# RSV vaccination in the elderly

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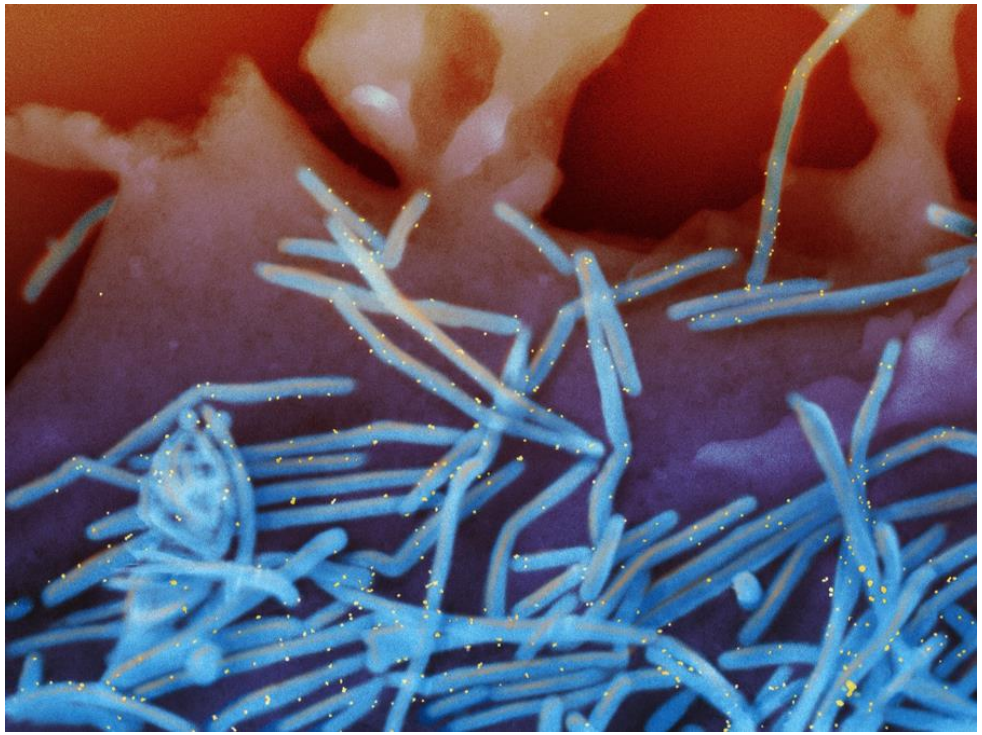
# Respiratory syncytial virus (RSV)

- **Respiratory syncytial virus (RSV)** was discovered in 1956 and was initially dubbed "*chimpanzee coryza agent*"

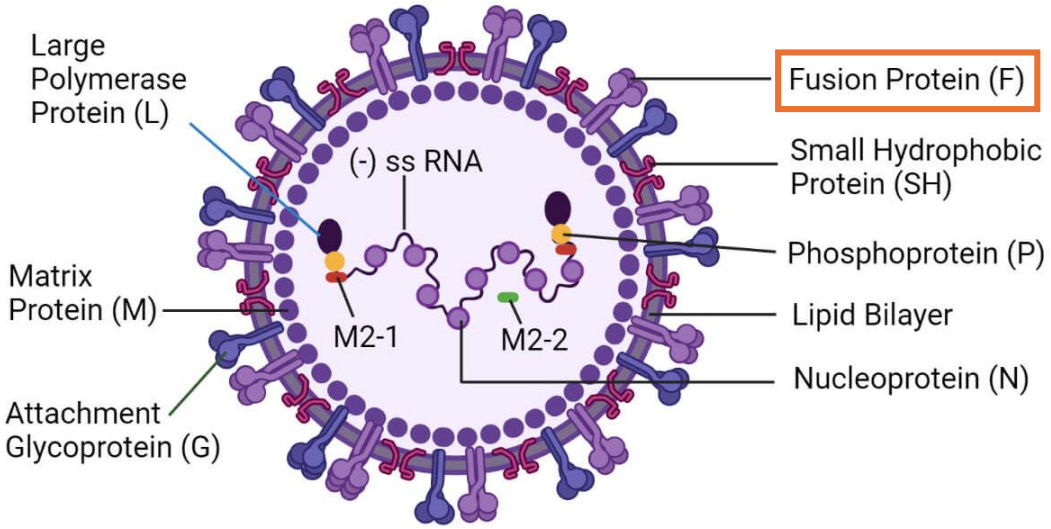
- In 1957, it was found to be the cause of **bronchiolitis**



Scanning electron micrograph of RSV virions (colorized blue) and labeled with anti-RSV F protein/gold antibodies (colorized yellow) shedding from the surface of human lung epithelial A549 cells.
Credit: NIAID/NIH

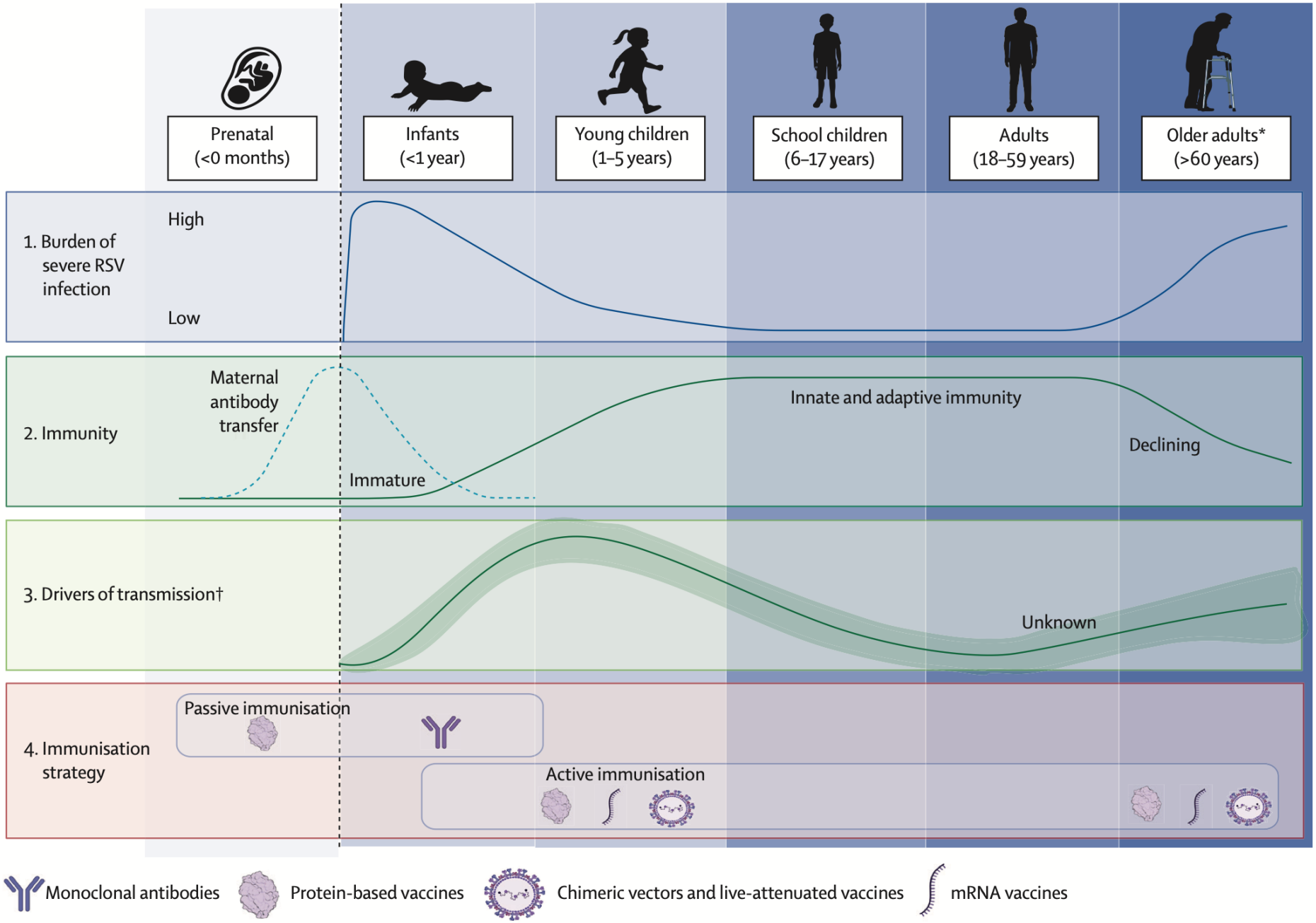
Graham, *NEJM* 2023

# Respiratory syncytial virus (RSV)




- **PreF is the active form** of the F protein on the **virion surface**; it is ***metastable***, meaning that is triggered easily and unpredictably **to refold to its postF conformation**
- **PostF** is extremely ***stable*** and cannot return to its functional preF form
- Briefly, once a virion is bound to a target cell via its G protein, preF is triggered and refolds in a dramatic structural rearrangement that links and fuses the virion and host cell membranes, becoming postF

Mejias et al, *Ann Allergy Asthma Immunol* 2020




Terstappen et al, *Lancet Infect Dis.* 2024

# Respiratory syncytial virus (RSV)

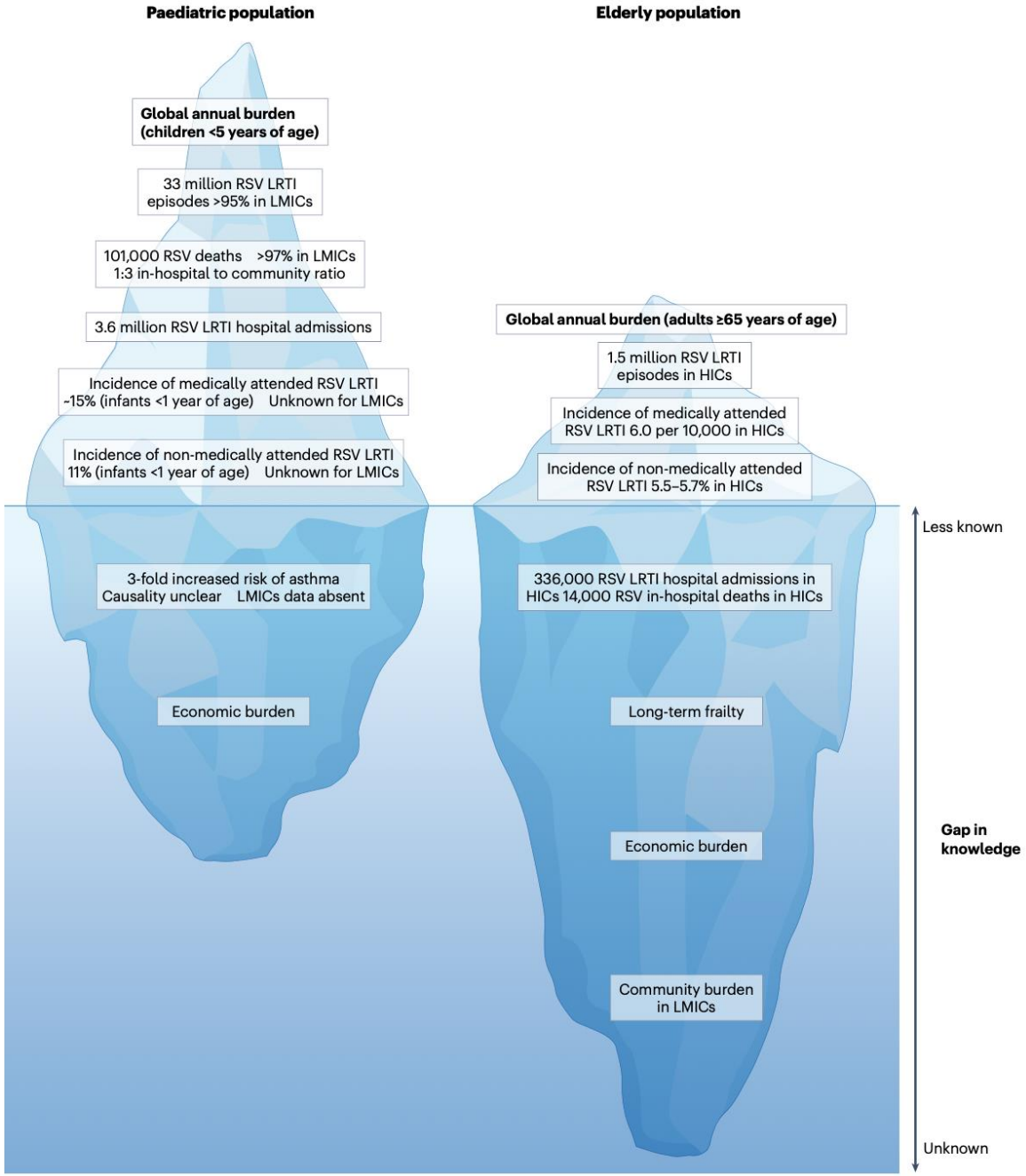
- RSV **infects everyone by 3 years of age** and **repeatedly infects people every few years** throughout life

- Although most infections result in **mild or no disease**, **2–3% of infants are hospitalized with RSV during their first year of life**, which makes RSV a **leading cause of hospitalization in children younger than 5 years of age**

- It is also a **major cause of death**, rivaling seasonal influenza, among **frail older adults**

Graham, *NEJM* 2023

# The burden of RSV disease




Langedijk et al, *Nat Rev Microbiol* 2023

# The burden of RSV disease in elderly

- **RSV illness** develops in approximately **3–7% of healthy older adults** in the United States and Europe each year, with an estimated **177,000 hospitalizations** and **14,000 deaths** each year in the United States
- The **severity of illness among older adults** who are hospitalized with RSV disease is substantial: **18%** are admitted to an **intensive care unit**, **31%** receive **home health services at discharge**, and **26% die** within 1 year after admission
- Older adults are at increased risk for RSV-related complications and death owing to **age-related immunosenescence** and a higher prevalence of **underlying conditions**
- **RSV shedding** also occurs at **higher levels** and for a **longer duration** in **older adults** than in younger adults

Falsey et al, *NEJM* 2005
Korsten et al, *Eur Respir J* 2021
Ackerson et al, *Clin Infect Dis* 2019

# The journey to RSV vaccines

- To address the disease burden, especially in infants younger than 6 months of age, **vaccine-development efforts began within a few years after the virus was discovered**

- At the time, the **whole-inactivated polio vaccine** developed by Salk was a **new and promising intervention**. It had been licensed in 1955, and by the early 1960s, cases of paralytic polio in the United States had dropped from tens of thousands to a few dozen per year

