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The Society for Healthcare Epidemiology of America

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The SHEA Podcast

SHEA & ASM on The Ramifications of Testing – Why Dx Stewardship is Critical
Dr. Francesca Lee interviews Dr. Laura Filkins from ASM and Dr. Dan Morgan from SHEA. Listen as our guests discuss how the overuse or misuse of diagnostic tests impacts patient care and the potential ramifications in a healthcare setting, as well as common challenges or misconceptions surrounding diagnostic testing.

Existing Public Health Infrastructure for HAI/AR
Dr. Jorge Salinas is joined by Joseph Perz and Melissa Cumming for a conversation on the existing public health infrastructure for addressing healthcare associated infections and antimicrobial resistance.

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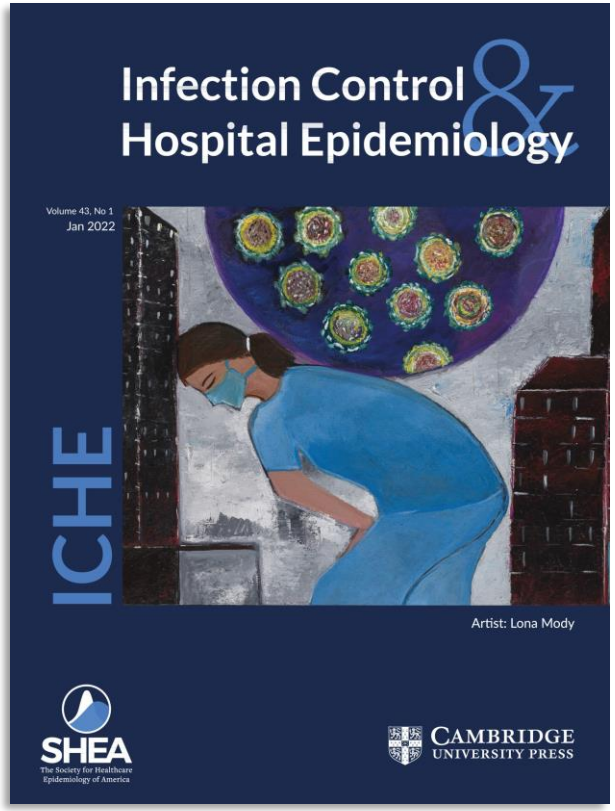

Infection Control & Hospital Epidemiology publishes scientifically authoritative, clinically applicable, peer-reviewed research on control and evaluation of the transmission of pathogens in healthcare institutions and on the use of epidemiological principles and methods to evaluate and improve the delivery of care. Major topics covered include infection control practices, surveillance, antimicrobial stewardship, cost-benefit analyses, resource use, occupational health, and regulatory issues.

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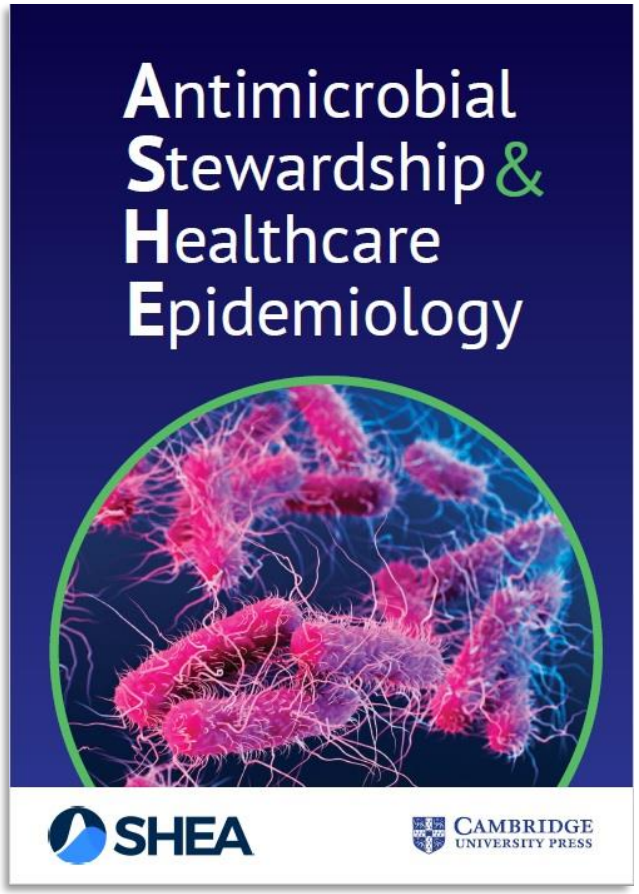
ASHE JOURNAL



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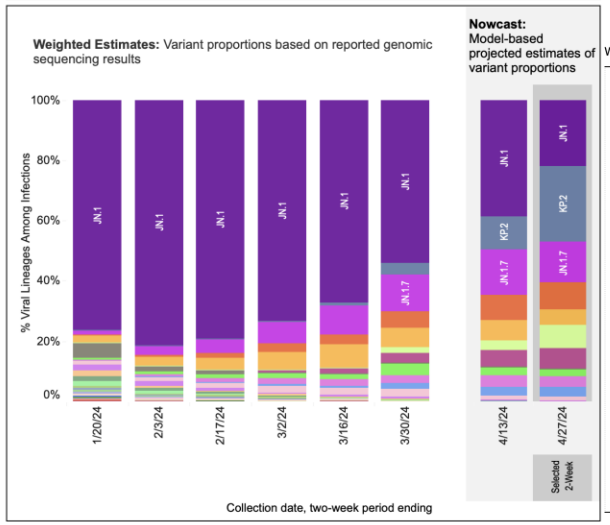
- Zoom Q&A and Chat

SHEA Town Hall 97
Overview

SARS-CoV-2 Variants, US, CDC

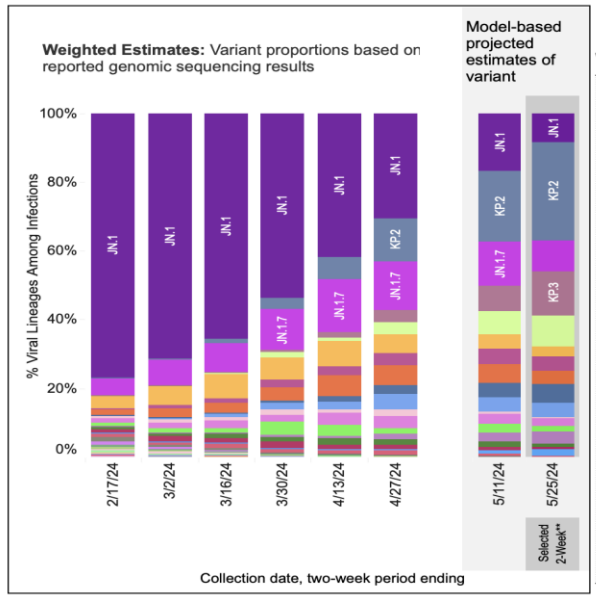


USA

WHO label	Lineage #	%Total	95%PI
Omicron	KP.2	24.9%	12.9-42.1%
	JN.1	22.0%	17.2-27.7%
	JN.1.7	13.7%	9.8-18.6%
	JN.1.13.1	8.8%	4.8-15.3%
	KP.1.1	7.5%	2.8-17.3%
	JN.1.16	6.9%	4.5-10.2%
	JN.1.8.1	5.3%	3.6-7.8%
	KQ.1	3.6%	2.1-6.1%
	JN.1.11.1	3.4%	1.9-5.8%
	JN.1.18	2.5%	1.6-3.9%
	BA.2	0.1%	0.0-0.5%
	GE.1	0.0%	0.0-0.1%
	BA.2.86	0.0%	0.0-0.1%
	JG.3	0.0%	0.0-0.0%
	XBB	0.0%	0.0-0.0%
	HV.1	0.0%	0.0-0.0%
	JD.1.1	0.0%	0.0-0.0%
	EG.5	0.0%	0.0-0.0%
	HK.3	0.0%	0.0-0.0%

* 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 all 2-week periods displayed.
** These data include Nowcast estimates, which are modeled projections that may differ from weighted estimates generated at later dates
# XDP was aggregated to JN.1.4(same spike as JN.1, but recombinants are always difficult). While all lineages are tracked by CDC, those named lineages not enumerated in this graphic are aggregated with their parent lineages, based o
Pango lineage definitions, described in more detail here: https://www.pango.network/the-pango-nomenclature-system/statement-of-nomenclature-rules/.

Data from 4/14/24 – 4/27/2024



USA

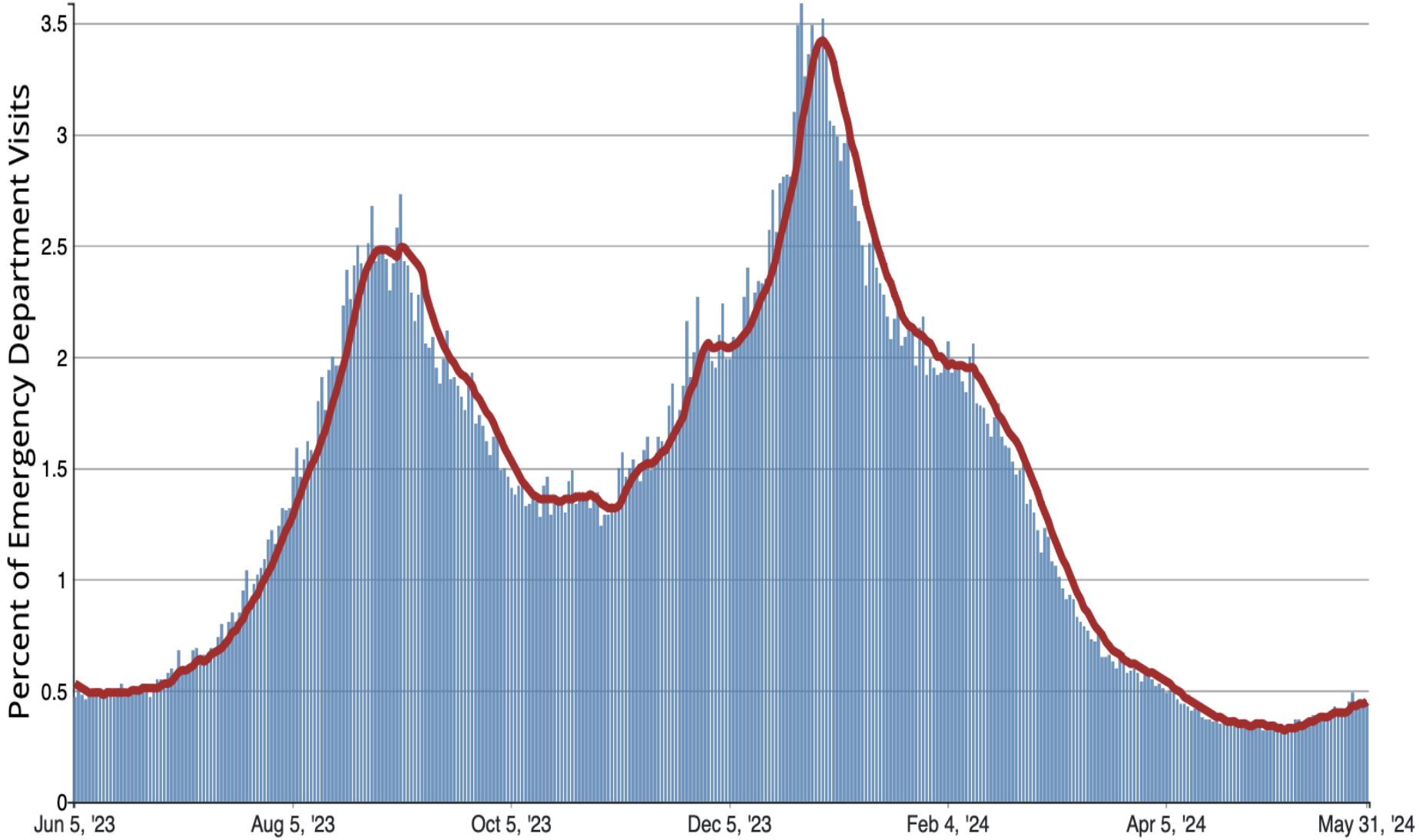
WHO label	Lineage #	%Total	95%PI
Omicron	KP.2	28.5%	23.0-34.7%
	KP.3	12.7%	7.8-19.6%
	JN.1.7	9.2%	7.3-11.6%
	KP.1.1	9.2%	6.5-12.8%
	JN.1	8.4%	6.8-10.3%
	JN.1.16.1	5.4%	3.3-8.8%
	JN.1.16	4.2%	2.6-6.8%
	JN.1.13.1	4.0%	2.8-5.7%
	JN.1.11.1	3.9%	2.6-5.9%
	KS.1	3.5%	2.0-6.1%
	JN.1.8.1	2.7%	2.0-3.6%
	KQ.1	2.2%	1.2-4.0%
	KW.1.1	1.7%	0.7-4.2%
	JN.1.18	1.7%	1.1-2.5%
	JN.1.32	1.0%	0.7-1.5%
	XDP	0.6%	0.4-1.0%
	KV.2	0.4%	0.2-0.7%
	GE.1	0.0%	0.0-0.0%
	BA.2	0.0%	0.0-0.1%
	BA.2.86	0.0%	0.0-0.0%
	JG.3	0.0%	0.0-0.0%
	HV.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 du
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 defini
described in more detail here: https://web.archive.org/web/20240116214031/https://www.pango.network/the-pango-nomenclature-system/statement-of-nomenclature-rules.

