Updates in Respiratory Viral Infections in Children

Ian C. Michelow, MD

Professor of Pediatrics

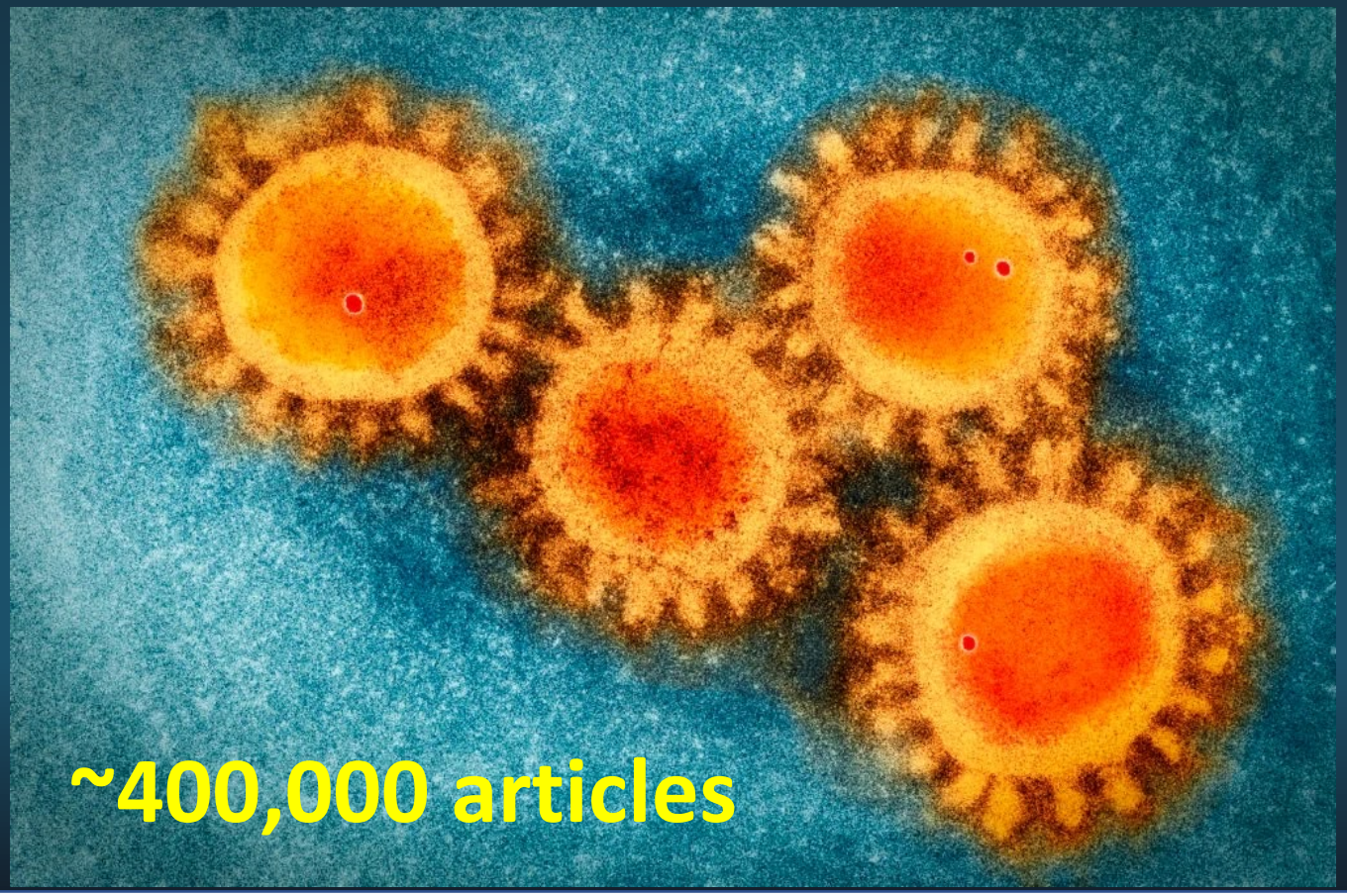
Head of Division, Pediatric Infectious Diseases & Immunology

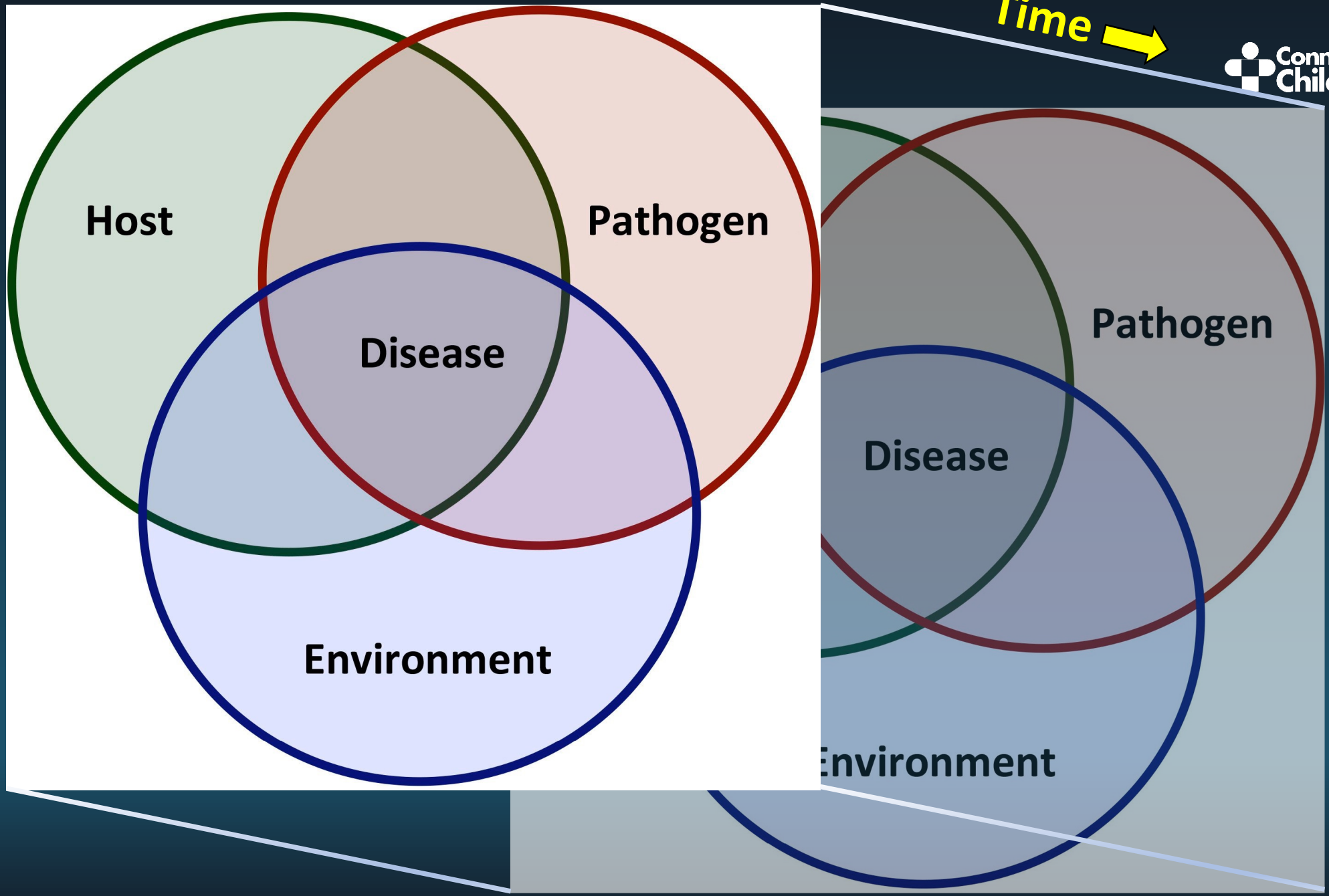
May 11, 2023

Disclosures

Dr Ian Michelow has no financial disclosures or conflicts of interest

What have we learned during the COVID-19 epidemic?




Host
Pathogen
Disease
Environment
Time
Pathogen
Disease
Environment

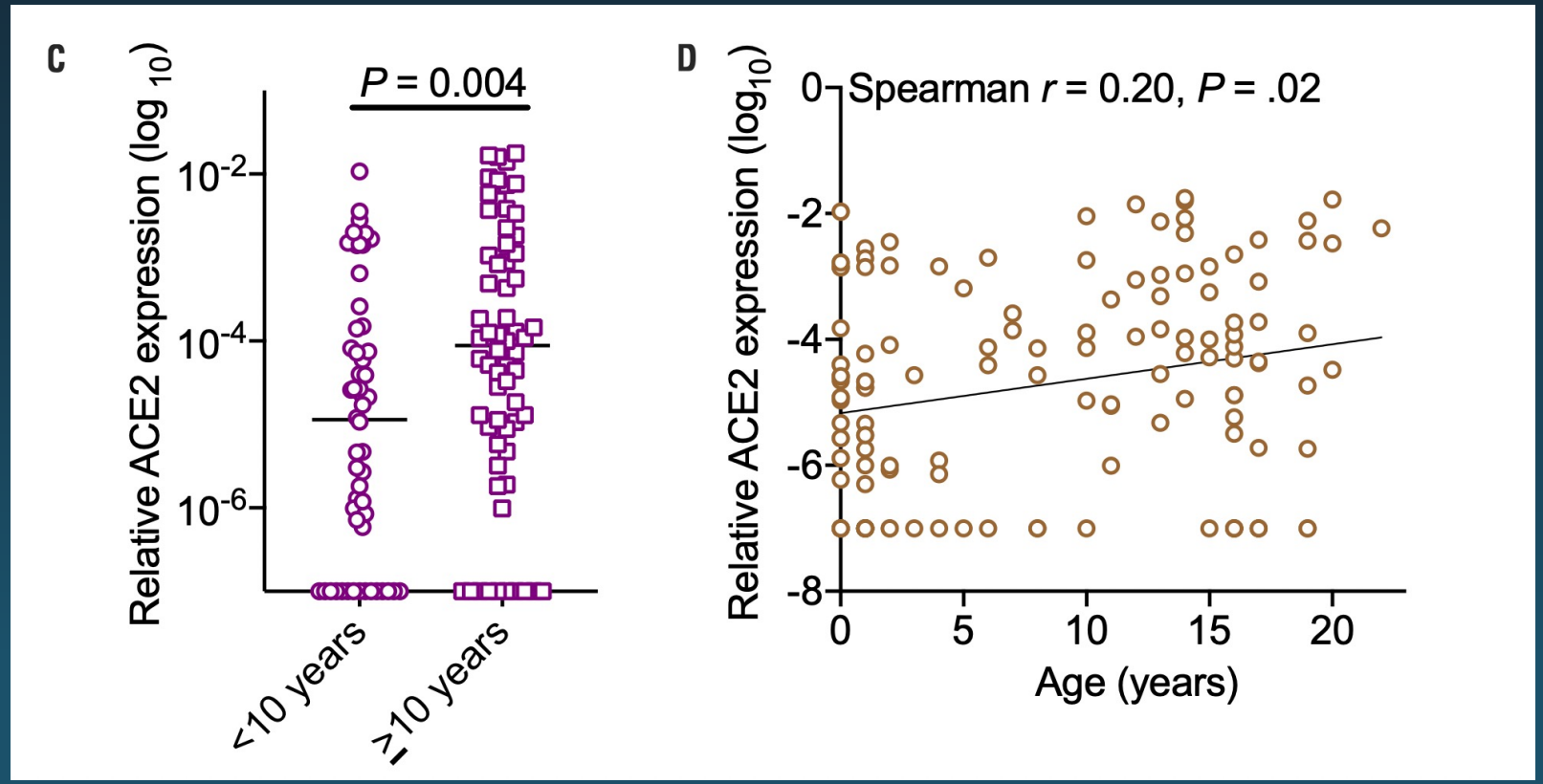
Why do children have milder disease than adults?

-some theories-

- fewer comorbidities (obesity, diabetes, etc)
- pre-existing protective antibodies against seasonal coronaviruses
- competition with other respiratory viruses
- BCG and MMR vaccination (off target effect of live vaccines)
- more robust innate immune systems (neutrophils, cytokines, IFNg)
- differences in respiratory tract microbiota
- lower intensity of exposure to SARS-CoV-2
- **less ACE2 receptors** in respiratory tract (esp lower tract)

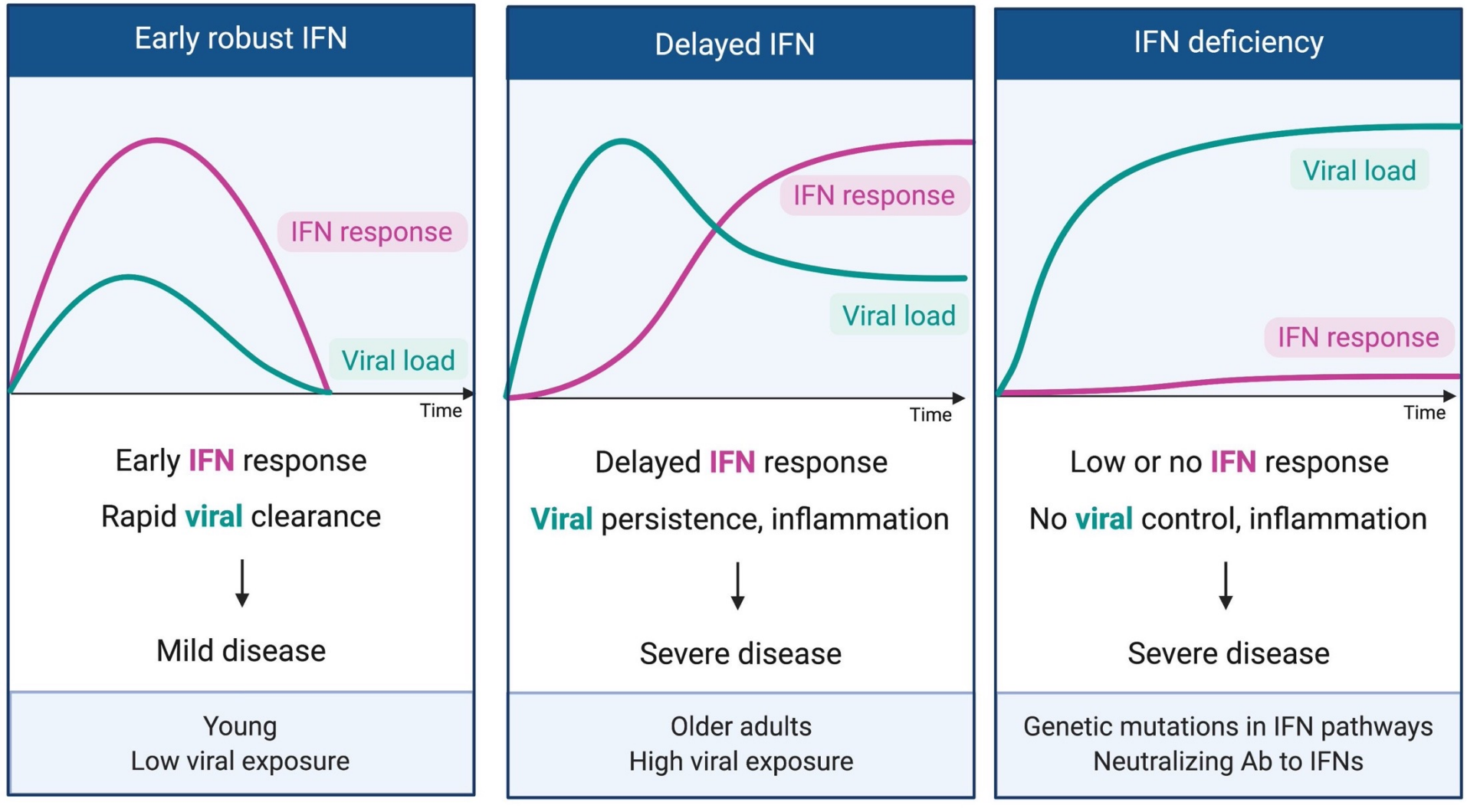
Zimmermann P, Curtis N. *Arch Dis Child* 2021;**106**:429–439

Less ACE2 receptors in upper respiratory tract

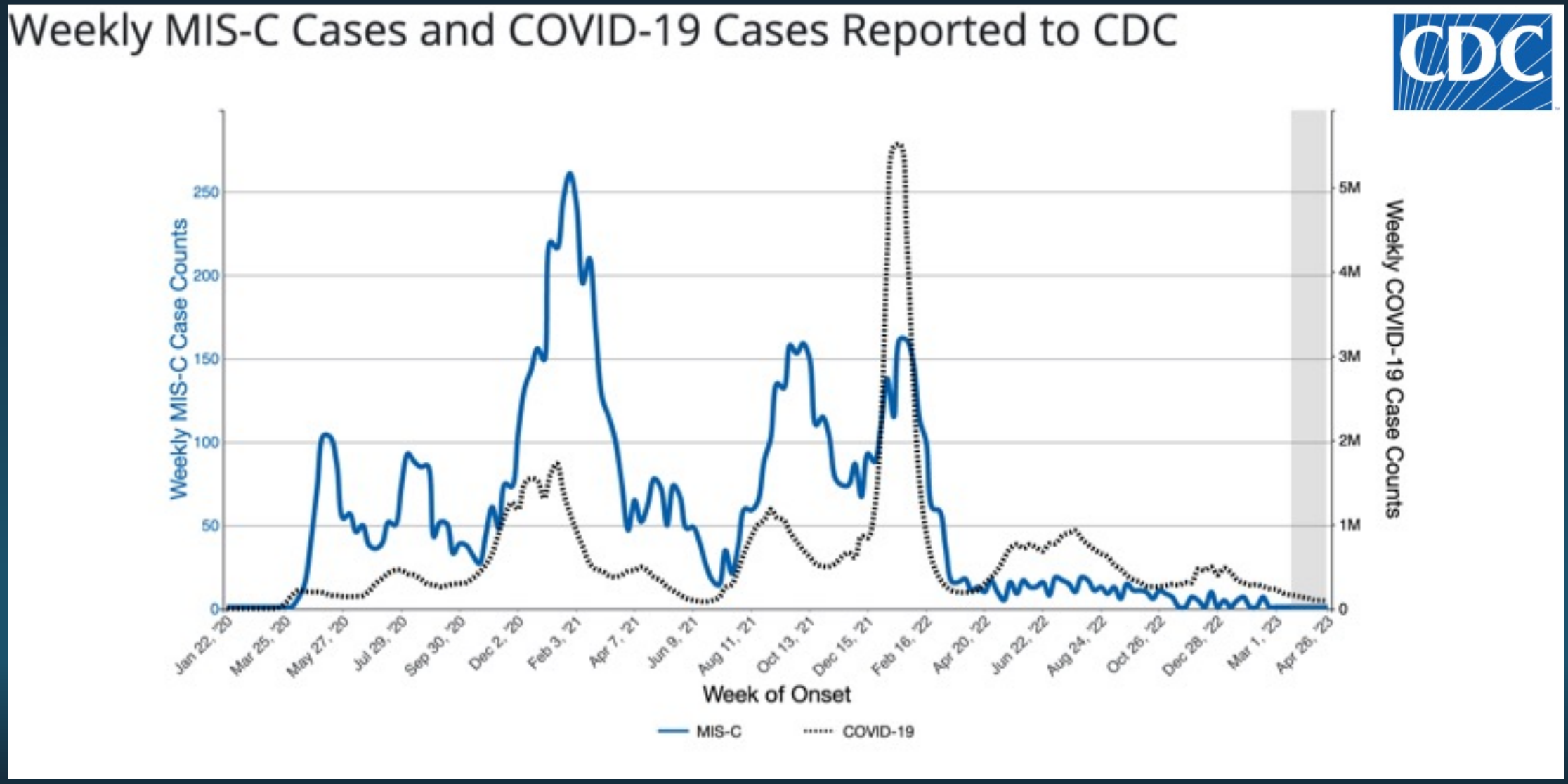


Yonker J Peds 2020

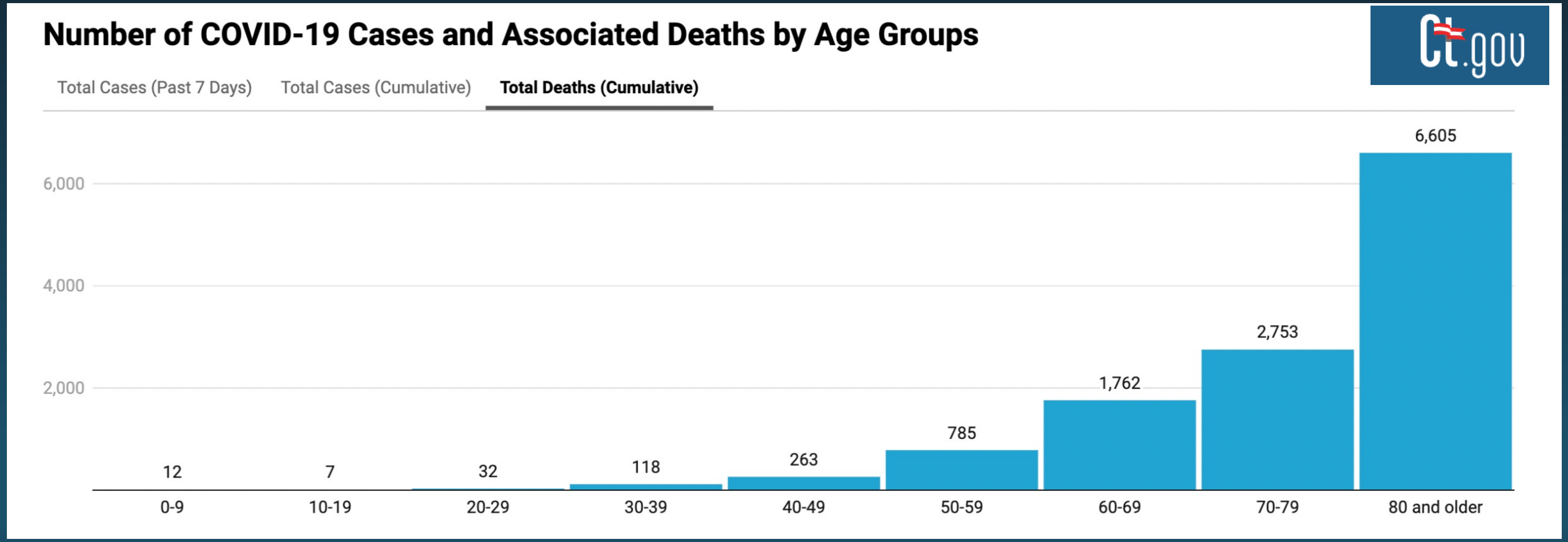
Children have potent innate immune systems



COVID-19 Epidemiology in Children <18 years

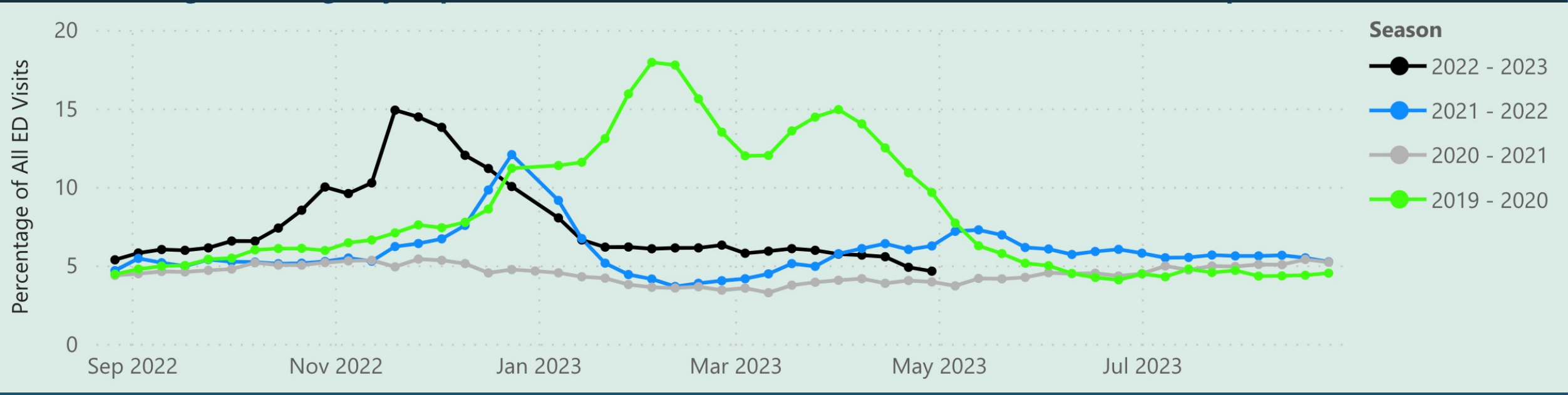


Low childhood COVID-19 death rates: CT



How did non-pharmaceutical interventions impact other respiratory viruses in children?