Graham, *NEJM* 2023

# The journey to RSV vaccines

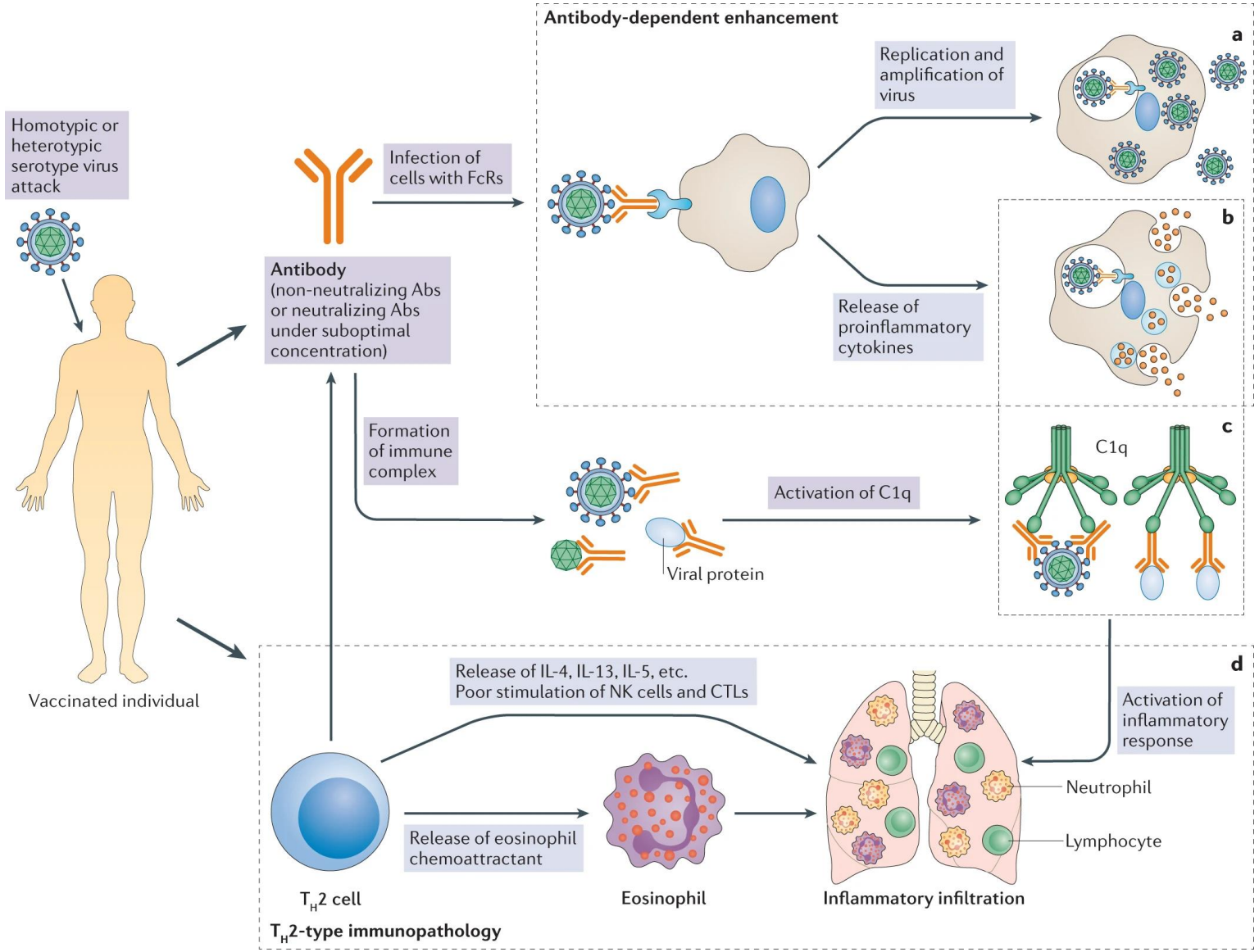
- **Informed and encouraged by that success, researchers developed a whole-inactivated RSV vaccine** and conducted four large studies in 1965 and 1966

- The **youngest cohort of children** was immunized before 6 months of age and before their first RSV infection. During the **winter of 1966–1967**, there was an **outbreak of RSV in the youngest age group**, and **of the 31 vaccinated infants, 20 were infected, 16 were hospitalized, and 2 died**

- This tragedy put an **end to RSV vaccine development for decades**

Graham, *NEJM* 2023

# Vaccine-associated enhanced disease (VAED)




Su et al, *Nat Rev Microbiol* 2020

# The journey to RSV vaccines

- After nearly **30 years of work** to elucidate the **immunologic events** that resulted in **RSV-vaccine–enhanced disease**, **vaccine development efforts were cautiously reinitiated**

- **Greater understanding of how to avoid RSV-vaccine–enhanced disease**, along with the availability of **new technologies**, led to the **exploration of multiple vaccine approaches**, including live virus, chimeric viruses, vector-based delivery, subunit proteins, peptides, virus-like particles, and nanoparticle display

Graham, *NEJM* 2023

# The journey to RSV vaccines

- Five phase 3 trials were conducted using **F protein in the postfusion conformation**, *which was known to be a target of neutralizing antibodies*
- Two trials used **virus-derived protein**, and three were based on **recombinant proteins**, one from insect cells and two from Chinese hamster ovary cells
- None of these candidate vaccines boosted neutralizing activity by more than a factor of five, and **trials did not achieve their primary efficacy objectives**

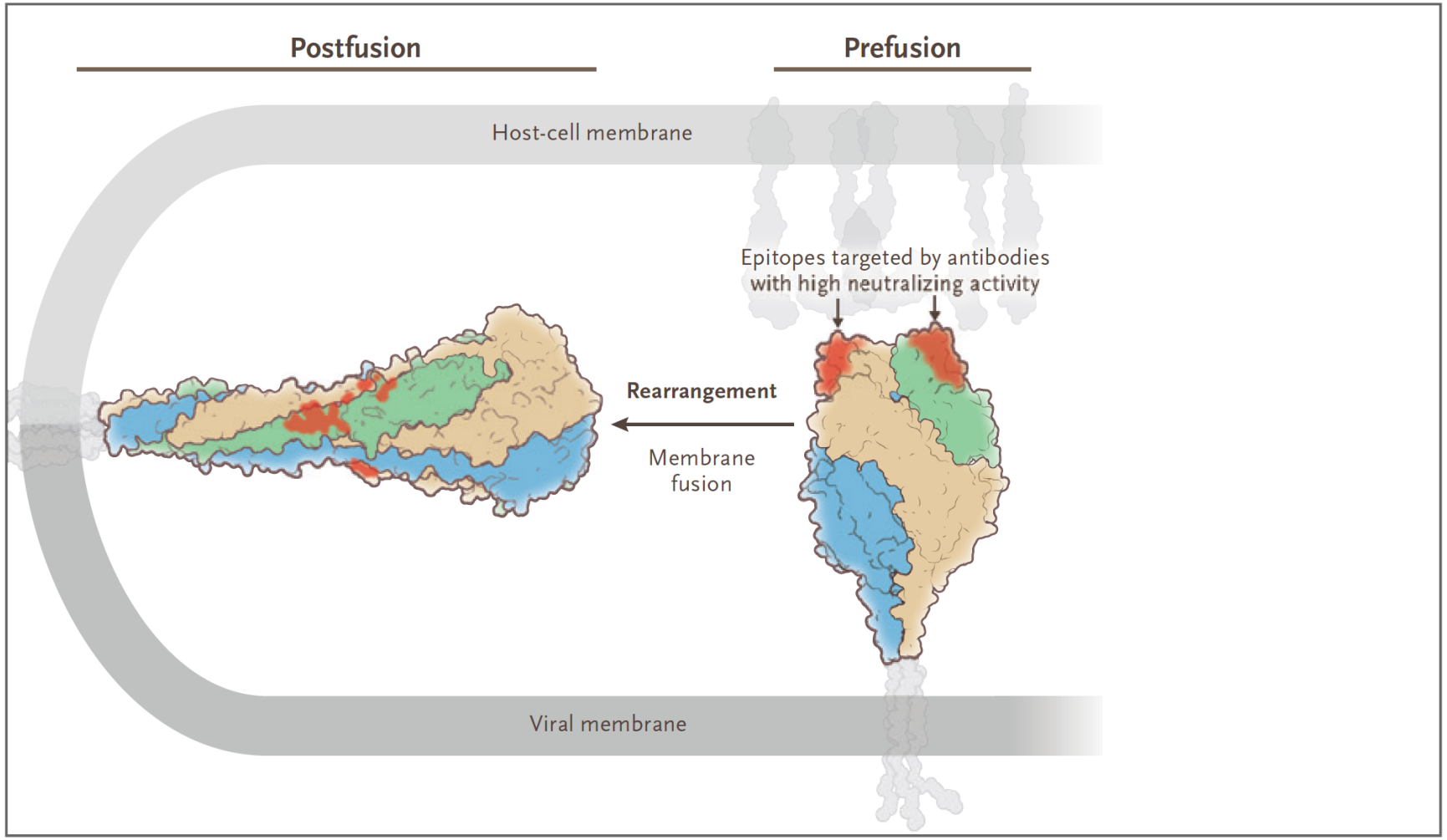
Graham, *NEJM* 2023

# The journey to RSV vaccines

- *In vitro* studies conducted by Melero and colleagues suggested that **antibodies specific for the prefusion form of F (preF)** may be responsible for **most of the neutralizing activity** in human serum

- Collectively, these studies suggested that the **protein structure of F** could be a **key factor in the antigenicity of RSV**

Graham, *NEJM* 2023




**The Effect of Respiratory Syncytial Virus (RSV) Fusion Glycoprotein (F) Structure on Antigenicity.**

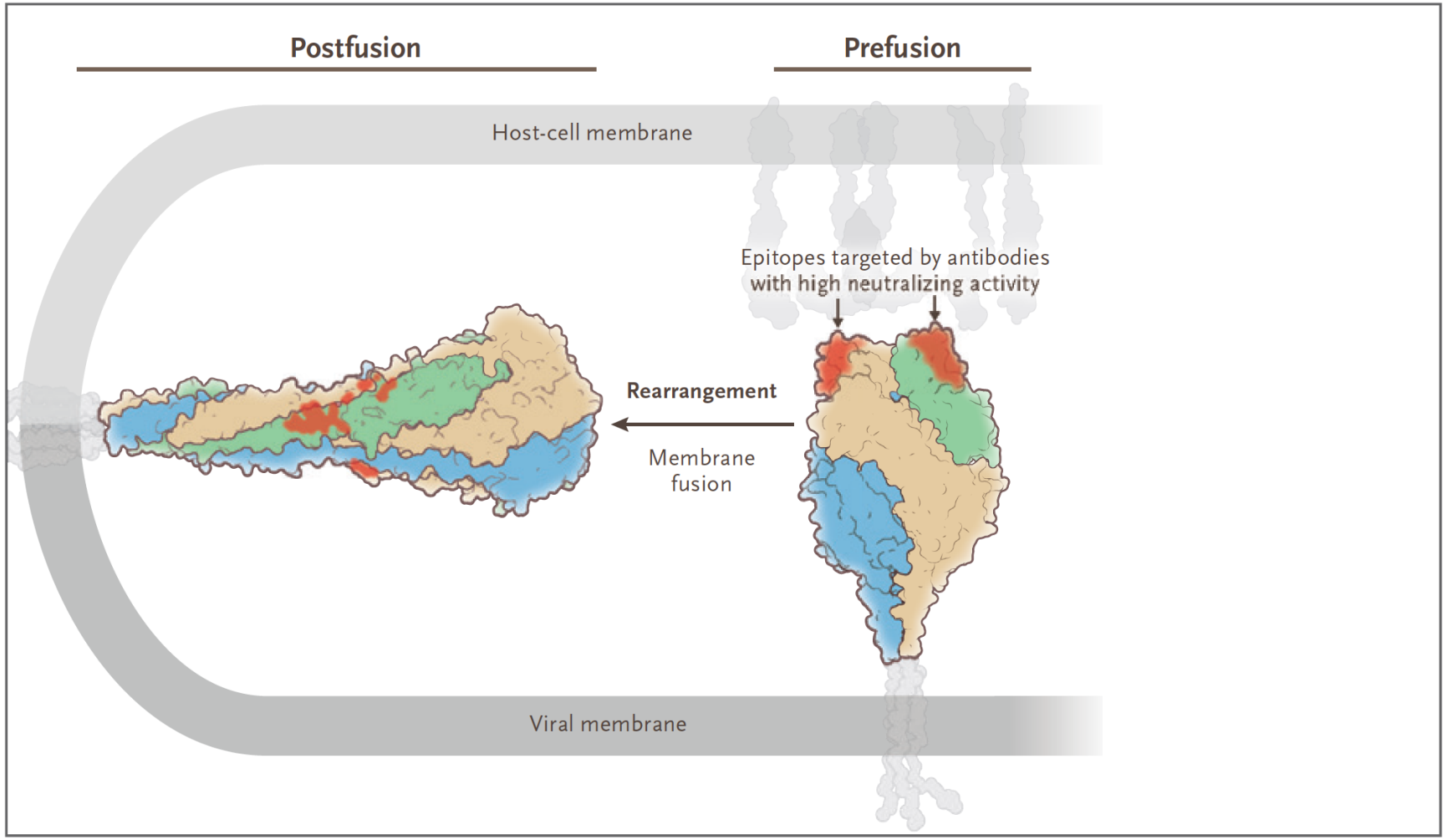
The trimeric RSV F protein in its prefusion state (middle) is anchored on the viral envelope by a transmembrane domain at the C-terminus. At the apex of the prefusion F protein, there is an epitope (denoted in red) targeted by antibodies with high neutralizing activity. When F protein rearranges into the postfusion form (left), either spontaneously on the viral membrane or after creating a fusion pore with the host-cell membrane, the epitope is lost. Stabilizing mutations can be introduced on the interior of the protein (right, small circled areas) to hold it in the prefusion conformation and preserve neutralization-sensitive epitopes at the apex for use as a vaccine antigen. The ectodomain of RSV F vaccines can be delivered as a soluble trimeric protein (right) by constraining the C-terminus (right, large circled area) or, if expressed by gene delivery, the membrane of the protein can be anchored by retaining the transmembrane domain.

Graham, *NEJM* 2023

# The journey to RSV vaccines

- Obtaining **RSV preF crystals** was difficult, because **the unmodified and untethered protein spontaneously rearranges into its highly stable postfusion conformation**
- Ultimately, a **trimerization domain derived from the fibritin protein from T4 phage** was used **at the C-terminal domain**, and **antibody Fab fragments that could form a complex by binding the apex of preF** were used to stabilize the trimer
- Having **preF as a reagent** allowed **detailed mapping of the antigenic surface of F** in all its conformations, **defining of the contribution of each epitope to virus neutralization**

Graham, *NEJM* 2023

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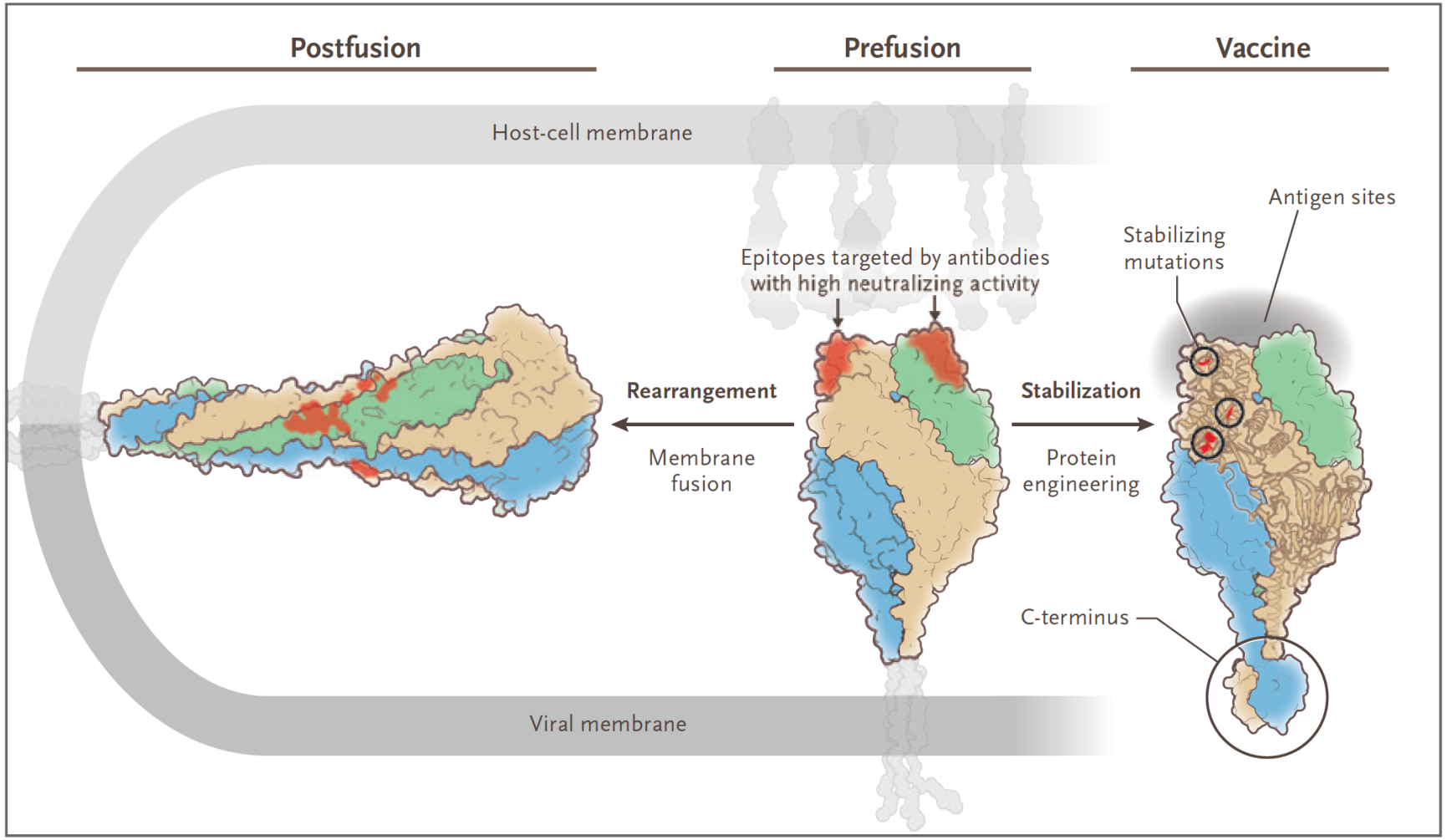
Graham, *NEJM* 2023

