



Updates in Respiratory Viral Infections in Children

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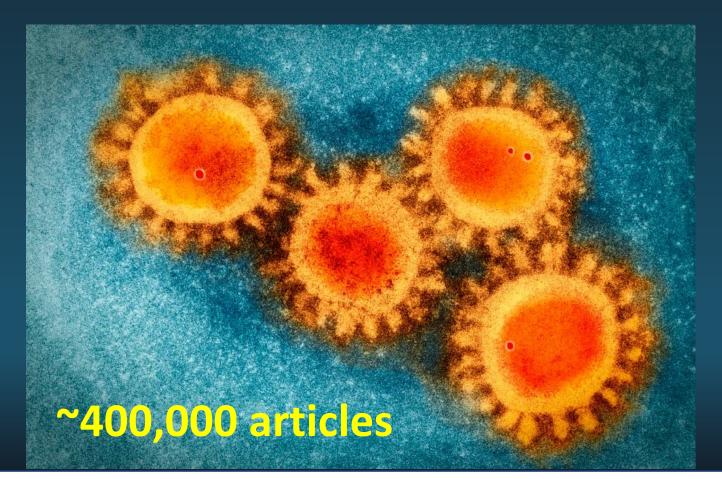


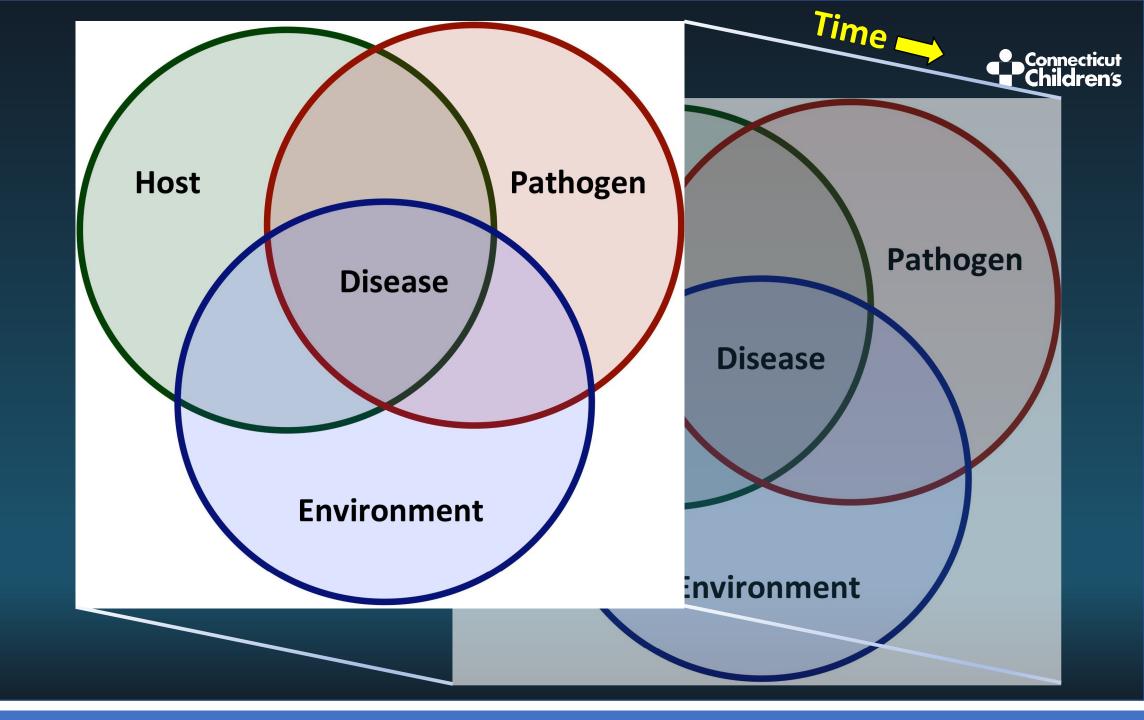
Disclosures

Dr Ian Michelow has no financial disclosures or conflicts of interest



What have we learned during the COVID-19 epidemic?



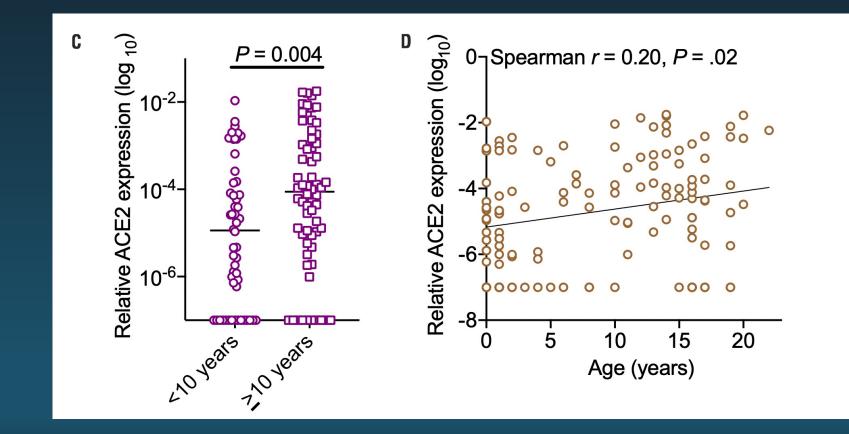


Why do children have milder disease than adults? Connecticut -some theories-

- 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)



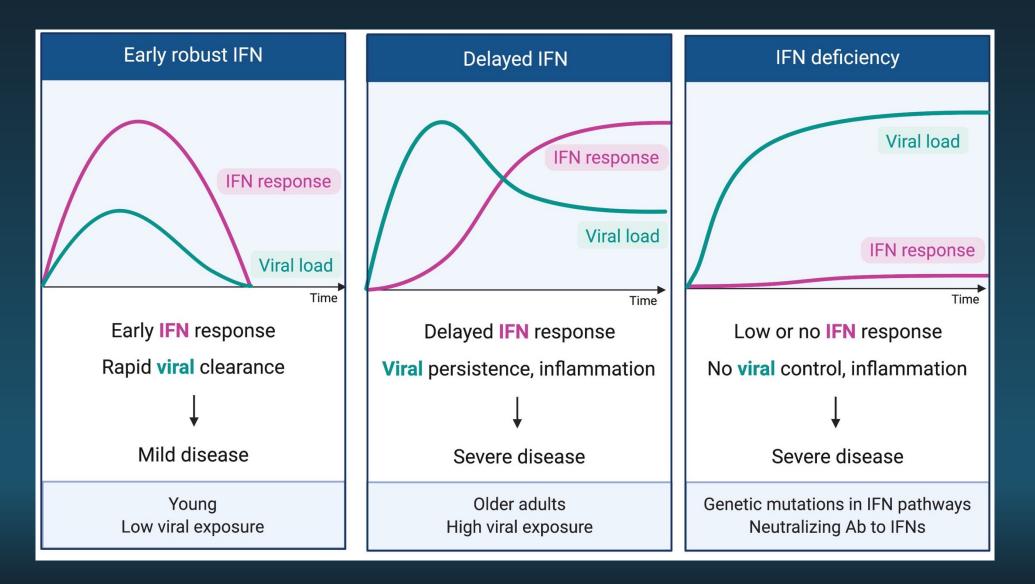
Less ACE2 receptors in upper respiratory tract



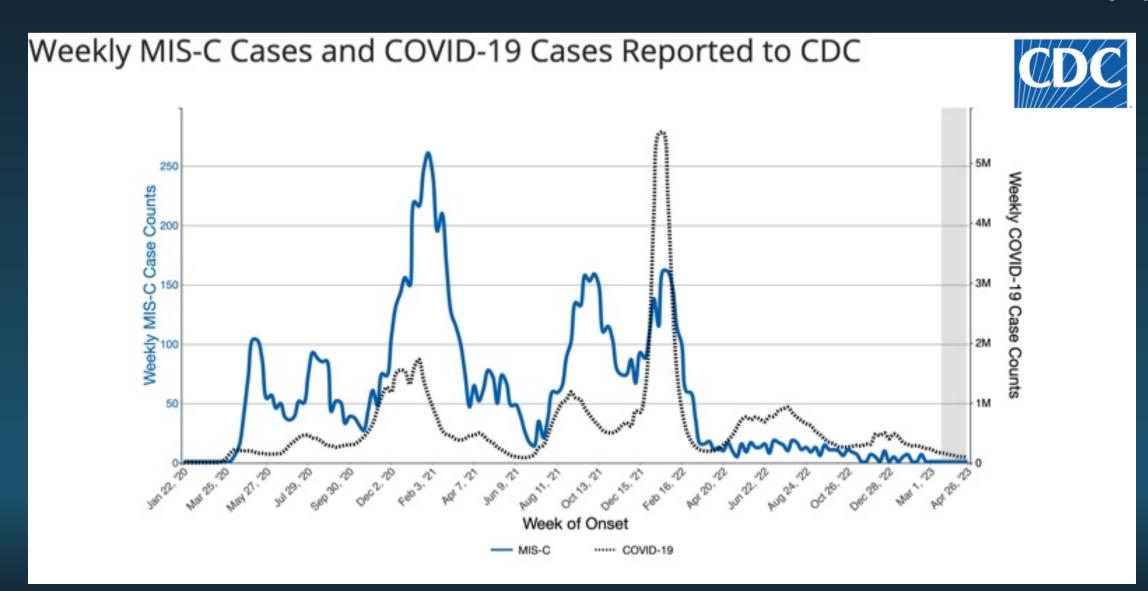
Yonker J Peds 2020

Children have potent innate immune systems





COVID-19 Epidemiology in Children <18 years





Low childhood COVID-19 death rates: CT



Number of COVID-19 Cases and Associated Deaths by Age Groups						Ct .000	
Total Cases (Past 7 Days)	Total Cases (Cumulative)	Total Deaths (Cumulative)					C C.gov
							6,605
5,000							
,000							
						2,753	
2,000					1,762		
				785			
12	7	32 118	263				
0-9	10-19 20)-29 30-39	40-49	50-59	60-69	70-79	80 and older