Influenze-like-illness (ILI) incidence in CT by season



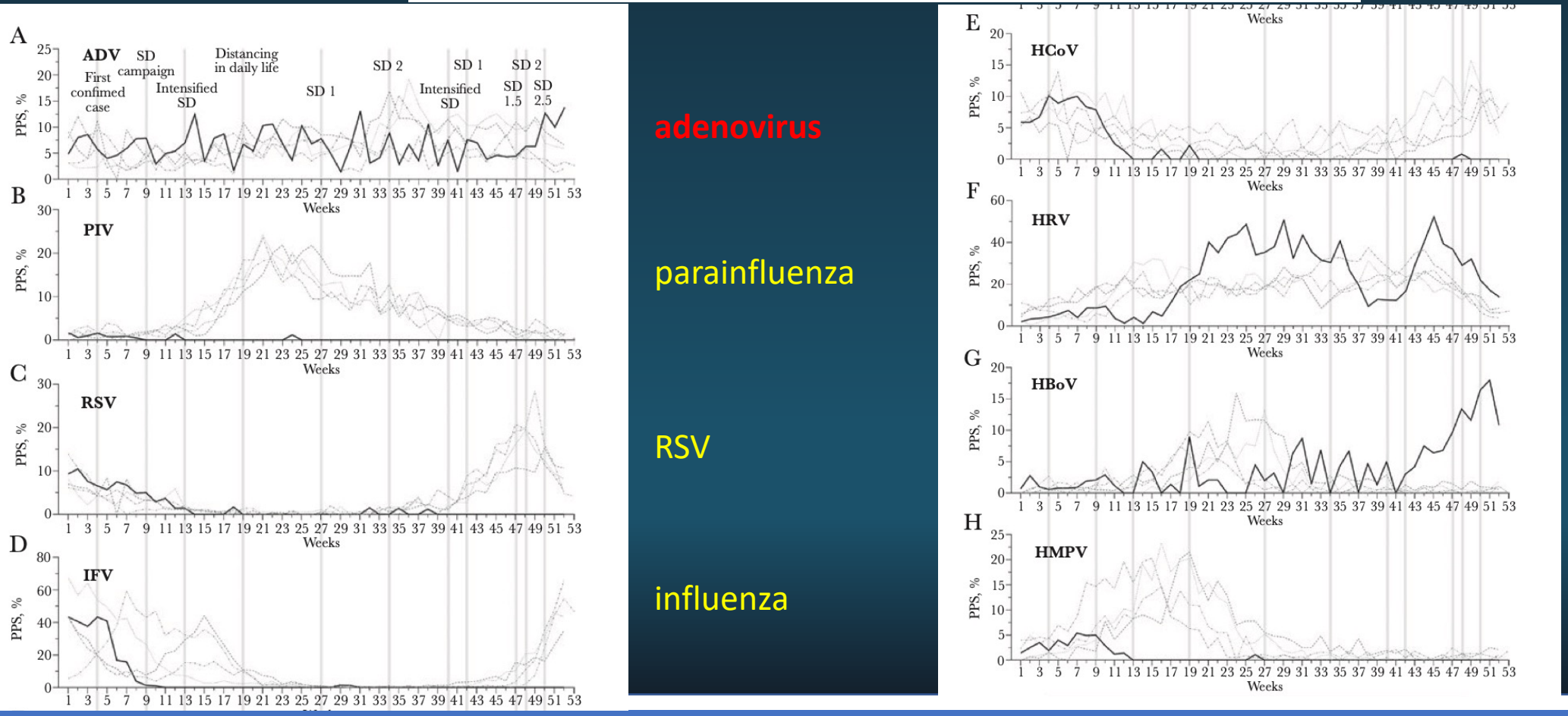
Korean Surveillance System
Monthly inpatient viral rates

The Journal of Infectious Diseases
MAJOR ARTICLE

Shifting Patterns of Respiratory Virus Activity Following Social Distancing Measures for Coronavirus Disease 2019 in South Korea

Sangshin Park,[1] Ian C. Michelow,[2,3] and Young June Choe[4]

2016 2017 2018 2019 2020



adenovirus

parainfluenza

RSV

influenza

Seasonal coronoviruses

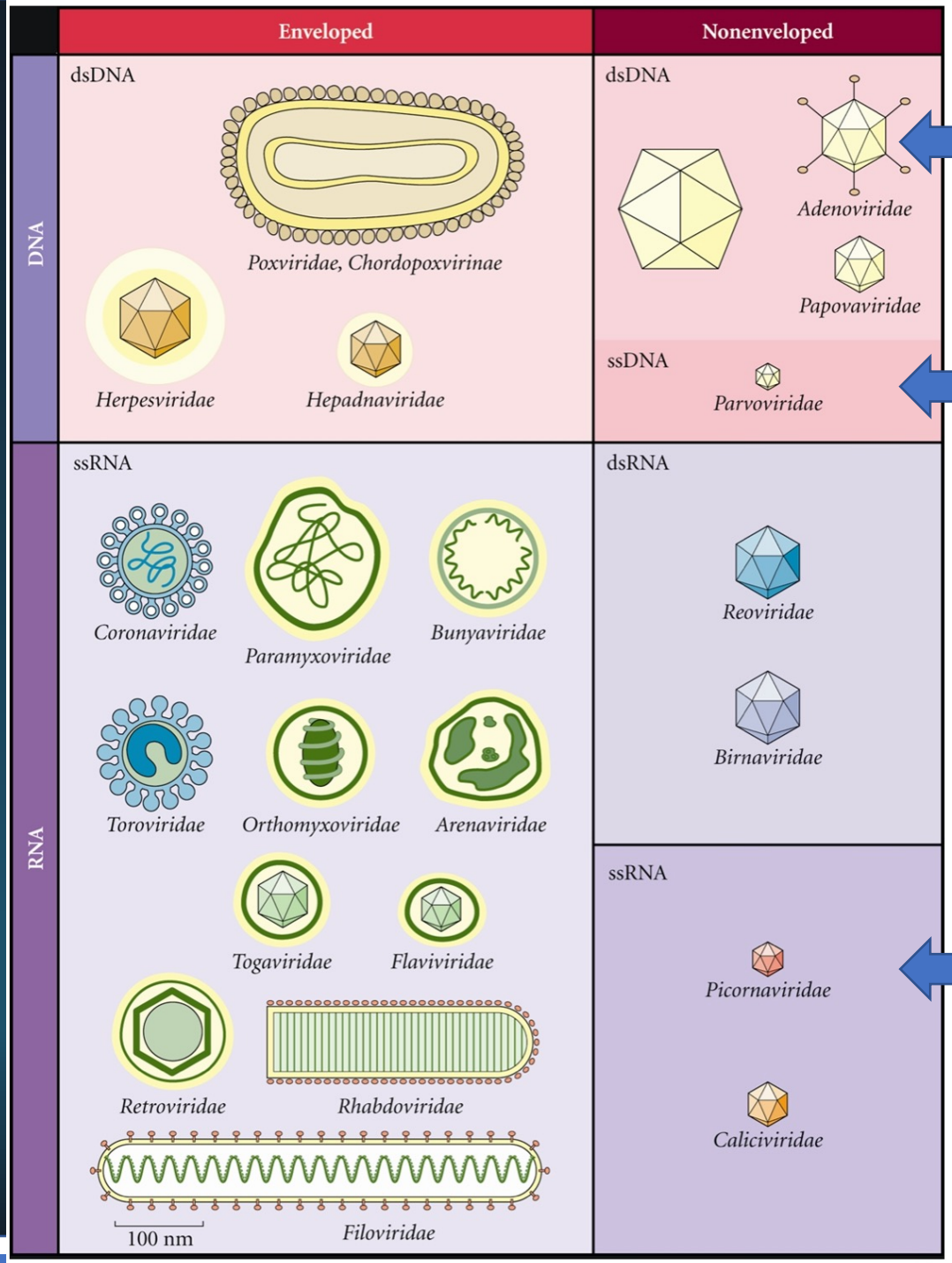
rhinovirus

bocavirus

Meta-pneumovirus

non-enveloped
viruses lack a lipid-bilayer membrane

not easily inactivated
by routine surface cleaning and disinfection



adenovirus

bocavirus

rhinovirus

https://ppdictionary.com/viruses.htm

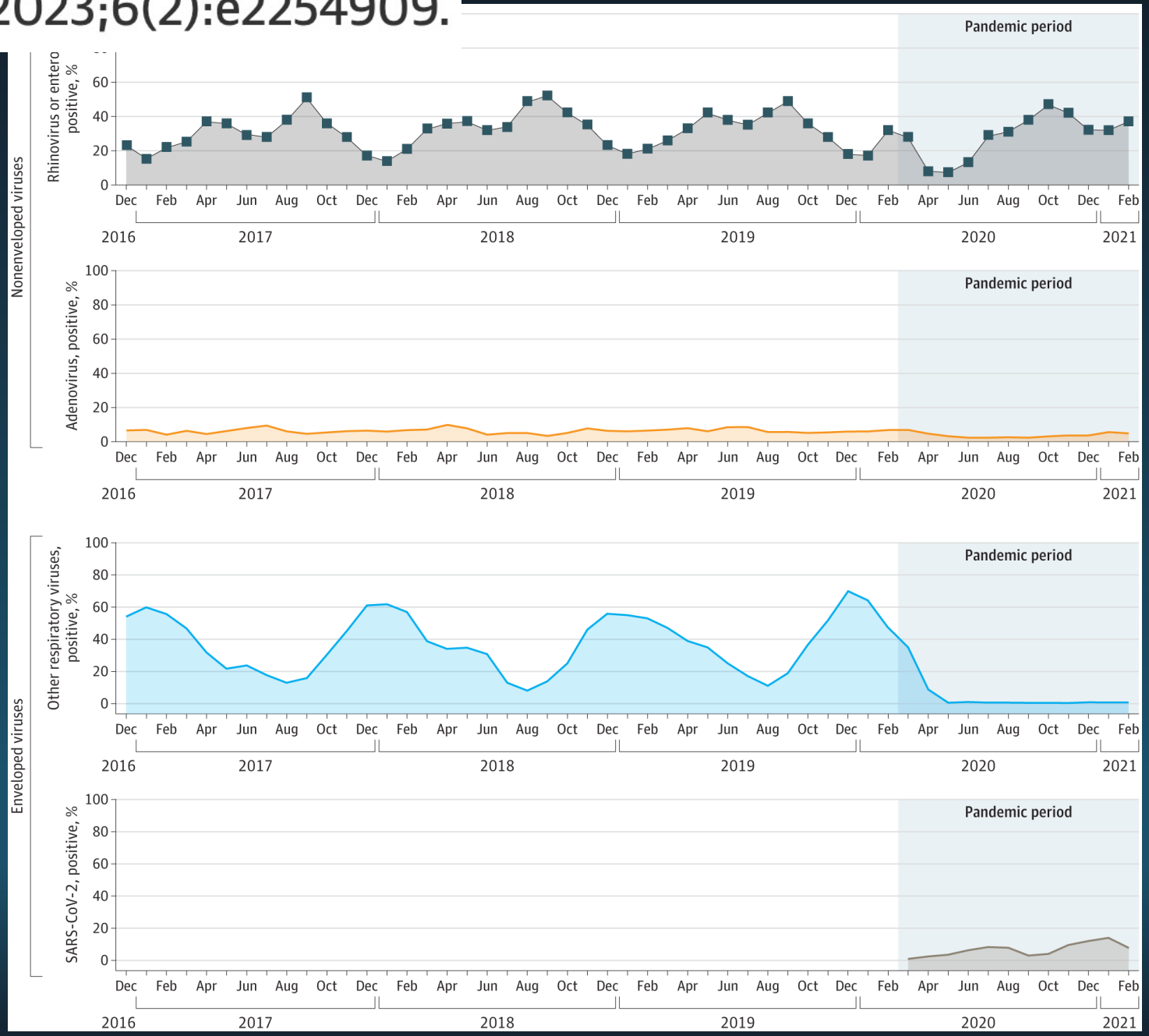
JAMA Netw Open. 2023;6(2):e2254909.

Rhino/entero

Adenovirus

Other resp viruses

SARS-CoV-2



7 centers (New Vaccine Surveillance Network)

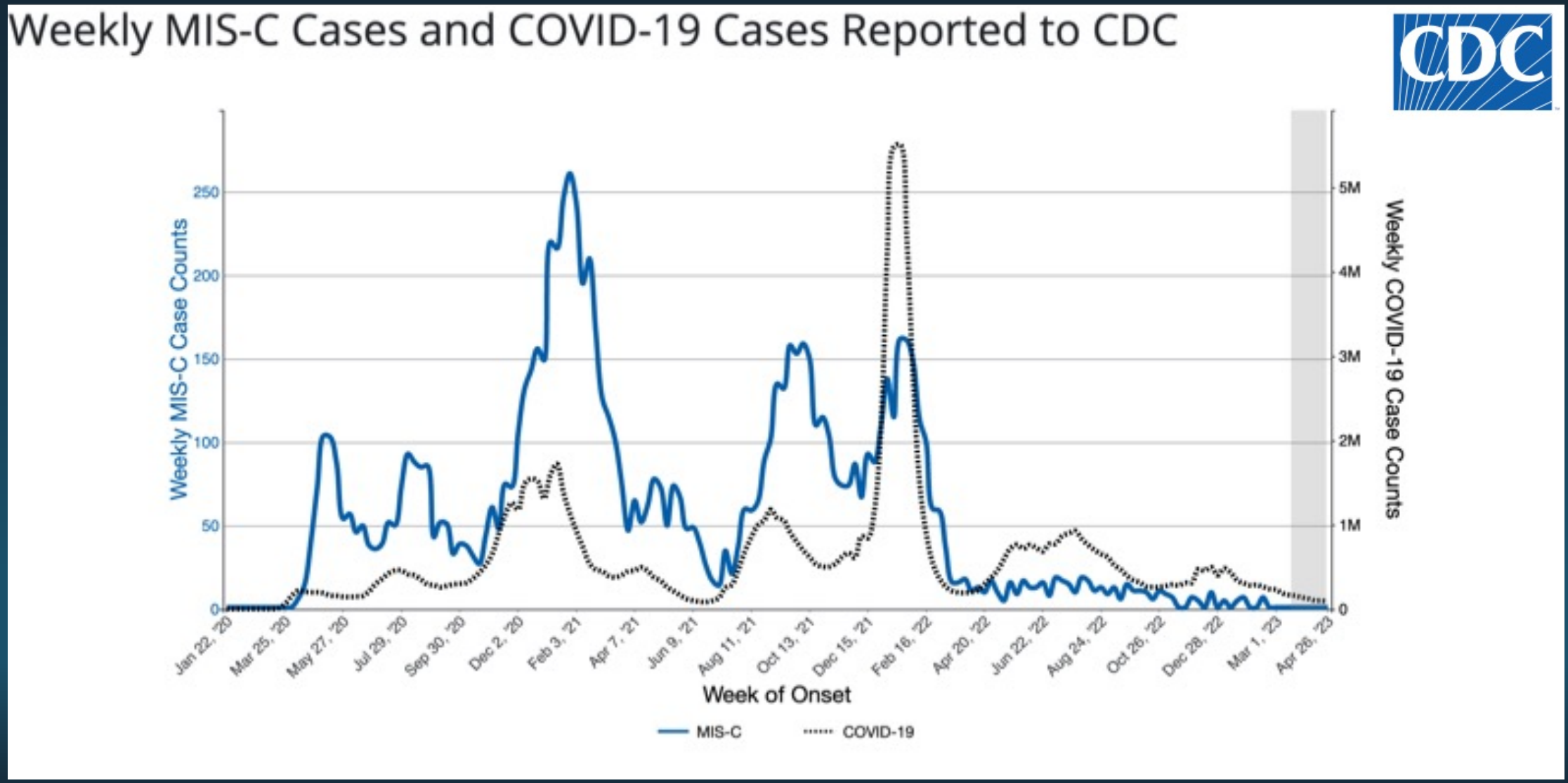
Have numbers of MIS-C cases decreased and if so why?