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Graham, *NEJM* 2023

Science

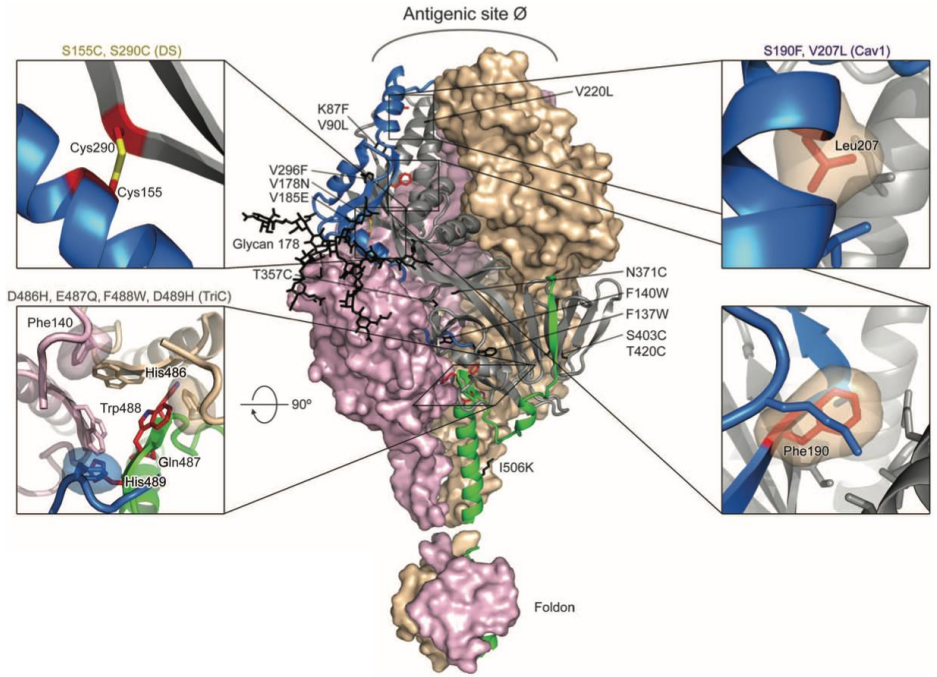


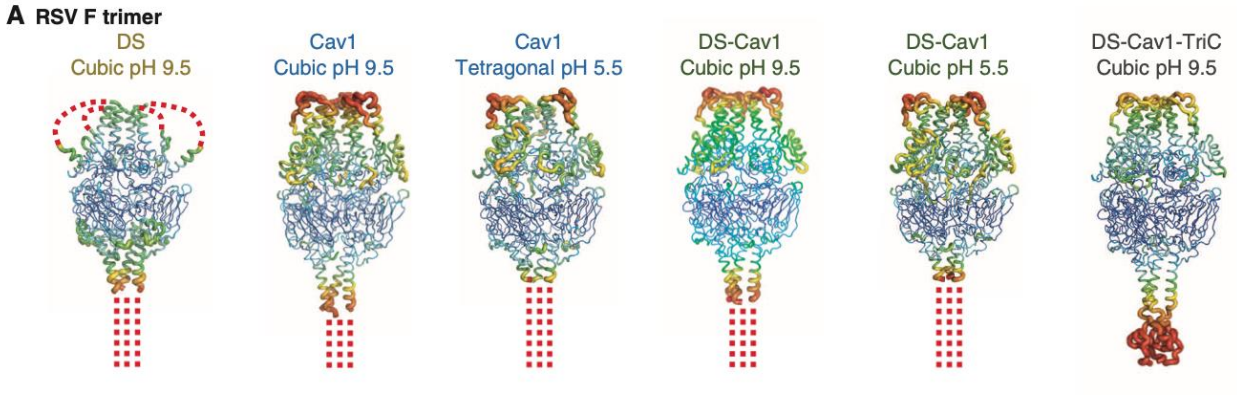
RESEARCH ARTICLE

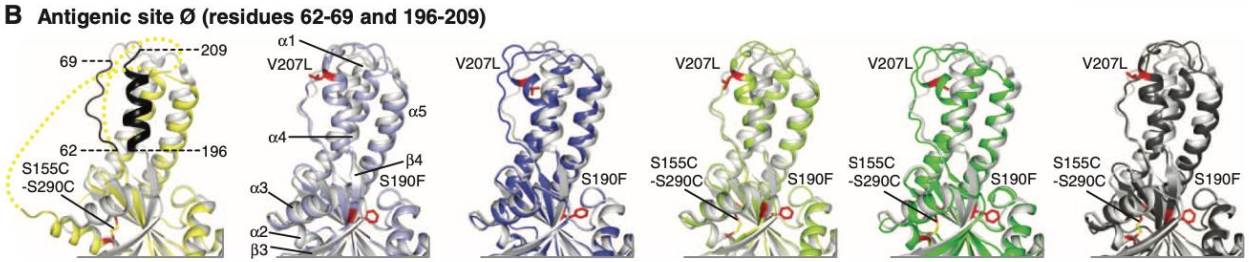
# Structure-Based Design of a Fusion Glycoprotein Vaccine for Respiratory Syncytial Virus

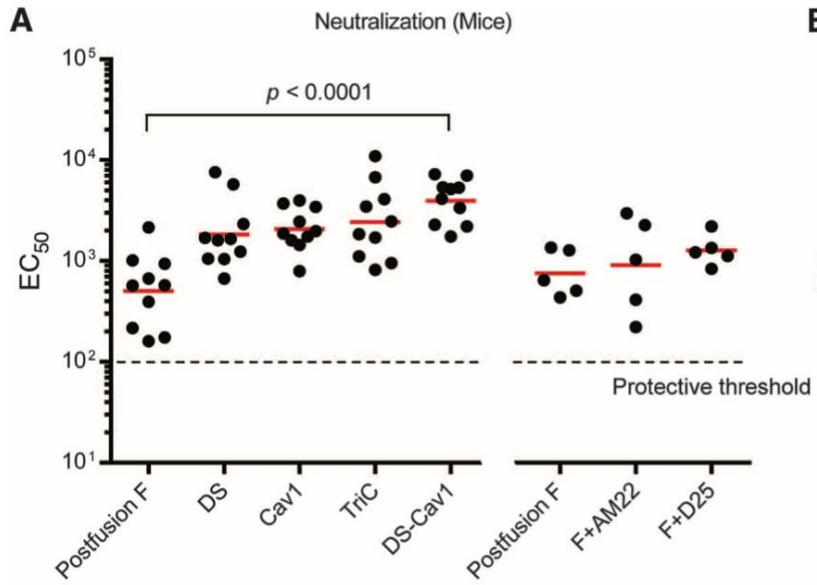
JASON S. MCLELLAN, MAN CHEN, M. GORDON JOYCE, MALLIKA SASTRY, GUILLAUME B. E. STEWART-JONES, YONGPING YANG, BAOSHAN ZHANG, LEI CHEN, SANJAY SRIVATSAN, ANQI ZHENG, TONGQING ZHOU, KEVIN W. GRAEPEL, AZAD KUMAR, SYED MOIN, JEFFREY C. BOYINGTON, GWO-YU CHUANG, CINQUE SOTO, ULRICH BAXA, ARJEN Q. BAKKER, HERGEN SPITS, TIM BEAUMONT, ZIZHENG ZHENG, NINGSHAO XIA, SUNG-YOUL KO, JOHN-PAUL TODD, SRINIVAS RAO, BARNEY S. GRAHAM, AND PETER D. KWONG fewer Authors Info & Affiliations

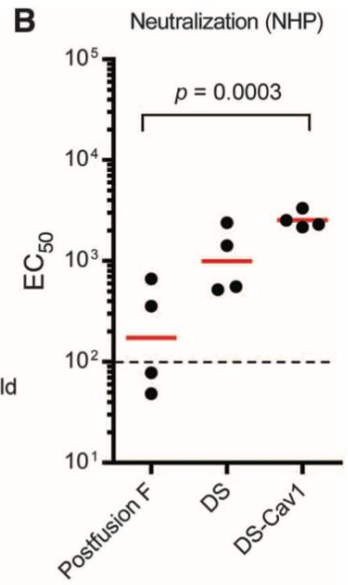
*SCIENCE* • 1 Nov 2013 • Vol 342, Issue 6158 • pp. 592-598 • DOI: 10.1126/science.1243283



nature COMMUNICATIONS

ARTICLE

Received 12 Mar 2015 | Accepted 23 Jul 2015 | Published 3 Sep 2015

DOI: 10.1038/ncomms9143 OPEN

# A highly stable prefusion RSV F vaccine derived from structural analysis of the fusion mechanism

Anders Krarup[1,*], Daphné Truan[1,*], Polina Furmanova-Hollenstein[1,*], Lies Bogaert[1], Pascale Bouchier[1], Ilona J.M. Bisschop[1], Myra N. Widjojoatmodjo[1], Roland Zahn[1], Hanneke Schuitemaker[1], Jason S. McLellan[2] & Johannes P.M. Langedijk[1]

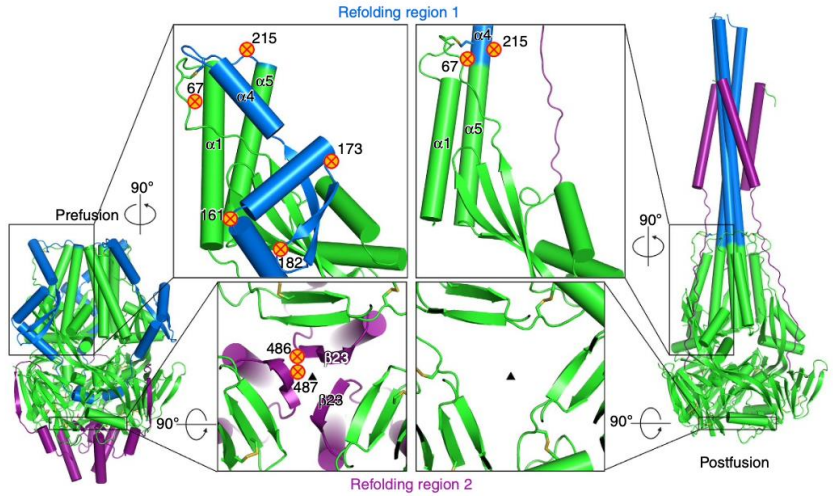
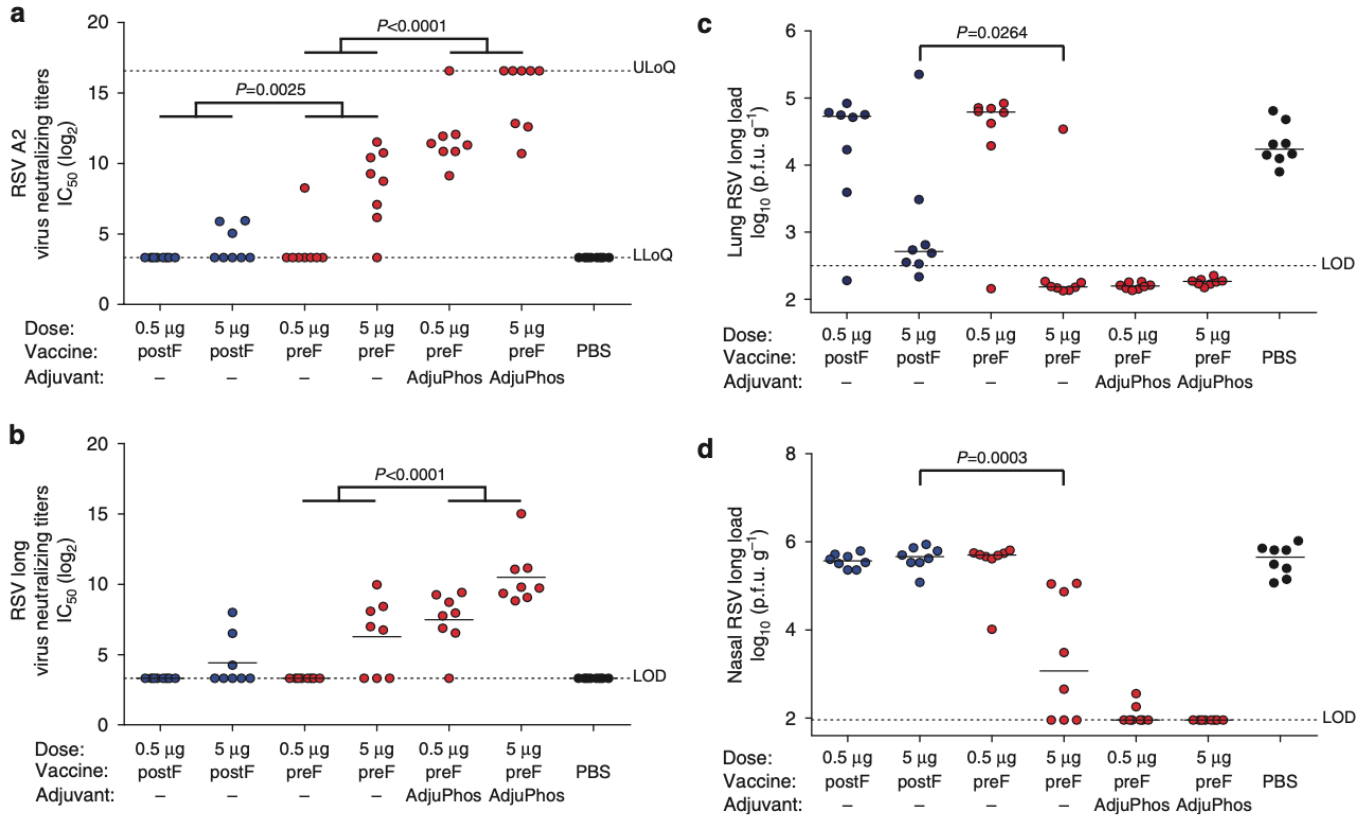



**Figure 2 | Strategy for prefusion F protein stabilization.** RSV F trimer and magnified views of prefusion F (left) and postfusion F protein (right) indicating refolding region 1 (RR1, blue) and refolding region 2 (RR2, purple) and location of amino acid substitutions indicated by crossed circles. The substitutions in the RR1 are designed to prevent the formation of the long helix. The substitutions in the RR2 are designed to reduce the negative charge repulsion between the β23 strands.