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

ADV SD

confimed

case

3 5

PIV

RSV

IFV

3 5

First campaign

Α 25

20

10

30

» 20-

PPS, 10

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30

» 20·

PPS,

D

%

PPS, 40 20

80

60-

~ 15

PPS,

В

The Journal of Infectious Diseases

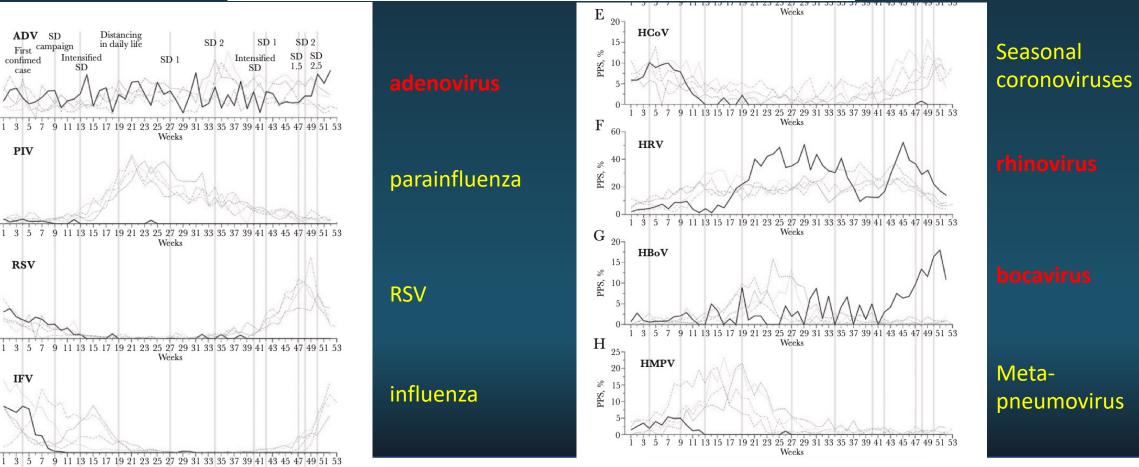
MAJOR ARTICLE



Shifting Patterns of Respiratory Virus Activity Following Social Distancing Measures for Coronavirus Disease 2019 in South Korea Sangshin Park,^{1,0} Ian C. Michelow,^{2,3} and Young June Choe^{4,0}

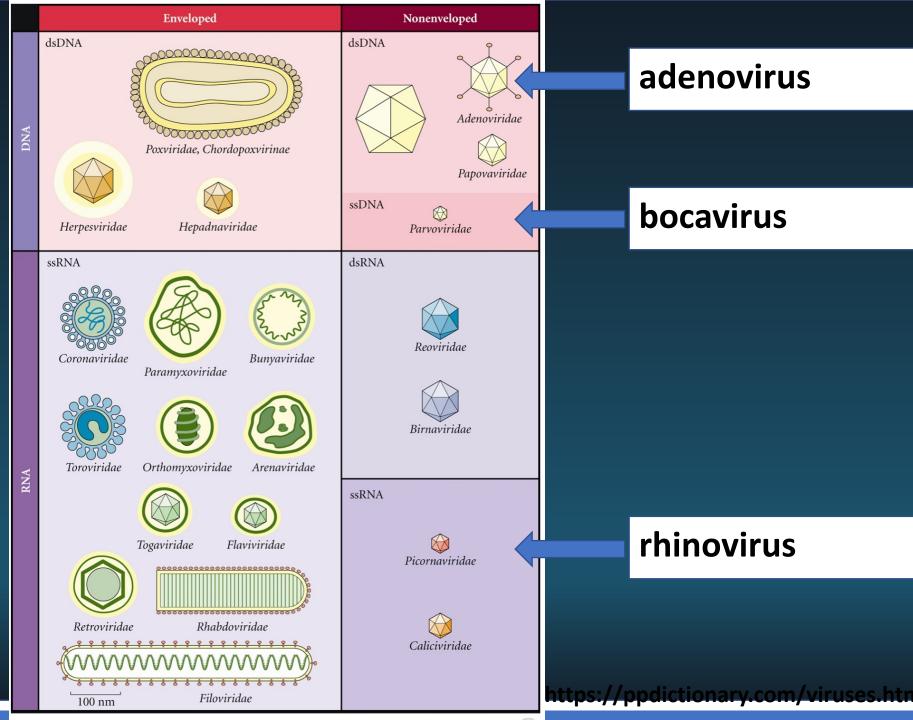
----- 2016 ----- 2017 ----- 2018 ----- 2019 2020





non-enveloped viruses lack a lipidbilayer membrane

not easily inactivated by routine surface cleaning and disinfection



adenovirus

bocavirus

rhinovirus

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

Nonenveloped viruses

Enveloped

Rhino/entero

Adenovirus

Other resp viruses

Pandemic period Rhinovirus or entero positive, % 60 40 20 Aug Oct Feb Dec Feb Dec Feb Apr Jun Aug Oct Dec Feb Apr Jun Oct Dec Feb Apr Jun Aug Dec Apr Jun Aug Oct 2020 2021 2016 2017 2018 2019 100 Pandemic period % positive, 80 60 Adenovirus, 40 20 0 Feb Dec Oct Dec Feb Apr Oct Oct Dec Feb Dec Feb Apr Jun Aug Jun Aug Dec Feb Apr Jun Aug Apr Jun Aug Oct 2017 2018 2019 2020 2016 2021 100 Other respiratory viruses, positive, % Pandemic period 80 60 40 20 0 Dec Feb Apr Jun Aug Oct Dec Feb Apr Jun Oct Dec Feb Apr Jun Aug Oct Dec Feb Apr Jun Aug Oct Dec Feb Αιια 2016 2017 2018 2019 2020 2021 100 positive, % Pandemic period 80 60 SARS-CoV-2, 40 20 Ω Dec Feb Dec Feb Apr Jun Aug Oct 2016 2017 2018 2019 2020 2021



7 centers (New Vaccine Surveillance Network)

SARS-CoV-2



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



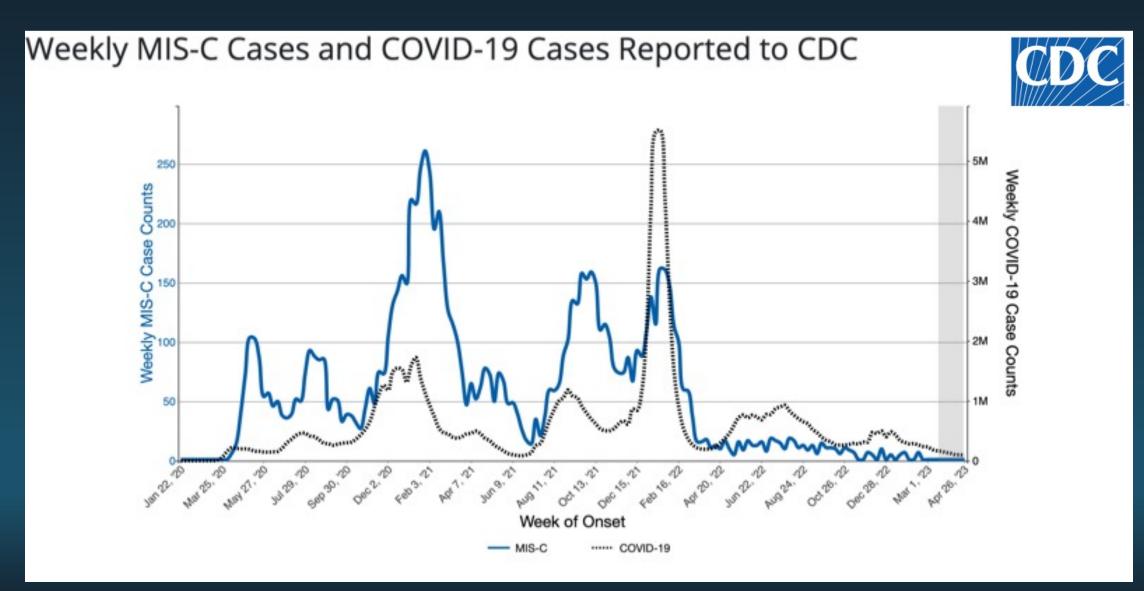


Surveillance definition:

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)

