IMMUNISATION COALITION

New technology vaccines: Safety and efficacy

3:40 pm

Prof Margie Danchin

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New vaccine technology - safety and efficacy?

Immunisation Coalition Conference 5th Feb 2024

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Outline

- Review vaccine technology, safety and efficacy
  - mRNA vaccines in the pipeline
  - Pre-fusion F protein RSV vaccines
    - Older adults
    - Babies
      - Vaccines (maternal product)
      - Immunization with monoclonal antibody (infant product)

- New needle free dermal high density vaccine microarray patches

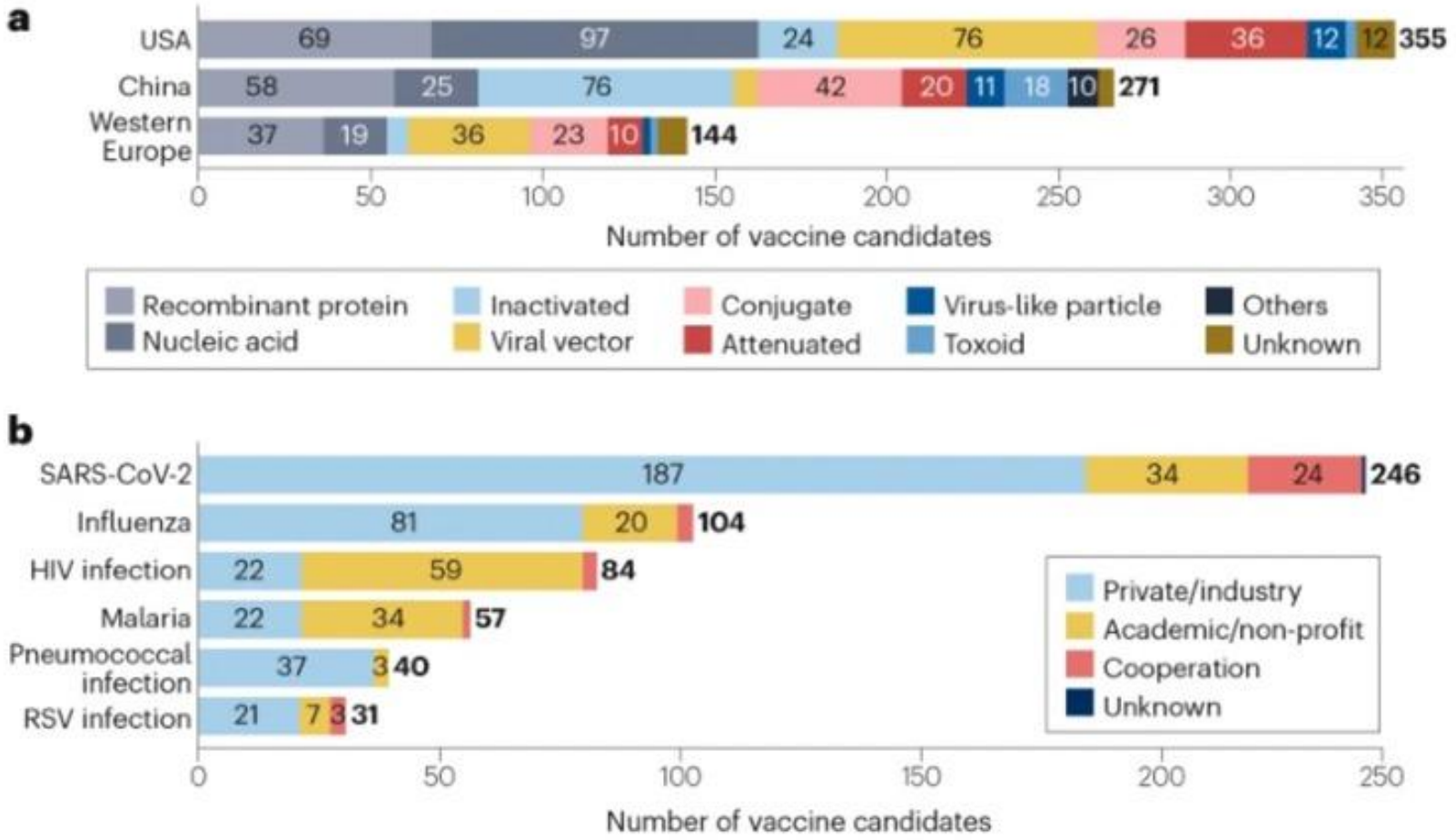


Fig. 2 | Distribution of vaccine candidates by geographic location and type of developer. **a**, Vaccine candidates with developers from the USA, China and western Europe, categorized by technical platform. **b**, Candidates for the top six diseases for vaccine development, by type of developer. See Supplementary information for details.

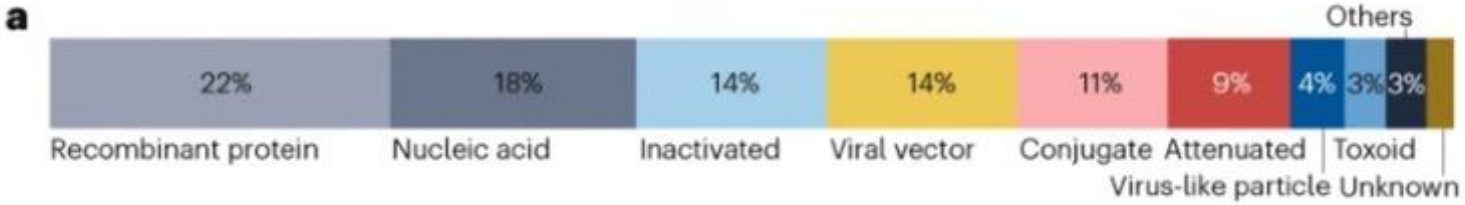
US/China/W Europe - Strong R&D capabilities and regulatory policy support

Only 25% developed by academic or other non-profit organizations

The R&D landscape for infectious disease vaccines

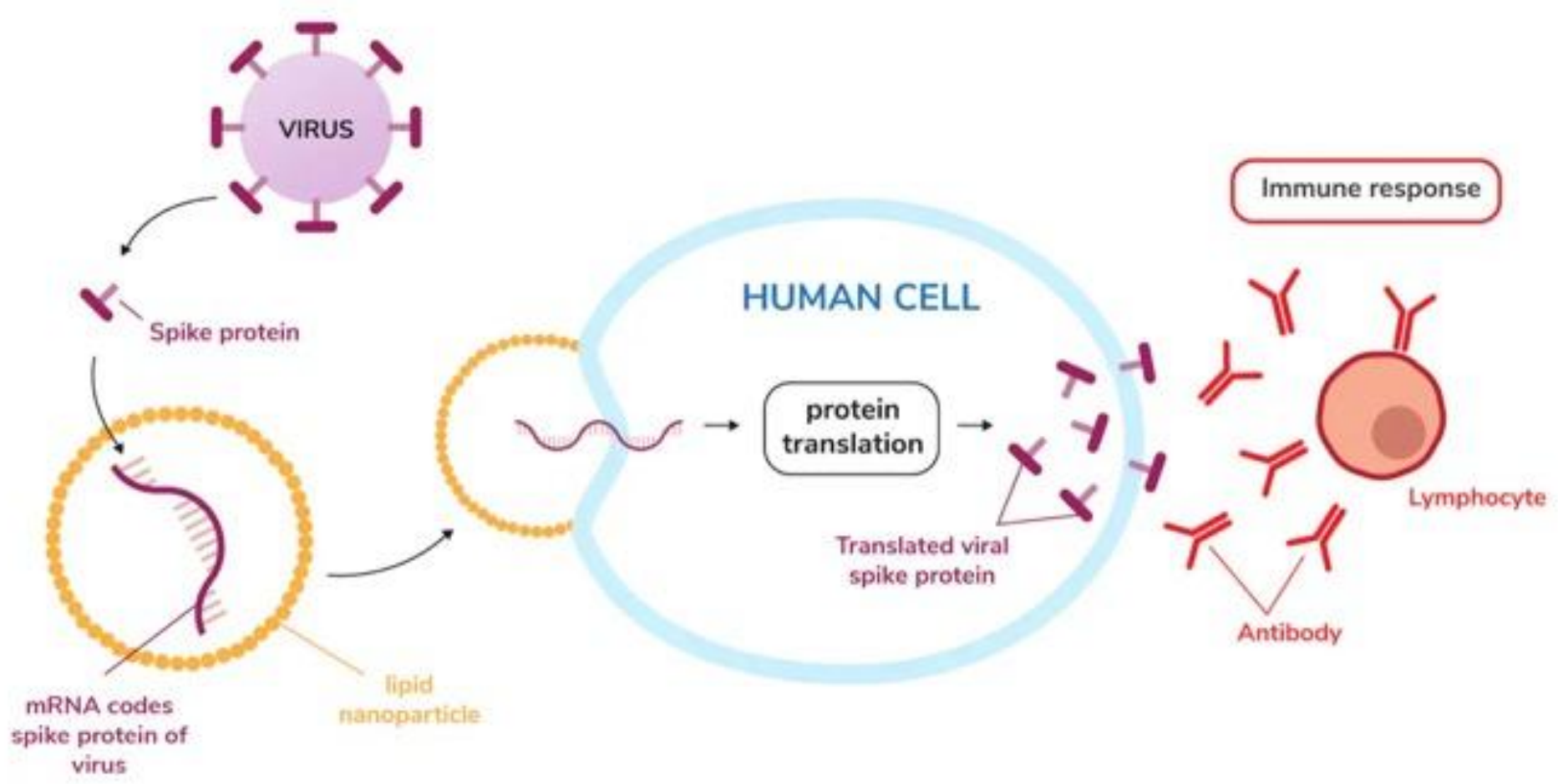
As of 1 January 2023, the global vaccine R&D landscape includes 966 candidates

