# RSV vaccinations and pregnancy


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# Acknowledgement of country

I would like to acknowledge the
traditional custodians of the land,
the Noongar Whadjuk people,
and pay my respects to their elders,
past, present and future.

# Declaration of Conflicts of Interest

- Membership of Immunisation committees
  - Australian Technical Advisory Group on Immunisation, 2005-14
  - Chair, WA Vaccine Safety Advisory Committee, 2011 - present
- Vaccine Scientific Advisory Boards
  - GlaxoSmithKline - Pertussis, pneumococcal, RSV vaccines, maternal immunisation, meningococcal & NTHi vaccines
  - Pfizer - Meningococcal, pneumococcal & RSV vaccines
  - Janssen – Bacterial vaccines
  - Sanofi – influenza vaccines, RSV mAb
  - Merck – pneumococcal vaccines, RSV mAb
  - Astra-Zeneca – COVID-19, RSV mAb
  - Resvinet Board member –RSV advocacy not-for profit organisation
  - *No personal remuneration*
- Vaccine Research
  - Investigator of industry sponsored multi-centre studies for Baxter, CSL, GSK, Medimmune, Merck, Pfizer, Sanofi, Novartis, Moderna,
  - Travel support to present at scientific conferences
    - Sanofi, Pfizer, Baxter, GSK
  - Research funding for Investigator initiated studies
    - GSK, Merck, Novartis, CSL

  - Views expressed during this presentation are mine only

# Talk outline

- Infant RSV burden and epidemiology
- Development of RSV vaccines and monoclonal antibodies
- Progress with maternal RSV vaccination
- Comparison with other RSV prevention strategies

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# Global Burden of RSV Disease

- ~95% infected by 2 years of age
- ~ 25% of RSV infected infants have lower respiratory tract infection
  - 34 million new episodes with >200,000 deaths globally (in low-income countries)
- In Australia, estimated 15, 000 children admitted to hospital each year
  - **One in 50 babies in the first year**
  - AIHW Hospitalisation data underestimates RSB burden by at least ~30%
- Compared to influenza, RSV is associated with higher rates of ED visits, hospitalizations and carer resource use
  - Twice as many ED visits (23.6% vs 11.2%)
  - Six times more hospitalizations (8.5 vs 1.4 per 1000 term children)
  - Caregivers lose 3 times more workdays

Fisher et al. *Pediatrics* 1997; Glezen et al. *NEJM* 1973; Broughton et al. *Thorax* 2005; Brandt et al. *Am J Epidem.* 1973; Henderson et al. *J Pediatr.* 1979; La Via et al. *J Pediatr.* 1992; Bourgeois et al. Pediatrics 2009; Nair et al. *Lancet* 2010.
Evohealth report 2023

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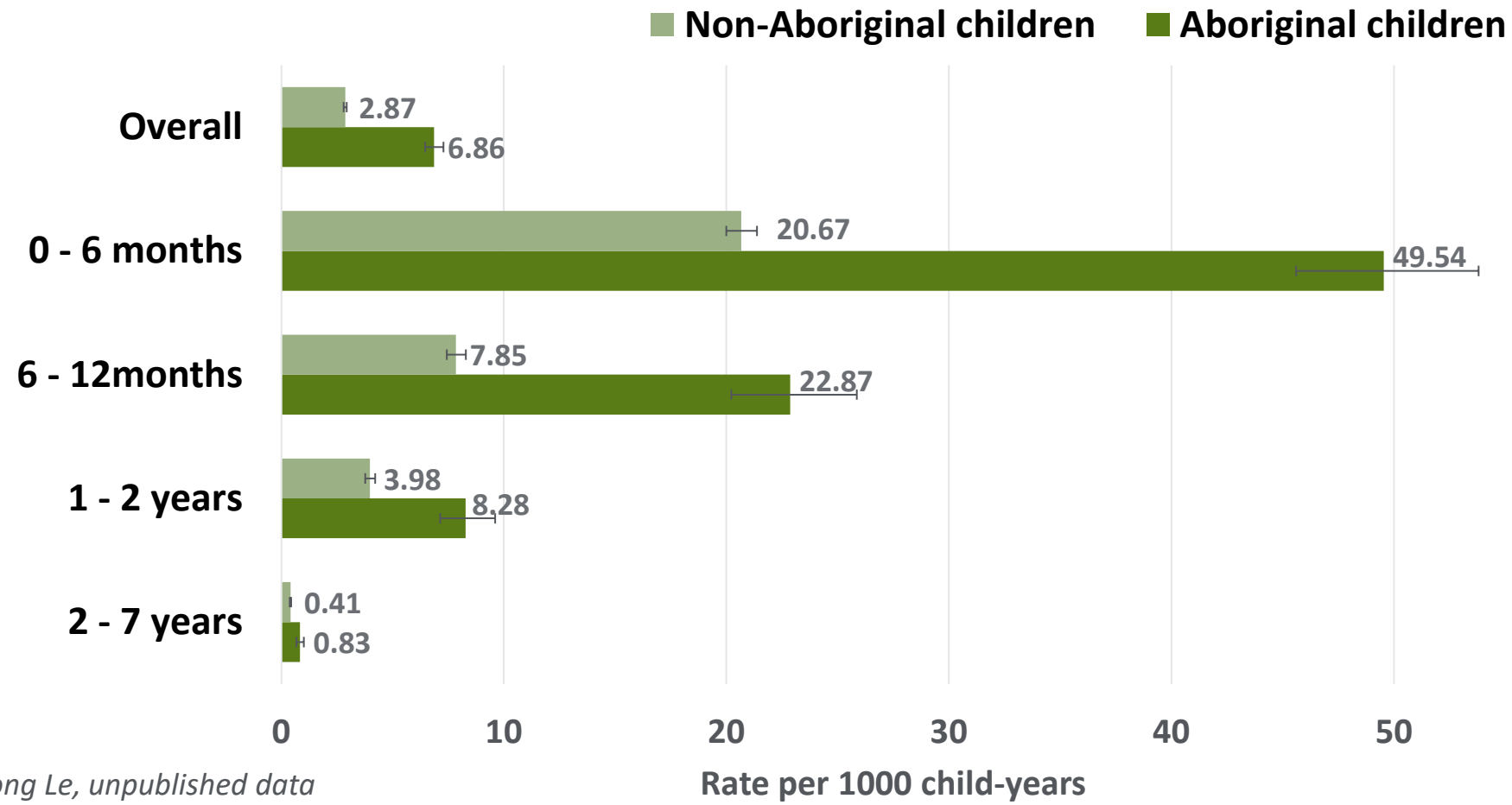
# RSV-hospitalisation in WA