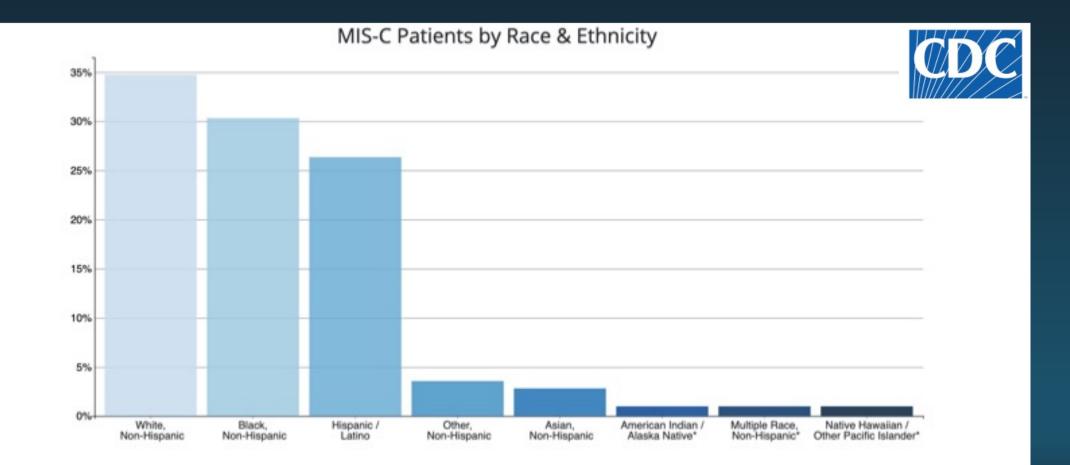
MIS-C Epidemiology in Children <18 years

Connecticut Children's



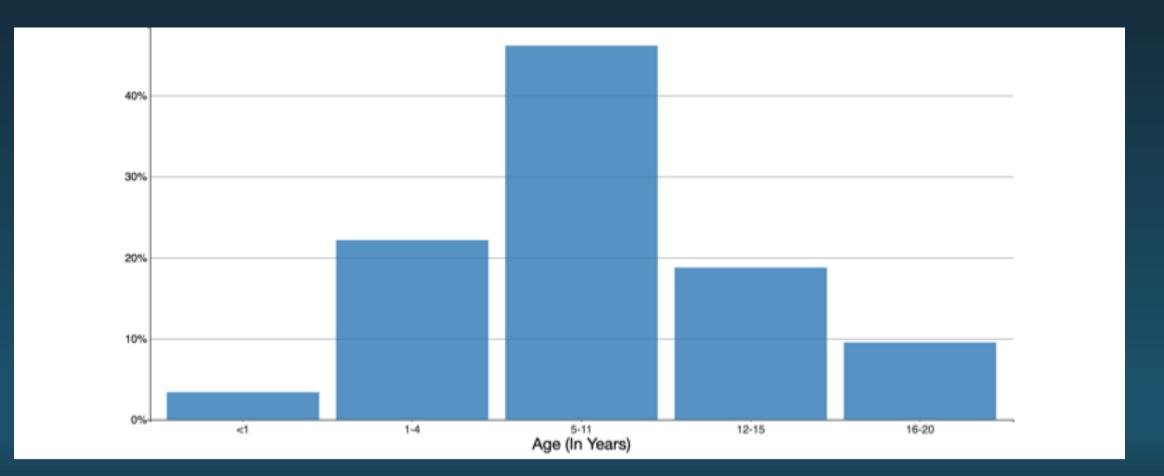
MIS-C by Race and Ethnicity





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%

Connecticut Children's

MIS-C: spectrum of severity



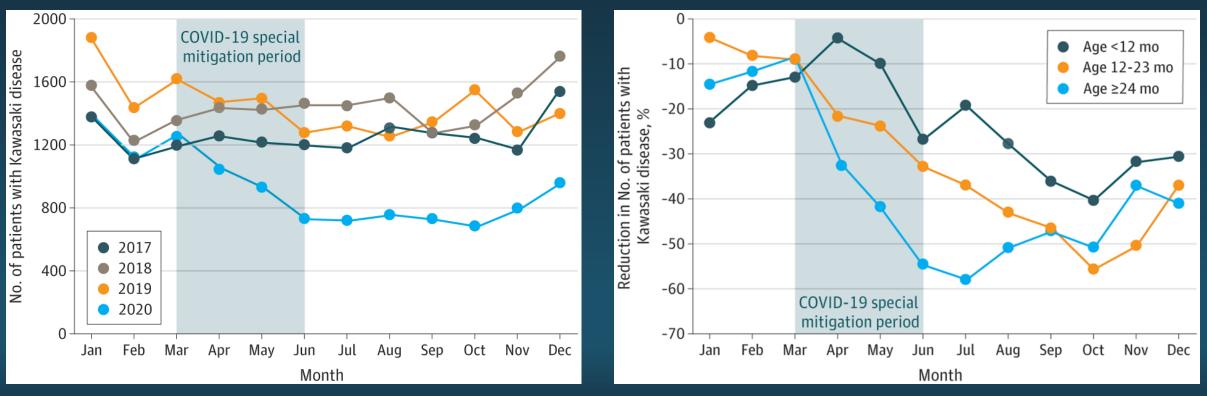
COVID-19-associated MIS-C					
Febrile inflammatory state	KD-like illness	Severe MIS-C			
Some children may present with persistent fevers and mild symptoms (eg, headache, fatigue). Inflammatory markers may be elevated, but signs of severe multisystem involvement are lacking.	Some children meet criteria 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.			

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





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





Is COVID-19 infectivity linked to virulence?

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



Volume 21 | March 2023 | 162–177

Infection-induced immunity

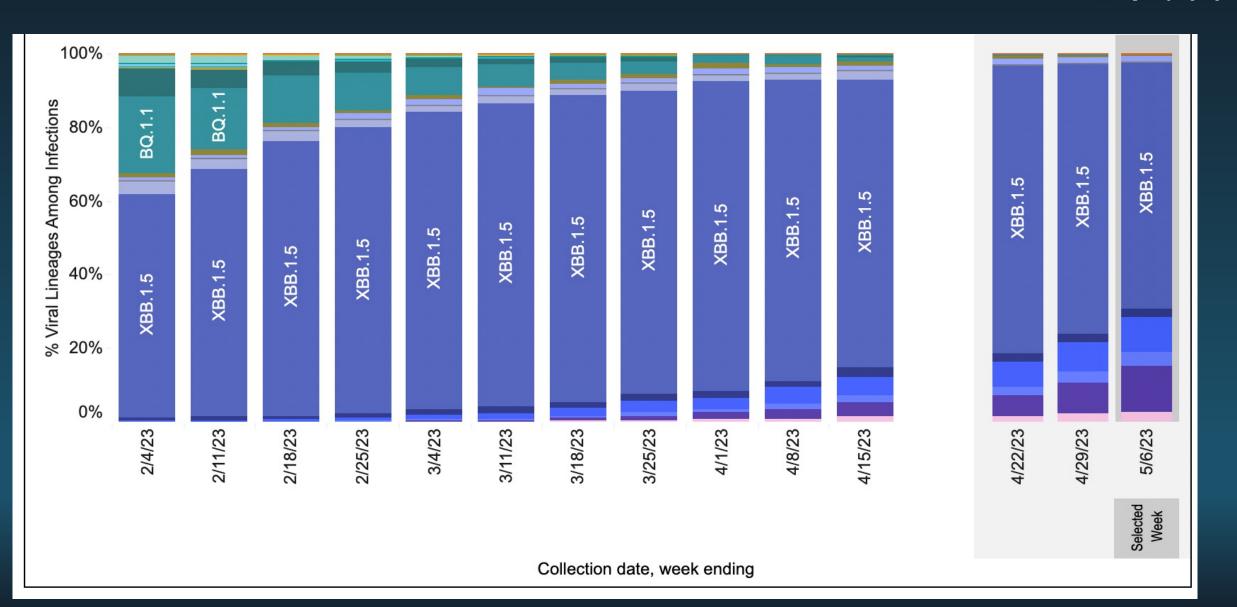
Vaccine-induced immunity

Immunologically naive hosts

Importance of antigenic novelty

Time

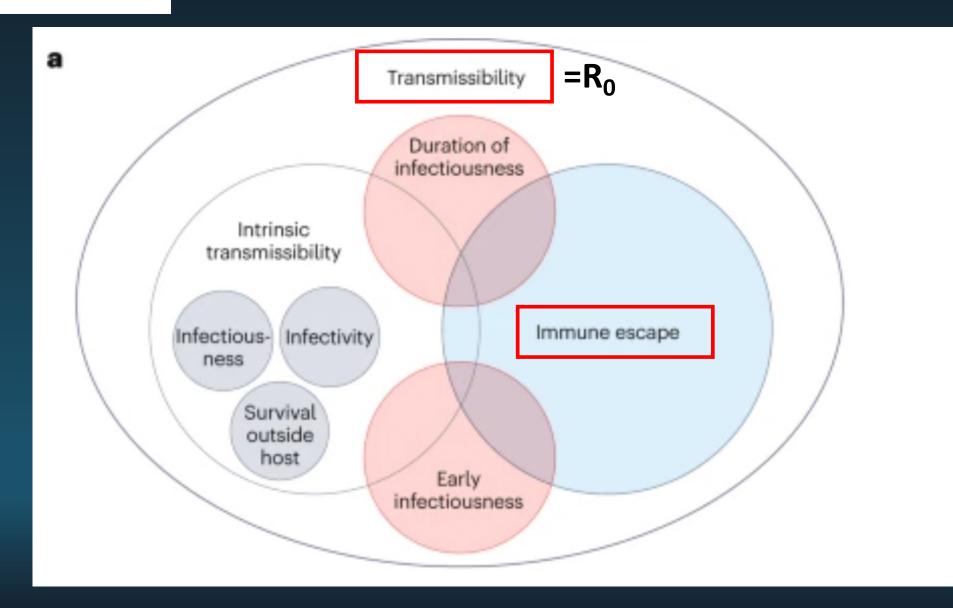
Circulating SARS-CoV-2 variants in the U.S.