Top 3 viruses – COVID, Flu, HIV



Yue J, Liu Y, Zhao M, Bi X, Li G, Liang W. The R&D landscape for infectious disease vaccines. Nat Rev Drug Discov. 2023 Jul 20.

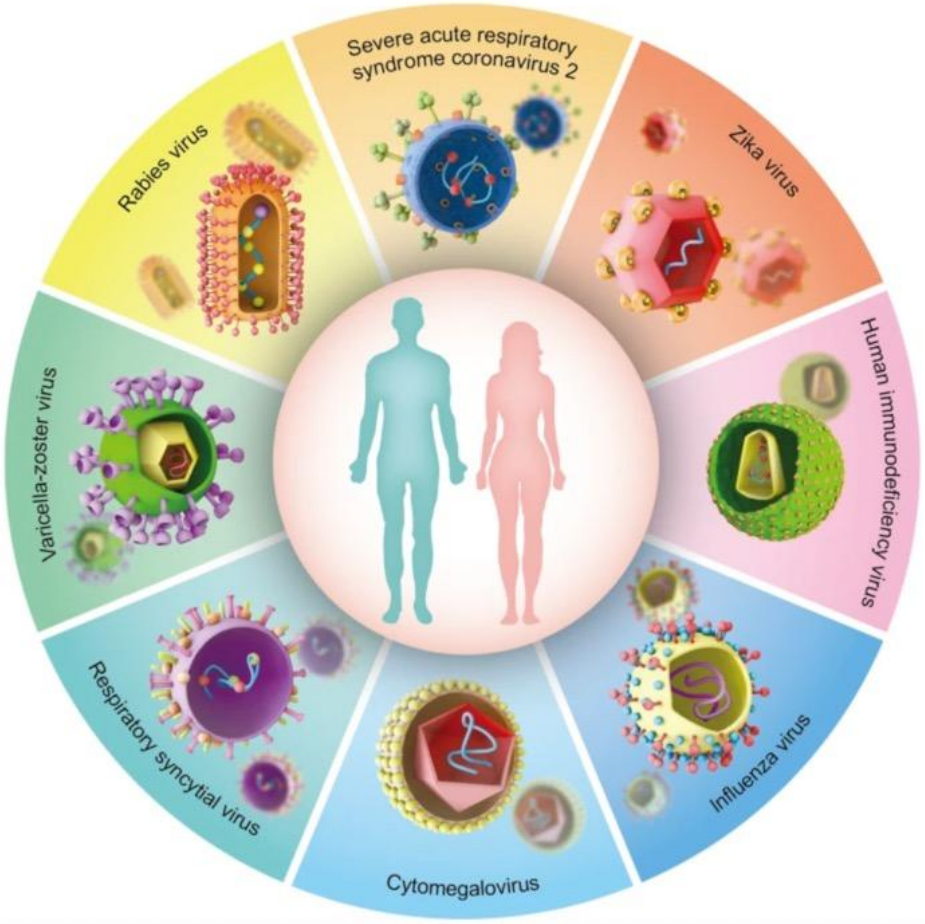
mRNA vaccines

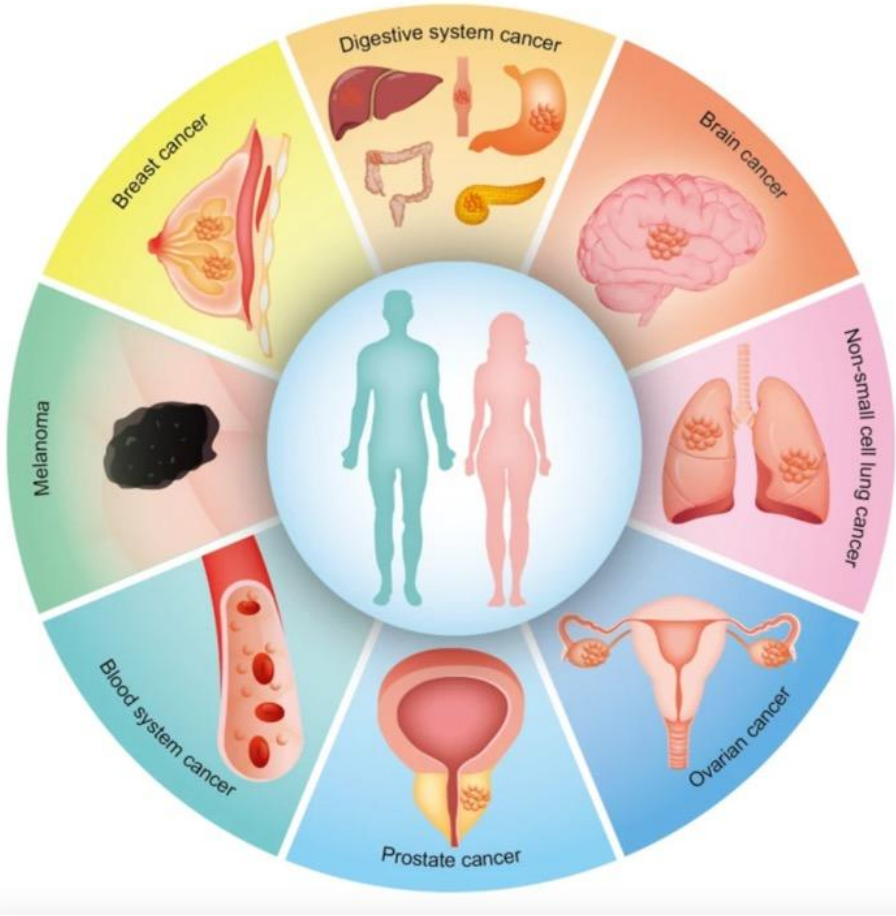


Messenger RNA vaccines get the recipient's body to produce a viral protein that then stimulates the desired immune response.

mRNA vaccines in the pipeline

- mRNA vaccines used in a diverse array of medical conditions ie **infectious diseases, cancers, immunological diseases, tissue damages and rare diseases**



