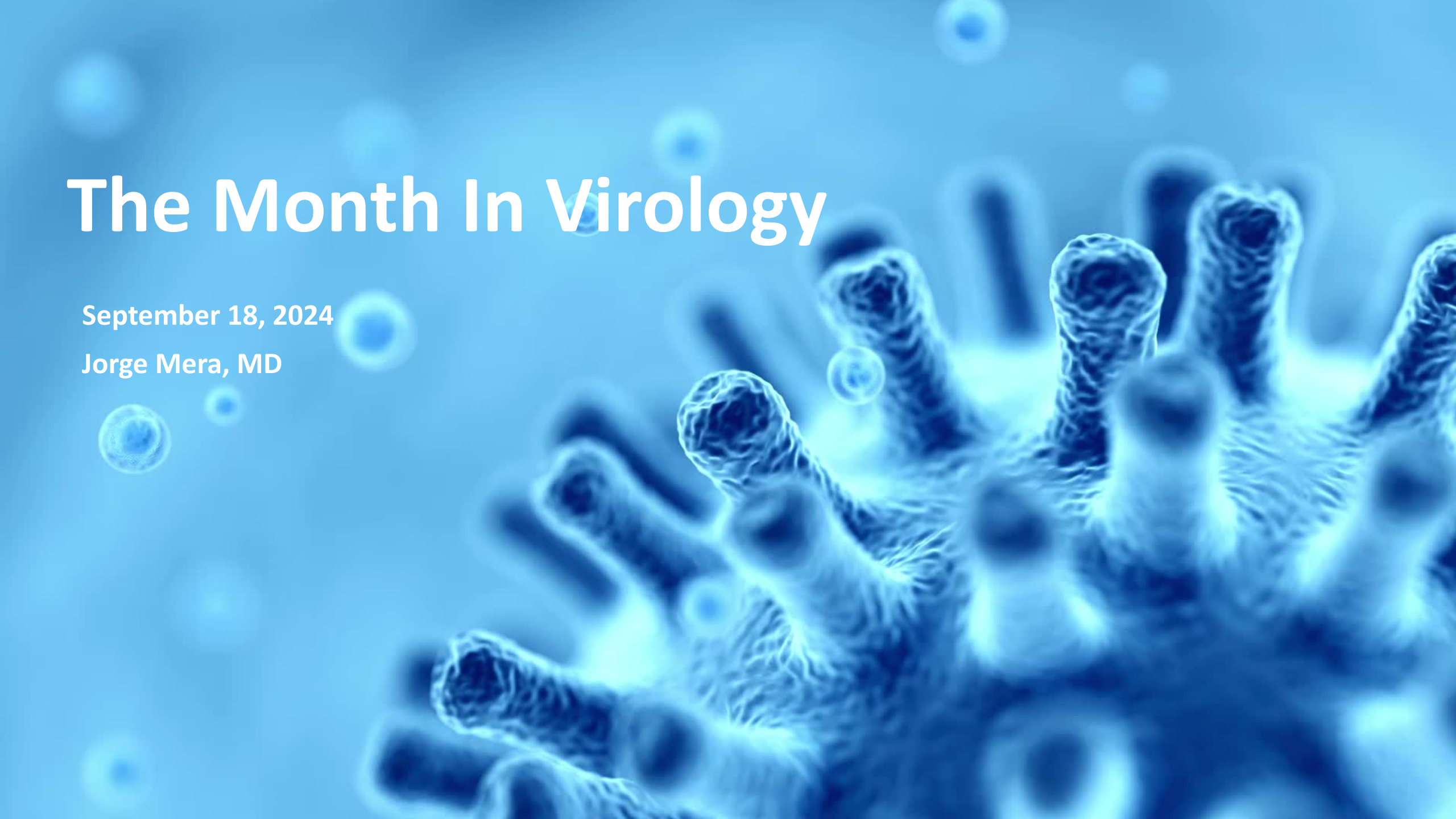
The Month In Virology

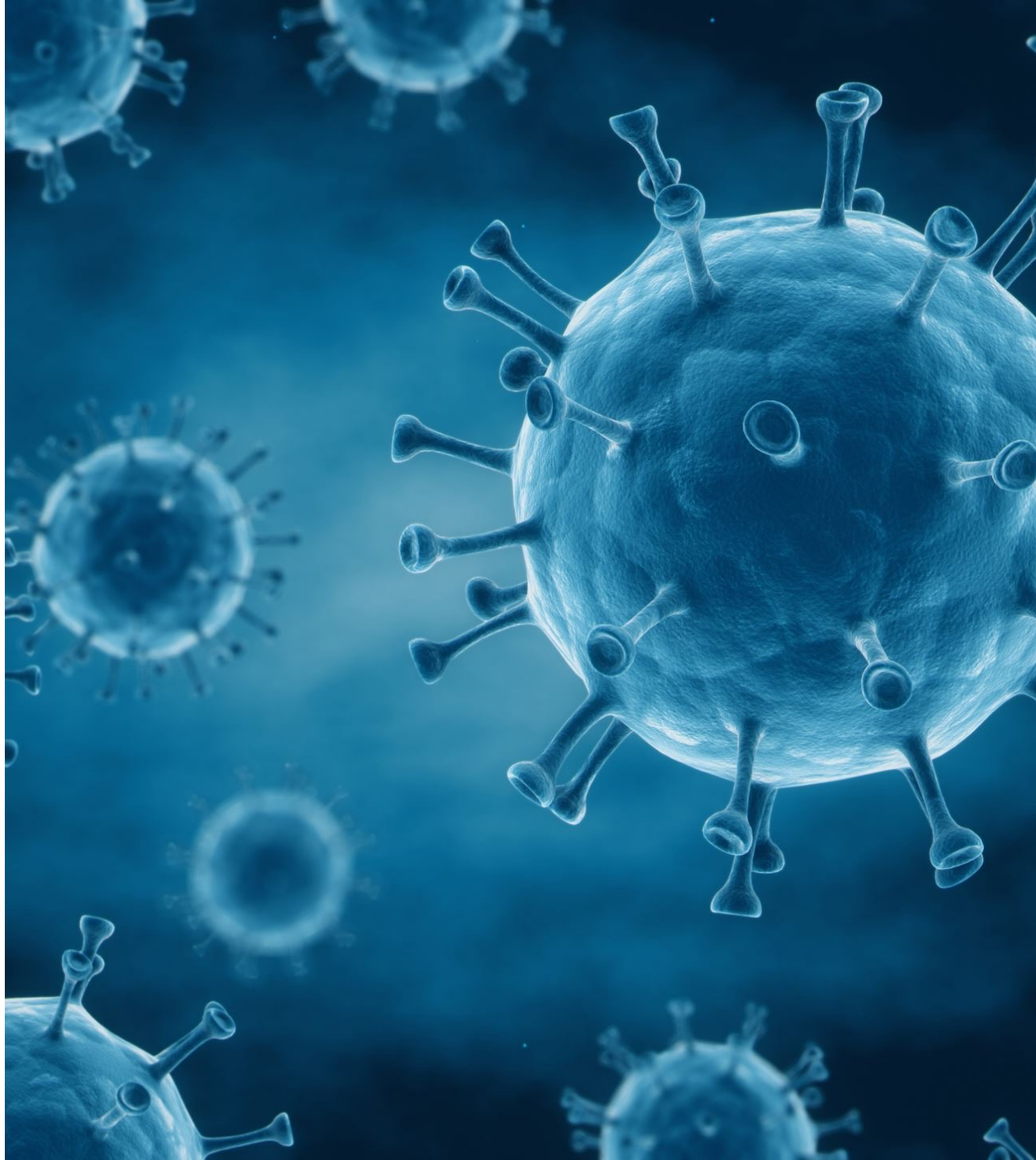
September 18, 2024

Jorge Mera, MD



Outline

- **Oropouche Virus Disease**
- **Avian Influenza in the US**
- **COVID-19 updates**
  - **Epidemiology**
  - **Vaccines**
  - **Long COVID**



Oropouche Virus Disease (OVD) Among U.S. Travelers — United States, 2024

- **What is already known about this topic?**
  - Oropouche virus is an emerging arthropod-borne virus in the Americas.
  - Recent reports of outbreaks in areas without previous endemic transmission, fatal cases, and vertical transmission associated with adverse pregnancy outcomes have raised concerns about human health risks.
- **What is added by this report?**
  - As of August 16, 2024, a total of 21 Oropouche virus disease cases among U.S. travelers returning from Cuba have been reported.
  - Most patients had self-limited illness.
  - At least three patients experienced recurrent symptoms after resolution of the initial illness.