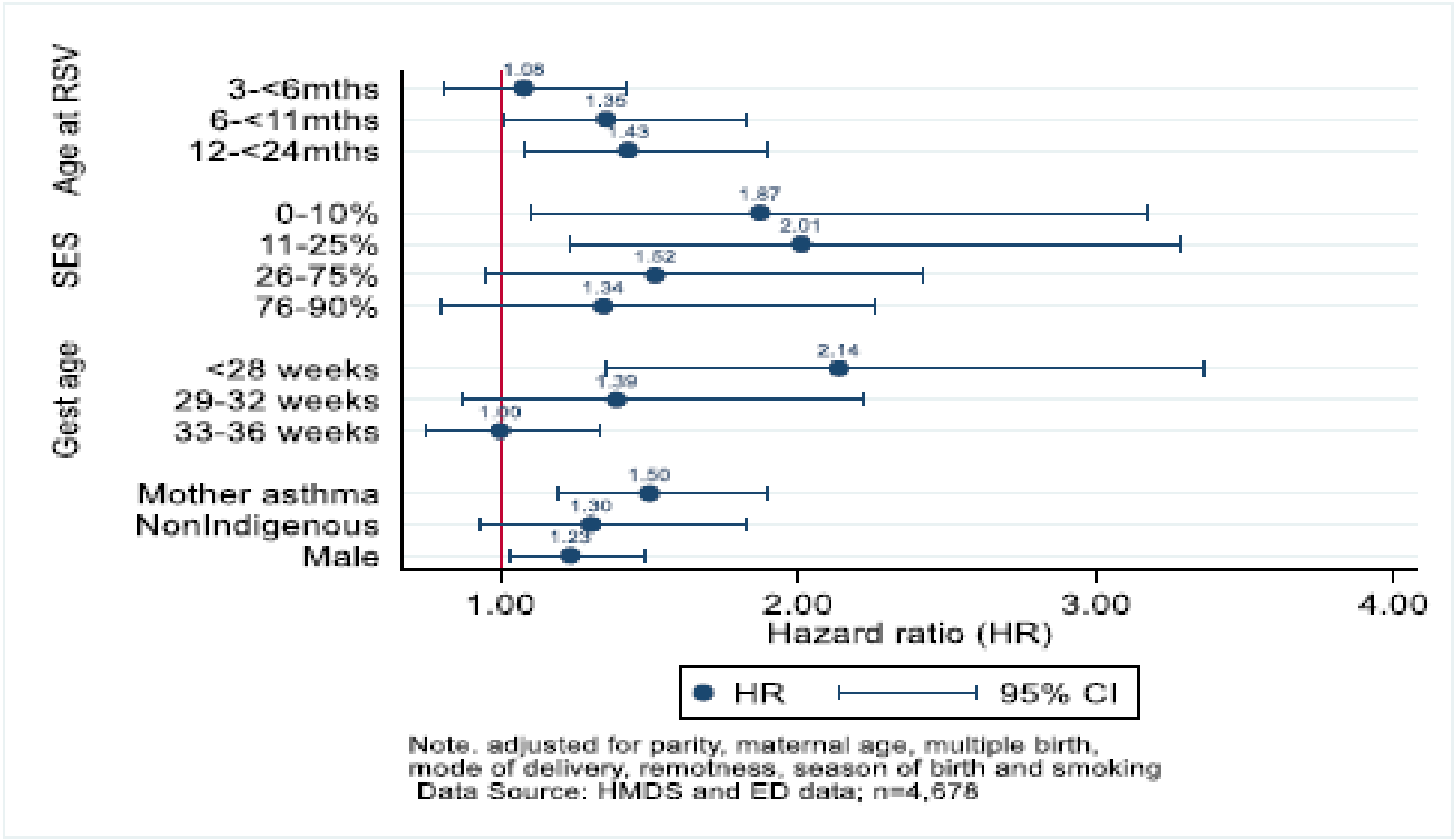



- RSV incidence is approximately twice the rate in Aboriginal children than non-Aboriginal children

*Huong Le, unpublished data*

# Long-term consequences of RSV disease

Recurrent viral-induced wheeze and asthma more common after RSV hospitalisation



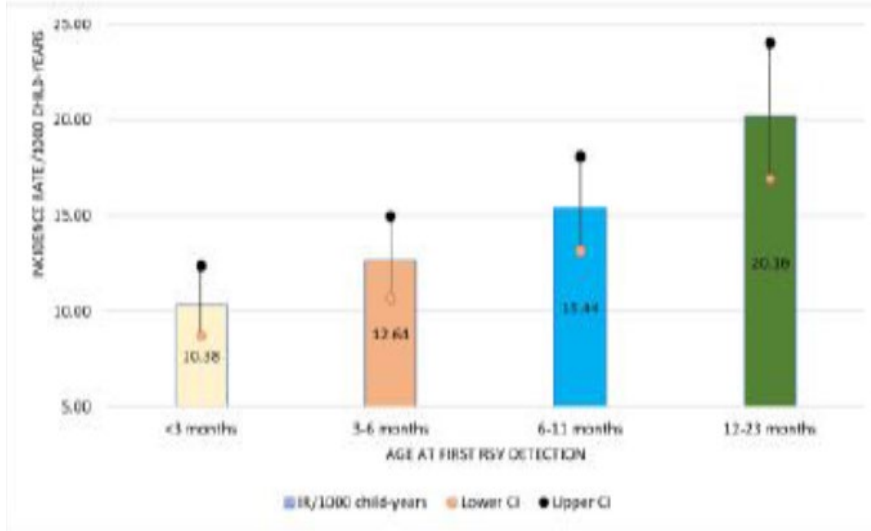




**Figure 3.** Relative risk of asthma and wheezing after age 2 during the follow-up for children with RSV-confirmed detections before age 2 years, 2000-2012, WA

Gebremedhin RSVVW 2021

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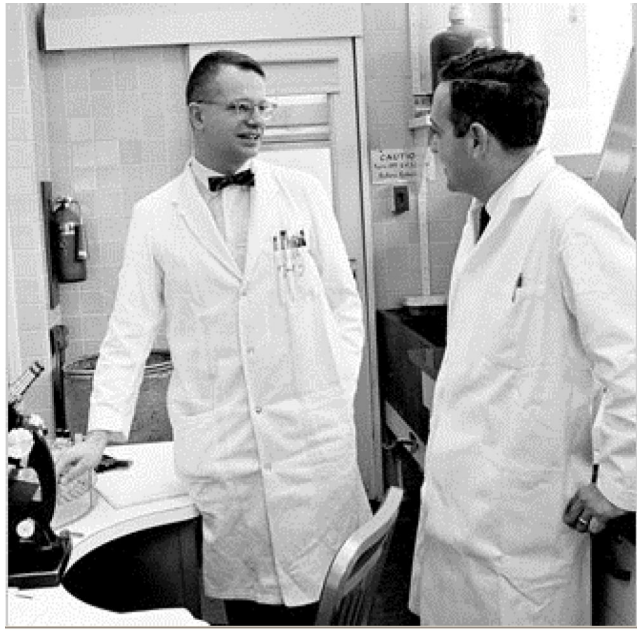


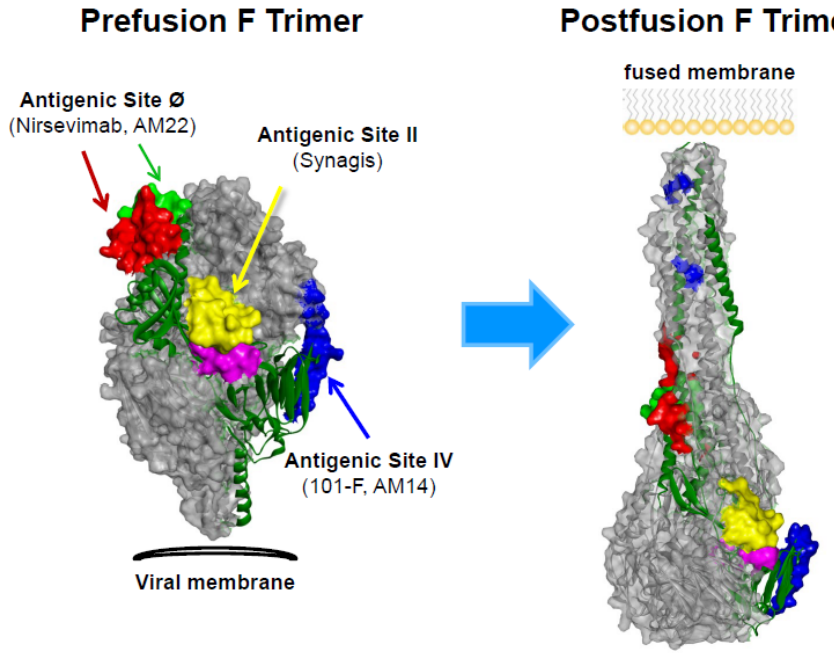
# The journey to RSV prevention

AMERICAN JOURNAL OF EPIDEMIOLOGY
Vol. 89, No. 4

Printed in U.S.A.

AN EPIDEMIOLOGIC STUDY OF ALTERED CLINICAL REACTIVITY TO RESPIRATORY SYNCYTIAL (RS) VIRUS INFECTION IN CHILDREN PREVIOUSLY VACCINATED WITH AN INACTIVATED RS VIRUS VACCINE

ALBERT Z. KAPIKIAN,[1] REGINALD H. MITCHELL,[2] ROBERT M. CHANOCK,[1] RUTH A. SHVEDOFF[1] AND C. ELEANOR STEWART[1]




**Only prefusion F can bind host cells for RSV to infect**

**Antibodies specific to the prefusion form are most effective at blocking virus infection**

McLellan et al Science Nov 2013

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# RSV Vaccine and mAb Snapshot