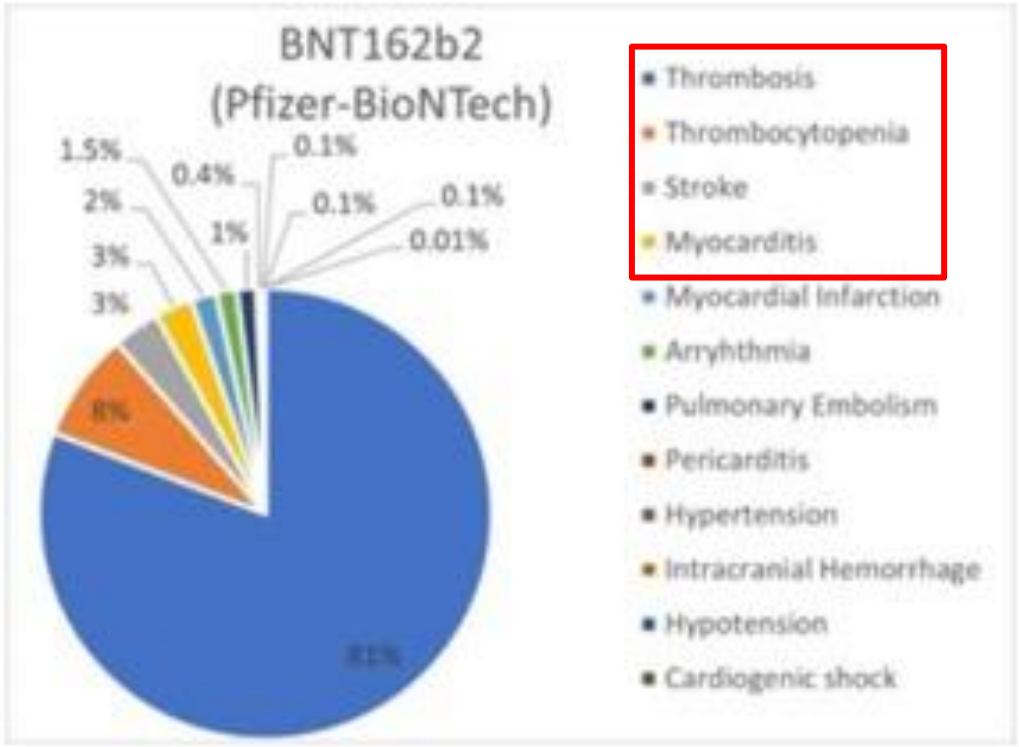


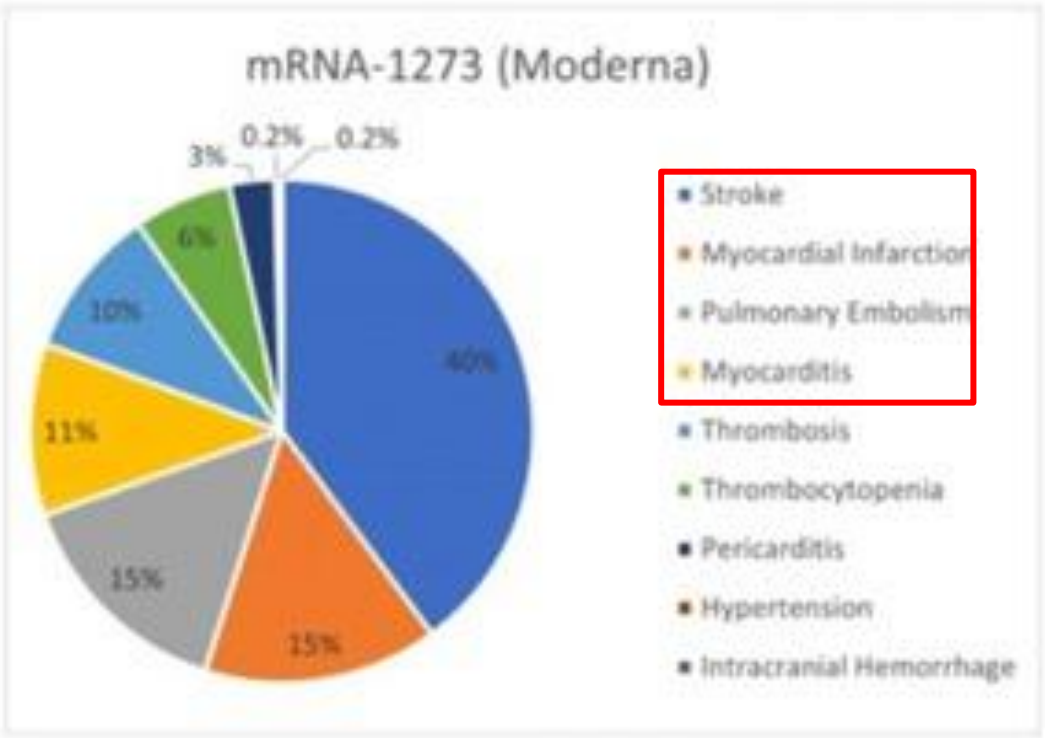
Cancers: melanoma, brain cancer, non-small cell lung cancer, ovarian cancer, prostate cancer, blood system cancer, digestive system cancer, and breast cancer

Zhang, G., Tang, T., Chen, Y. *et al.* mRNA vaccines in disease prevention and treatment. *Sig Transduct Target Ther* **8**, 365 (2023).

Cardiac and vascular events observed with mRNA vaccines, any dose

81 articles analyzed confirmed cardiovascular complications post-COVID-19 mRNA vaccines in 17,636 individuals and reported 284 deaths with any mRNA vaccine: 228 Pizer and 56 Moderna

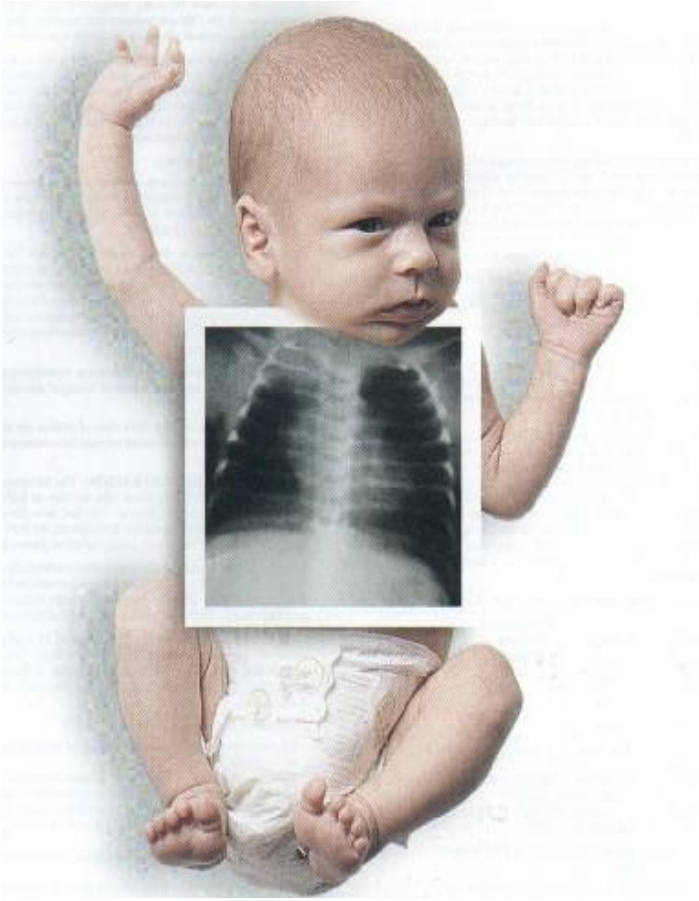




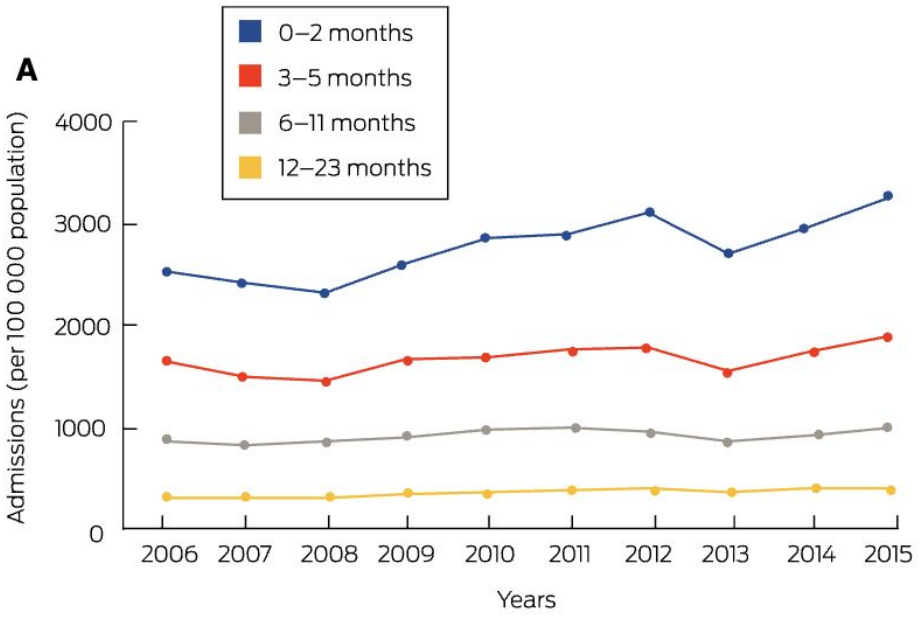
Asghar MS et al. Adverse events following COVID-19 mRNA vaccines: A systematic review of cardiovascular complication, thrombosis, and thrombocytopenia. Immun Inflamm Dis. 2023 Mar; 11(3): e807.