Weekly / September 5, 2024 / 73(35);769–773

Oropouche virus

Oropouche virus infections are caused

- By bites from **tiny flies known as midges.**

These midges breed in piles of rotting banana stumps and cacao husks

- Exposure to bananas and cacao appear to be at increased risk for transmission

Risk of transmission

- **I**s greatest during the rainy season

Climate change, deforestation, and unplanned urbanization

- Have facilitated the spread of the virus from the Amazon region into new areas of Brazil

(*Culicoides paraensis*)

Published Online: August 30, 2024. doi:10.1001/jama.2024.15885

Oropouche virus

Genus *Orthobunyavirus*	In the family Bunyavirus Four genotypes have been identified
First described in 1961	In Vega de Oropouche, Trinidad .
First epidemic	Occurred in Belem, Brazil (1961)
Has been **associated with large epidemics:**	**And sporadic disease** in Brazil, Peru, Panama, Haiti, Colombia, and French Guiana

(*Culicoides paraensis*)

Published Online: August 30, 2024. doi:10.1001/jama.2024.15885

Oropouche Viral Disease

Incubation period	• 4 to 8 days (range 3 to 12 days)
Presentation	• Fever, chills, headache, myalgias, arthralgias, retro-orbital pain, photophobia, and rash.
Laboratory	• Include leukopenia and neutropenia.
Symptoms course	• usually last 4 to 5 days, but recurrence up to 10 days following initial recovery has been observed

Source: Up To Date

Oropouche Viral Disease

Asymptomatic infection

- Frequency is unknown

Immunity

- Following infection is likely lifelong

Complications:

- Hemorrhagic manifestations reported in 16% percent of patients in one series
- Meningoencephalitis is rare

Oropouche fever outbreak, Manaus, Brazil, 2007-2008. Mourãão MP, Bastos MS, Gimaqu JB, et al. Emerg Infect Dis. 2009 Dec;15(12):2063-4

Oropouche Viral Disease

Diagnosis	• Antibody on acute and convalescent sera • Viral RNA in blood via RT-PCR
Differential diagnosis	• Dengue, yellow fever, chikungunya, Zika, malaria, leptospirosis, ehrlichiosis, and influenza.
Treatment	• Supportive
Prevention	• Use of mesh screens and other interventions to prevent insect bites.

Source: Up To Date

Oropouche virus Disease

Distribution

- At the end of July, there were more than 8000 confirmed cases and 2 confirmed deaths throughout 5 countries in Latin America.

PAHO recommendations

- Bolstering surveillance and diagnosis in the region
- Draining standing water
- Widespread use of mosquito nets and repellents.

Published Online: August 30, 2024. doi:10.1001/jama.2024.15885

Oropouche Virus Disease Among U.S. Travelers — United States, 2024

- **What are the implications for public health practice?**
  - Clinicians and public health jurisdictions should be aware of the occurrence of Oropouche virus disease in U.S. travelers and request testing for suspected cases.
  - Travelers should prevent insect bites when traveling
  - Pregnant persons should consider deferring travel to areas experiencing outbreaks of Oropuche Virus Disease

- *Weekly* / September 5, 2024 / 73(35);769–773

Oropouche Virus Disease

CDC has developed an Interim Guidance for Evaluating and Managing Infants Born to Pregnant People with Confirmed or Probable Oropouche Virus Disease.

- **Summary points from the guidance are:**
  - Data on congenital Oropouche virus disease is currently limited.
  - In Brazil Oropouche during pregnancy has been reported to cause **still birth and severe microcephaly**.
  - Infants born to people with confirmed or probable Oropouche during pregnancy should receive a comprehensive evaluation by a healthcare provider at birth and at each well-child visit.
  - Infants and children with congenital anomalies might benefit from multidisciplinary care.

WHO Announces Project to Develop an mRNA H5N1 Vaccine for Humans

In 2021 the WHO launched the mRNA Technology Transfer Programme

To help develop and produce mRNA vaccines in lower-resource countries

To be able to mount a more effective and equitable response in the next pandemic

In late July

The WHO plans to develop a highly pathogenic A(H5N1) virus mRNA vaccine

To protect people in low- and middle-income countries

Argentinian manufacturer Sinergium Biotech is leading the effort.

The company's mRNA vaccine is still being tested for effectiveness against the H5N1

If successful, the technology will be shared with vaccine manufacturers in other low- to middle-income countries

Cluster of Influenza A(H5) Cases Associated with Poultry Exposure at Two Facilities — Colorado, July 2024

- **What is already known about this topic?**
  - Humans who have contact with influenza A(H5N1) virus–infected cattle or poultry can become infected.
  - Before this outbreak, five human cases of influenza A(H5) had been reported in the United States
    - One in 2022 in Colorado associated with poultry exposure and four among dairy workers reported during April–July 2024

Weekly / August 29, 2024 / 73(34);734–739

Cluster of Influenza A(H5) Cases Associated with Poultry Exposure at Two Facilities — Colorado, July 2024

- **What is added by this report?**
  - The first known cluster of human influenza A(H5) cases in the United States associated with poultry exposure occurred in Colorado
  - 109 (16.4%) of 663 workers performing poultry depopulation reported symptoms and received testing, and nine (8.3%) of the workers who received testing for influenza A(H5) received a positive result.
  - All nine cases were associated with mild illness, with conjunctivitis as the most common symptom.

Weekly / August 29, 2024 / 73(34);734–739

Cluster of Influenza A(H5) Cases Associated with Poultry Exposure at Two Facilities — Colorado, July 2024

- **What are the implications for public health practice?**
  - As the prevalence of highly pathogenic avian influenza A(H5N1) virus clade 2.3.4.4b genotype B3.13 increases, U.S. public health agencies should prepare to rapidly investigate and respond to illness in agricultural workers, including workers with limited access to health care.

Weekly / August 29, 2024 / 73(34);734–739

Highly pathogenic avian influenza (HPAI) A(H5) CDC Recommendations

- **People should avoid unprotected exposures to sick or dead animals**
  - Including wild birds, poultry, other domesticated birds, and other wild or domesticated animals (including cows).
- **People should also avoid unprotected exposures**
  - To animal feces, bedding, unpasteurized milk, or materials that have been touched by, or close to, birds or other animals with suspected or confirmed A(H5N1) virus.
- **CDC has interim recommendations** for prevention, monitoring, and public health investigations of A(H5N1) virus infections in people.
- CDC also has updated recommendations for worker protection and use of PPE.
- **Following these recommendations is central to reducing a person's risk and containing the overall public health risk.**

For immediate release: July 25, 2024 http://www.cdc.gov/media

Perspective

August 8, 2024

Déjà Vu All Over Again — Refusing to Learn the Lessons of Covid-19

Michael S. Sinha, M.D., J.D., M.P.H., Wendy E. Parmet, J.D., and Gregg S. Gonsalves, Ph.D.

COVID-19 Update for the United States

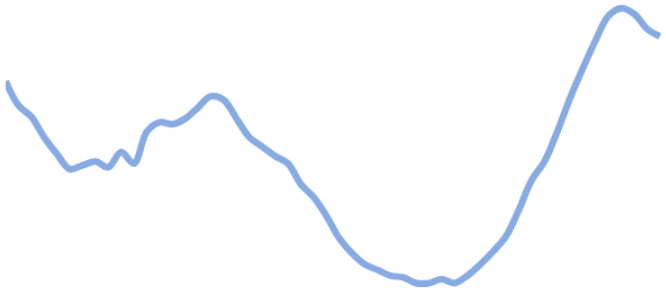
Early Indicators

Test Positivity

% Test Positivity

16.3%

Week ending August 31, 2024
Previous week 16.7%



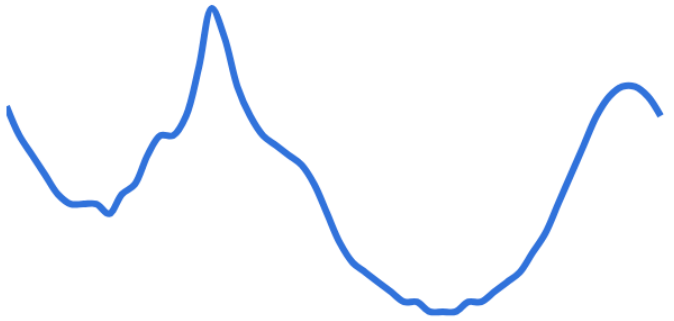
Sep 9, 2023 Aug 31, 2024

Emergency Department Visits

% Diagnosed as COVID-19

2.3%

Week ending August 31, 2024
Previous week 2.5%



Sep 9, 2023 Aug 31, 2024

These early indicators represent a portion of national COVID-19 tests and emergency department visits. Wastewater information also provides early indicators of spread.

