“Novel Vaccines for Respiratory Viral Infections: Can They Reduce Both Viral Disease Burden and Antibiotic usage?”

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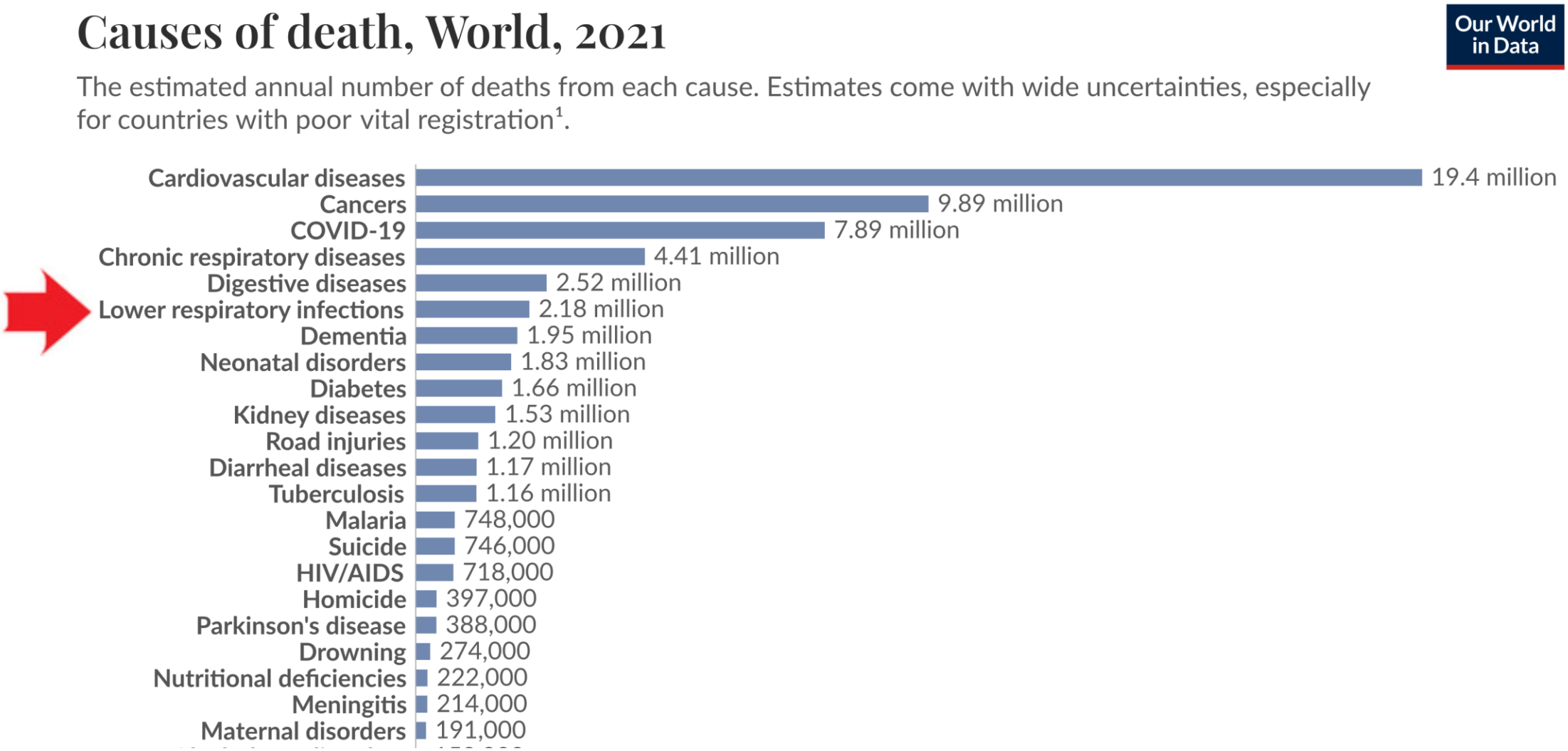
Disclosure: P. Delputte has recent and/or ongoing contracts with MSD, Pfizer, Gilead, Janssen and GSK

