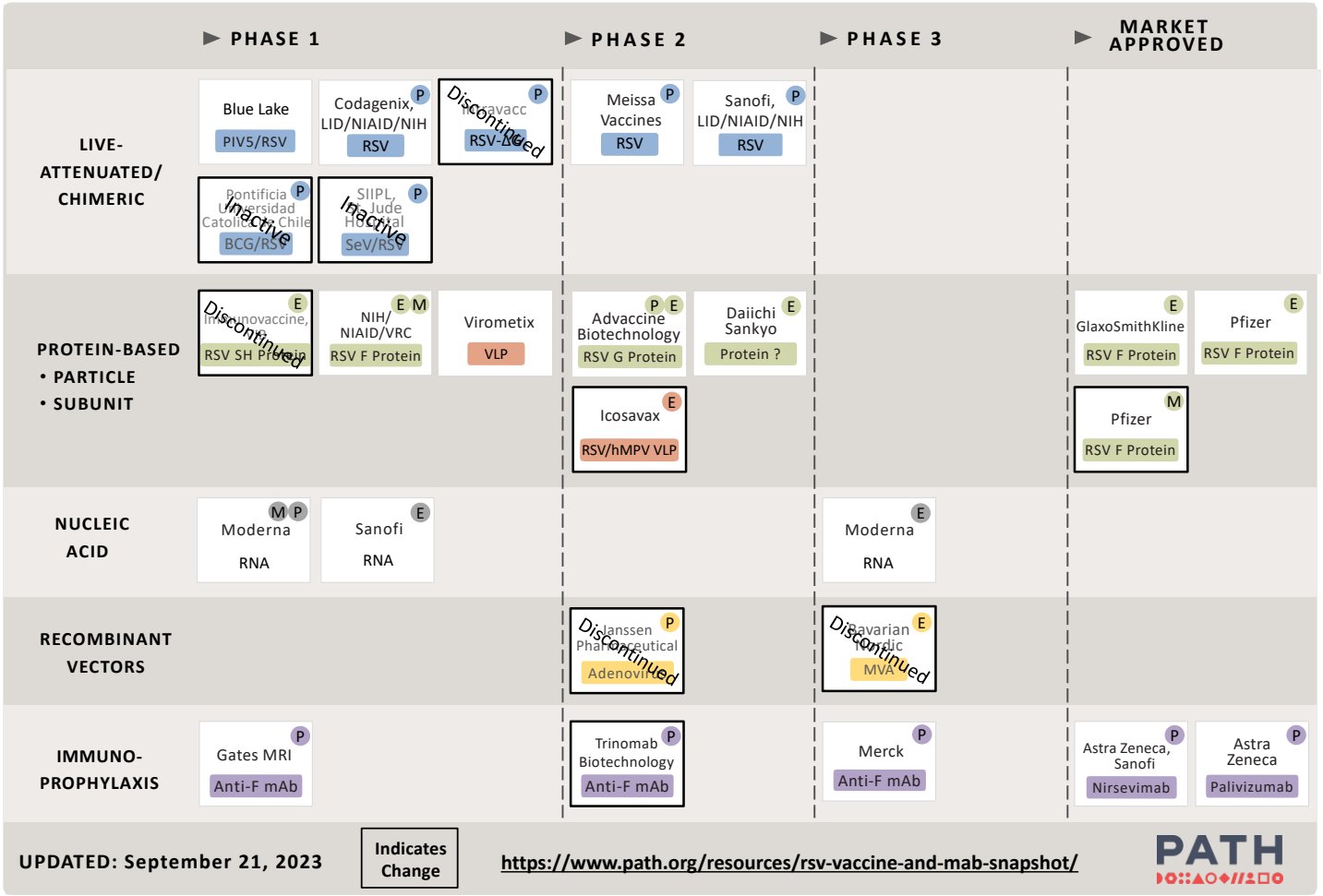
Older adults

Pregnant women

Immunoglobulin

RSV Vaccine and mAb Snapshot

TARGET INDICATION: P=PEDIATRIC M=MATERNAL E=ELDERLY



Vaccines in older adults

Two vaccines have been approved by the FDA and the European Commission

- Pfizer - **ABRYSVO™**
  - **[protein subunit]**

Efficacy and Safety of a Bivalent RSV Prefusion F Vaccine in Older Adults

Edward E. Walsh, M.D., Gonzalo Pérez Marc, M.D., Agnieszka M. Zareba, M.D., Ph.D., Ann R. Falsey, M.D., Qin Jiang, M.S., Michael Patton, B.Sc., Fernando P. Polack, M.D., Conrado Llapur, M.D., Pablo A. Doreski, M.D., Kumar Ilangovan, M.D., Mika Rämet, M.D., Ph.D., Yasushi Fukushima, M.D., Ph.D., et al., for the RENOIR Clinical Trial Group*

- GSK – **AREXVY**
  - **[protein subunit]**

Respiratory Syncytial Virus Prefusion F Protein Vaccine in Older Adults

Alberto Papi, M.D., Michael G. Ison, M.D., Joanne M. Langley, M.D., Dong-Gun Lee, M.D., Ph.D., Isabel Leroux-Roels, M.D., Ph.D., Federico Martinon-Torres, M.D., Ph.D., Tino F. Schwarz, M.D., Ph.D., Richard N. van Zyl-Smit, M.D., Ph.D., Laura Campora, M.D., Nancy Dezutter, Ph.D., Nathalie de Schrevel, Ph.D., Laurence Fissette, M.S., et al., for the AReSVi-006 Study Group*

What is the evidence?

- Clinical Trials
  - Looked at: *Definitions varied between trials:*
    - Acute Respiratory Infection (ARI)
    - Lower Respiratory Tract Infection (LRTI)
    - Severe Lower Respiratory Tract Infection (SLRTI)
  - Adverse events following vaccinations

- Post marketing surveillance (nil data available)

- Co-administration with other vaccines

Older adults – clinical trial outcome definitions

	GSK (Arexvy®) RSVPreF3-AE01 [1*]	Pfizer Abrysvo® RSVPreF [2,3**]	Moderna RSV mRNA-1345 [4]
N participants Vaccine (n, %) Placebo (n, %)	N= 24,960 (2 full seasons) RSVPreF3 (12,466, 49.9%) Placebo (12,494, 50.1%)	N=32,614 RSVpreF (16,306, 50.0%) Placebo (16,308, 50.0%)	N=35,541 RSVmRNA-1345 (17,793, 50.1%) Placebo (17,748, 49.9%)

Older adults - vaccine efficacy (VE) summary

VE generally higher against more severe outcomes > LRTI > general infection

Vaccine, sponsor, study phase	Age group	VE against RSV-ARI
Arexvy® GSK[1] (RSVPreF3-AE01 adjuvanted) vaccine Phase 3	60 and over	**71.7%** (56.2%, 82.3%); ≥2 sx at **10m**
Abrysvo® Pfizer[2] (RSVPreF unadjuvanted) vaccine Phase 3	60 and over	**62.1%** (37.1%, 77.9%); ≥1 sx at **10m**
RSV mRNA-1345[3] **Moderna** vaccine Phase 2/3	60 and over	Data not yet available.

