Infectious Diseases Watch

March 2023

Ed Septimus, MD

General Infectious Diseases

Nipah Outbreak in Bangladesh

To date, there have been confirmed cases of Nipah virus in six districts in Bangladesh. Out of the ten people who have been diagnosed with Nipah virus infection, seven of them have died. Nipah virus is most commonly transmitted to humans from contact with bats and their secretions. Symptoms typically appear 4-14 days after infection and include fever, headache, vomiting, and cough; however, severe symptoms such as seizures and encephalitis can also occur. There have been no reports of person-to-person transmission in this current outbreak. However, person-to-person spread is possible with close contact and through nasal and respiratory secretions, blood, and urine. There is no approved treatment for Nipah virus infection, although the use of monoclonal antibody therapy for Nipah virus is currently being studied. Some drugs such as ribavirin and remdesivir have shown promise in animal models and select case reports. It is crucial that the steps to prevent Nipah virus infection be taken, as this is a severe and highly lethal infection. Case fatality rates in previous outbreaks range from 40-75 percent.

Comment: Nipah virus infection is a viral zoonotic disease caused by the Nipah virus (NiV) from the genus Henipavirus. Fruit bats, also known as flying foxes, are the primary zoonotic host and can transmit the virus to humans and animals—particularly livestock such as pigs and horses. The virus can spread to people through consumption of raw date palm sap and fruit that has been contaminated with bat secretions (saliva, urine). Transmission can also occur through close contact with an infected animal or its bodily fluids.

<u>Infection Control Measures</u>

Because NiV can spread person-to-person, CDC recommends standard infection control practices including contact and droplet precautions: The recommended PPE for health care workers caring for patients suspected or confirmed to be infected with Nipah virus (NiV) includes N95 mask, isolation gown AAMI PB70 Level 1 –3 have increasing levels of resistance to fluids, and Level 4 is tested for viral penetration, gloves non-sterile medical exam gloves; double gloving and the use of extended cuff gloves may be advised, and eye protection. Like Ebola virus, NiV is a Tier 1 enveloped virus—the easiest to inactivate with the right

disinfectant. Waste generated in the care of patients with NiV infection, including laboratory waste and used PPE, is considered Category A waste.

Marburg virus Equatorial Guinea February 28, 2023

Equatorial Guinea announced its first outbreak of Marburg virus. The WHO has confirmed 11 deaths and 16 other possible infections. According to news sources, neighboring Cameroon also suspects two cases of the virus.

The virus causes extreme fatigue, blood in the vomit, and diarrhea. The WHO reports that the virus spreads quickly and causes a high fatality rate. The virus comes from fruit bats and can easily be spread from person-to-person. Incubation period is up to 21 days. The virus can easily be transmitted and HCWs are at high risk. Body fluids including breast milk and semen can also carry the virus.

According to the CDC, fruit bats don't show signs of infection. The only other virus that is related to Marburg is Ebola. There is no vaccine or medication to treat the virus.

Comment: Marburg virus, like Ebola, spreads through contact with an infected patient's body fluids. It has a fatality rate as high as 88%, and there are no approved vaccines or treatments, though some vaccines are in clinical trials.

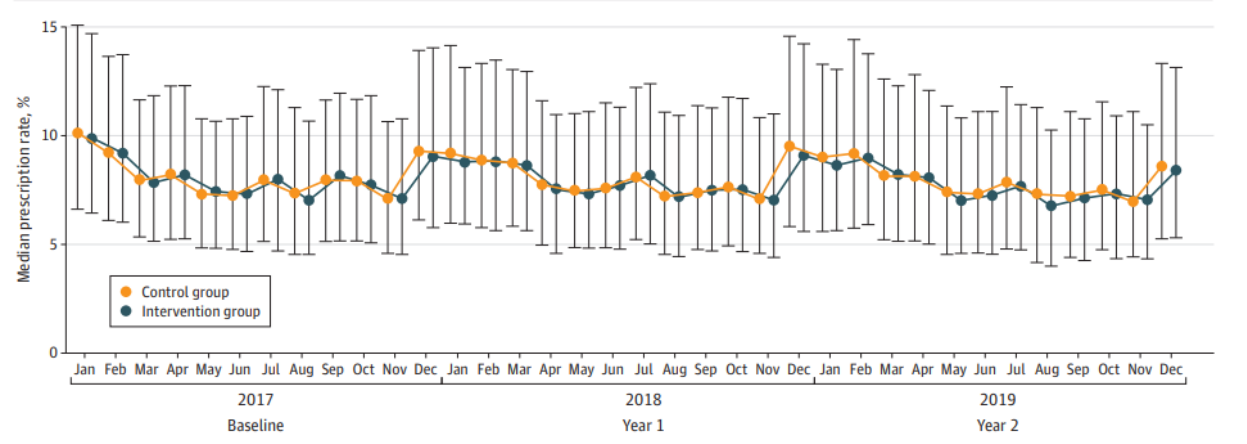
Effect of Antibiotic Prescription Audit and Feedback on Antibiotic Prescribing in Primary Care A Randomized Clinical Trial. JAMA Intern Med published online February 6, 2023