Burden of respiratory infections

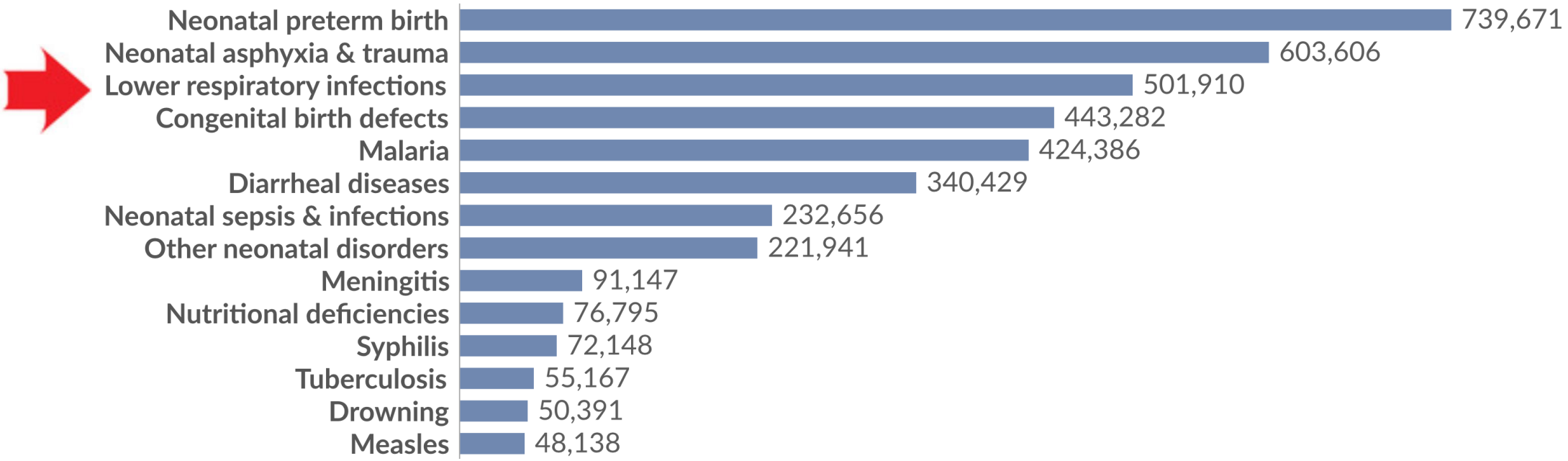


Burden of respiratory infections

Causes of death in children under five, World, 2021

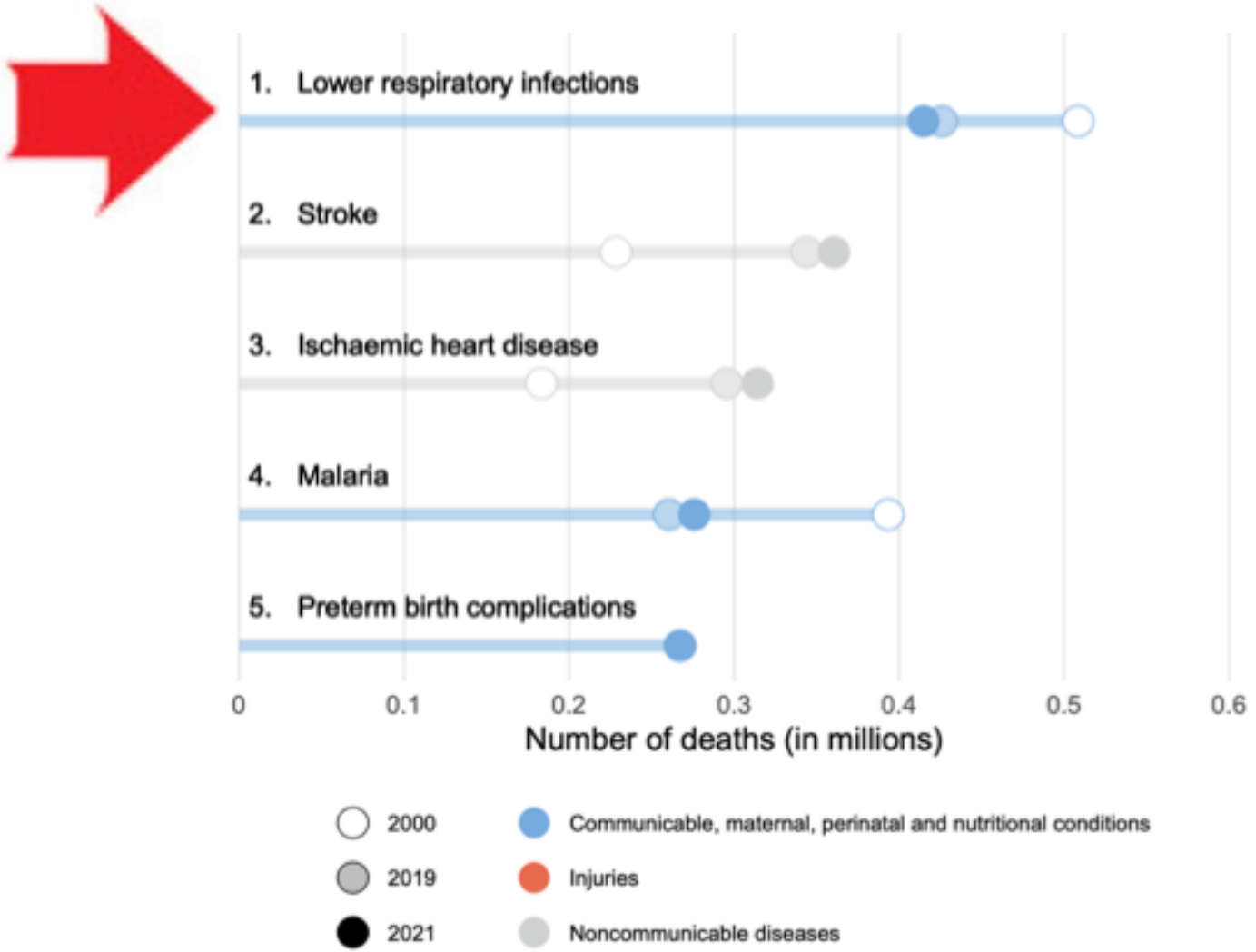
Our World in Data

The estimated annual number of deaths from each cause. Estimates come with wide uncertainties especially for countries with poor vital registration[1].



Burden of respiratory infections

Leading cause of death in low-income countries



World Health Organization

University of Antwerp

Antibiotic usage in respiratory infections and AMR

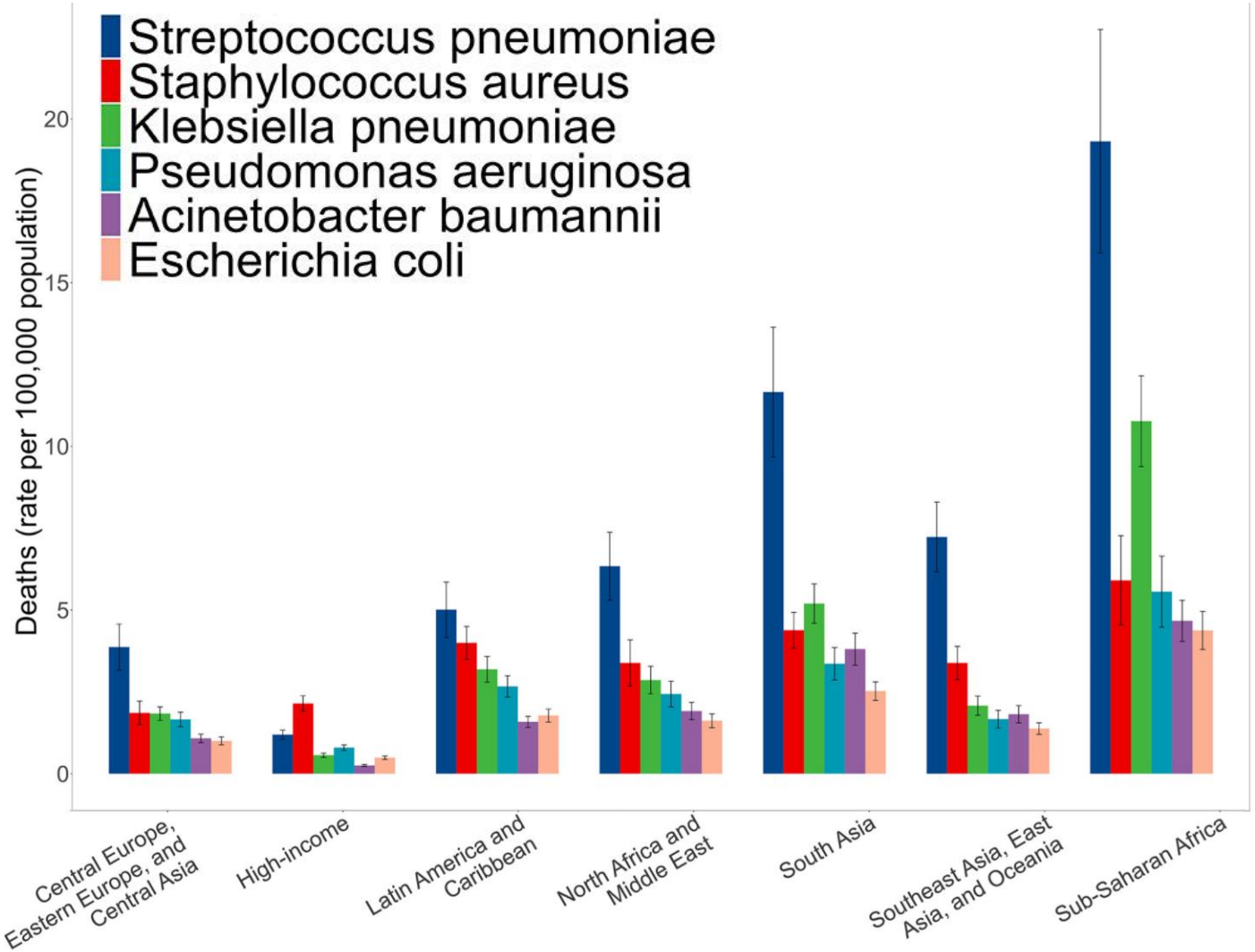
respiratory infections account for a large proportion of antibiotic prescriptions in primary care settings

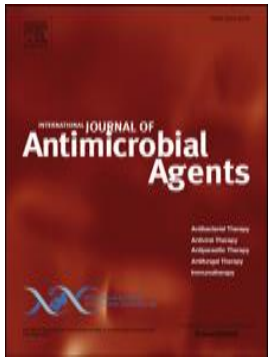
the **mismanagement of respiratory infections** contributes considerably to increased antimicrobial resistance, with URIs being a **major contributor to antibiotic prescriptions**

THE LANCET
Infectious Diseases

Global, regional, and national burden of upper respiratory infections and otitis media, 1990–2021: a systematic analysis from the Global Burden of Disease Study 2021
Sirota, Sarah Brooke et al.
The Lancet Infectious Diseases, Volume 25, Issue 1, 36 - 51