Multisystem inflammatory Syndrome in Children (MIS-C) up to 60 days after COVID-19 infection

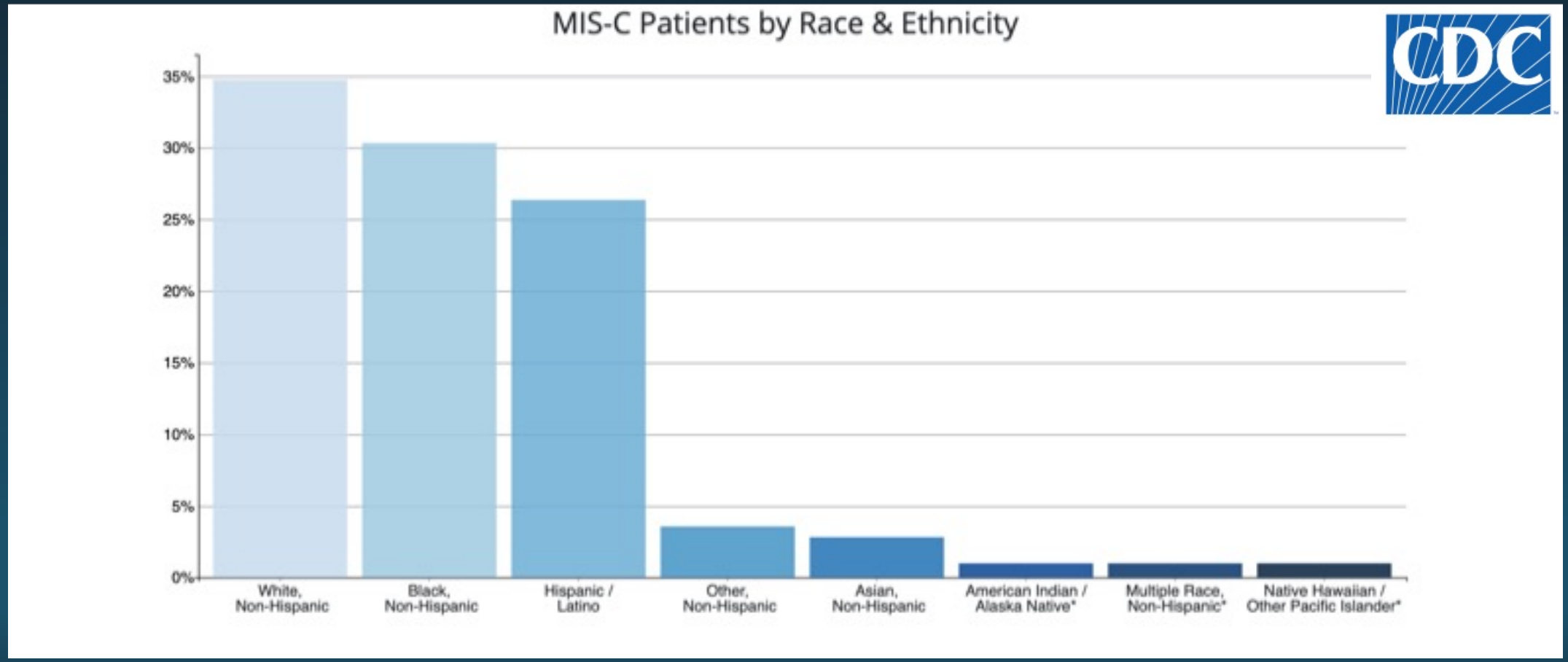
Surveillance definition:

Any illness in a person <21 years that meets:
•The clinical AND the laboratory criteria (Confirmed),
OR
•The clinical criteria AND epidemiologic linkage criteria (Probable)

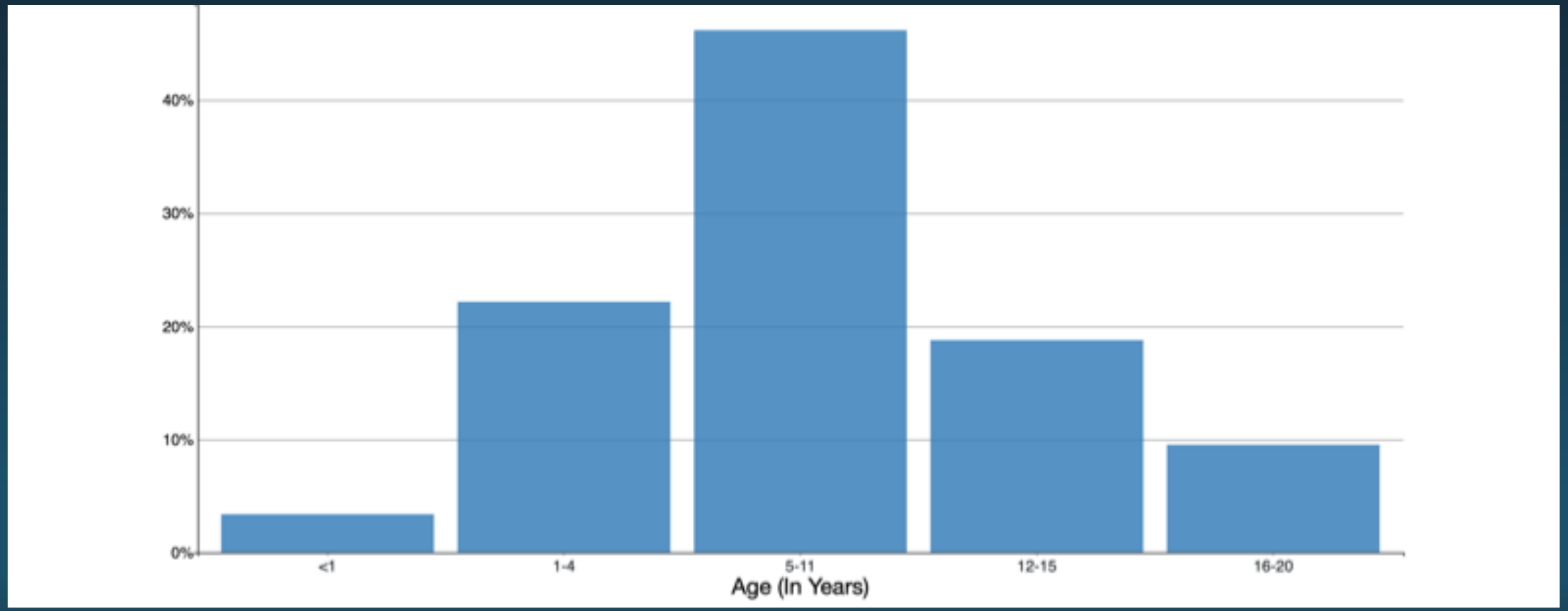
MIS-C Epidemiology in Children <18 years



MIS-C by Race and Ethnicity



MIS-C by Age



Did rates of Kawasaki Disease change?

	MIS-C	KD
Age	Older children and adolescent, Median age 8–11 years	Infant and young children, 76% of affected children <5 years
Sex ratio	Male/Female 1:1 to 1.2:1	Male/Female 1.5:1 to 1.7:1
Race and ethnicity	Black and Hispanic descent	Asian descent
Gastrointestinal symptoms	Very Common (53–92%)	Less common (≈20%)
Myocardial dysfunction and shock	Common, 73% elevated BNP, 50% elevated troponin levels, 48% receive vasoactive support	Less common, 5% receive vasoactive support
Organ dysfunction	Multiorgan dysfunction common	Multiorgan dysfunction not common
Inflammatory markers	Highly elevated CRP, ferritin, procalcitonin, and D-dimer, lymphopenia and thrombocytopenia	Elevated CRP, D-dimer, and thrombocytosis, usually normal ferritin; thrombocytopenia is rare
Treatment	IVIG, Corticosteroids, IL-1 blocker, IL-6 inhibitors	IVIG, Corticosteroids, IL-1 blockers
Outcome	Fatality rate 1.4–1.7%	Fatality rate 0.01%

MIS-C: spectrum of severity

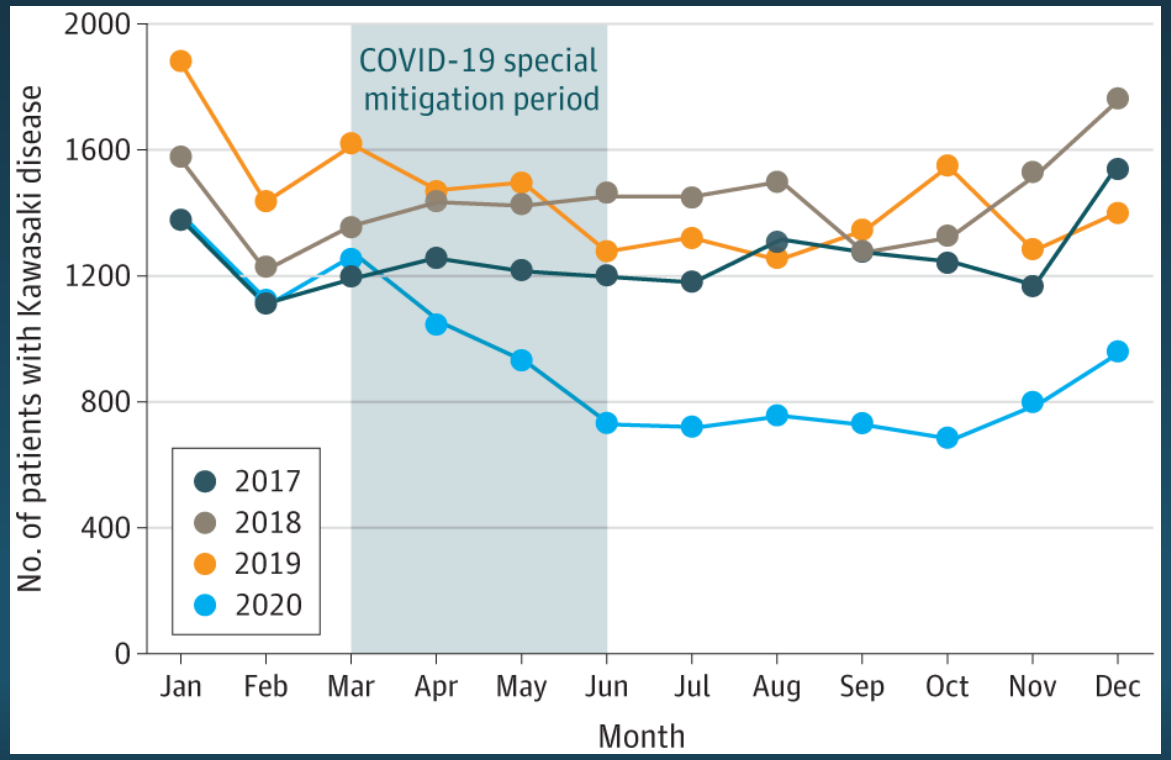
COVID-19-associated MIS-C		
Febrile inflammatory state	**KD-like illness**	**Severe MIS-C**
Some children may present with persistent fevers and mild symptoms (eg, headache, fatigue). Inflammatory markers may be elevated, but signs of severe multisystem involvement are lacking.	Some children meet criteria for complete or incomplete KD and do not develop shock and severe multisystem involvement.	Children with severe MIS-C have markedly elevated inflammatory markers and severe multisystem involvement. Cardiac involvement and shock are common.

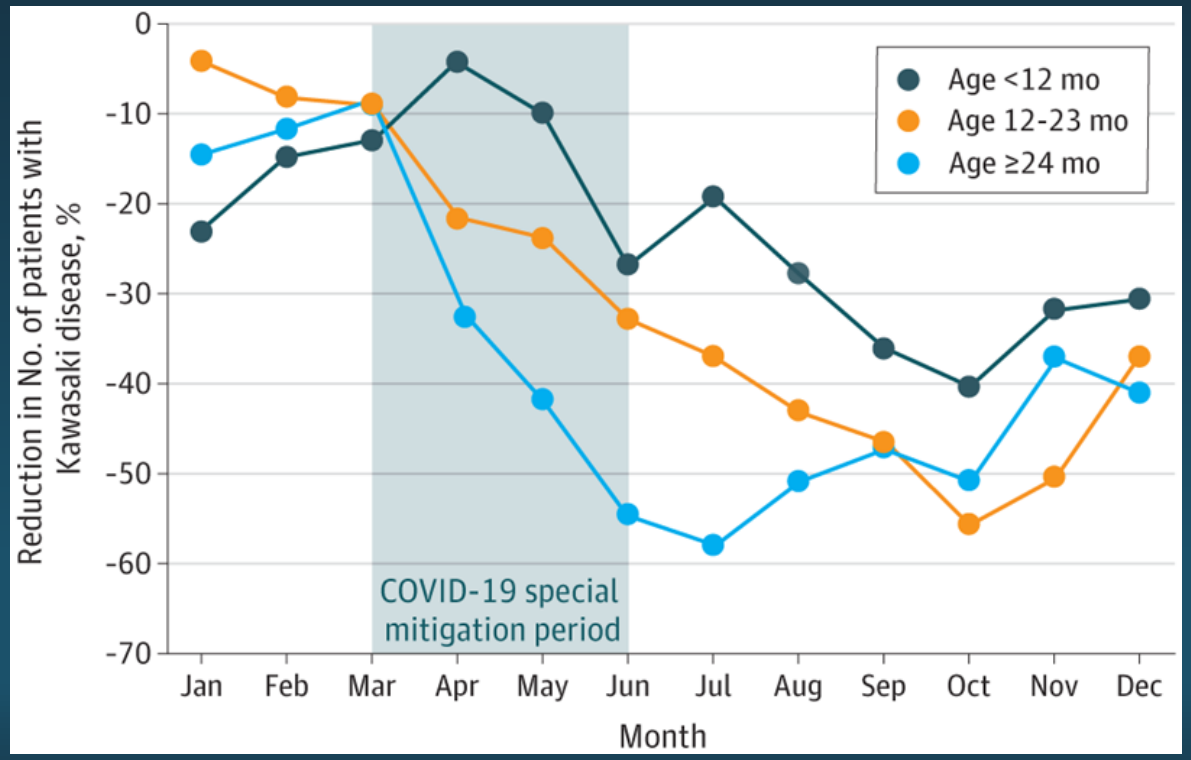
UpToDate®

What happened to KAWASAKI DISEASE during the COVID-19 pandemic? Japan experience

JAMA Network

JAMA Pediatr. 2022;176(12):1217-1224



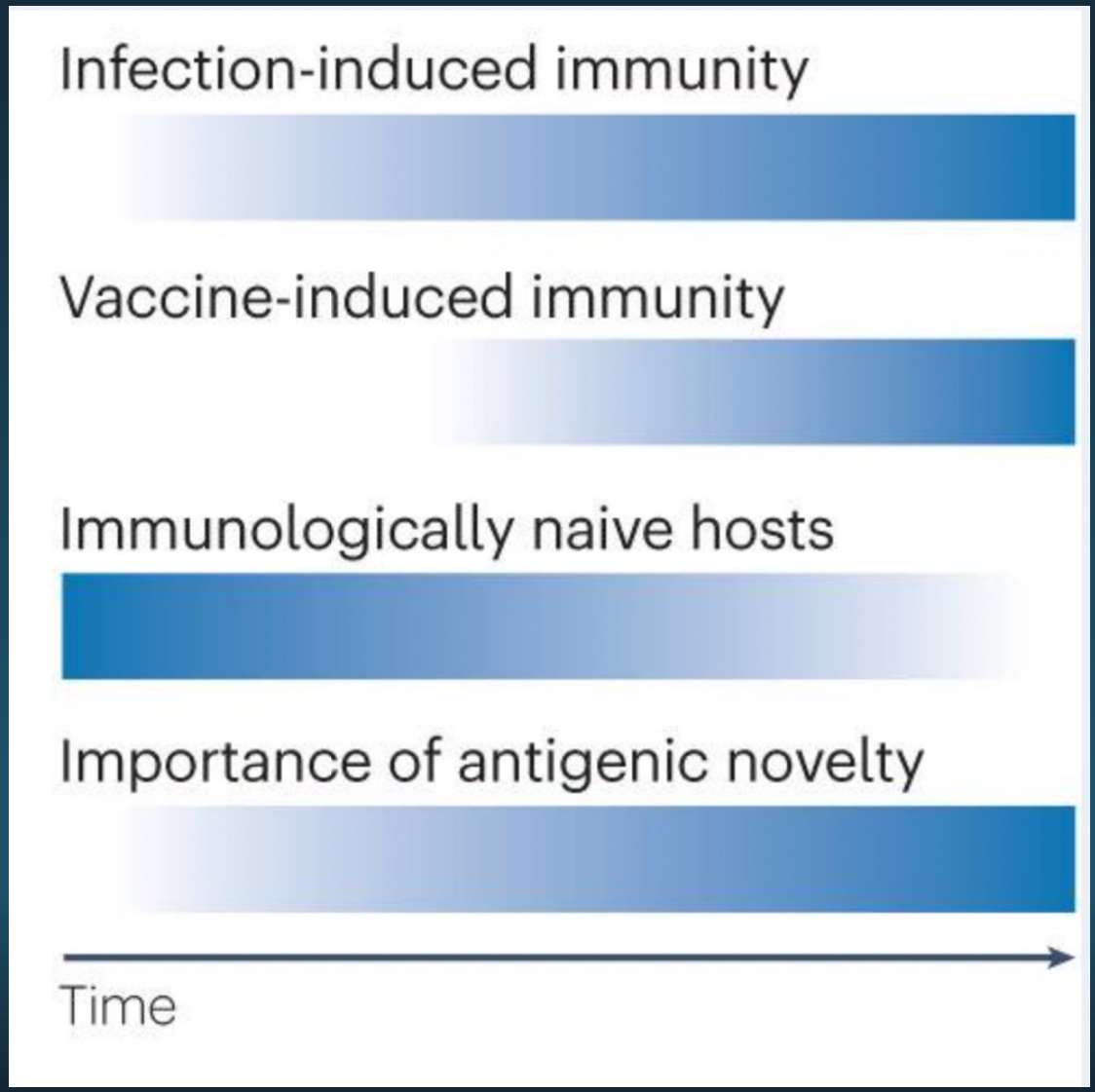


Is COVID-19 infectivity linked to virulence?

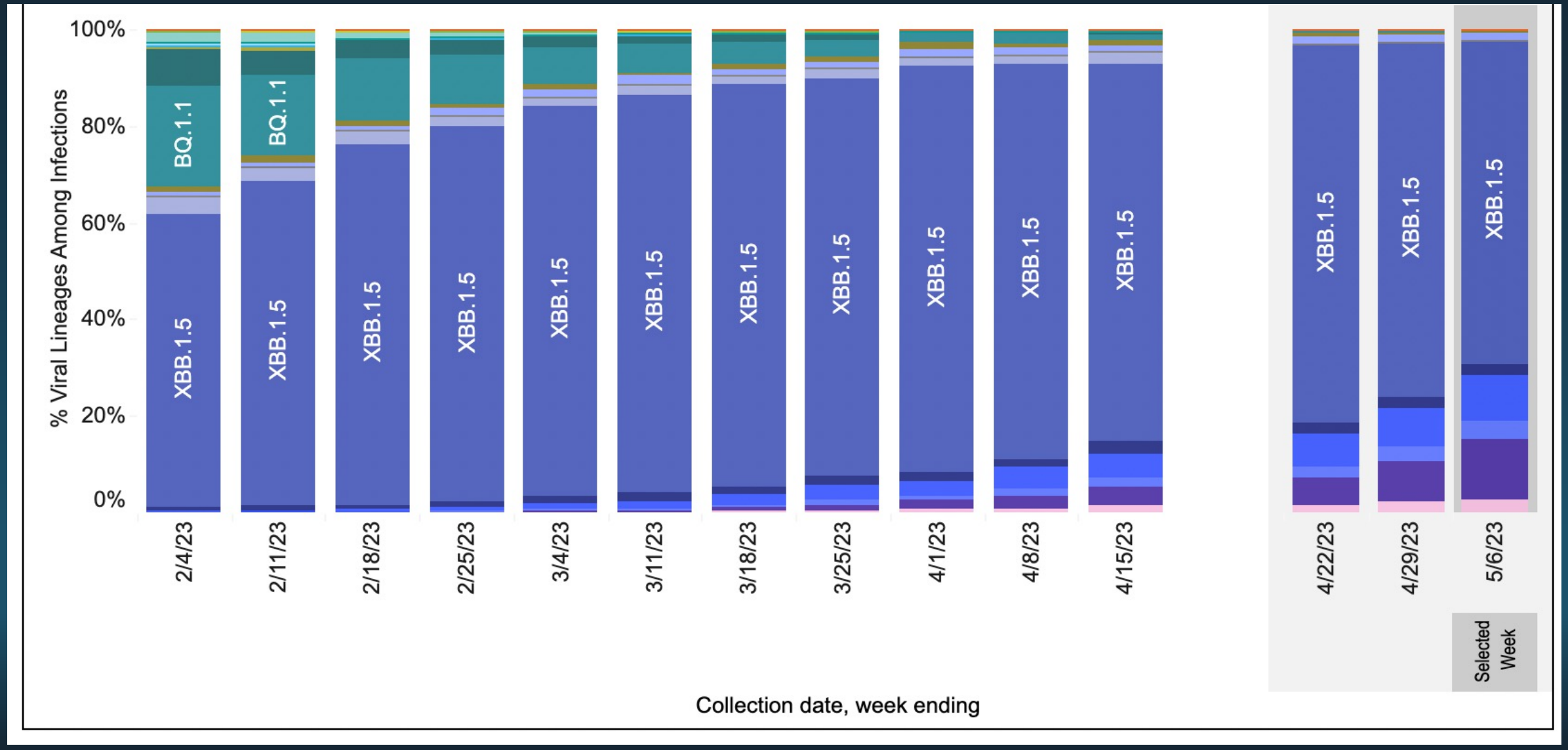
nature reviews microbiology

Volume 21 | March 2023 | 162–177

SARS-CoV-2 variant biology: immune escape, transmission and fitness



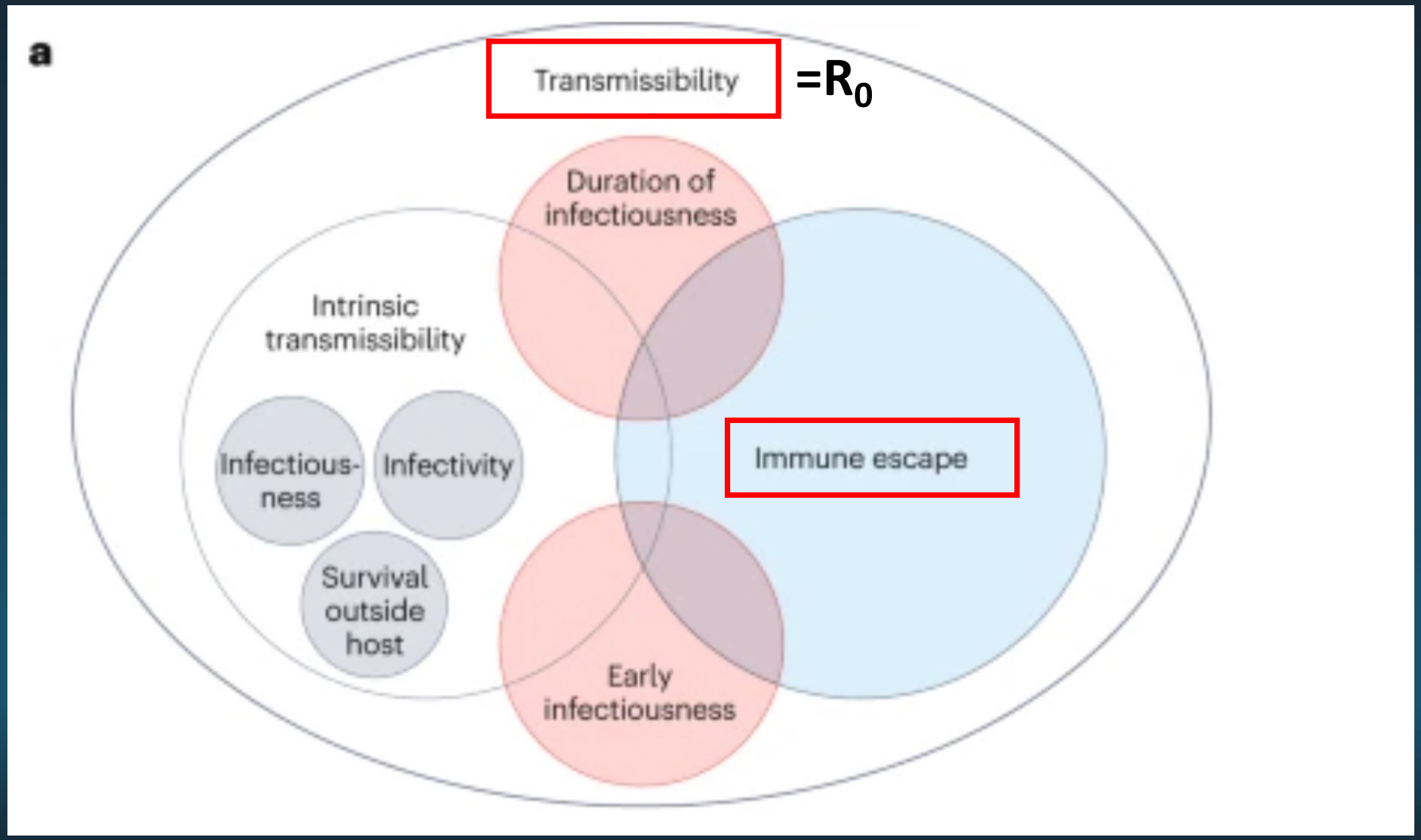
Circulating SARS-CoV-2 variants in the U.S.