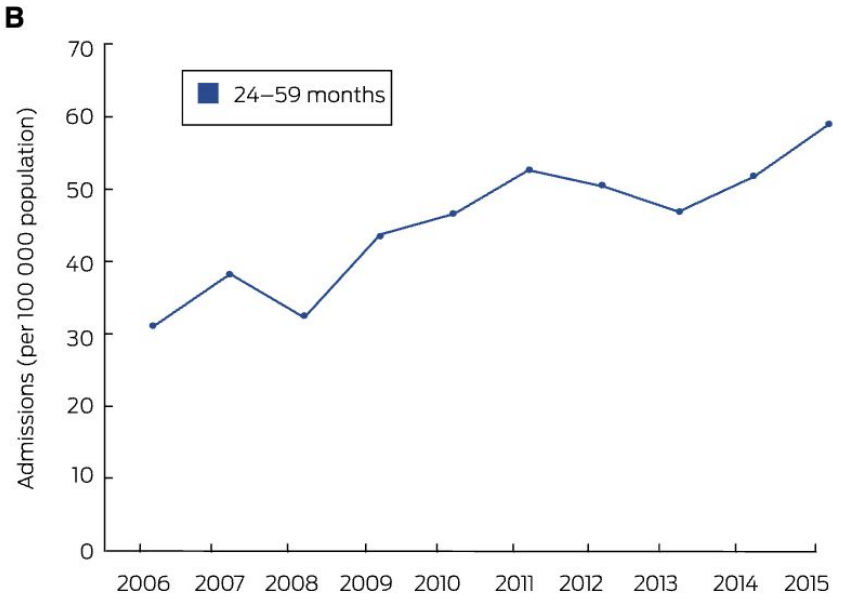
Preventing Infant RSV Disease in infants

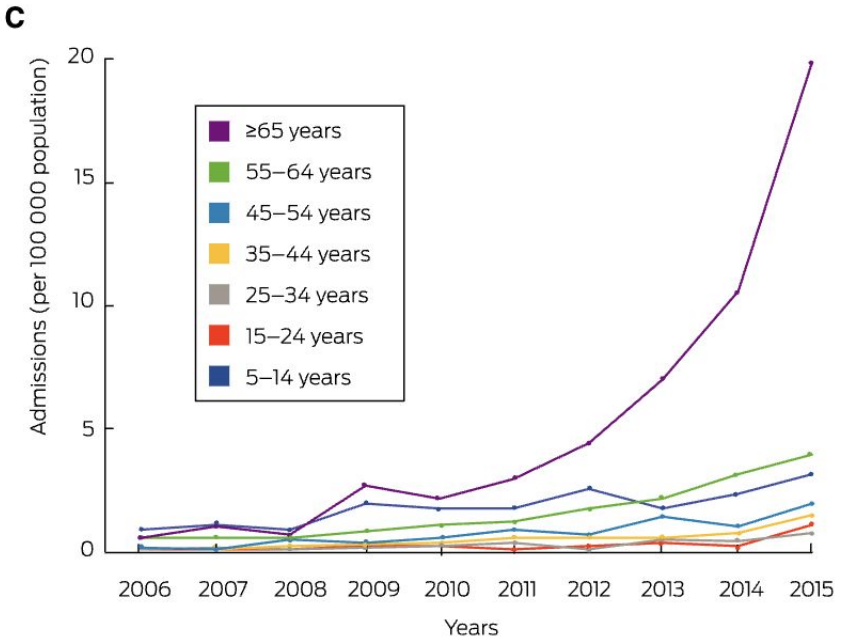
- Most (68%) infants are infected in the first year of life and nearly all (97%) by age 2
- Most urgent need for protection against RSV is during first few months of life
  - Premature infants <30 weeks gestation have hospitalization rates ~ 3x higher than term infants
  - >75% of RSV disease hospitalization occurs in full term, healthy infants.
- 2-3% of all infants will be hospitalized for RSV, up to 8% Aboriginal babies
- Efficient RSV-specific IgG transfer from mothers to neonates



Australia Burden of RSV







Saravanos et al. Medical Journal of Australia. 2019;
Saravanos et al. Journal of Paediatrics and Child Health. 2021

Societal Costs of RSV

- RSV leading cause of hospitalisation in young children.

- **The societal cost (i.e. hospital care, productivity loss and out-of-pocket expenses) of hospitalisation of Australian children < 5 years with RSV is estimated at $193 million per year**

- More than 90% load is from developing world but no costing data exists?

THE CONVERSATION

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RSV is everywhere right now. What parents need to know about respiratory syncytial virus

Published: July 26, 2023 10.32am AEST

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This winter, we're having to get our heads around another respiratory virus – RSV.

It's less well known than COVID or flu, but it's also responsible for unplanned visits to the GP or emergency department, and days off school, childcare and work.

It's the most common cause of hospitalisation in infants. Most children have at least one RSV infection by the age of three years and yet, many Australians have not heard of RSV or know little about this potentially serious winter virus.

Read more: Monday's medical myth: you can catch a cold by getting cold

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What is RSV?

RSV stands for respiratory syncytial (pronounced sin-CITY-al) virus. This common respiratory virus usually causes a mild cold with symptoms such as a

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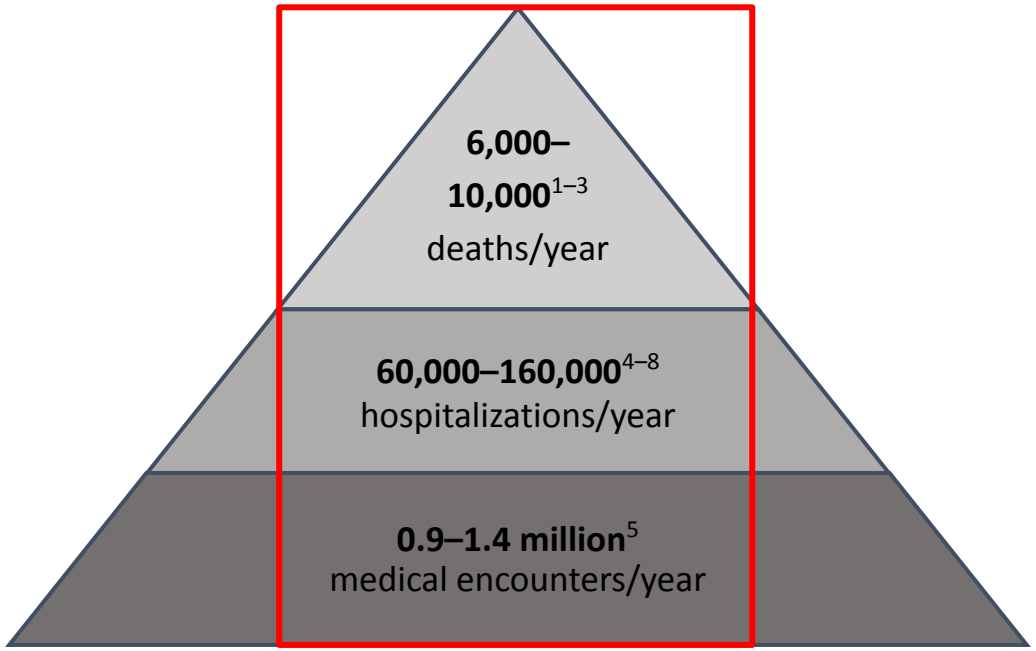
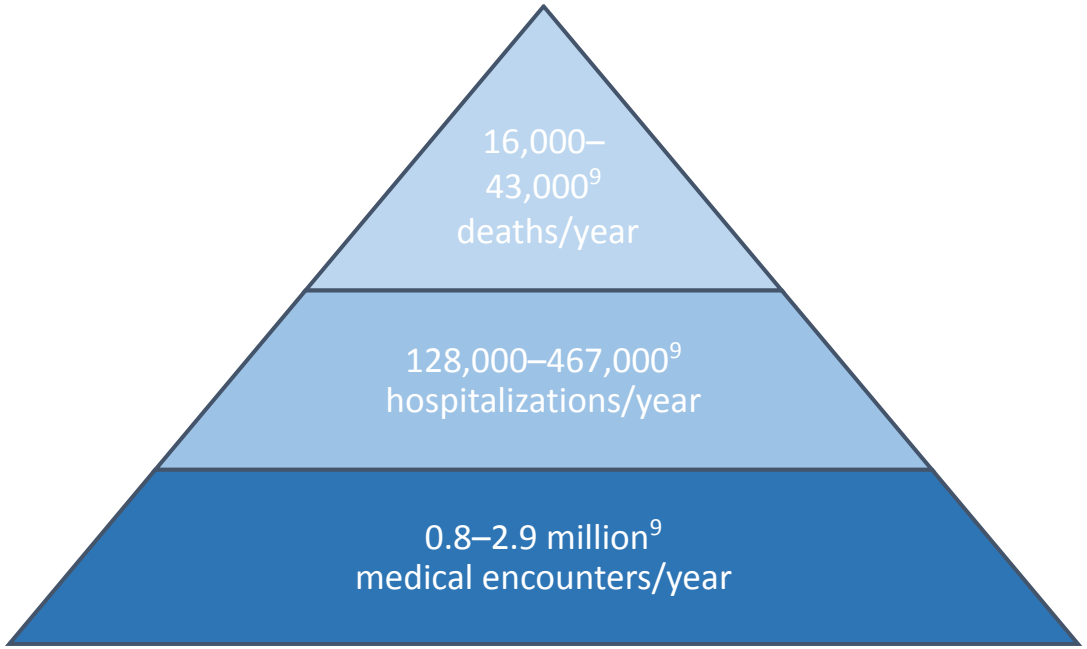
Can Respir J. 2011 Mar-Apr; 18(2): e10–e19