AMR-related mortality, related to respiratory infections





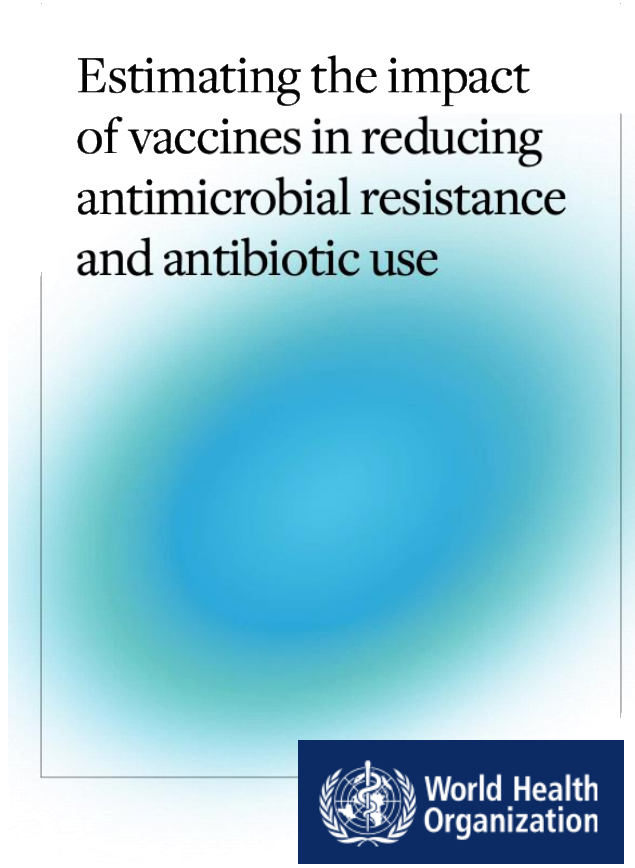
Global burden of antimicrobial resistance in lower respiratory infections in 2021: A systematic analysis

Xingyu Wan[a,b,†], Run Miao[b,†], Ning Zhang[c,d,†], Wei Huang[d], Zhengyang Wu[d], Haiwei Wang[d], Yang Yang[d], Yinyin Xie[e,*], Yinan Du[a,*]

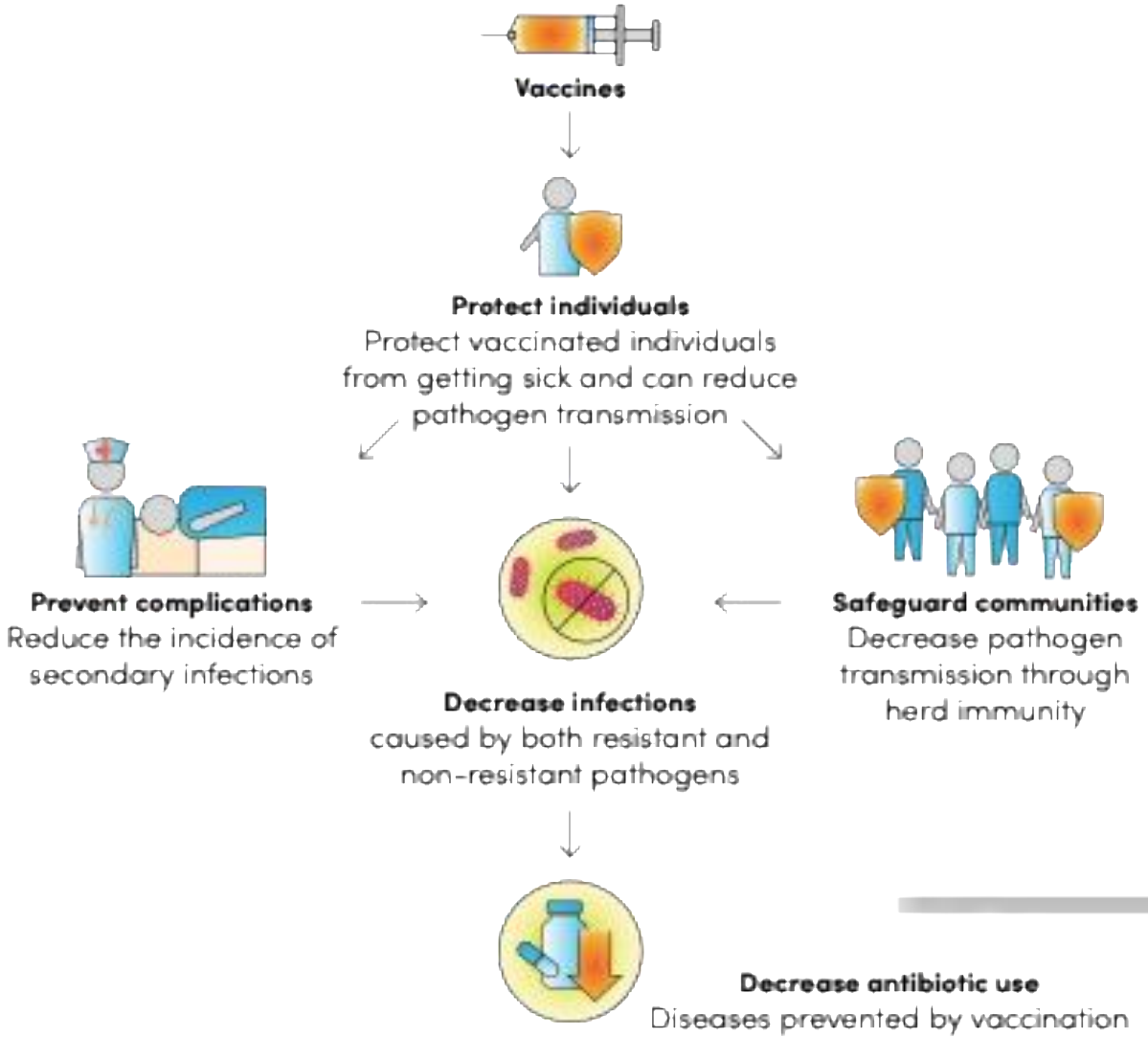
Vaccines can reduce antibiotic prescription and AMR

- The WHO report covers 44 vaccines & 24 priority pathogens
  - currently licensed vaccines
  - vaccines in early and late stages of clinical development

- The 24 pathogens, selected a.o. for large volume of antimicrobials used in their treatment, include
  - 19 bacteria
  - 4 viruses
  - malaria parasite Plasmodium falciparum



Vaccines can reduce antibiotic prescription and AMR

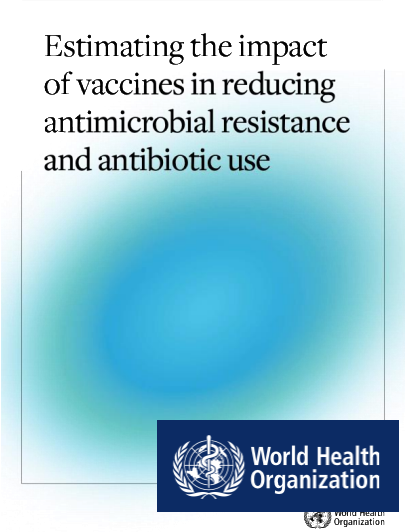


Estimating the impact of vaccines in reducing antimicrobial resistance and antibiotic use

World Health Organization

Vaccines can reduce antibiotic prescription and AMR

Vaccines that prevent ‘community-acquired’ infections & ‘hospital-acquired’ infections’

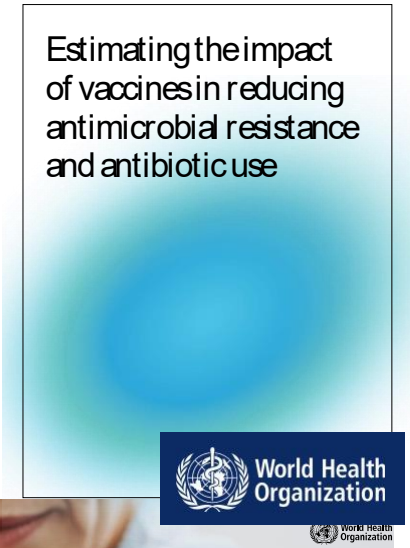


- Antibiotic usage reduced by **22% or 2.5 billion defined daily doses** globally every year
- **~515 000** less deaths **associated with AMR**
- annual **hospital costs related to AMR down by 1/3th**
- ***Streptococcus pneumoniae* vaccines** could **save 33 million antibiotic doses**, if the ‘Immunization Agenda 2030’ target of 90% of the world’s children were vaccinated, as well as older adults

Impact of vaccines in reducing antimicrobial resistance
Jesudason, Timothy; The Lancet Microbe, Volume 6, Issue 1, 101040