Adverse events following immunisation

- The most common reactions pain at the injection site (61%), fatigue (34%), myalgia (29%), and headache (27%) (1).

- Grade 3 reactions (severe enough to prevent normal daily activities) occurred in 4% of vaccine recipients.

- 3 inflammatory neurologic events (two cases of Guillain-Barré syndrome, including one case of the Miller-Fisher variant, and one case of undifferentiated motor-sensory polyneuropathy) were reported within 42 days after vaccination among 20,255 investigational vaccine recipients aged ≥60 years,

Additional end points – for LRTI

- RSV subtype:
  - Efficacy similar between RSV A and RSV B differed with different vaccines: Similar for GSK Arexy but some differences with Pfizer Abryso; small numbers

- Age Group:
  - Similar efficacy in 60-69 yrs, 70-79 yrs, 80+ (small numbers in 80+ age group)

- Presence of 2+ comorbidities
  - Efficacy 60-95%; higher for severe disease

Coadministration

- CDC: Acceptable; acknowledging that data is limited
- ? increase local or systemic reactogenicity

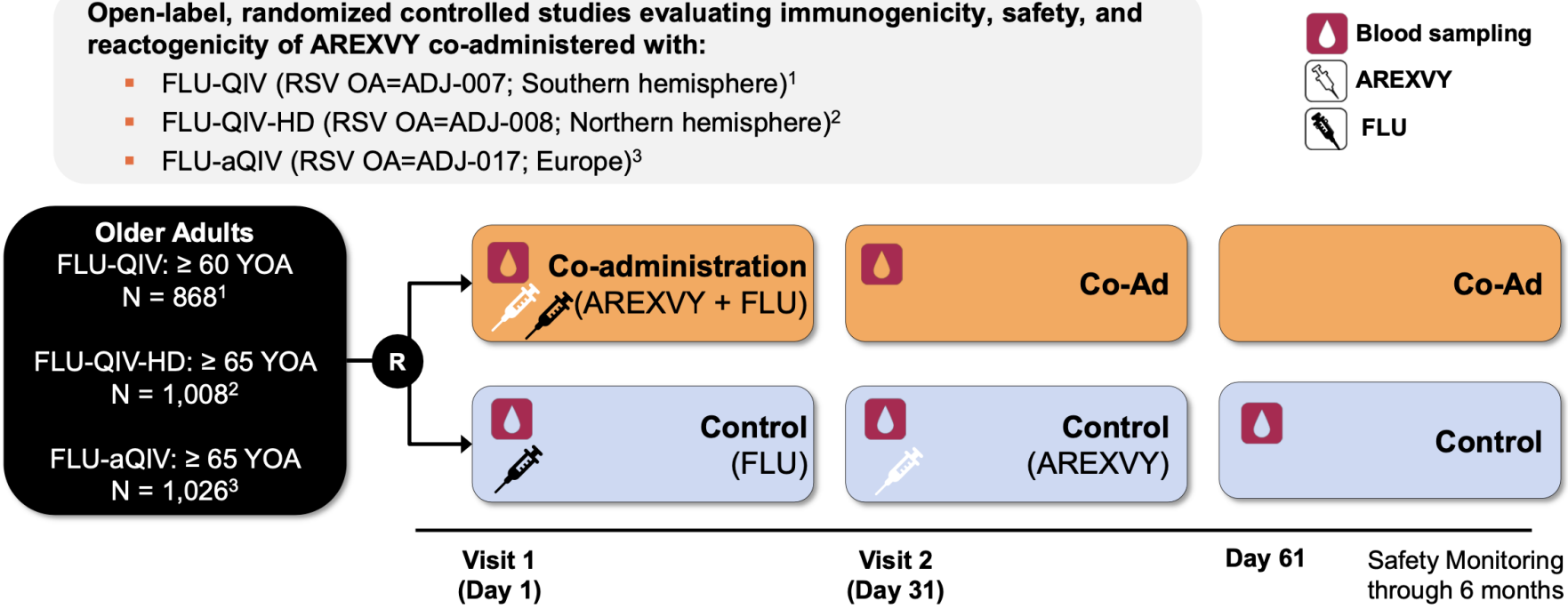
- RSV + Influenza vaccines:
  - Non-inferior for overall immunogenicity
  - RSV and influenza antibody titres were somewhat lower with coadministration; however, the clinical significance of this is unknown.

Co-administration with Flu vaccine

Phase 3 Influenza Vaccine Co-Administration Studies: Designs[1–3]

Open-label, randomized controlled studies evaluating immunogenicity, safety, and reactogenicity of AREXVY co-administered with:

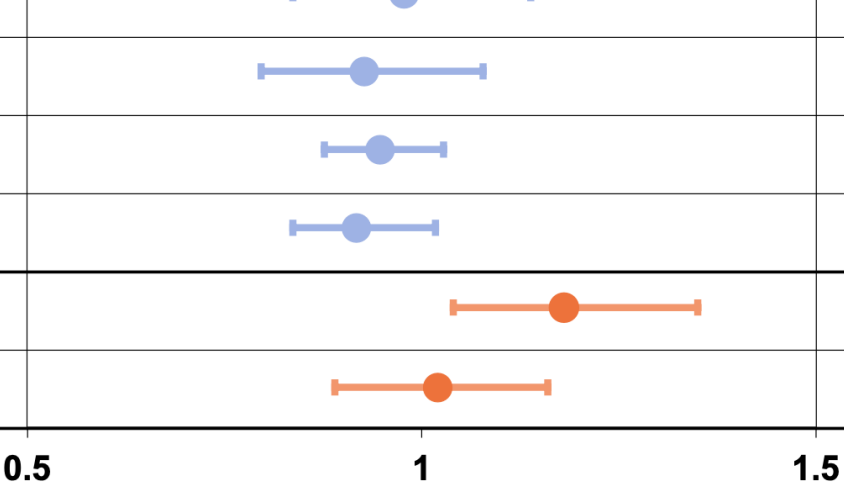
- FLU-QIV (RSV OA=ADJ-007; Southern hemisphere)[1]
- FLU-QIV-HD (RSV OA=ADJ-008; Northern hemisphere)[2]
- FLU-aQIV (RSV OA=ADJ-017; Europe)[3]