RSV and influenza burden compared – Adults ≥ 65 years



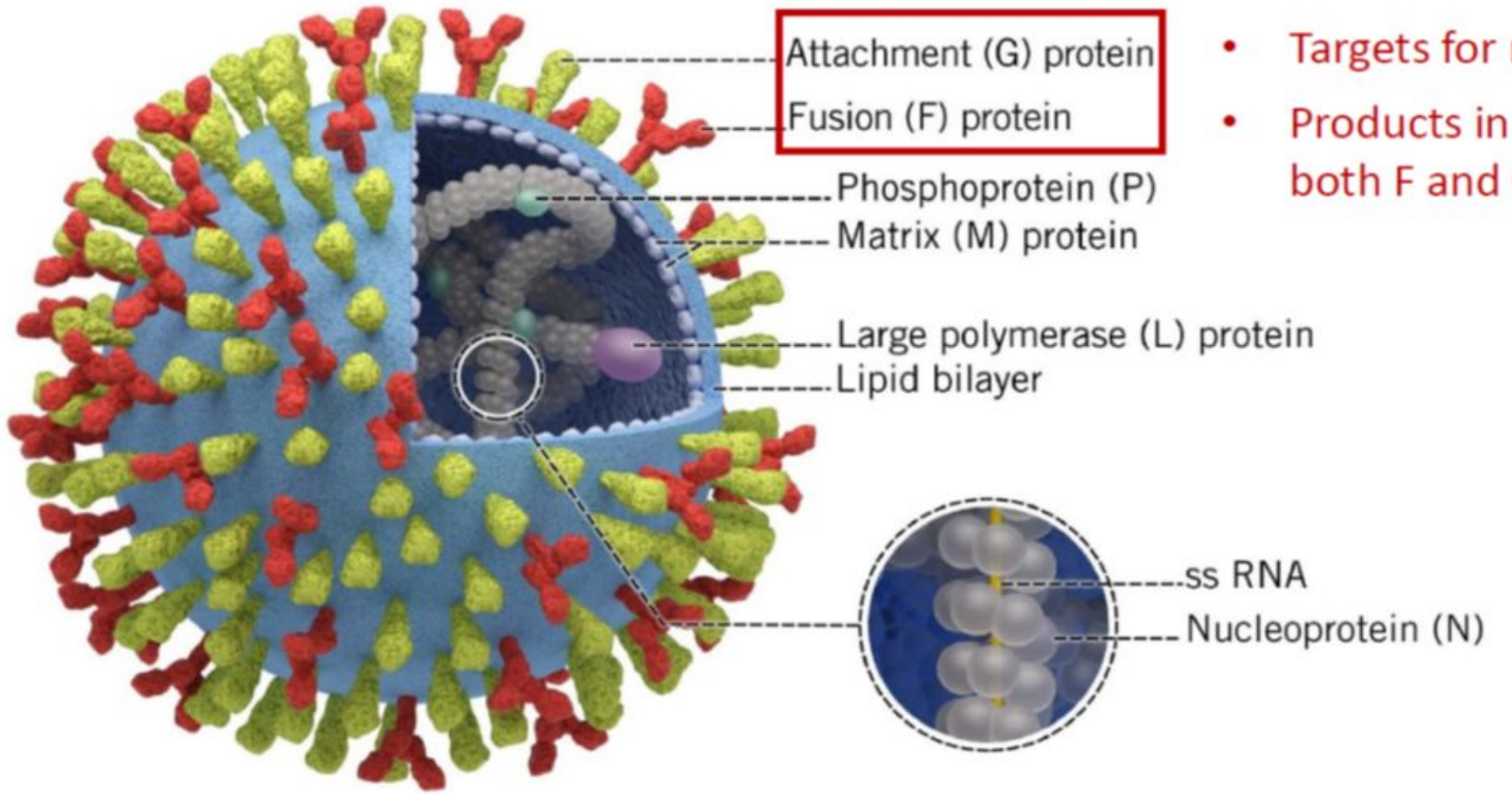
RSV



Influenza

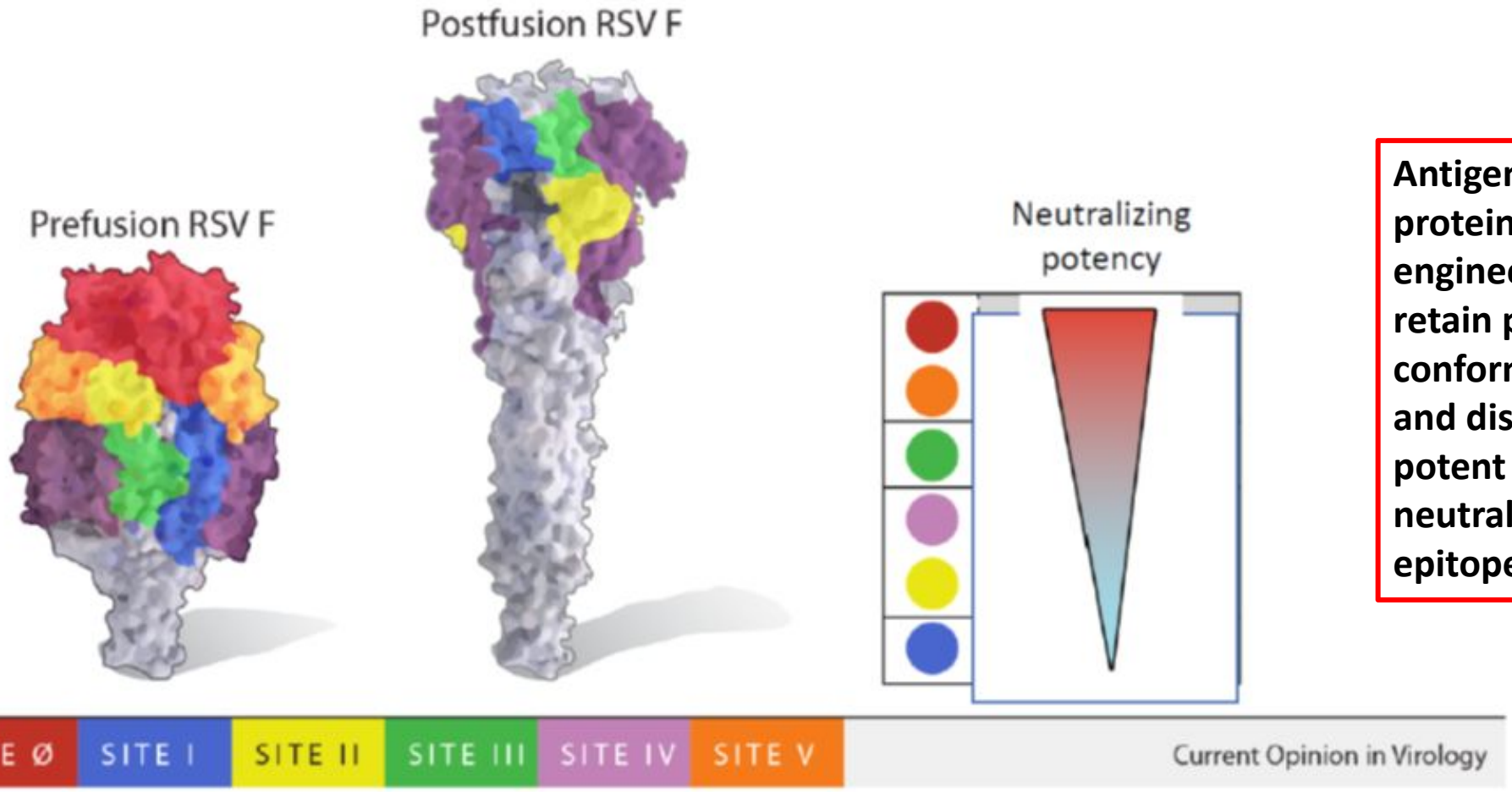
1. Thompson et al, JAMA (2003): https://doi.org/10.1001/jama.289.2.179
2. Matias et al, Influenza Other Respi Viruses (2014): https://doi.org/10.1111/irv.12258
3. Hansen et al, JAMA Network Open (2022): https://doi.org/10.1001/jamanetworkopen.2022.0527
4. Widmer et al, JAMA Network Open (2012): https://doi.org/10.1093/infdis/jis309
5. McLaughlin et al, Open Forum Infect Dis (2022): https://doi.org/10.1093/ofid/ofac300
6. Zheng et al, Pneumonia (2022): https://doi.org/10.1186/s41479-022-00098-x
7. Branche et al, Clinical Infect Dis (2022): https://doi.org/10.1093/cid/ciab595
8. CDC RSV-NET data 2016–2020 (unpublished)
9. CDC Influenza Burden 2015-2020: https://www.cdc.gov/flu/about/burden/past-seasons.html

RSV Virion Structure



- Targets for neutralizing antibodies
- Products in target F alone or have both F and G

The Fusion Protein exists in two or more structural forms, which bind different antibodies



Graham B. Current Opinion in Virology. 23: 107-112. 2017.