COVID-19 Update for the United States

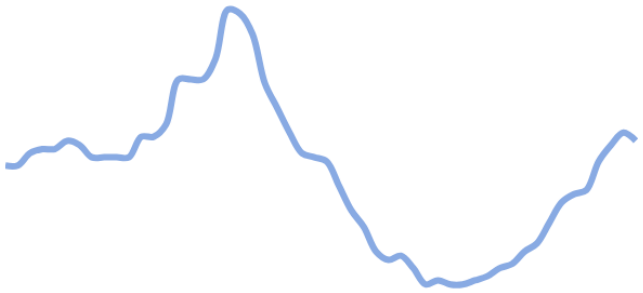
Severity Indicators

Hospitalizations

Rate per 100,000 population

4.6

Week ending August 17, 2024
Previous week 4.8



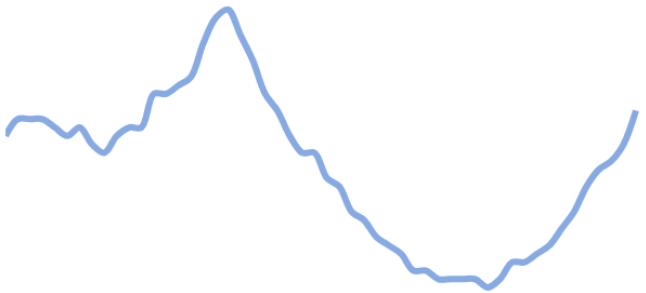
Aug 26, 2023 Aug 17, 2024

Deaths

% of All Deaths in U.S. Due to COVID-19

2.6%

Week ending August 31, 2024
Previous week 2.2%

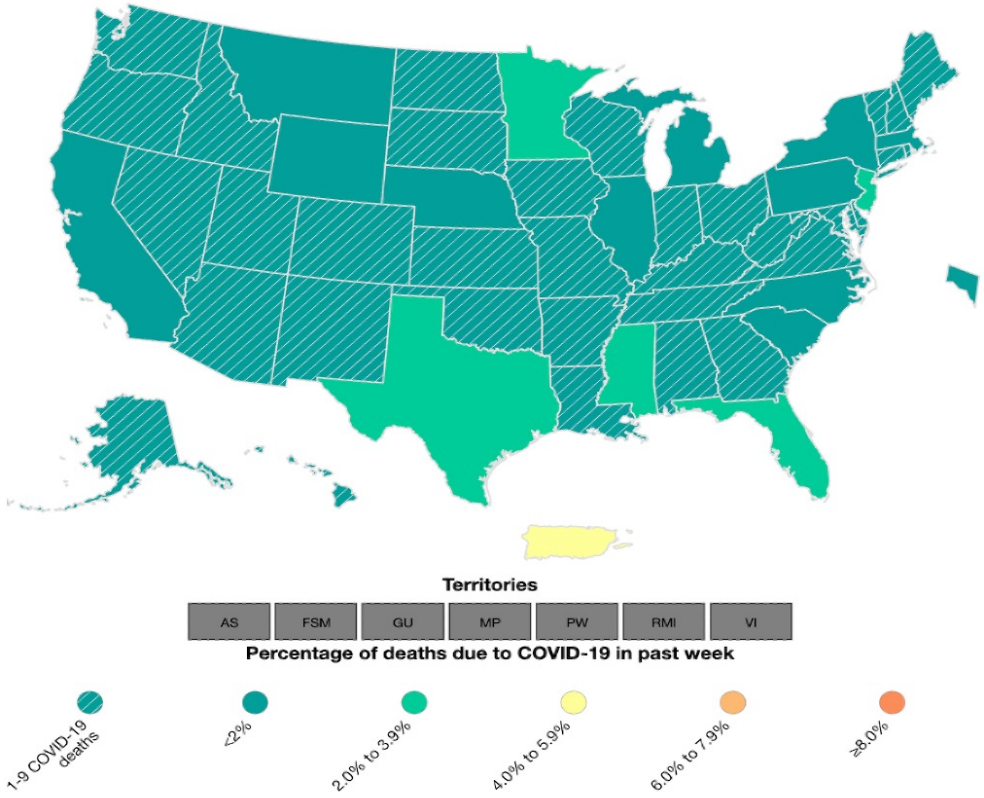


Sep 9, 2023 Aug 31, 2024

CDC | Test Positivity data through: August 31, 2024; Emergency Department Visit data through: August 31, 2024; Hospitalization data through: August 17, 2024; Death data through: August 31, 2024.

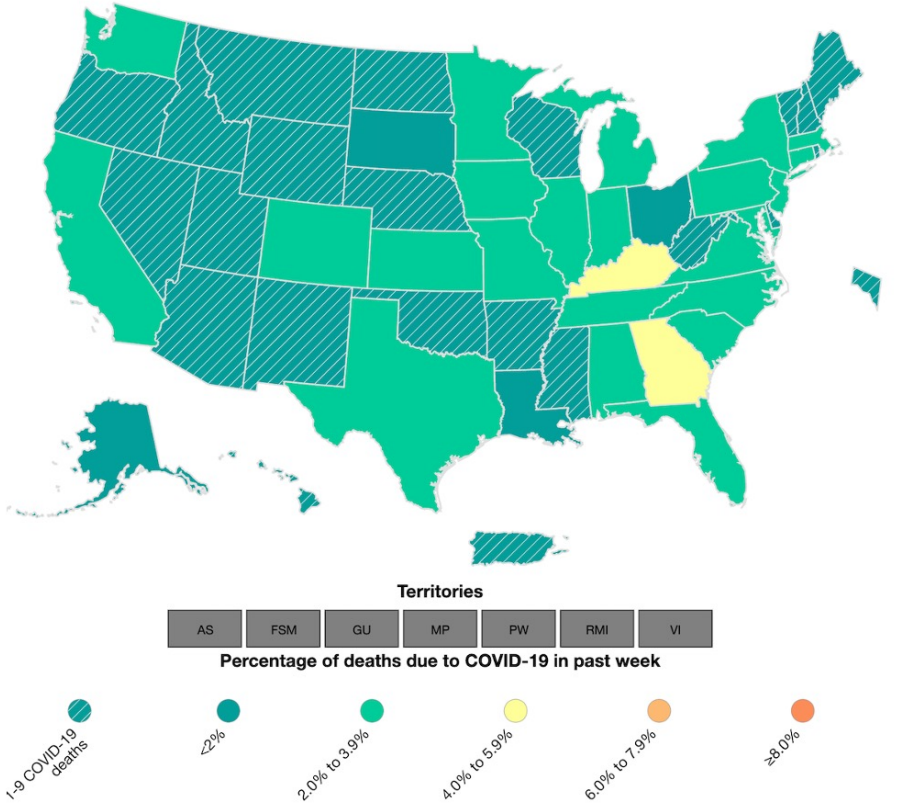
Percentage of Provisional Deaths Due to COVID-19 in the Past week, by State/Territory-United States