Co-Administration of AREXVY and Licensed FLU-QIV-HD

Non-inferior

Antibody	Co-Ad N	Control N	GMT Ratio (Control Over Co-Administration) 1 Month After Vaccination Per Protocol Set	GMT Ratio (95% CI)
Flu A/Darwin H3N2	458	441		**0.98** (0.84, 1.14)
Flu A/Victoria H1N1	452	435		**0.93** (0.80, 1.08)
Flu B/Austria/Victoria	458	441		**0.95** (0.88, 1.03)
Flu B/Phuket/Yamagata	456	441		**0.92** (0.84, 1.02)
RSV-A*	459	358		**1.18** (1.04, 1.35)
RSV-B	459	357		**1.02** (0.89, 1.16)

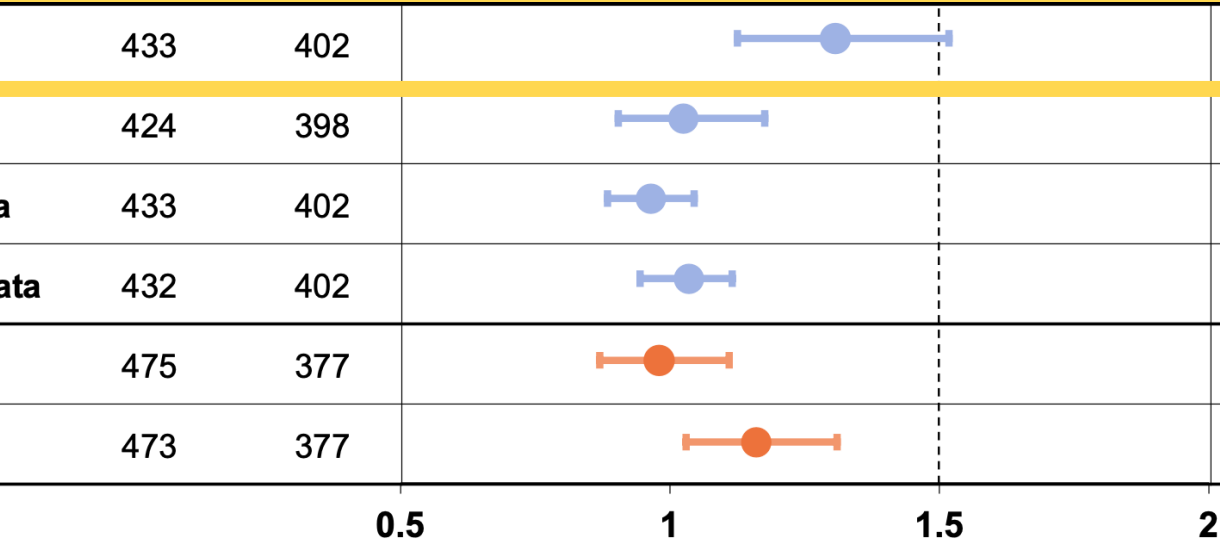


Success Criteria: Upper limit ≤ 1.5 of 2-sided 95% CI for Group GMT Ratio (Control Group divided by Co-Ad Group) for RSV vaccine and for each of FLU vaccine strains

Co-Administration of AREXVY and Licensed Flu-Adjuvanted QIV

GMT Ratio (Control Over Co-Administration)
1 Month After Vaccination
Per Protocol Set

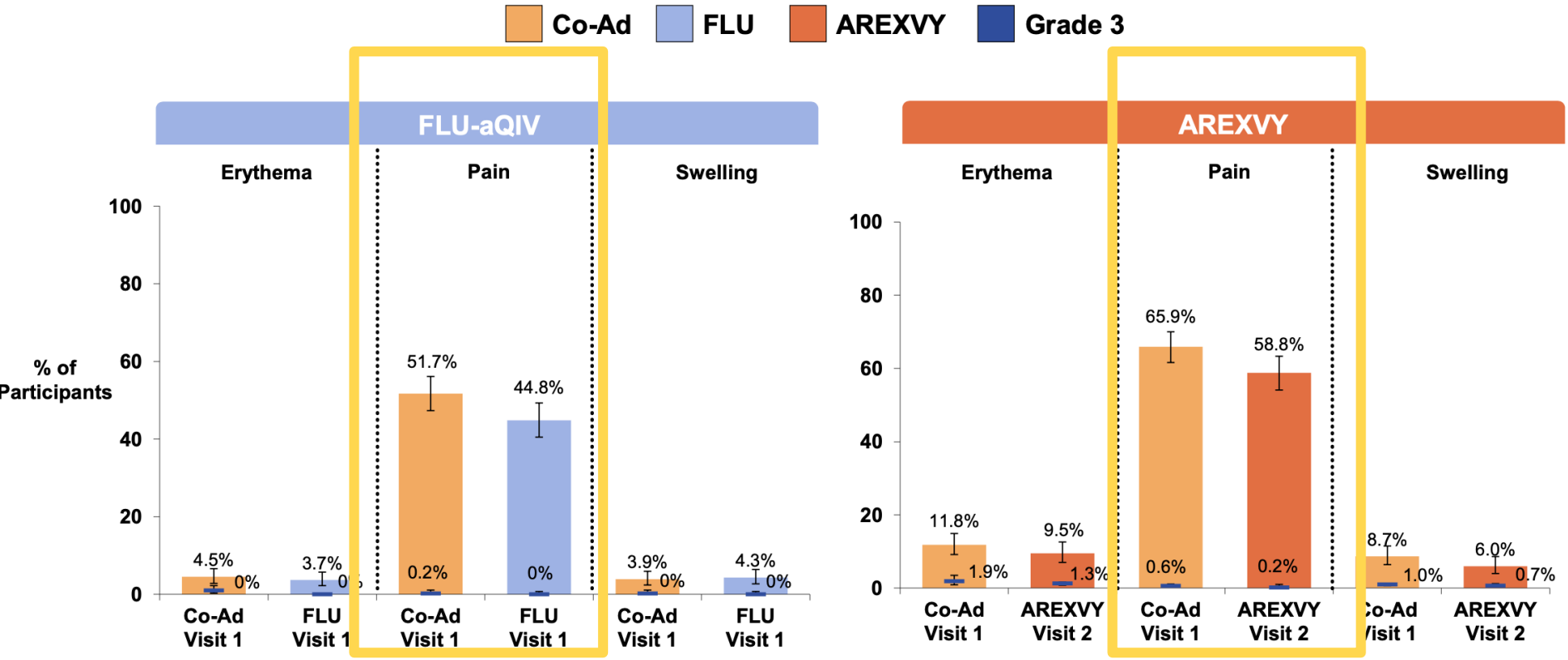
Antibody	Co-Ad N	Control N	GMT Ratio (95% CI)
Flu A/Darwin H3N2*	433	402	**1.31** (1.13, 1.52)
Flu A/Victoria H1N1	424	398	**1.03** (0.91, 1.18)
Flu B/Austria/Victoria	433	402	**0.97** (0.89, 1.05)
Flu B/Phuket/Yamagata	432	402	**1.04** (0.95, 1.12)
RSV-A**	475	377	**0.98** (0.87, 1.11)
RSV-B	473	377	**1.16** (1.03, 1.31)