Data from 5/12/2024 – 5/25/2024

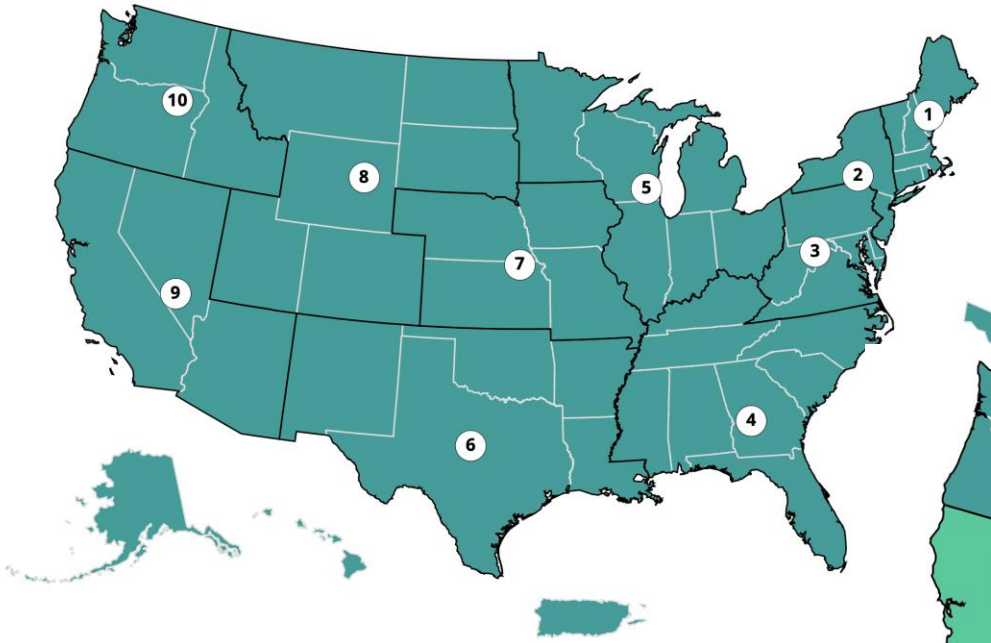
https://covid.cdc.gov/covid-data-tracker/#variant-proportions

EMERGENCY DEPARTMENT VISITS DUE TO COVID-19

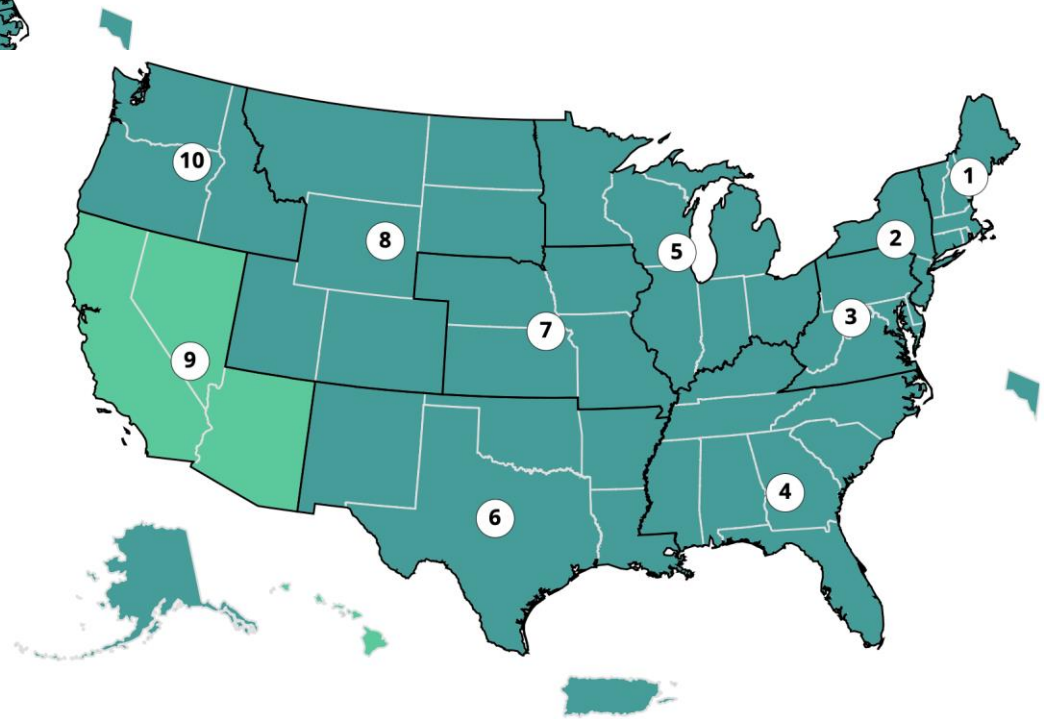


Source: CDC https://covid.cdc.gov/covid-data-tracker/#ed-visits_all_ages_combined 5-4-2024

COVID-19 Test Positivity Rates



Week of 5/5/2024

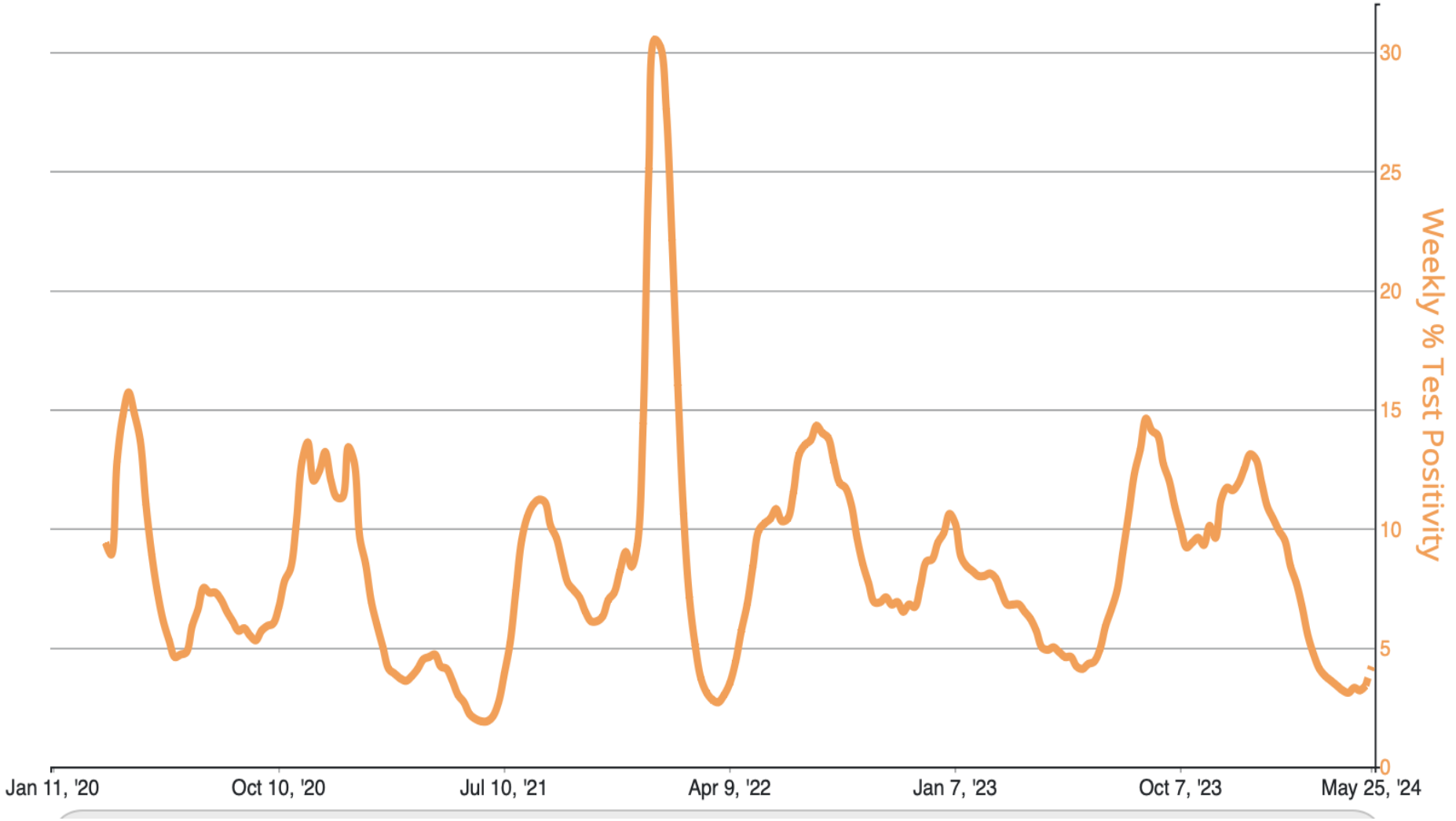


Week of 6/2/2024

Insufficient data | <5% | 5.0% to 9.9% | 10.0% to 14.9% | 15.0% to 19.9% | ≥20.0%

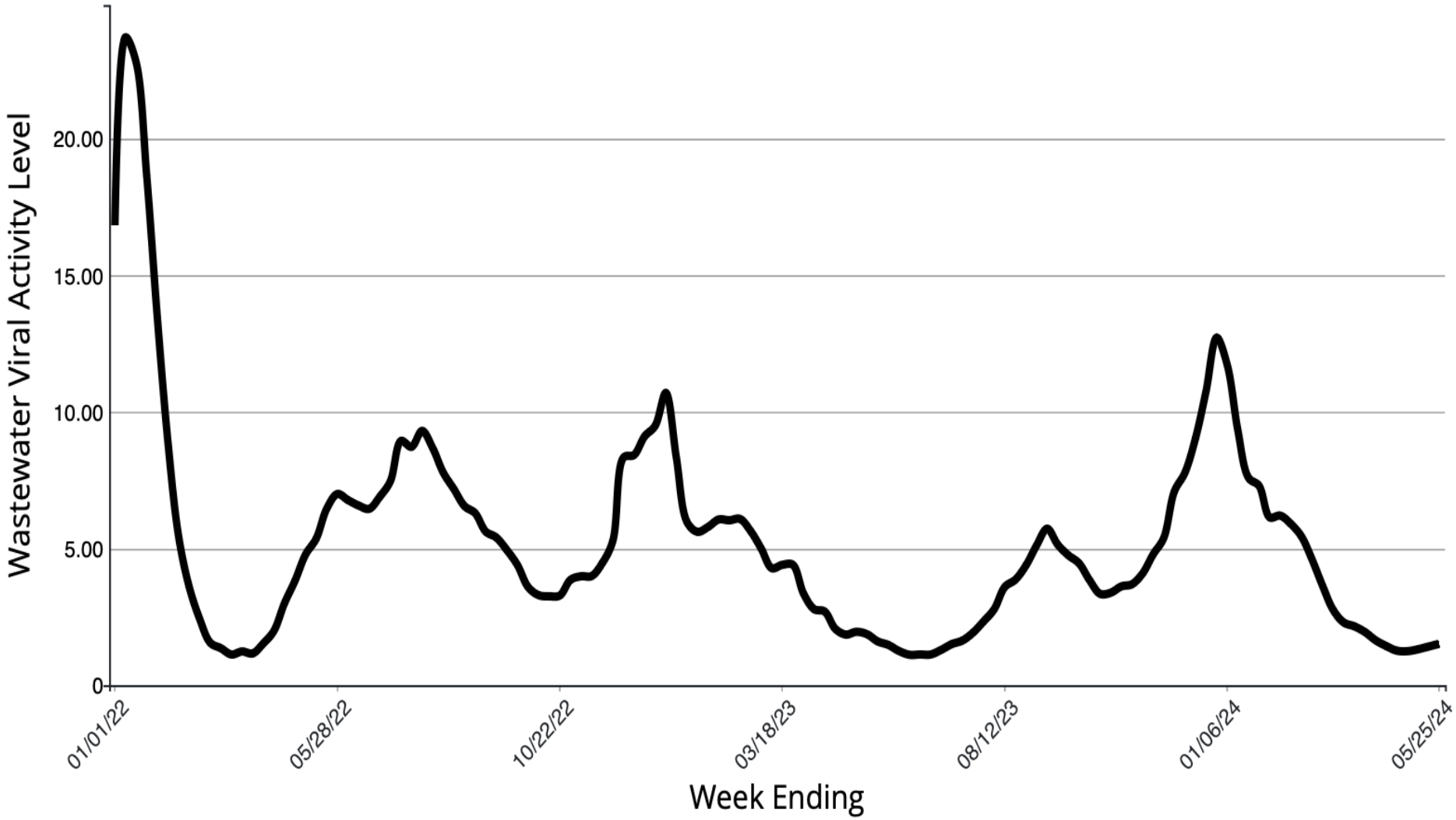
Source: CDC https://covid.cdc.gov/covid-data-tracker/#maps_positivity-week 5-4-2024