Week of August 15



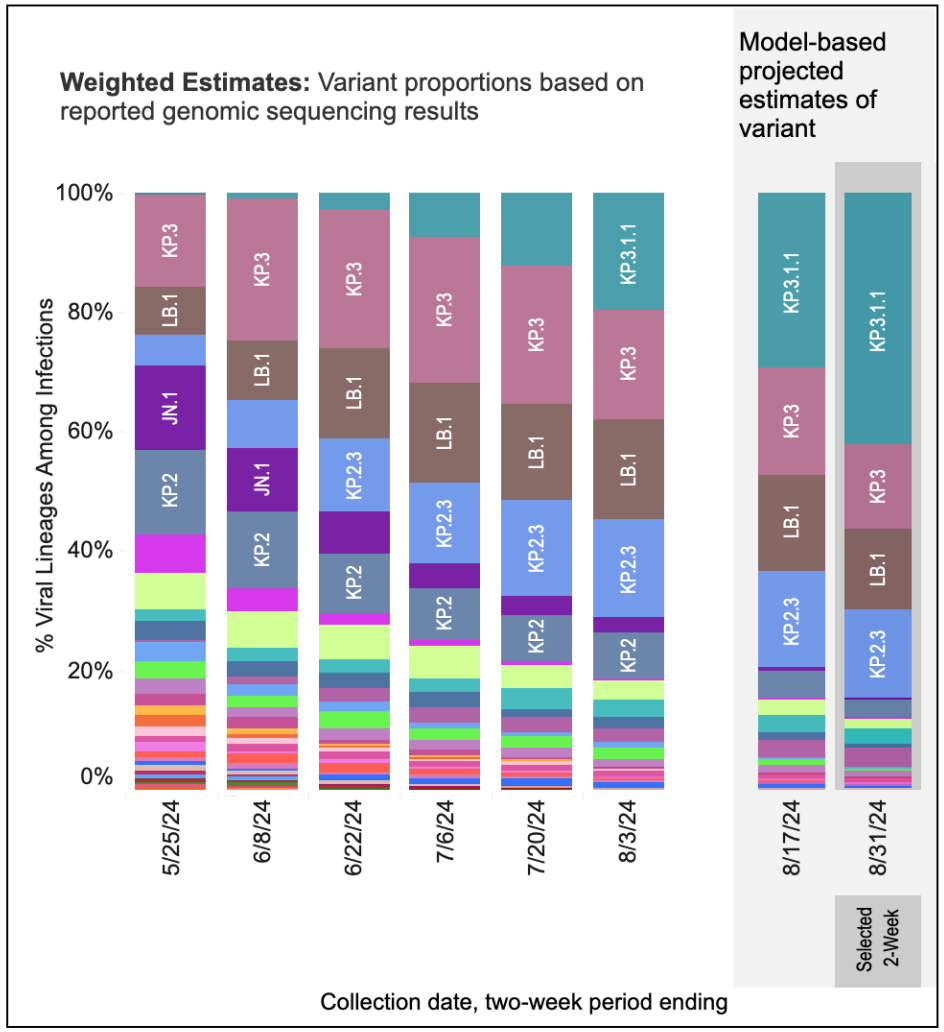
Centers for Disease Control and Prevention. COVID Data Tracker. Atlanta, GA: U.S. Department of Health and Human Services, CDC; 2024, August 15. https://covid.cdc.gov/covid-data-tracker

Week of September 12



Centers for Disease Control and Prevention. COVID Data Tracker. Atlanta, GA: U.S. Department of Health and Human Services, CDC; 2024, September 12. https://covid.cdc.gov/covid-data-tracker

Variant Proportions



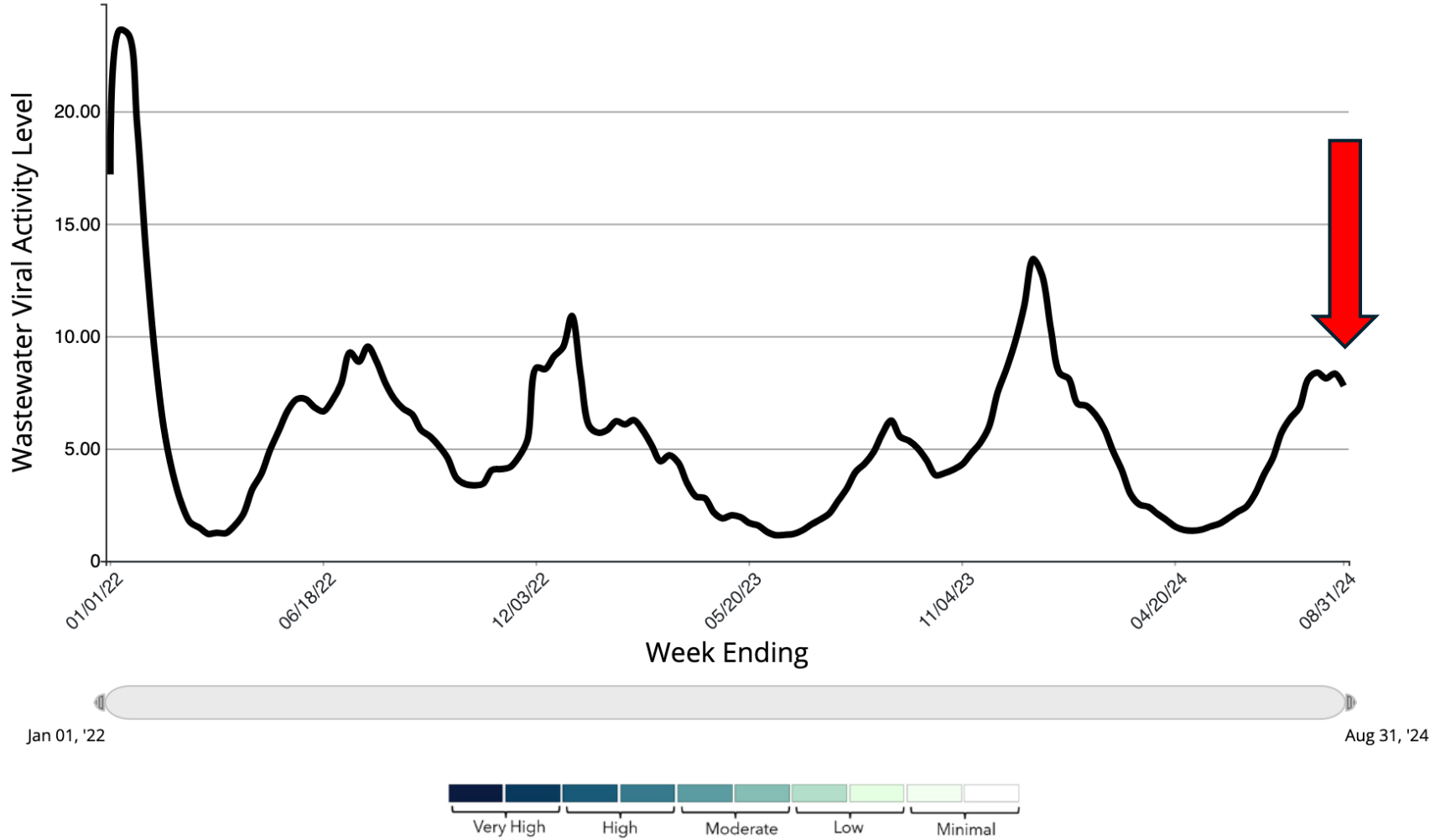
USA

WHO label	Lineage #	%Total	95%PI
Omicron	KP.3.1.1	42.2%	37.7-46.9%
	KP.2.3	14.6%	12.4-17.0%
	KP.3	14.2%	12.8-15.8%
	LB.1	13.5%	11.3-16.0%
	KP.2	3.1%	2.4-4.0%
	LP.1	3.1%	2.0-4.7%
	KP.1.1.3	2.6%	1.9-3.6%
	KP.1.1	2.0%	1.5-2.6%
	KS.1	1.0%	0.6-1.7%
	KP.2.15	0.8%	0.4-1.4%
	LF.3.1	0.7%	0.5-1.1%
	JN.1.16.1	0.7%	0.5-0.9%
	JN.1.18	0.5%	0.4-0.8%
	KP.4.1	0.3%	0.1-0.7%
	JN.1	0.2%	0.1-0.3%
	JN.1.11.1	0.2%	0.1-0.3%
	XDV.1	0.1%	0.0-0.2%
	KW.1.1	0.1%	0.0-0.2%
	JN.1.16	0.1%	0.0-0.1%
	KP.1.2	0.0%	0.0-0.1%
	JN.1.7	0.0%	0.0-0.1%
	KQ.1	0.0%	0.0-0.0%
	JN.1.13.1	0.0%	0.0-0.0%
	JN.1.4.3	0.0%	0.0-0.0%
	XDP	0.0%	0.0-0.0%
	JN.1.8.1	0.0%	0.0-0.0%