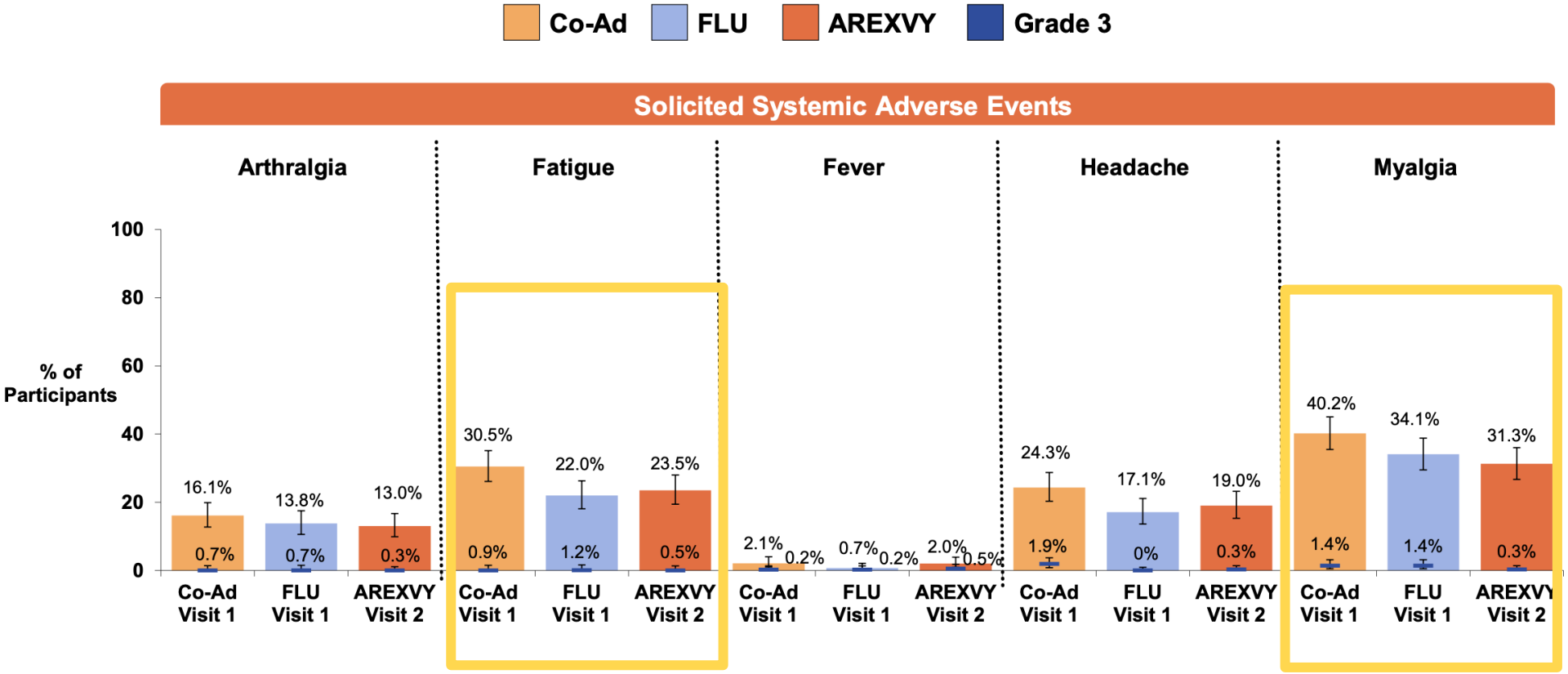
Success Criteria: Upper limit ≤ 1.5 of 2-sided 95% CI for Group GMT Ratio (Control Group divided by Co-Ad Group) for RSV vaccine and for each of FLU vaccine strains

Reactogenecity

Exposed Set: Solicited Local AEs Within 7 Days Post Vaccination



Modified Set: Solicited Systemic AEs Within 4 Days Post Vaccination



Vaccines in pregnancy

1 vaccine has been approved by the FDA and the European Commission

- Pfizer - **ABRYSVO™**
  - **Bivalent vaccine**

Bivalent Prefusion F Vaccine in Pregnancy to Prevent RSV Illness in Infants

Beate Kampmann, M.D., Ph.D., Shabir A. Madhi, M.B., B.Ch., Ph.D., Iona Munjal, M.D., Eric A.F. Simões, M.D., Barbara A. Pahud, M.D., M.P.H., Conrado Llapur, M.D., Jeffrey Baker, M.D., Gonzalo Pérez Marc, M.D., David Radley, M.S., Emma Shittu, Ph.D., Julia Glanternik, M.D., Hasra Snaggs, M.D., et al., for the MATISSE Study Group*

- GSK's **Arexvy –** stopped the Phase 3 trial early due to increase in premature births.
  - Contains adjuvant

What is the evidence?