Antigen (fusion protein) engineered to retain pre-fusion conformation and display potent neutralizing epitopes

New Immunizations to Protect Against Severe RSV

Who Does It Protect?	Type of Product	Is It for Everyone in Group?
 Adults 60 and over	RSV vaccine	Talk to your doctor first
 Babies	RSV antibody given to baby	All infants entering or born during RSV season. Small group of older babies for second season.
	OR	
 Babies	RSV vaccine given during pregnancy	Can get if you are 32–36 weeks pregnant during September–January

www.cdc.gov/rsv

CDC

Bivalent RSV Prefusion F Vaccine

ABRYSVO™
Respiratory Syncytial Virus Vaccine

Proposed Indication:

Prevention of acute respiratory disease and lower respiratory tract disease caused by respiratory syncytial virus (RSV)

Individuals 60 years of age and older

DOSE LEVEL

- **120 µg without an adjuvant**
- **Dose contains 60 µg dose of each prefusion protein antigen, in a 0.5 mL injection**

PRESENTATION

- **Single dose 2 mL vial**
- **1 mL Pre-filled syringe**
- **Vial adaptor**

STORAGE

- **Refrigeration at 2°C to 8°C (36°F to 46°F)**
- **After reconstitution: 15ºC to 30ºC (used within 4 hours of reconstitution)**

Pfizer RSVpreF efficacy and safety – Adults >=60 years

TABLE 3. Efficacy of 1 dose of Pfizer respiratory syncytial virus RSVpreF vaccine against respiratory syncytial virus–associated disease among adults aged ≥60 years — multiple countries, 2021–2023

Efficacy evaluation period	Vaccine efficacy against outcome, % (95% CI)*	
	RSV-associated LRTD†	RSV-associated medically attended LRTD§
Season 1¶	88.9 (53.6–98.7)	84.6 (32.0–98.3)
Season 2 (interim)**	78.6 (23.2–96.1)	—††
Combined seasons 1 and 2 (interim)§§	84.4 (59.6–95.2)	81.0 (43.5–95.2)

TABLE 4. Safety* of 1 dose of Pfizer respiratory syncytial virus RSVpreF vaccine in adults aged ≥60 years — multiple countries, 2021–2023

Safety event	Risk for event		
	RSVpreF recipients no./No. (%)†	Placebo recipients no./No. (%)§	Relative risk (95% CI)¶
Serious AE**	792/18619 (4.3%)	749/18334 (4.1%)	1.04 (0.94–1.15)
Severe reactogenicity events††	36/3673 (1.0%)	24/3491 (0.7%)	1.43 (0.85–2.39)
Inflammatory neurologic events§§	3/18622 (—)¶¶	0/18335 (—)	—¶¶

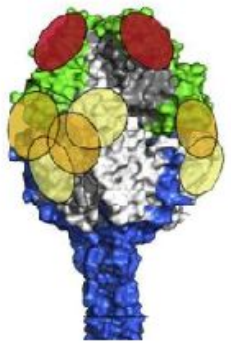
Use of Respiratory Syncytial Virus Vaccines in Older Adults: Recommendations of the Advisory Committee on Immunization Practices — United States, 2023 | MMWR (cdc.gov)

GSK's RSV older adult vaccine

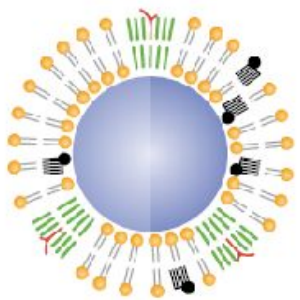
The combination of RSVPreF3 (120 µg) and AS01$_E$ is designed to induce a robust humoral and cellular immune response, to help protect older adults and those with underlying comorbidities

RSVPreF3 OA Vaccine

RSVPreF3 Antigen (120 µg) + **AS01$_E$ Adjuvant System**



Antigen engineered to preferentially maintain the pre-fusion conformation and display potent neutralizing epitopes to boost humoral immune response in older adults[1,2]



Boosts cellular immune response and restores the RSVPreF3 CD4+ T-cell level in older adults[2]

AREXVY
(RESPIRATORY SYNCYTIAL VIRUS VACCINE, ADJUVANTED)

AS01$_E$, Adjuvant System 01$_E$ (25 µg *Quillaja saponaria* Molina, fraction 21, 25 µg 3-Odesacyl-4'- monophosphoryl lipid A); OA, older adults.
Image of F protein reproduced from Graham BS, et al. *Curr Opin Immunol* 2015;35:30–38. Copyright 2015, with permission from Elsevier

1. Graham BS, et al. *Curr Opin Immunol.* 2015;35:30–38; 2. Leroux-Roels I, et al. *J Infect Dis.* 2022:jiac327.

GSK RSVpreF vaccine efficacy and safety - Adults >=60 years

TABLE 1. Efficacy of 1 dose of GSK respiratory syncytial virus RSVpreF3 vaccine against respiratory syncytial virus–associated disease among adults aged ≥60 years — multiple countries, 2021–2023

	Vaccine efficacy against outcome*	
Efficacy evaluation period	RSV-associated LRTD†	RSV-associated medically attended LRTD§
Season 1¶	82.6 (57.9–94.1)**	87.5 (58.9–97.6)††
Season 2§§	56.1 (28.2–74.4)††	—¶¶
Combined seasons 1 and 2 (interim)***	74.5 (60.0–84.5)†††	77.5 (57.9–89.0)††

TABLE 2. Safety* of 1 dose of GSK respiratory syncytial virus RSVPreF3 vaccine in adults aged ≥60 years — multiple countries, 2021–2023

	Risk for event		
Safety event	RSVPreF3 recipients no./No. (%)†	Placebo recipients no./No. (%)§	Relative risk (95% CI)¶
Serious AE**	549/12,570 (4.4)	540/12,604 (4.3)	1.02 (0.91–1.15)
Severe reactogenicity events††	37/979 (3.8)	9/976 (0.9)	4.10 (1.99–8.45)
Inflammatory neurologic events§§	3 events in trials without placebo recipients¶¶	—¶¶	—¶¶

Use of Respiratory Syncytial Virus Vaccines in Older Adults: Recommendations of the Advisory Committee on Immunization Practices — United States, 2023 | MMWR (cdc.gov)

Cases of Guillain Barre syndrome were reported after vaccination with both investigational vaccines

- All cases had onset during the 42-day risk window post-vaccination used in CDC surveillance
- The significance of 1-2 cases in safety databases of 15,000-26,000 persons is unclear
- Population-based rates of GBS increase with age
- Postmarketing studies required

USA – ACIP RSV vaccine recommendations adults ≥ 60 years

Morbidity and Mortality Weekly Report

Use of Respiratory Syncytial Virus Vaccines in Older Adults: Recommendations of the Advisory Committee on Immunization Practices — United States, 2023

Michael Melgar, MD[1]; Amadea Britton, MD[1]; Lauren E. Roper, MPH[1]; H. Keipp Talbot, MD[2]; Sarah S. Long, MD[3]; Camille N. Kotton, MD[4]; Fiona P. Havers, MD[1]

Recommendations for Use of RSV Vaccines in Older Adults

On June 21, 2023, ACIP recommended that adults aged ≥60 years may receive a single dose of RSV vaccine, using shared clinical decision-making.[§§§§]

Comparison of Different Strategies to Protect Infants During Their First RSV Season

	Immunisation with licensed mAbs	Immunisation with extended half-life mAbs	Maternal immunisation
Antibody Transfer	• Not affected by mother's health or transplacental transfer[1]	• Not affected by mother's health or transplacental transfer[1]	• Various factors like mother's health and preterm birth can impact antibody production and transplacental transfer[6-8]
Consistency of Protection	• Consistent and robust, antibodies delivered by IM injection and rapidly reach the bloodstream[2-4] • Rapid waning[5]	• Consistent and robust, antibodies delivered by IM injection and rapidly reach the bloodstream[2-4]	• Not consistent in all infants as it depends on timing of mother's immunisation prior to delivery, mother's comorbidities (HIV, malaria)[6,7,9]
Flexibility and Timing of Immunisation	• Can time immunisation to the start of RSV circulation[1,2] • Requirement for monthly dosing can present a barrier to compliance[1,2]	• Can time immunisation to the start of the RSV circulation[1]	• Must be administered during third trimester of pregnancy, regardless of timing of RSV circulation[1,3]

IM: intramuscular; mAbs: monoclonal antibodies

1. Esposito S et al. *Front Immunol.* 2022;13:880368. 2. Robbie GJ et al. *Antimicrob Agents Chemother.* 2012;56(9):4927-4936. 3. Domachowske JB et al. *Pediatr Infect Dis J.* 2018;37(9):886-892. 4. Aliprantis AO et al. *Clin Pharmacol Drug Dev.* 2021;10(5):556-566. 5. Subramanian KN, et al. *Pediatr Infect Dis J.* 1998;17(2):110-115. 6. Saso A et al. *Front Microbiol.* 2020;11:1499. 7. Pou C et al. *Nat Med.* 2019;25(4):591-596. 8. Eichinger KM et al. *Ther Adv Vaccines Immunother.* 2021;9:2515135520981516. 9. Malek A et al. *Am J Reprod Immunol.* 1996;36(5):248-255.