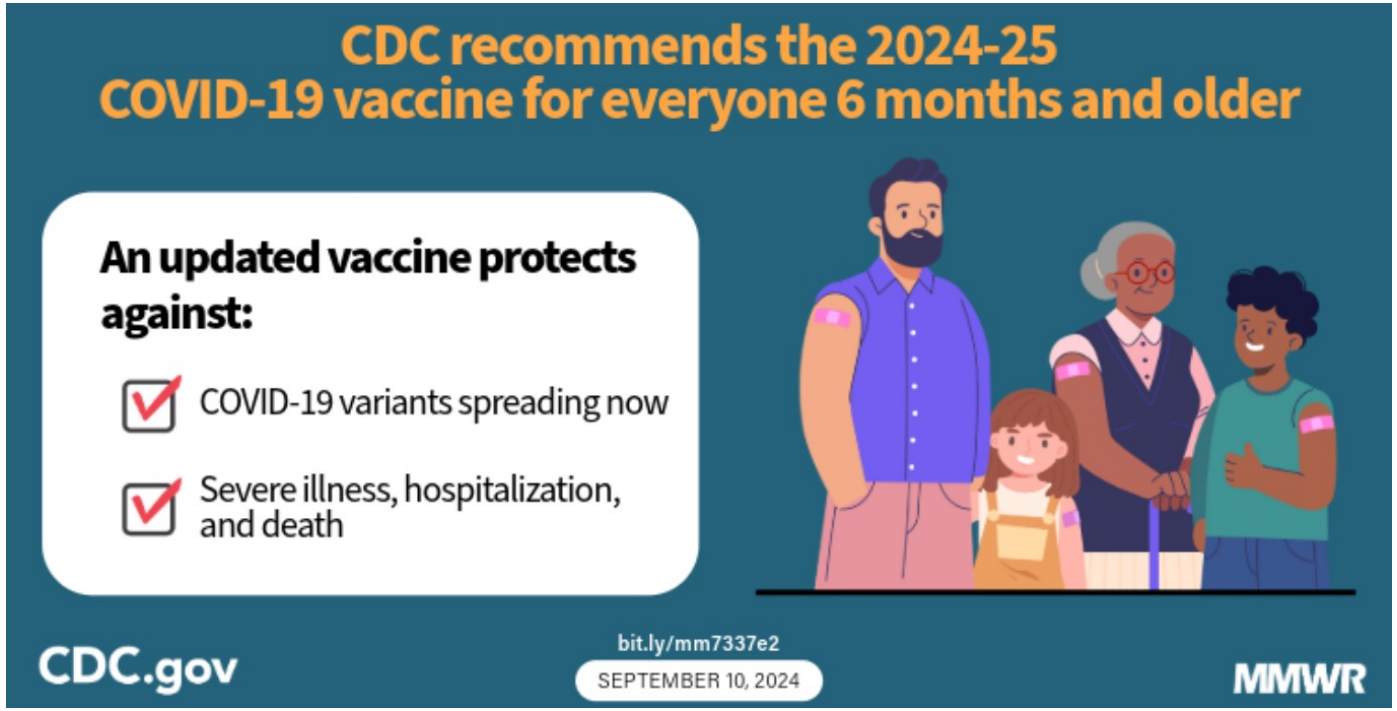
** These data include Nowcast estimates, which are modeled projections that may differ from weighted estimates generated at later dates
# Enumerated lineages are US VOC and lineages circulating above 1% nationally in at least one 2-week period. "Other" represents the aggregation of lineages which are circulating <1% nationally during a 2-week periods displayed. While all lineages are tracked by CDC, those named lineages not enumerated in this graphic are aggregated with their parent lineages, based on Pango lineage definitions, described in more detail here: https://web.archive.org/web/20240116214031/https://www.pango.network/the-pango-nomenclature-system/statement-of-nomenclature-rules.

Nowcast Estimates for 8/18/2024 – 8/31/2024 by HHS Region

COVID-19 Wastewater Viral Activity Level Over Time, United States



Use of COVID-19 Vaccines for Persons Aged ≥6 Months: Recommendations of the Advisory Committee on Immunization Practices — United States, 2024–2025



Panagiotakopoulos L, Moulia DL, Godfrey M, et al. Use of COVID-19 Vaccines for Persons Aged ≥6 Months: Recommendations of the Advisory Committee on Immunization Practices — United States, 2024–2025. MMWR Morb Mortal Wkly Rep. ePub: 10 September 2024. DOI: http://dx.doi.org/10.15585/mmwr.mm7337e2

Use of COVID-19 Vaccines for Persons Aged ≥6 Months: Recommendations of the Advisory Committee on Immunization Practices — United States, 2024–2025

What is already known about this topic?

- The 2023–2024 COVID-19 vaccines provided protection against SARS-CoV-2 XBB-sublineage strains;
- However, these strains are no longer predominant in the United States.

What is added by this report?

- On June 27, 2024, the ACIP recommended 2024–2025 COVID-19 vaccination with a FDA authorized and approved vaccine for all persons aged ≥6 months.
- In August 2024, the FDA approved and authorized the Omicron JN.1 lineage (JN.1 and KP.2), 2024–2025 COVID-19 vaccines by Moderna and Pfizer-BioNTech (KP.2 strain) and Novavax (JN.1 strain).

What are the implications for public health practice?

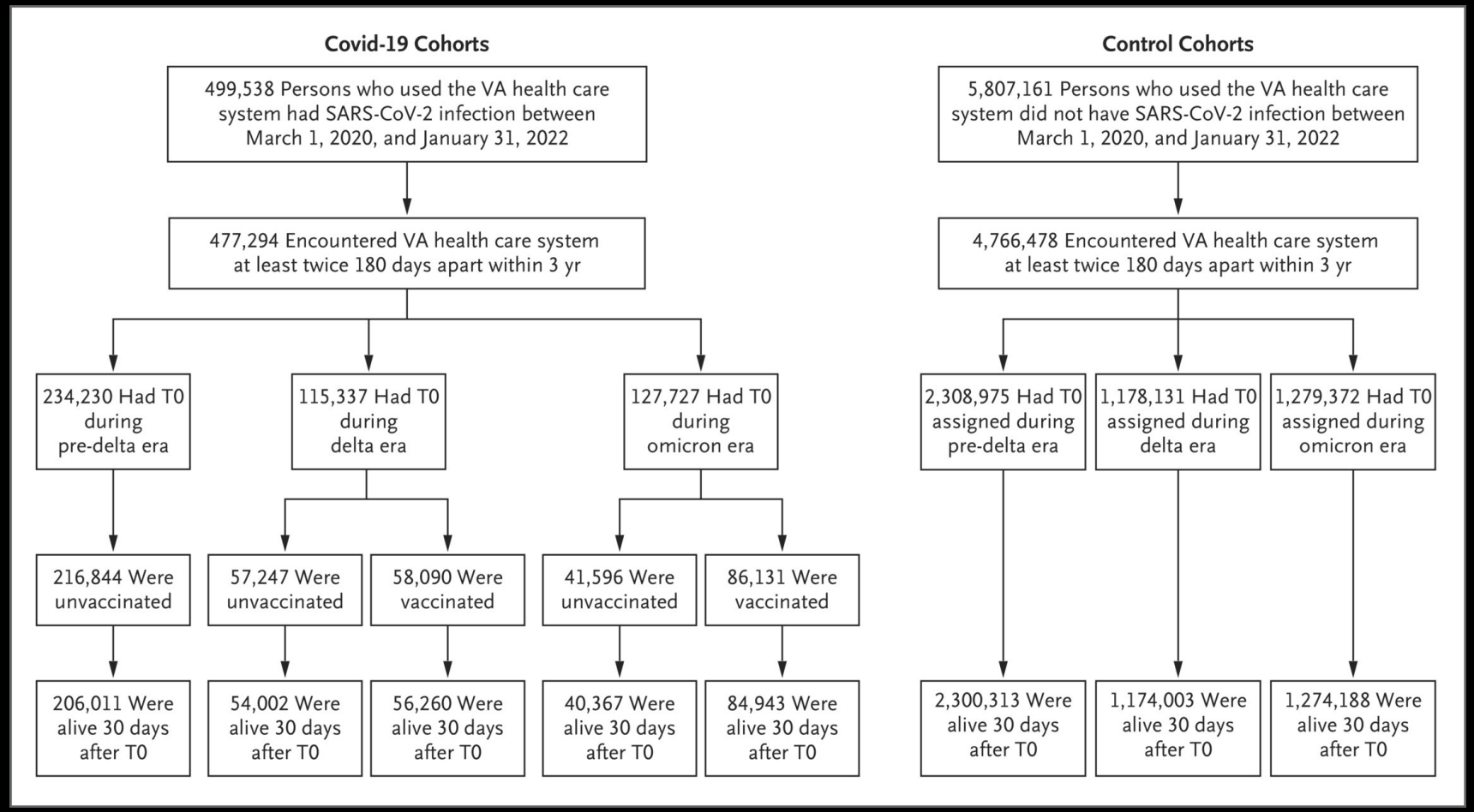
- The 2024–2025 COVID-19 vaccines are recommended for all persons aged ≥6 months to target currently circulating SARS-CoV-2 strains and provide additional protection against severe COVID-19–associated illness and death.