Connecticut Children's

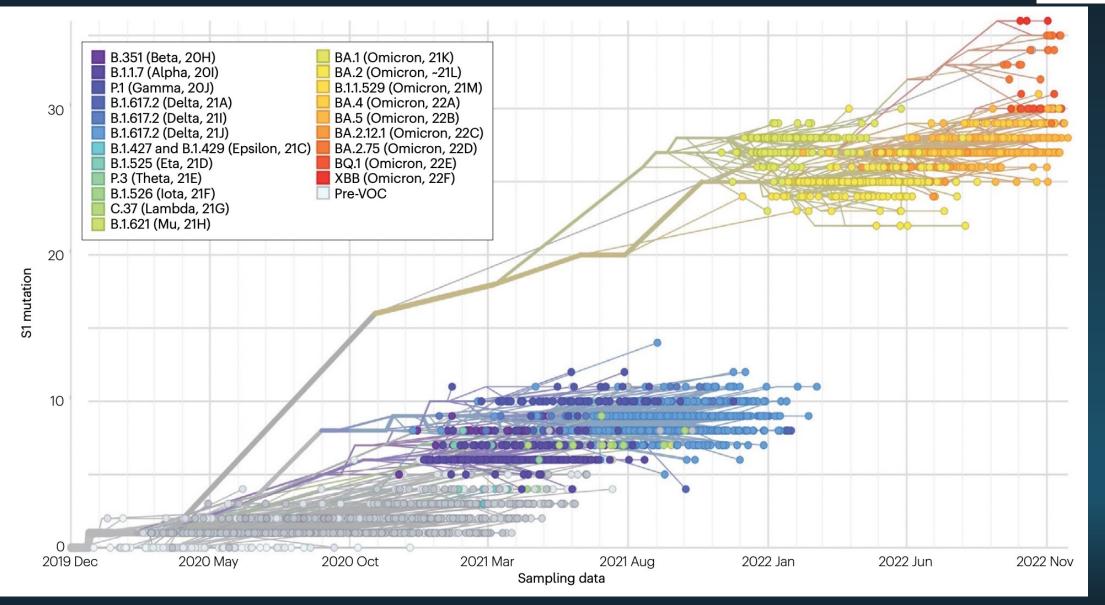
The evolution of SARS-CoV-2





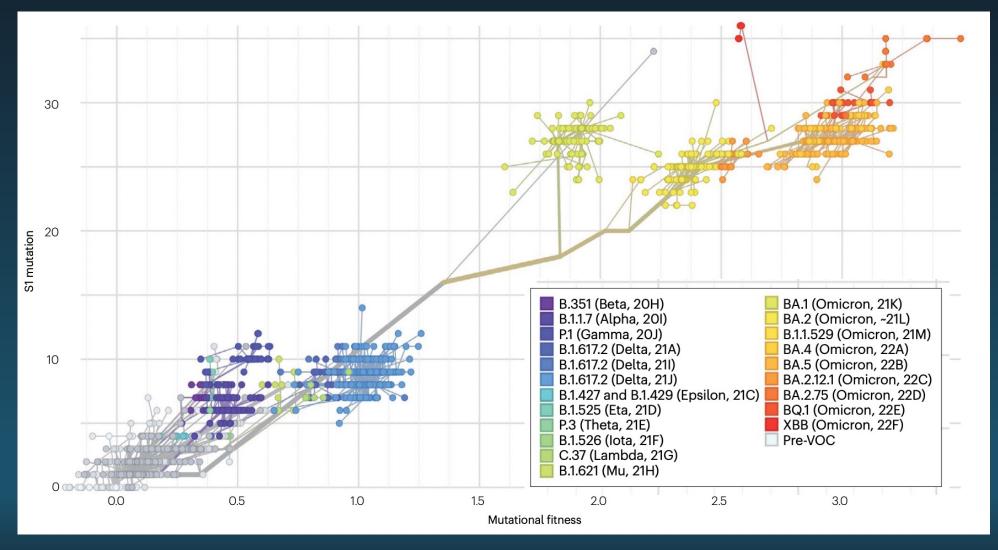
Viral Fitness

05 April 2023



Survival of the fittest

05 April 2023



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

20, pages251–252 (2022)

Intrinsic transmissibility (evolutionary pressure)

Burden of future variants escape (evolutionary pressure)

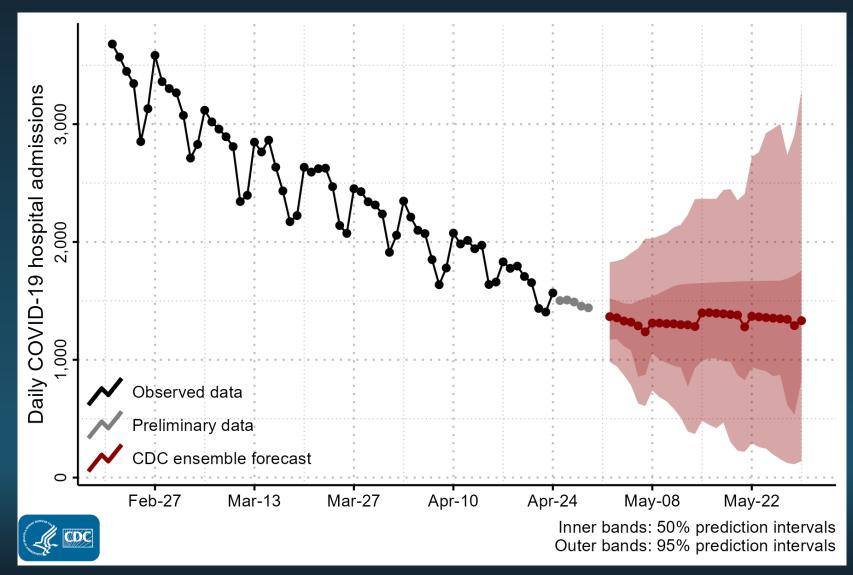
Disease severity (evolutionary by-product) Connecticut Children's



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 systema review and meta-analyses

scientific reports

(2022) 12:9950

atic	Lo	ng CO'	VID (P	ASC)
		ropsychiatric (%)	_2	5.24%
	_	.50 (sad, tense, angry,		Card
	anxiety, de			• Respira
	• Fatigue			• Sputum
	-	order (8.42) (insomnia,	(20)	 Option Orthost
		nia, poor sleep quality)	(S. 2)	
	Headache	e (7.84)	Chines	o Exercis
	Cognition	6.27 (confusion, impaired		• Chest p
	concentrat	ion, learning difficulties,		• Rhinorr
	memory lo	ss)	~	o Cough
	• Dizziness	4.40		• Sore th
	Neurologi	ical abnormalities 0.86	JE E	• Chest t
		needles, tremor, numbness)	A A A A A A A A A A A A A A A A A A A	• Variatio
		oroblems 0.54		o Palpitat
		testinal (%)		Dermat
			ARKEN I	
		al pain (2.91)		• Hyper
	 Constipa 			• Derma
	• Diarrhea	(1.68)		itchy s
	• Vomiting	/nausea 1.53		• Hair lo
	Speech disturbances	-		Oth
	Dysphagia Balance problems	-		
	Urinary symptoms Neurological abnormalities			• Loss of appetite
	Hair loss Changes in menstruation	=		• Altered smell 🤅
	Palpitations			hyposmia, anosn
	Vomiting/nausea Diarrhea			 Body weight ch
	Musculoskeletal other Fever			• Myalgia/arthral
	Dysphonia			o Altered taste 3
	Constipation Variations in heart rate			o Otalgia (3.41) (ti
	Sore throat Chest tightness			• Ophtalmologic
	Swollen lymph nodes			
	Dermatologic Abdominal pain		Lee Lund	eyes, problems s
	Ophtalmologic Otalgia			photophobia, pai
	Altered taste			o Swollen lymph
	Myalgia/arthralgia Cough			• Dysphonia (1.89
	Body weight changes Rhinorrhea			• Fever (1.87)
	Dizziness			• Musculoskeleta
	Chest pain Hyperhidrosis			• Changes in me
	Altered smell Exercise intolerance			 Urinary sympto
	Loss of appetite			
	Cognition Orthostatic intolerance		-	• Dysphagia 0.46
	Sputum/nasal congestion Respiratory symptoms			 Speech disturb

8.00 - 17.00% 4.00 - 7.99% 2.00 - 3.99 % 0.00 - 1.99%

Cardiorespiratory (%) • Respiratory symptoms (7.62) Sputum/nasal congestion 7.53 Orthostatic intolerance (6.92) • Exercise intolerance (5.73)