- Clinical Trials
  - Looked at:
    - Medically attended **severe** RSV-associated Lower Respiratory Tract Infection
    - Medically attended RSV-associated Lower Respiratory Tract Infection
  - Adverse events following vaccinations in mother and baby

- Post marketing surveillance (nil data available)

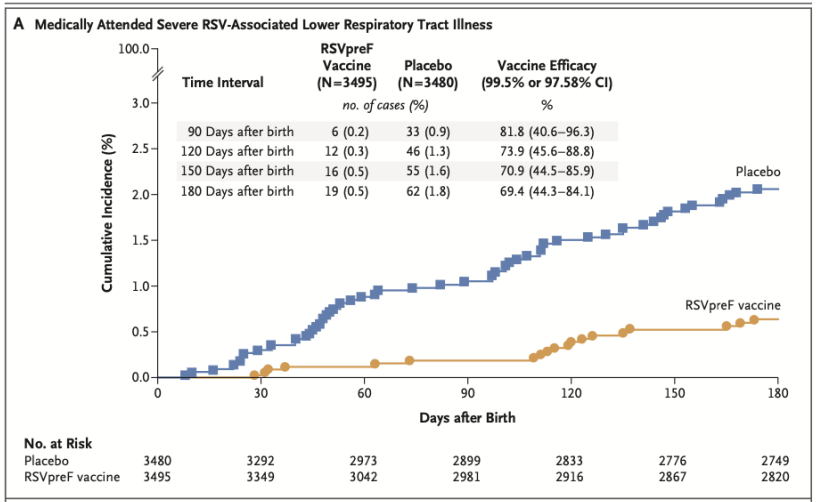
- Co-administration with other vaccines

Clinical Trial:

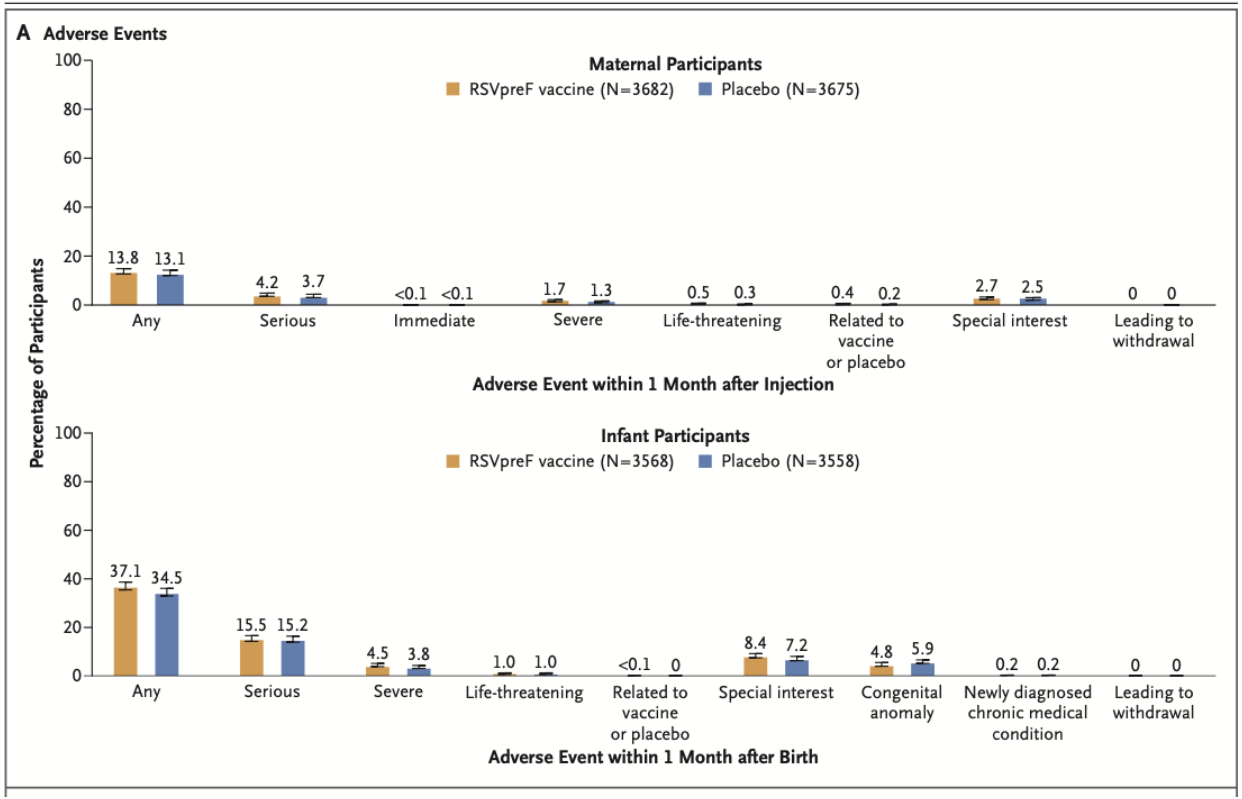
- 7358 women across 18 countries
  - Vaccine given at 24-36 weeks
  - 120 ug RSV preF (60 ug of RSV A and RSV B antigens each)
  - Majority of infants (94%) born at term (37-42 weeks)

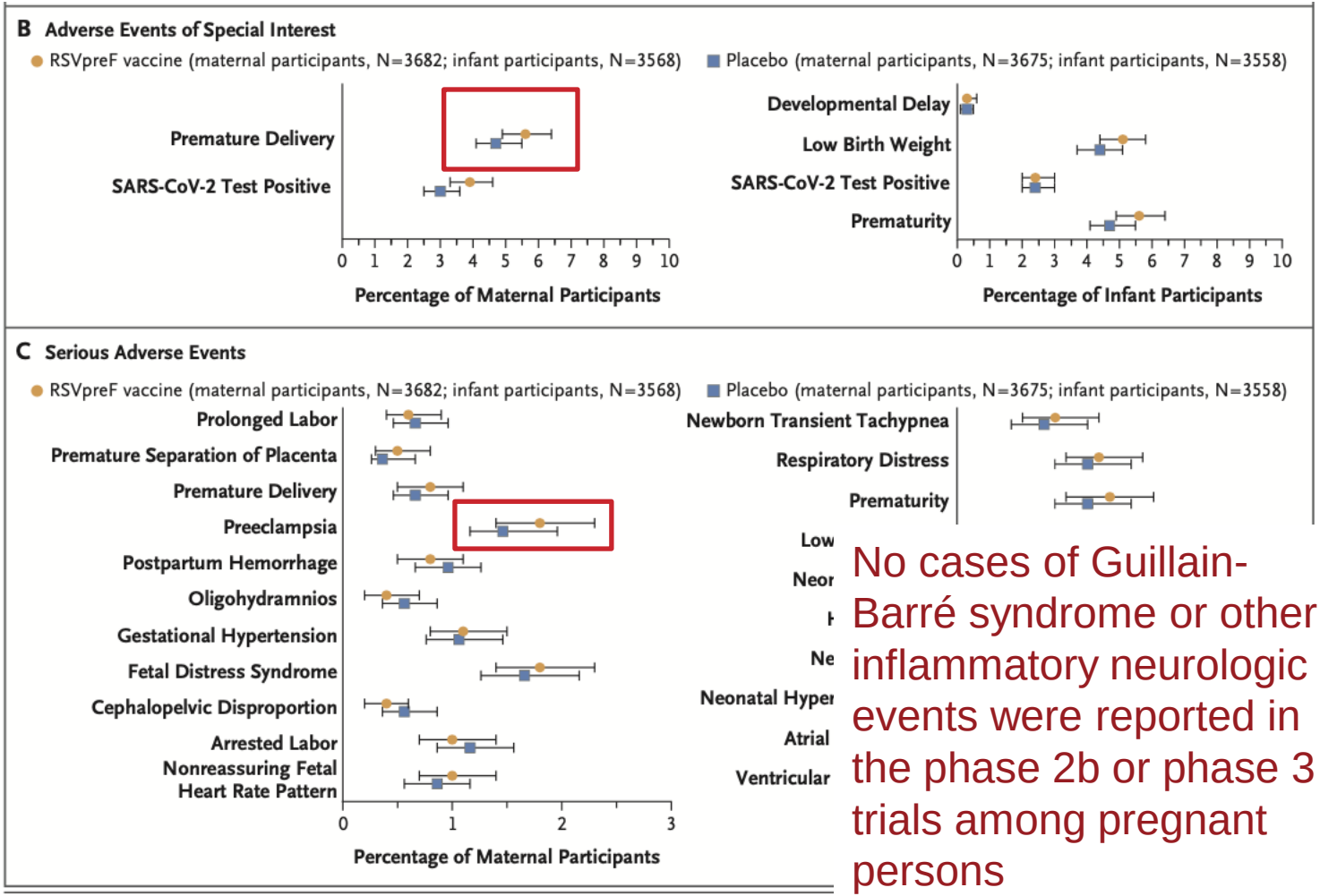
Efficacy: (medically attended)