Panagiotakopoulos L, Moulia DL, Godfrey M, et al. Use of COVID-19 Vaccines for Persons Aged ≥6 Months: Recommendations of the Advisory Committee on Immunization Practices — United States, 2024–2025. MMWR Morb Mortal Wkly Rep. ePub: 10 September 2024. DOI: http://dx.doi.org/10.15585/mmwr.mm7337e2

Postacute Sequelae of SARS-CoV-2 Infection in the Pre-Delta, Delta, and Omicron Eras

N Engl J Med, Volume 391(6):515-525, August 8, 2024

Study Cohorts.



Xie Y et al. N Engl J Med2024;391:515-525

The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med, Volume 391(6):515-525, August 8, 2024

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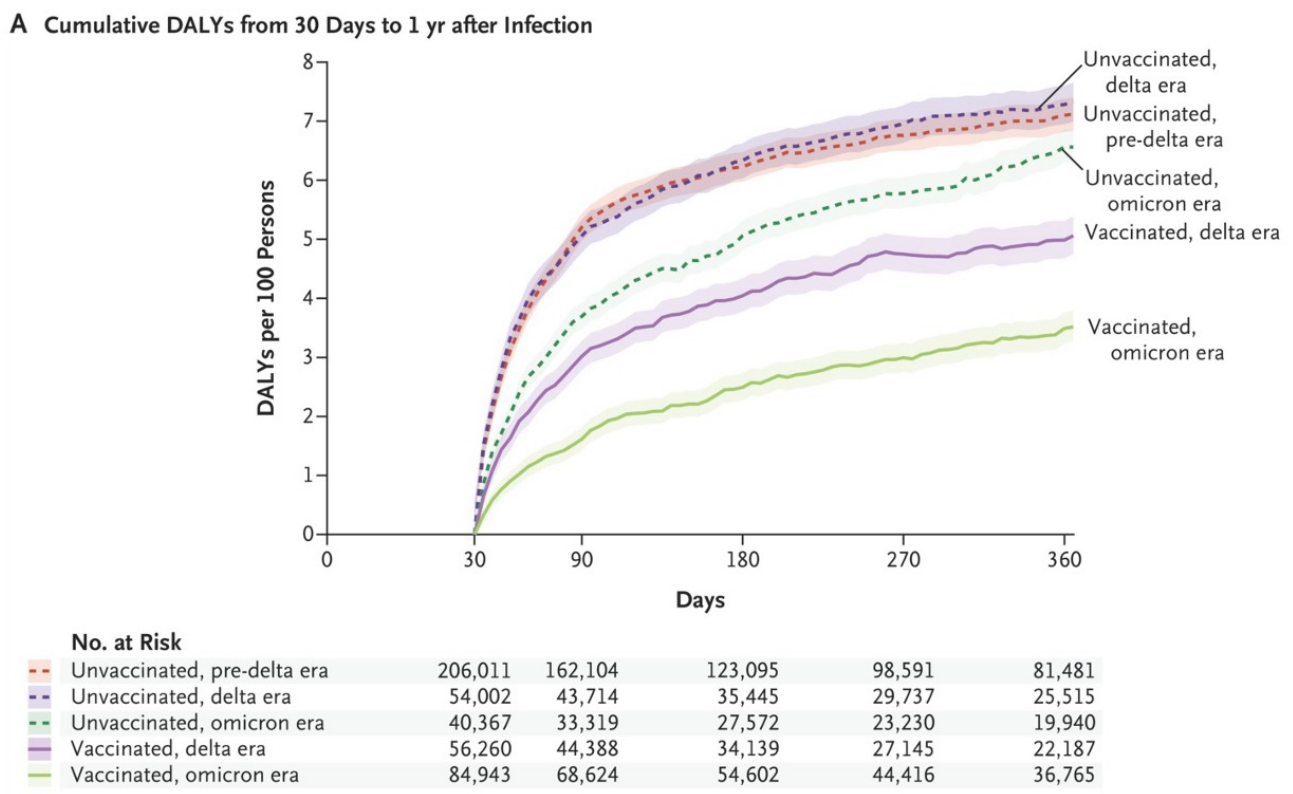

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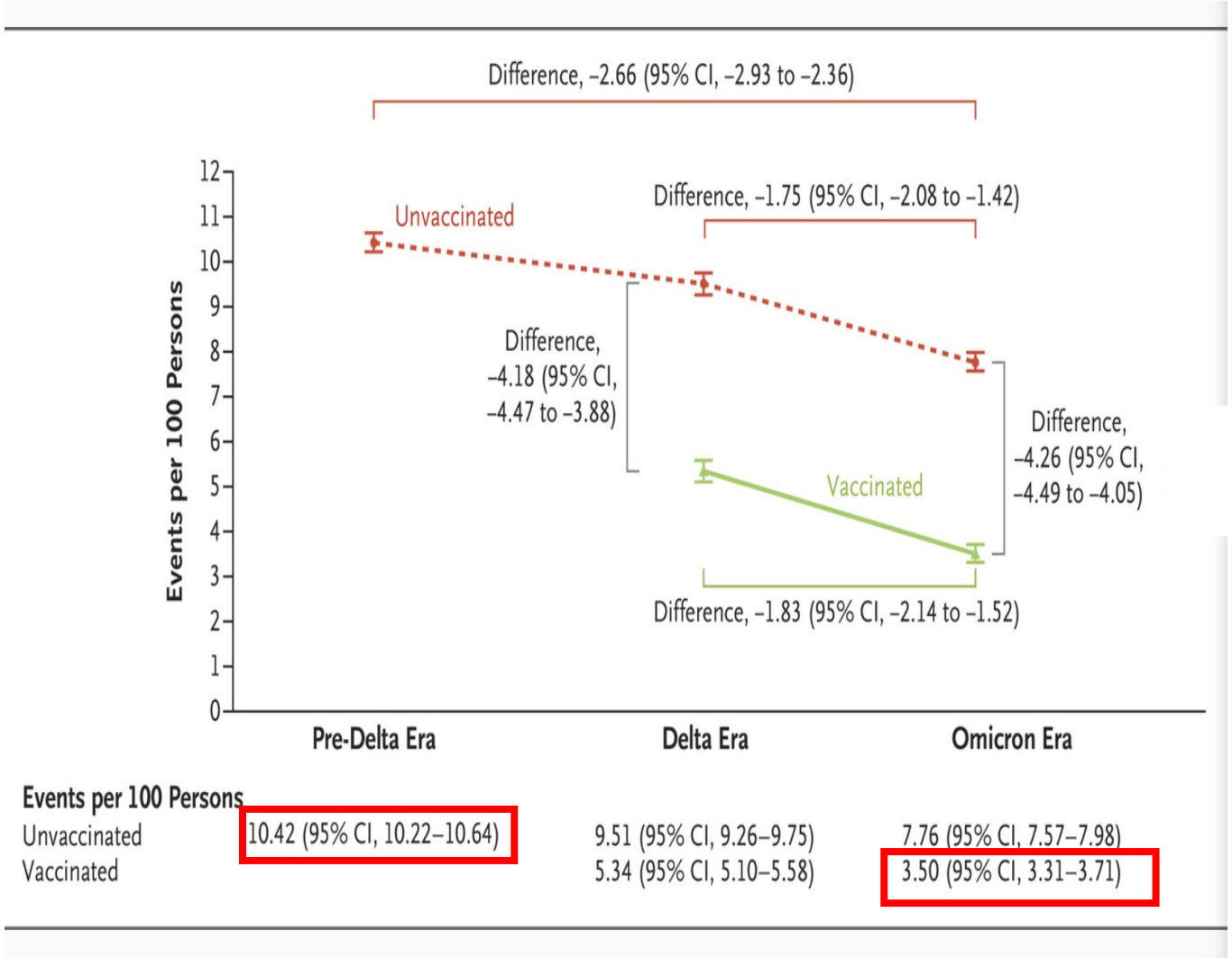


N Engl J Med, Volume 391(6):515-525, August 8, 2024

In this study, the risk of postacute sequelae decreased over time but remained substantial even among vaccinated persons infected in the omicron era

Viral Variants, Vaccinations, and Long Covid New Insights

- Vaccinations can prevent many but not all cases of long Covid
- Viral variants influence the risk of PASC
- New cases of PASC may continue unabated
- Changes in the clinical presentation of long Covid are a function of “points in time”
- Limitations:
  - This study provides a snapshot across only the first 2 years of the pandemic (March 2020 through January 2022)
  - Focuses primarily on male U.S. veterans
  - Due to the nature of the study (EHR data), confounding variables may have been missed and lead to the misclassification of SARS- CoV-2 infection status

NEJM 391;6: August 8, 2024

Autoimmune Sequelae After Delta or Omicron Variant SARS-CoV-2 Infection in a Highly Vaccinated Cohort

This study aimed to estimate the 300-day risk of new-incident autoimmune sequelae after SARS-CoV-2 Delta (B.1.617.2) and Omicron BA.1 or BA.2 variant infection

Adults who received COVID-19 vaccines and boosters compared with a contemporary control group without infection.