Vaccines can reduce antibiotic prescription and AMR

Vaccines that prevent respiratory viral infections

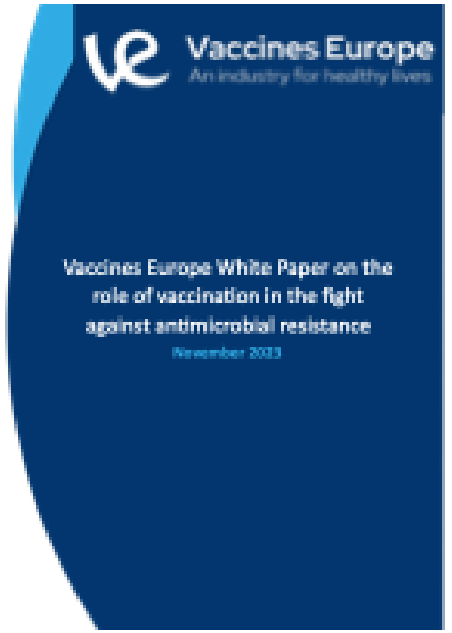


These viral vaccines are important because of ***secondary bacterial infections***

and

because a ***large proportion of unnecessary prescribing of antibiotics occurs for patients who have viral infections****, even though the drugs will not help in these cases.*

Influenzavirus and AMR

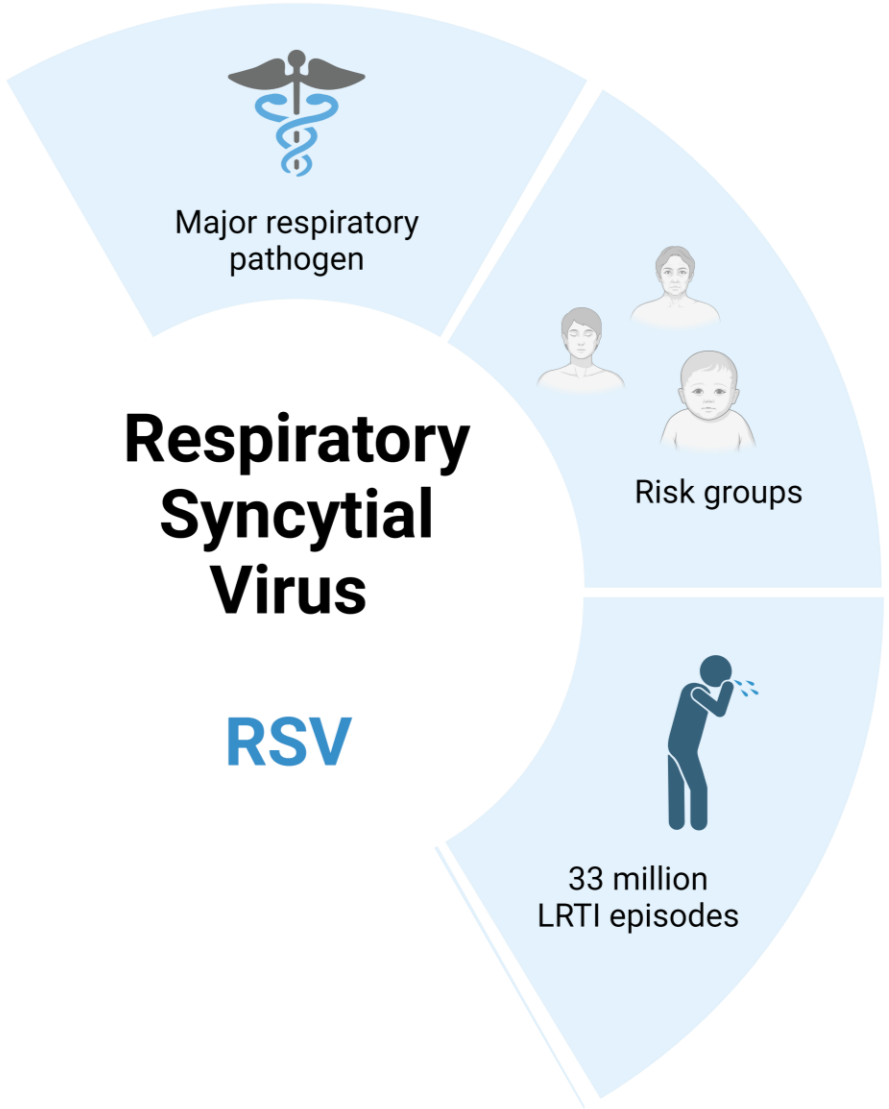


antibiotics prescribed to children with influenza in 28% to 55% of cases

- Influenza vaccines reduce the number of secondary bacterial infections
- up to 64% less antibiotic use in vaccinated individuals
- 10% increase influenza vaccination -> 6.5% decrease antibiotic use, notably in the paediatric and elderly populations
- reduced erroneous prescription of antibiotics

Respiratory Syncytial Virus (RSV)

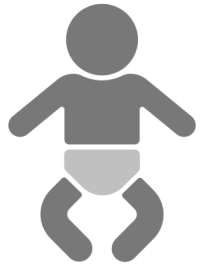
- **Major respiratory pathogen globally present**
- **Two antigenic subtypes (RSV-A and RSV-B)**
- **Risk groups**
  - Children 25 days – 6 months
  - Children < 5 years
  - Elderly (>65 years old)
  - Immunocompromised adults
- **33 million of LRTI episodes**



RSV burden

Children < 5 years

- 90% of children infected first 2 years of life
- 33 million RSV-associated cases
- ~ 10% requiring hospitalization
- 26.300 RSV acute LRI in hospital deaths
- 101 400 RSV-attributable overall deaths



Children 25 days – 6 months

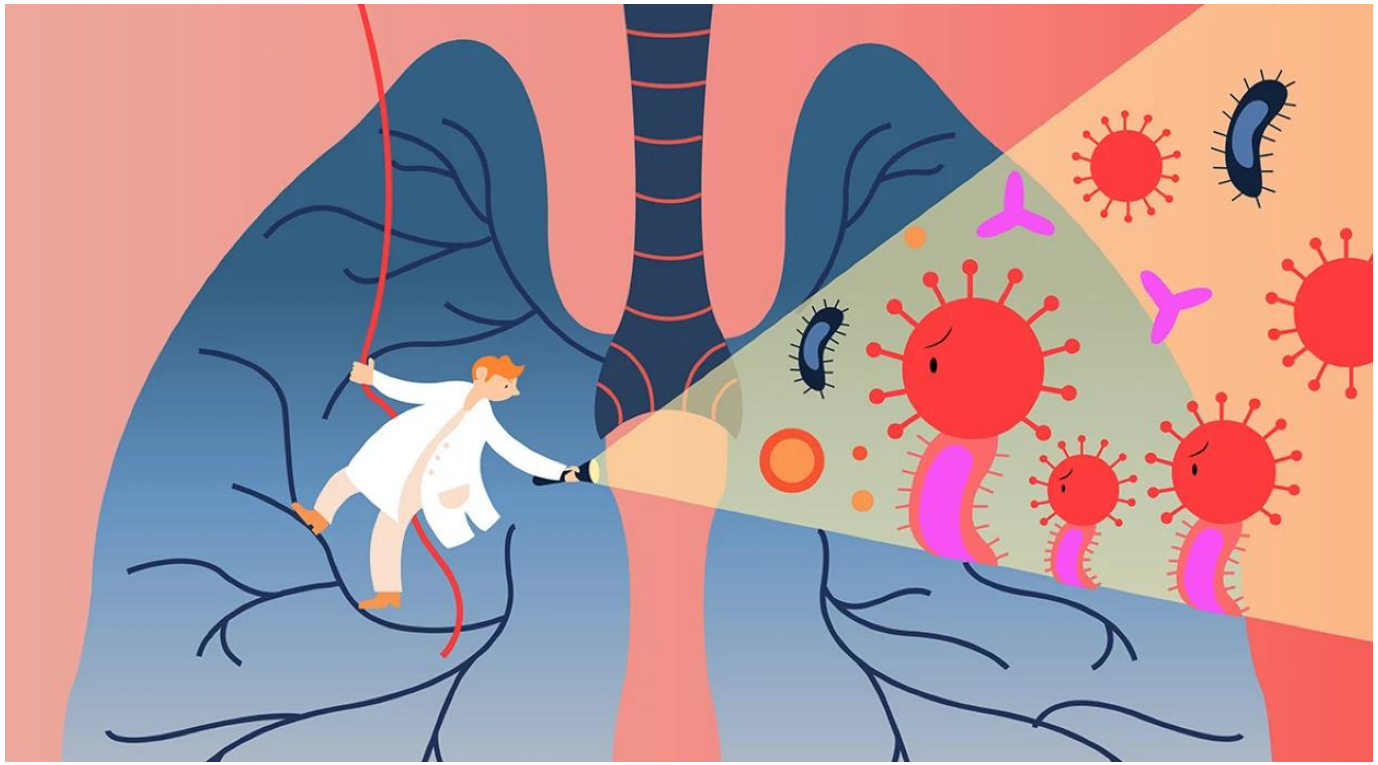
- 1·4 million RSV-associated acute LRI hospital admissions
- 1 in 28 deaths attributable to RSV