Maternal Pfizer RSV vaccine

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 20, 2023 VOL. 388 NO. 16

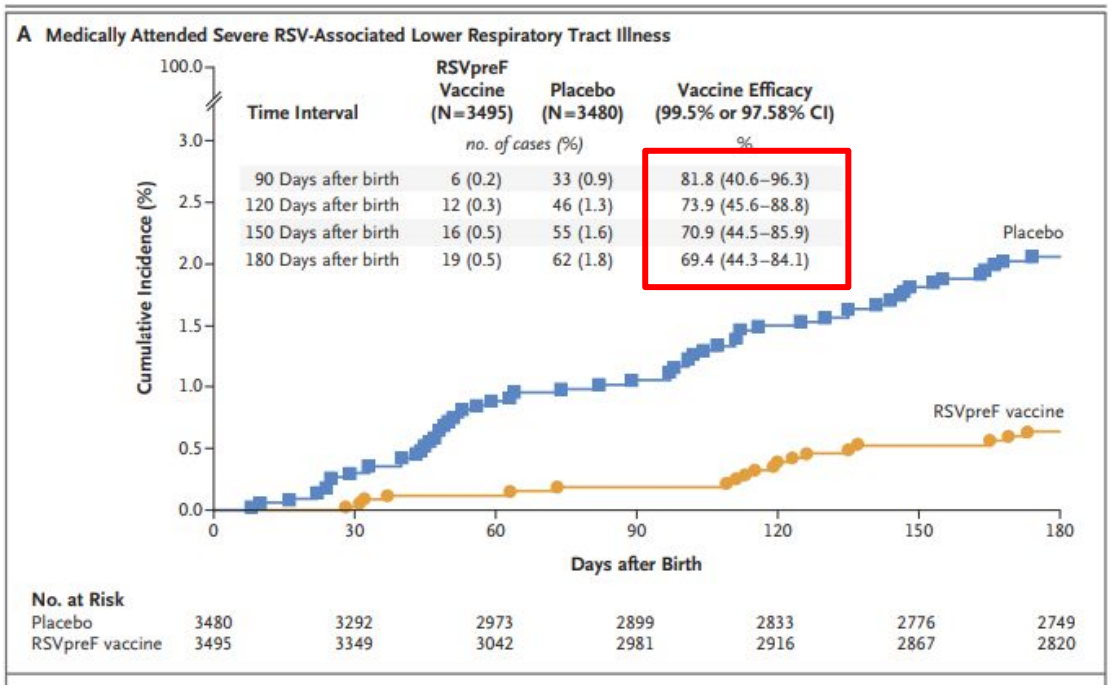
Bivalent Prefusion F Vaccine in Pregnancy to Prevent RSV Illness in Infants

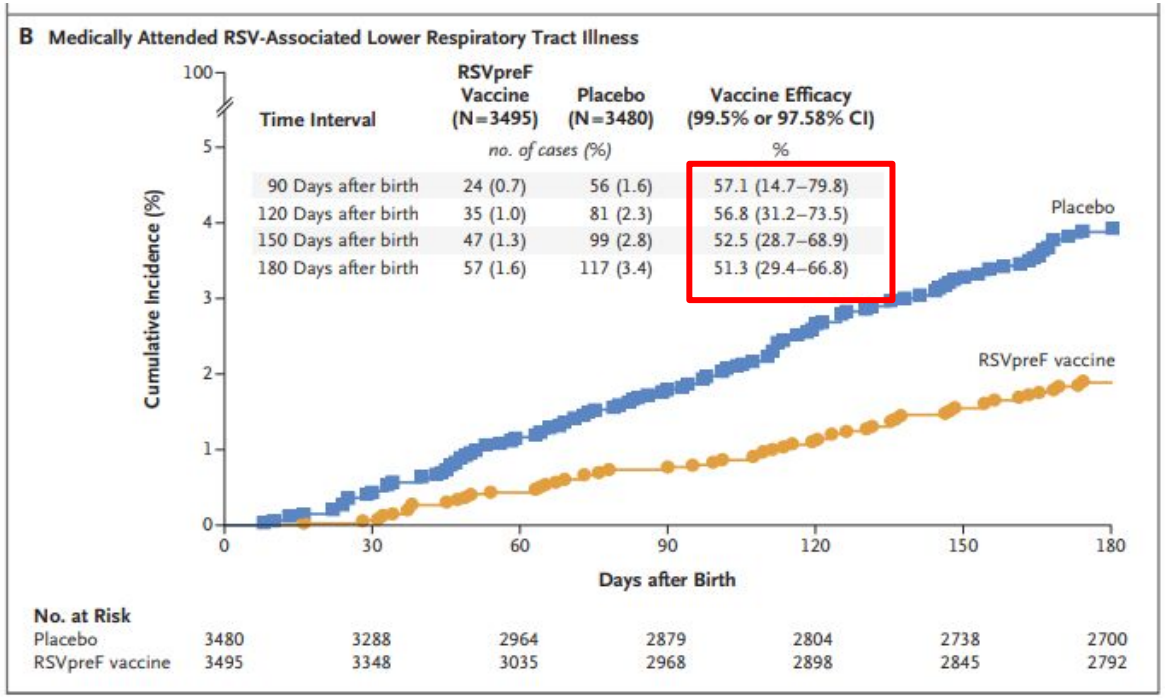
B. Kampmann, S.A. Madhi, I. Munjal, E.A.F. Simões, B.A. Pahud, C. Llapur, J. Baker, G. Pérez Marc, D. Radley, E. Shittu, J. Glanternik, H. Snaggs, J. Baber, P. Zachariah, S.L. Barnabas, M. Fausett, T. Adam, N. Perreras, M.A. Van Houten, A. Kantele, L.-M. Huang, L.J. Bont, T. Otsuki, S.L. Vargas, J. Gullam, B. Tapiero, R.T. Stein, F.P. Polack, H.J. Zar, N.B. Staerke, M. Duron Padilla, P.C. Richmond, K. Koury, K. Schneider, E.V. Kalinina, D. Cooper, K.U. Jansen, A.S. Anderson, K.A. Swanson, W.C. Gruber, and A. Gurtman, for the MATISSE Study Group*

- Phase 3, double-blind trial
- 7392 Maternal participants in 18 countries
- Pregnant women < 50 years between 24-38 weeks gestation, inclusive
- Randomized 1:1 to Pfizer bivalent RSV Prefusion F vaccine or placebo
- Well-tolerated
- **Effective against medically attended severe RSV-associated lower respiratory tract illness in infants**

Kampmann wt al. Bivalent Prefusion F Vaccine in Pregnancy to Prevent RSV Illness in Infants. NEJM, April 2023

Primary Endpoints: Vaccine efficacy by cumulative days after birth for two primary endpoints