nature reviews microbiology

The evolution of SARS-CoV-2

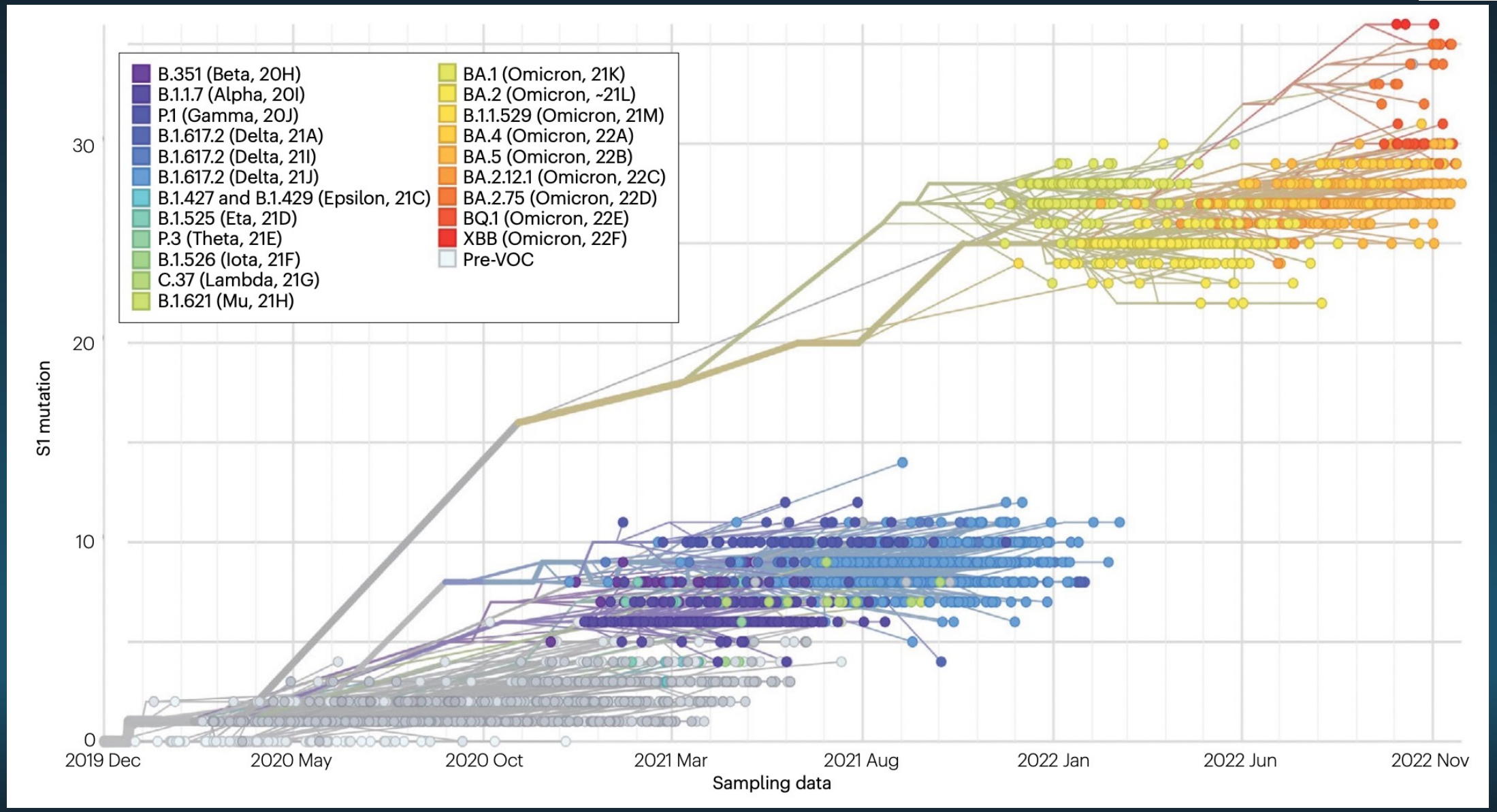
05 April 2023



nature reviews microbiology

Viral Fitness

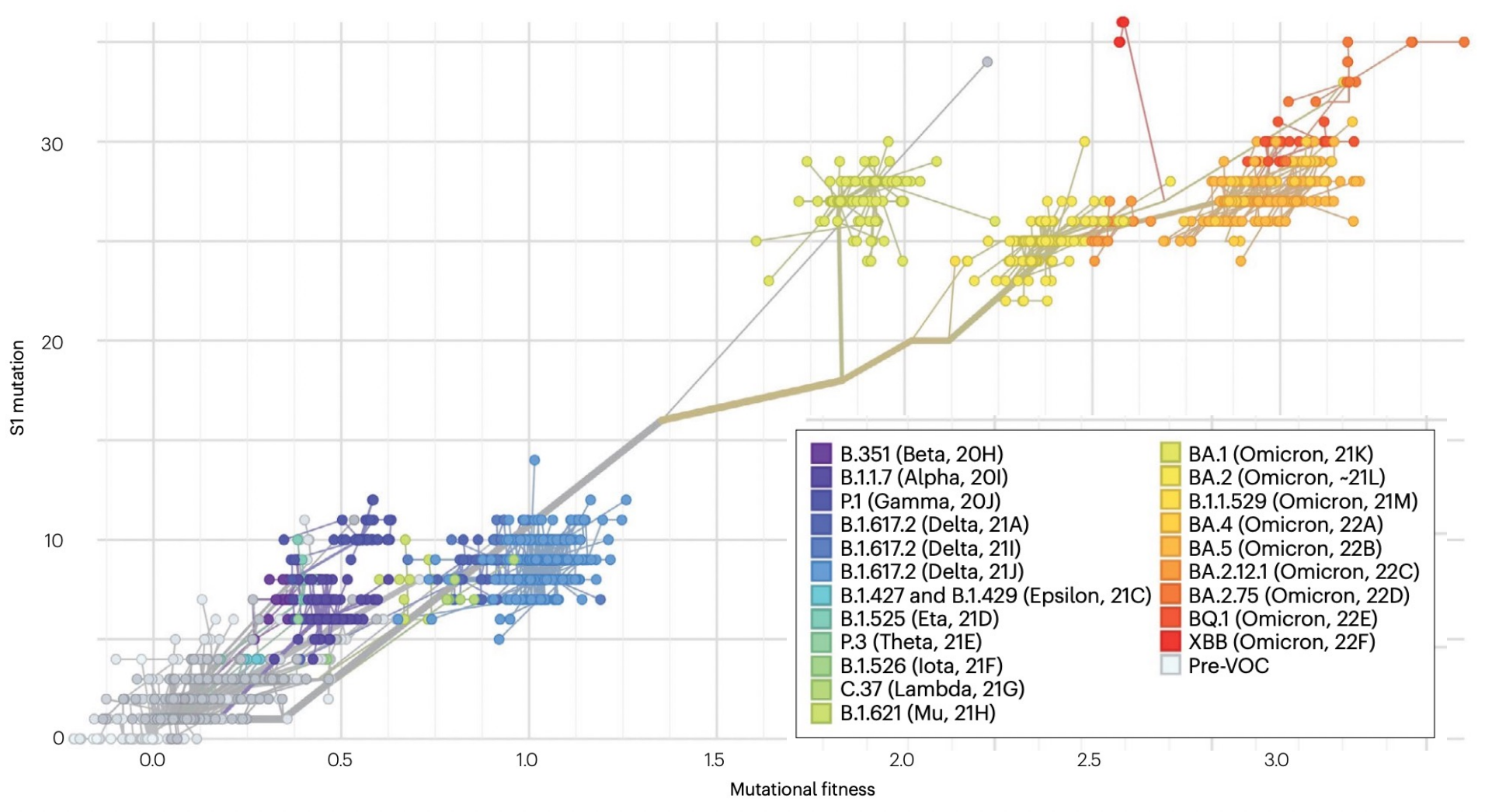
05 April 2023



nature reviews microbiology

Survival of the fittest

05 April 2023

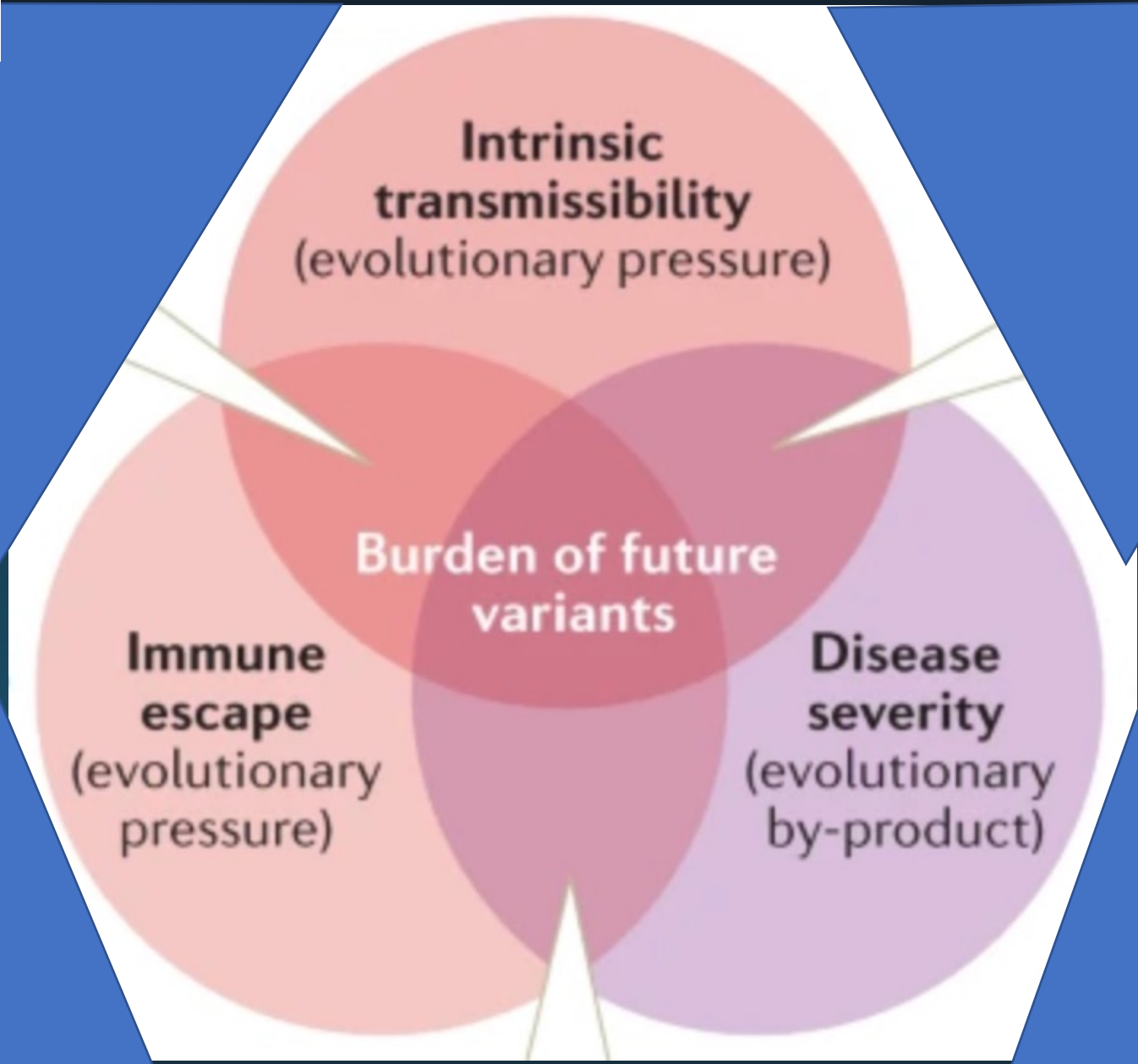


- Lineages diversify and sub-lineages compete
- If successful→ antigenically distinct strain
- If fail→ extinct

nature reviews microbiology

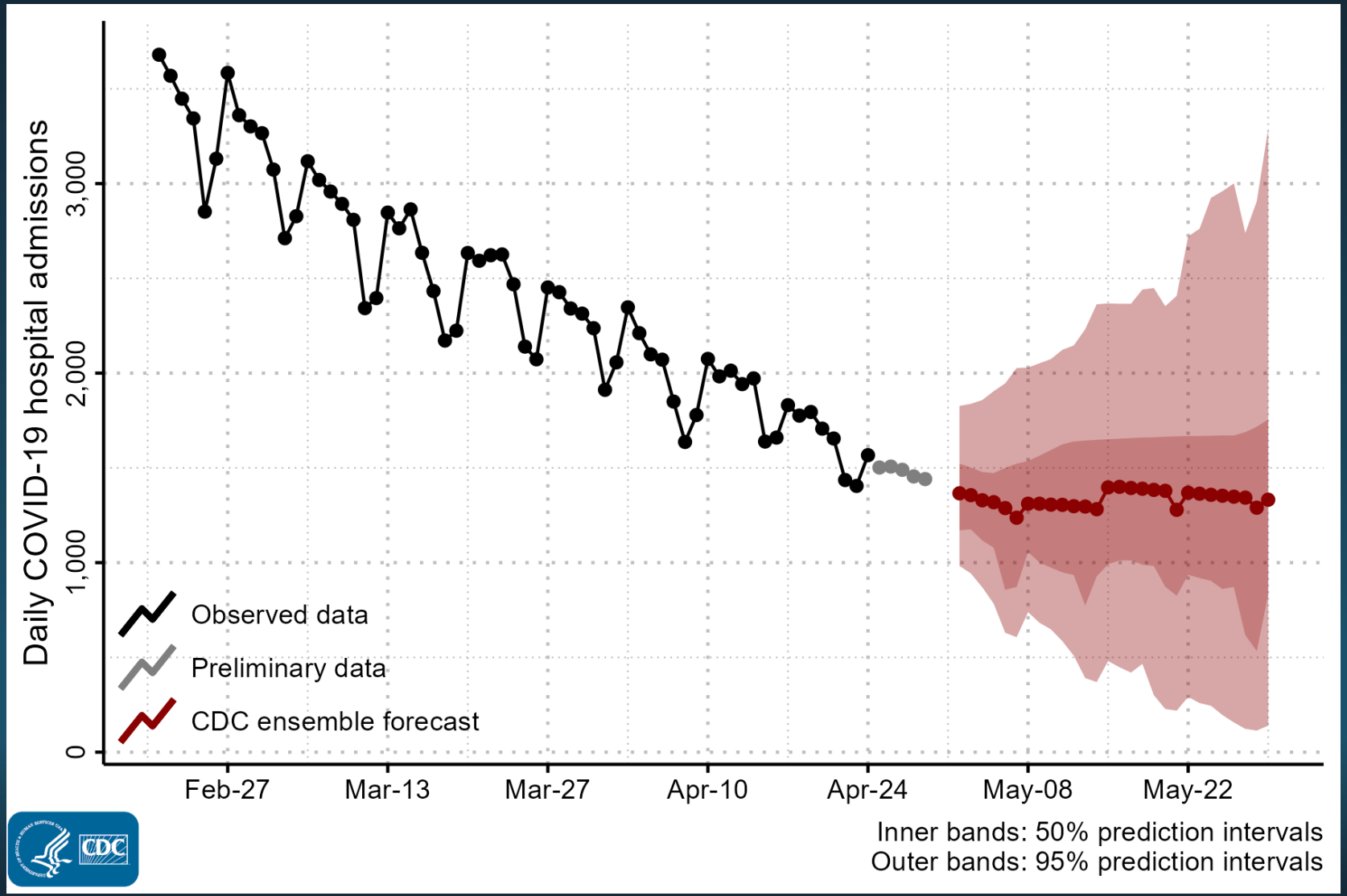
20, pages251–252 (2022)

Connecticut Children's



Can we forecast respiratory viral seasons accurately in future?

COVID-19 forecasting: inexact science

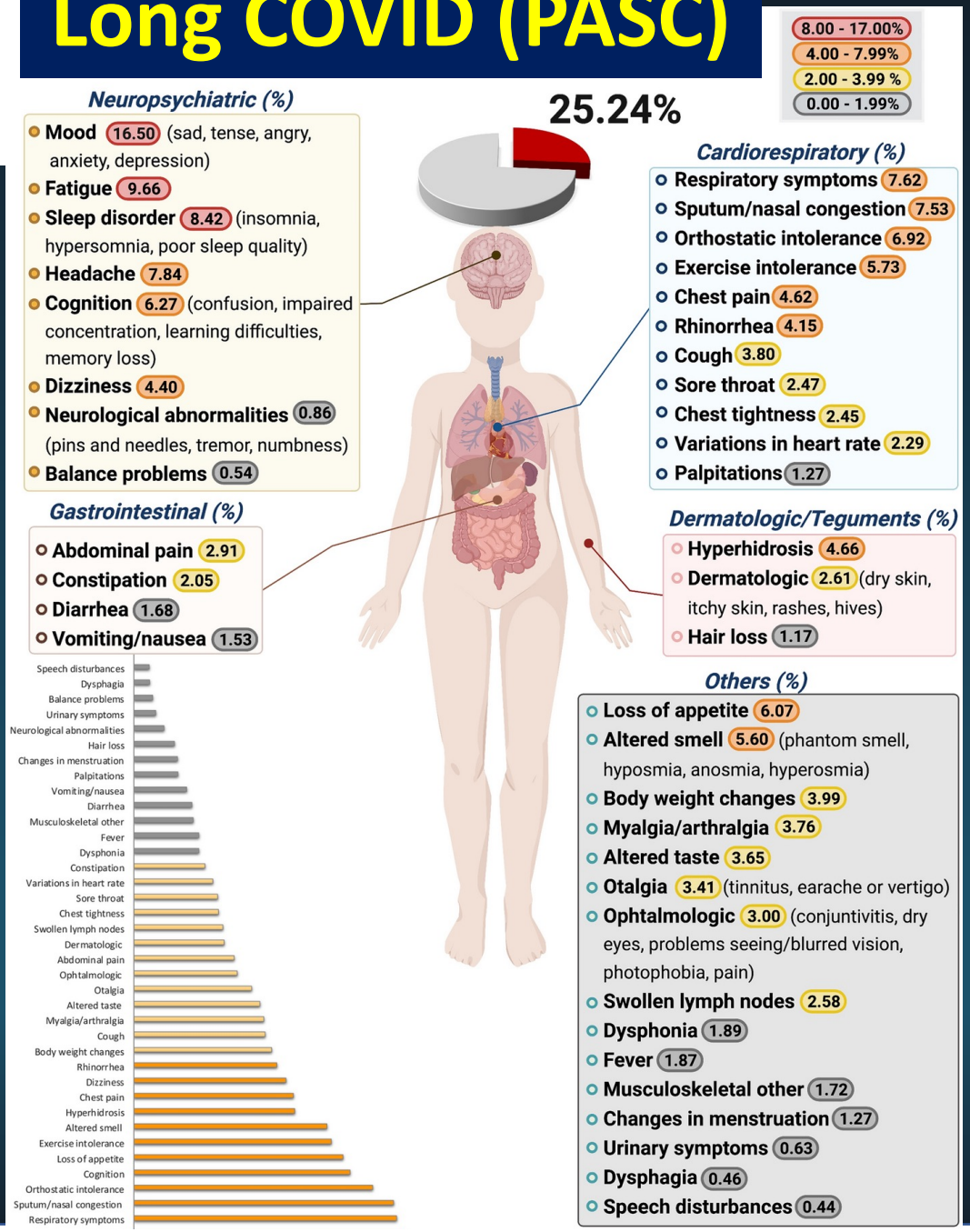


Does long COVID-19 affect children and adults similarly?