Elderly (> 65 years)

- 336.000 RSV acute LRI hospital admissions
- 14.000 in hospital deaths

Li et al. The Lancet, 2022; Shi et al. J Infect Dis, 2020

RSV and bacterial co-infections



- 10 – 20% RSV ARI have bacterial co-infections -> more severe outcome
- ~ Streptococcus pneumonia, Haemophilus influenza, Staphylococcus aureus, Pseudomonas aeruginosa, and Moraxella catarrhalis

RSV and AMR

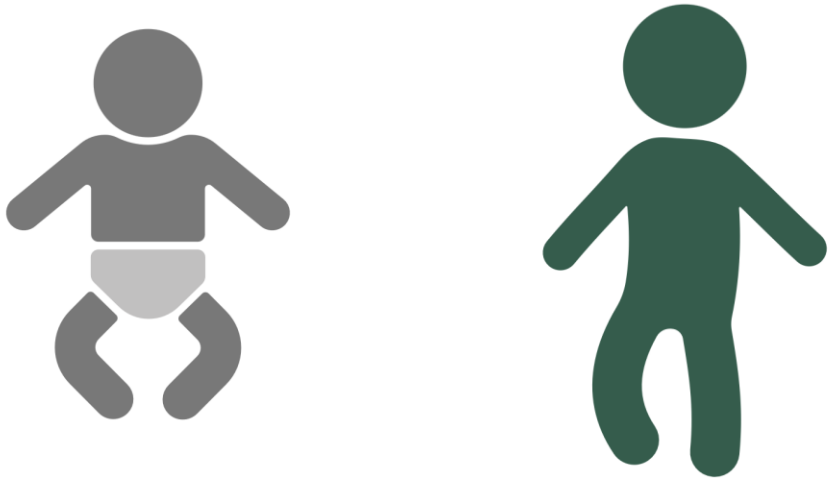
- 2.1% of antibiotic prescriptions in English GPs were attributable to RSV infections
- An estimated 2.1% of antibiotics were attributable to RSV, equating to an average of 640,000 prescriptions annually
- **adults ≥75 years** contributed to the greatest volume, with an annual average of 149,078 prescriptions
- **Infants 6-23 months** had the highest average annual rate at 6,580 prescriptions per 100,000 individuals
- Most RSV-attributable antibiotic prescriptions were penicillins, macrolides or tetracyclines

J Antimicrob Chemother 2025; **80**: 1116–1126
https://doi.org/10.1093/jac/dkaf043 Advance Access publication 19 February 2025

Journal of Antimicrobial Chemotherapy 50 years

General practice antibiotic prescriptions attributable to respiratory syncytial virus by age and antibiotic class: an ecological analysis of the English population

Lucy Miller [1,2*], Thomas Beaney [1], Russell Hope [2], Mark Cunningham[3], Julie V. Robotham[2,4], Koen B. Pouwels[4,5] and Cèire E. Costelloe[1,6]



Why is there no RSV vaccine (for children < 5 years) ?

RSV vaccines

- **The first RSV vaccine trial failed**

FIELD EVALUATION OF A RESPIRATORY SYNCYTIAL VIRUS VACCINE AND A TRIVALENT PARAINFLUENZA VIRUS VACCINE IN A PEDIATRIC POPULATION1

JAMES CHIN ✉, ROBERT L. MAGOFFIN, LOIS ANN SHEARER, JACK H. SCHIEBLE, EDWIN H. LENNETTE

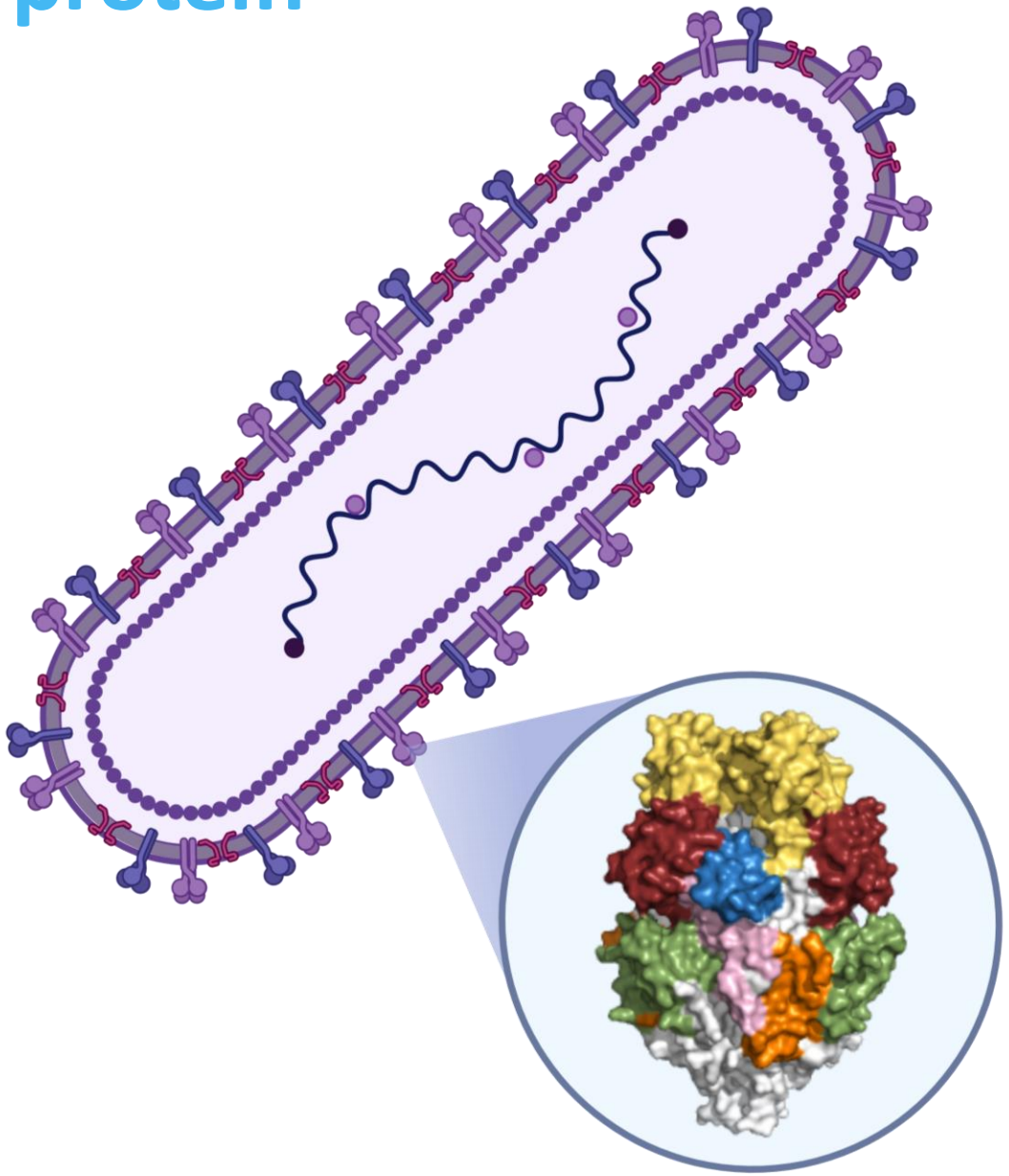
American Journal of Epidemiology, Volume 89, Issue 4, 1 April 1969, Pages 449–463,