doi:10.1001/jamainternmed.2022.6529

This a RCT included 3,426 primary care physicians and pediatricians in Switzerland who were among the top 75% prescribers of antibiotics. The researchers conducted the trial from January 1, 2018, to December 31, 2019. The physicians were randomly assigned in a 1:1 ratio to undergo quarterly antibiotic prescribing audit and feedback with peer benchmarking or no intervention for 2 years. Those in the intervention group received evidence-based guidelines for UTI and respiratory tract infection management and information about community antibiotic resistance. For audit and feedback, the researchers used anonymized patient-level claims data from the health insurers that serve roughly 50% of people insured in Switzerland. The researchers noted that those in the intervention group were blinded regarding the nature of the trial, and those in the control group did not know of the trial. The primary outcome was the overall antibiotic prescription rate per 100 consultations in the second year of intervention (long-term intervention effect). The secondary outcomes were (1) overall antibiotic use per 100 patient consultations in the first year (short-term intervention effect) (2) and over 2 years while considering 2 repeated measurements, over the first and the second year of intervention; (3) use of broad-spectrum antibiotics (FQ and oral cephalosporins) per 100 patient consultations;

(4) all-cause hospitalizations and infection-related hospitalizations; (5) antibiotic use in 3 specific patient age groups (≤5 years, 6-65 years, and >65 years). The last 3 secondary outcomes were to be evaluated separately over the second and first years of the intervention.

A total of 3426 physicians were randomized to the intervention (n = 1713) and control groups (n = 1713) serving 629,825 and 622,344 patients, respectively, with a total of 4,790,525 consultations in the baseline year of 2017. In the entire cohort, a 4.2% (95% CI, 3.9%-4.6%) relative increase in the antibiotic prescribing rate was noted during the second year of the intervention compared with 2017. In the intervention group, the median annual antibiotic prescribing rate per 100 consultations was 8.2 (IQR, 6.1-11.4) in the second year of the intervention and was 8.4 (IQR, 6.0-11.8) in the control group. Relative to the overall increase, a –0.1% (95% CI, –1.2% to 1.0%) lower antibiotic prescribing rate per 100 consultations was found in the intervention group compared with the control group. No relevant reductions in specific antibiotic prescribing rates were noted between groups except for FQ in the second year of the intervention (–0.9% [95% CI, –1.5% to –0.4%]).



Comment: Previous trials that were conducted in selected general practices used antibiotic prescription feedback in combination with personalized expert feedback, academic detailing, or in combination with decision support systems and found a relative reduction in antibiotic prescriptions of approximately 5%. In a recent trial investigator in primary care practices performed a cluster-randomized trial of 3 behavioral interventions intended to reduce inappropriate prescribing for acute respiratory infections (ARI). They found that 2 socially motivated interventions—accountable justification and peer comparison— resulted in statistically significant reductions in inappropriate antibiotic prescribing (5-7%), while suggested alternatives, which lacked a social component, had no statistically significant effect). [JAMA. 2016;315(6):562-570] A follow-up study 12 months after removing behavioral interventions, found inappropriate antibiotic prescribing for ARIs increased relative to control practices—whose inappropriate prescribing rates continued to decrease. [JAMA. 2017;318(14):1391-1392] Swiss primary health care setting already had low antibiotic use when compared with other European countries. In this current study due to the long processing time of claims data by health insurers, prescription feedback was sent to physicians with a delay of 6 months[!], making it likely less relevant or more difficult to interpret in the actual clinical situation. Swiss claims data do not contain any diagnostic information from primary care; therefore, it was not possible to provide feedback on the appropriateness of antibiotic prescriptions. Whether health

system–wide antimicrobial stewardship programs with more individually tailored information on the appropriateness of antibiotic prescriptions, eventually combined with individual physician-targeted incentives, might achieve further reductions in antibiotic use should be evaluated in future trials. Such trials need much more detailed, routinely collected diagnostic and laboratory patient data. See next review.