COVID-19 Rates of Test Positivity



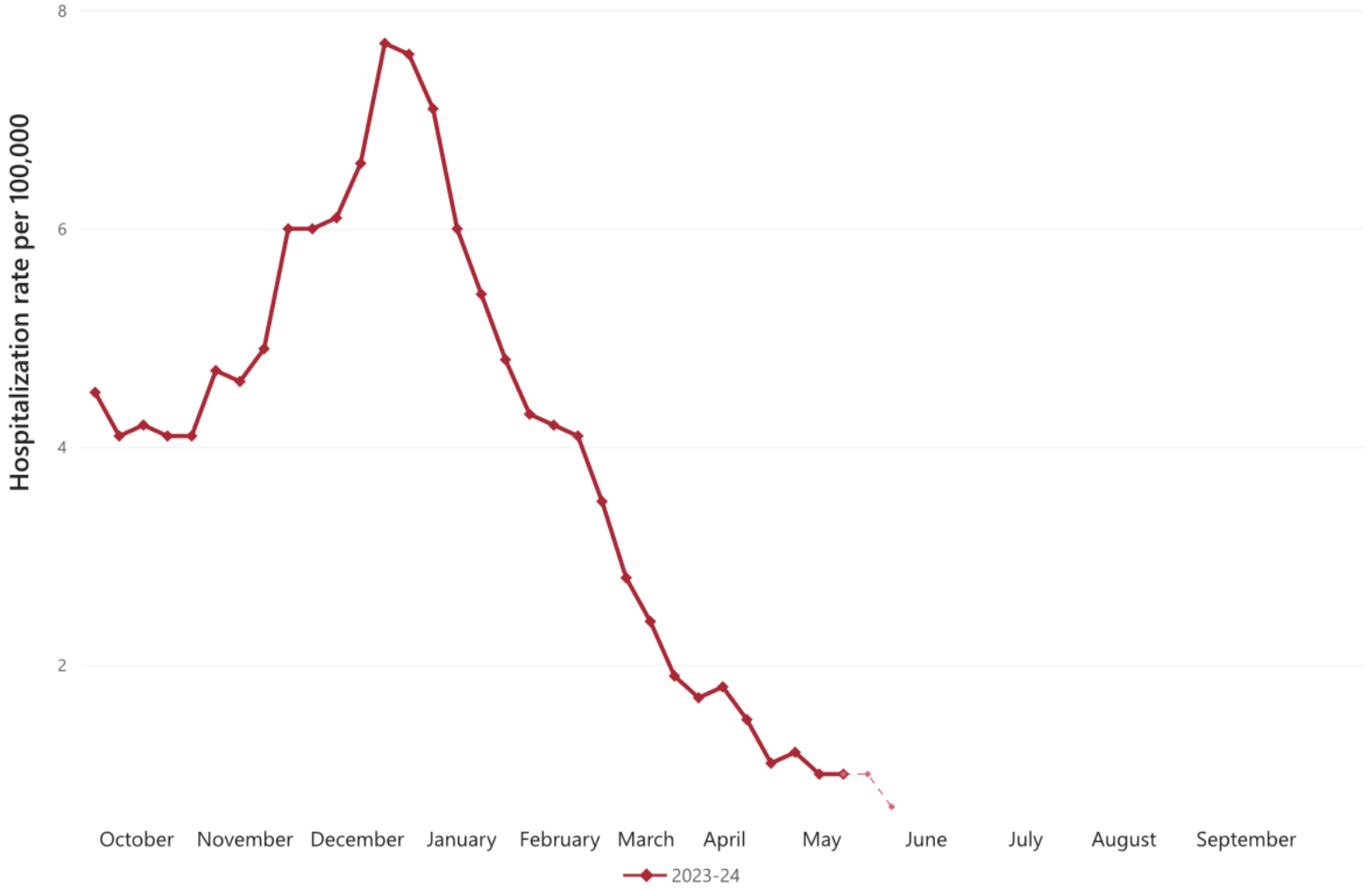
Source: CDC https://covid.cdc.gov/covid-data-tracker/#trends_weeklyhospitaladmissions_testpositivity_00
6/7-2024

COVID-19 WASTEWATER VIRAL ACTIVITY



Source: CDC https://covid.cdc.gov/covid-data-tracker/#wastewater-surveillance 5-4-2024

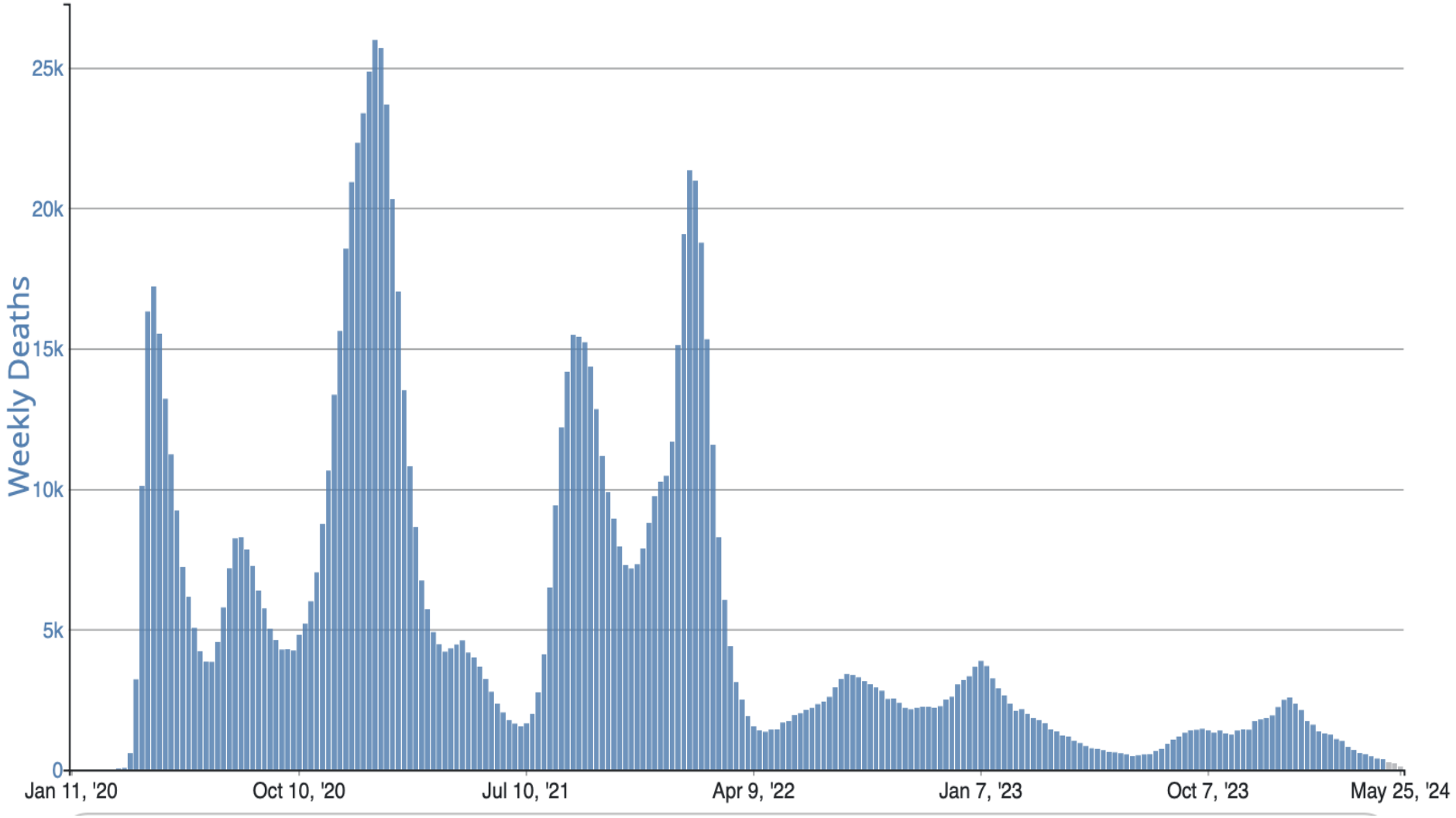
HOSPITALIZATIONS FOR COVID-19 IN THE UNITED STATES



Hospitalizations decreased by 30 % from our last Town Hall

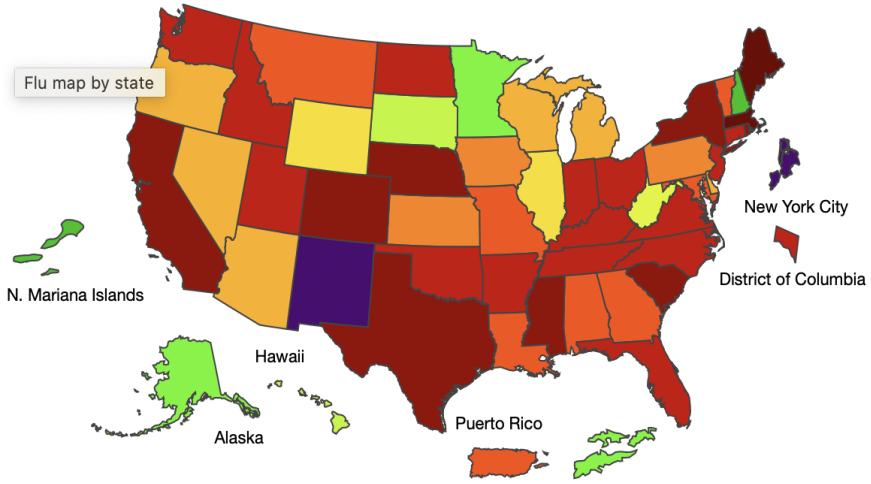
Source: https://covid.cdc.gov/covid-data-tracker/#covidnet-hospitalization-network 5-4-24

Weekly Provisional Deaths from COVID-19 in the United States

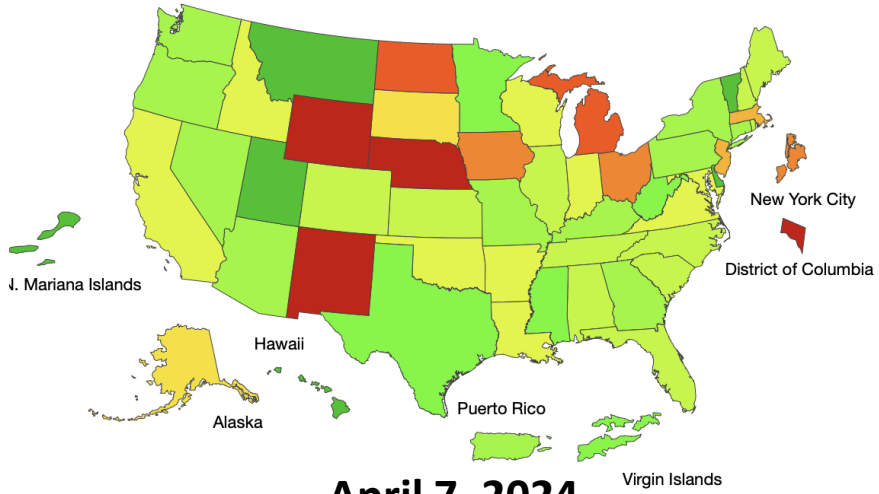


https://covid.cdc.gov/covid-data-tracker/#trends_weeklydeaths_select_00

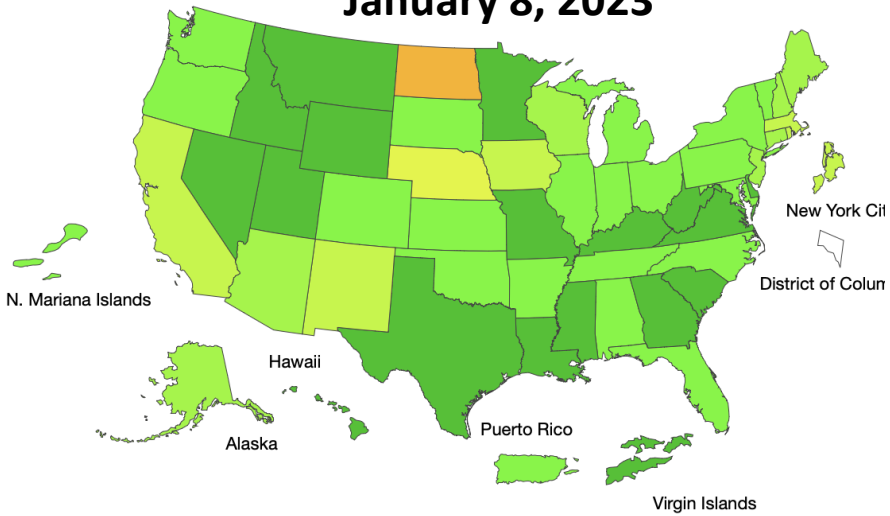
Influenza Activity by State in the United States



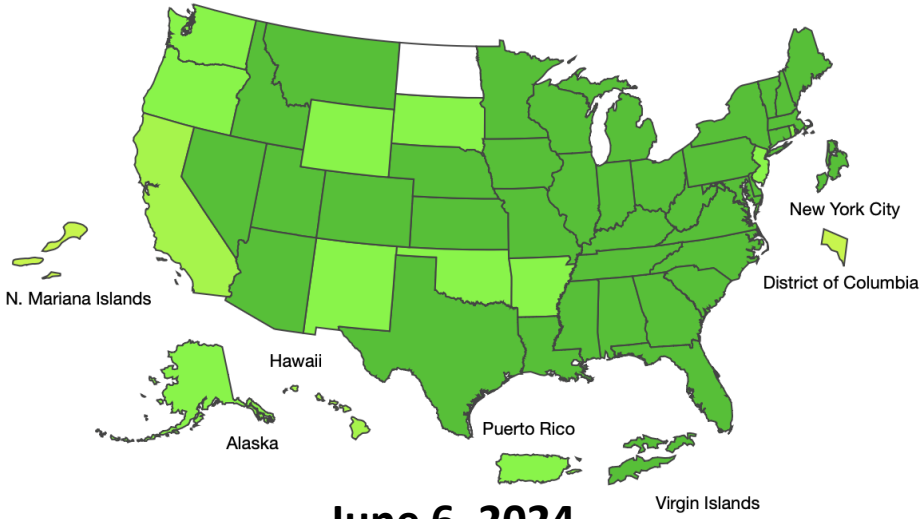
January 8, 2023



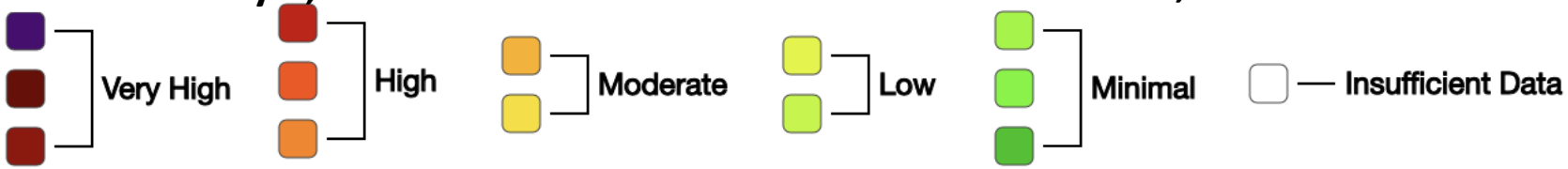
April 7, 2024



May 4, 2024



June 6, 2024



Source: CDC https://www.cdc.gov/flu/weekly/usmap.htm 6-6-2024

Today's Emerging Infectious Disease News

1. A study published in **e-Biomedicine** evaluated masks and respirators for source control of exhaled viral burdens in volunteer patients with COVID-19 infections and showed that all masks and respirators significantly reduced exhaled viral load, without fit tests or training, but N95 respirators outperformed all others significantly.
2. A paper in **Nature Communications** evaluated the safety, immunogenicity and efficacy of the self-amplifying mRNA ARCT-154 COVID-19 vaccine: in pooled phase 1, 2, 3a and 3b randomized, controlled trials, finding the efficacy to be 56.6% against SARS-CoV-2 infection and 95.3% against severe COVID-19.
3. A paper in **Nature** describes a new antibiotic (lolamicin) that has activity against a panel of more than 130 multidrug-resistant clinical isolates, while sparing the normal gut flora,.
4. A paper in the **Lancet Microbe** found that patients admitted to hospital with less favorable 5-day biomarker trajectories (i.e., low anti-nucleocapsid antibody, high plasma nucleocapsid antigen, and high first 5 day-inflammatory markers) had worse prognoses, identifying patients that might benefit from antiviral or anti-inflammatory escalation.
5. A study of 35 California hospitals and nursing homes published in **JAMA**, found that chlorhexidine bathing and nasal decolonization were associated with lower prevalence of multiply-drug-resistant organisms and incident positive MDRO clinical cultures.
6. A study published in **Pediatrics** found that, among 3,082,626 COVID-19 diagnoses in 2,949,118 children between March 7, 2020 and December 31, 2022. Hydroxychloroquine and ivermectin were prescribed in 0.03% and 0.14% of COVID-19 cases.