Science Immunology

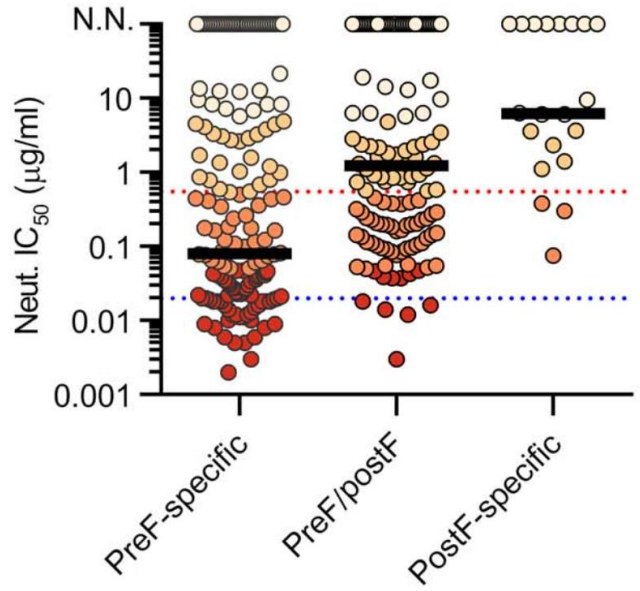


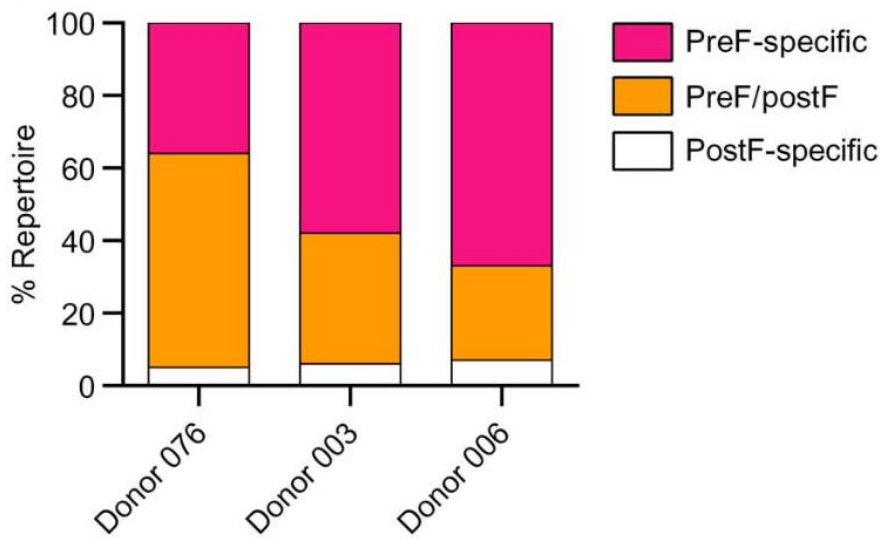
RESEARCH ARTICLE | INFECTIOUS DISEASE

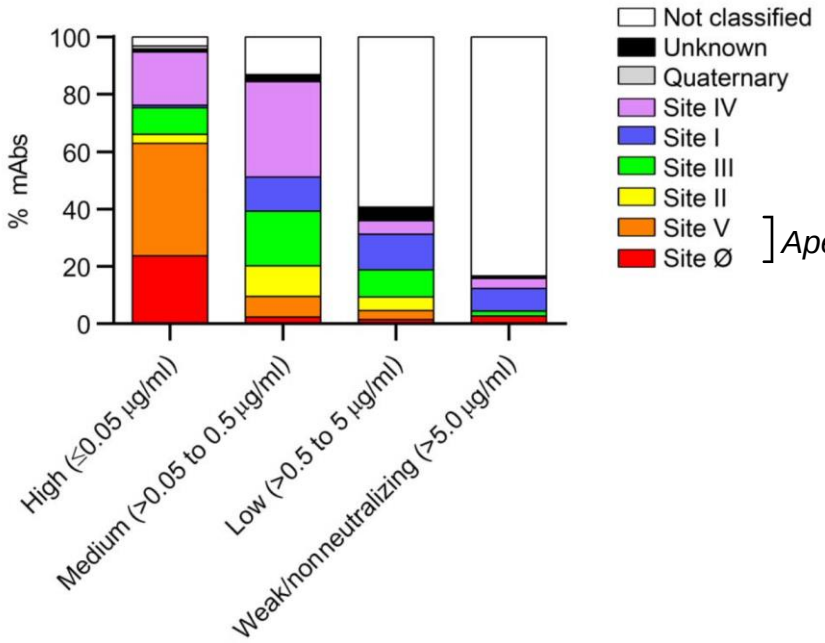
# Rapid profiling of RSV antibody repertoires from the memory B cells of naturally infected adult donors

MORGAN S. A. GILMAN, CARLOS A. CASTELLANOS, MAN CHEN, JOAN O. NGWUTA, EILEEN GOODWIN, SYED M. MOIN, VICENTE MAS, JOSÉ A. MELERO, PETER F. WRIGHT, BARNEY S. GRAHAM, JASON S. MCLELLAN, AND LAURA M. WALKER fewer Authors Info & Affiliations

*SCIENCE IMMUNOLOGY* • 23 Dec 2016 • Vol 1, Issue 6 • DOI: 10.1126/sciimmunol.aaj1879




*Apex of the preF trimer*

Science

HOME > SCIENCE > VOL. 365, NO. 6452 > A PROOF OF CONCEPT FOR STRUCTURE-BASED VACCINE DESIGN TARGETING RSV IN HUMANS

REPORT

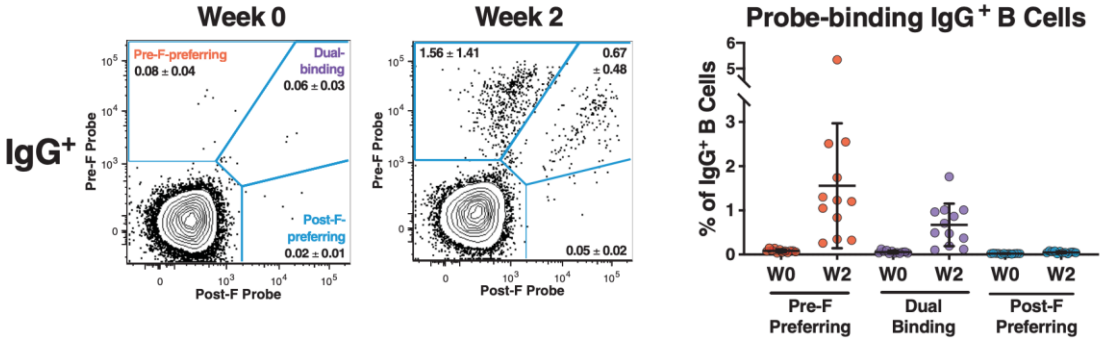
# A proof of concept for structure-based vaccine design targeting RSV in humans

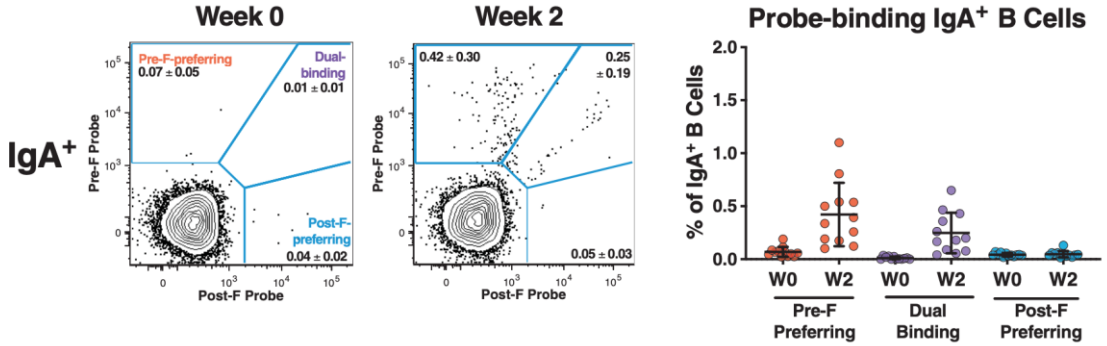
MICHELLE C. CRANK, TRACY J. RUCKWARDT, MAN CHEN, KAITLYN M. MORABITO, EMILY PHUNG, PAMELA J. COSTNER, LASONJI A. HOLMAN, SOMIA P. HICKMAN, NINA M. BERKOWITZ, [...], AND THE VRC 317 STUDY TEAM +22 authors Authors Info & Affiliations

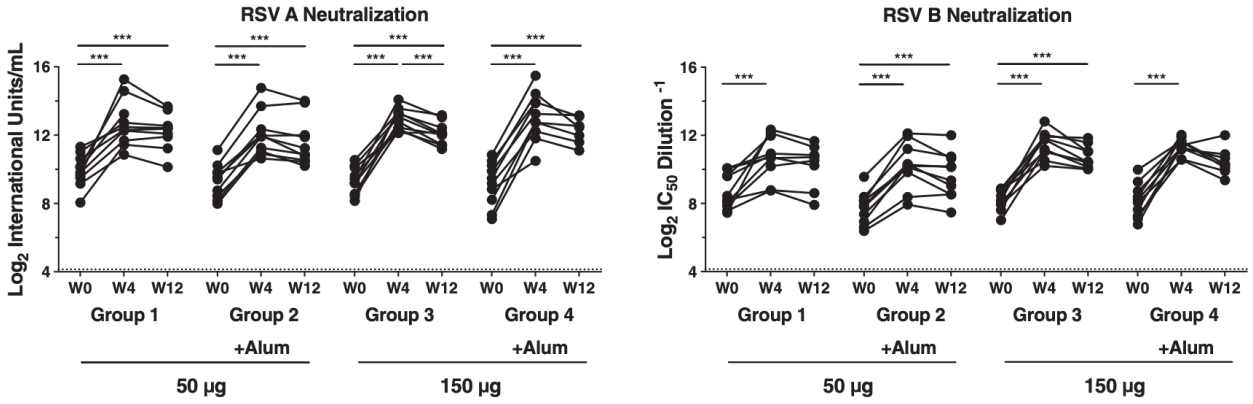
SCIENCE • 2 Aug 2019 • Vol 365, Issue 6452 • pp. 505-509 • DOI: 10.1126/science.aav9033

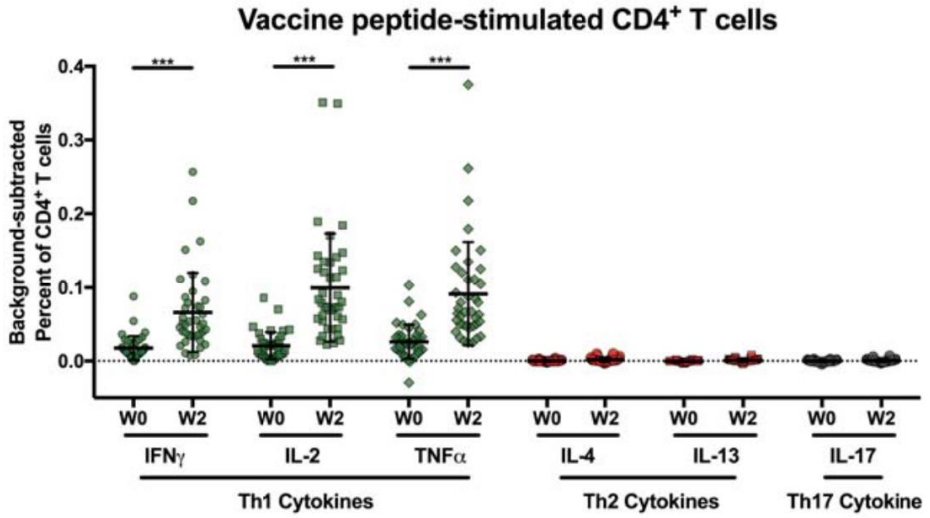
Randomized, open-label phase I dose-escalation clinical trial [Vaccine Research Center (VRC) 317] to evaluate two administrations of **DS-Cav1** (stabilized subunit vaccine candidate) with and without aluminum hydroxide (alum) formulation at three different dose levels in **healthy adults between 18 and 50 years of age**

*Interim analysis, evaluating immune responses to the first administration of 50 or 150 µg of DS-Cav1 with or without alum (n = 10 subjects per group)*



GSK

AREXVY
(RESPIRATORY SYNCYTIAL VIRUS VACCINE, ADJUVANTED)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Respiratory Syncytial Virus Prefusion F Protein Vaccine in Older Adults

A. Papi, M.G. Ison, J.M. Langley, D.-G. Lee, I. Leroux-Roels, F. Martinon-Torres, T.F. Schwarz, R.N. van Zyl-Smit, L. Campora, N. Dezutter, N. de Schrevel, L. Fissette, M.-P. David, M. Van der Wielen, L. Kostanyan, and V. Hulstrøm, for the AReSVi-006 Study Group*

Pfizer

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Respiratory Syncytial Virus Vaccine

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

E.E. Walsh, G. Pérez Marc, A.M. Zareba, A.R. Falsey, Q. Jiang, M. Patton, F.P. Polack, C. Llapur, P.A. Doreski, K. Ilangovan, M. Rämet, Y. Fukushima, N. Hussen, L.J. Bont, J. Cardona, E. DeHaan, G. Castillo Villa, M. Ingilizova, D. Eiras, T. Mikati, R.N. Shah, K. Schneider, D. Cooper, K. Koury, M.-M. Lino, A.S. Anderson, K.U. Jansen, K.A. Swanson, A. Gurtman, W.C. Gruber, and B. Schmoele-Thoma, for the RENOIR Clinical Trial Group*

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*

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mRESVIA®
(Respiratory Syncytial Virus Vaccine)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Efficacy and Safety of an mRNA-Based RSV PreF Vaccine in Older Adults

E. Wilson, J. Goswami, A.H. Baqui, P.A. Doreski, G. Perez-Marc, K. Zaman, J. Monroy, C.J.A. Duncan, M. Ujiie, M. Rämet, L. Pérez-Breva, A.R. Falsey, E.E. Walsh, R. Dhar, L. Wilson, J. Du, P. Ghaswalla, A. Kapoor, L. Lan, S. Mehta, R. Mithani, C.A. Panozzo, A.K. Simorellis, B.J. Kuter, F. Schödel, W. Huang, C. Reuter, K. Slobod, S.K. Stoszek, C.A. Shaw, J.M. Miller, R. Das, and G.L. Chen, for the ConquerRSV Study Group*

AREXVY (RESPIRATORY SYNCYTIAL VIRUS VACCINE, ADJUVANTED)

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ORIGINAL ARTICLE

# Respiratory Syncytial Virus Prefusion F Protein Vaccine in Older Adults

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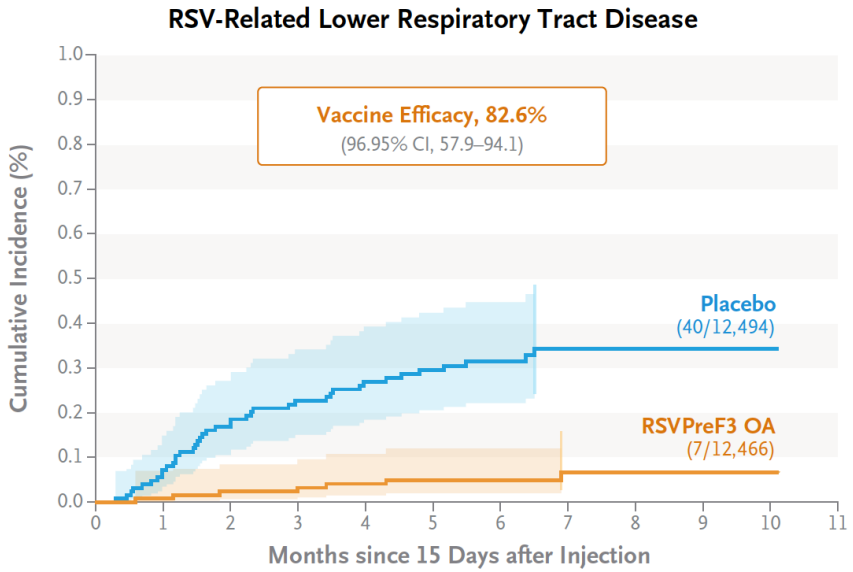
## CLINICAL TRIAL

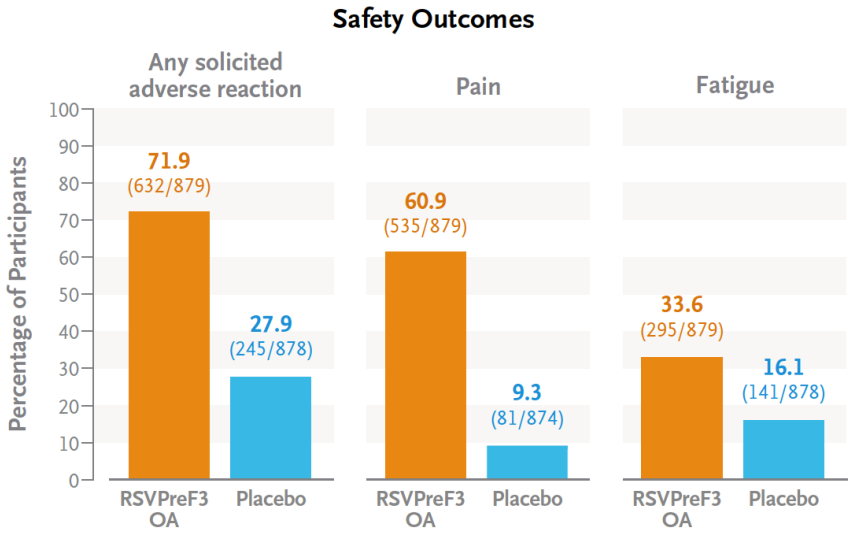
**Design:** An ongoing phase 3, international, randomized, placebo-controlled trial assessed the efficacy and safety of an AS01$_E$-adjuvanted respiratory syncytial virus (RSV) prefusion F protein–based candidate vaccine (RSVPreF3 OA) among adults ≥60 years of age.