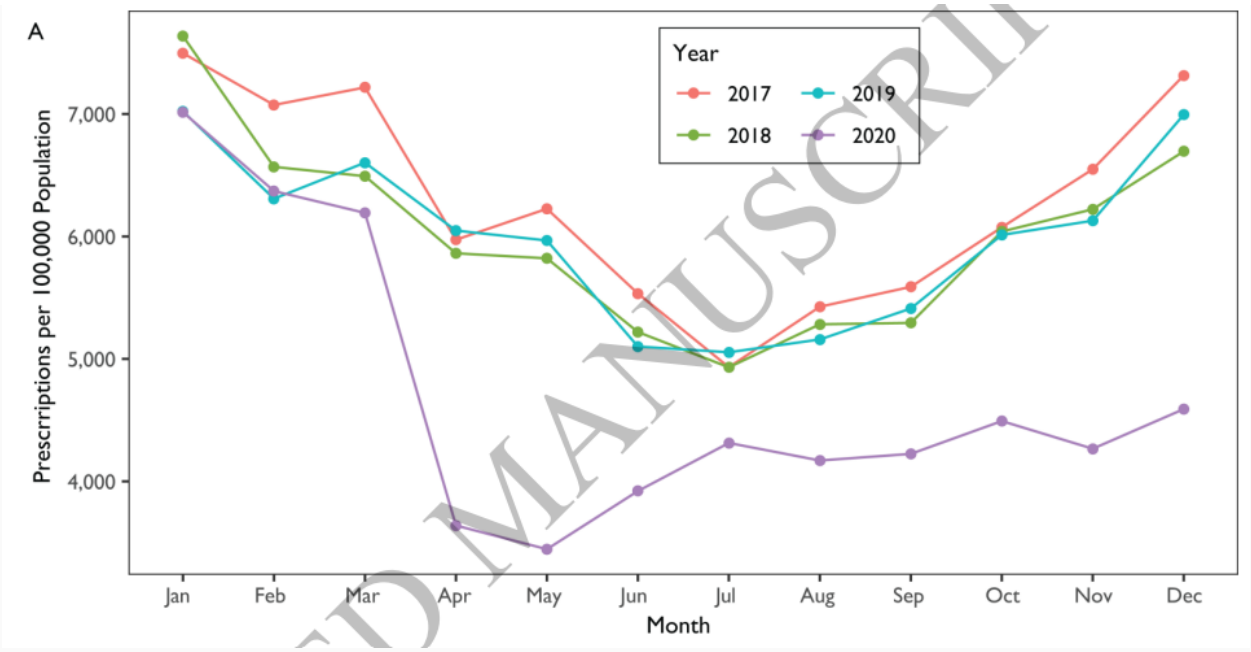
COVID-19 and Outpatient Antibiotic Prescriptions in the United States: A County-level Analysis OFID published online February 24, 2023