JAMA Netw Open. 2024;7(8):e2430983.doi:10.1001/jamanetworkopen.2024.30983

Autoimmune Sequelae After Delta or Omicron Variant SARS-CoV-2 Infection in a Highly Vaccinated Cohort

Table 2. Risks and Excess Burdens of Prespecified New-Incident Autoimmune Diagnoses in SARS-CoV-2 Cases and Controls During Delta and Omicron BA.1 or BA.2 Variant Periods

Autoimmune diagnosis	Cases with autoimmune diagnosis, No. (%)[a]	Cases, No.[a]	Controls with autoimmune diagnosis, No. (%)[a]	Controls, No.[a]	Excess burden, weighted, per 1000 persons (95% CI)[b]	AHR (95% CI)[c,d]	*P* value
Delta variant period							
Systemic lupus erythematosus	2 (<0.01)	104 125	47 (0.01)	666 367	−0.04 (−0.10 to 0.02)	0.31 (0.08 to 1.30)	.11
Rheumatoid arthritis	34 (0.03)	103 902	250 (0.04)	665 098	−0.06 (−0.24 to 0.11)	0.83 (0.58 to 1.20)	.33
Sjögren syndrome	1 (<0.01)	104 162	11 (<0.01)	666 463	−0.01 (−0.04 to 0.03)	0.54 (0.07 to 4.25)	.56
Systemic sclerosis	1 (<0.01)	104 170	6 (<0.01)	666 535	NA[e]	NA[e]	NA[e]
Dermatomyositis or polymyositis	0	104 168	28 (<0.01)	666 515	NA[e]	NA[e]	NA[e]
Other connective tissue diseases[f]	2 (<0.01)	104 169	8 (<0.01)	666 531	0.01 (−0.03 to 0.05)	1.90 (0.40 to 9.13)	.42
Vasculitis	2 (<0.01)	104 144	37 (0.01)	666 363	−0.04 (−0.10 to 0.02)	0.32 (0.08 to 1.33)	.12
Inflammatory bowel disease	66 (0.06)	103 806	422 (0.06)	664 169	−0.03 (−0.27 to 0.21)	0.95 (0.73 to 1.24)	.71
Spondyloarthropathies	10 (0.01)	104 125	64 (0.01)	666 265	−0.02 (−0.11 to 0.07)	0.83 (0.42 to 1.63)	.59
Psoriasis	31 (0.03)	103 883	210 (0.03)	665 114	−0.07 (−0.24 to 0.10)	0.81 (0.56 to 1.19)	.29
Bullous skin disorders	11 (0.01)	104 139	62 (0.01)	666 401	−0.03 (−0.12 to 0.07)	0.79 (0.42 to 1.51)	.48
Autoimmune thyroid disease	20 (0.02)	104 050	142 (0.02)	665 825	−0.02 (−0.16 to 0.11)	0.89 (0.55 to 1.43)	.63
Omicron BA.1 or BA.2 variant period							
Systemic lupus erythematosus	31 (0.01)	375 722	58 (0.01)	619 189	−0.01 (−0.06 to 0.05)	0.91 (0.58 to 1.41)	.66
Rheumatoid arthritis	151 (0.04)	374 920	221 (0.04)	618 087	0.05 (−0.06 to 0.17)	1.15 (0.93 to 1.41)	.20
Sjögren syndrome	21 (0.01)	375 833	18 (<0.01)	619 290	0.03 (−0.01 to 0.06)	1.91 (1.01 to 3.63)	.04
Systemic sclerosis	10 (<0.01)	375 873	12 (<0.01)	619 348	0.01 (−0.02 to 0.03)	1.25 (0.53 to 2.90)	.61
Dermatomyositis or polymyositis	6 (<0.01)	375 863	24 (<0.01)	619 338	−0.02 (−0.05 to 0.01)	0.40 (0.16 to 1.00)	.05
Other connective tissue diseases[f]	11 (<0.01)	375 859	8 (<0.01)	619 320	0.02 (−0.01 to 0.05)	2.44 (0.96 to 6.15)	.06
Vasculitis	22 (0.01)	375 772	26 (<0.01)	619 198	0.02 (−0.03 to 0.06)	1.35 (0.76 to 2.39)	.31
Inflammatory bowel disease	261 (0.07)	374 520	406 (0.07)	617 308	0.05 (−0.10 to 0.20)	1.08 (0.92 to 1.26)	.36
Spondyloarthropathies	44 (0.01)	375 711	74 (0.01)	619 113	−0.01 (−0.07 to 0.05)	0.93 (0.63 to 1.35)	.70
Psoriasis	121 (0.03)	374 902	203 (0.03)	618 085	−0.02 (−0.12 to 0.09)	0.95 (0.75 to 1.19)	.65
Bullous skin disorders	52 (0.01)	375 762	49 (0.01)	619 243	0.05 (−0.01 to 0.11)	1.57 (1.06 to 2.33)	.03
Autoimmune thyroid disease	106 (0.03)	375 426	170 (0.03)	618 744	−0.00 (−0.10 to 0.09)	0.98 (0.77 to 1.26)	.89

Abbreviations: AHR, adjusted hazard ratio; NA, not available.

[a] Numbers in each subcohort for each specific autoimmune diagnosis do not add up to the original number of SARS-CoV-2 cases and controls because, for estimation of risks for each new-incident autoimmune diagnosis, a subcohort of individuals without history of the diagnosis in the past 5 years was constructed.

[b] Excess burden greater than 0 denotes excess burden in a respective autoimmune diagnosis among infected cases vs controls.

[c] AHR greater than 1 denotes higher risk of a respective autoimmune diagnosis among cases vs controls.

[d] Each model was overlap weighted and regression adjusted based on demographic characteristics (age, sex, ethnicity), socioeconomic status (housing type), vaccination status (not fully vaccinated, fully vaccinated, fully vaccinated and received boosters), and comorbidities.

[e] Risks could not be estimated due to too few numbers of a new-incident autoimmune diagnosis for that subcategory.

[f] Included mixed connective tissue disease, Behçet disease, and polymyalgia rheumatica.

JAMA Netw Open. 2024;7(8):e2430983.doi:10.1001/jamanetworkopen.2024.30983

Autoimmune Sequelae After Delta or Omicron Variant SARS-CoV-2 Infection in a Highly Vaccinated Cohort

- **Findings**
  - In this cohort study of 1 766 036 adults in Singapore, no significantly elevated risk of autoimmune sequelae after infection from Delta and Omicron BA.1 or BA.2 variants was observed.
  - A modest increase in risk of inflammatory bowel disease and bullous skin disorders was found in the hospitalized subgroup during the predominance of the Omicron variant.
- **Meaning**
  - Findings of this study suggest that booster vaccination may mitigate the risk of long-term autoimmune sequelae after Omicron variant infection.

JAMA Netw Open. 2024;7(8):e2430983.doi:10.1001/jamanetworkopen.2024.30983

COVID-19 Updates

What is going on with vaccines?