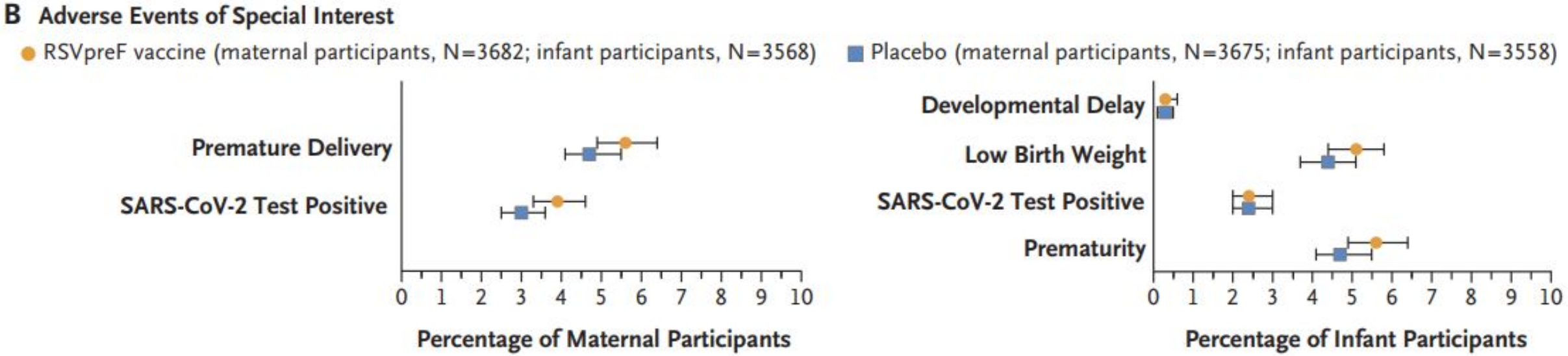
Medically attended severe lower respiratory tract illness occurred within 90 days after birth

- VE 81.8%; 99.5% CI, 40.6 to 96.3

Medically attended RSV-associated lower respiratory tract illness occurred within 90 days after birth

- VE 57.1%; 99.5% CI, 14.7 to 79.8 – NOT significant

Safety



Prematurity:
201 babies (5.6%) were born prematurely to vaccinated mothers *v* 169 babies (4.7%) in the placebo group

- not statistically significant
- no imbalance of neonatal deaths observed

No safety signals were detected in maternal participants or in infants and toddlers up to 24 months of age


SCIENCEINSIDER | HEALTH

FDA advisers agree maternal RSV vaccine protects infants, but are divided on its safety

Some have concerns about premature births after vaccination against respiratory syncytial virus

19 MAY 2023 · 1:35 PM · BY MEREDITH WADMAN

Maternal RSV vaccine: Further analysis is urged on preterm births. *BMJ* 2023;381:p1021

Approval for RSVpreF vaccine for pregnant women

- **Licensures:** FDA, Argentina (32-36 weeks), EMA (24-36 weeks)
- FDA approved as a single dose - 32-36 weeks gestation
  - reduce potential risk of and complications from preterm birth
  - Similar vaccine efficacy in 32-36 wks gestation compared to overall study pop
  - Avoids risk of extremely preterm births
  - FDA has required manufacturer to conduct post-marketing studies to assess preterm birth and hypertensive disorders of pregnancy, including pre-eclampsia
- **Recommendations:**
  - ACIP
    - US (32-36 weeks, seasonal)
  - JVAC, UK
    - All year administration, no gestational age restrictions noted
  - Low and middle resource countries?
    - SAGE working group….coming soon

Nirsevimab - Outcomes through 150 days after injection

Table 3. Outcomes through 150 Days after the Injection.*

Outcome	Nirsevimab (N=686)	Placebo (N=342)	Efficacy (95% CI)†	Cases Averted per 1000 Infants Treated (95% CI)‡	Number Needed to Treat (95% CI)§
	no. (%)				
Medically attended RSV-associated lower respiratory tract infection on any test result¶	17 (2.5)	37 (10.8)	77.0 (59.8 to 86.8)	83.4 (62.0 to 105.0)	12 (10 to 17)
Medically attended RSV-associated lower respiratory tract infection on central test result¶	15 (2.2)	33 (9.6)	77.2 (58.7 to 87.5)	74.7 (53.0 to 95.0)	14 (11 to 19)
Medically attended lower respiratory tract infection of any cause¶	60 (8.7)	62 (18.1)	51.5 (32.6 to 65.2)	93.6 (63.0 to 124.0)	11 (9 to 16)
Hospitalization for any respiratory illness due to RSV on any test result	9 (1.3)	11 (3.2)	59.0 (2.1 to 82.9)	19.0 (5.5 to 32.0)	53 (32 to 182)
Hospitalization for any respiratory illness due to RSV on central test result	7 (1.0)	9 (2.6)	61.1 (–3.7 to 85.4)	16.1 (4.5 to 28.0)	62 (36 to 223)
Hospitalization for any respiratory illness of any cause	16 (2.3)	14 (4.1)	42.8 (–15.8 to 71.7)	17.7 (2.0 to 33.0)	57 (31 to 500)

- Nirsevimab for Prevention of RSV in Healthy Late-Preterm and Term Infants (nejm.org)

ACIP and AAP recommendations for the use of the monoclonal antibody nirsevimab for the prevention of RSV disease

Approved by US FDA on July 17, 2023

- Long-acting monoclonal antibody for use in newborns and infants
- Recommended for:
  - All infants younger than 8 months born during or entering their first RSV season
  - Infants and children aged 8 through 19 months who are at increased risk of severe RSV disease and entering their second RSV season
  - Increased risk: chronic lung disease of prematurity who required medical support; severely immunocompromised; cystic fibrosis with severe lung disease American Indian and Alaska Native children
- Regulatory approval in UK and Europe (June 2023)
- Australia – ? nirsevimab and maternal vaccine programs work together

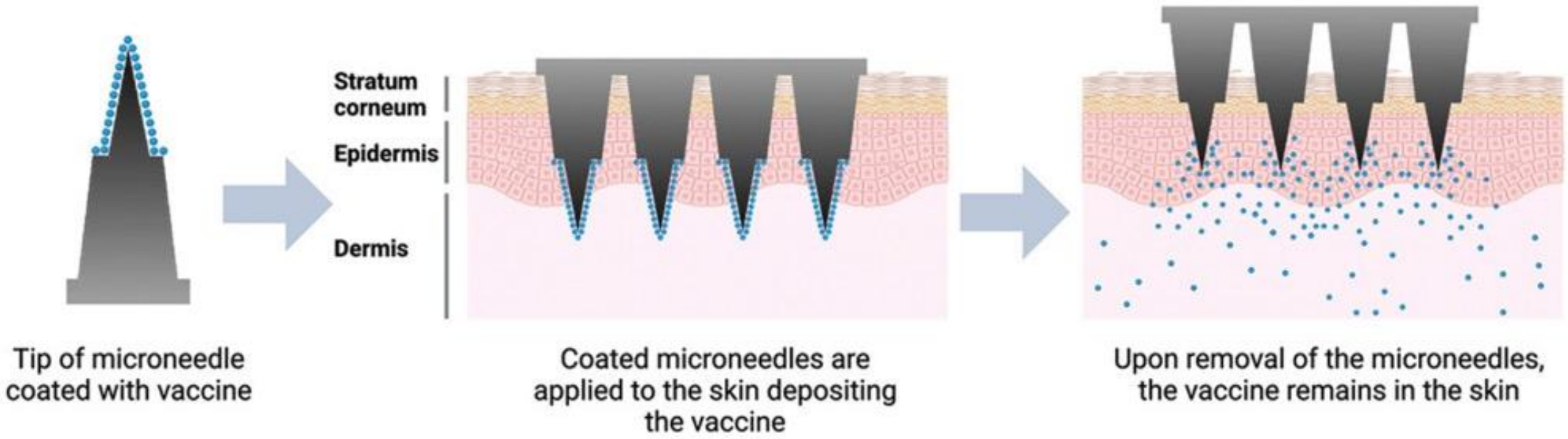
Needle free dermal high density vaccine microarray patches

- Novel vaccination strategies with needle-free technologies - microarray patches (MAPs)
- Rapid development last 10 years
- **MAPs categorized into five main types: solid, coated, dissolvable, hollow and hydrogel-forming:**
  - house an array of microprojections 100–1500 µm in length
  - breach outer layer of the skin to deliver antigen into the epidermal and dermal layers
  - applied either by pressing onto the skin or with applicators
  - compatible with a variety of vaccine modalities (DNA, live attenuated virus, mRNA, conjugate, subunit, inactivated virus, chimeric virus)

Jovin J. Y. et al. (2023) Microarray patches: scratching the surface of vaccine delivery, Expert Review of Vaccines, 22:1, 937-955,

Coated MAPs

- Vaccines are dry coated onto the tips of the microprojections before application to the skin



- Coated MAPs are one of the more popular choices for vaccine delivery, short wear time <2 mins
- Been evaluated with viral vaccine candidates such as Influenza, SARS-CoV-2, dengue, Ebola, poliovirus, measles, hepatitis C, HPV, and RSV
- 3 phase I clinical trials for influenza using coated MAPs have been conducted by Vaxxas Pty Ltd
  - significantly higher antibody response using MAPs over the traditional N&S method
  - HD-MAP delivery of flu vaccine well tolerated with only mild and moderate AEs reported

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