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

| | PHASE 1 | PHASE 2 | PHASE 3 | MARKET APPROVED |
|---|---|---|---|---|
| LIVE-ATTENUATED/ CHIMERIC | Blue Lake — PIV5/RSV (P)<br>Codagenix, LID/NIAID/NIH — RSV (P)<br>Intravacc — RSV-ΔG (P)<br>Pontificia Universidad Catolica de Chile — BCG/RSV (P)<br>SIIPL, St. Jude Hospital — SeV/RSV (P) | Meissa Vaccines — RSV (P)<br>Sanofi, LID/NIAID/NIH — RSV (P) | | |
| PROTEIN-BASED • PARTICLE • SUBUNIT | Icosavax — RSV/hMPV VLP (E)<br>Immunovaccine, VIB — RSV SH Protein (E)<br>NIH/ NIAID/VRC — RSV F Protein (E M)<br>Virometix — VLP | Advaccine Biotechnology — RSV G Protein (P E)<br>Daiichi Sankyo — Protein ? (E) | Pfizer — RSV F Protein (M) | GlaxoSmithKline — RSV F Protein (E)<br>Pfizer — RSV F Protein (E) |
| NUCLEIC ACID | Moderna — RNA (M P)<br>Sanofi — RNA (E) | | Moderna — RNA (E) | |
| RECOMBINANT VECTORS | | Janssen Pharmaceutical — Adenovirus (P) | Bavarian Nordic — MVA (E) | |
| IMMUNO-PROPHYLAXIS | Gates MRI — Anti-F mAb (P)<br>Trinomab Biotechnology — Anti-F mAb (P) | | Merck — Anti-F mAb (P) | Astra Zeneca, Sanofi — Nirsevimab (P)<br>Astra Zeneca — Palivizumab (P) |

UPDATED: June 2, 2023

Indicates Change

https://www.path.org/resources/rsv-vaccine-and-mab-snapshot/

PATH

# Addressing RSV in children and adults : what is the best approach?


RSV, respiratory syncytial virus

*PATH, 2023. RSV Vaccine and mAb Snapshot. https://www.path.org/resources/rsv-vaccine-and-mab-snapshot/ (accessed May 2023)*

# Lessons from Novavax prepare study – close but yet so far …

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Respiratory Syncytial Virus Vaccination during Pregnancy and Effects in Infants

S.A. Madhi, F.P. Polack, P.A. Piedra, F.M. Munoz, A.A. Trenholme, E.A.F. Simões, G.K. Swamy, S. Agrawal, K. Ahmed, A. August, A.H. Baqui, A. Calvert, J. Chen, I. Cho, M.F. Cotton, C.L. Cutland, J.A. Englund, A. Fix, B. Gonik, L. Hammitt, P.T. Heath, J.N. de Jesus, C.E. Jones, A. Khalil, D.W. Kimberlin, R. Libster, C.J. Llapur, M. Lucero, G. Pérez Marc, H.S. Marshall, M.S. Masenya, F. Martinón-Torres, J.K. Meece, T.M. Nolan, A. Osman, K.P. Perrett, J.S. Plested, P.C. Richmond, M.D. Snape, J.H. Shakib, V. Shinde, T. Stoney, D.N. Thomas, A.T. Tita, M.W. Varner, M. Vatish, K. Vrbicky, J. Wen, K. Zaman, H.J. Zar, G.M. Glenn, and L.F. Fries, for the Prepare Study Group*

N Engl J Med 2020;383:426-39.

# Unexplained Novavax Efficacy results

## Geographic imbalance in efficacy

Primary Endpoint Cases

| Day 90 Vac. Efficacy (%) Placebo, Vaccine cases | All | U.S. | S. Africa | ROW* |
|---|---|---|---|---|
| MS RSV LRTI | 39.4<br>35/1430<br>41/2765 | 11.6<br>6/346<br>10/652 | 42.5<br>22/732<br>25/1447 | 54.7<br>7/352<br>6/666 |

U.S. efficacy was low compared to other countries by most measures and appears to be related to timing of immunization, including the negative effects of late gestational age immunization and short intervals to birth, conditions which were more common in U.S. subjects.

- larger proportion of infants vaccinated several months before start of RSV season
- FDA required repeat Phase 3 study – Novavax has discontinued RSV program
- Provides proof of principle of safety and efficacy of maternal RSV vaccination

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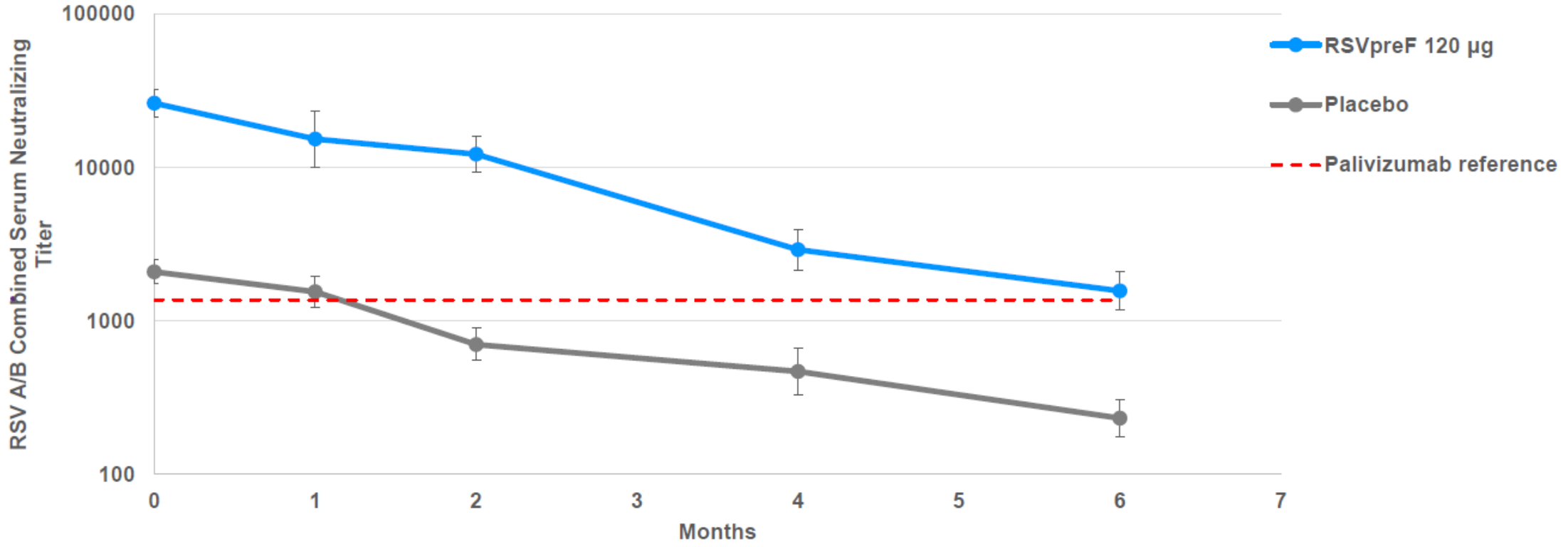
# Maternal RSV vaccination results in protective antibody levels in infants

RSV A/B Combined 50% Geometric Mean Neutralizing Titers by Month in Infants born to Mothers Vaccinated at 24-36 weeks




---*Palivizumab reference line = 50% A/B neutralizing titer of a 100ug/mL palivizumab dose, demonstrated to be efficacious in preventing infant RSV-associated ICU admission (Forbes ML, Kumar VR, Yogev R, et al. Hum Vaccin Immunother 2014;10:2789-94.)*

# New Maternal RSV Vaccine Efficacy Studies

- GSK pre-F3 protein unadjuvanted vaccine:
  - Recruiting up to 20,000 healthy pregnant mothers
  - Study discontinued due to possible increase in preterm babies in LMICs
  - *ClinicalTrials.gov Identifier: NCT04605159*

GRACE
InvestiGational RSV MAternal VaCcinE

- Pfizer bivalent preF protein vaccine

Matisse

  - Recruited 7,300 healthy pregnant mothers
  - randomized 1:1 between ≥24 and ≤36 weeks gestation
  - Efficacy outcome medically attended ALRTI up to 6 months

(*ClinicalTrials.gov Identifier: NCT04424316)*

# Grace study: Increase in preterm births after GSK PreF3 maternal vaccination

- Enrolment ceased after 3557 women enrolled (2:1 randomisation)
  - Excess preterm births and neonatal deaths related to prematurity in vaccine group
  - Associated with mothers in LMCI countries (RR1.57 (CI:1.17-2.1) vs RR 1.04 (CI: 0.68-1.58)

**Table. Preterm births in the RSV MAT-009 study (exposed set – infants)**

| Category | RSVPreF3 Mat N=3,496 | | Placebo N=1,739 | | RSVPreF3 Mat/ Placebo | |
|---|---|---|---|---|---|---|
| | n | % (95% CI) | n | % (95% CI) | RR (95% CI) | p-value |
| **Any preterm (<37 weeks)** | 238 | 6.81 (6.0–7.7) | 86 | 4.95 (4.0–6.1) | 1.38 (1.08–1.75) | 0.009 |
| Moderate–late preterm (32– <37 weeks) | 225 | 6.44 (5.6–7.3) | 84 | 4.83 (3.9–5.9) | 1.33 (1.04–1.70) | 0.021 |
| Very preterm (28– <32 weeks) | 11 | 0.31 (0.2–0.6) | 2 | 0.12 (0.0–0.4) | 2.74 (0.61–12.33) | 0.190 |
| Extremely preterm (<28 weeks) | 2 | 0.06 (0.0–0.2) | 0 | 0.00 (0.0–0.2) | NE | |

N, number of infants in the exposed set – infants; n/%, number/percentage of preterm births; CI, confidence interval; RR, relative risk; NE, could not be estimated. Data for the pre-specified day 43 post-delivery safety analysis, with data lock point 4 October 2022.