Chest tightness (2.45)

- Variations in heart rate (2.29)
- o Palpitations (1.27)

• Chest pain (4.62) • Rhinorrhea (4.15)

• Cough (3.80) Sore throat (2.47)

Dermatologic/Teguments (%) Hyperhidrosis (4.66) Dermatologic (2.61) (dry skin, itchy skin, rashes, hives) Hair loss (1.17)

Others (%)

o Loss of appetite (6.07) • Altered smell (5.60) (phantom smell, hyposmia, anosmia, hyperosmia) Body weight changes (3.99) o Myalgia/arthralgia (3.76) Altered taste (3.65) • Otalgia (3.41) (tinnitus, earache or vertigo) • Ophtalmologic (3.00) (conjuntivitis, dry eyes, problems seeing/blurred vision, photophobia, pain) o Swollen lymph nodes (2.58) Dysphonia (1.89) • Fever (1.87) Musculoskeletal other (1.72) Changes in menstruation (1.27) • Urinary symptoms (0.63) o Dysphagia (0.46)

Speech disturbances (0.44)



PASC: Postacute 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	Þ
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



Rank	Name	IRR	95% CI	Þ
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

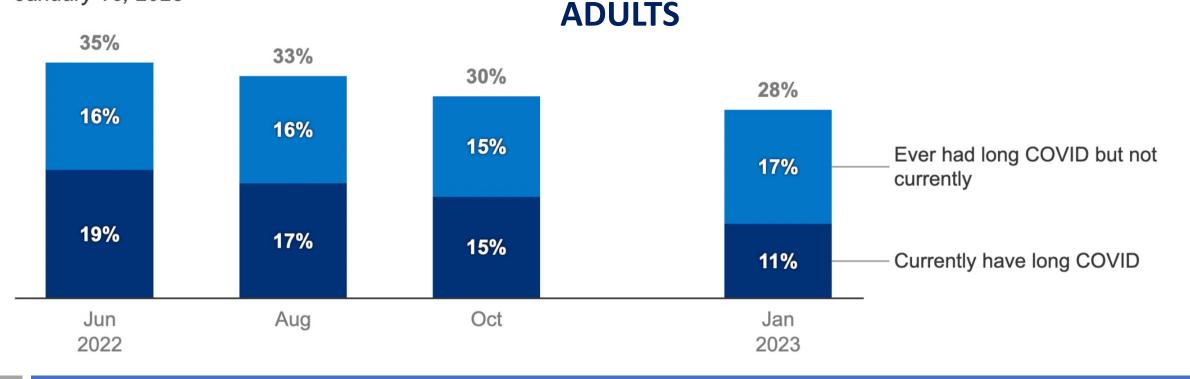
Adults





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

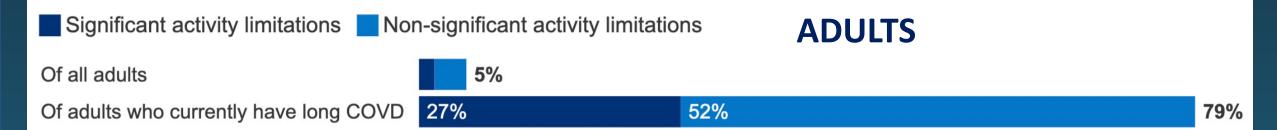




Alice Burns

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



INTERNATIONAL SOCIETY FOR INFECTIOUS

DISEASES

Zaid Alhinai^{1,#}, Sangshin Park^{2,#}, Young-June Choe³, Ian C. Michelow^{4,*}

Sources: Our World in Data; publications; newspaper articles

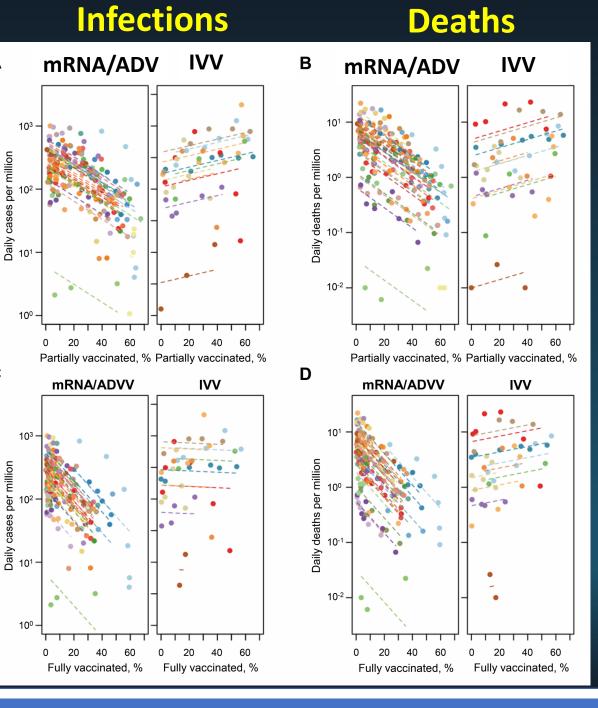
Country ^a mRNA-based vaccines		Adenovirus-vectored vaccines				Inactivated virus vaccines							
	Woderna	Pfilet	n ^{RWA ON^W}	Janseen	Astaleneca	constield	Spatniky	Anyatenorine	man and lot adenovitus	Balascori	Colonavac	ectivated virus vaccines	olofcountrisvectures
Austria Bahrain Belgium Bhutan]		>60 ^b
Canada Chile Croatia Cyprus Czechia													78 ^c
Denmark Dominican Republic Estonia Finland France			· · ·			- - -							~95 ^d
Germany Greece Hungary Ireland Israel]		21 ^c
Italy Latvia Lithuania Maldives Mauritius			-										~35 ° >50 ^f
Mongolia Netherlands Norway Poland													87 ^g
Portugal Qatar Serbia Singapore Slovakia]		>50 ^h
Slovenia Spain Sweden Switzerland													. .
Turkey United Kingdom Uruguay USA													>90 ⁱ 74 ^c

Partially vaccinated

Α

С

Fully vaccinated

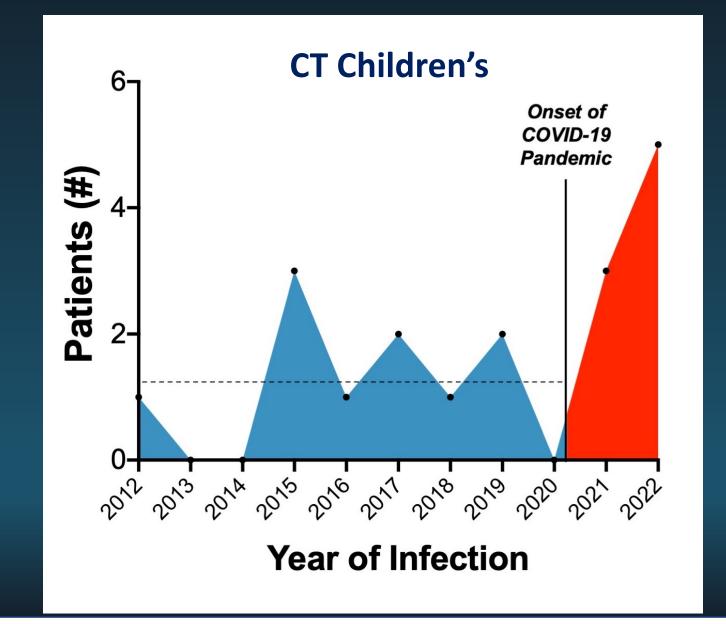






Was there a change in rates of secondary bacterial infections?

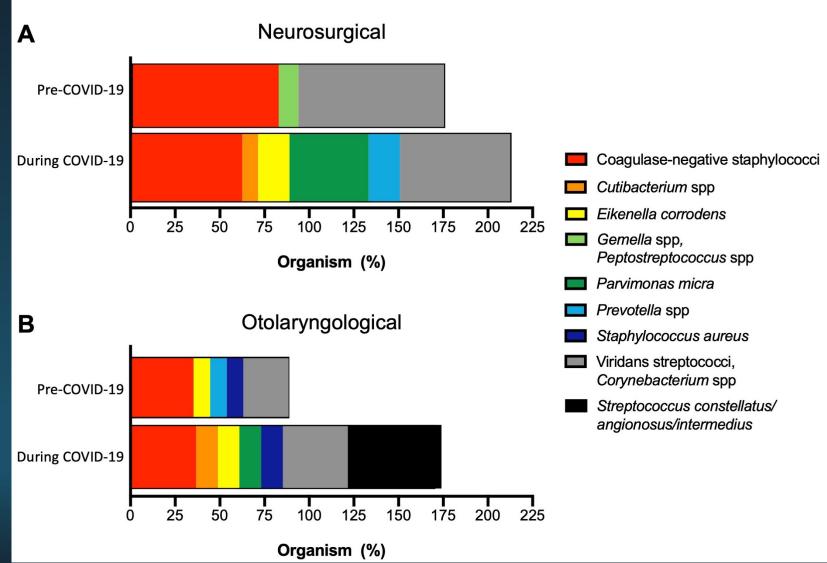
Rates of secondary bacterial infections: intracranial



J Neurosurg-<u>Pe</u>diatr (in press)