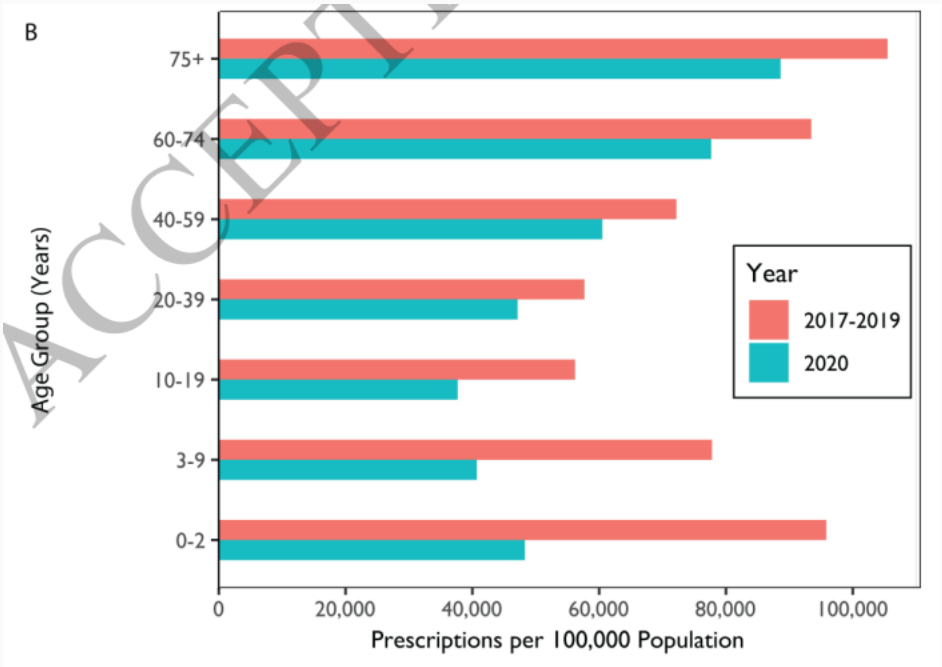
DOI: 10.1093/ofid/ofad096

Data on systemic antibiotic prescriptions (ATC code J01) collected from retail pharmacies in the US from January through December were obtained from IQVIA's Xponent database for the period from 2017 to 2020. The database contains the total number of outpatient prescriptions and the quantity of each antibiotic dispensed at the zip code and month level disaggregated by age group and sex. They excluded topical agents that are not systemically absorbed (e.g., Bacitracin) and medications not recommended for treatment of respiratory infections in the outpatient setting (e.g., Cefepime, Vancomycin, and Telavancin). Because defined daily doses (DDDs) are a standardized international measure of drug consumption, they were included as a sensitivity analysis. Data on Covid-19 cases were obtained from the New York Times via the Dartmouth Data Analytic Core (DAC). To standardize case rates and control for county- and state-level differences in demographics and healthcare access , population data, including each county's total population, age group-stratified population, the percentage of the population of people of color, the percentage of the population living in poverty, and the number of physicians' offices by county, were obtained from the US Census Bureau.

Total antibiotic prescriptions fell 26.8% between March and December 2020 compared to the same period from 2017 to 2019. Prescriptions fell significantly in April and May 2020. While there was some rebound in June and July, prescribing remained below average between July and December. States in the Southeast had the lowest percentage declines in prescribing from prior years. Overall prescribing of FQ dropped 28.9% from a mean of 6,738.3 prescriptions per 100,000 in previous years to 4,787.1 per 100,000 in 2020. In comparison, tetracyclines dropped 3.13%, while other antibiotics showed marginal changes. The largest change in prescriptions by age group was observed among children 0-2 years old, dropping 49.6% from 95,804.6 per 100,000 in previous years to 4,8276.0 per 100,000 in 2020.

Outpatient prescribing dispensed to all ages was positively correlated with monthly county-level Covid-19 cases; however, there was an inverse correlation between monthly cases and prescriptions dispensed to children. While the percentage increase per 100,000 population was not large at the county level, the total increase in the number of prescriptions attributable to Covid-19 cases was approximately 1,000 prescriptions for every 1% increase in Covid-19 cases.





Comment: These results suggest surges in cases were primarily associated with increased prescribing among adults. Since bacterial co-infection in Covid-19 patients is rare and other studies have identified antibiotic overuse [Internal and Emergency Medicine. 2021 Jun 29], it is likely that some of outpatient antibiotic prescribing in 2020 was inappropriate. This analysis also supports prior findings of decreased outpatient antibiotic prescribing due to reduced healthcare-seeking behavior at the beginning of the pandemic. They also found a strong correlation with prior prescribing suggesting that social norms could be the most important factors driving prescribing. Available data on school mandates did not allow for a detailed understanding of the

heterogeneity of instruction within counties or states or among different age groups. In addition, potential changes in county urban-rural classification since 2013 (the most recent classification scheme) or the small percentage of counties dropped from the analysis due to missingness could have biased results. They used data from the only source of large-scale antibiotic use in the US, and data provided by IQVIA is an estimation of total use. IQVIA data do not provide diagnostic decision information from the prescribing physician or the results of diagnostic tests, so they excluded antibiotics that are not typically used to treat respiratory infections in the outpatient setting.

The results demonstrate that providers may have inappropriately prescribed antibiotics for Covid-19, although more information on the prescribing physician's diagnosis or results of diagnostic tests is needed. While inappropriate treatment of viral infections remains common, the assumption has been that reducing diagnostic uncertainty as to the etiology of infection would reduce antibiotic use [ID Watch February 2023 reviewed a paper that found use of RIDT reduced antibiotic prescribing Clin Infect Dis published online February 1, 2023] however, the evidence here suggests that antibiotic use may have continued even when infections were likely viral. Further research is needed to understand why clinicians continue to prescribe antibiotics in these situations and how to modify their prescribing behavior. Second, while inappropriate prescribing remains a common problem in the outpatient setting, the results from this analysis bolster similar studies suggesting there remain unknown factors – —prescribing norms – driving variation in use. Lastly, as in prior studies pediatrics outperforms adult prescribing.