Long-COVID in children and adolescents: a systematic review and meta-analyses

scientific reports

(2022) 12:9950



PASC: Post-acute sequelae of COVID-19

Post-COVID-19-associated morbidity in children, adolescents, and adults: A matched cohort study including more than 157,000 individuals with COVID-19 in Germany

PLOS Medicine | https://doi.org/10.1371/journal.pmed.1004122 November 10, 2022

Children

Rank	Name	IRR	95% CI	*p*
1	Malaise/fatigue/exhaustion	2.28	(1.71–3.06)	<0.01
2	Cough	1.74	(1.48–2.04)	<0.01
3	Throat/chest pain	1.72	(1.39–2.12)	<0.01
4	Adjustment disorder	1.71	(1.42–2.06)	<0.01
5	Somatization disorder	1.62	(1.30–2.02)	<0.01
6	Headache	1.58	(1.35–1.84)	<0.01
7	Fever	1.56	(1.30–1.87)	<0.01
8	Anxiety disorder	1.54	(1.23–1.92)	<0.01
9	Abdominal pain	1.45	(1.27–1.64)	<0.01
10	Depression	1.45	(1.12–1.87)	<0.01

5 identical outcomes in children and adults: cough, fever, headache, malaise/fatigue/exhaustion, and throat/chest pain

Connecticut Children's

Adults

Rank	Name	IRR	95% CI	*p*
1	Disturbances of smell and taste	6.69	(5.88–7.60)	<0.01
2	Fever	3.33	(3.01–3.68)	<0.01
3	Dyspnea	2.88	(2.74–3.02)	<0.01
4	Cough	2.80	(2.64–2.97)	<0.01
5	Respiratory insufficiency	2.47	(2.28–2.69)	<0.01
6	Throat/chest pain	2.20	(2.09–2.31)	<0.01
7	Hair loss	2.02	(1.88–2.18)	<0.01
8	Malaise/fatigue/exhaustion	1.97	(1.89–2.06)	<0.01
9	Dysphagia	1.95	(1.78–2.12)	<0.01
10	Headache	1.74	(1.67–1.82)	<0.01

KFF
HENRY J KAISER FAMILY FOUNDATION

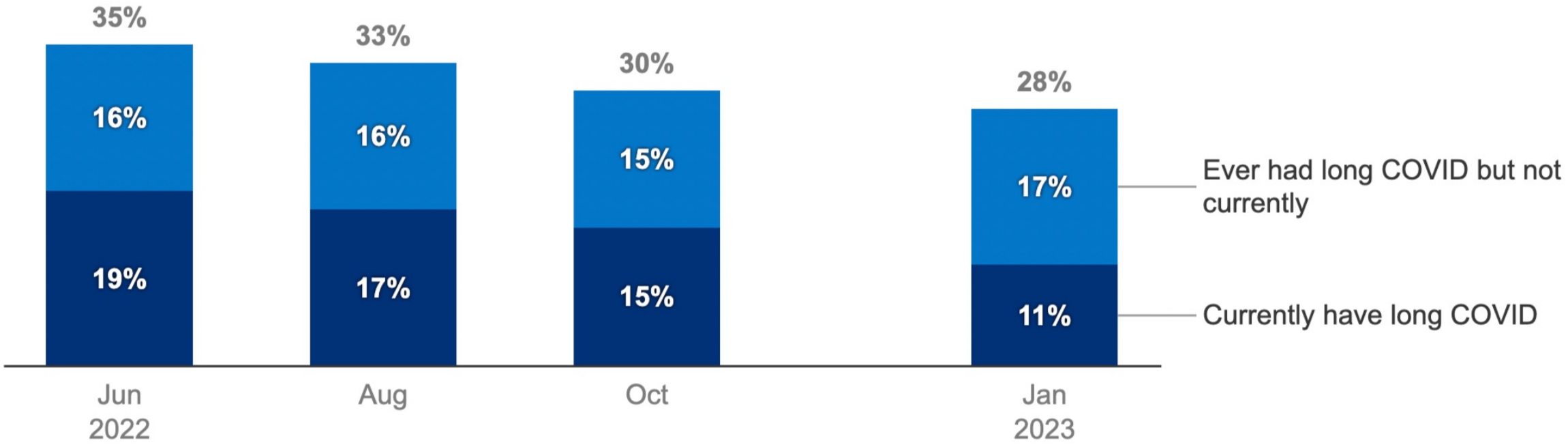
Connecticut Children's

Alice Burns

Among People Who Have Had COVID, the Percentage who Currently Have Long COVID is Declining

Percentage of people reporting that they currently have or ever had long COVID among those who have had COVID as of January 16, 2023

ADULTS



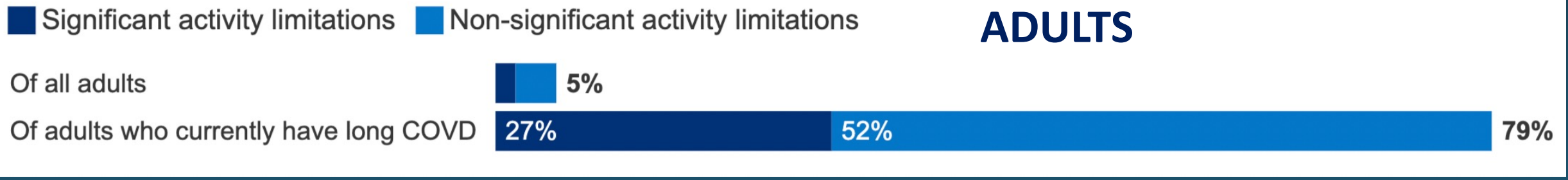
KFF
HENRY J KAISER FAMILY FOUNDATION

Connecticut Children's

Alice Burns

Many People with Long COVID Have Activity Limitations but Most are Not Significant

Percentage of people reporting that they have activity limitations from long COVID as of January 16, 2023



Management of Long Covid ©

Relaxation techniques: massage, meditation, yoga, visualization, etc
Identify /address racial, ethnic, socioeconomic disparities
Social interaction: in-person
Exclude mood and other organic disorders
&
Sleep hygiene: limit daytime naps; aim for 8-10 hours sleep
Hydration: set goals; manage POTS with water and electrolytes
internet: limit time; avoid use before bed
Nutrition: balanced diet; high fiber; fruit; vegetables
Exercise: graded reconditioning

Are inactivated COVID-19 vaccines as effective as other types?

Contents lists available at ScienceDirect

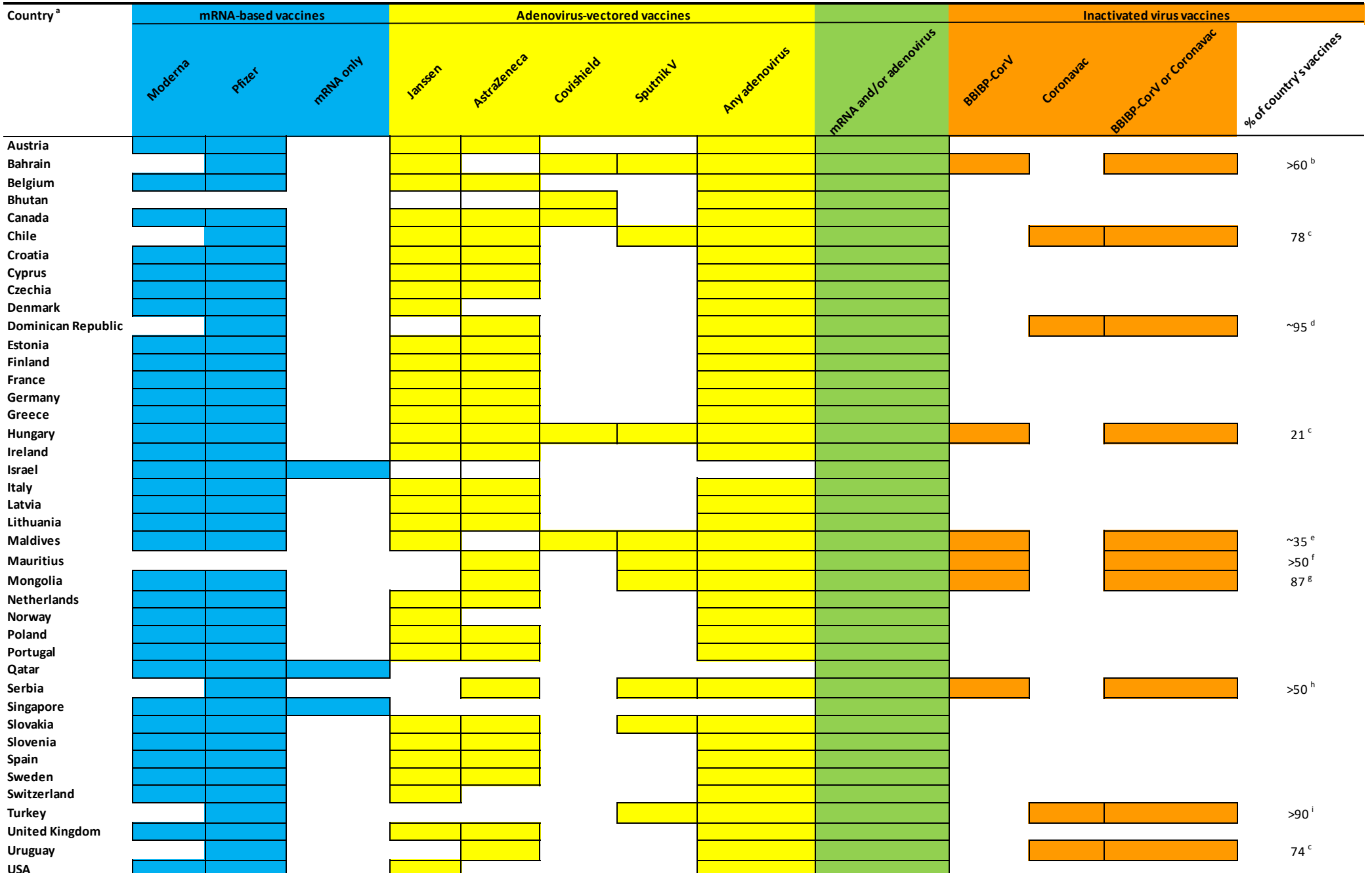
International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

A global epidemiological analysis of COVID-19 vaccine types and clinical outcomes

Zaid Alhinai[1,#], Sangshin Park[2,#], Young-June Choe[3], Ian C. Michelow[4,*]

Sources: Our World in Data; publications; newspaper articles

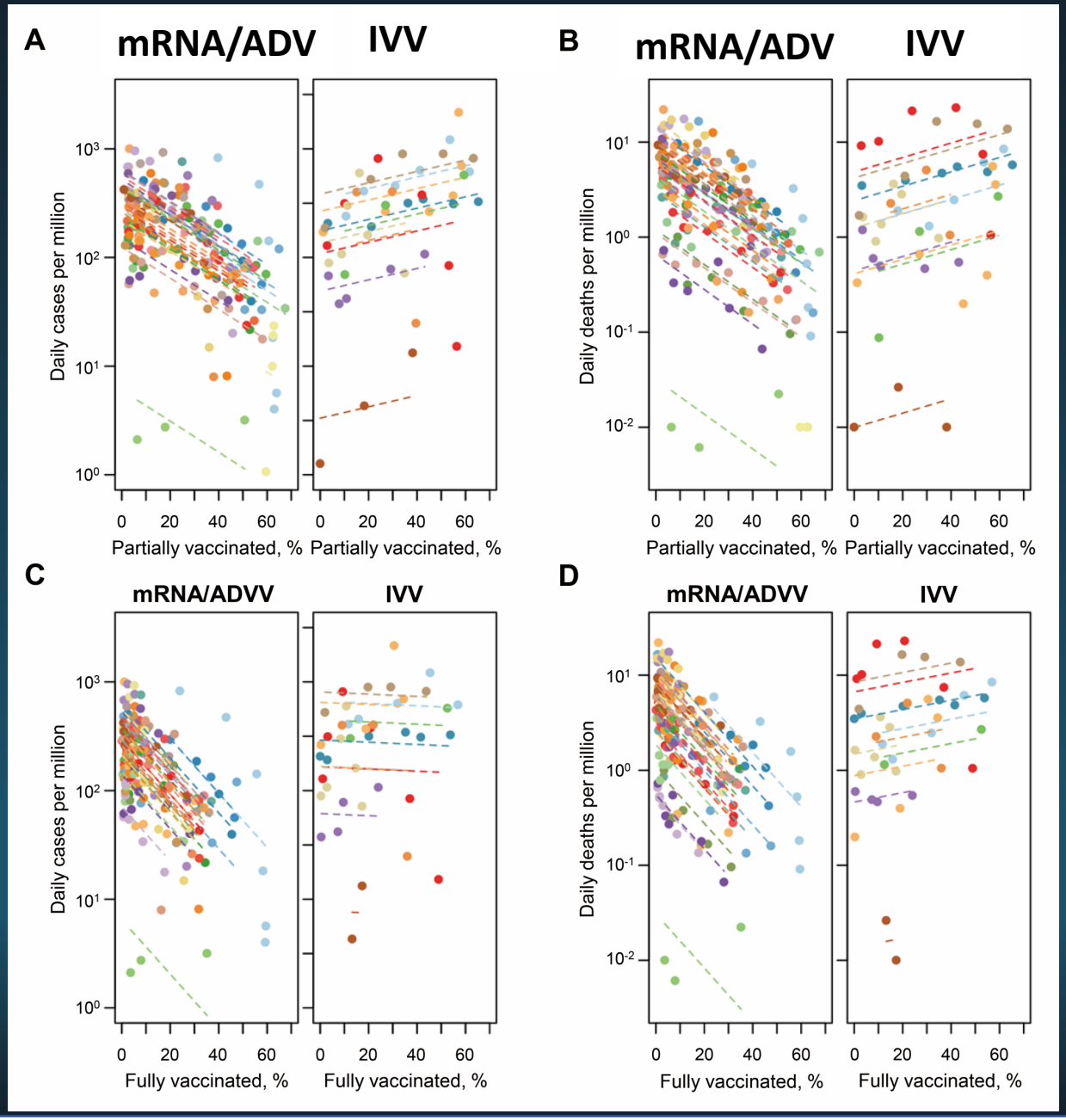


Infections

Deaths

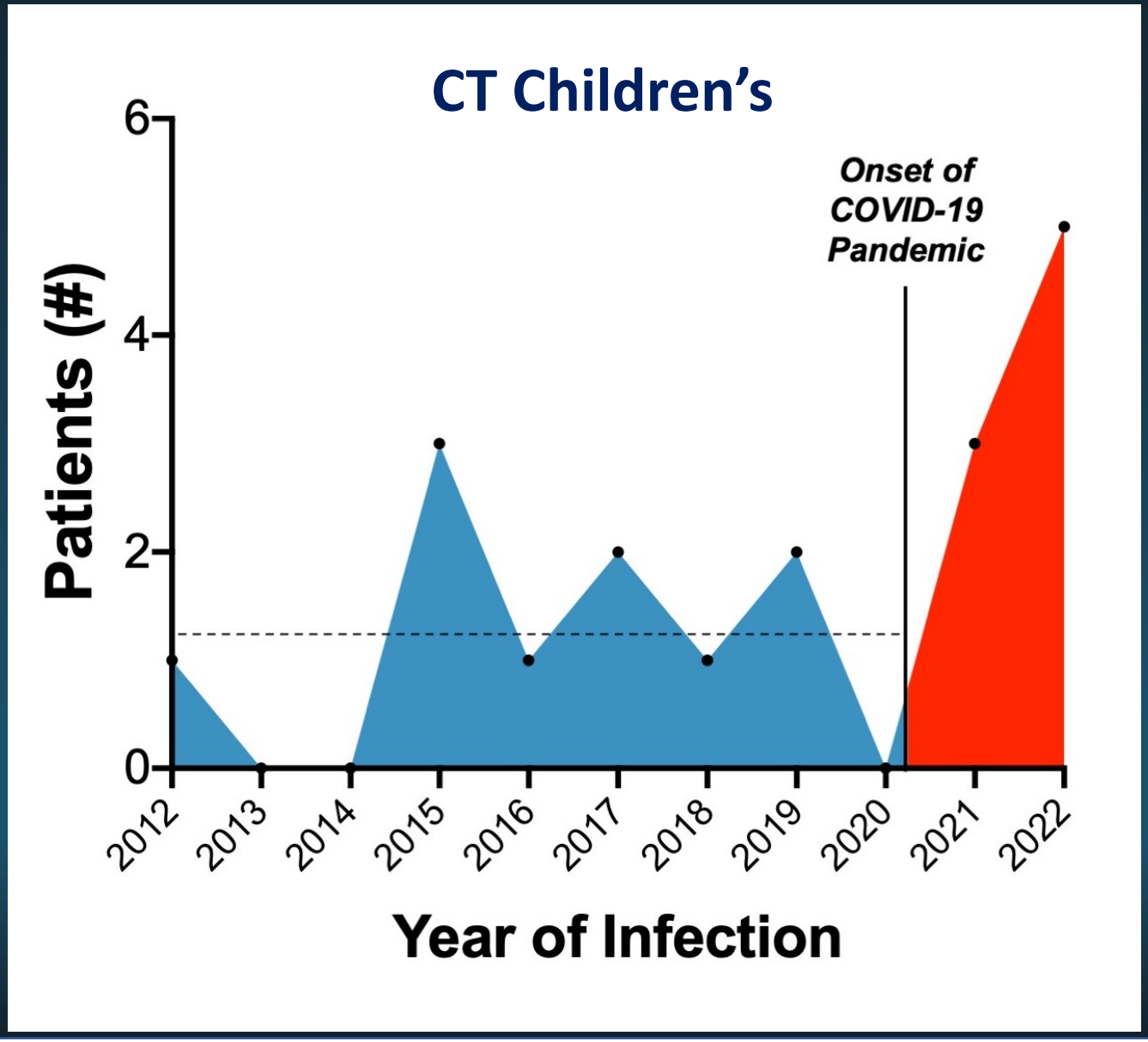
Partially vaccinated

Fully vaccinated



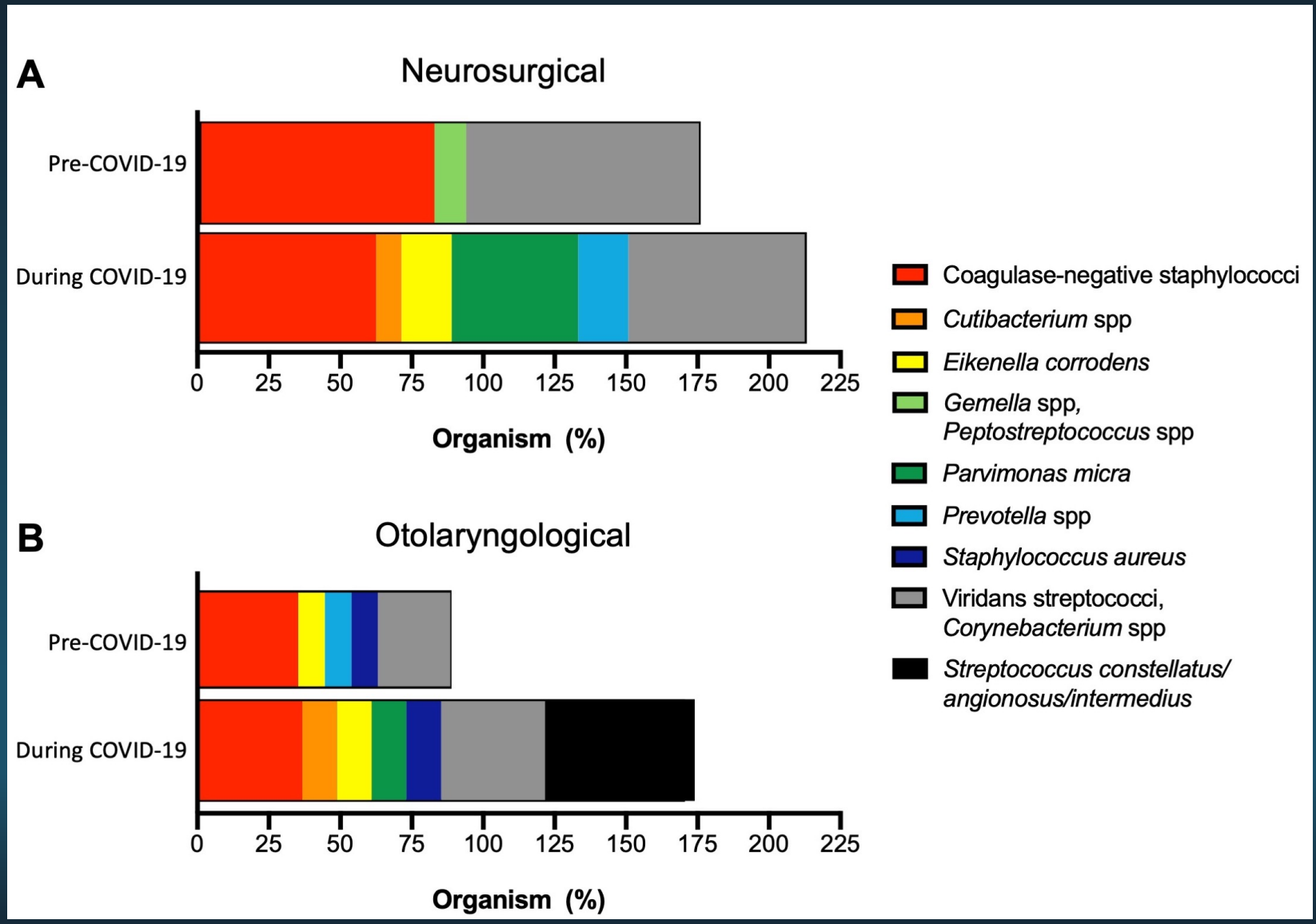
Was there a change in rates of secondary bacterial infections?