- **In 1969, a formalin-inactivated RSV vaccine (FI-RSV) was administered to healthy infants and young children in a clinical phase I trial**

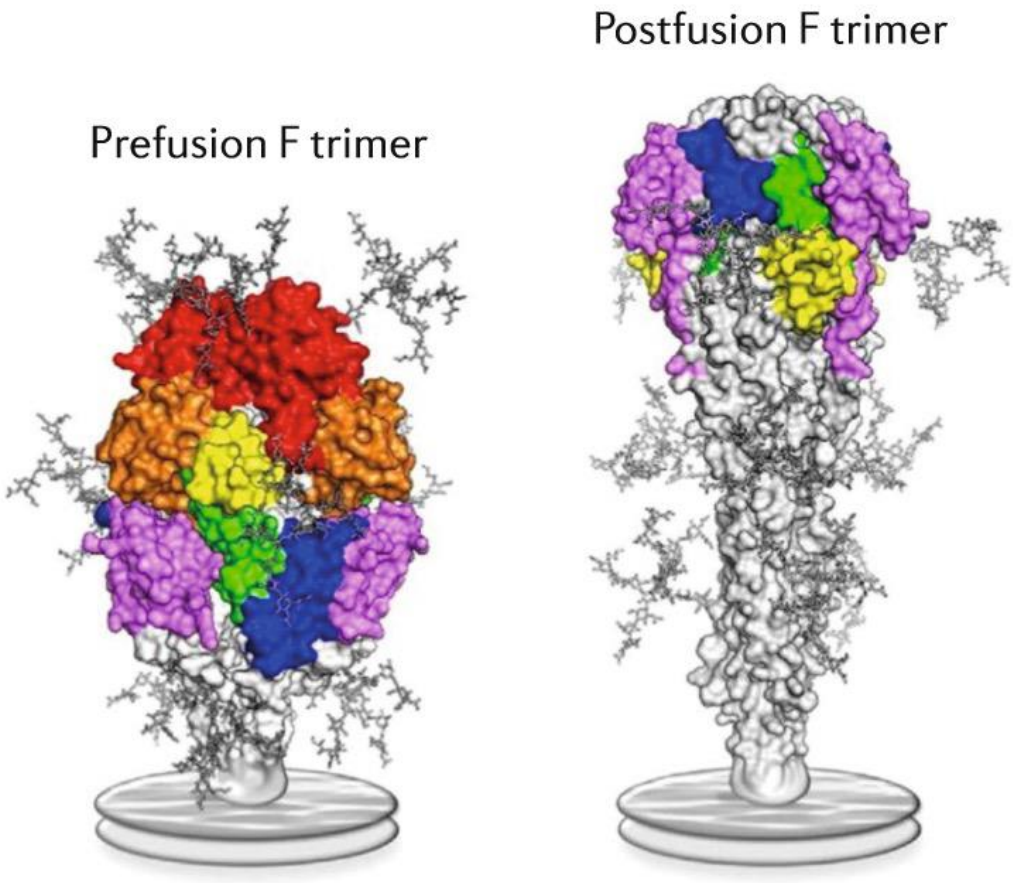
Vaccine	Category	Total No. of infants
FI-RSV lot 100 (N= 31)	RSV infection	20 (65%)
	Hospitalized	16 (80%)
Total FI-PIV (N= 40)	RSV infection	21 (53%)
	Hospitalized	1 (5%)

2 vaccinated children died

RSV fusion (F) protein



RSV F protein



Structure of RSV Fusion Glycoprotein Trimer Bound to a Prefusion-Specific Neutralizing Antibody

Jason S. McLellan[1,*], Man Chen[1], Sherman Leung[1], Kevin W. Graepel[1], Xiulian Du[1], Yongping Yang[1], Tongqing Zhou[1], Ulric…
+ See all authors and affiliations

Science 31 May 2013:
Vol. 340, Issue 6136, pp. 1113-1117
DOI: 10.1126/science.1234914

Two forms of F

1. In the viral envelope, the F protein exists in a metastable, high-energy state (**prefusion trimer**)

2. This form undergoes a major rearrangement to a stable state (**postfusion trimer**) by an irreversible and complex process

RSV prevention

Prefusion stabilized F protein-based vaccines

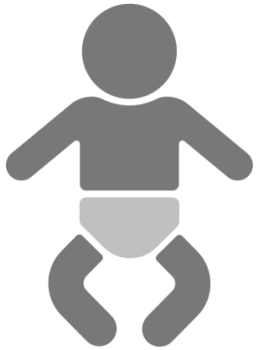
Published in final edited form as:
Science. 2013 November 1; 342(6158): 592–598. doi:10.1126/science.1243283.

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

Jason S. McLellan[1], Man Chen[1,#], M. Gordon Joyce[1,#], Mallika Sastry[1,#], Guillaume B. E. Stewart-Jones[1,#], Yongping Yang[1,#], Baoshan Zhang[1,#], Lei Chen[1], Sanjay Srivatsan[1], Anqi Zheng[1], Tongqing Zhou[1], Kevin W. Graepel[1], Azad Kumar[1], Syed Moin[1], Jeffrey C. Boyington[1], Gwo-Yu Chuang[1], Cinque Soto[1], Ulrich Baxa[2], Arjen Q. Bakker[3], Hergen Spits[3], Tim Beaumont[3], Zizheng Zheng[4], Ningshao Xia[4], Sung-Youl Ko[1], John-Paul Todd[1], Srinivas Rao[1], Barney S. Graham[1,*], and Peter D. Kwong[1,*]

RSV prevention: different target groups

P



M

O

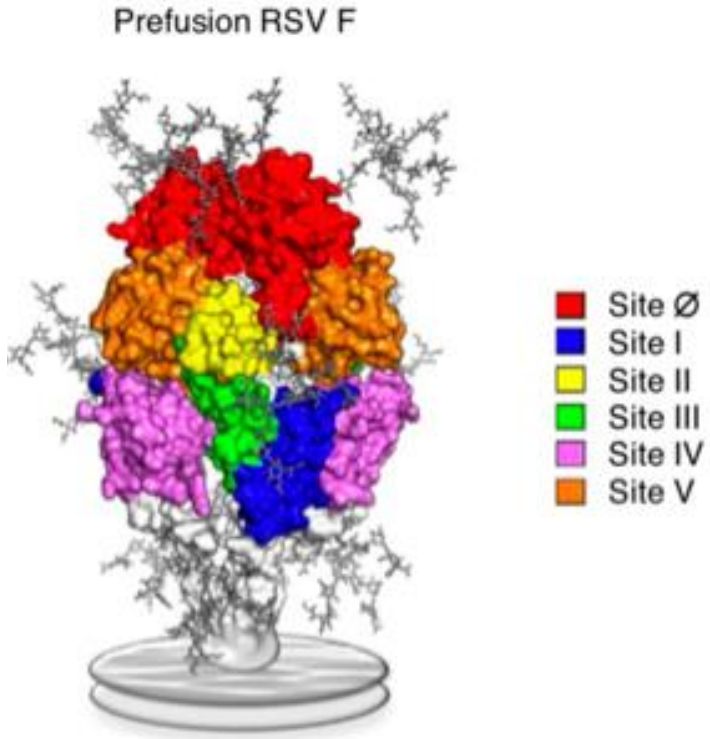
RSV prevention: monoclonal antibodies

Palivizumab (Synagis)

- Humanized mAb, given to high-risk infants, monthly injections
- 55% overall reduction in hospitalization as a result of RSV

Nirsevimab (MEDI8897)

- Humanized mAb, Site Ø specific
- Extended serum half-life (t1/2), one injection



Clesrovimab (phase III)

- Humanized mAb, Site IV specific
- Extended serum half-life (t1/2), one injection

RSV vaccines - ELDERLY

O

AREXVY (RESPIRATORY SYNCYTIAL VIRUS VACCINE, ADJUVANTED) GSK

- **RSVpreF3 OA**
  - 120 µg recombinant subunit soluble prefusion F antigen from RSV A2, RSVPreF3, based on McClellan et al. Science, 2013
  - AS01E adjuvant (QS-21 + MPL)