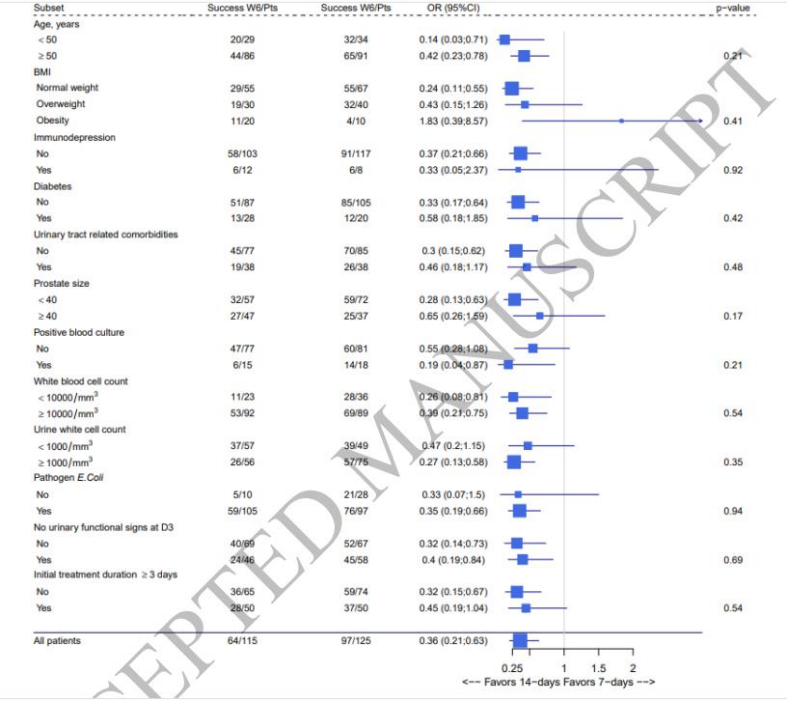
Antimicrobial for 7 or 14 days for febrile urinary tract infection in men: a multicenter noninferiority double blind placebo-controlled, randomized clinical trial Clin Infect Dis published online February 14, 2023

DOI: 10.1093/cid/ciad070

In men with afebrile urinary tract infection (UTI), a 7-day course of antibiotics may be sufficient [*JAMA* 2021; 326:324-331] — but what about a sicker population? In a noninferiority trial, investigators in France randomized men with febrile UTI to 7 or 14 days of antibiotics and evaluated treatment success at 6 weeks as defined by clinical success (lack of fever), microbiologic success (negative urine culture), and absence of subsequent antibiotics against the isolated pathogen. Men were eligible if they had a febrile urinary tract infection and urine culture showed a single pathogen. Participants were treated with ofloxacin or third generation cephalosporin at day 1, then randomized at day 3-4 to either continue ofloxacin for 14 days total treatment, or for 7 days followed by placebo until day 14. Randomization occurred at day three or day four after antibiotic treatment initiation. Randomization criteria were a positive urine culture (≥103 CFU/mL) with a single pathogen susceptible to nalidixic acid, FQ, and 3rd generation cephalosporins, the possibility of oral treatment, a temperature <38°C under empirical antimicrobial therapy, no prostatic abscess and no post-voiding residual volume >100 mL on ultrasound.

Among 240 participants (median age, 60.4) the most common pathogen was *E coli*, and among 196 participants with blood cultures, results were positive in 17%. At baseline, certain comorbidities were more prevalent in the 7-day than the 14-day group (e.g., obesity [17% vs.

8%], immunosuppression [10% vs. 6%], diabetes [24% vs. 16%], kidney disease [11% vs. 5%]). At 6 weeks, rates of treatment success were 56% (7-day) compared with 78% (14-day) and rates of clinical success were 96% and 100%. There were no between-group differences in acquisition of drug-resistant *Enterobacterales* on rectal swab testing or in recurrence of UTI.



Comment: This trial demonstrates that a shorter course of 7 days of antibiotic therapy with ofloxacin was inferior to a longer course of 14 days in the treatment of febrile UTI in men and resulted in unfavorable outcomes in a higher percentage of participants. These results differ from those reported in other studies. However, most were all observational and most of them involved afebrile participants. A recent randomized trial found that among 272 men with afebrile UTI, treatment with ciprofloxacin or trimethoprim/sulfamethoxazole for 7 days was noninferior to 14 days of treatment, regarding resolution of UTI symptoms by 14 days after antibiotic therapy [*JAMA* 2021; 326:324-331]. This study included afebrile patients and the primary endpoint was assessed early (14 days) after completion of antibiotic treatment. The absence of fever may indicate a less severe UTI, thus allowing for a shorter treatment. However, in a post-hoc analysis of the subgroup of men with UTI from a trial on gram-negative bacteremia, no significant difference was demonstrated between 7 and 14 days of antibiotic therapy. [Clin Infect Dis. 2019; 13;69:1091-1098]