*www.resvinet.org/uploads/2/2/2/7/22271200/rsvvw23_abstract_booklet_v2.pdf Abstract 126 P 60*

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# Efficacy of RSV Vaccine in Pregnancy

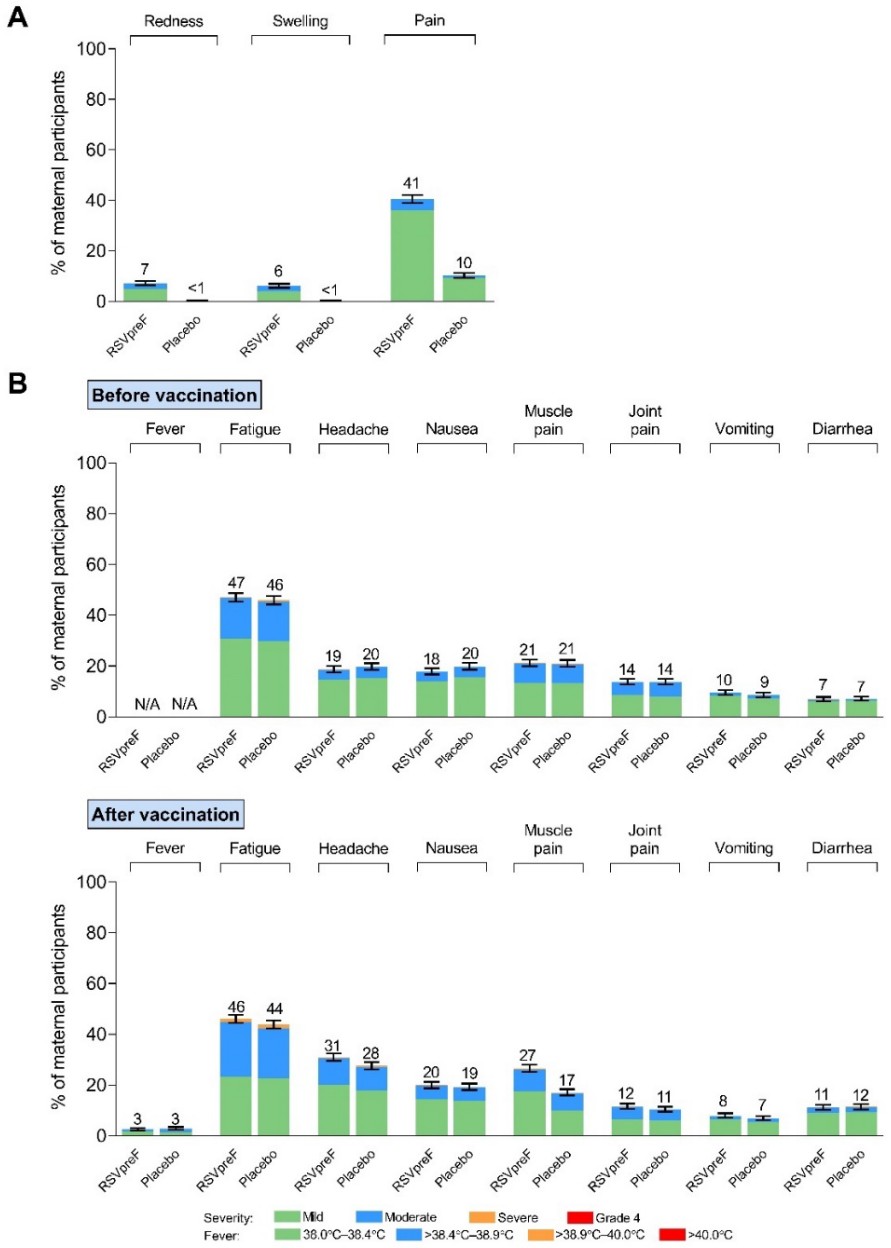
The NEW ENGLAND JOURNAL of MEDICINE

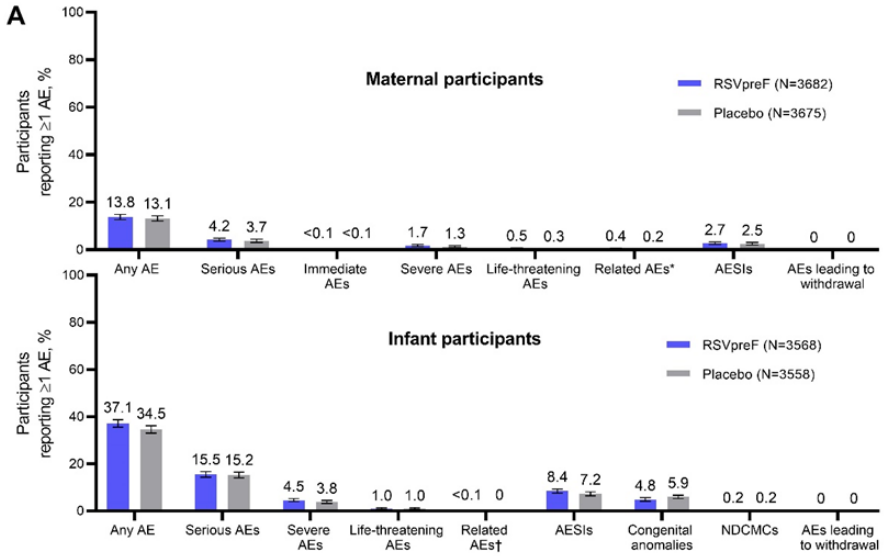
ESTABLISHED IN 1812 APRIL 20, 2023 VOL. 388 NO. 16

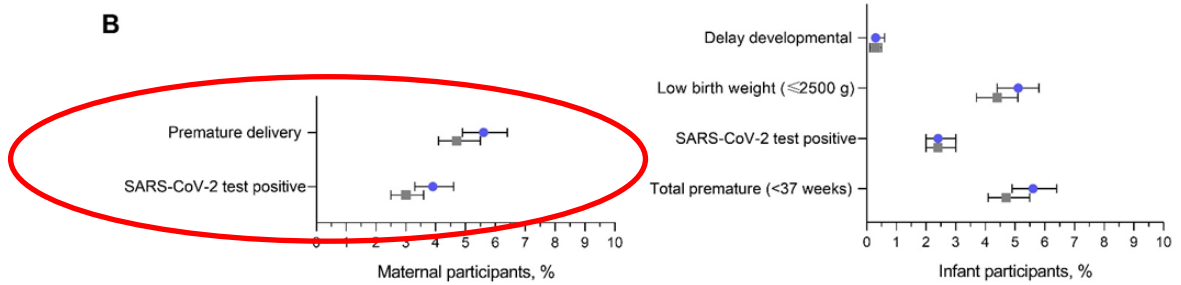
## Bivalent Prefusion F Vaccine in Pregnancy to Prevent RSV Illness in Infants

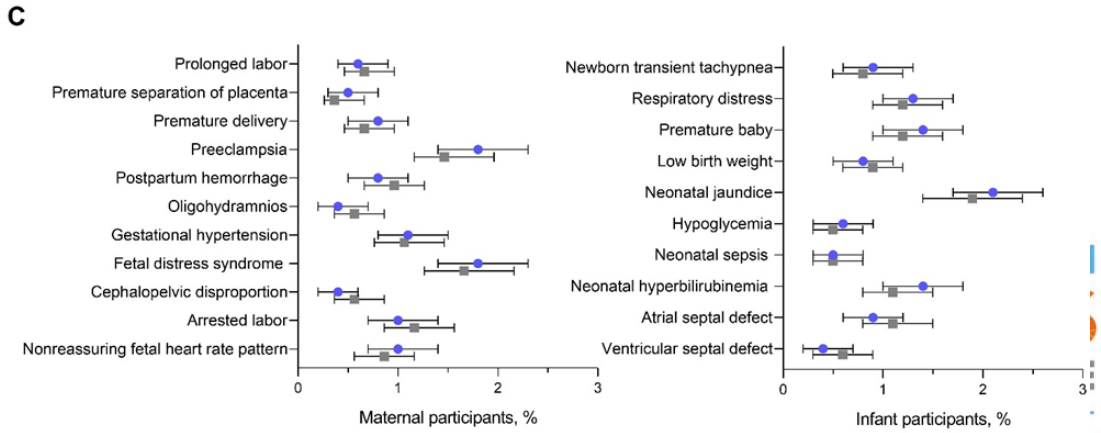
B. Kampmann, S.A. Madhi, I. Munjal, E.A.F. Simões, B.A. Pahud, C. Llapur, J. Baker, G. Pérez Marc, D. Radley, E. Shittu, J. Glanternik, H. Snaggs, J. Baber, P. Zachariah, S.L. Barnabas, M. Fausett, T. Adam, N. Perreras, M.A. Van Houten, A. Kantele, L.-M. Huang, L.J. Bont, T. Otsuki, S.L. Vargas, J. Gullam, 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*