References available in the chat

Today's Emerging Infectious Disease News

7. A study from Hong Kong, published in **The Lancet Infectious Diseases** found the administration of nirmatrelvir/ritonavir to be associated with significant reductions in risks for post-acute mortality and the occurrence of 13 post-acute sequelae among patients with COVID admitted to hospitals in Hong Kong.
8. A **JAMA** study of US VA patients found that in fall-winter 2023-2024, the risk of death in patients hospitalized for COVID-19 was greater than the risk of death in patients hospitalized for influenza (5.70% vs. 4.24%).
9. A **JAMA** study of COVID-Vaccine-related postings on X (Previously Twitter) recommended that healthcare professionals add 'Community Notes' to posts that provide misinformation about adverse events and conspiracy.
10. A press release issued by**AstraZeneca** issued noting that its investigational long-acting monoclonal, sipavibart, met its primary endpoint in the 'Supernova' trial (i.e., preventing COVID-19 in immunocompromised patients).
11. A study published in **Infection Control and Hospital Epidemiology** provided a comparative analysis of sampling and detection methods for fungal contamination on common healthcare environment surface materials finding that that sponge sampling and qPCR detection performed best.
12. A **JAMA Pediatrics** study asked if the COVID-19 pandemic was associated with changes in children's developmental milestone attainment and found very modest decreases.

References available in the chat

Today's Emerging Infectious Disease News

13. A **BMC Infectious Diseases** study found early uptake of COVID-19 vaccines associated with older age, greater numeracy skills, higher COVID-19 risk perceptions, and positive attitudes towards vaccines;, younger age, negative attitudes towards vaccines, low trust in healthcare, and medical minimizing predicted vaccine refusal..
14. A paper published in **JAMA Network Open** concludes that COVID-19 surges were associated with declines in hospital quality, highlighting the importance of identifying and implementing strategies to maintain care quality during periods of high hospital use.
15. A **JAMA Internal Medicine** paper evaluated the frequency and severity of acute cardiac events among adults $\geq$ 50 years admitted with laboratory confirmed RSV infection; acute cardiac events are common and are associated with severe clinical outcomes.
16. An editorial accompanying this paper in **JAMA Internal Medicine** emphasizes that the 'juice' of RSV vaccination of older adults is truly 'worth the squeeze'.
17. A study published in **Infection Control and Hospital Epidemiology** evaluated the characteristics of healthcare personnel who acquired SARS-CoV-2 infection at 10 emerging infections program sites in the United States.
18. The **FDA Vaccines and Related Biological Products Advisory Committee (VRBPAC)** unanimously recommended basing this fall's COVID vaccine on the JN.1 strain.

References available in the chat

Panelists:

Dr. David Henderson
NIH Consultant

Dr. Kristina Bryant
University of Louisville

Dr. Debbie Yokoe
UCSF Health-UCSF Medical Center

Dr. David Weber
UNC School of Medicine

COVID-19 POTPOURRI:
WASTEWATER SURVEILLANCE, PEMGARDA, SELF-REPLICATING mRNA VACCINE

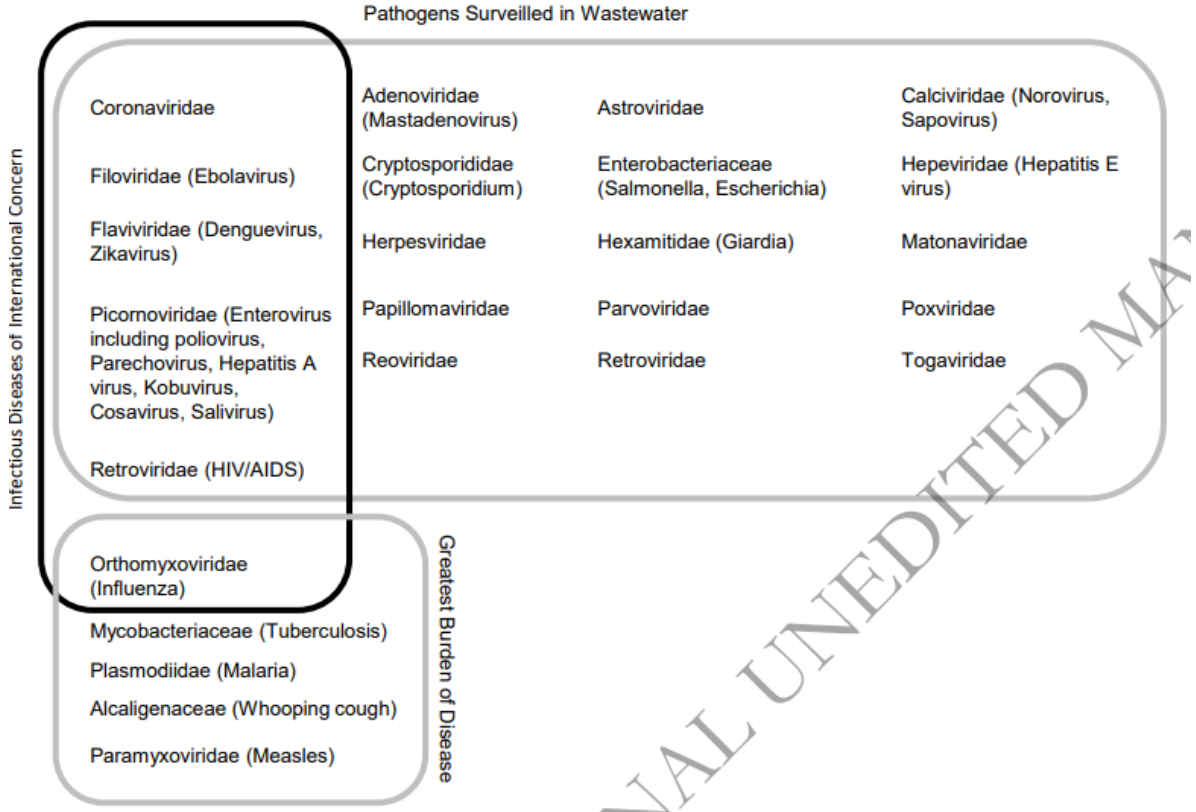
David J. Weber, MD, MPH, FIDSA, FSHEA, FRSM (London)
Sanders Distinguished Professor of Medicine, Pediatrics and Epidemiology
Associate Chief Medical Officer, UNC Medical Center
Medical Director, Hospital Epidemiology, UNC Medical Center
University of North Carolina at Chapel Hill

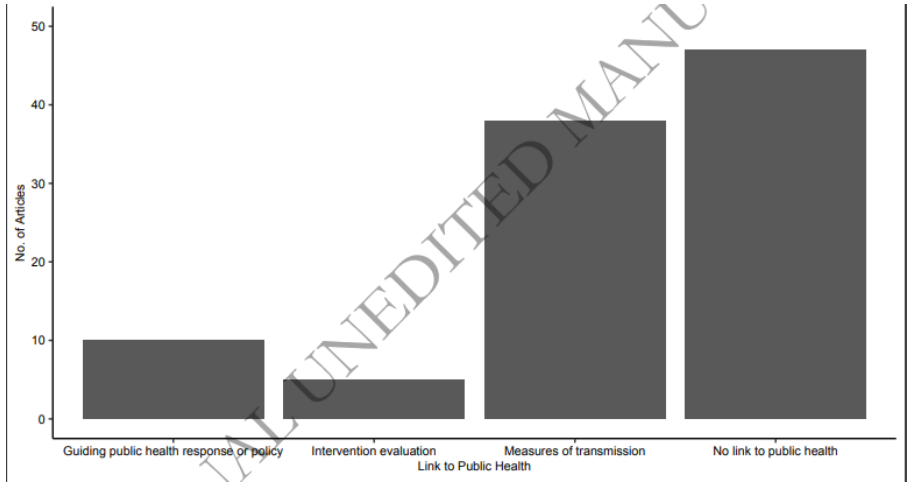
UNC SCHOOL OF MEDICINE

Disclosures: Consultancy-Pfizer, GSK, PDI, BD, Germitec; Speaker's Bureau-Merck, BD, GAMA

WASTEWATER SURVEILLANCE FOR INFECTIOUS DISEASES

- Demonstrated value in monitoring SARS-CoV-2
- May predict impending surges
- Useful for assessing prevalence
- Not dependent on treatment-seeking behavior or access to care
- Challenges
  - Ensuring equity
  - Ensuring timeliness
  - Target selection: Pathogens public health significance, analytic feasibility, usefulness
- Studies: >100 papers, 38 countries
- Utility still under investigation
- Future: Assessing MDROs





Mello MM, et al NEJM 2023;388:1441; Kilaru P, et al. Am J Epidemiol 2023

Wastewater-based epidemiology for surveillance of infectious diseases in healthcare settings

KEY POINTS

- Wastewater provides anonymous and untapped disease data repository in hospitals.
- In hospitals, wastewater RNA-signal trends to nosocomial COVID-19 cases/outbreaks and is sensitive enough to detect new outbreaks.
- Wastewater sampling can help to reduce hospitals' large-scale clinical testing requirements, as it is inexpensive.
- Routine sampling using wastewater provides a platform for risk-based sampling and enables scaled resource allocation in response to outbreaks.
- Hospital monitoring in low-income settings is a priority for future research.

Hassard F, et al
Curr Opin Infect Dis 2023;36:288-295

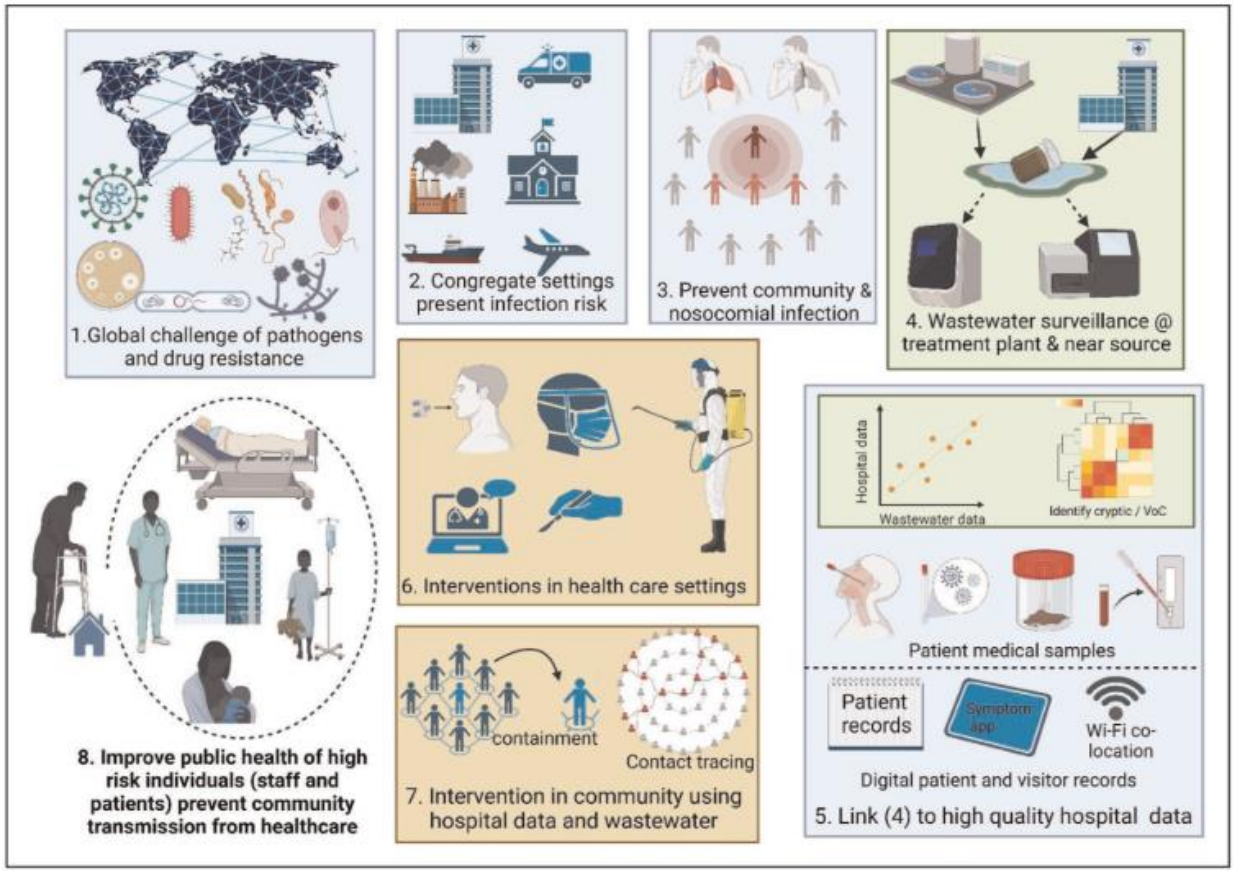
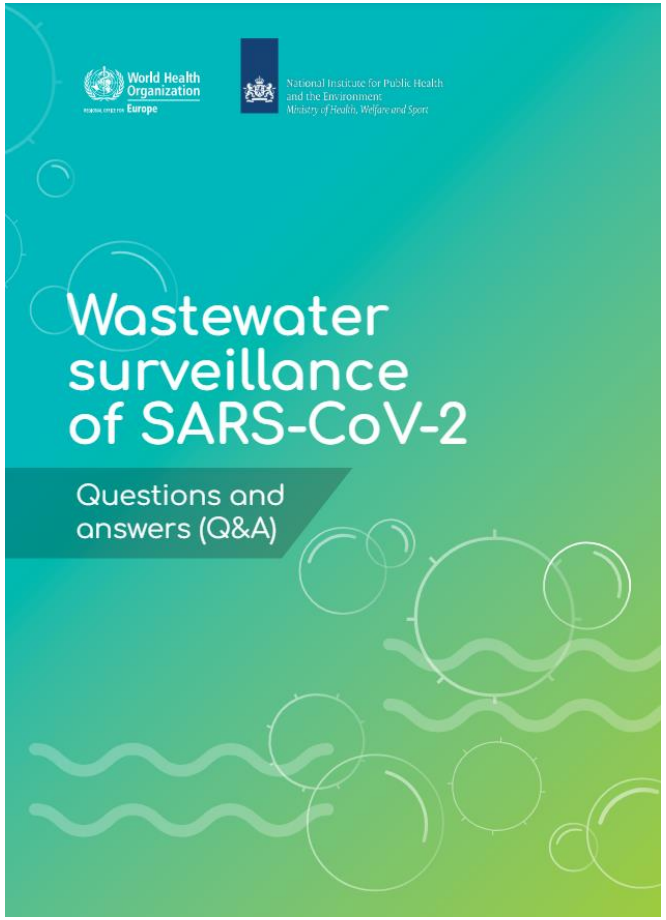


FIGURE 1. Roadmap for using wastewater-based surveillance and near source sampling to better characterize infection risks in hospitals and care homes.