**Intervention:** 25,040 participants in 17 countries were assigned to receive a single dose of the RSVPreF3 OA vaccine or placebo before the RSV season. The primary objective was to show vaccine efficacy against RSV-related lower respiratory tract disease during one RSV season.

**Efficacy:** During a median follow-up of 6.7 months, among 24,960 participants with evaluable data, vaccine efficacy against RSV-confirmed lower respiratory tract disease was >80%.




**Safety:** Solicited adverse events occurred more often with the vaccine than with placebo; most were mild to moderate in severity and resolved within the 4-day solicitation period. Pain was the most common solicited injection-site reaction with the vaccine, and fatigue was the most common solicited systemic reaction.




## LIMITATIONS AND REMAINING QUESTIONS

- A small number of frail participants and participants ≥80 years of age were included; longer follow-up is needed to determine efficacy in these subgroups.
- The trial had limited ability to detect rare side effects.
- Public health measures to limit Covid-19 transmission reduced the spread of RSV and altered the RSV season.
- Additional RSV seasons need to be studied to better understand vaccine efficacy.

## CONCLUSIONS

A single dose of an AS01$_E$-adjuvanted RSV prefusion F protein–based candidate vaccine (RSVPreF3 OA) given before the RSV season showed high efficacy against RSV-related lower respiratory tract disease and had an acceptable safety profile in adults ≥60 years of age.

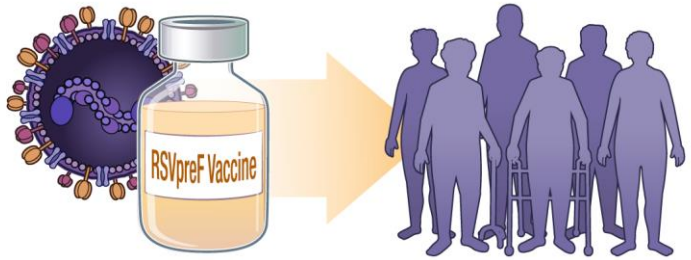
Pfizer ABRYSVO™ Respiratory Syncytial Virus Vaccine

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

E.E. Walsh, G. Pérez Marc, A.M. Zareba, A.R. Falsey, Q. Jiang, M. Patton, F.P. Polack, C. Llapur, P.A. Doreski, K. Ilangovan, M. Rämet, Y. Fukushima, N. Hussen, L.J. Bont, J. Cardona, E. DeHaan, G. Castillo Villa, M. Ingilizova, D. Eiras, T. Mikati, R.N. Shah, K. Schneider, D. Cooper, K. Koury, M.-M. Lino, A.S. Anderson, K.U. Jansen, K.A. Swanson, A. Gurtman, W.C. Gruber, and B. Schmoele-Thoma, for the RENOIR Clinical Trial Group*

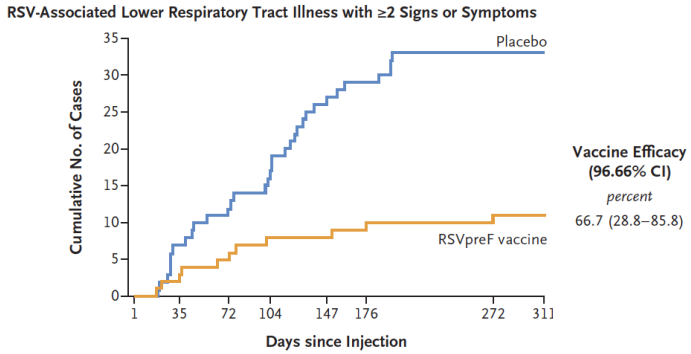


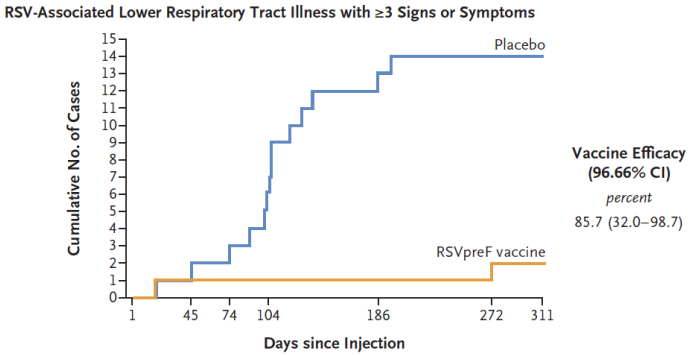

## CLINICAL TRIAL

**Design:** An ongoing, phase 3, multinational, double-blind, randomized, placebo-controlled trial evaluated the efficacy and safety of RSVpreF vaccine in adults ≥60 years of age during a single RSV season.

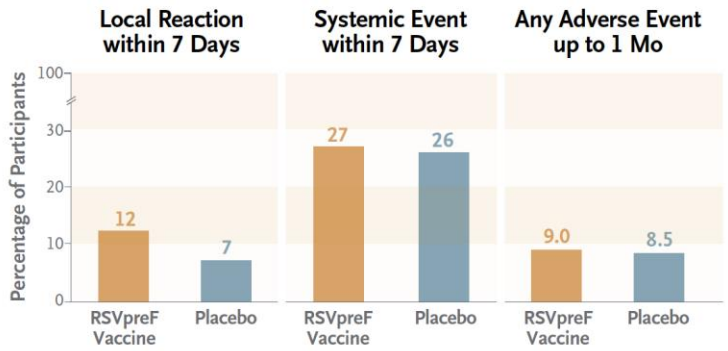
**Intervention:** 34,284 participants received one intramuscular 120-$\mu$g dose of RSVpreF vaccine (containing 60 $\mu$g each of RSV A and RSV B antigens) or placebo. The two primary end points were vaccine efficacy against RSV-associated lower respiratory tract illness with either ≥2 signs or symptoms or ≥3 signs or symptoms in the first RSV season (starting on day 15 after the injection).

**Efficacy:** The RSVpreF vaccine was effective in preventing RSV-associated lower respiratory tract illness with ≥2 or ≥3 signs or symptoms.




**Safety:** Local reactions were more common with RSVpreF vaccine than with placebo within 7 days after injection; incidences of systemic events were similar in the two groups. Incidences of adverse events through 1 month after injection were also similar in the two groups.




## LIMITATIONS AND REMAINING QUESTIONS

- Immunocompromised persons were excluded from the trial.
- Given the sample size, additional safety data are needed.
- The current prespecified interim analysis was limited to one RSV season; future analyses may assess whether vaccine efficacy persists beyond one season.

## CONCLUSIONS

**In adults ≥60 years of age, one dose of RSVpreF vaccine prevented RSV-associated symptomatic lower respiratory tract illness, with no apparent safety concerns, during a single RSV season.**

moderna mRESVIA® (Respiratory Syncytial Virus Vaccine)

The NEW ENGLAND JOURNAL of MEDICINE

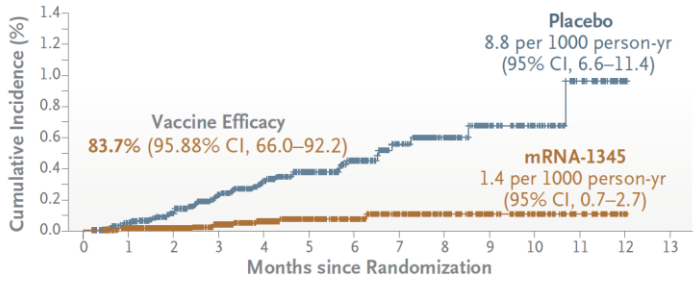
ORIGINAL ARTICLE

# Efficacy and Safety of an mRNA-Based RSV PreF Vaccine in Older Adults

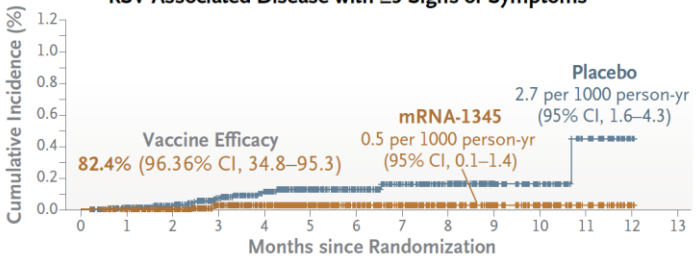
E. Wilson, J. Goswami, A.H. Baqui, P.A. Doreski, G. Perez-Marc, K. Zaman, J. Monroy, C.J.A. Duncan, M. Ujiie, M. Rämet, L. Pérez-Breva, A.R. Falsey, E.E. Walsh, R. Dhar, L. Wilson, J. Du, P. Ghaswalla, A. Kapoor, L. Lan, S. Mehta, R. Mithani, C.A. Panozzo, A.K. Simorellis, B.J. Kuter, F. Schödel, W. Huang, C. Reuter, K. Slobod, S.K. Stoszek, C.A. Shaw, J.M. Miller, R. Das, and G.L. Chen, for the ConquerRSV Study Group*

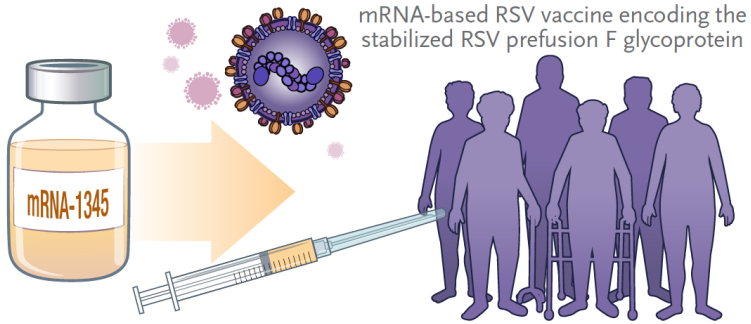
**Efficacy:** During a median follow-up of 112 days, the mRNA-1345 vaccine showed efficacy against RSV-associated lower respiratory tract disease with ≥2 and with ≥3 lower respiratory signs or symptoms.

**RSV-Associated Disease with ≥2 Signs or Symptoms**

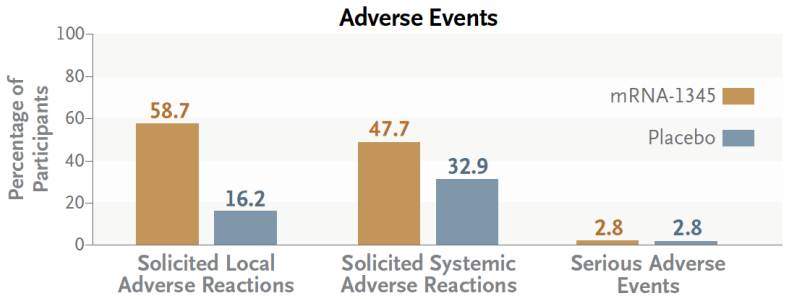



**RSV-Associated Disease with ≥3 Signs or Symptoms**




**Safety:** Solicited local and systemic adverse reactions were reported more often with the mRNA-1345 vaccine than with placebo; most adverse reactions were mild to moderate in severity and were transient. The incidence of serious adverse events did not differ between the groups.




## CLINICAL TRIAL

**Design:** An ongoing, phase 2–3, international, double-blind, randomized, placebo-controlled trial assessed the efficacy and safety of the mRNA-1345 vaccine in preventing RSV-associated lower respiratory tract disease in adults ≥60 years of age.

**Intervention:** 35,541 participants were assigned to receive a single intramuscular injection of mRNA-1345 or saline placebo. The two primary efficacy end points were the prevention of a first episode of RSV-associated lower respiratory tract disease with ≥2 signs or symptoms and with ≥3 signs or symptoms within 14 days to 12 months after injection.

## LIMITATIONS AND REMAINING QUESTIONS

- Participants with certain immunocompromising conditions were excluded from the trial.
- There were low case numbers in some subgroups, including participants ≥80 years of age and frail participants.
- Ongoing follow-up will assess the duration of protection from the vaccine, and the need for and appropriate timing of a booster are under study.