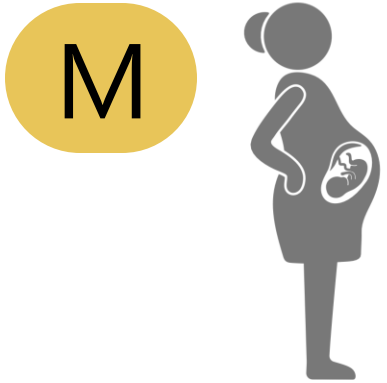
ABRYSVO® Respiratory Syncytial Virus Vaccine Pfizer

- **RSVpreF**
  - 60 µg recombinant RSVPreF of both RSV-A and RSV-B subtype, no adjuvant

mRESVIA® (Respiratory Syncytial Virus Vaccine) moderna

- **mRNA-1345**
  - 50µg mRNA coding for a full length prefusion F antigen from RSV A2
  - same lipid nanoparticles (LNPs) as in the Moderna COVID-19 vaccines

RSV vaccines - MATERNAL

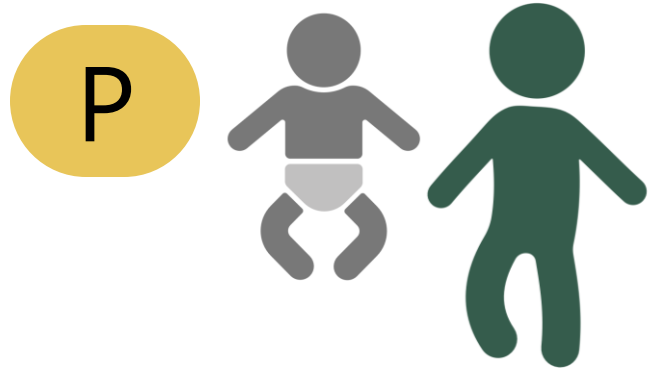


ABRYSVO®
Respiratory Syncytial Virus Vaccine

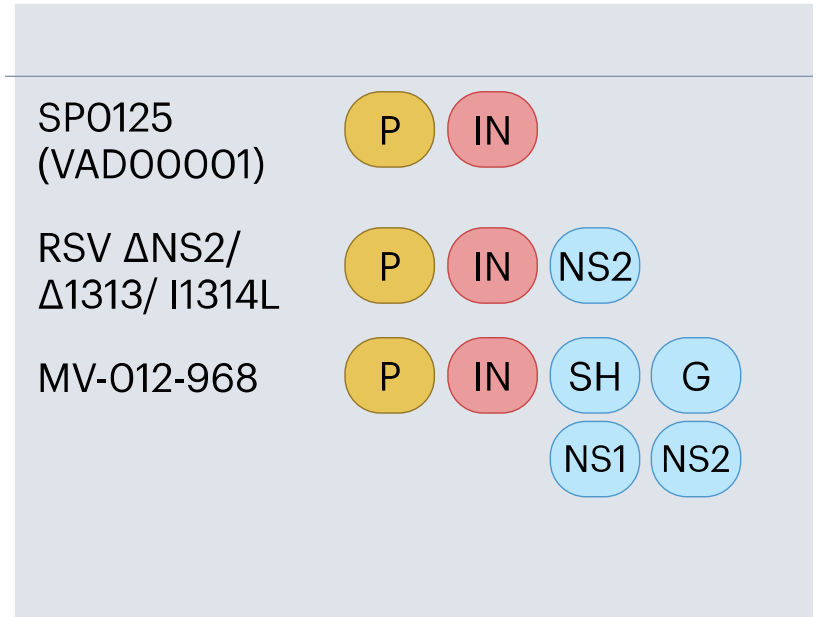
Pfizer

- **RSVpreF**
  - 60 µg recombinant RSVPreF of both RSV-A and RSV-B subtype, no adjuvant

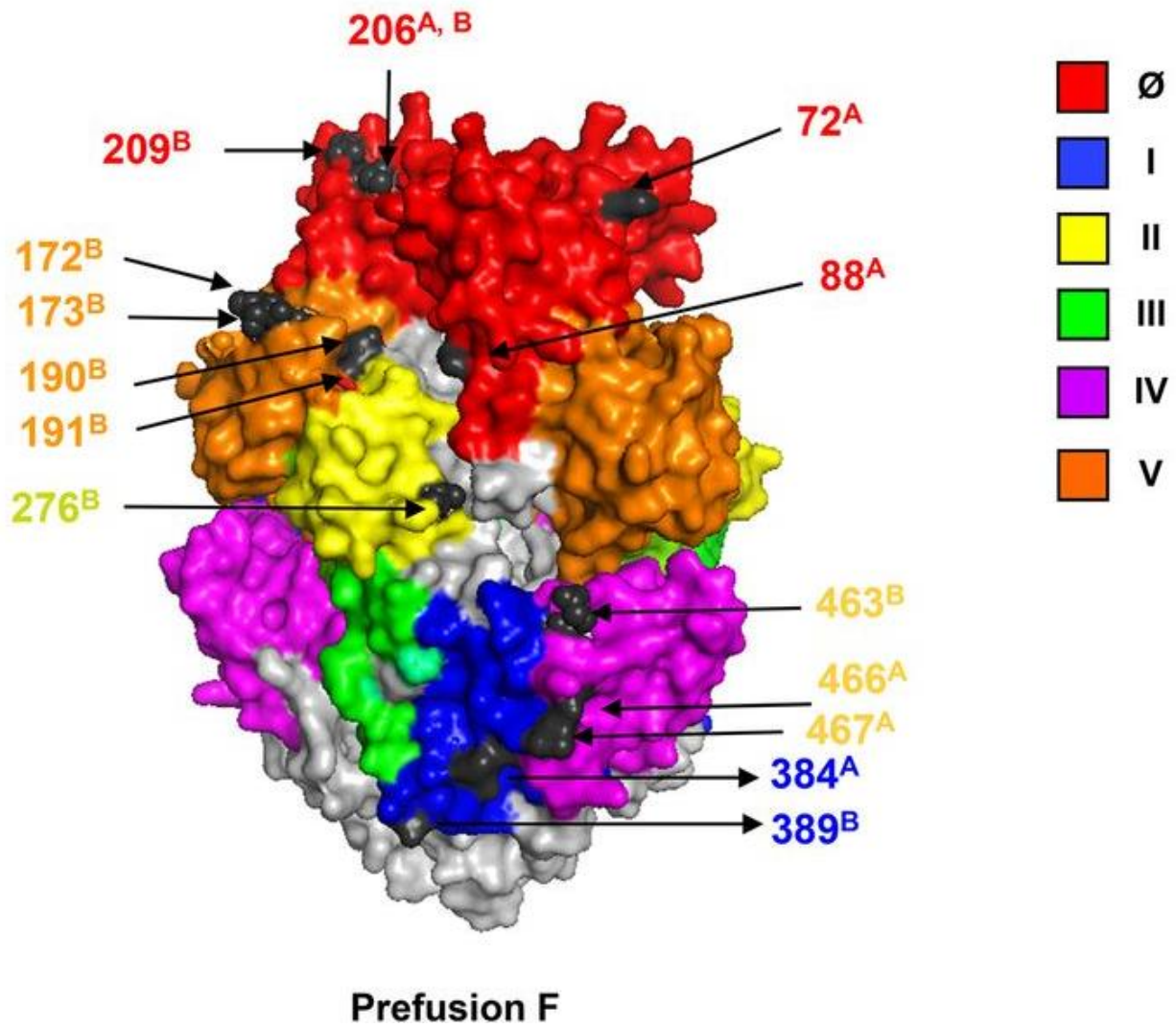
Other vaccine candidates in development



- **Still no effective vaccine for use in children**
  - Risk for enhanced disease in RSV naïve infants
  - Live RSV vaccines not expected to cause enhanced disease
- **Live attenuated vaccines in development**
  - Sanofi SP-0125 (VAD00001)
  - Sanofi /NIH RSV ΔNS2/Δ1313/I1314L
  - Meissa Vaccines MV-012-968
- **Sufficient attenuation vs. breadth of protection?**
- **Viral escape mutants?**