WASTEWATER SURVEILLANCE OF SARS-COv2, WHO, 2022



https://iris.who.int/bitstream/handle/10665/353058/WHO-EURO-2022-5274-45038-64164-eng.pdf?sequence=4

- Wastewater surveillance involves the systematic sampling and testing of untreated wastewater and sewer sludge for fragments of non-infective RNA of SARSCoV-2, its so-called genetic fingerprint.
- By analyzing wastewater for RNA fragments that are present, health authorities can identify trends at the population level and detect where SARS-CoV-2 is circulating to inform the public health response. Wastewater surveillance does not monitor for live virus and is a non-invasive way of monitoring the circulation of SARS-CoV-2 in a community.
- Wastewater surveillance is not a standalone surveillance approach, and it is critical to partner with epidemiologists, environmental engineers and other public health partners to best understand and make use of wastewater data in public health decision making and response alongside other surveillance indictors. Such surveillance represents a complementary adjunct to clinical testing for assessing infection trends in the wider community. In addition, wastewater surveillance may help overcome known limitations of clinical surveillance, such as low population coverage, high costs, testing and reporting delays, and the uncertain likelihood of an individual to seek health care.
- Limitations: 1) It may be difficult for wastewater surveillance to detect low levels of infection in a community as the lower limits of detection of current testing methods are not well understood. The absence of SARS-Cov-2 in wastewater does not indicate a lack of the virus in the community. 2) There is no unified standard method for sampling or testing of wastewater. 3) There remains limited experience and understanding of both the interpretation of data and subsequent actions that public health authorities may take based on wastewater surveillance alone

NATIONAL WASTEWATER SURVEILLANCE SYSTEM (NWSS)

COVID-19 NWSS Wastewater Monitoring in the U.S.

Print

LOW

Nationally, the wastewater viral activity level for COVID-19 is currently **low**.

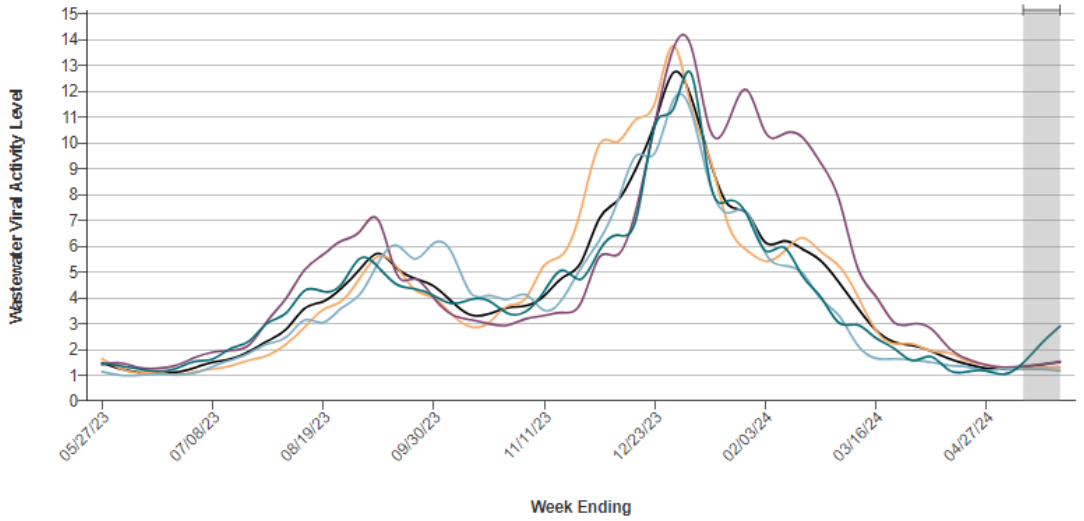
Region with the highest wastewater viral activity level for COVID-19:
West

See individual state and territory trends.

This chart shows national and regional trends of SARS-COV-2 viral activity levels in wastewater.

Make a selection from the filters to change the visualization information.

1 Year



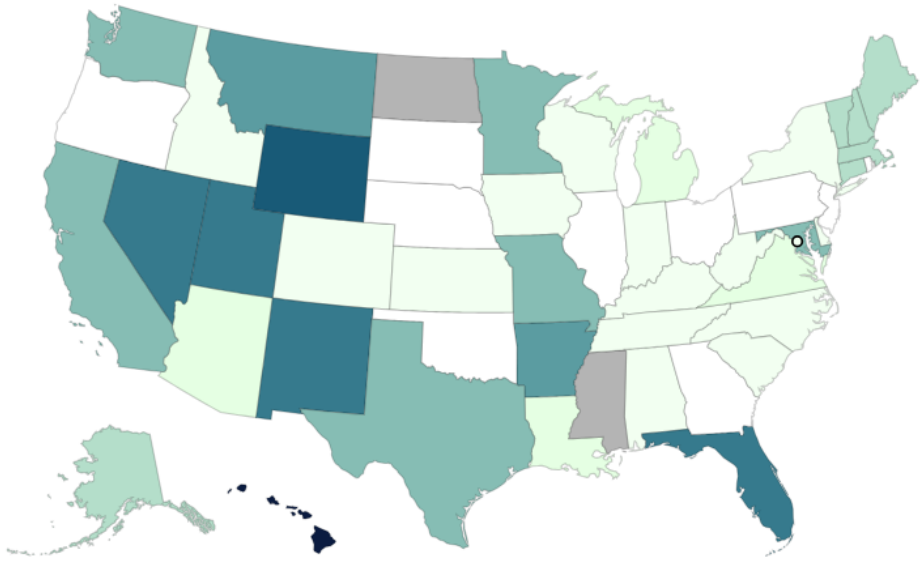
Select a geography to add or remove it from the visualization.

National Midwest South Northeast West

Data from the most recent two weeks may be incomplete due to delays in data reporting. These data sets are subject to change and are indicated by the gray shading.

Data last updated 2024-05-30

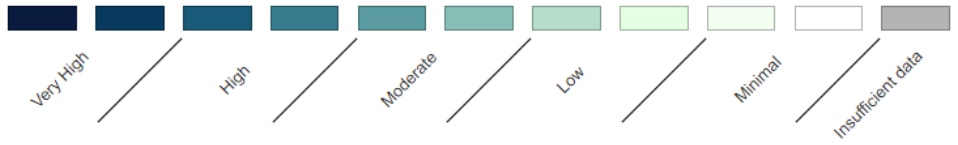
This interactive map shows current viral activity levels of SARS-COV-2 in wastewater.



Territories GU PR VI

Current SARS-CoV-2 Wastewater Viral Activity Level

Select a level to add or remove it from the visualization.



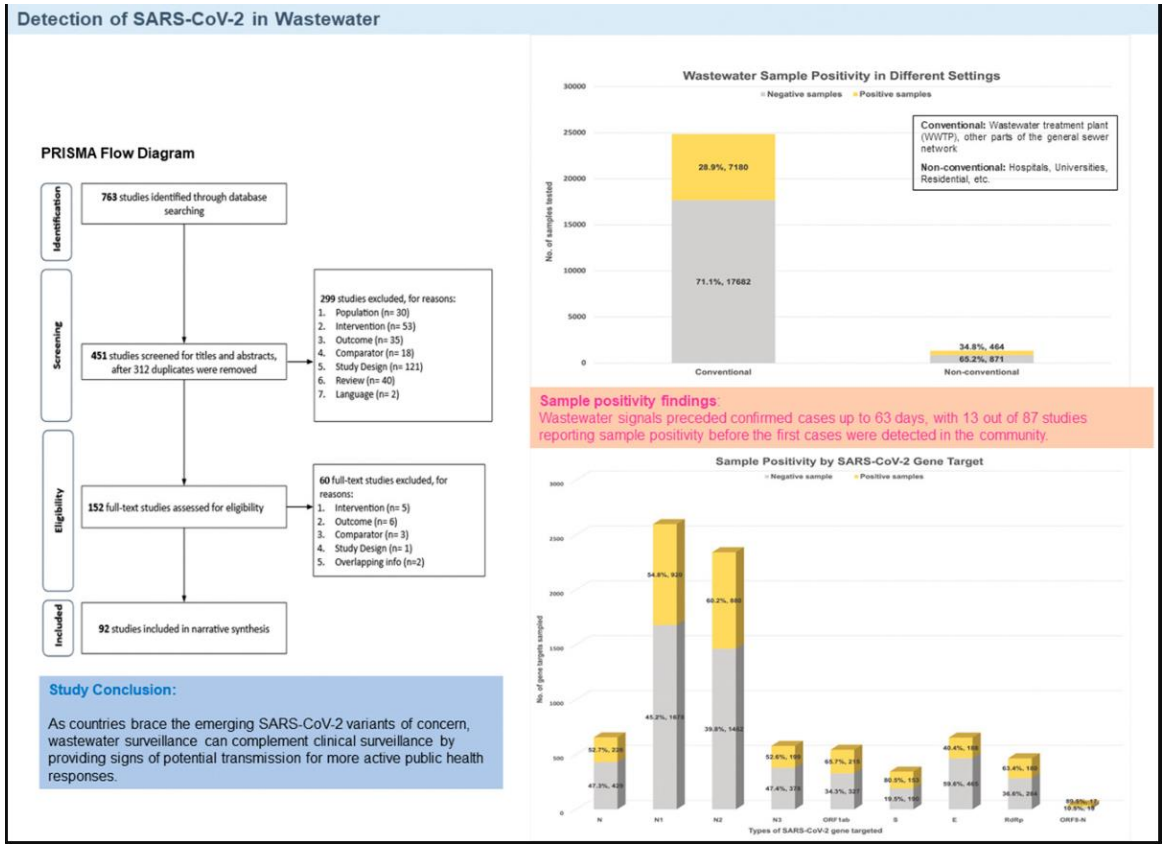
Testing has resumed for commercial contract wastewater sites (about 350 sites) that have had a temporary delay since September 15, 2023. Once sites have six weeks of data, the wastewater viral activity levels will be displayed.

Data last updated 2024-05-30

https://www.cdc.gov/nwss/rv/COVID19-nationaltrend.html; https://www.cdc.gov/nwss/rv/COVID19-currentlevels.html

Wastewater surveillance to infer COVID-19 transmission: A systematic review

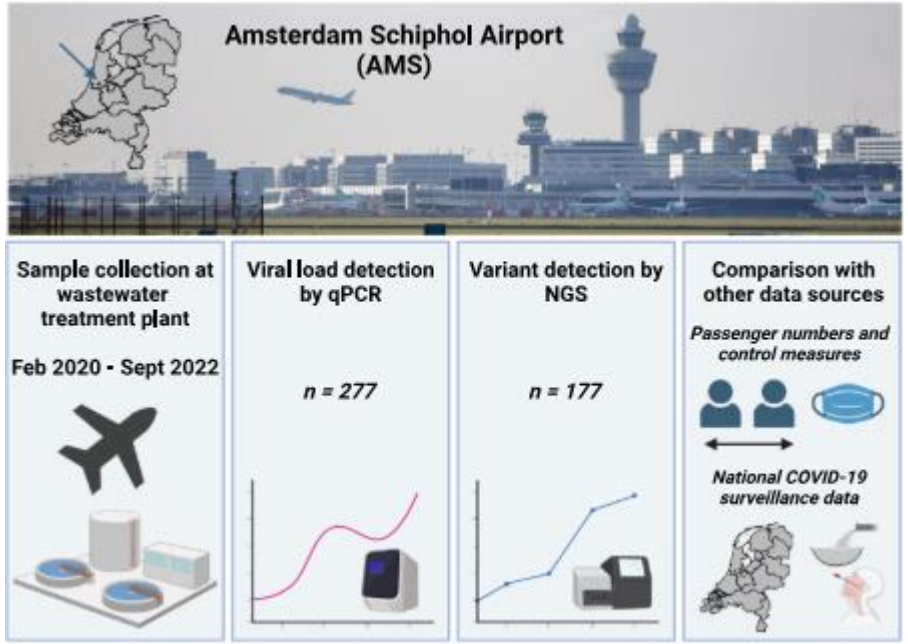
Successful detection of SARS-COV-2 in wastewater suggests the potential utility of wastewater-based epidemiology (WBE) for COVID-19 community surveillance. This systematic review aims to assess the performance of wastewater surveillance as early warning system of COVID-19 community transmission. A systematic search was conducted in PubMed, Medline, Embase and the WBE Consortium Registry according to PRISMA guidelines for relevant articles published until 31st July 2021. Relevant data were extracted and summarized. Of 763 studies identified, 92 studies distributed across 34 countries were shortlisted for qualitative synthesis. A total of 26,197 samples were collected between January 2020 and May 2021 from various locations serving population ranging from 321 to 11,400,000 inhabitants. Overall sample positivity was moderate at 29.2% in all examined settings with the spike (S) gene having maximum rate of positive detections and nucleocapsid (N) gene being the most targeted. Wastewater signals preceded confirmed cases by up to 63 days, with 13 studies reporting sample positivity before the first cases were detected in the community. At least 50 studies reported an association of viral load with community cases. While wastewater surveillance cannot replace large-scale diagnostic testing, it can complement clinical surveillance by providing early signs of potential transmission for more active public health responses. However, more studies using standardized and validated methods are required along with risk analysis and modelling to understand the dynamics of viral outbreaks.