## CONCLUSIONS

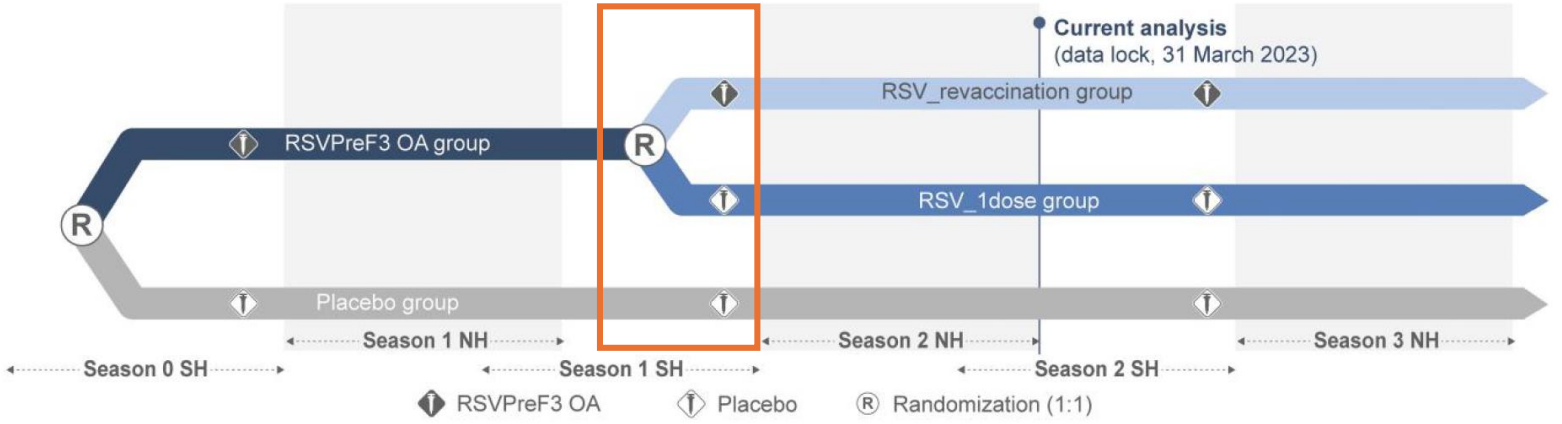
**Among adults ≥60 years of age, a single dose of the mRNA-1345 vaccine led to a lower incidence of RSV-associated lower respiratory tract disease than placebo and resulted in no apparent safety concerns.**

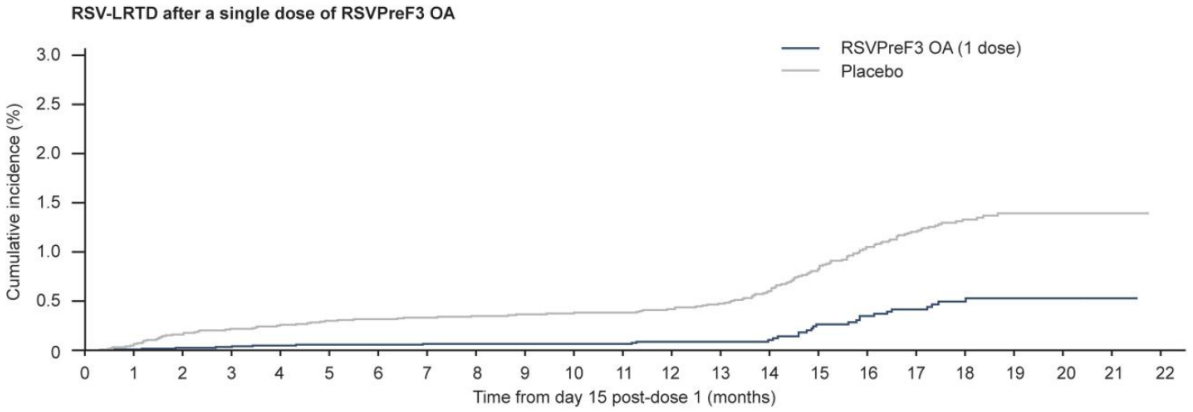
AREXVY (RESPIRATORY SYNCYTIAL VIRUS VACCINE, ADJUVANTED)

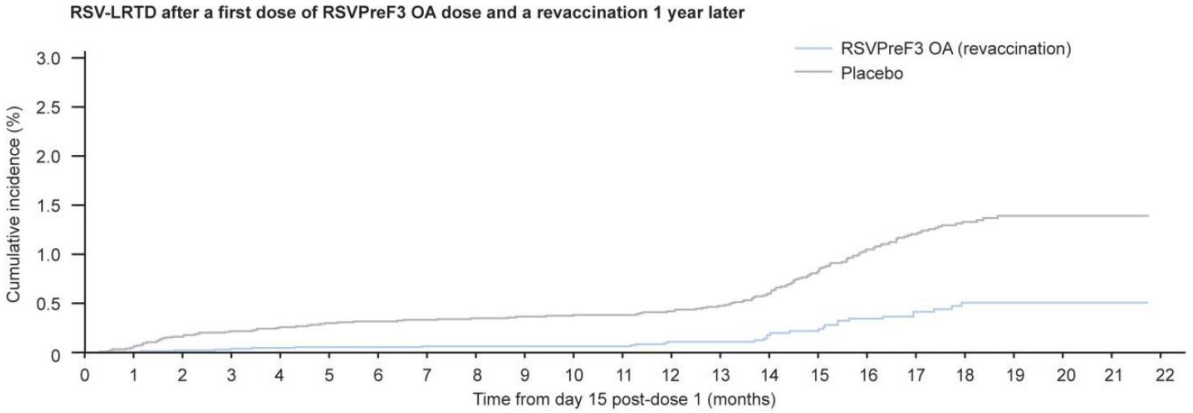
*Clinical Infectious Diseases*
MAJOR ARTICLE

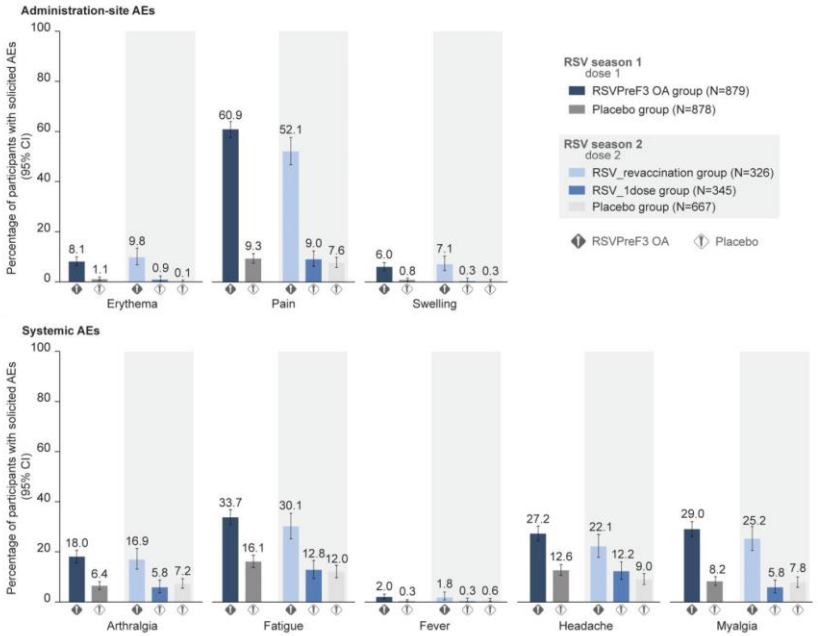
# Efficacy and Safety of Respiratory Syncytial Virus (RSV) Prefusion F Protein Vaccine (RSVPreF3 OA) in Older Adults Over 2 RSV Seasons

Michael G. Ison,[1,a] Alberto Papi,[2,a] Eugene Athan,[3,4] Robert G. Feldman,[5] Joanne M. Langley,[6] Dong-Gun Lee,[7] Isabel Leroux-Roels,[8] Federico Martinon-Torres,[9,10,11] Tino F. Schwarz,[12] Richard N. van Zyl-Smit,[13] Céline Verheust,[14] Nancy Dezutter,[14] Olivier Gruselle,[14] Laurence Fissette,[14] Marie-Pierre David,[14] Lusine Kostanyan,[14] Veronica Hulstrøm,[14] Aurélie Olivier,[14] Marie Van der Wielen,[14,©] and Dominique Descamps[14]; for the AReSVi-006 Study Group[b]



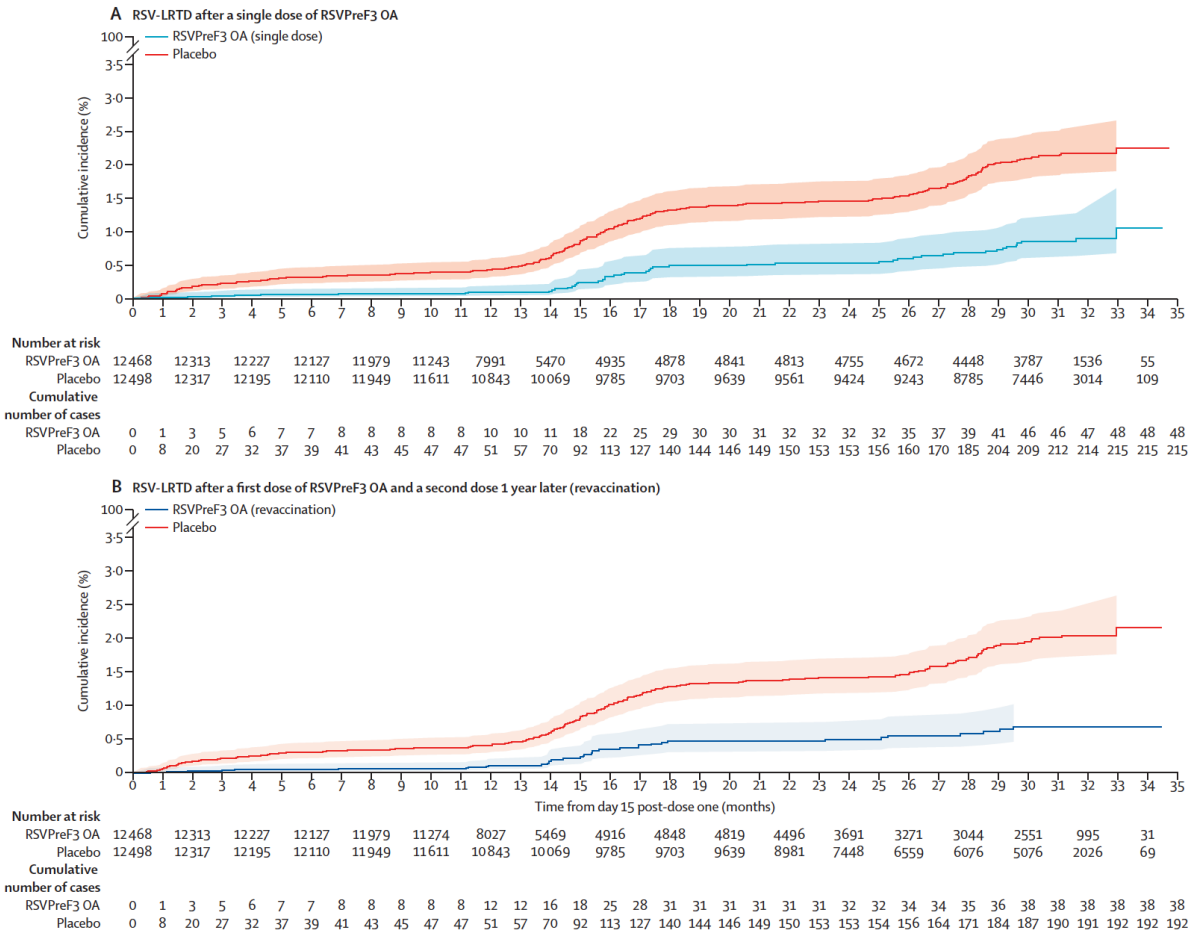

## Conclusions

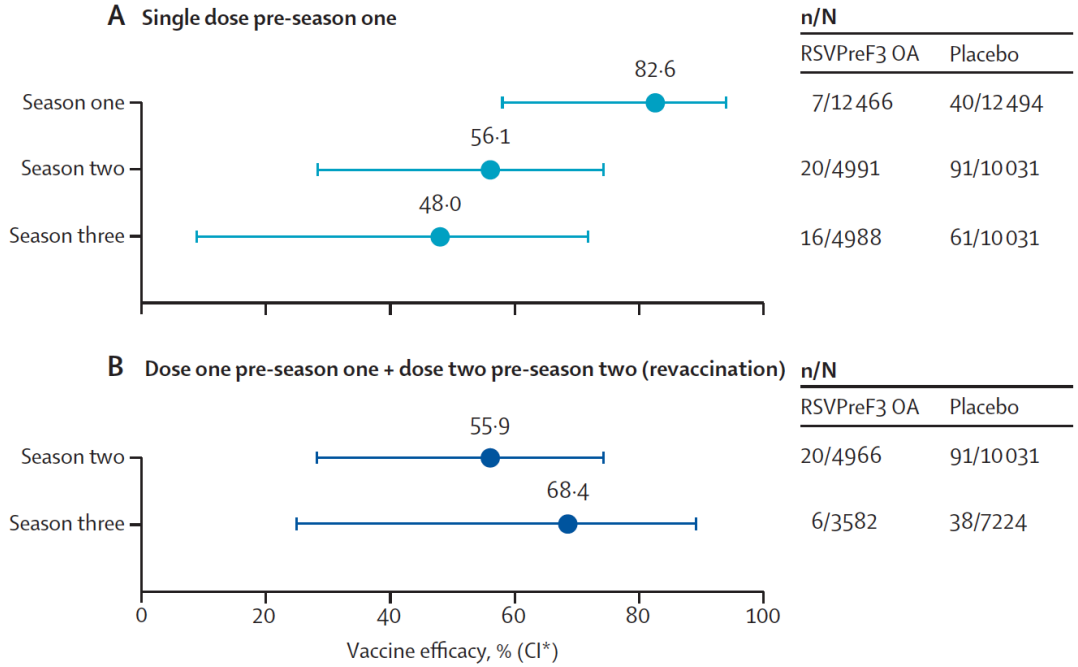
- One RSVPreF3 OA dose was efficacious against RSV-LRTD (RSV-related lower respiratory tract disease) over 2 RSV seasons in ≥60-year-olds
- Revaccination 1 year post–dose 1 was well tolerated but did not seem to provide additional efficacy benefit in the overall study population

GSK AREXVY (RESPIRATORY SYNCYTIAL VIRUS VACCINE, ADJUVANTED)

# Efficacy, safety, and immunogenicity of the AS01$_E$-adjuvanted respiratory syncytial virus prefusion F protein vaccine (RSVPreF3 OA) in older adults over three respiratory syncytial virus seasons (AReSVi-006): a multicentre, randomised, observer-blinded, placebo-controlled, phase 3 trial

*Michael G Ison*, Alberto Papi*, Eugene Athan, Robert G Feldman, Joanne M Langley, Dong-Gun Lee, Isabel Leroux-Roels, Federico Martinon-Torres, Tino F Schwarz, Richard N van Zyl-Smit, Susanna Cuadripani, Quentin Deraedt, Nancy Dezutter, Catherine Gerard, Laurence Fissette, Stebin Xavier, Marie-Pierre David, Aurélie Olivier, Marie Van der Wielen, Dominique Descamps, on behalf of the AReSVi-006 study group†*




## Conclusions

- A single RSVPreF3 OA dose was efficacious against RSV-LRTD over three RSV seasons in people aged 60 years or older, despite a decrease in efficacy over time
- Efficacy over three seasons of a first RSVPreF3 OA dose followed by revaccination 1 year later was in the same range as that of a single dose
- Further research is needed to establish the optimal revaccination strategy

Pfizer ABRYSVO™ Respiratory Syncytial Virus Vaccine

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

## RENOIR Trial — RSVpreF Vaccine Efficacy over Two Seasons

**Table 1. Efficacy of RSVpreF Vaccine Assessed in Two RSV Seasons.***

| End Point | End of Season One | | | End of Season Two | | | Seasons One and Two | | |
|---|---|---|---|---|---|---|---|---|---|
| | RSVpreF Vaccine | Placebo | Vaccine Efficacy (95% CI) | RSVpreF Vaccine | Placebo | Vaccine Efficacy (95% CI) | RSVpreF Vaccine | Placebo | Vaccine Efficacy (95% CI) |
| | *no. of cases/ no. at risk* | | % | *no. of cases/ no. at risk* | | % | *no. of cases/ no. at risk* | | % |
| RSV LRTI, ≥3 symptoms | 2/18,050 | 18/18,074 | 88.9 (53.6–98.7) | 8/16,164 | 36/16,059 | 77.8 (51.4–91.1) | 10/18,050 | 54/18,074 | 81.5 (63.3–91.6) |
| RSV LRTI, ≥2 symptoms | 15/18,050 | 43/18,074 | 65.1 (35.9–82.0) | 39/16,164 | 88/16,059 | 55.7 (34.7–70.4) | 54/18,050 | 131/18,074 | 58.8 (43.0–70.6) |
| RSV-associated ARI | 37/18,050 | 98/18,074 | 62.2 (44.4–74.9) | 149/16,164 | 236/16,059 | 36.9 (22.2–48.9) | 186/18,050 | 334/18,074 | 44.3 (33.2–53.7) |

* ARI denotes acute respiratory illness, LRTI lower respiratory tract illness, RSV respiratory syncytial virus, and RSVpreF RSV prefusion F protein–based.