Connecticut

Change in microbiology of intracranial infections

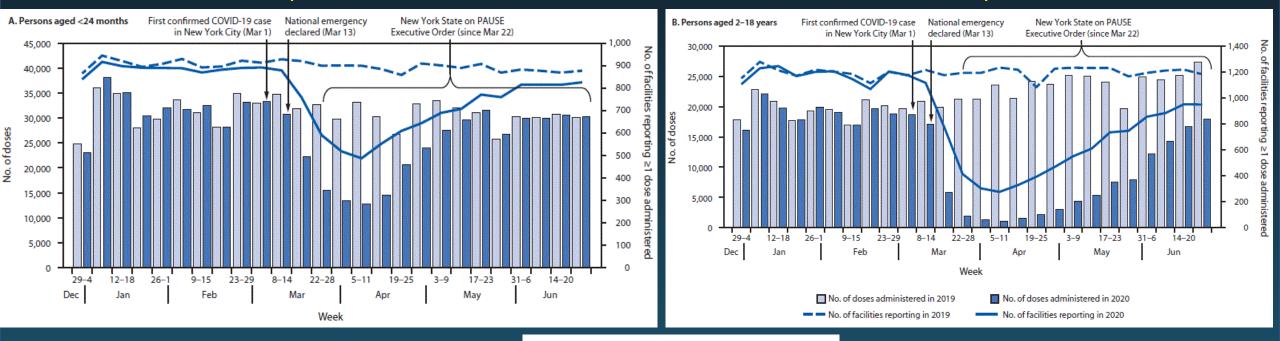


J Neurosurg-Pediatr (in press)



How did COVID-19 impact routine childhood vaccines?

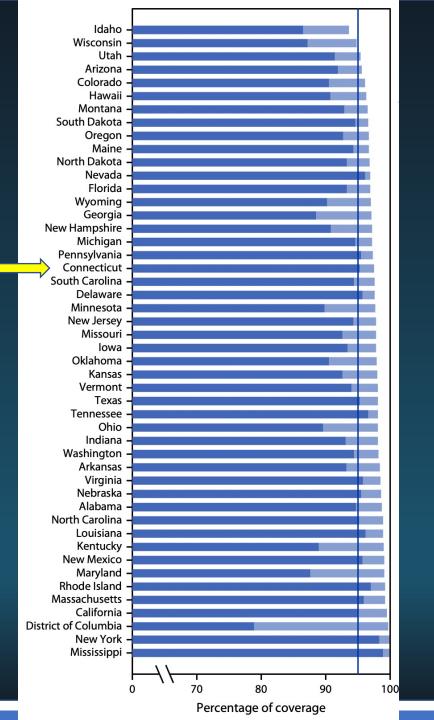
COVID-19 disrupted delivery of childhood vaccinations 2 yrs 2020 2-18 yrs



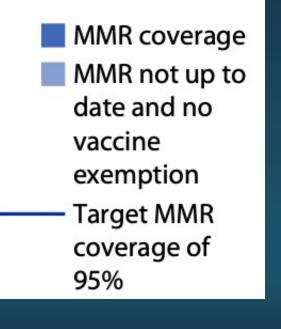




Centers for Disease Control and Prevention CDC 24/7: Saving Lives, Protecting People™ CT — 2021-22: 95.7%



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









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



444

- Increase in Adverse Childhood Experiences (ACEs)



Do RNA or DNA viruses pose a greater pandemic threat?

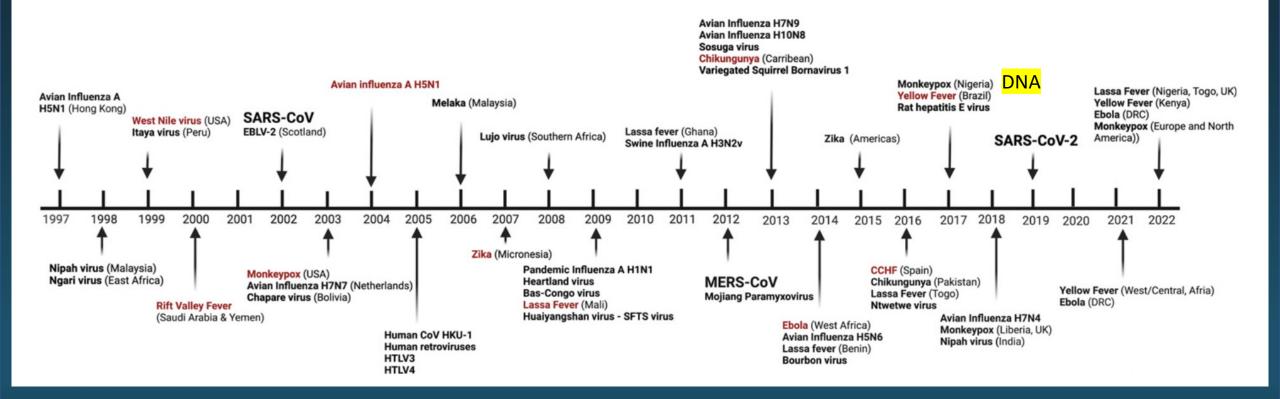
Emerging infectious Diseases





RNA >> DNA viruses cause zoonoses and outbreaks

they are have error-prone replication and high mutation rates

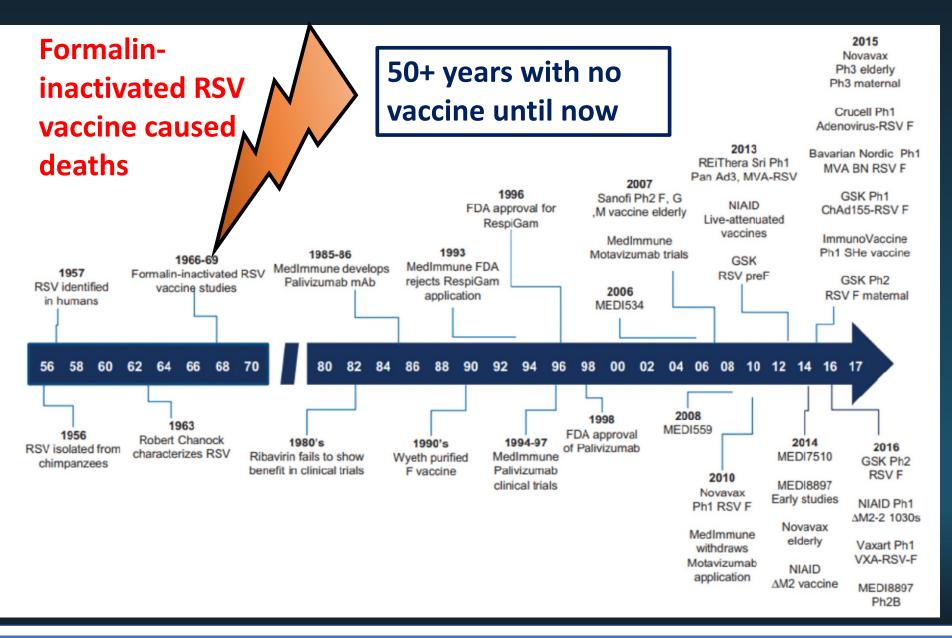




What's new in RSV vaccine development?

Long saga of RSV vaccine development





FDA NEWS RELEASE



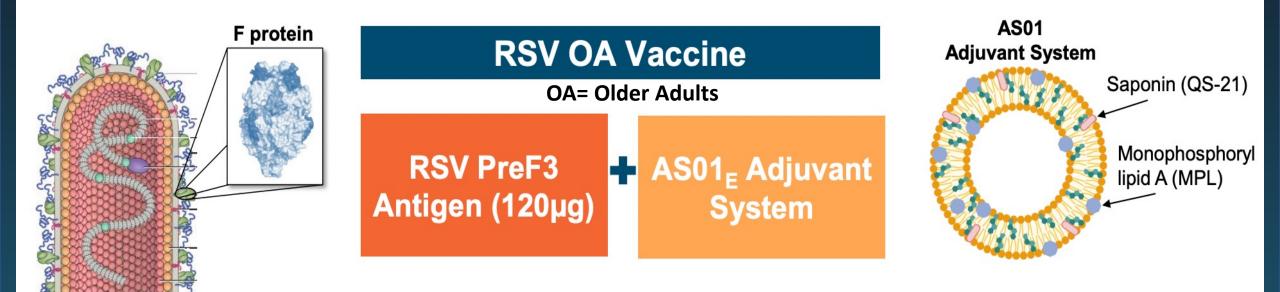
FDA Approves First Respiratory Syncytial Virus (RSV) Vaccine

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
- o mild colds to pneumonia and respiratory failure

RSV Vaccine: 120 µg RSVPreF3 + AS01_E Adjuvant Formulation Selected for Phase 3 Development



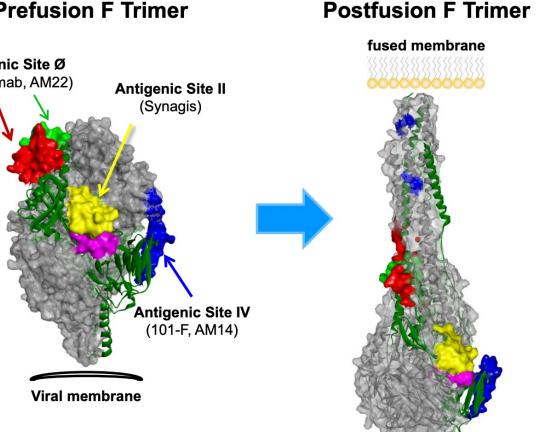
- High serum neutralization titers for RSV-A and RSV-B
- High polyfunctional RSVPreF3 specific CD4+ T-cell responses in OAs approaching levels seen in young adults following vaccination
- Th1 dominant response
- Well tolerated with acceptable safety profile