- **After vaccination with the 2023-2024 vaccines** (XBB.1.5 variant)
  - Vaccine effectiveness peaked four weeks after vaccination and then gradually waned
  - Protection is for about 3-4 months

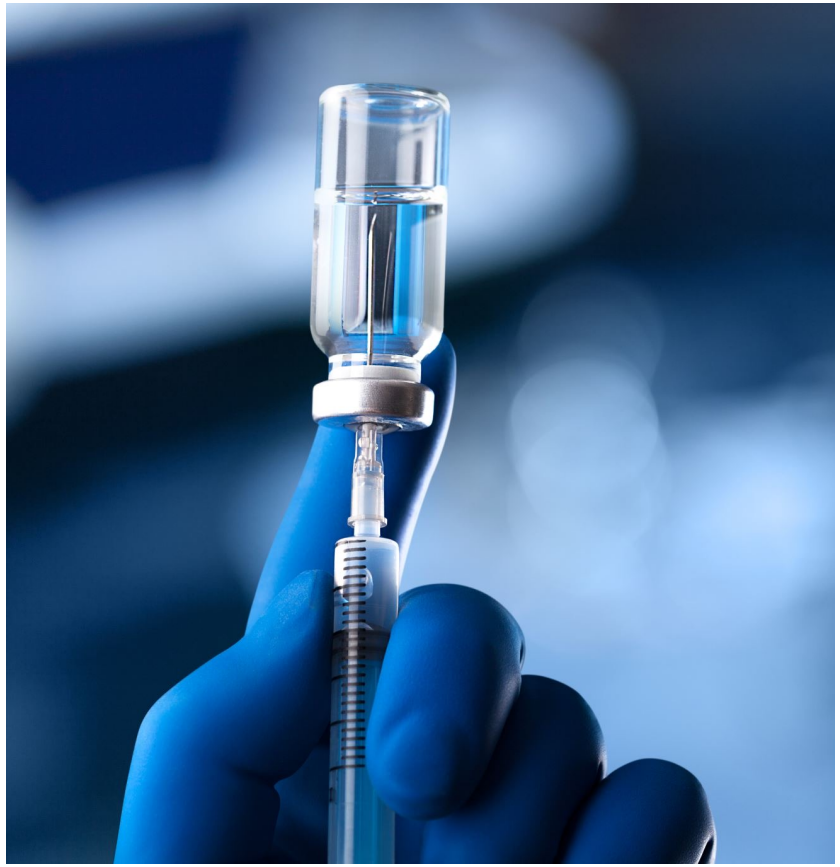
- **As of May, only 22.5% of adults** received the updated 2023-24 vaccine

COVID-19 Updates: *Recommendations*

- **On June 27, 2024, the ACIP recommended 2024–2025 COVID-19 vaccination**
  - For all persons aged ≥6 months.

- **In August 2024 the FDA approved and authorized the Omicron JN.1 lineage (JN.1 and KP.2), 2024–2025 COVID-19 vaccines**
  - By Moderna and Pfizer-BioNTech (KP.2 strain)
  - Novavax (JN.1 strain).

- **The CDC recommends that people in high-risk categories**
  - Get a second dose of vaccine at least four months after their last booster
  - Get the updated 2024-2025 vaccine once it is available.



COVID-19 Updates

What's going on with the variants?

SARS-CoV-2 KP.2.3, KP.3 and KP.3.1.1

- Accounted for most infections in the United States as of the first week of September.

The surge is occurring probably due to a:

- Greater transmissibility
- Partial escape from immunity
- Waning immunity from previous vaccinations and infections

COVID-19 Updates

What's going on with the clinical impact?

- **ED visits and hospitalizations** due to COVID-19 have increased
- **Deaths have increased to 2.6% in the last week of August but still remain far below** the weekly rates during previous surges

Week ending date in which the death occurred	All Deaths involving COVID-19 [1]	Deaths from All Causes	Percent of Expected Deaths [2]	Deaths involving Pneumonia [3]	Deaths involving COVID-19 and Pneumonia [3]	All Deaths involving Influenza [4]	Deaths involving Pneumonia, Influenza, or COVID-19 [5]
9/7/2024	535	22,921	45	1,270	200	14	1,617
8/31/2024	953	38,451	75	2,065	330	25	2,711
8/24/2024	1,041	46,831	93	2,546	405	26	3,205

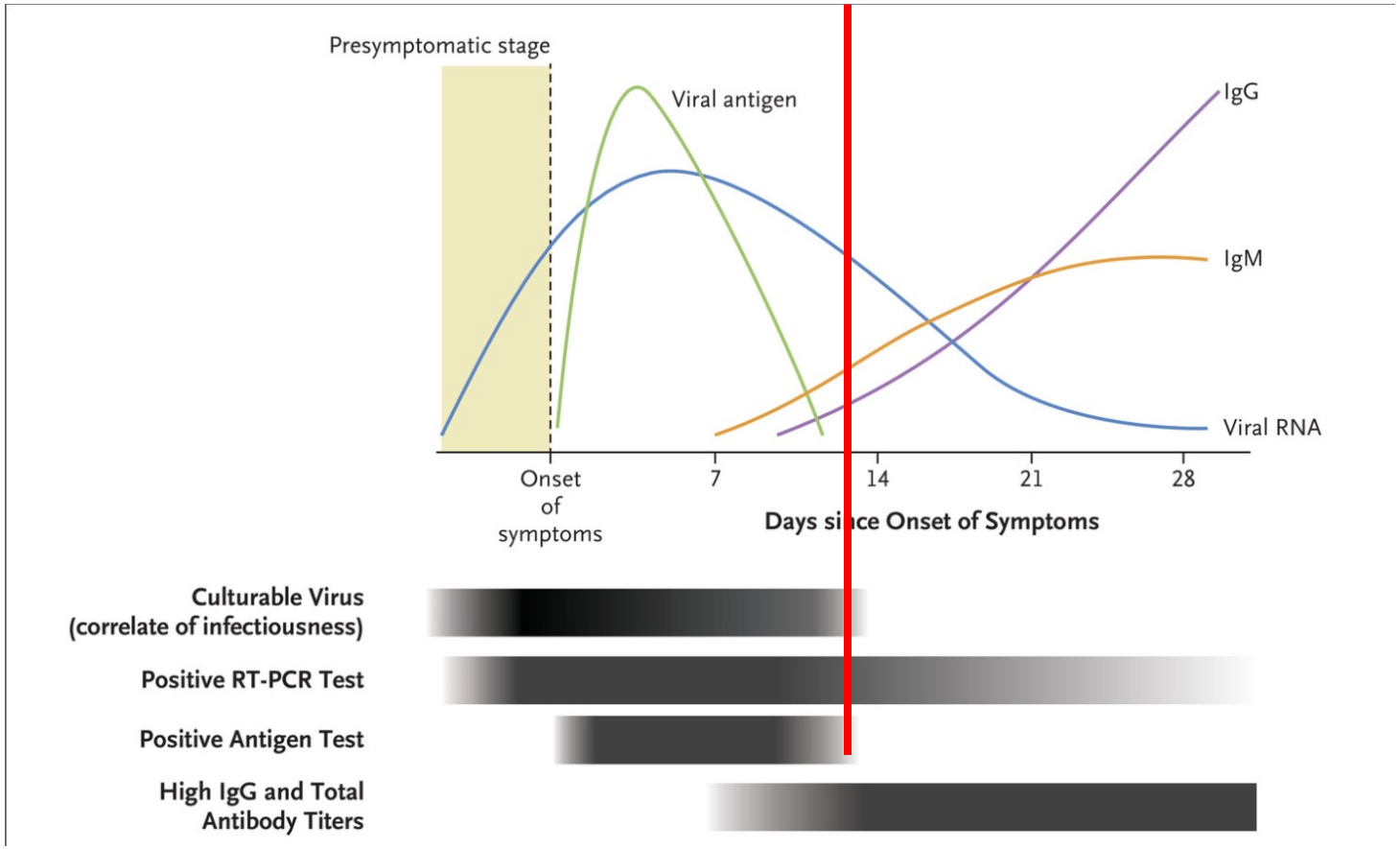
https://www.cdc.gov/nchs/nvss/vsrr/covid19/index.htm

COVID-19 Updates

- ***What is going on with masks?***
  - Especially useful in high-risk environments
  - Specially when the virus is surging
  - Specially indoors and crowded conditions
  - N95 > surgical > cloth

COVID-19 Updates

- ***What is going on with isolation?***
  - According to CDC guidelines you can resume normal activity if your symptoms have improved for 24 hours and you haven't had a fever in 24 hours without taking a fever suppressant, but you should continue to take extra precautions, like masking, for an additional five days.



N Engl J Med 2020;383: e120DOI: 10.1056/NEJMp2025631

COVID-19 Updates

- ***What is going on with treatment?***
  - Those in high-risk groups (people 65 and older or anyone over age 12 with a condition that is a risk factor for severe COVID, including diabetes, asthma, heart disease, obesity, or pregnancy) still benefit from an antiviral
  - It must be started within five to seven days of developing symptoms.


Questions?