- 90d;severe disease: VE: 81.8% (99.5% CI 40.6-96.3)
- 180 d; severe disease: VE: 69.4%; (97.58% CI, 44.3 to 84.1)
- 90d; non severe: 57.1%; (99.5% CI, 14.7 to 79.8) *did not meet statistical significance criterion)



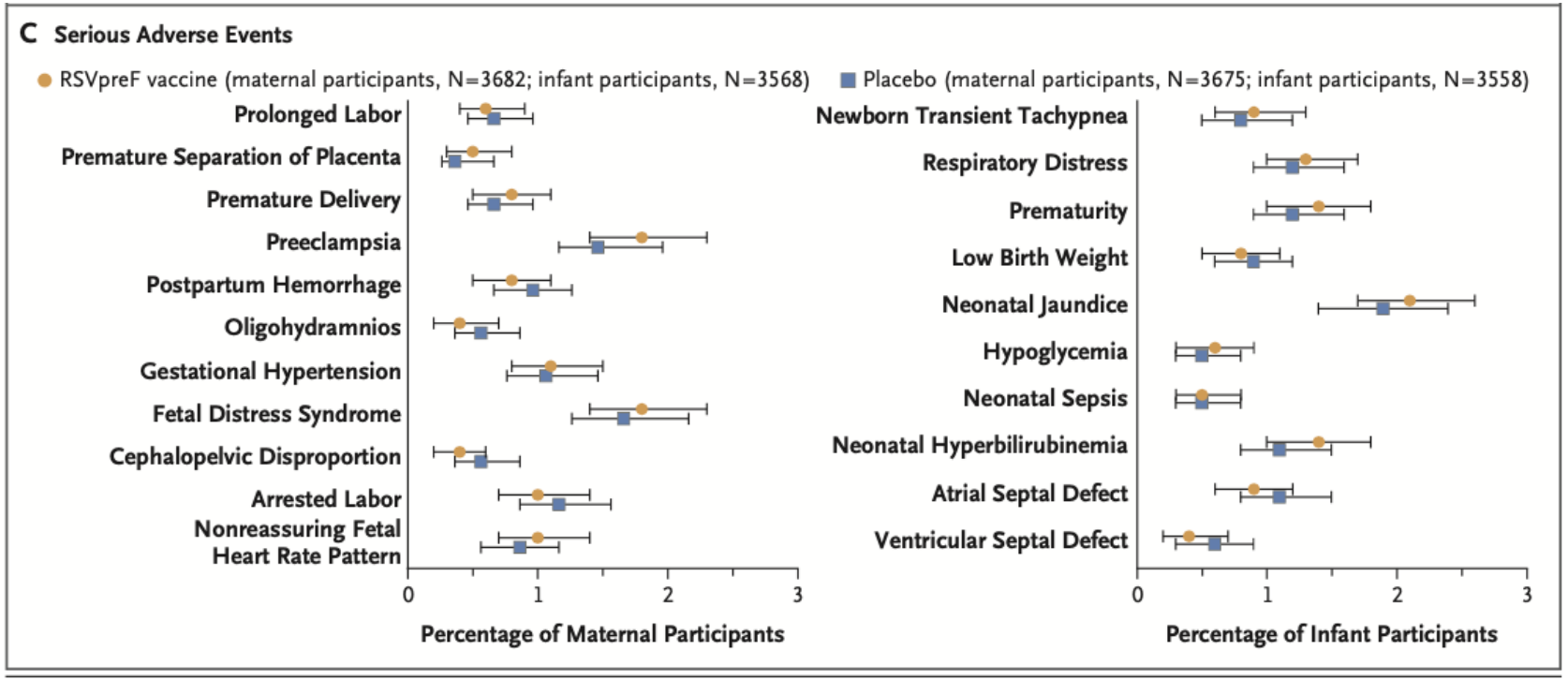
Adverse events following immunisation





No cases of Guillain-Barré syndrome or other inflammatory neurologic events were reported in the phase 2b or phase 3 trials among pregnant persons