Rates of secondary bacterial infections: intracranial



J Neurosurg-Pediatr (in press)

Change in microbiology of intracranial infections



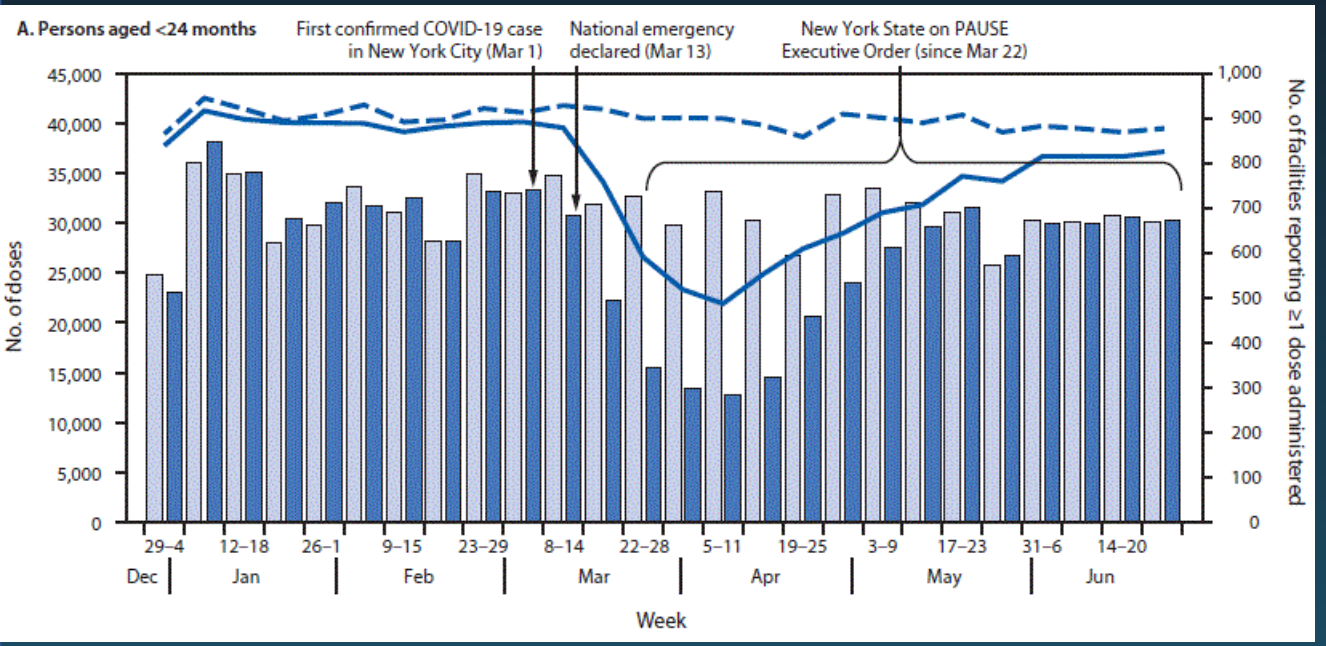
J Neurosurg-Pediatr (in press)

How did COVID-19 impact routine childhood vaccines?

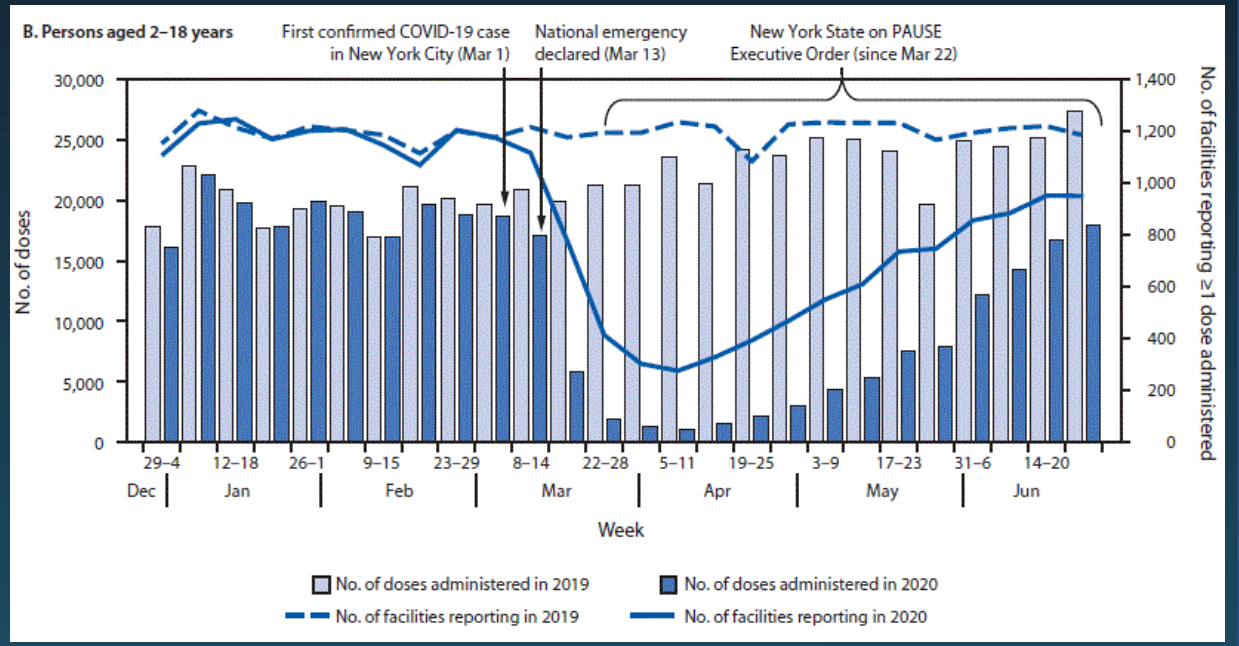
COVID-19 disrupted delivery of childhood vaccinations 2020

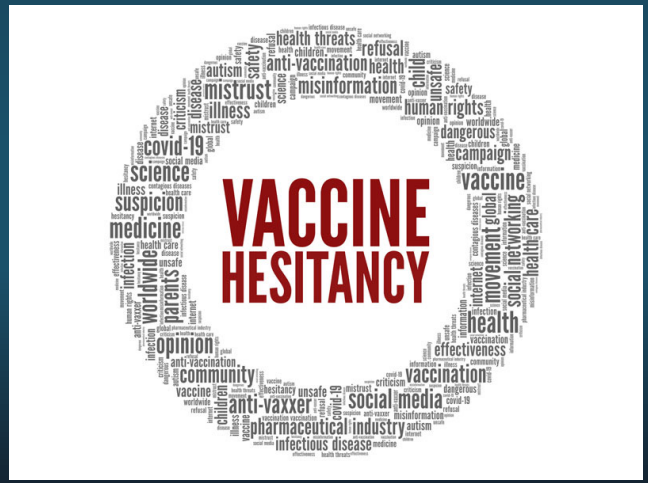
Connecticut Children's

<2 yrs



2-18 yrs

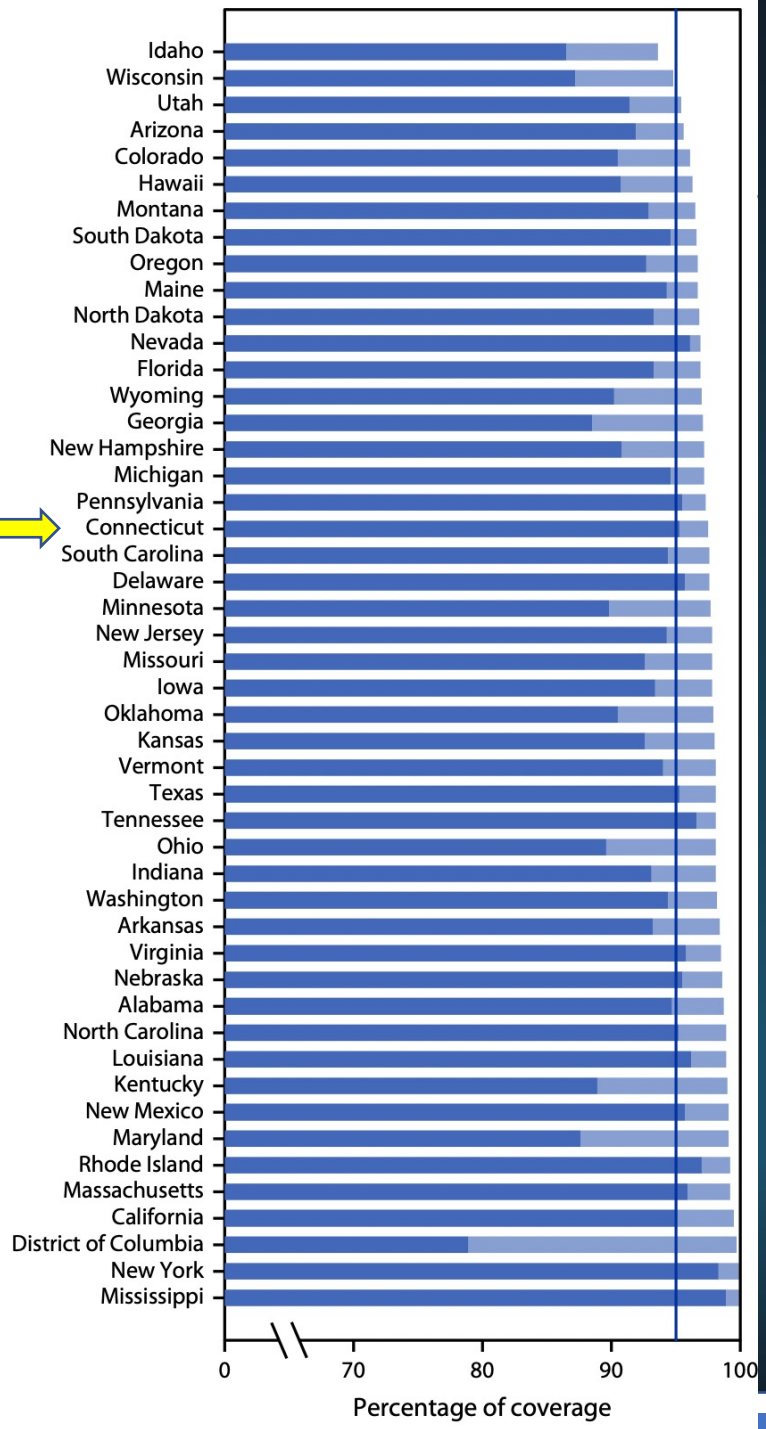




CDC Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

MMR vaccine rates in kindergarteners in US states for 2020-21 school year

CT
2021-22:
95.7%



MMR coverage

MMR not up to date and no vaccine exemption

Target MMR coverage of 95%

Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

Connecticut Children's

Other indirect impacts of COVID-19 pandemic on children

Widened racial, ethnic and socioeconomic disparities

- Worsening of mental or emotional health

- Widening of existing education gaps

- Decreased physical activity and increased body mass index (BMI)

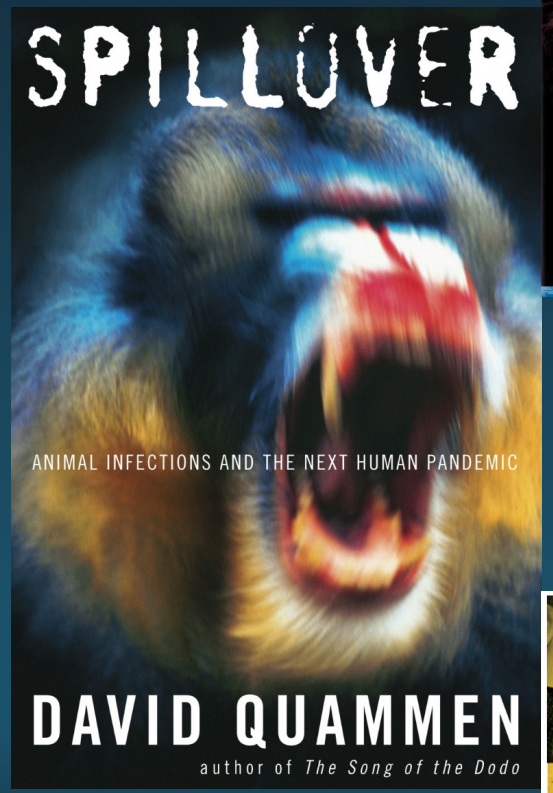
- Decreased healthcare utilization

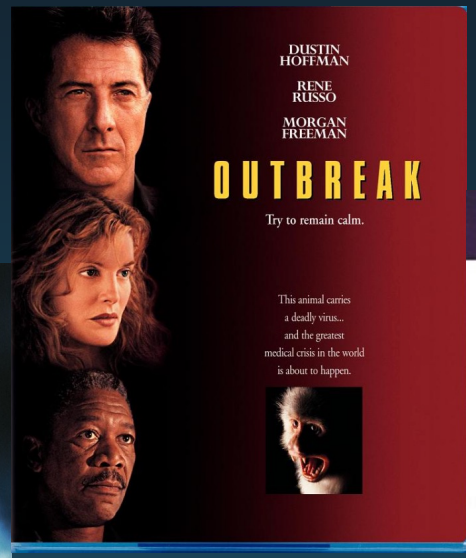
- Decreased routine immunizations

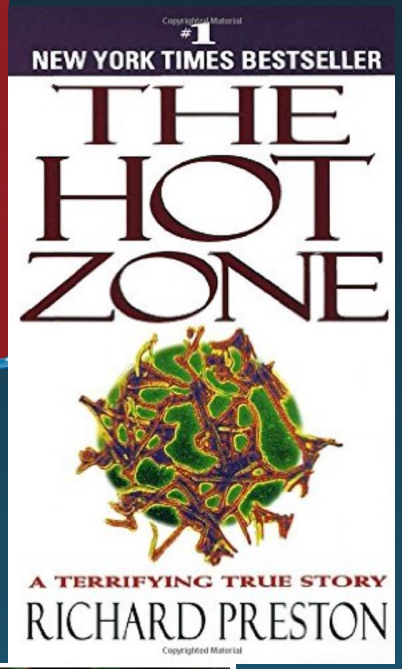
- Increase in Adverse Childhood Experiences (ACEs)

Do RNA or DNA viruses pose a greater pandemic threat?

Emerging infectious Diseases

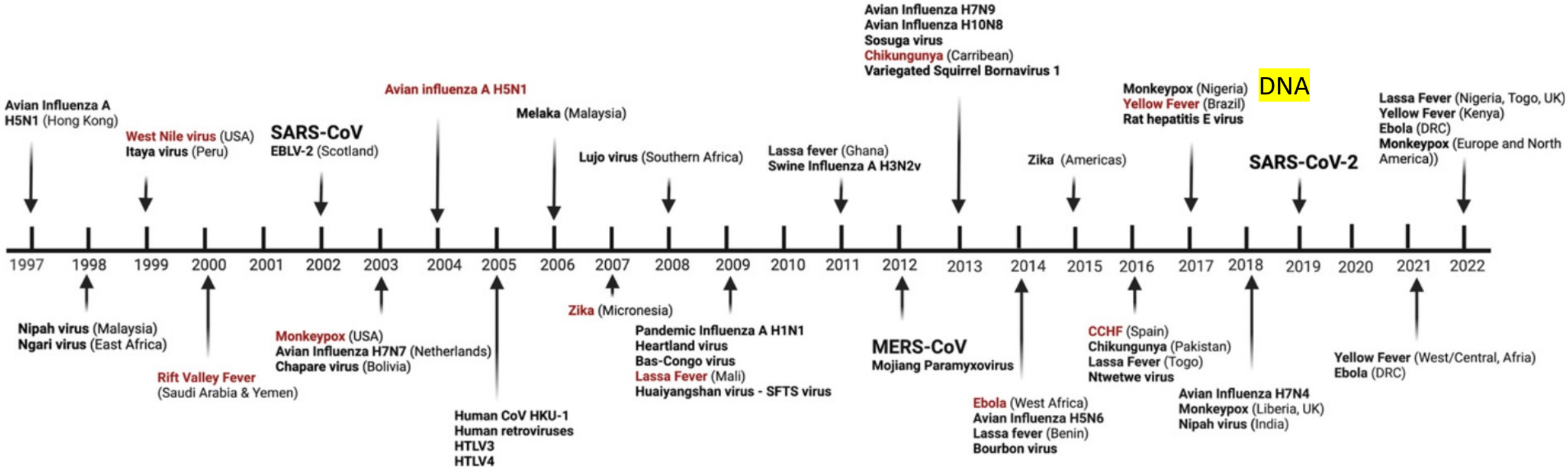






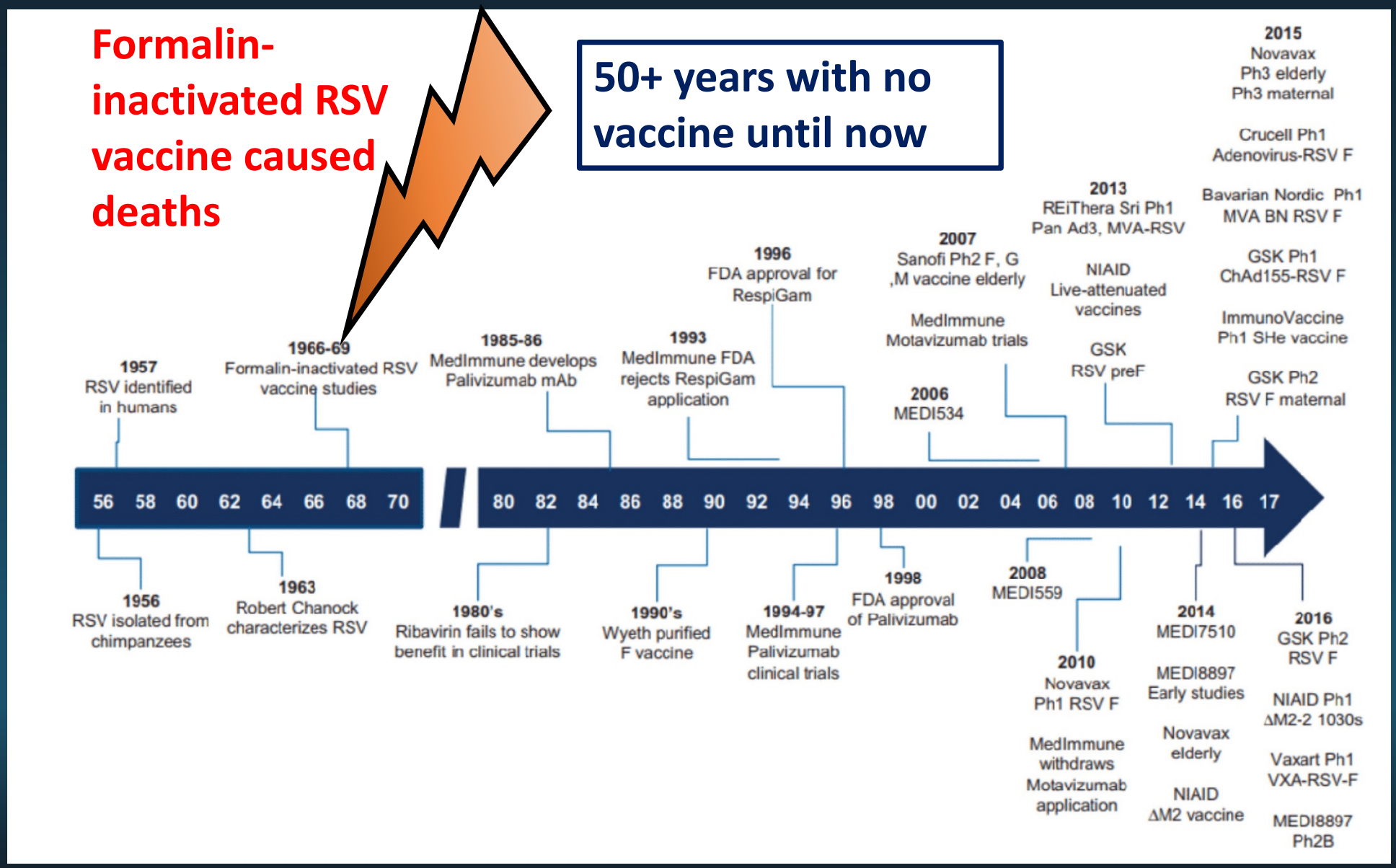
RNA >> DNA viruses cause zoonoses and outbreaks

they are have error-prone replication and high mutation rates



What’s new in RSV vaccine development?