# Safety of Maternal bivalent RSV vaccine

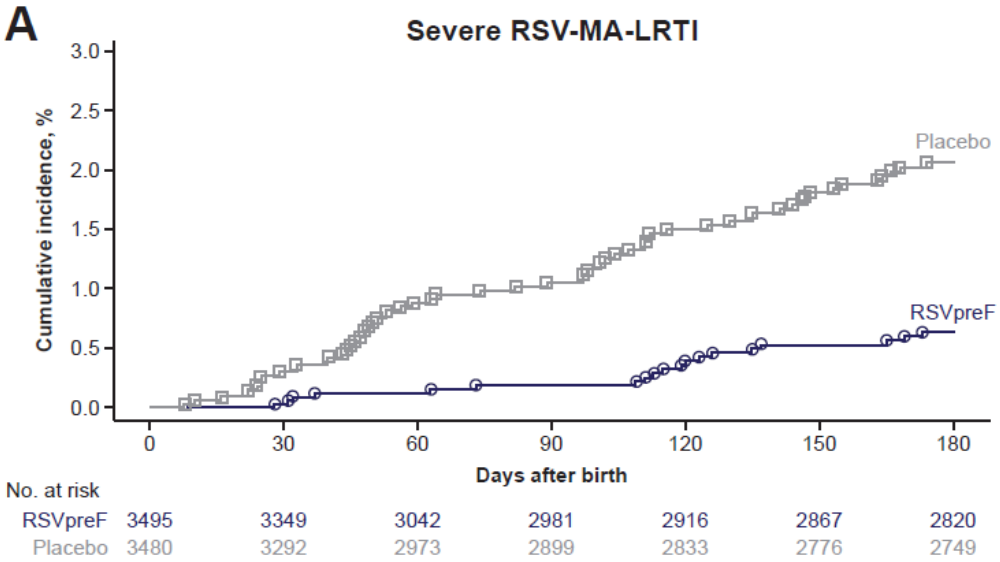


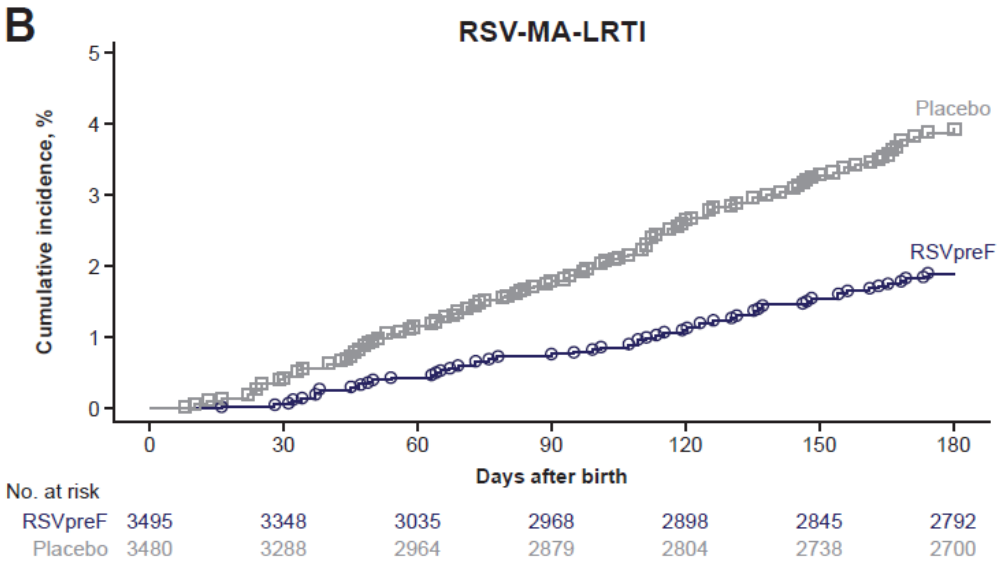



# Maternal RSV Vaccine Efficacy against LRTI




| Time interval | RSVpreF (N=3495) Number of cases (%) | Placebo (N=3480) Number of cases (%) | VE, % (CI) |
|---|---|---|---|
| 90 days after birth | 6 (0.2) | 33 (0.9) | 81.8 (40.6–96.3) |
| 120 days after birth | 12 (0.3) | 46 (1.3) | 73.9 (45.6–88.8) |
| 150 days after birth | 16 (0.5) | 55 (1.6) | 70.9 (44.5–85.9) |
| 180 days after birth | 19 (0.5) | 62 (1.8) | 69.4 (44.3–84.1) |




| Time interval | RSVpreF (N=3495) Number of cases (%) | Placebo (N=3480) Number of cases (%) | VE % (CI) |
|---|---|---|---|
| 90 days after birth | 24 (0.7) | 56 (1.6) | 57.1 (14.7–79.8) |
| 120 days after birth | 35 (1.0) | 81 (2.3) | 56.8 (31.2–73.5) |
| 150 days after birth | 47 (1.3) | 99 (2.8) | 52.5 (28.7–68.9) |
| 180 days after birth | 57 (1.6) | 117 (3.4) | 51.3 (29.4–66.8) |

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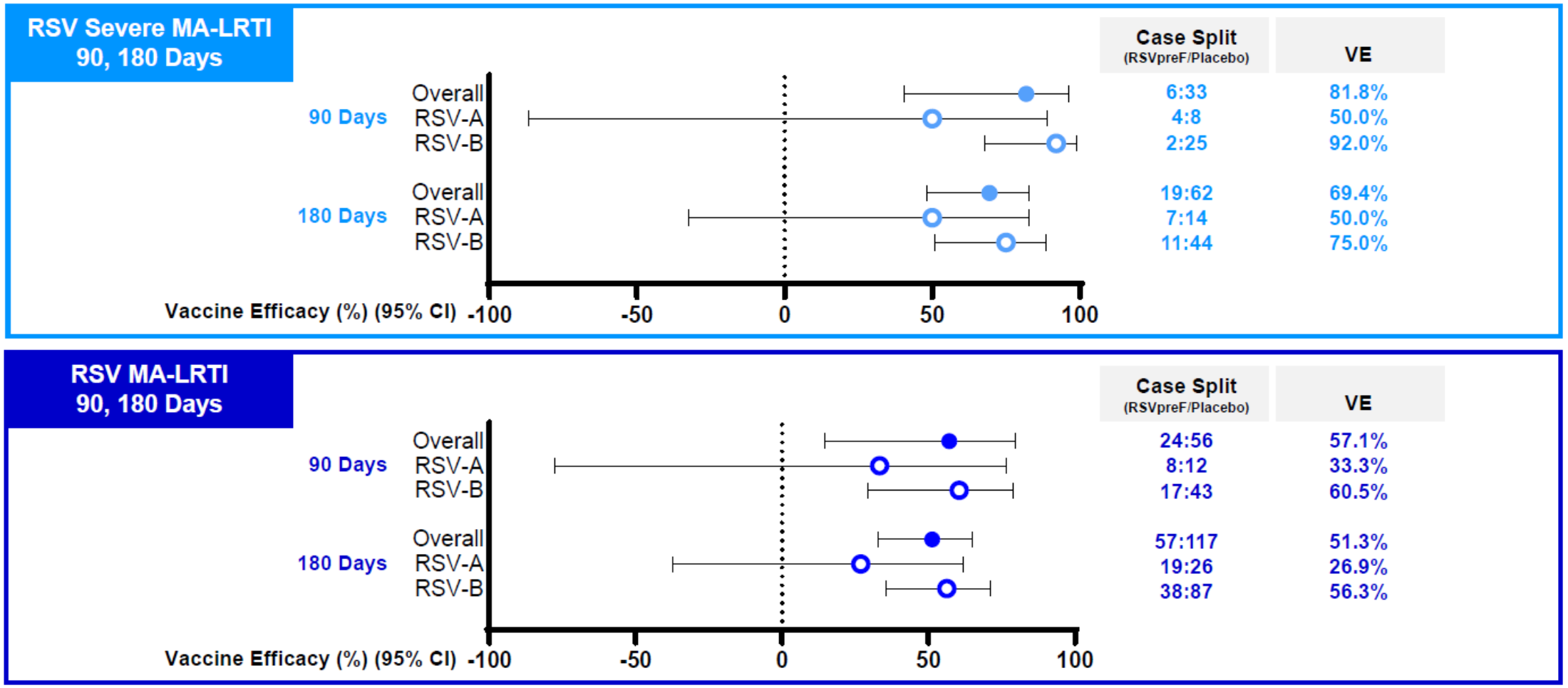
# Maternal Bivalent pre-F RSV vaccine efficacy