In the current trial, the success rate in the reference arm (14 days) was below the estimated success rate used to calculate the sample size. This could be related to the stringent definition of success used in this trial, which combined several criteria (clinical and microbiological cure and no use of antibiotics even for a reason other than UTI) and the time at which primary endpoint was assessed (6 weeks rather than 2 weeks as usually reported in other studies). Some imbalances between groups regarding obesity, immunodepression, diabetes, chronic kidney disease and *E. coli* infection were observed, likely due to the stratification of the randomization on type of patients and center resulting in 54 lists; however multivariate analysis showed that the adjusted treatment effect was not modified. Positive blood cultures were fairly

high indicating a sicker patient population. Bottom line, fever in men may represent a sicker population with the potential need for longer duration of therapy.

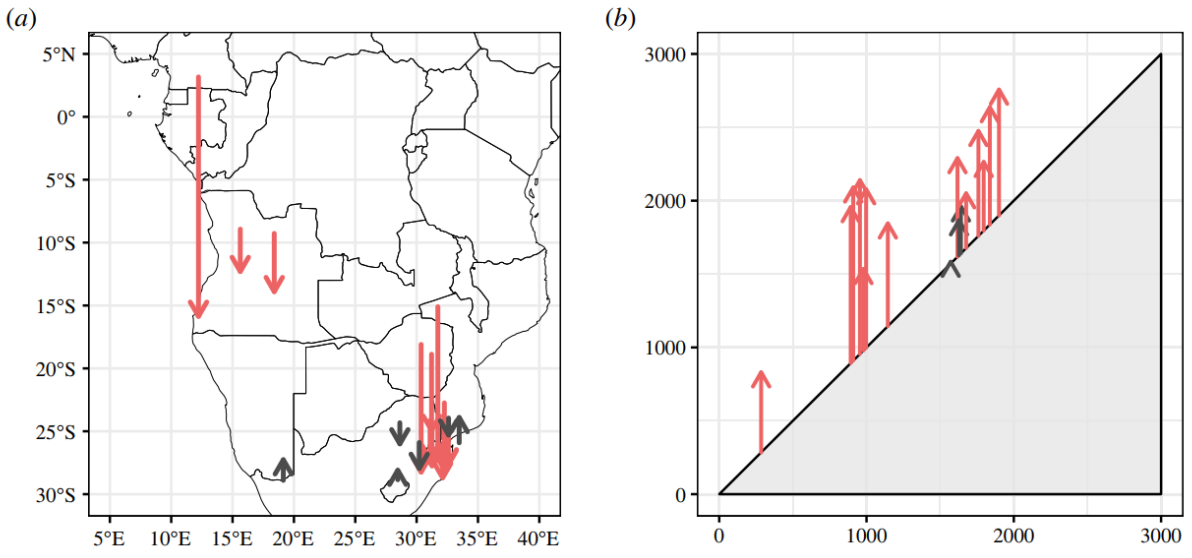
How Climate Change Is Spreading Malaria in Africa NY Times February 15, 2023

Warmer climates are expected to be advantageous for mosquitoes because they, and the parasites they carry, reproduce faster at higher temperatures. In a recent study (see below) from 1898-2016 Anopheles mosquitoes expanded their range by a cumulative average of 2,300 feet in elevation and to more than 300 miles south of the Equator.

Rapid range shifts in African Anopheles mosquitoes over the last century Biol. Lett. 2023;19: 20220365.

https://doi.org/10.1098/rsbl.2022.0365

The investigators used a recently published compendium of occurrence data for 22 species of *Anopheles* mosquitoes vectors of malaria in Africa. The dataset comprises over a century's (1898–2016) worth of long-term, systematic entomological surveys from malaria programmers, as well as other opportunistic data collected by researchers, gathered from a mix of peer-reviewed publications, technical reports, theses, and archival records. Using a simple regression approach, they estimate that these species' ranges gained an average of 6.5 m of elevation per year, and the southern limits of their ranges moved polewards 4.7 km per year. In both elevational and latitudinal maxima, they observed a strong and unambiguous signal consistent with long-term range expansion. (see figure below)



Comment: They found clear evidence that *Anopheles* mosquitoes have undergone rapid range shifts over the twentieth century, challenging a long-standing assumption in historical

epidemiology that mosquito ranges are mostly stationary over decades or centuries. Their findings were consistent with expectations for the direction and pace of climate linked range shifts, including previous estimates of climate velocity in sub-Saharan Africa. These findings also suggest a new facet of the complex and contentious relationship between climate change and shifting malaria endemicity in Africa. Confirming that climate change underlies these shifts, and applying similar methods to other disease vectors, are important directions for future research.