Shah S, et al. Science of Total Environ 2022;804;15 Jan.

Long-term wastewater monitoring of SARS-CoV-2 viral loads and variants at the major international passenger hub Amsterdam Schiphol Airport: A valuable addition to COVID-19 surveillance

- Wastewater surveillance for SARS-CoV2 was performed at Amsterdam Schiphol Airport.
- Airport wastewater monitoring feasible throughout pandemic irrespective of measures
- Viral load trends parallel and sometimes predates Dutch national viral load trends.
- Viral loads rose simultaneously with the emergence of new variants.
- VOC emergence mirrors and at times predates those reported in clinical samples.



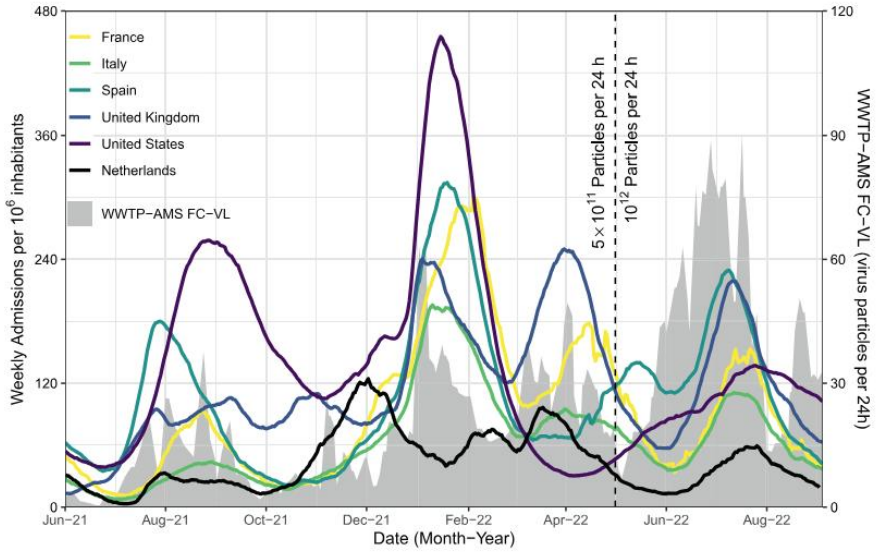


Fig. 3. Hospital admissions per million inhabitants per week in six countries over time compared to the trend in viral load at Amsterdam Schiphol Airport (FC-VL shown in grey area). Weekly hospital admissions per million are given per country. A selection of countries is made based on where most passengers are arriving from at Amsterdam Schiphol Airport (France, Italy, Spain, the United Kingdom and the United States of America) as well as the country where the study is performed (the Netherlands). The trend in FC-VL at Schiphol Airport is scaled separately for the period before and after May 1, 2022, shown by the dashed vertical line.

Van der Drift A-M, et al. Science Total Environ 2024;937:173535

COVID-19 Update: An EUA for Pemivibart (Pemgarda) for Pre-Exposure Prophylaxis

- The FDA has issued an Emergency Use Authorization (EUA) for the long-acting investigational IV monoclonal antibody pemivibart (Pemgarda – Invivyd) for pre-exposure prophylaxis of COVID-19 in persons ≥12 years old (weight ≥40 kg) who have moderate to severe immune compromise and are unlikely to respond adequately to COVID-19 vaccination (see Table 1).1 Pemgarda is the only drug that is currently authorized in the US for pre-exposure prophylaxis of COVID-19. Tixagevimab/cilgavimab (Evusheld) was previously available under an EUA for this indication, but it lacks activity against currently circulating SARS-CoV-2 variants.
- Pemivibart has activity against the currently dominant JN.1 Omicron lineage of SARS-CoV-2.4 Pemivibart is catabolized slowly (median half-life 44.8 days).cab
- No clinical efficacy data were required for authorization of pemivibart. Issuance of the EUA was based on the results of an unpublished immunobridging trial (CANOPY Cohort A; summarized in the FDA Fact Sheet) in 306 adults with moderate to severe immune compromise. Titer levels of anti-SARS-CoV-2 JN.1 neutralizing antibodies 28 days after administration of one dose of pemivibart were compared to extrapolated titer levels of anti-SARS-CoV-2 B.1.617.2 (Delta) neutralizing antibodies 28 days after administration of a single adintrevimab dose in historical controls.
- A hypersensitivity or infusion-related reaction occurred in 9% of patients in CANOPY Cohort A. Anaphylaxis occurred in 0.6% of 623 patients who received pemivibart in clinical trials. Pemivibart contains polysorbate 80, which is similar in structure to polyethylene glycol and has been associated with hypersensitivity reactions to COVID-19 vaccines; an immunology consult should be considered before use in patients who had a severe hypersensitivity reaction to a COVID-19 vaccine.

Table 1. Some Immunocompromising Conditions[1]

- Moderate or severe primary immunodeficiency
- Advanced or untreated HIV infection
- Active treatment for a solid-tumor or hematologic malignancy
- Hematologic malignancy associated with poor vaccine response (e.g., acute leukemia, chronic lymphocytic leukemia, non-Hodgkin lymphoma, multiple myeloma)
- Use of immunosuppressive therapy after a solid-organ or islet transplant
- Receipt of CAR T-cell therapy or hematopoietic stem cell transplant within previous 2 years
- Active treatment with other immunosuppressive or immunomodulatory drugs, such as high-dose corticosteroids (≥20 mg/day of prednisone or equivalent for ≥2 weeks) and tumor necrosis factor (TNF) inhibitors

1. FDA. Fact sheet for healthcare providers: Emergency Use Authorization for Pemgarda (pemivibart). March 2024. Available at: https://bit.ly/3Q3K5AL. Accessed April 25, 2024.

Medical Letter, 3 May 2024; Issue 1702

PEMGARDA: CANOPY TRIAL DATA

Background: The safety and PK data to support the authorization of pemivibart were generated from the ongoing Phase 3 multicenter trial (CANOPY).

Methods: Immunobridging/PK safety trial. Cohort A, single arm; Cohort B, randomized. Analyses updated to assess JN.1.

Results: Following a single dose administration of pemivibart 4500 mg, the geometric mean titers at the end of infusion on Day 1, at Month 1, and at Month 3 are 22552 (%CV:123.42), 7204 (%CV:37), and 3451 (%CV:39) respectively5. The range of titers achieved with pemivibart for 3 months following administration of 4500 mg IV were consistent with the titer levels associated with efficacy in prior clinical trials with other mAbs.

Safety: AEs through Day 28 were reported more frequently with pemivibart (Cohort A+B) compared to placebo. While more participants in Cohort A reported an AE through Day 28, most events were considered unrelated to study drug. Nonetheless, drug-related AEs through Day 28 were more frequently reported in Cohort A compared to Cohort B/pemivibart, while no drug-related AEs were reported with placebo.

Administration: Q3 month dosing; Cost = $5,000 to $6,000 per dose; requires post-infusion monitoring for 2 hours.

https://www.fda.gov/media/177333/download?attachment

Figure 1. Comparison Between Titer-Response Relationship Based on a Meta-Analysis and the Range of Titer Following the Administration of Pemivibart 4500 mg IV (Green Box)

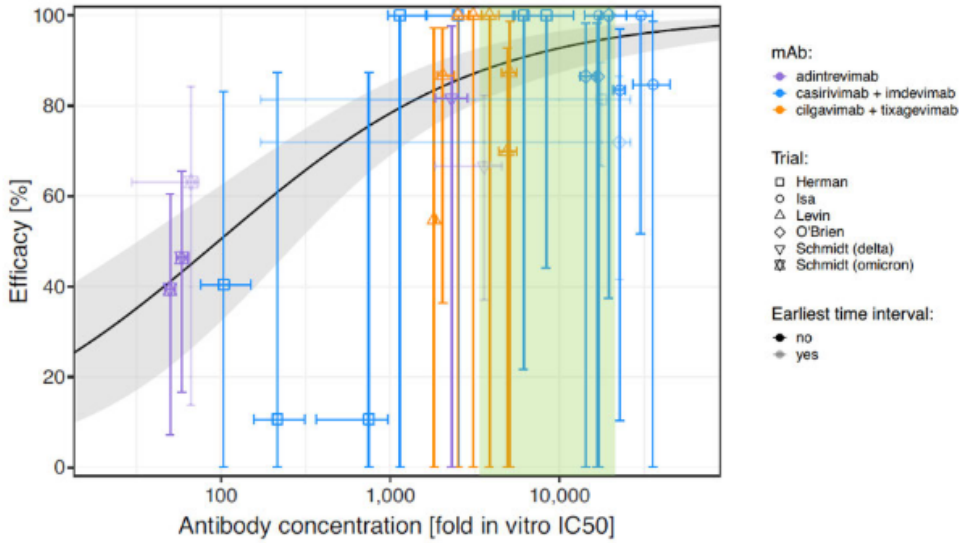
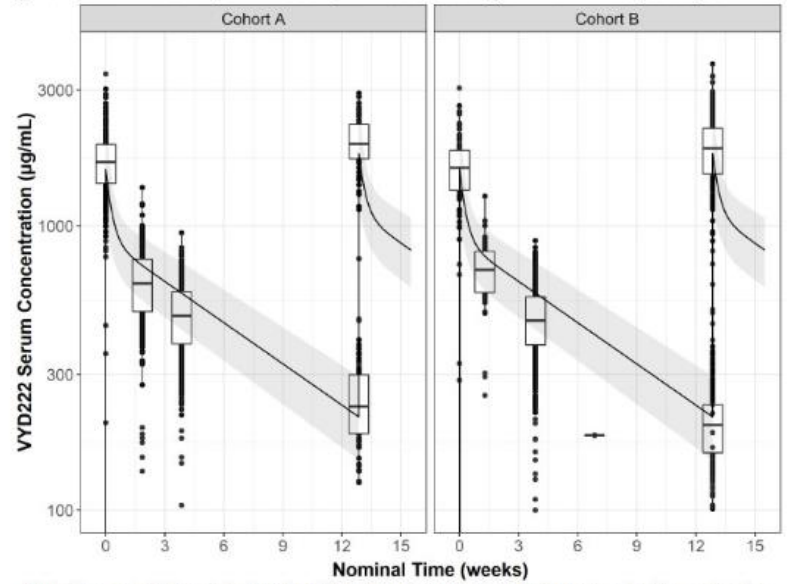


Figure 6. Pemivibart PopPK Model Qualification Using CANOPY Data, Study 001



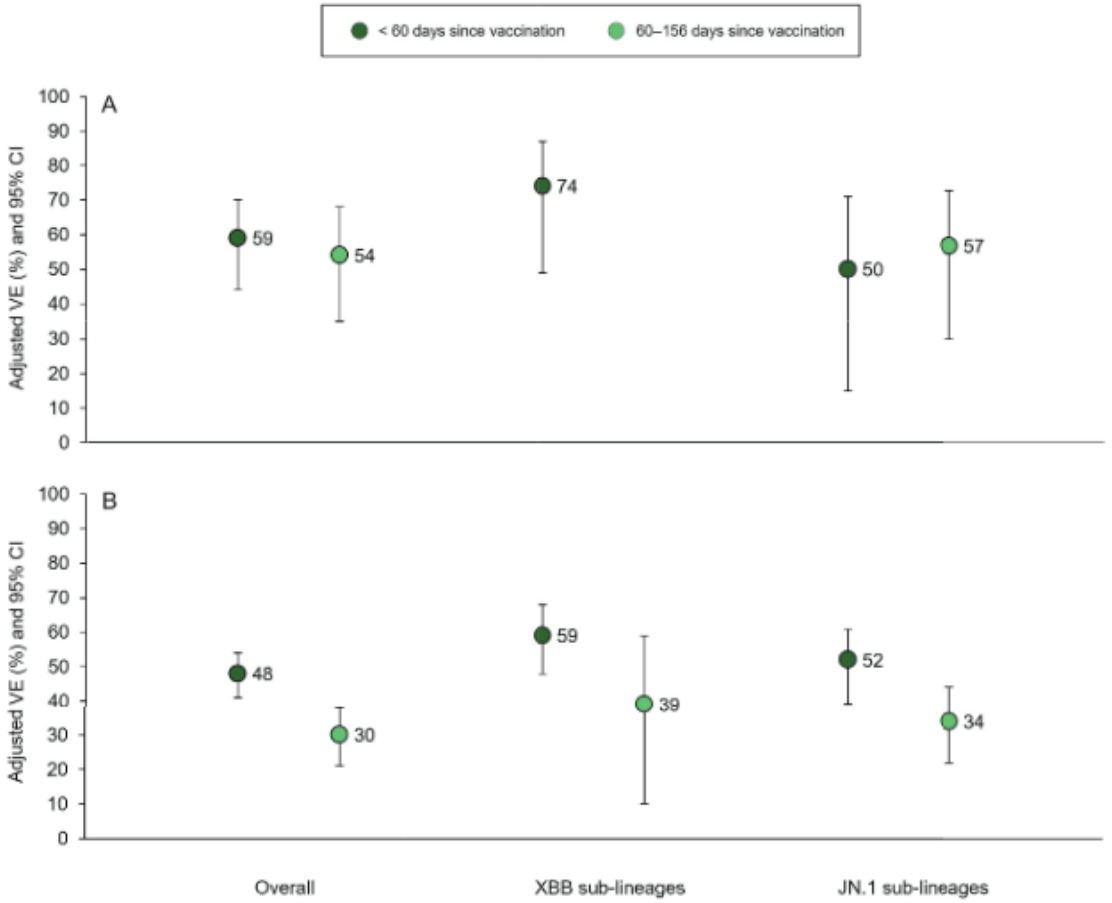
Note: Box-and-whisker plots show the distribution of serum concentrations at nominal time points for subjects enrolled in the Phase 3 study. The black lines and grey shaded regions show the median and 5th – 95th percentiles of the simulated concentrations using the Phase 1 Population PK Model and the demographics of the Phase 3 subjects. Abbreviations are provided in the Abbreviation Listing.