RSV fusion (F) glycoprotein



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

Prefusion F Trimer Antigenic Site Ø (Nirsevimab, AM22)



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

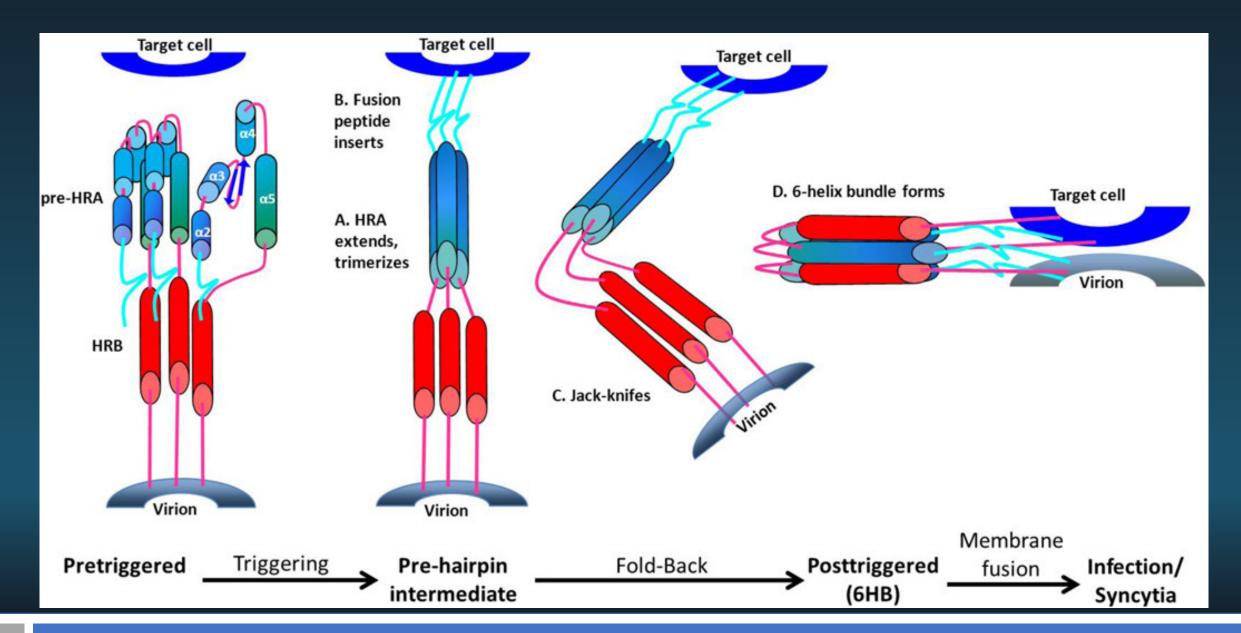


Worldwide Research, Development and Medical Vaccine Research and Developmer

McLellan et al. Science, Nov 2013

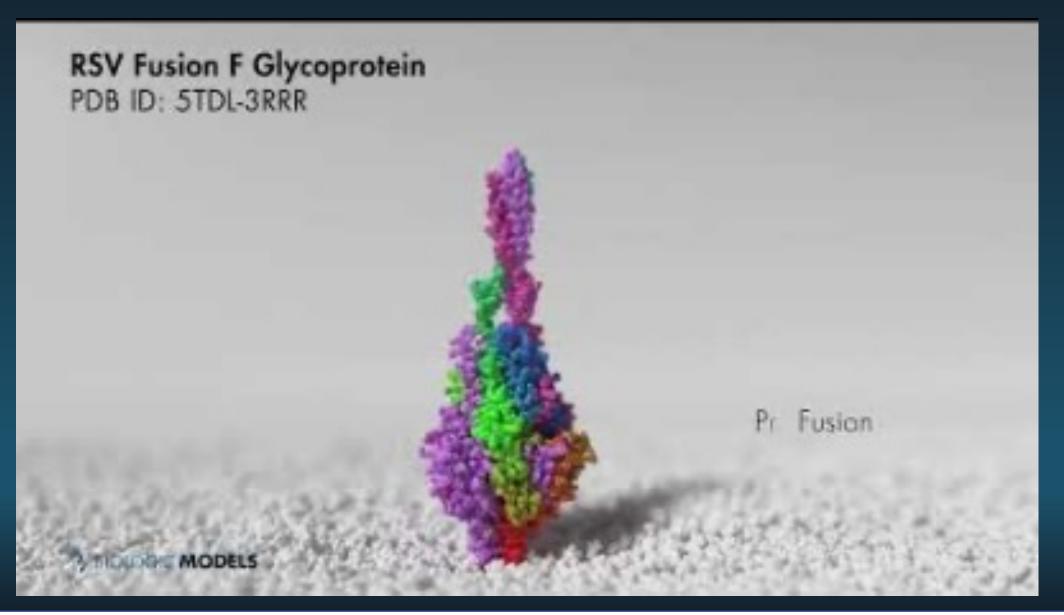
Structure of RSV fusion (F) glycoprotein

Connecticut Children's



Function of RSV fusion (F) glycoprotein





RSVPreF vaccine protects against clinical disease

N ENGL J MED 388;7 NEJM.ORG

FEBRUARY 16, 2023

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*

> A RSV-Related Lower Respiratory Tract Disease 1.0 -**RSV-LRTI** 0.9-0.8-Cumulative Incidence (%) 0.7-0.6-0.5 0.4 Placebo 0.3 0.2 0.1 **RSVPreF3 OA** 0.0 10 11 Months since 15 Days after Injection No. at Risk Placebo 12,403 12,290 11,887 12.494 11,640 11,022 8291 5464 2709 559 2 0 12,286 11,892 571 2 RSVPreF3 OA 12.466 12.392 11,655 11,046 8320 5495 2727 0 Cumulative No. of Cases Placebo 0 9 21 28 33 36 38 40 40 40 40 3 RSVPreF3 OA 0 5 6 7 7 7 7



Study 006: Consistent Efficacy Against RSV Disease (mES)

	RSV Vaccine (N = 12,466) Number	Placebo (N = 12,494) of events			Vaccine Efficacy (Cl*)
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)
		() 20	40 60 80 1	00



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

	Expos	ed Set		
SOC occurring in ≥ 0.5% of participants	RSV Vaccine N = 12,467	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%	F	0.99 (0.77, 1.27)
		() 1	2

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



Studies 004 and 007: pIMDs of Medical Interest

Potential immune-mediated diseases

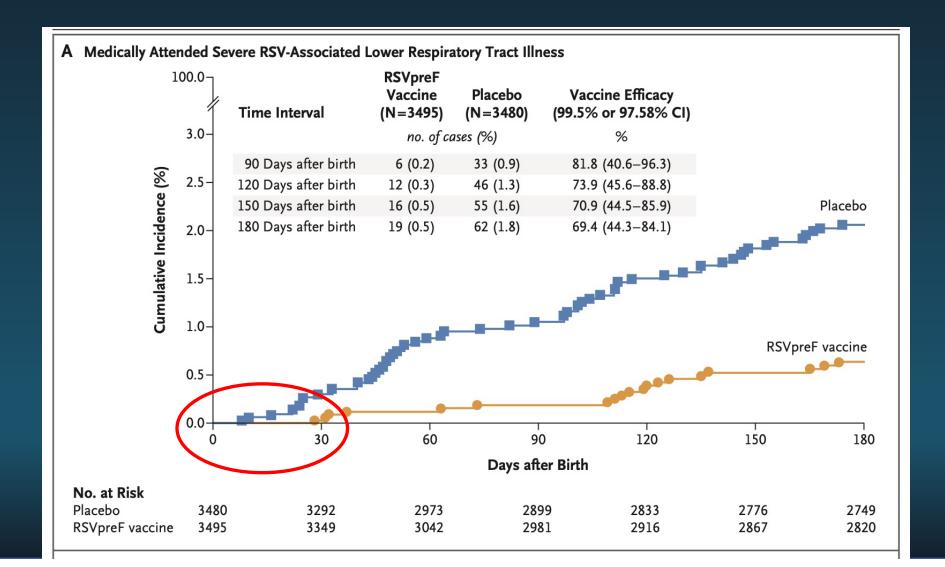
Event	Age/ Sex	Country	Time to Onset (Days)	Comment
Guillain Barre Syndrome	78/F	JP	9	Elevated CSF protein, serum GM1-IgG positive; BC Level 3
ADEM	71/M	ZA	7	2 prior strokes with Wallerian demyelination; fatal outcome; BC Level 3
ADEM	71/F	ZA	22	Recovered; no investigations performed; BC Level 3



- Phase 3, double-blind RCT
- o 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