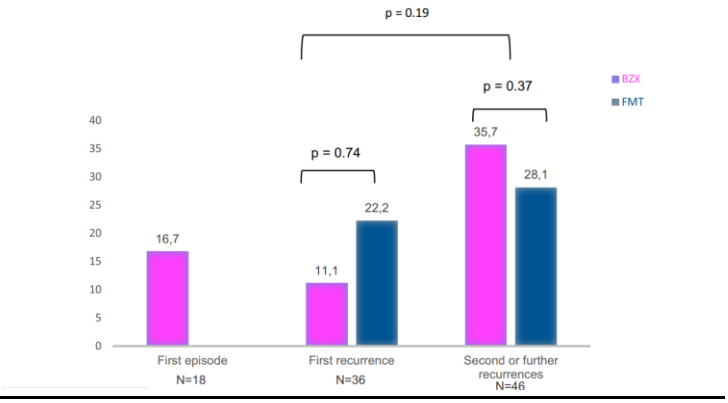
Real-world Use of Bezlotoxumab and Fecal Microbiota Transplantation for the Treatment of *Clostridioides difficile* Infection OFID published January 25, 2023

https://doi.org/10.1093/ofid/ofad028

This was a retrospective study conducted in a university hospital in which adult patients treated with BZX or FMT from January 2018 to April 2021 were included. The primary objective was to evaluate the effectiveness of BZX and FMT in preventing early (within 8 weeks) and late (within 1 year) CDI recurrences (rCDI). A multivariate analysis of risk factors for early recurrence was performed.

Of 1377 consecutive CDI episodes, 117 (8.5%) received BZX or FMT, with full information available for 100 of the episodes: 51 received BZX, and 49 received FMT. BZX was used mostly in immunosuppressed patients (66.7%) and in first episodes or first recurrences in 70.6% of the cases. FMT was prescribed only in rCDI. Despite the different conditions of the patients, there were no significant differences between BZX and FMT in preventing early rCDI (19.6% vs 24.5%; *P* = .55) or late rCDI (9.8% vs 18.4%; *P* = .31). In the multivariate analysis, risk factors for recurrence were presence of ≥2 previous rCDI episodes (odds ratio [OR], 2.90; 95% CI, 1.03–8.63) and use of non-CDI antibiotics (OR, 3.45; 95% CI, 1.24–9.57)

Percentage of recurrences at 8 weeks following BZX or FMT for each type of episode.



Comments: BZX and FMT were infrequently used in real-world practice (8.5% in this series) and in very different clinical scenarios, as BZX was more frequently assigned to patients with immunosuppression and for first and severe episodes, while FMT was indicated in cases with several prior CDI recurrences. Second, despite these differences, both strategies of treatment

had equivalent effectiveness, assessed in terms of early and late rCDI episodes. Third, BZX and FMT appeared to be more effective in the treatment of first recurrences compared with second or further rCDI episodes. At 1-year follow-up, BZX had a trend toward fewer late CDI episodes compared with FMT (9.8% vs 18.4%; *P* = .31), but they believe that this effect could be partially explained by the higher non-CDI-related mortality rate observed in the BZX group at 1 year of follow-up (27.5% vs 14.3%; *P* = .10). Current guidelines advocate the use of BZX for first recurrences and FMT for second or subsequent recurrences. [Clin Infect Dis 2018**;** 66:e1–48; Clin Microbiol Infect 2021; 27:S1–21] In a recent clinical trial comparing the use of SER-109 with standard treatment in patients with multiple rCDIs, the subgroup that previously received fidaxomicin had the lowest recurrence rates. [N Engl J Med 2022; 386:220–9] In this current study, they= investigators could not establish the effect of the combination of fidaxomicin with either FMT or BZX. They also observed an improvement in recurrence rates when FMT or BZX were administrated earlier in the course of disease (first episodes). This is in accordance with a recent publication [OFID 2020; 7:ofaa097]. This study used a retrospective design and there was considerable heterogeneity of patients selected in each arm of treatment. There was no control group making it difficult to estimate the effectiveness of BZX and FMT. Nevertheless, the recurrence rate in both groups was high which is in agreement with the results obtained in previous studies. [J Clin Gastroenterol 2021**;** 55:300–8; Clin Infect Dis 2022; 74: 1572–8. They could not determine if these treatments were effective in CDI episodes caused by 027 ribotypes, because in this series there were no 027-confirmed strains. See next review.