| Outcome | Vaccine Efficacy | | |
|---|---|---|---|
| | Over 3 months | Over 6 months | Over 12 months |
| Any Medically Attended RSV LRTI | **57.1%** (CI: 14.7%, 79.8%) | **51.3%** (29.4%, 66.8%) | **41.0%** (16.2 – 58.9%) |
| Severe Medically attended RSV LRTI | **81.8%** (CI: 40.6%, 96.3%) | **69.4%** (44.3%, 84.1%) | N/A |
| Hospitalisations with RSV ALRTI | **67.7%** (15.9 – 89.5%) | **56.4%** (10.1 – 80.7%) | **33.3%** (-17.6 – 62.9%) |
| Any Medically Attended RSV RTI | **39.1%** (16.7 – 55.7%) | **37.9%** (24 – 49.5%) | N/A |

- Vaccine well-tolerated with no safety concerns for vaccinated mothers and their newborns
- Submission for FDA registration in Feb 2023, approved by advisory committee May 2023
- Confirms efficacy of RSV maternal immunisation though duration critical

# Bivalent RSV vaccine protects against both strains

## Consistent efficacy Was Observed Across RSV Subgroup A and B*




* Exploratory Endpoint – no prespecified criterion for RSV A and B

# Maternal RSV immunisation Summary

- No safety concerns and well tolerated in pregnant women
- Is immunogenic with passive antibody transfer to the infant
- Is likely to be effective in the first 180 days
- Prevents both lower and upper respiratory infections
- Timing of vaccination during pregnancy and related to season is important
- No evidence of disease enhancement in subsequent year

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# RSV Immunoprophylaxis

- RSV protection for infants to young to be vaccinated:
  - Maternal vaccines:
    - Mothers more influenced by protection of baby than themselves
    - Accepted NIP strategy for the prevention of maternal and infant disease with Influenza, Pertussis
  - Monoclonal antibodies
    - complements maternal vaccination strategy especially for premature infants as most of IgG transfer occurs in the last trimester of gestation
    - Able to target other groups including older at-risk infants
    - Maybe easier to implement but not considered as part of NIP
    - Acceptance of new technology

# RSV vaccine for older adults

Promising results from recent studies

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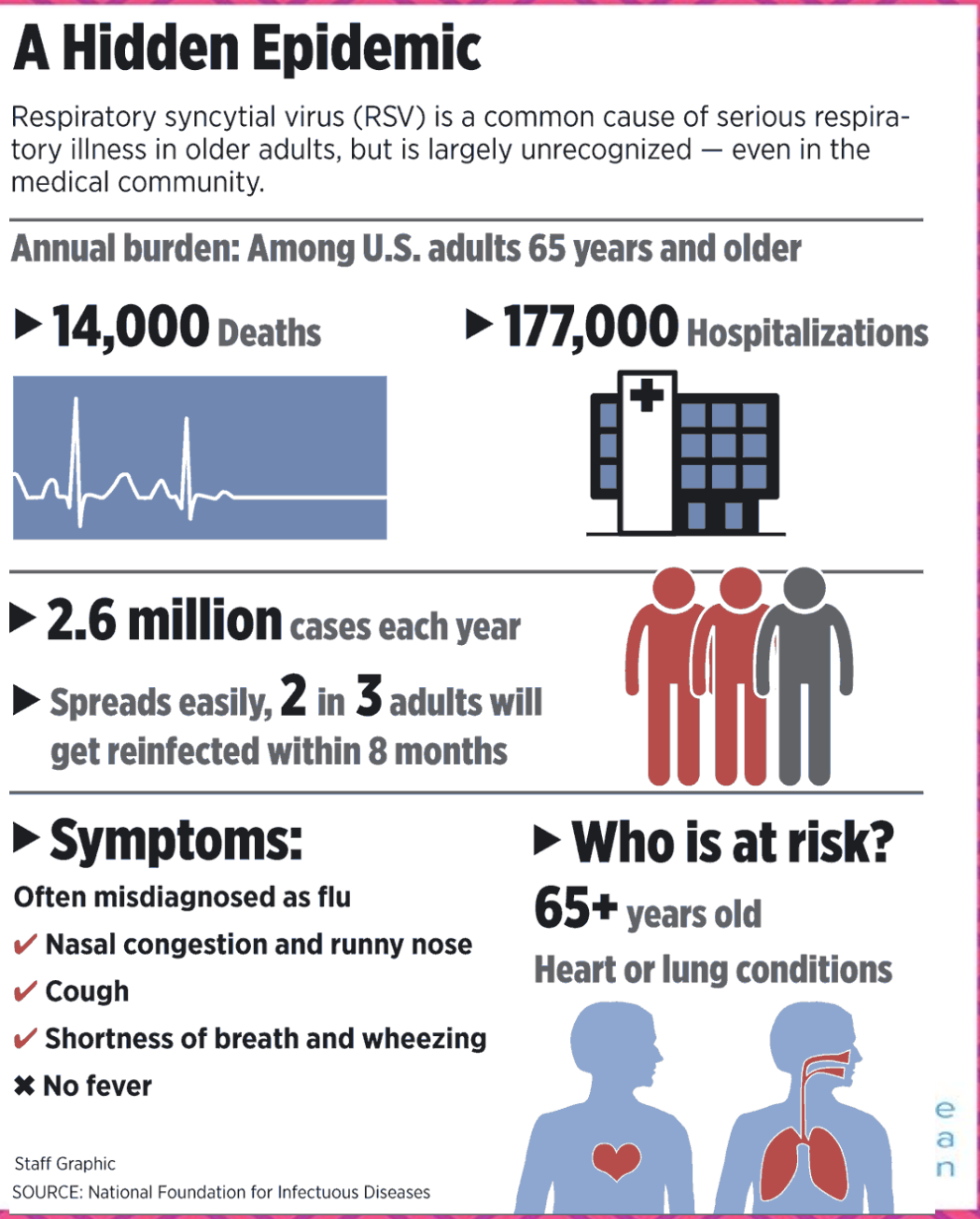


# Comparison of RSV Vaccine efficacy in older adults

Increasing severity

| GlaxoSmithkline (n=24,966) | | Pfizer (n=34,283) | | Moderna[1] (n=37,500) | | Janssen[2] (n=5782) | |
|---|---|---|---|---|---|---|---|
| **Outcome** | **Efficacy** | **Outcome** | **Efficacy** | **Outcome** | **Efficacy** | **Outcome** | **Efficacy** |
| RSV Acute RTI | 71.7% | RSV ARTI | 62.1% | RSV ARTI | N/A | RSV ARTI | N/A |
| RSV Acute LRT disease with ≥2 LRT Sx/signs inc 1 LR sign or 2 LR signs or 3 LR Sx | 82.6% | RSV LRTI with ≥2 Sx/signs | 66.7% | RSV LRTI with ≥2 Sx/signs | 83.7% (CI: 66%, 92%) | RSV LRTI with ≥2 Sx/signs | 75% (CI: 50-88%) |
| | | RSV LRTI with ≥3 Sx / signs | 85.7% | RSV LRTI with ≥3 Sx / signs | 82.4% (CI: 35%, 95%) | RSV LRTI with ≥3 Sx / signs | 80% (CI: 52-93%), |
| RSV LRTI with ≥2 lower resp. signs or assessed as severe by PI | 94.1% | | | | | RSV LRTI with ≥2 Sx or ≥1 LRTI Sx with ≥1 systemic Sx | 70% (CI: 44-85%) |