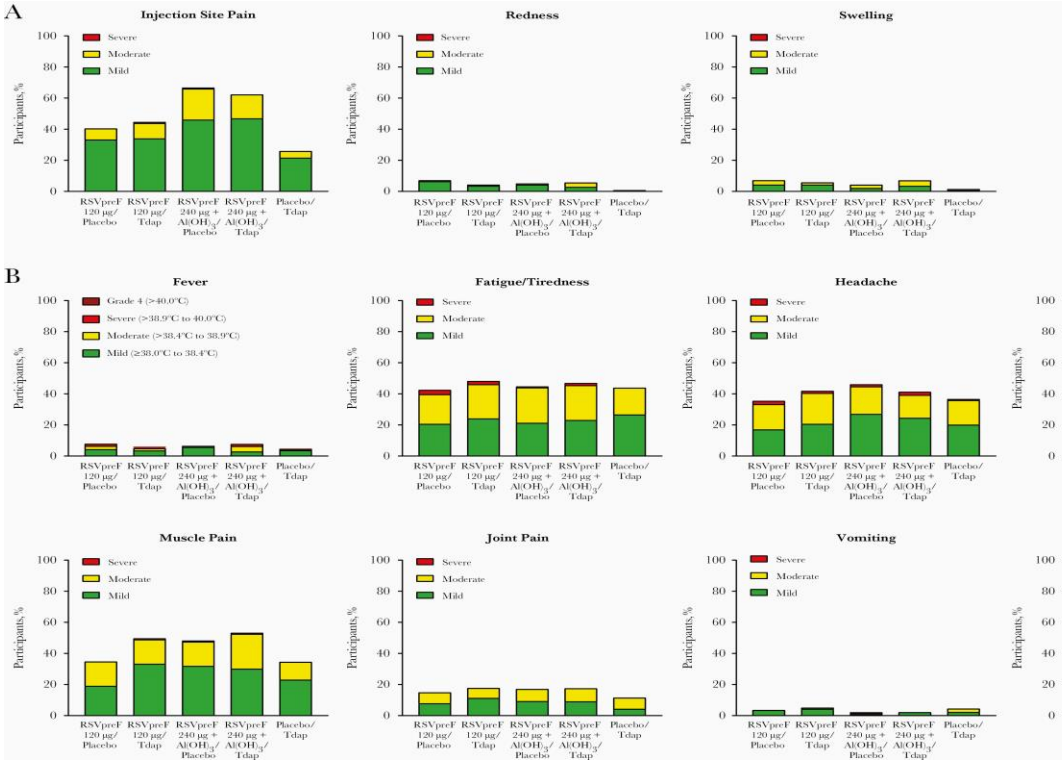
No difference in Serious Adverse Events in mum and bub



Registered for:

- Vaccination between 32 weeks – 36 weeks of pregnancy
- Can be administered to pregnant persons with other recommended vaccines, such as tetanus, diphtheria, and pertussis (Tdap), influenza, and COVID-19 vaccines, without regard to timing, including simultaneous vaccination at different anatomic sites on the same day

Co-admin with dTaP: No difference in solicited AEFIs



JOURNAL ARTICLE

Safety and Immunogenicity of a Respiratory Syncytial Virus Prefusion F Vaccine When Coadministered With a Tetanus, Diphtheria, and Acellular Pertussis Vaccine

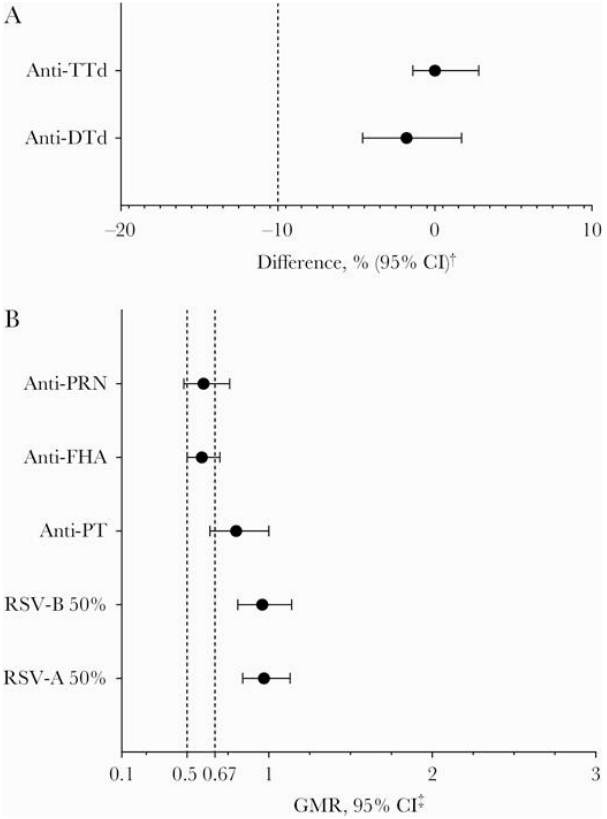
James T Peterson, Agnieszka M Zareba ✉, David Fitz-Patrick, Brandon J Essink, Daniel A Scott, Kena A Swanson, Dhawal Chelani, David Radley, David Cooper, Kathrin U Jansen ... Show more

The Journal of Infectious Diseases, Volume 225, Issue 12, 15 June 2022, Pages 2077–2086, https://doi.org/10.1093/infdis/jiab505

Published: 12 October 2021 **Article history** ▾

Immunogenecity:

- Non-inferior for tetanus
- Response to pertussis occurred post vaccination, but decreased immunogenicity when given combined with RSV compared to ;placebo; unsure of clinical relevance



Long acting monoclonal antibody

- Nirsevimab
  - Produced by AstraZeneca/Sanofi

Nirsevimab

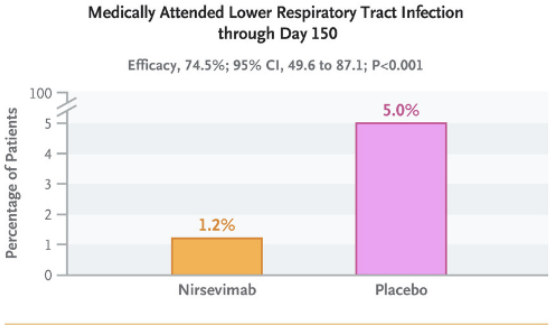
- Nirsevimab is a **monoclonal antibody** with an **extended half-life** to protect infants for an **entire RSV season with a single intramuscular dose**.
- Compares with Palivizumab which requires monthly injections.

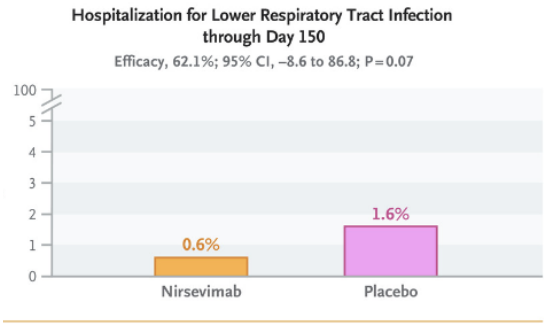
- Nirsevimab targets highly conserved site 0 epitope present on the prefusion conformation of the RSV fusion protein. Improved neutralisation

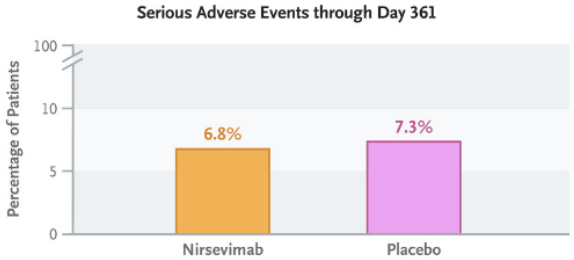
- Fc region modification promotes longer half-life.