Long saga of RSV vaccine development



FDA NEWS RELEASE

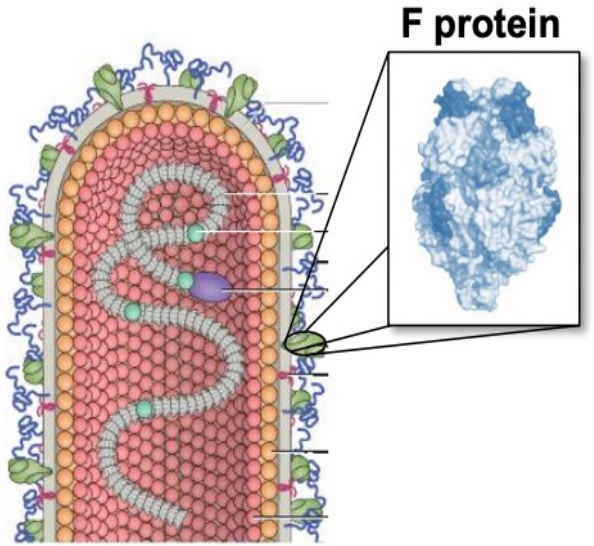
FDA Approves First Respiratory Syncytial Virus (RSV) Vaccine

Arexvy Approved for Individuals 60 Years of Age and Older

May 3, 2023

- **CDC:** RSV causes 60,000-120,000 hospitalizations and 6,000-10,000 deaths among adults ≥ 60 years annually
- 2 major subtypes: RSV A and B that may co-circulate
- Infection does not confer long-term immunity
- Reinfection is common at all ages
- mild colds to pneumonia and respiratory failure

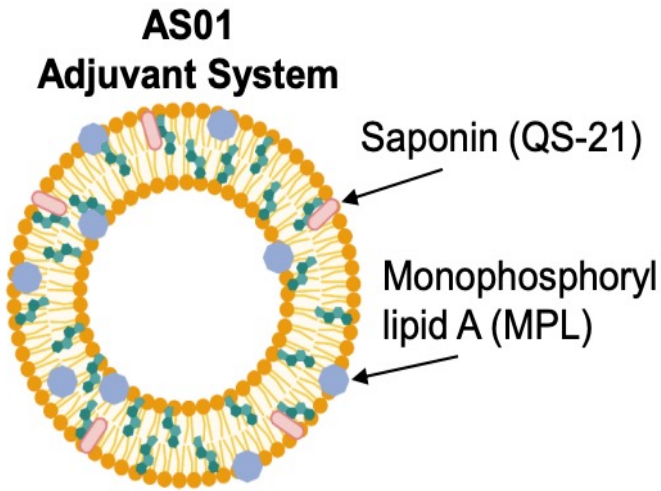
RSV Vaccine: 120 µg RSVPreF3 + AS01$_E$ Adjuvant Formulation Selected for Phase 3 Development



RSV OA Vaccine

OA= Older Adults

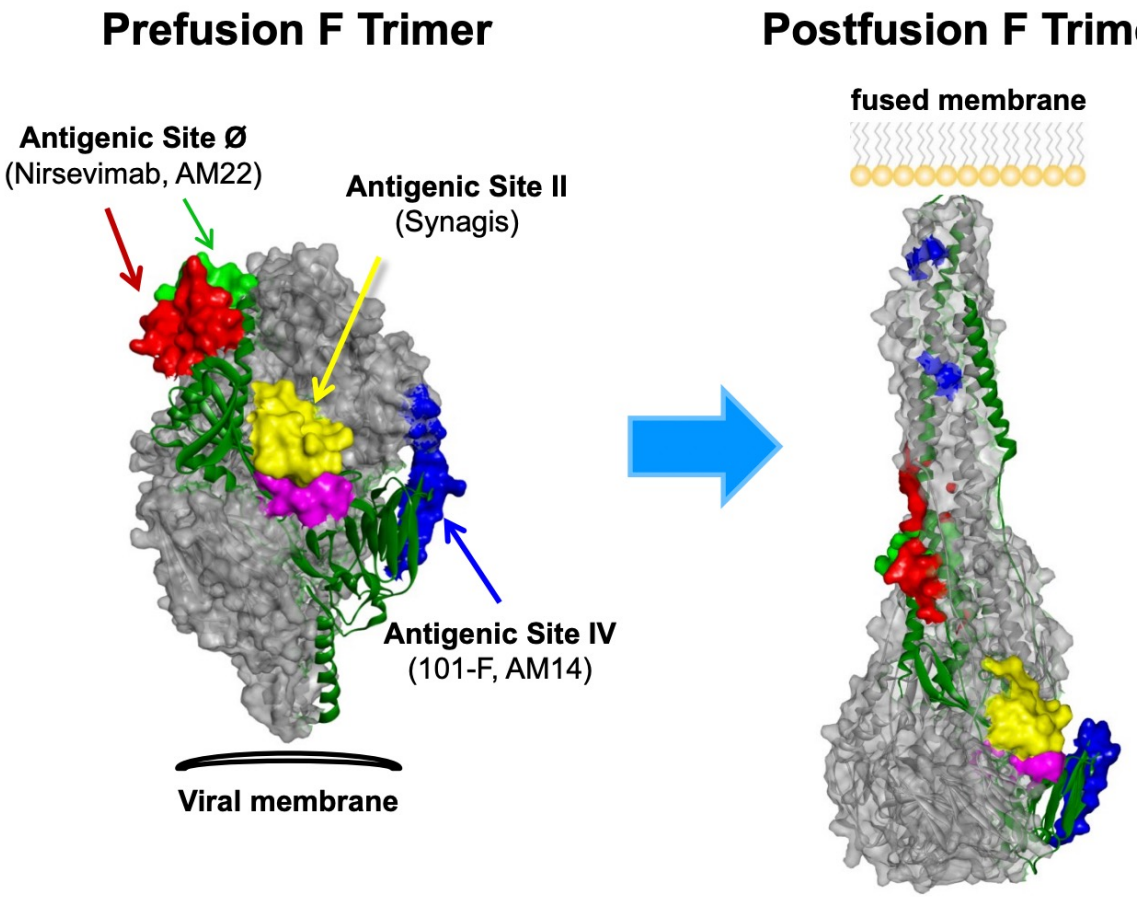
RSV PreF3 Antigen (120µg) + **AS01$_E$ Adjuvant System**



- High serum neutralization titers for RSV-A and RSV-B
- High polyfunctional RSVPreF3 specific CD4+ T-cell responses in OAs approaching levels seen in young adults following vaccination
- Th1 dominant response
- Well tolerated with acceptable safety profile

RSV fusion (F) glycoprotein

Groundbreaking Structural Work by NIH Elucidated that RSV F on the Virus Exists as an Unstable Prefusion Form



Barney Graham
Jason McLellan

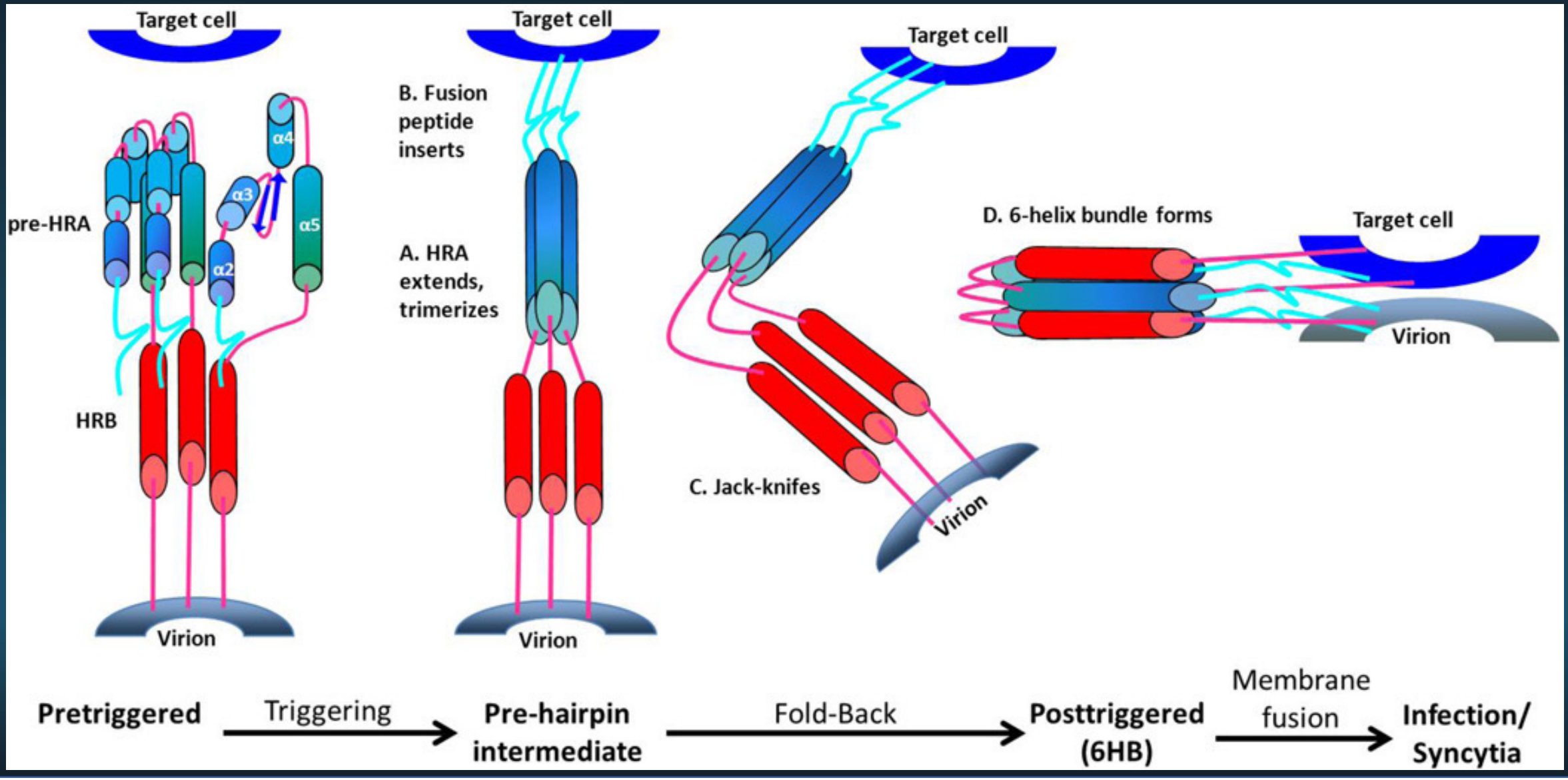
Only prefusion F can bind host cells for RSV to infect

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

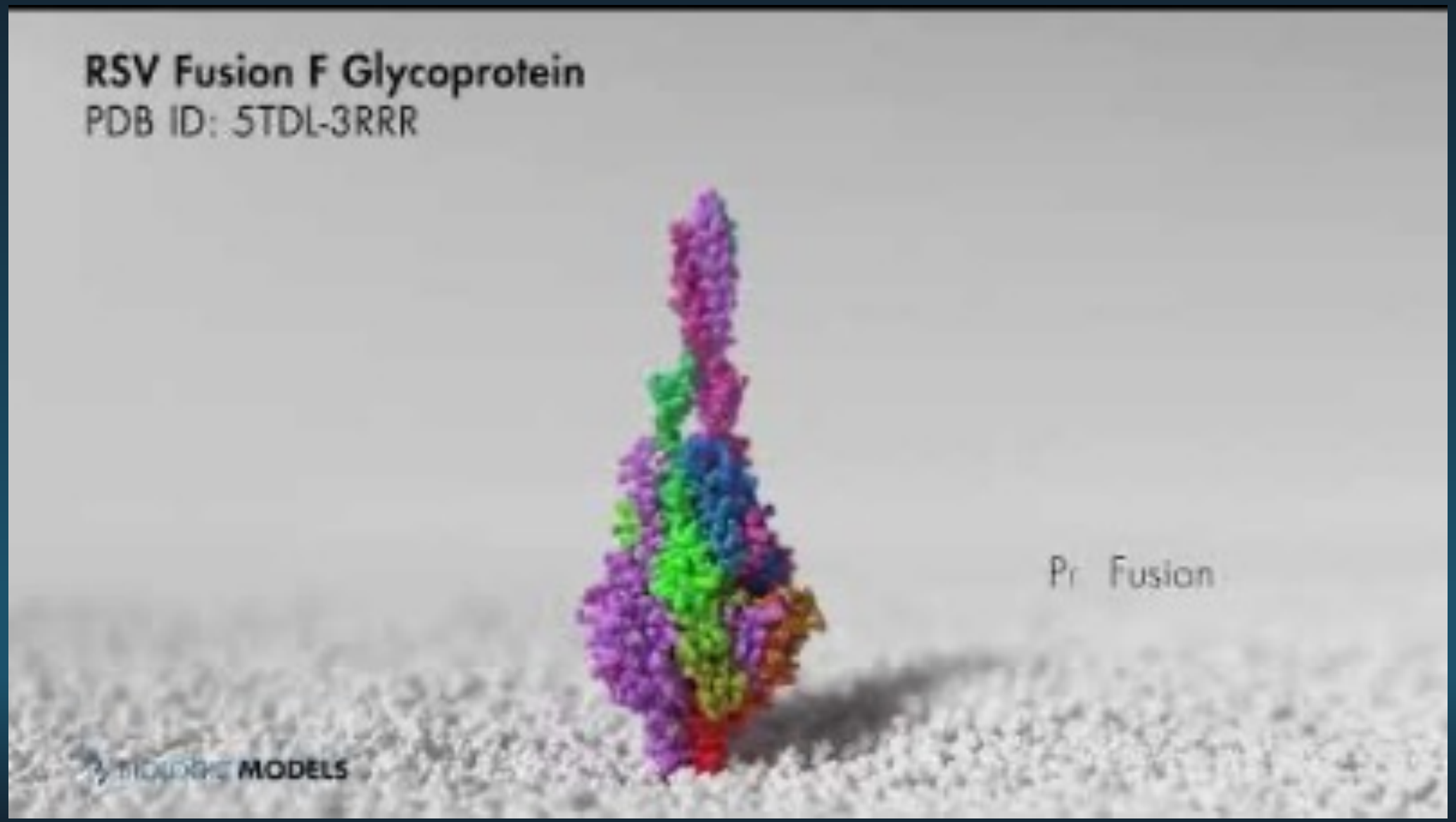
Vaccine=stabilized prefusion F protein trimer

McLellan et al. *Science*, Nov 2013

Structure of RSV fusion (F) glycoprotein



Function of RSV fusion (F) glycoprotein



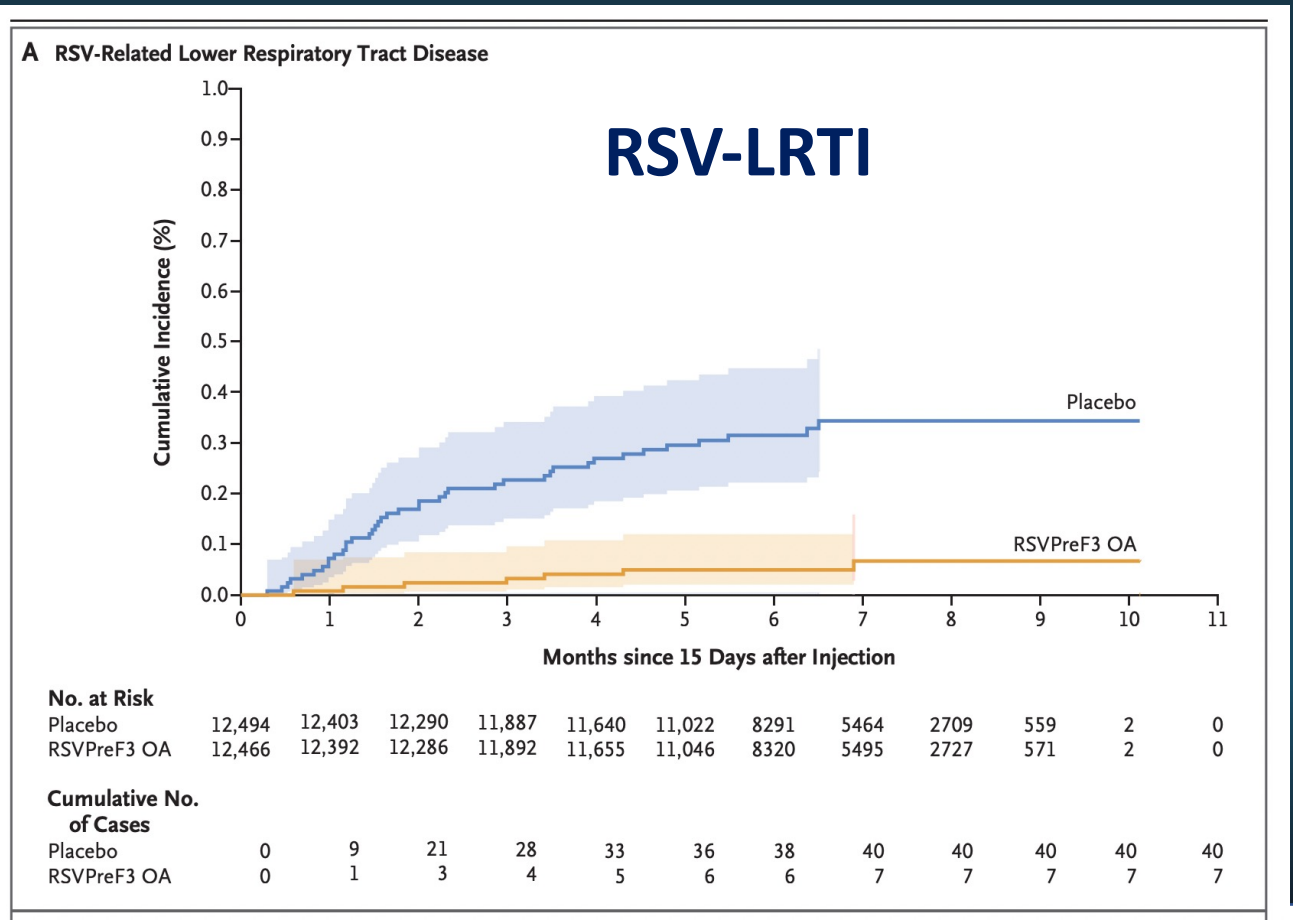
RSVPreF vaccine protects against clinical disease

Connecticut Children's

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*

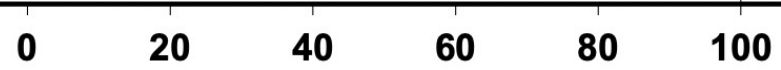
N ENGL J MED 388;7 NEJM.ORG FEBRUARY 16, 2023



No. at Risk												
Placebo	12,494	12,403	12,290	11,887	11,640	11,022	8291	5464	2709	559	2	0
RSVPreF3 OA	12,466	12,392	12,286	11,892	11,655	11,046	8320	5495	2727	571	2	0
Cumulative No. of Cases												
Placebo	0	9	21	28	33	36	38	40	40	40	40	40
RSVPreF3 OA	0	1	3	4	5	6	6	7	7	7	7	7

Study 006: Consistent Efficacy Against RSV Disease (mES)

	RSV Vaccine (N = 12,466)	Placebo (N = 12,494)	Vaccine Efficacy (CI*)
	Number of events		
RSV-confirmed ARI	**27**	**95**	**71.7%** (56.2, 82.3)
RSV-confirmed LRTD	**7**	**40**	**82.6%** (57.9, 94.1)
RSV-confirmed severe LRTD[1]	**1**	**17**	**94.1%** (62.4, 99.9)



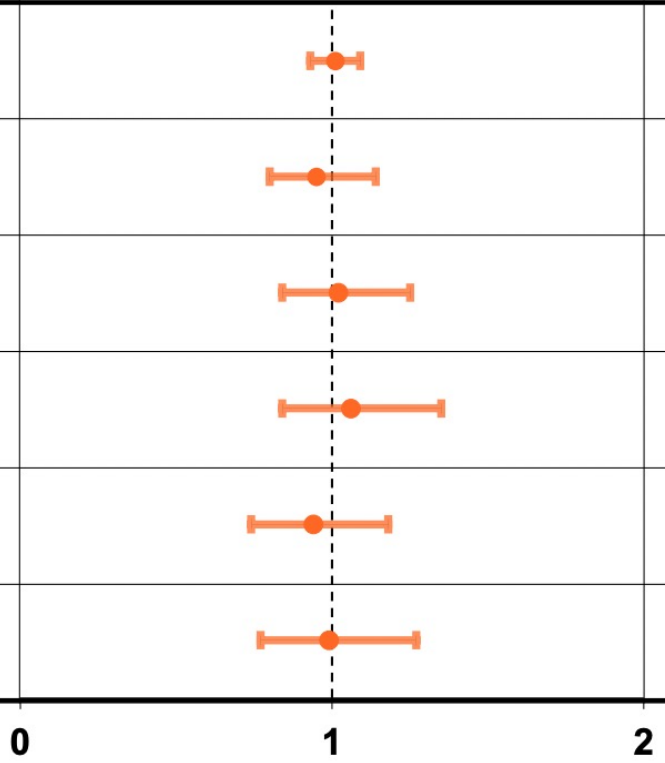
Clinical Program Supports Efficacy and Safety of RSV Vaccine

- Efficacy of 82.6% in prevention of RSV LRTD in adults ≥ 60 YOA
- Consistent protection regardless of
  - RSV disease severity
  - Advancing age
  - Comorbidities of interest
  - RSV-A and RSV-B subtypes
- Well tolerated with acceptable safety profile

Severe Adverse Events (SAE)

Study 006: SAEs Balanced Between Groups

SOC occurring in ≥ 0.5% of participants	Exposed Set: RSV Vaccine N = 12,467	Exposed Set: Placebo N = 12,499	Relative Risk (80% CI)	RR (80% CI)
Any SAE (within 6 months)	**4%**	**4%**		**1.01** (0.93, 1.09)
Infections and infestations	**0.9%**	**0.9%**		**0.95** (0.80, 1.14)
Cardiac disorders	**0.8%**	**0.7%**		**1.02** (0.84, 1.25)
Neoplasms benign, malignant, and unspecified	**0.6%**	**0.5%**		**1.06** (0.84, 1.35)
Nervous system disorders	**0.5%**	**0.5%**		**0.94** (0.74, 1.20)
Injury, poisoning, and procedural complications	**0.5%**	**0.5%**		**0.99** (0.77, 1.27)



Post-marketing enhanced surveillance is planned

Study 006: Atrial Fibrillation Events Within 30 Days Post-Vaccination

Preferred Term	RSV Vaccine N = 12,467	Placebo N = 12,499
Atrial fibrillation	10 **(0.1%)**	4 **(< 0.1%)**
New onset	4	2
Recurrence	6	2
Outcome		
Recovered	8	3
Not recovered	2	1
Time to Onset, median (min, max)	**18.5** (1 – 30)	**10.5** (1 – 24)

- All participants with new onset have risk factors for development of atrial fibrillation
- IDMC reviewed all events
- Similar incidence in both groups at 6 months post-vaccination (14 RSV Vaccine vs 16 Placebo)

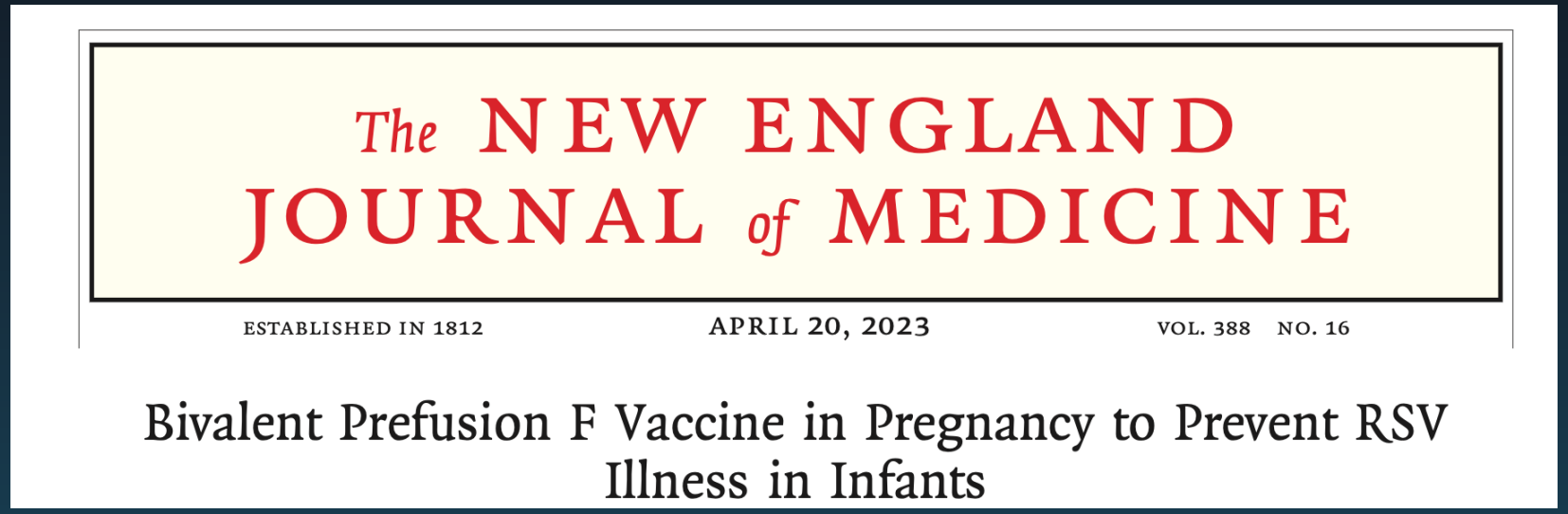
Post-marketing enhanced surveillance is planned