Effectiveness of BNT162b2 XBB Vaccine against XBB and JN.1 Sub-lineages

Methods: we provide updated results (October 11, 2023 through February 29, 2024) from our previously conducted test-negative case-control study in Kaiser Permanente Southern California to evaluate sub-lineage-specific effectiveness of the BNT162b2 XBB1.5-adapted vaccine.

Results: Overall (including all sub-lineages) adjusted BNT162b2 XBB VE was 57% (95% CI: 45–66%) against COVID-19-related hospital admission and 40% (34–45%) against ED/UC visits. Against XBB sub-lineages, VE was 65% (41–79%) for hospitalization and 55% (45–64%) for ED/UC; compared to 54% (33–69%) and 41% (32–49%) against JN.1 sub-lineages, respectively.

When stratified by time since vaccination, VE <60 days post-vaccination against XBB sub-lineages was 74% (49–87%) for hospitalization and 59% (48–68%) for ED/UC; whereas VE against JN.1 sub-lineages for the same two outcomes was 50% (15–71%) and 52% (39–61%), respectively



(A) Effectiveness against hospital admission. (B) Effectiveness against ED/UC visits. VE ≥2 months after vaccination could not be calculated for XBB sub-lineages due to small sample size. Models adjusted for week of encounter, age, sex, self-reported race/ethnicity, BMI, Charlson comorbidity index, prior SARS-CoV-2 infection, and utilization history (flu and pneumococcal vaccination, inpatient, ED, and outpatient encounters in prior year

Tartof SY, et al. https://www.medrxiv.org/content/10.1101/2024.05.04.24306875v1.full.pdf

Rise of the RNA machines – self-amplification in mRNA vaccine design

mRNA vaccines have won the race for early COVID-19 vaccine approval, yet improvements are necessary to retain this leading role in combating infectious diseases. A next generation of self-amplifying mRNAs, also known as replicons, form an ideal vaccine platform. Replicons induce potent humoral and cellular responses with few adverse effects upon a minimal, single-dose immunization. Delivery of replicons is achieved with virus-like replicon particles (VRPs), or in nonviral vehicles such as liposomes or lipid nanoparticles. Here, we discuss innovative advances, including multivalent, mucosal, and therapeutic replicon vaccines, and highlight novelties in replicon design. As soon as essential safety evaluations have been resolved, this promising vaccine concept can transform into a widely applied clinical platform technology taking center stage in pandemic preparedness.

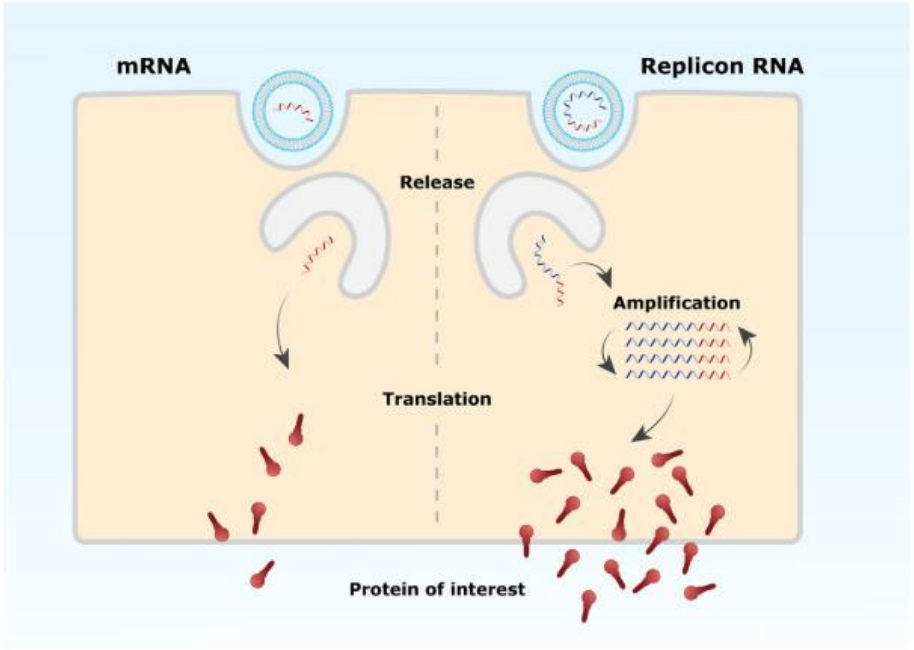


Figure 1. Schematic representation of the protein of interest expression induced by a conventional mRNA and a replicon vaccine. Once released in the cell, the mRNA is translated to produce the protein of interest. In contrast to mRNA, replicon RNA encodes alongside the protein of interest, self-amplifying genes (depicted in blue) that amplify the replicon RNA. This intracellular amplification will subsequently result in higher expression levels of the protein of interest.

Comes JDG, et al. Trends Biotechnol 2023;June 14

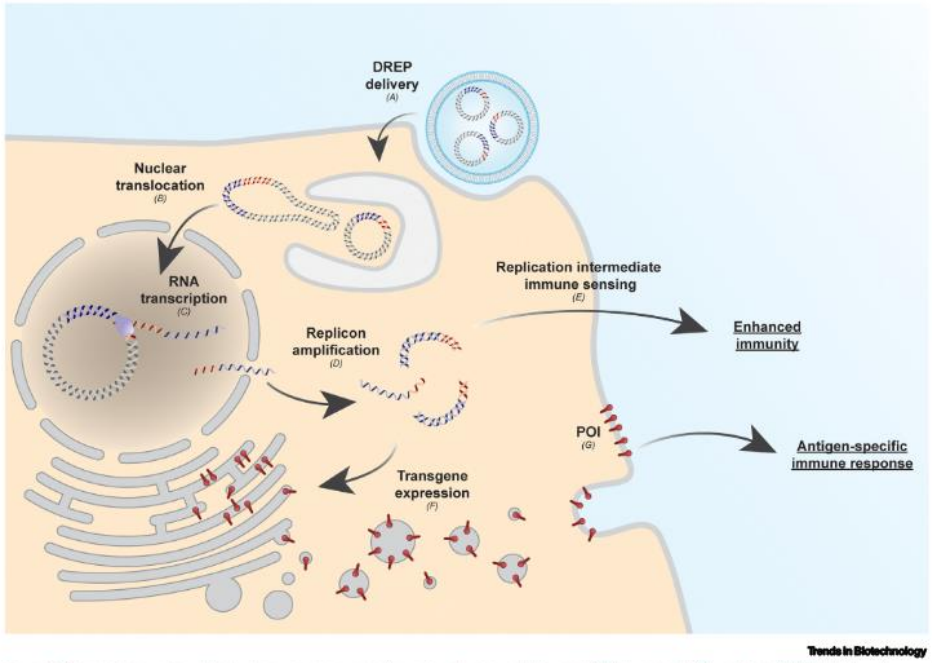


Figure 3. Schematic overview of heterologous gene expression using a liposomal-delivered DNA-launched RNA replicon (DREP). (A) Upon liposomal delivery to a cell, (B) the DREP migrates to the nucleus where (C) it serves as a template for the RNA polymerase II-mediated transcription of replicon RNA. (D) Subsequently, the replicon RNA is transported to the cytoplasm where the self-amplification, mediated by replicase proteins, occurs. (E) During amplification, cellular sensors recognize amplification intermediates (double-stranded RNA), enhancing host immunity. (F) At the same time, translation of the replicon RNA produces the protein of interest (POI). (G) This will induce an antigen-specific immune response.

UNC SCHOOL OF MEDICINE

Immunogenicity and safety of a booster dose of a self-amplifying RNA COVID-19 vaccine (ARCT-154) versus BNT162b2 mRNA COVID-19 vaccine: a double-blind, multicentre, randomised, controlled, phase 3, noninferiority trial

Methods: Double-blind, multicentre, RCT, controlled, phase 3, non-inferiority trial, conducted at 11 outpatient clinical sites in Japan, enrolled healthy adults aged at least 18 years who had previously been immunized with two doses of an mRNA COVID-19 vaccine (BNT162b2 or mRNA-1273 [Spikevax; Moderna]) followed by a third dose of BNT162b2 at least 3 months before enrolment. Participants were randomly assigned, in a 1:1 ratio to receive either ARCT-154 or BNT162b2 as a fourth-dose booster via deltoid intramuscular injection.

Results: Randomized 828 participants to receive ARCT-154 (n=420) or BNT162b2 (n=408) vaccines as a 4th-dose booster. The GMTs of surrogate neutralising antibodies induced against the Wuhan-Hu-1 SARS-CoV-2 strain in the ARCT-154 group (5641 [95% CI 4321–7363]) were non-inferior to those in the BNT162b2 group (3934 [2993–5169]) when measured at 28 days after boosting, with a GMT ratio of 1·43 (95% CI 1·26–1·63). Seroresponse rates were 65·2% (95% CI 60·2–69·9) in the ARCT-154 group versus 51·6% (46·4–56·8) in the BNT162b2 group, a difference of 13·6% (95% CI 6·8–20·5). GMTs against the omicron BA.4/5 variant on day 29 were 2551 (1687–3859) in the ARCT-154 group and 1958 (1281–2993) in the BNT162b2 group—a GMT ratio of 1·30 (1·07–1·58)—with seroresponse rates of 69·9% (65·0–74·4) and 58·0% (52·8–63·1). Both boosters were equally well tolerated.

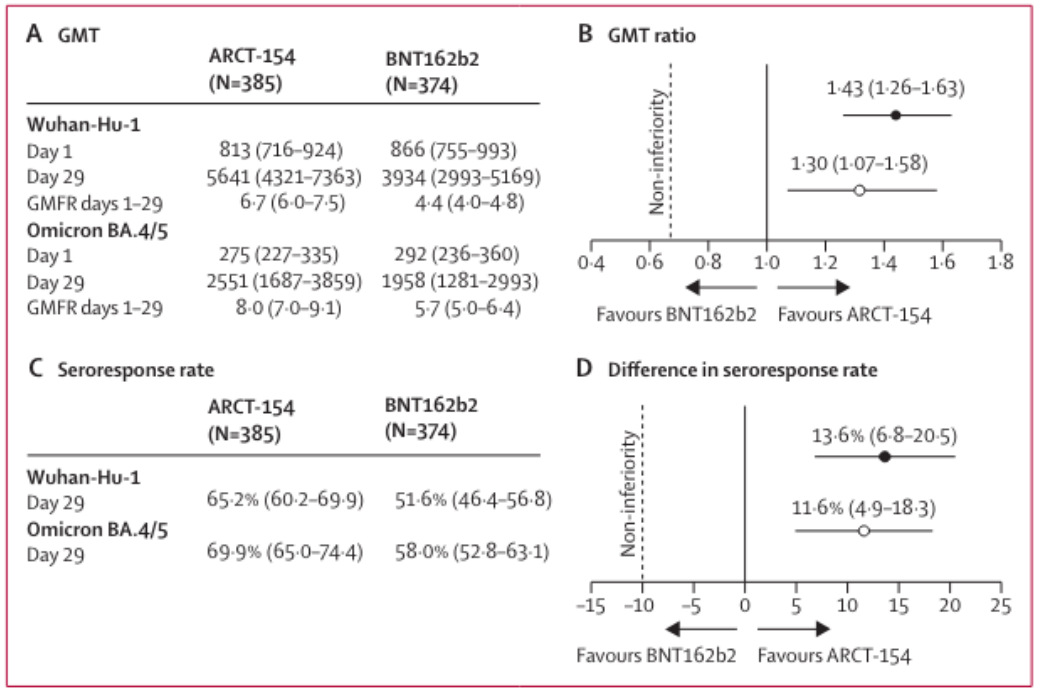


Figure 2: **Surrogate neutralising antibody titres and seroresponse rates**
(A) GMTs of surrogate neutralising antibodies at day 1 (baseline) and day 29, and GMFRs in titres from day 1 to day 29. (B) GMT ratio. (C) Seroresponse rates at day 29. (D) Seroresponse difference. All data are from per-protocol set 1 and are shown with 95% CIs in parentheses. Solid circles represent the Wuhan-Hu-1 variant of SARS-CoV-2, open circles represent the omicron BA.4/5 variant. Vertical dashed lines represent the threshold for non-inferiority. GMT=geometric mean titre. GMFR=geometric mean fold rise.