These data indicate that bivalent RSVpreF vaccine remains efficacious against more severe lower respiratory tract illness due to RSV A and RSV B over two RSV seasons

# Vaccine effectiveness studies can help address limitations of clinical trials data

## Randomized RSV vaccine clinical trials (adjuvanted RSVPreF3 and RSVpreF)[1–3]

- Few (<8%) ≥80 YOA
- No immunocompromised patients
- Less than half (<52%) had chronic conditions

**Key endpoint:**
Symptomatic RSV-LRTD

## Observational RSV vaccine effectiveness studies[3,4]

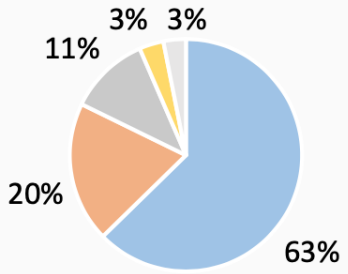
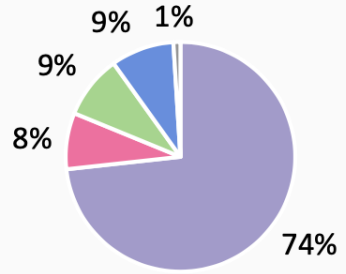
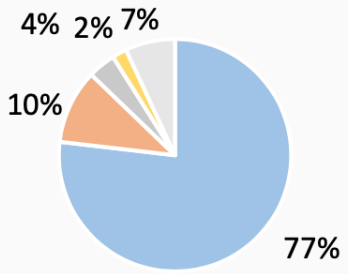
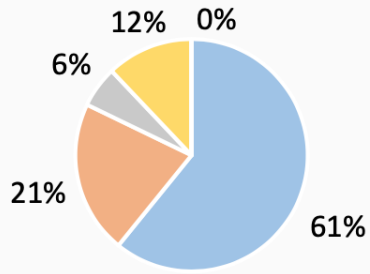
- ≥25% were ≥80 years YOA
- Included immunocompromised patients
- ≥94% had chronic conditions
- Both adjuvanted RSVPreF3 and RSVpreF were analyzed

**Key endpoints:** RSV-associated ED visits, hospitalization, critical illness*

*Critical illness is defined as ICU admissions or death (or both for VISION).
ED, emergency department; ICU, intensive care unit; LRTD, lower respiratory tract disease; YOA, years of age.

1. Papi A *et al. N Engl J Med* 2023;388:595–608; 2. Walsh EE *et al. N Engl J Med.* 2023;388:1465–1477; 3. Surie D. Effectiveness of adult respiratory syncytial virus (RSV) vaccines, 2023–2024. Presented at ACIP, 26 June. https://www.cdc.gov/acip/downloads/slides-2024-06-26-28/07-RSV-Adult-Surie-508.pdf (accessed December 2024); 4. Payne AB *et al. Lancet* 2024;404:1547–1559.

# Overview of RSV vaccine effectiveness studies: study design and demographic characteristics

| | IVY[1] | VISION[2] | VHA[1] | Medicare/ESRD[1] |
|---|---|---|---|---|
| | Investigating respiratory viruses in the acutely ill | Electronic health records from the CDC and 9 US healthcare systems and research centers | Veterans Health Administration | CMS Fee-for-Service Claims data |
| | (N=2978) | (N=36,706) | (N=293,704) | (N=69,279) |
| **Design** | Test-negative, case-control design | Test-negative design analysis | Target trial emulation | Retrospective cohort |
| **Number of hospitals** | 26 hospitals | 230 hospitals; 245 emergency rooms | 172 medical centers; 18 systems of care, 1138 outpatient sites of care | Data source: Medicare fee-for-service claims data |
| **Period** | October 1, 2023 – March 31, 2024 | October 1, 2023 – March 31, 2024 | September 1, 2023 – March 31, 2024 | October 1, 2023 – February 24, 2024 |
| **Population** | Adults ≥60 YOA hospitalized with ARI* | Adults ≥60 YOA visiting a participating ED for or hospitalized with RLI with RSV test† | VHA enrollees ≥60 YOA engaged in VHA care§ | Persons aged ≥65 with ESRD¶ |
| **Race/ethnicity**<br>White non-Hispanic<br>Black non-Hispanic<br>Hispanic or Latino any race<br>Other race non-Hispanic**<br>Unknown†† |  |  |  |  |

*RSV test results within 10 days of illness onset and 3 days of admission; †RSV test result within 10 days before or 72 hours after encounter; §Engaged in VHA care: ≥1 primary care encounter within 18 months prior to the first day of each trial month; ¶At least 1 dialysis encounter (excluding acute kidney injury) in the 90 days before the index date; **For VISION, includes patients with missing race and ethnicity in their electronic health records. For IVY, "Other race, non-Hispanic" includes Asian, American Indian or Alaska Native, and Native Hawaiian or other Pacific Islander; because of small numbers, these categories were combined; ††For VISION, "Unknown" includes patients reporting non-Hispanic ethnicity and any of the following for race: American Indian or Alaska Native, Asian, Native Hawaiian, or other Pacific Islander, other races not listed, and multiple races. Because of smaller numbers, these categories were combined. For IVY, "Unknown" includes patients who self-reported their race and ethnicity as "Other" and those for whom race and ethnicity were unknown. For VHA "Unknown" includes missing, unknown, or declined race or ethnicity. ARI, acute respiratory illness; ED, emergency department; EHR, electronic health record; EMR, electronic medical records; ESRD, end stage renal disease; NAAT, nucleic acid amplification testing; RLI, RSV-like illness; RT-PCR, reverse transcription polymerase chain reaction; VHA, Veterans Health Administration; YOA, years of age.

1. Surie D. Effectiveness of adult respiratory syncytial virus (RSV) vaccines, 2023–2024. Presented at ACIP, 26 June 2024. https://www.cdc.gov/acip/downloads/slides-2024-06-26-28/07-RSV-Adult-Surie-508.pdf (accessed December 2024); 2. Payne AB *et al. Lancet* 2024;404:1547–1559.

# Overview of RSV vaccine effectiveness studies: study populations

| | IVY[1,2] (N=2978) | VISION[3] (N=36,706) | VHA[1] (N=293,704) | Medicare/ESRD[1] (N=69,279) |
|---|---|---|---|---|
| **Median age (range)** | 72 years (66–80) | 76 years (69–84) | 76 years (72–80) | 75 years (70–80) |
| **≥4 chronic medical conditions** | 28% | 42% | 21% | 84% |
| **Immuno-compromised** | 24% | 23% | 11% | 25% |
| **Chronic lung disease** | 48% | 48% | 30% | 56% |
| **Cardiovascular disease** | 84% | 79% | 42% | 97% |
| | **9%** RSV-vaccinated | **9%** RSV-vaccinated | **50%** RSV-vaccinated† | **10%** RSV-vaccinated |
| | 61%* | 74% | 30% | 68% |
| | RSVPreF3 OA / RSVpreF | RSVPreF3 OA / RSVpreF | RSVPreF3 OA / RSVpreF | RSVPreF3 OA / RSVpreF |

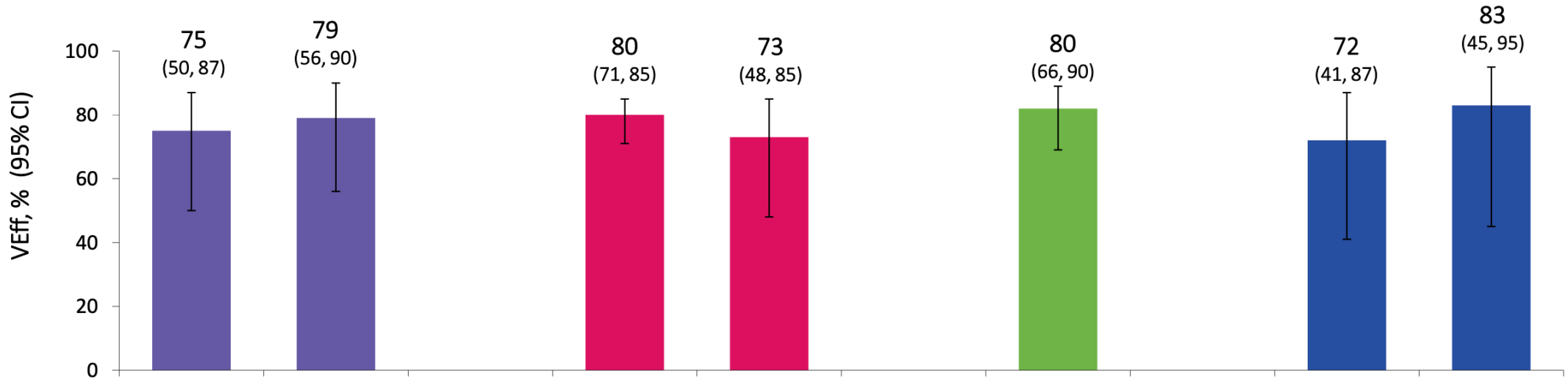
**Compared with clinical trials, real-world studies are more inclusive of patients at increased risk for severe RSV disease**

*Of 265 RSV-vaccinated patients in IVY, 226 (85%) had known vaccine type, which is used as the denominator for these percentages; †Each RSV-vaccinated patient matched to up to 4 unvaccinated, equally-weighted patients, resulting in 50% of matched persons having an RSV vaccination. Among match-eligible patients, 4.5% received RSV vaccination.

ESRD, end-stage renal disease; VHA, Veterans Health Administration.

1. Surie, D. Effectiveness of adult respiratory syncytial virus (RSV) vaccines, 2023–2024. Presented at ACIP, 26 June 2024. https://www.cdc.gov/acip/downloads/slides-2024-06-26-28/07-RSV-Adult-Surie-508.pdf (accessed December 2024); 2. Surie D *et al. JAMA* 2024:332:1105–1107; 3. Payne AB *et al. Lancet* 2024;404:1547–1559.

# Vaccine effectiveness against RSV-associated hospitalization




| Group (All RSV vaccines unless stated otherwise): | ≥60 YOA, unweighted* | ≥60 YOA, IPVW† | ≥60 YOA, Immunocompetent‡ | ≥60 YOA, Immunocompromised‡ | ≥60 YOA | ≥65 YOA, Immunocompetent§ | ≥65 YOA, Immunocompromised§¶ |
|---|---|---|---|---|---|---|---|
| Study: | IVY[1,2] | | VISION[3] | | VHA[1] | Medicare/ESRD[1] | |
| **Number of events/N:** | | | | | | | |
| Vaccinated | **9** / 367 | **9** / 367 | **35** / 2455 | **10** / 820 | **15** / 51,298 | **<11** / 4603 | **<11** / 2128 |
| Unvaccinated | **256** / 2611 | **256** / 2611 | **1567** / 25,816 | **314** / 7615 | **80.3** / 50,975 | **342** / 47,177 | **161** / 15,371 |

CCI, Charlson Comorbidity Index; CI, confidence interval; ESRD, end-stage renal disease; IPVW, inverse probability of vaccination weighting; SVI, social vulnerability index; VEff, effectiveness; VHA, Veterans Health Administration; YOA, year of age.

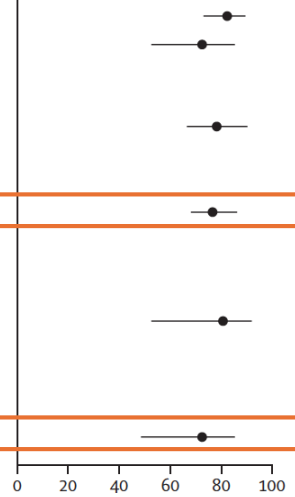
1. Surie, D. Effectiveness of adult respiratory syncytial virus (RSV) vaccines, 2023–2024. Presented at ACIP, 26 June 2024. https://www.cdc.gov/acip/downloads/slides-2024-06-26-28/07-RSV-Adult-Surie-508.pdf (accessed December 2024); 2. Surie D *et al*. *JAMA* 2024:332:1105–1107; 3. Payne AB *et al*. *Lancet* 2024;404:1547–1559.

# Respiratory syncytial virus (RSV) vaccine effectiveness against RSV-associated hospitalisations and emergency department encounters among adults aged 60 years and older in the USA, October, 2023, to March, 2024: a test-negative design analysis

*Amanda B Payne, Janet A Watts, Patrick K Mitchell, Kristin Dascomb, Stephanie A Irving, Nicola P Klein, Shaun J Grannis, Toan C Ong, Sarah W Ball, Malini B DeSilva, Karthik Natarajan, Tamara Sheffield, Daniel Bride, Julie Arndorfer, Allison L Naleway, Padma Koppolu, Bruce Fireman, Ousseny Zerbo, Julius Timbol, Kristin Goddard, Brian E Dixon, William F Fadel, Colin Rogerson, Katie S Allen, Suchitra Rao, David Mayer, Michelle Barron, Sarah E Reese, Elizabeth A K Rowley, Morgan Najdowski, Allison Avrich Ciesla, Josephine Mak, Emily L Reeves, Omobosola O Akinsete, Charlene E McEvoy, Inih J Essien, Mark W Tenforde, Katherine E Fleming-Dutra, Ruth Link-Gelles*

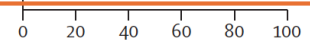
## Estimated vaccine effectiveness against respiratory syncytial virus-associated hospitalization among adults aged at least 60 years

| | Total | Positive RSV test result (number [%]) | Median interval since dose (days [IQR]) | Unadjusted vaccine effectiveness (% [95% CI]) | Adjusted* vaccine effectiveness (% [95% CI]) |
|---|---|---|---|---|---|
| **Immunocompetent—hospitalisation** | | | | | |
| **≥60 years** | | | | | |
| Unvaccinated | 25 816 | 1567 (6%) | NA | 0 (ref) | 0 (ref) |
| Vaccinated† | 2455 | 35 (1%) | 74 (44–109) | 78 (69–84) | 80 (71–85) |
| 14–59 days earlier | 934 | 7 (1%) | 37 (26–48) | 88 (75–94) | 90 (79–95) |
| ≥60 days earlier | 1520 | 27 (2%) | 100 (79–125) | 72 (59–81) | 73 (60–82) |
| GSK, Arexvy | 1812 | 21 (1%) | 73 (43–105) | 82 (72–88) | 83 (73–89) |
| Pfizer, Abrysvo | 642 | 13 (2%) | 81 (48–116) | 68 (44–82) | 73 (52–85) |
| **60–74 years** | | | | | |
| Unvaccinated | 11 048 | 670 (6%) | NA | 0 (ref) | 0 (ref) |
| Vaccinated | 836 | 11 (1%) | 75 (46–110) | 79 (62–89) | 81 (66–90) |
| **≥75 years** | | | | | |
| Unvaccinated | 14 768 | 897 (6%) | NA | 0 (ref) | 0 (ref) |
| Vaccinated | 1619 | 24 (1%) | 74 (43–108) | 77 (65–85) | 79 (68–86) |
| **Critical illness** | | | | | |
| **≥60 years** | | | | | |
| Unvaccinated | 24 506 | 257 (1%) | NA | 0 (ref) | 0 (ref) |
| Vaccinated | 2425 | 5 (<1%) | 74 (44–109) | 81 (53–92) | 81 (52–92) |
| **With immunocompromise–hospitilisation** | | | | | |
| **≥60 years** | | | | | |
| Unvaccinated | 7615 | 314 (4%) | NA | 0 (ref) | 0 (ref) |
| Vaccinated | 820 | 10 (1%) | 72 (43–108) | 71 (46–85) | 73 (48–85) |