Connecticut Children's

Studies 004 and 007: pIMDs of Medical Interest

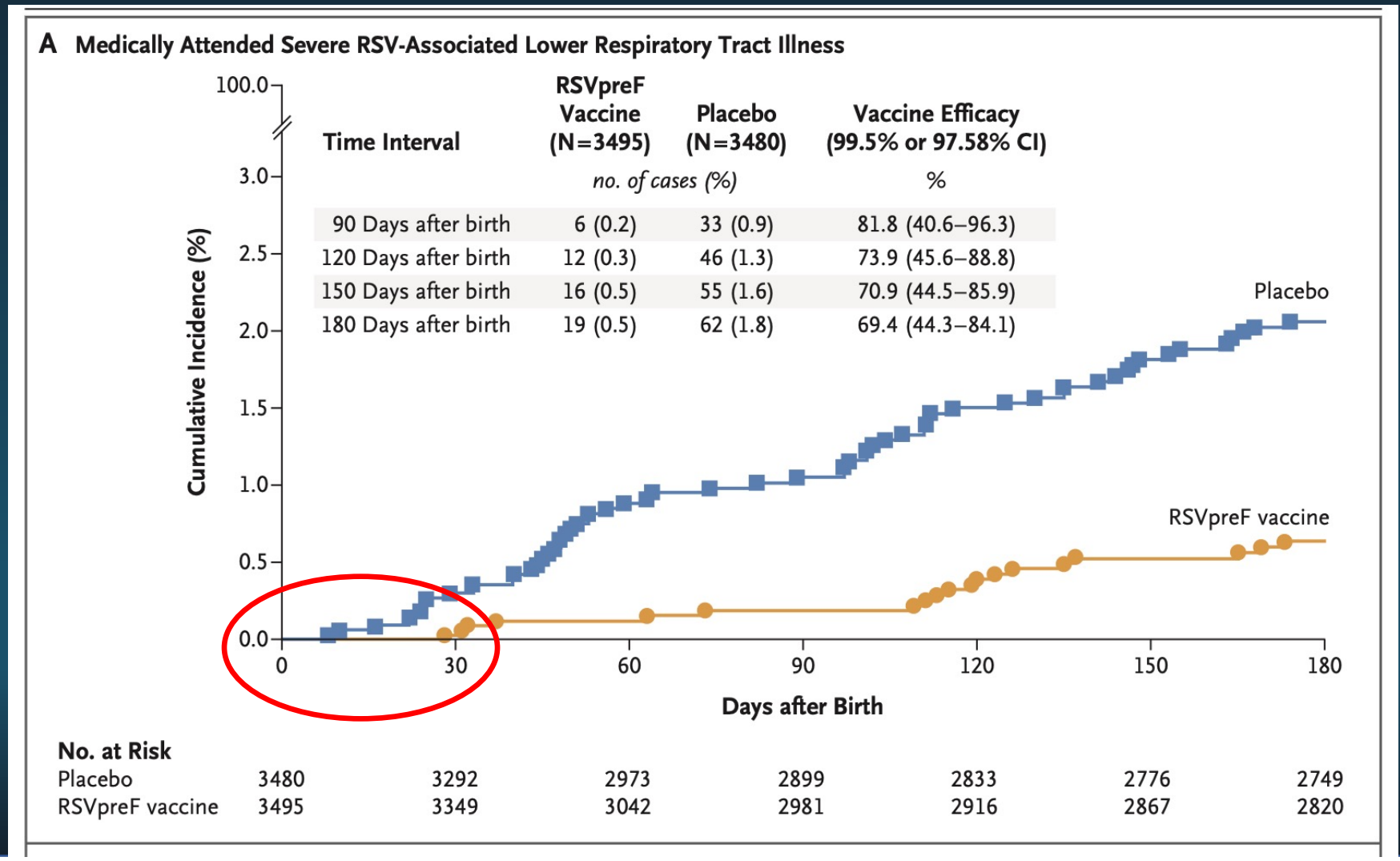
Potential immune-mediated diseases

Event	Age/ Sex	Country	Time to Onset (Days)	Comment
Guillain Barre Syndrome	78/F	JP	9	Elevated CSF protein, serum GM1-IgG positive; BC Level 3
ADEM	71/M	ZA	7	2 prior strokes with Wallerian demyelination; fatal outcome; BC Level 3
ADEM	71/F	ZA	22	Recovered; no investigations performed; BC Level 3



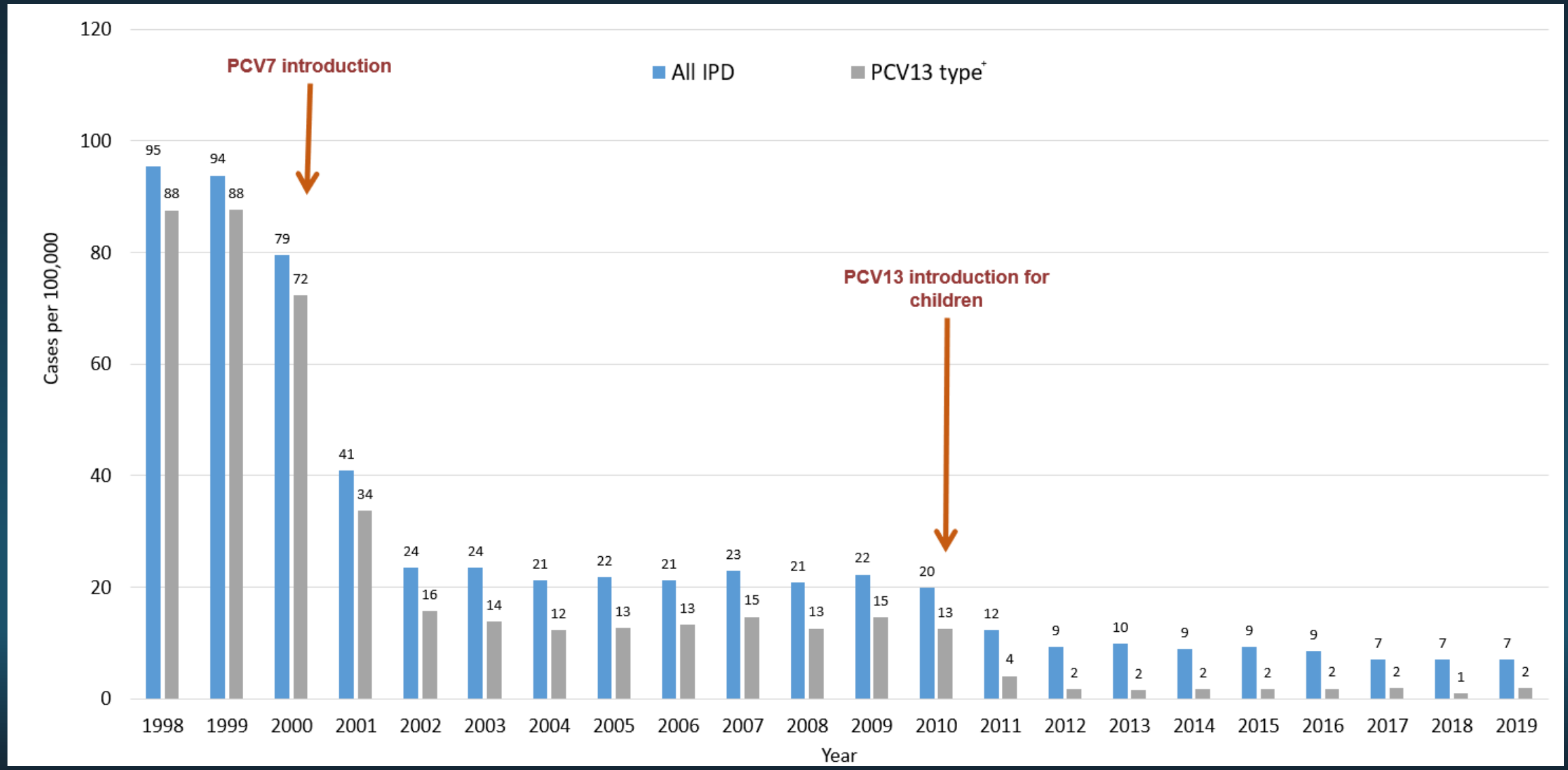
- Phase 3, double-blind RCT
- 18 countries
- Seasons: 2 in northern/2 in southern hemisphere
- Single IM vaccine (RSV A + B)
- 24-36 weeks gestation
- Infant follow-up: 1-2 years
- **Primary outcome:** medically-attended RSV LRTI

PreF vaccine reduced rate of severe RSV-LRTI in infants by 82% within 90 days

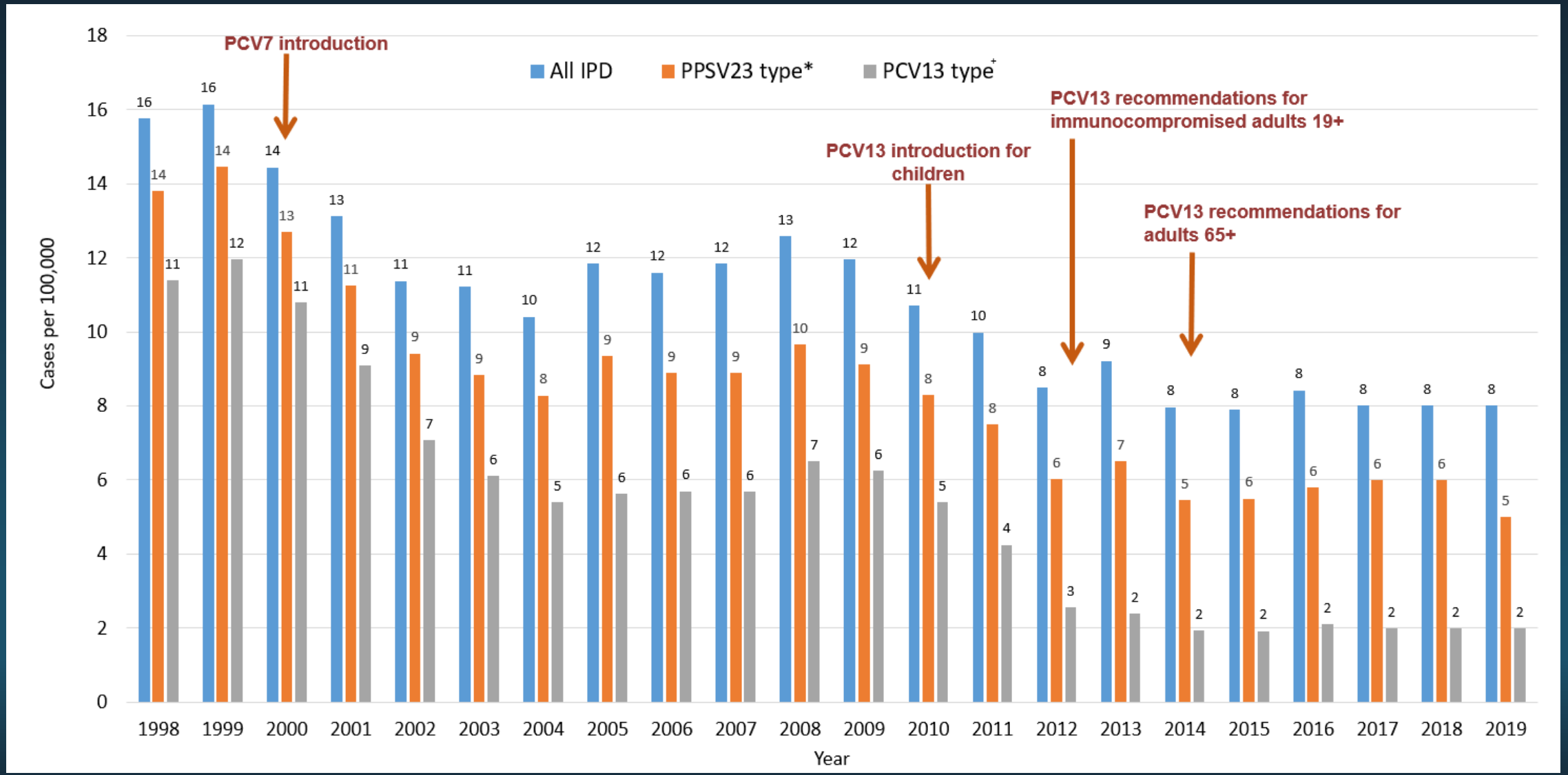


What's new in pneumococcal vaccine development?

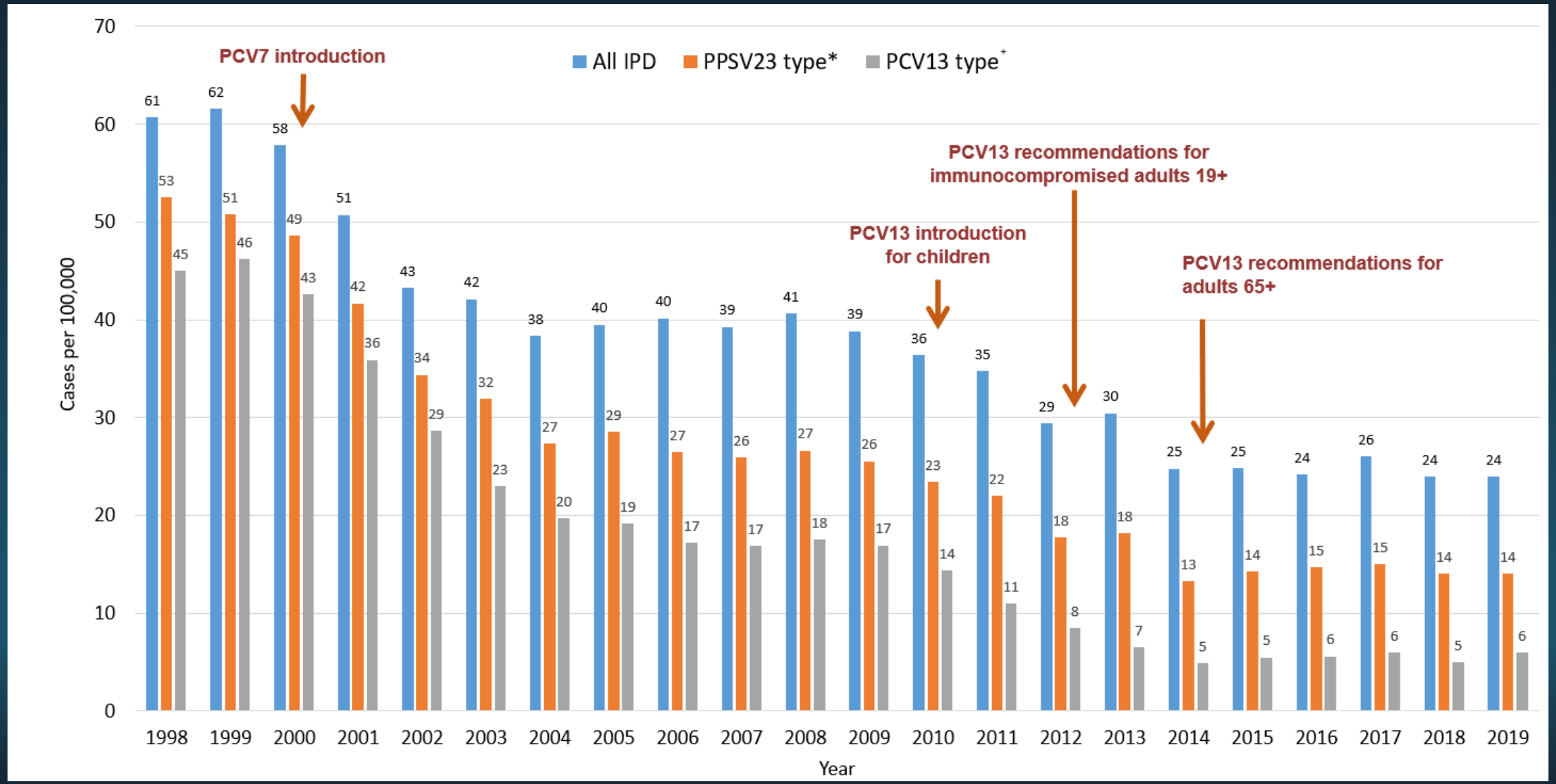
Trends in invasive pneumococcal disease <5 yrs



Trends in invasive pneumococcal disease 19-64 yrs



Trends in invasive pneumococcal disease >64 yrs



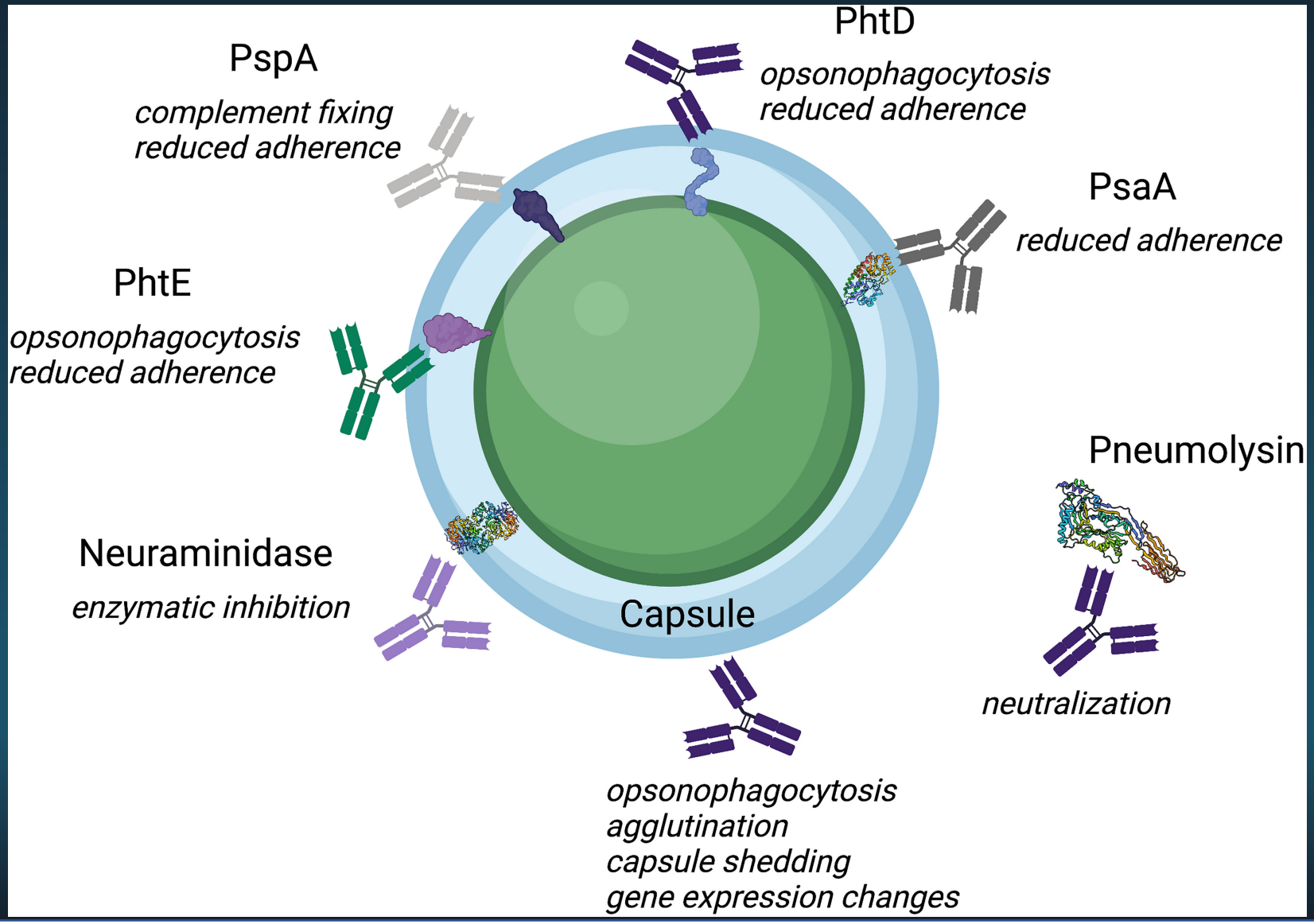
Streptococcus pneumoniae vaccine

FDA Approves Prevnar 20 Vaccine to Prevent Invasive Pneumococcal Disease in Children 6 Weeks Through 17 Years

Apr 28, 2023

This approval expands existing adult coverage (2021)

We need a universal protein-based pneumococcal vaccine!



Thank you

“Life or death for a young child too often depends on whether they are born in a country where vaccines are available or not…” Nelson Mandela

imichelow@connecticutchildrens.org