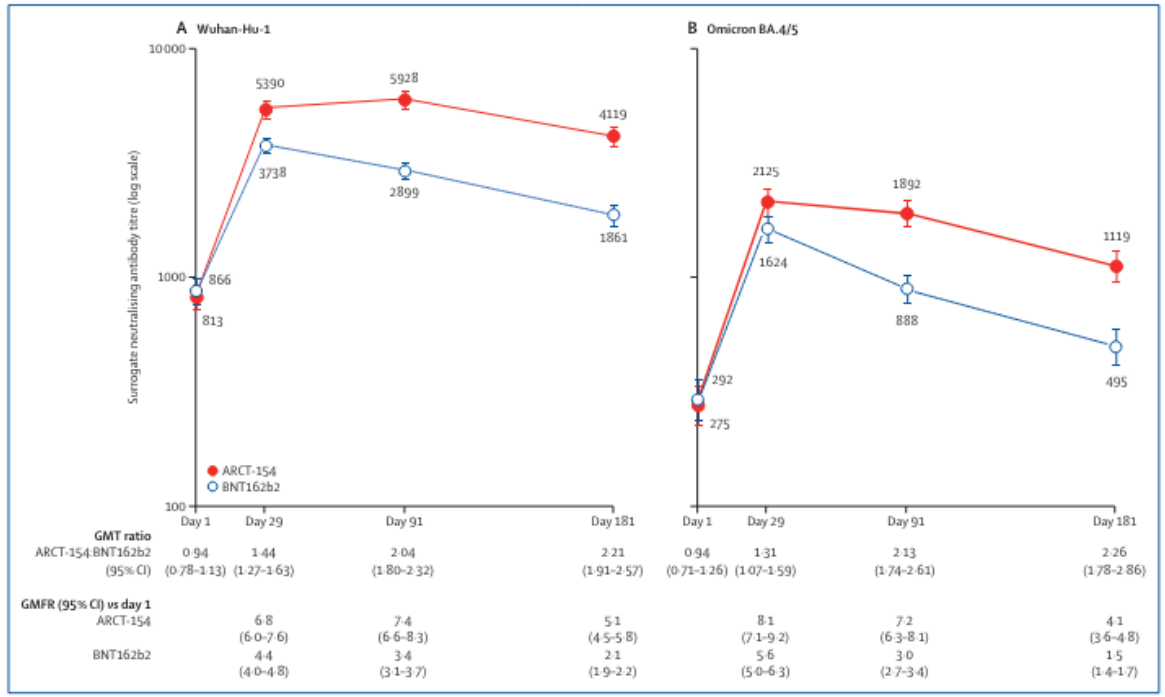
Oda Y, et al. Lancet ID 2024;24:351-60

Persistence of immune responses of a self-amplifying RNA COVID-19 vaccine (ARCT-154) versus BNT162b2

Context: We recently reported that a booster dose of the novel mRNA vaccine, ARCT-154, a self-amplifying mRNA (saRNA) vaccine based on the SARS-CoV-2 D614G variant (B.1), induced superior immunogenicity than BNT162b2 (Comirnaty; Pfizer–BioNTech) in BNT162b2-primed adults 1 month after administration.

Results: Day 91 titres were equal to or greater than day 29 titres in 205 of 369 (55·6% [95% CI 50·3–60·7]) ARCT-154 recipients, but in only 108 of 356 (30·3% [25·6–35·4]) BNT162b2 recipients. Due to different rates of antibody waning by day 181 GMTs were 4119 (95% CI 3723–4557, n=332) in the ARCT-154 group and 1861 (1667–2078, n=313) in the BNT162b2 group, maintaining a GMT ratio of 2·21 (1·91–2·57) between vaccine groups. GMTs against Wuhan-Hu-1 remained higher 180 days after ARCT-154 than GMTs observed 28 days after the BNT162b2 booster.

Conclusion: These data demonstrate the extended persistence of neutralising antibodies after the saRNA vaccine compared with conventional mRNA vaccine in the clinical setting, confirming the longer-lasting immunity.



	Wuhan-Hu-1				Omicron BA.4/5			
	Day 1	Day 29	Day 91	Day 181	Day 1	Day 29	Day 91	Day 181
GMT ratio								
ARCT-154:BNT162b2	0·94	1·44	2·04	2·21	0·94	1·31	2·13	2·26
(95% CI)	(0·78–1·13)	(1·27–1·63)	(1·80–2·32)	(1·91–2·57)	(0·71–1·26)	(1·07–1·59)	(1·74–2·61)	(1·78–2·86)
GMFR (95% CI) *vs* day 1								
ARCT-154		6·8 (6·0–7·6)	7·4 (6·6–8·3)	5·1 (4·5–5·8)		8·1 (7·1–9·2)	7·2 (6·3–8·1)	4·1 (3·6–4·8)
BNT162b2		4·4 (4·0–4·8)	3·4 (3·1–3·7)	2·1 (1·9–2·2)		5·6 (5·0–6·3)	3·0 (2·7–3·4)	1·5 (1·4–1·7)

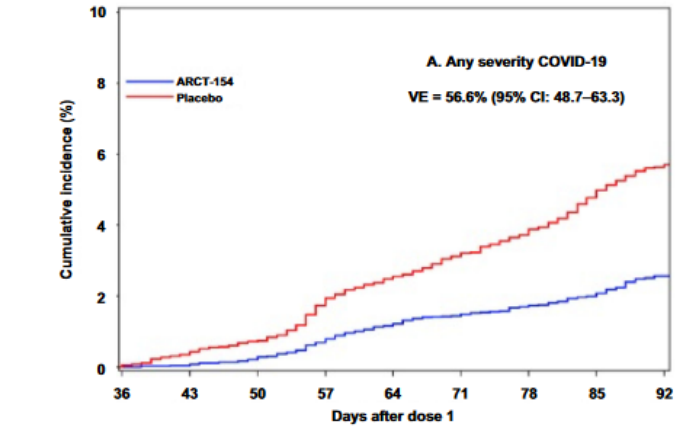
Figure: Geometric mean titres (with 95% CIs) of surrogate neutralising antibodies against the SARS-CoV-2 Wuhan-Hu-1 (A) and Omicron BA.4/5 (B) strains up to 6 months after vaccination with one booster dose of either ARCT-154 or BNT162b2

GMT ratios (95% CI) for ARCT-154:BNT162b2 are shown for days 1, 29, 91, and 181 and GMFR (95% CI) are shown for each group at days 29, 91 and 181. GMFR=geometric mean-fold rises over baseline. GMT=geometric mean titre.

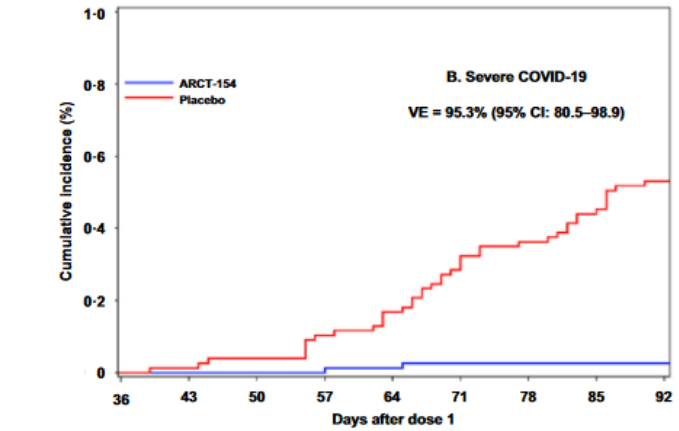
Oda Y, et al. Lancet ID 2024;24:341 (April)

Safety, immunogenicity and efficacy of the self-amplifying mRNA ARCT-154 COVID-19 vaccine: pooled phase 1, 2, 3a and 3b randomized, controlled trials

Combination of waning immunity and lower effectiveness against new SARS-CoV-2 variants of approved COVID-19 vaccines necessitates new vaccines. We evaluated two doses, 28 days apart, of ARCT-154, a self-amplifying mRNACOVID-19 vaccine, compared with saline placebo in an integrated phase 1/2/3a/3b controlled, observer-blind trial in Vietnamese adults. Primary safety and reactogenicity outcomes were unsolicited adverse events (AE) 28 days after each dose, solicited local and systemic AE 7 days after each dose, and serious AEs throughout the study. Primary immunogenicity outcome was the immune response as neutralizing antibodies 28 days after the second dose. Efficacy against COVID-19 was assessed as primary and secondary outcomes in phase 3b. ARCT-154 was well tolerated with generally mild–moderate transient AEs. Four weeks after the second dose 94.1% (95% CI: 92.1–95.8) of vaccinees seroconverted for neutralizing antibodies, with a geometric mean-fold rise from baseline of 14.5 (95% CI: 13.6–15.5). Of 640 cases of confirmed COVID-19 eligible for efficacy analysis most were due to the Delta (B.1.617.2) variant. Efficacy of ARCT-154 was 56.6% (95% CI: 48.7– 63.3) against any COVID-19, and 95.3% (80.5–98.9) against severe COVID-19. ARCT-154 vaccination is well tolerated, immunogenic and efficacious, particularly against severe COVID-19 disease.



No. at risk	7723	7673	7645	7565	7451	7372	7277	7184	2127	Placebo
Cases	4	33	57	150	197	248	300	384	440	
No. at risk	7787	7766	7752	7710	7626	7577	7512	7472	2254	ARCT-154
Cases	0	6	22	61	95	116	135	162	200	



No. at risk	7723	7699	7697	7687	7620	7580	7525	7505	2386	Placebo
Cases	0	1	3	8	13	25	28	35	41	
No. at risk	7787	7769	7768	7764	7714	7686	7640	7621	2386	ARCT-154
Cases	0	0	0	1	1	2	2	2	2	

Fig. 6 | Cumulative incidence curves of COVID-19 of any severity **(A)**, and severe COVID-19 **(B)** in vaccine and placebo groups from Day 36 (per protocol).

Ho NT, et al. Nature Communications 2024;14 May

Effectiveness of BNT162b2 BA.4/5 Bivalent COVID-19 Vaccine against Long COVID Symptoms: A US Nationwide Study

Background: Long COVID has become a central public health concern. This study characterized the effectiveness of BNT162b2 BA.4/5 bivalent COVID-19 vaccine (bivalent) against long COVID symptoms.

Methods: Symptomatic US adult outpatients testing positive for SARS-CoV-2 were recruited between 2 March and 18 May 2023. Symptoms were assessed longitudinally using a CDC-based symptom questionnaire at Week 4, Month 3, and Month 6 following infection. The odds ratio (OR) of long COVID between vaccination groups was assessed by using mixed-effects logistic models, adjusting for multiple covariates.

Results: At Week 4, among 505 participants, 260 (51%) were vaccinated with bivalent and 245 (49%) were unvaccinated. Mean age was 46.3 years, 70.7% were female, 25.1% had ≥1 comorbidity, 43.0% prior infection, 23.0% reported Nirmatrelvir/Ritonavir use. At Month 6, the bivalent cohort had 41% lower risk of long COVID with ≥3 symptoms (OR: 0.59, 95% CI, 0.36–0.96, p = 0.034) and 37% lower risk of ≥2 symptoms (OR: 0.63, 95% CI, 0.41–0.96, p = 0.030). The bivalent cohort reported fewer and less durable symptoms throughout the six-month follow-up, driven by neurologic and general symptoms, especially fatigue.

Conclusions: Compared with unvaccinated participants, participants vaccinated with the bivalent were associated with approximately 40% lower risk of long COVID and less symptom burden over the six-month study duration.

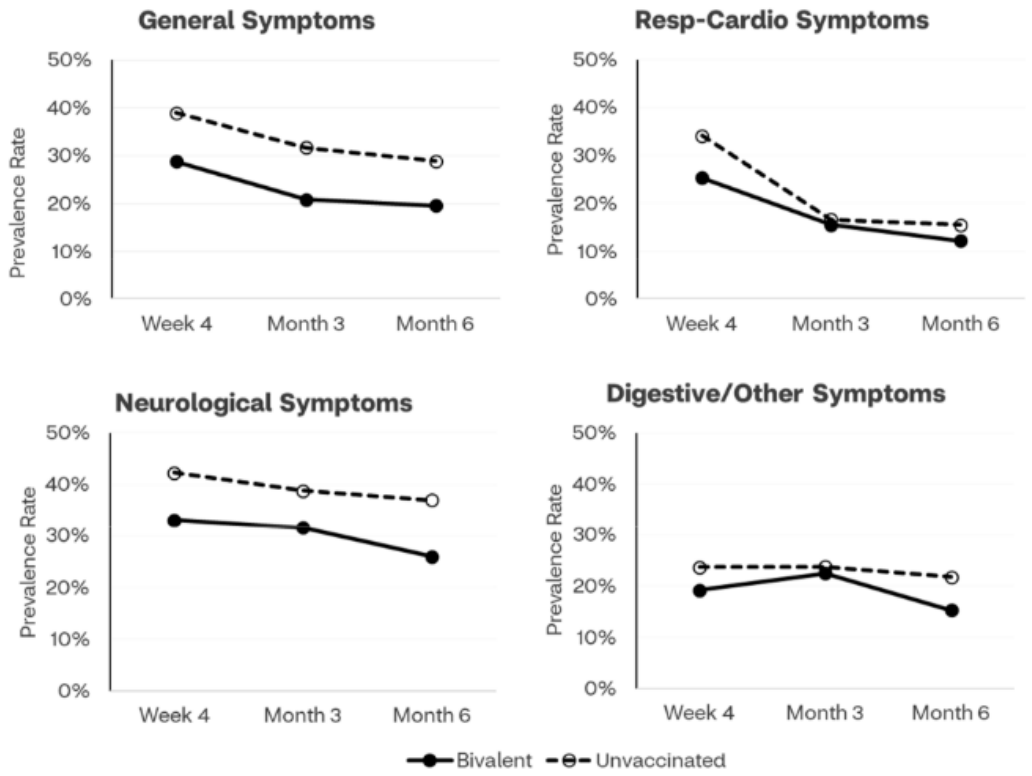


Figure 1. Prevalence of long COVID symptoms by COVID-19 vaccination status and symptoms category across time points (Week 4, Month 3, Month 6). The category "Other" included: rash, joint or muscle pain, hair loss, changes in menstrual cycles.

Di Fusco M, et al. Vaccines 2024;12:183

CONCLUSIONS

- Wastewater is useful but not perfect surveillance method for emerging diseases (e.g., Mpox, SARS-CoV-2, polio); in the future may be useful for monitoring MDROs
  - May predict surges, detect variants, and assess prevalence
  - Widely used to assess COVID-19
- Pemivibart (Pemgarda) if FDA approved for COVID-19 pre-exposure prophylaxis for immunocompromised patients
  - Approval based on immuno-bridging studies; no clinical trials available; no published papers
- Durability of currently available mRNA COVID-19 vaccines: 3 months for protection of infection; 6 months for protection against serious disease
- Self-replicating mRNA vaccines may improve durability of vaccine-induced immunity
  - ARCT-154 vaccine (a self-replicating COVID-19 vaccine approved in Japan) based on immunogenicity/safety data plus small clinical trial in Vietnam