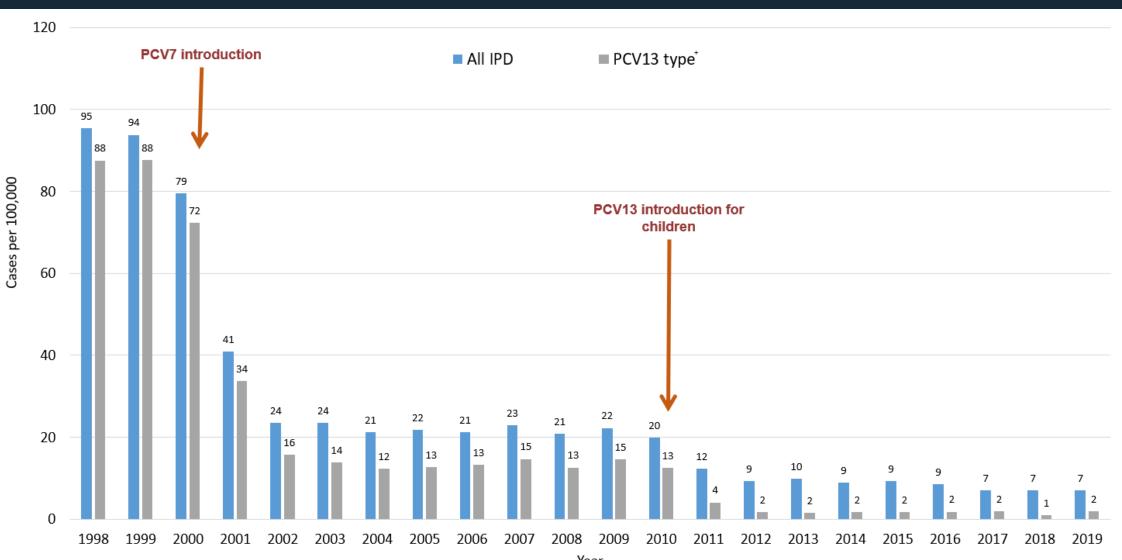




What's new in pneumococcal vaccine development?

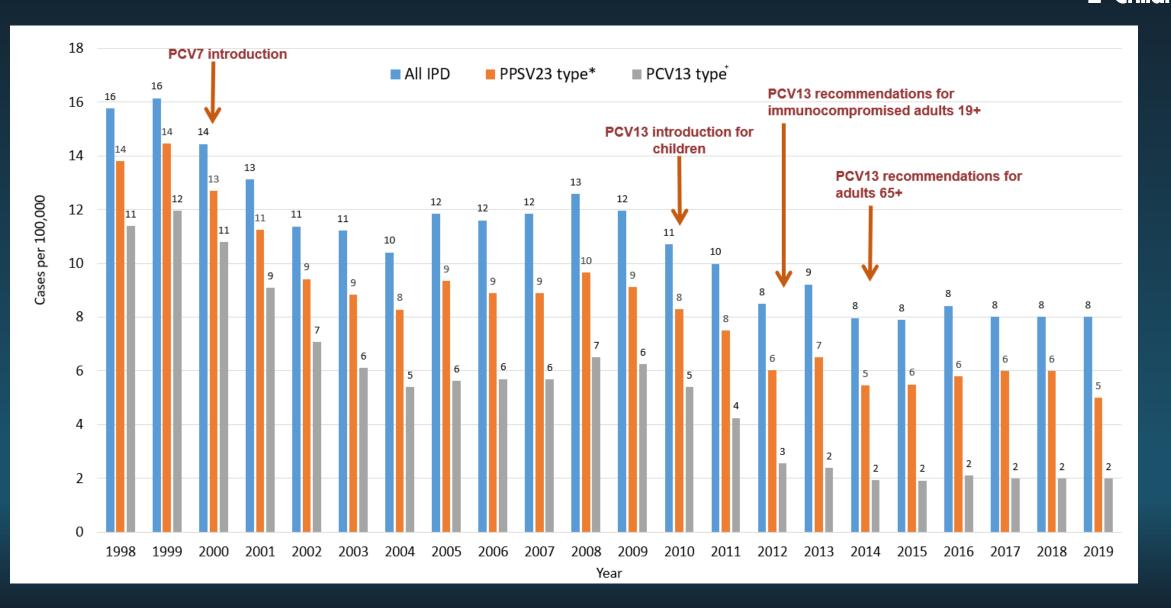
Trends in invasive pneumococcal disease <5 yrs

Connecticut



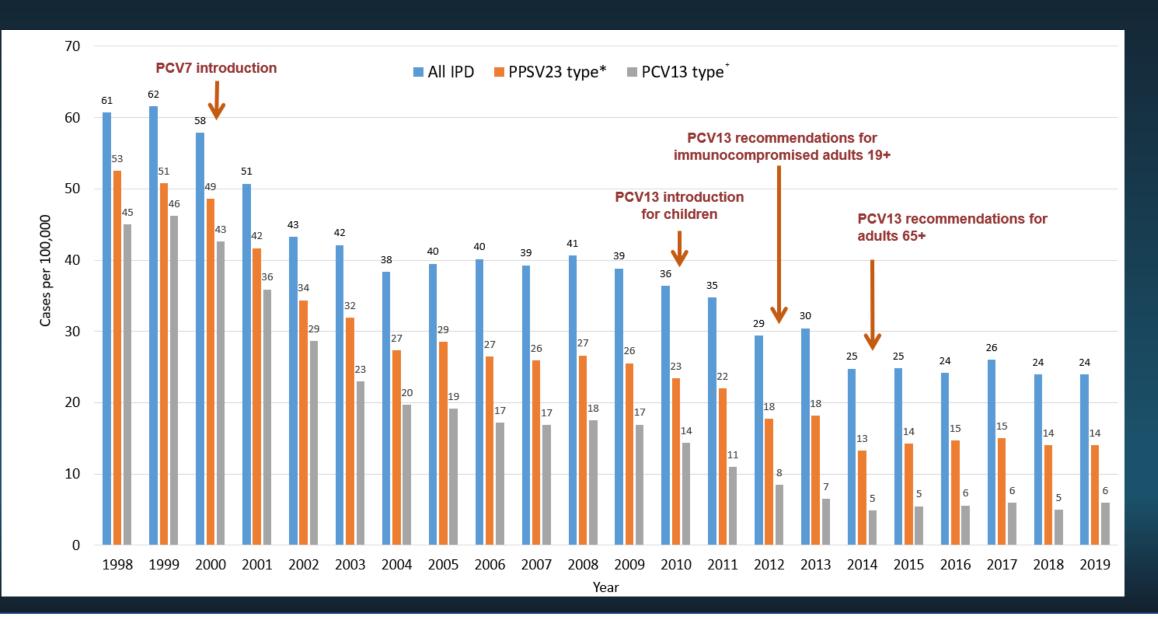
Year

Trends in invasive pneumococcal disease 19-64 yrs



Trends in invasive pneumococcal disease >64 yrs







Streptococcus pneumoniae vaccine

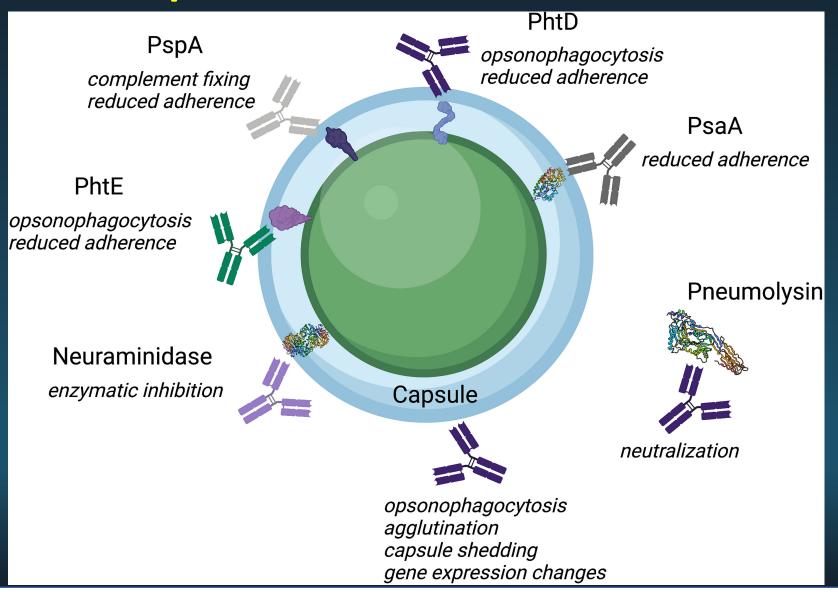
FDA Approves Prevnar 20 Vaccine to Prevent Invasive Pneumococcal Disease in Children 6 Weeks Through 17 Years

Apr 28, 2023

This approval expands existing adult coverage (2021)

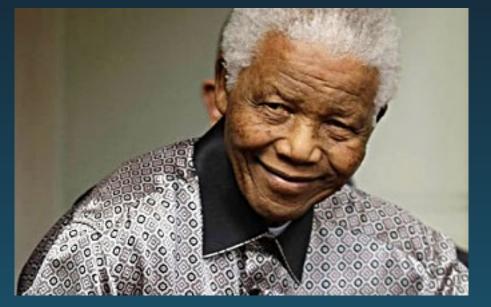
We need a universal protein-based pneumococcal vaccine!





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

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