## Estimated vaccine effectiveness against respiratory syncytial virus-associated emergency department encounters among adults aged at least ≥60 years without documented immunocompromise

| | Total* | Positive RSV test result (number [%]) | Median interval since dose (days [IQR]) | Unadjusted vaccine effectiveness (% [95% CI] | Adjusted† vaccine effectiveness, (% [95% CI]) |
|---|---|---|---|---|---|
| **≥60 years** | | | | | |
| Unvaccinated | 33 491 | 2645 (8%) | NA | 0 (ref) | 0 (ref) |
| Vaccinated‡ | 3030 | 57 (2%) | 67 (40–101) | 78 (71–83) | 77 (70–83) |
| 14–59 days earlier | 1300 | 19 (1%) | 36 (26–47) | 83 (73–89) | 85 (77–91) |
| ≥60 days earlier | 1728 | 37 (2%) | 95 (76–119) | 74 (65–82) | 70 (58–78) |
| GSK, Arexvy | 2522 | 47 (2%) | 67 (40–99) | 78 (70–83) | 77 (70–83) |
| Pfizer, Abrysvo | 506 | 9 (2%) | 71 (40–108) | 79 (59–89) | 79 (59–89) |
| **60–74 years** | | | | | |
| Unvaccinated | 16 985 | 1303 (8%) | NA | 0 (ref) | 0 (ref) |
| Vaccinated | 1139 | 23 (2%) | 66 (40–100) | 75 (62–84) | 75 (62–84) |
| **≥75 years** | | | | | |
| Unvaccinated | 16 506 | 1342 (8%) | NA | 0 (ref) | 0 (ref) |
| Vaccinated | 1891 | 34 (2%) | 69 (40–101) | 79 (71–85) | 78 (69–85) |



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Research Letter FREE

# RSV Vaccine Effectiveness Against Hospitalization Among US Adults 60 Years and Older

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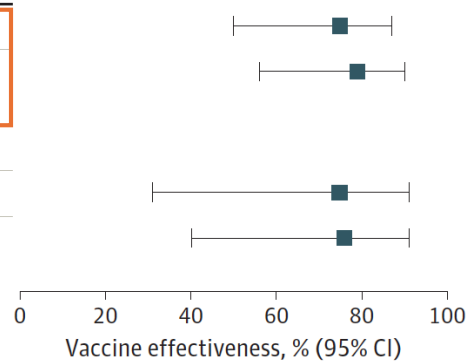
**Figure. Vaccine Effectiveness Against Respiratory Syncytial Virus (RSV)–Associated Hospitalization Among Adults 60 Years and Older**

| Group | Vaccinated RSV case patients, No./total No. (%) | Vaccinated control patients, No./total No. (%) | Days since RSV vaccination, median (IQR) | Vaccine effectiveness, % (95% CI) |
|---|---|---|---|---|
| Adults aged ≥60 y, unweighted[a] | 9/367 (2.5) | 256/2611 (9.8) | 84 (54-125) | 75 (50-87) |
| Adults aged ≥60 y, inverse probability of vaccination weighting[b] | 9/367 (2.5) | 256/2611 (9.8) | 84 (54-125) | 79 (56-90) |
| Age group, y, unweighted[a] | | | | |
| 60-74 | 4/214 (1.9) | 118/1542 (7.7) | 88 (57-128) | 75 (31-91) |
| ≥75 | 5/153 (3.3) | 138/1069 (12.9) | 81 (50-123) | 76 (40-91) |




[a]Multivariable logistic regression compared the odds of RSV vaccination among RSV case and control patients. Models were adjusted for a base set of *a priori* variables, including age, sex, race and ethnicity, US Department of Health and Human Services Region, and calendar month of admission. Vaccine effectiveness (VE) was computed as: (1 − adjusted odds ratio) × 100%.

[b]Propensity for vaccination was modeled with an expanded set of *a priori* covariates. Weights were computed as the inverse of the probability of vaccination. The standardized differences for covariates after weighting were all <0.1, except for Social Vulnerability Index, which was included in the final logistic regression model that compared the odds of RSV vaccination between RSV case and control patients (eMethods in Supplement 1).

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Infectious Diseases

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# Early evidence of RSV vaccination impact on hospitalisation rates of older people in Scotland

Safraj Shahul Hameed [a] · Chris Robertson [a,b] · Kirsty Morrison [a] · Ross McQueenie [a] · Jim McMenamin [a] · Sam Ghebrehewet [a] · et al. Show more

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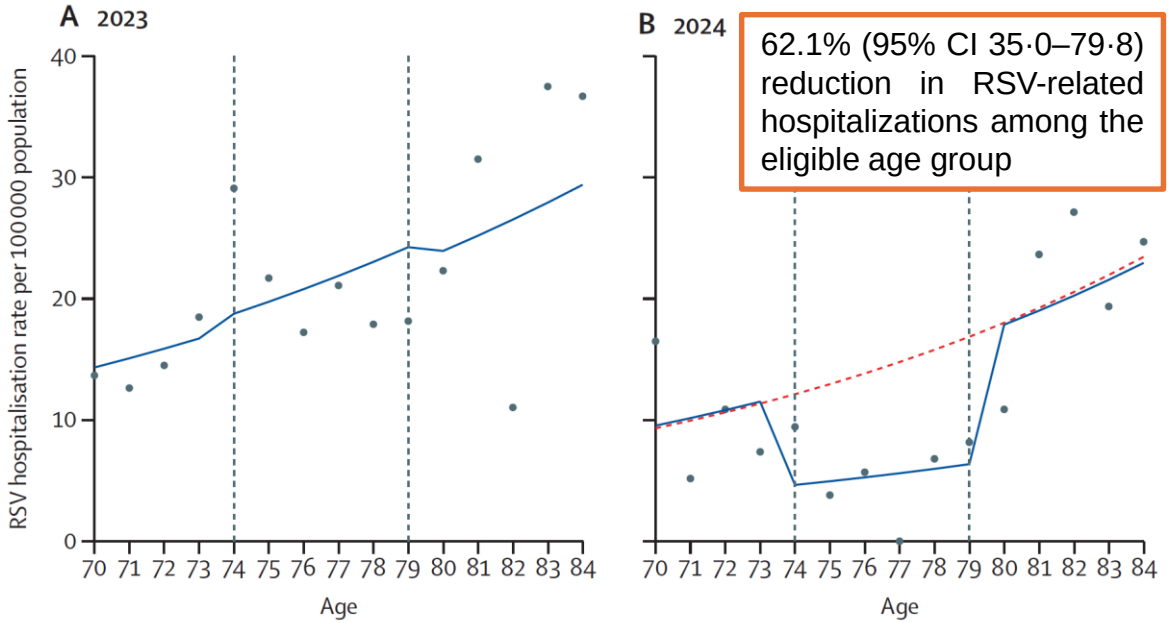


62.1% (95% CI 35·0–79·8) reduction in RSV-related hospitalizations among the eligible age group

***Figure:*** **Observed, modelled, and predicted rates of admission to hospital due to respiratory syncytial virus in Scotland**

(A) Hospitalisation rates before vaccination discontinuity for people aged 74–79 years from Oct 1 to Dec 8, 2023 and (B) hospitalisation rates after vaccination discontinuity for people aged 74–79 years from Oct 1 to Dec 8, 2024. Grey dot=admitted rate. Blue line=predicted rate. Dashed grey lines=vaccine eligible age groups. Red dashed line=modelled rate in the absence of vaccination. RSV=respiratory syncytial virus.

THE LANCET

CORRESPONDENCE · Volume 405, Issue 10485, P1139-1140, April 05, 2025

# Early impact of RSV vaccination in older adults in England

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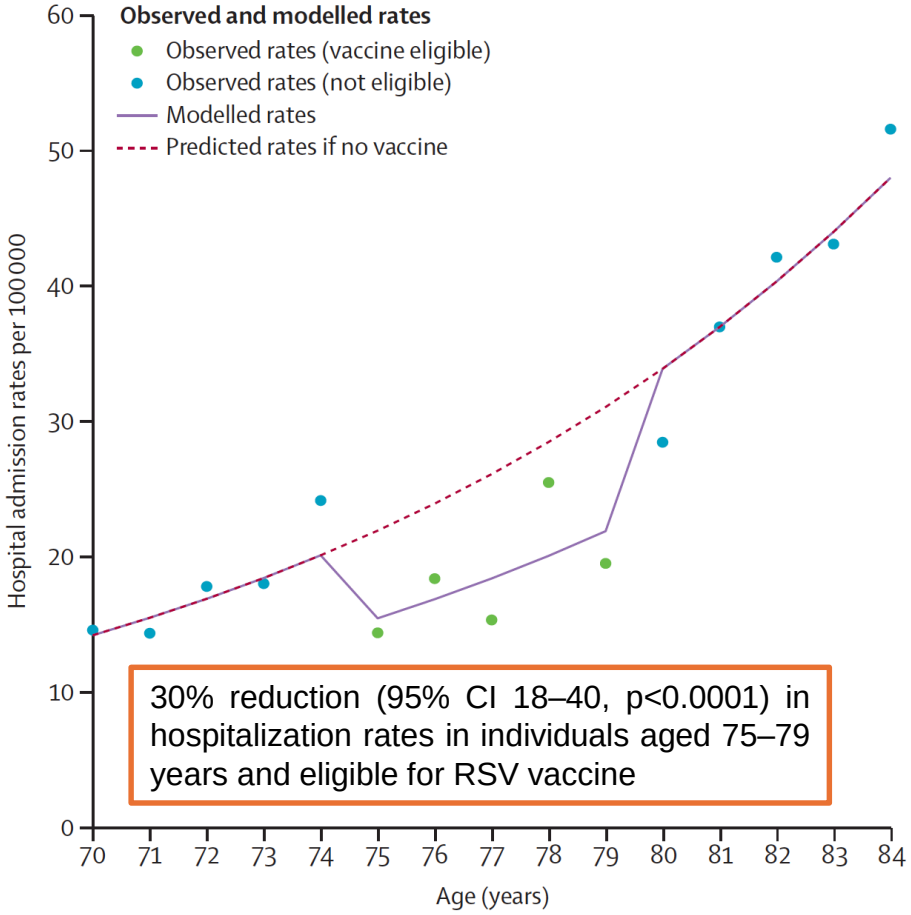
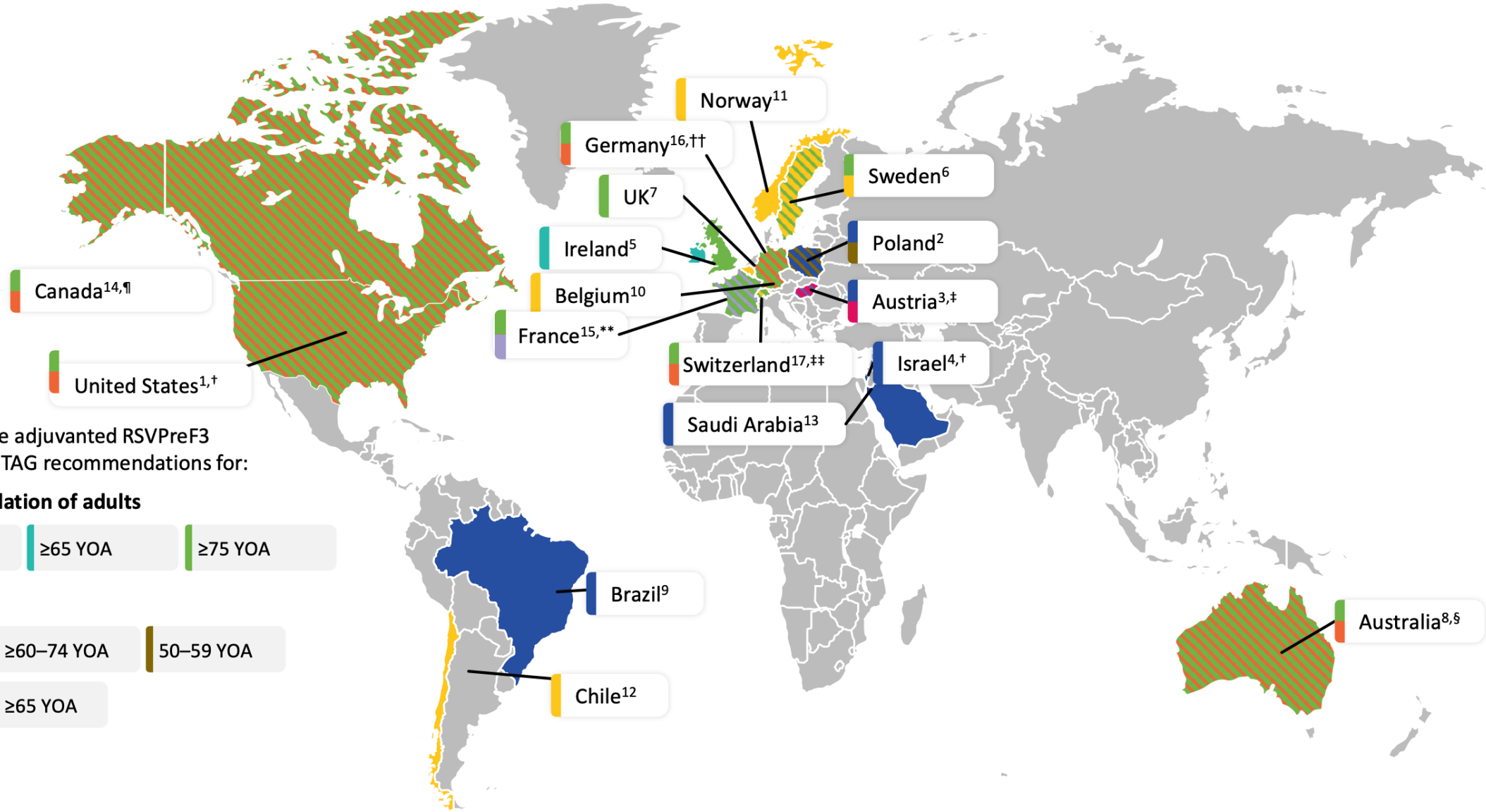



30% reduction (95% CI 18–40, p<0.0001) in hospitalization rates in individuals aged 75–79 years and eligible for RSV vaccine

# National recommendations for RSV vaccination in adult population




Markets where adjuvanted RSVPreF3 vaccine has NITAG recommendations for:

**General population of adults**

- ≥60 YOA
- ≥65 YOA
- ≥75 YOA

**People at risk**

- ≥18 YOA
- ≥60–74 YOA
- 50–59 YOA
- ≥60 YOA
- ≥65 YOA

**Raccomandazioni del Board del Calendario per la Vita sulla vaccinazione contro Virus Respiratorio Sinciziale (VRS o RSV) nella popolazione anziana e negli adulti a rischio**

**Il Board del Calendario della Vita, sulla base delle evidenze di efficacia e sicurezza ad oggi disponibili, e considerando le informazioni attualmente in fase di raccolta sulla durata della protezione conferita dai vaccini anti-RSV, ne raccomanda l'utilizzo ai soggetti di età pari o superiore ai 75 anni, popolazione nella quale è peraltro molto frequente la co-esistenza di condizioni di cronicità che rendono l'infezione da RSV ancora più a rischio di complicanze gravi. Per le stesse motivazioni, raccomanda l'estensione della vaccinazione ai soggetti affetti da patologie croniche di età superiore o uguale ai 60 anni.**

**Prevenzione delle infezioni da Virus Respiratorio Sinciziale nella popolazione italiana**

Società Scientifiche proponenti:

SItI- Società Italiana Igiene, Medicina Preventiva e Sanità Pubblica

SIMIT- Società Italiana Malattie Infettive e Tropicali

Panel di esperti coinvolti nella stesura del documento: Massimo Andreoni, Vincenzo Baldo, Paolo Castiglia, Rosita Cipriani, Giovanni Gabutti, Sandro Giuffrida, Roberto Parrella, Roberta Siliquini, Laura Sticchi, Maria Grazia Zuccali

Prevedere di inserire la vaccinazione contro RSV nel calendario vaccinale, raccomandando la vaccinazione negli adulti ≥60 anni di età con co-morbosità e negli anziani ≥75 anni di età