Sx – symptoms

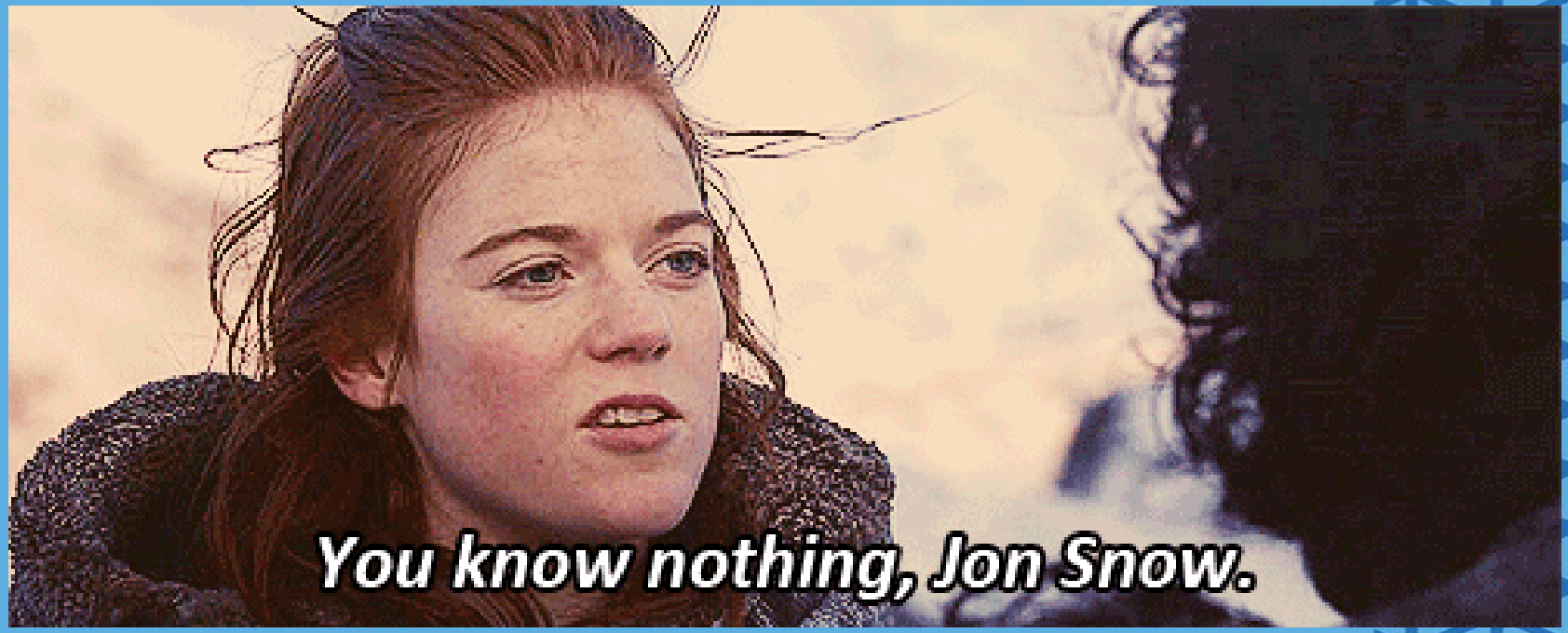

1. https://investors.modernatx.com/news/news-details/2023/Moderna-Announces-mRNA-1345-an-Investigational *RSV vaccine*
2. *https://www.janssen.com/janssen-announces-respiratory-syncytial-virus-rsv-adult-vaccine-candidate-maintains-high-efficacy*

# Summary

- RSV is a major cause of paediatric diseases and mortality
  - New technologies are delivering effective prevention strategies
- Maternal RSV vaccination
  - Well tolerated and immunogenic with passive antibody transfer
  - Is likely to be effective against ALRI in the short term (90 – 180 days)
  - No evidence of disease enhancement
- RSV vaccines for older adults appear highly effective against mild-moderate disease
- Paediatric RSV vaccines in early phase trials to reduce burden in older children

# Acknowledgements


- Telethon Kids Institute
  - Vaccine Trials Group
  - Hannah Moore Minda Sarna, Ruomei Xu, Parveen Fathima, Chris Blyth
- Australian and Overseas investigators  involved in trials
- ACIP for public provision of meeting data
- Wesfarmers Centre Community Reference Group
- Funding
  - Telethon-Perth Children's Hospital Research Fund
  - Merck IISP




# Questions?

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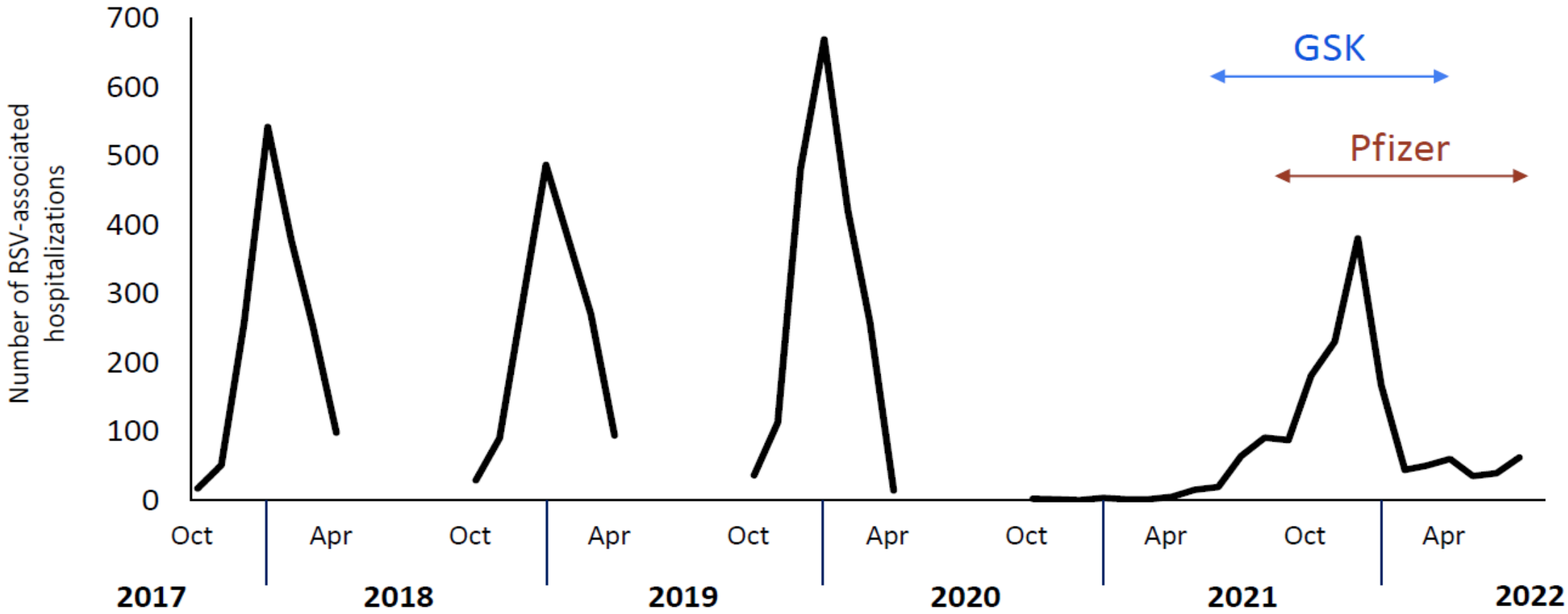
# Timing of RSV efficacy studies may affect point estimates