Nirsevimab for Prevention of RSV in Healthy Late-Preterm and Term Infants

Laura L. Hammitt, M.D., Ron Dagan, M.D., Yuan Yuan, Ph.D., Manuel Baca Cots, M.D., Miroslava Bosheva, M.D., Shabir A. Madhi, Ph.D., William J. Muller, Ph.D., Heather J. Zar, Ph.D., Dennis Brooks, M.D., Amy Grenham, M.Sc., Ulrika Wählby Hamrén, Ph.D., Vaishali S. Mankad, M.D., et al., for the MELODY Study Group*







Vaccine, sponsor, study phase	Age group	VE against MA-RSV-LRTI	VE against severe MA-RSV-LRTI	VE against hospitalisation
Nirsevimab (mAb against prefusion F protein)[2] Interim Phase 3 analysis	Infants born >35 weeks GA	**74.5%** (49.6 to 87.1) through 150 days post injection		**62.1%**; (−8.6, 86.8) through 150 days post injection
Combined Phase 2b and final Phase 3 analysis[3]	Infants born >35 weeks GA	**79.0%** (68.5%, 86.1%)	**86.2%**[#] (68.1%, 94.0%)	**80.6%** (62.3%, 90.1%)

Nirsevimab

- Shown to be effective at reducing lower respiratory tract disease caused by RSV in three main studies – during their first RSV season.

- **Comparison with placebo** in 1,490 healthy children born prematurely and at term (at 35 weeks gestation or more). In their first RSV season, 1.2% of children (12 out of 994) developed RSV-induced lung disease that required medical attention compared with 5%[1] (25 out of 496) in the placebo group.

- **Comparison with placebo** in 1,453 children born between 29 and 35 weeks gestation). 2.6% of children (25 out of 969) developed RSV-induced lung disease that required medical attention compared with 9.5% (46 out of 484) in the placebo group.

- **Comparison with palivizumab** in children who were either born prematurely, or born at full term but had heart or lung disease which put them at risk of RSV-induced lung disease. 4 children (out of 616) developed RSV-induced lung disease that required medical attention compared with 3 children (out of 309) in the group who had palivizumab.

Safety summary

Nirsevimab: Favorable Safety Profile Across All Infants (2569 Received Nirsevimab)

Safety	Ph2b[1] 29-<35 w GA		MELODY[2] ≥ >35 w GA		MEDLEY[3] Preterm		MEDLEY[3] CHD/CLD	
	Placebo (N=479)	Nirsevimab (N=968)	Placebo (N=491)	Nirsevimab (N=987)	Palivizumab (N=206)	Nirsevimab (N=406)	Palivizumab (N=98)	Nirsevimab (N=208)
Serious adverse events	16.9%	11.2%	7.3%	6.8%	5.3%	6.9%	20.4%	19.2%
Adverse events of Grade 3 or higher	12.5%	8.0%	4.3%	3.6%	3.4	3.4%	13.3%	14.4%
Adverse events of special interest (AESI)	0.6%	0.5%	0%	0.1%	0.0%	0.2%	0.0%	0.5%
Deaths	3	2	0	3	0	2	1	3

- None of the serious adverse events or deaths were considered as related to nirsevimab
- Overall, incidence of nirsevimab antidrug antibody was low across studies with no safety concerns
  - MELODY: single AESI case of hypersensitivity limited to cutaneous signs and symptoms
  - MEDLEY: 2 AESIs (nirsevimab arm): Maculopapular rash (preterm cohort) 92 days post nirsevimab dose and heparin-induced thrombocytopenia (CHD/CLD cohort) unrelated to treatment

sanofi AstraZeneca

1. Hammitt LL,et al N Engl J Med. 2022 Mar 3;386(9):837-846. 2. Domachowske Joseph et al. N Engl J Med 2022 Mar 386:9, 892-894. 3. Griffin MP, et al. N Engl J Med. 2020 Jul 30;383(5):415-425

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- **Nirsevimab (AZ/Sanofi)** is already recommended and approved for use in some countries. It has demonstrated a favourable safety profile
- **Clesrovimab** (MSD) is indicated for use in infants and children and is currently in phase 3 trials with estimated completion in 2025. Phase 1 trials in adults showed no safety concerns with AEs reported in 47.4% MK-1654–treated participants and 42.1% of placebo

ACIP June 2022 - https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2022-06-22-23/05-RSV-Felter-508.pdf

How is nirsevimab being used? (Beyfortus)

- In US:
  - 1 dose of nirsevimab for all infants aged <8 months born during or entering their first RSV season
  - 1 dose of nirsevimab for infants and children aged 8–19 months who are at increased risk for severe RSV disease and entering their second RSV season
  - https://www.cdc.gov/mmwr/volumes/72/wr/mm7234a4.htm#B1_down

- In UK:
  - Recommended for all high risk infants who would have qualified for palivizumab

https://www.sciencedirect.com/science/article/pii/S234128792300217X

Advantages and Disadvantages (US CDC table)

	Maternal RSV preF vaccine	Nirsevimab
Advantages	Provides protection immediately after birth Might be more resistant to potential mutations in F protein (*Maternal RSV vaccination results in a polyclonal immune response, which is expected to be more resistant to potential mutations in the RSV F protein than a monoclonal antibody product*.)	Studies of antibody levels suggest that protection might wane more slowly than protection from the maternal RSV vaccine Assures direct receipt of antibodies rather than relying on transplacental transfer No risk for adverse pregnancy outcomes
Disadvantages	Protection potentially reduced if fewer antibodies are produced or are transferred from pregnant person to baby (e.g., pregnant person is immunocompromised or infant born soon after vaccination) Potential risk for preterm birth and hypertensive disorders of pregnancy	Potentially limited availability during 2023–24 RSV season Requires infant injection

https://www.cdc.gov/mmwr/volumes/72/wr/mm7241e1.htm#B1_down

What is happening in Australia

- TGA reviewing the vaccines and monoclonal antibodies
- ATAGI will review and provide guidance.

- Opportunity to review post marketing surveillance studies from US and Europe.

National Centre for Immunisation Research and Surveillance

Thank you! Any Questions?

archana.Koirala@health.nsw.gov.au