Virus evolution – surveillance for immune escape

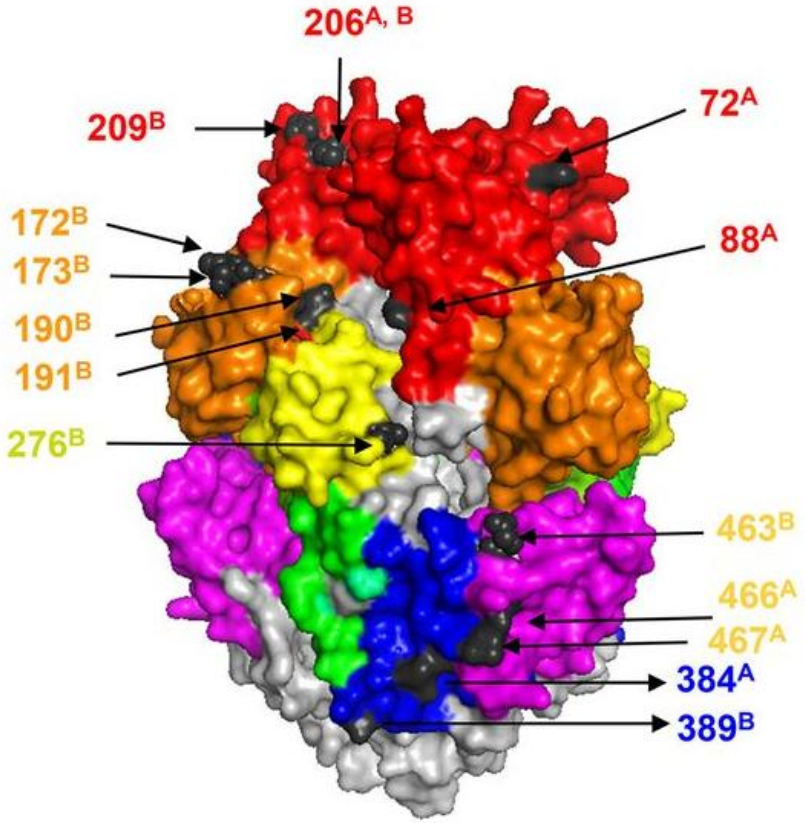


Tabor et al. JCM, 2020

Virus evolution – surveillance for immune escape

Antibody escape mutants

- Palivizumab (site II): K272E mutation confers resistance
- Suptavumab (site V): ineffective against novel RSV-B variant (mutations L172Q and S173L)
- Nirsevimab (MEDI8897; Site Ø): resistant strains exist, yet are rare
- Clesrovimab (Site IV): generally less variation, not clear if known variants confer resistance



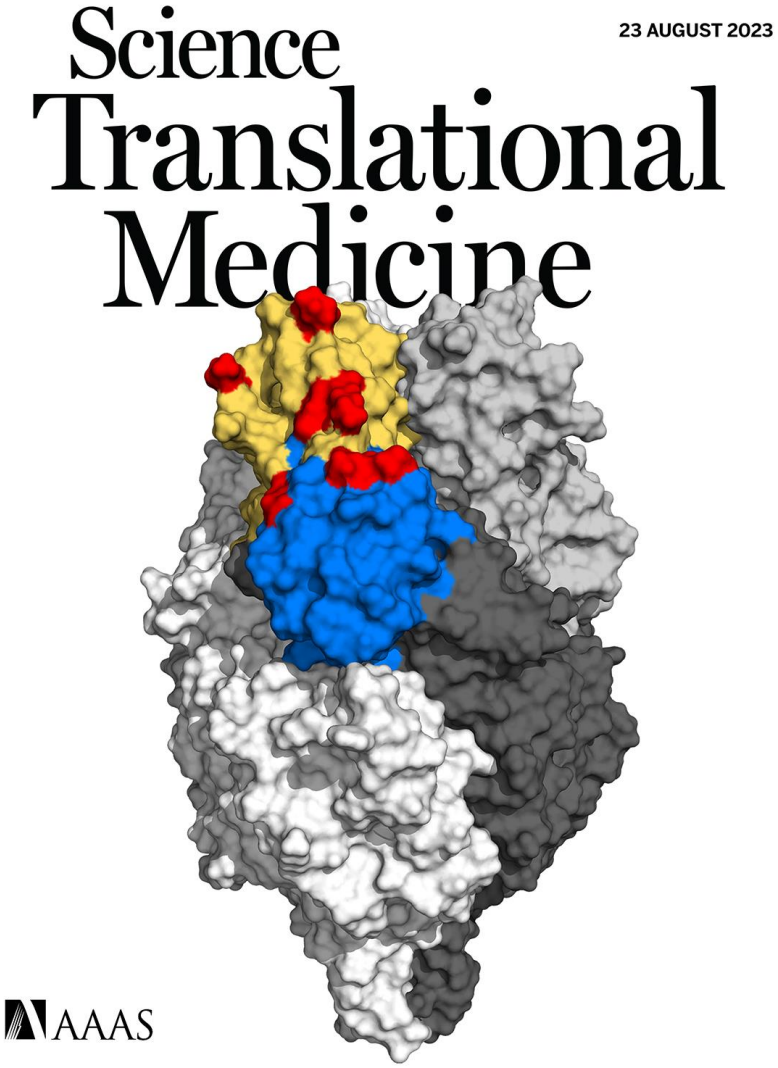
Simões et al. Clinical Infectious Diseases, 2023; Wilkins et al. The Lancet Infectious Diseases, 2023; Mosscrop et al. Nature Reviews Immunology, 2022; Zhu et al. JID, 2018; Tabor et al. JCM, 2020

Virus evolution – surveillance for immune escape

- **Genomic analysis**
  - Protein variability

- **Functional analysis: genotype to phenotype (G to P)**
  - Sensitivity to neutralization by panel of different mAbs
  - Viral 'fitness'

Virus evolution – surveillance for immune escape



REVIRANT
ANTWERP RESPIRATORY VIRUS REPOSITORY

Viral variants affecting vaccine efficacy

- Efficacy against RSV-A versus RSV-B
- Breadth of the vaccine-induced neutralizing antibodies, evaluation against an panel of clinical isolates representing ongoing variability

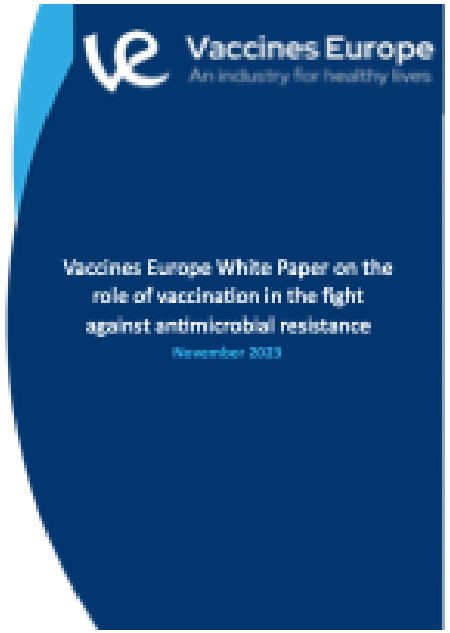
Sacconnay et al. STM, 2023

RSV vaccines and AMR

- In a double-blind, randomized, placebo-controlled trial, administering an RSV vaccine to pregnant mothers **reduced antimicrobial prescribing** among their infants by **12.9% over the first 3 mo of life**

- Over the first 3 mo of life, **maternal vaccination prevented 3.6 antimicrobial prescription courses for every 100 infants** born in high-income countries and **5.1 courses per 100 infants** in low- and middle-income countries, representing **20.2 and 10.9%** of all antimicrobial prescribing in these settings, respectively

- Clear vaccine **efficacy (71.3%)** was also observed against **acute otitis media–associated antimicrobial prescription** among infants in high-income countries.



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University of Antwerp

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