RSVNet unpublished preliminary data – presented at ACIP meeting Oct 2022

# Exploring under-ascertainment of RSV hospital burden

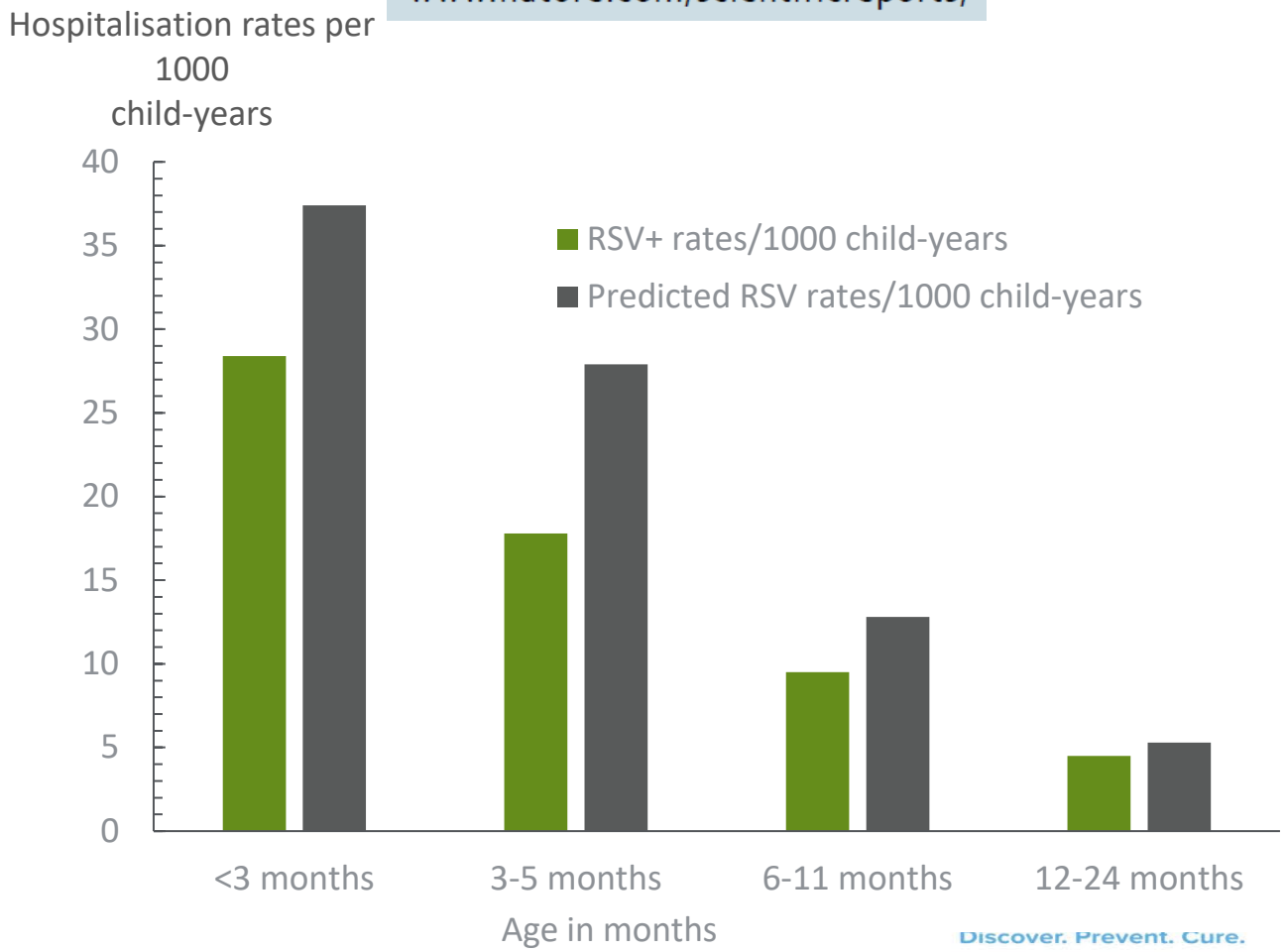
**Developing a prediction model to estimate the true burden of respiratory syncytial virus (RSV) in hospitalised children in Western Australia**

Amanuel Tesfay Gebremedhin[1✉], Alexandra B. Hogan[2], Christopher C. Blyth[1,3,4,5], Kathryn Glass[6] & Hannah C. Moore[1]

www.nature.com/scientificreports/

Linked hospital + perinatal + RSV laboratory testing: 2000-2012

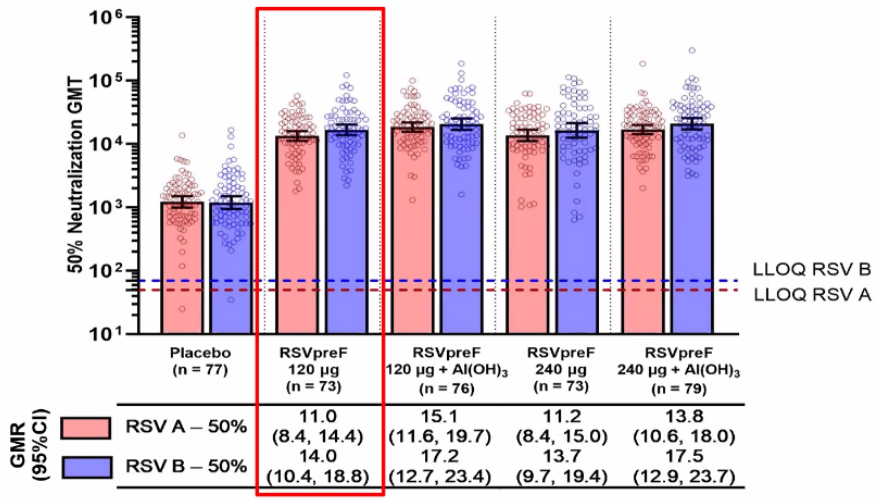
- Prediction model of RSV test positivity <5 years
  - Perinatal, clinical and socio-demographic factors
- Applied predicted probabilities to full hospitalisation dataset to estimate "true burden of RSV"
- Laboratory testing data may be underestimating RSV incidence by 30-57%




*Gebremedhin et al (2022) SciReports*

## RSVpreF elicits neutralizing GMR 11-14 at chosen dose in pregnant women

RSV-A and RSV-B 50% neutralizing geometric mean titers at delivery and geometric mean ratio versus placebo

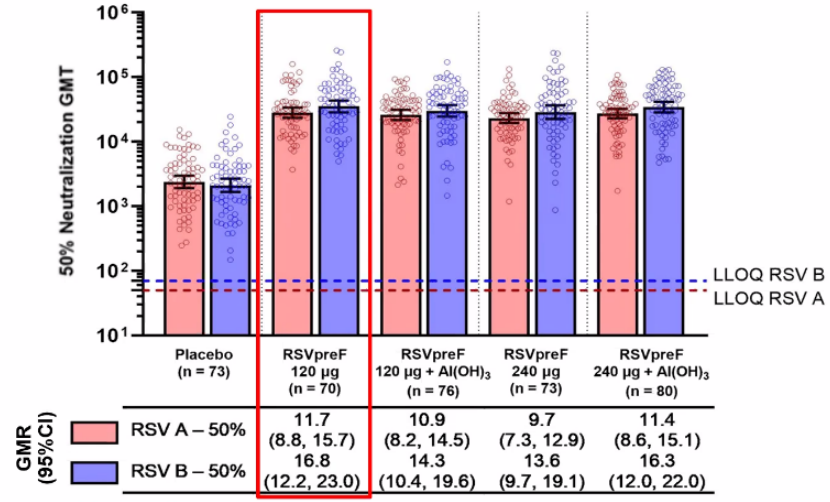



Pfizer Worldwide Research, Development and Medical
Vaccine Clinical Research and Development



## High cord blood neutralizing titers in infants

RSV-A and RSV-B 50% neutralizing geometric mean titers at birth and geometric mean ratio versus placebo




Pfizer Worldwide Research, Development and Medical
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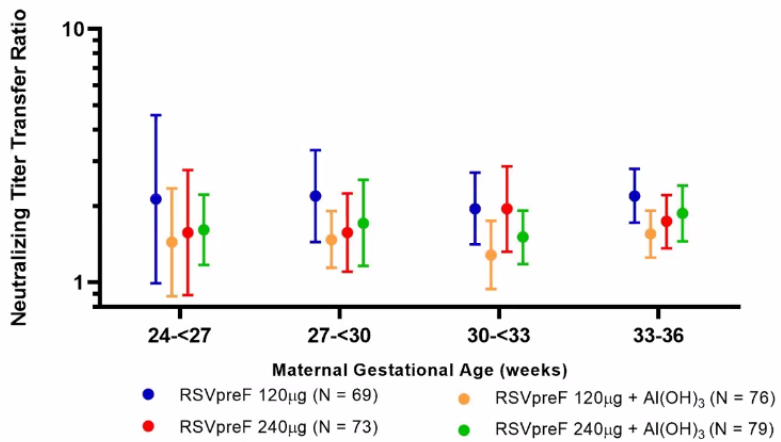
## Transplacental transfer consistent across broad range of gestational age at vaccination




## RSVpreF given to pregnant women prevents infant RSV-positive LRTI

*4:1 vaccine to placebo ratio*

| | RSVpreF (N=405) | Placebo (N=103) | Vaccine Efficacy (95% CI) |
|---|---|---|---|
| **Analyses and Definitions** | | | |
| **Medically attended LRTI**<br>Medically attended visit and ≥1:<br>• tachypnea (RR ≥60 (<2 m [60 days]) or ≥50 (≥2 to 12 m);<br>• peripheral capillary oxygen saturation (SpO2) measured in room air <95%;<br>• chest wall indrawing | 3 | 5 | 84.7%<br>(21.6%, 97.6%) |
| **Medically attended severe LRTI**<br>Medically attended visit and ≥1:<br>• tachypnea (RR ≥70 (<2 m [60 days]) or ≥60 (≥2 to 12 m);<br>• SpO2 measured in room air <93%;<br>• high-flow nasal cannula or mechanical ventilation;<br>• ICU admission for >4 hours; unresponsive/unconscious | 1 | 3 | 91.5%<br>(-5.6%, 99.8%) |