Safety and Tolerability of SER-109 as an Investigational Microbiome Therapeutic in Adults With Recurrent *Clostridioides difficile* Infection **A Phase 3, Open-Label, Single-Arm Trial.** JAMA Network Open. 2023;6(2):e2255758.

doi:10.1001/jamanetworkopen.2022.55758

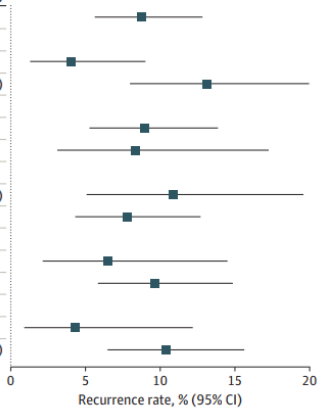
SER-109 is an investigational, oral microbiome therapeutic composed of purified Firmicutes spores, which has recently been found to be superior to placebo in reducing risk of recurrent CDI at 8 weeks in patients with 2 or more CDI recurrences. [N Engl J Med. 2022;386(3):220-229]

This study is a phase 3, single-arm, open-label trial (ECOSPOR IV) conducted at 72 US and Canadian outpatient sites from October 2017 to April 2022. SER-109 given orally as 4 capsules daily for 3 days following symptom resolution after antibiotic treatment for CDI. The main outcomes were safety, measured as the rate of treatment-emergent adverse events (TEAEs) in all patients receiving any amount of SER-109, and cumulative rates of recurrent CDI (toxin-positive diarrhea requiring treatment) through week 24 in the intent-to-treat population. There were 2 cohorts: (1) rollover patients from the ECOSPOR III trial who had CDI recurrence diagnosed by toxin enzyme immunoassay (EIA) and (2) patients with at least 1 CDI recurrence (diagnosed by polymerase chain reaction [PCR] or toxin EIA), inclusive of their acute infection at study entry.

263 were enrolled (180 [68.4%] female; mean [SD] age, 64.0 [15.7] years); 29 were in cohort 1 and 234 in cohort 2. Overall, 23 patients (8.7%; 95% CI, 5.6%-12.8%) had recurrent CDI at week 8 (4 of 29 [13.8%; 95% CI, 3.9%-31.7%] in cohort 1 and 19 of 234 [8.1%; 95% CI, 5.0%-12.4%] in cohort 2), and recurrent CDI rates remained low through 24 weeks (36 patients [13.7%; 95% CI, 9.8%-18.4%]). At week 8, recurrent CDI rates in patients with a first recurrence

were similarly low (5 of 77 [6.5%; 95% CI, 2.1%-14.5%]) as in patients with 2 or more recurrences (18 of 186 [9.7%; 95% CI, 5.8%-14.9%]). Analyses by select baseline characteristics showed consistently low recurrent CDI rates in patients younger than 65 years vs 65 years or older (5 of 126 [4.0%; 95% CI, 1.3%-9.0%] vs 18 of 137 [13.1%; 95% CI, 8.0%-20.0%]) and patients enrolled based on positive PCR results (3 of 69 [4.3%; 95% CI, 0.9%-12.2%]) vs those with positive toxin EIA results (20 of 192 [10.4%; 95% CI, 6.5%-15.6%]). Overall, 141 patients (53.6%) had TEAEs, which were mostly mild to moderate and gastrointestinal.

Baseline characteristic	Patients, No./ total No.	Recurrence rate, % (95% CI)
Overall	23/263	8.7 (5.6-12.8)
Age, y		
<65	5/126	4.0 (1.3-9.0)
≥65	18/137	13.1 (8.0-20.0)
Antibiotic regimen		
Vancomycin	17/191	8.9 (5.3-13.9)
Fidaxomicin	6/72	8.3 (3.1-17.3)
Sex		
Male	9/83	10.8 (5.1-19.6)
Female	14/180	7.8 (4.3-12.7)
Prior CDI episodes (including qualifying), No.		
2	5/77	6.5 (2.1-14.5)
≥3	18/186	9.7 (5.8-14.9)
Qualifying episode definition		
PCR alone	3/69	4.3 (0.9-12.2)
Toxin with or without PCR	20/192	10.4 (6.5-15.6)



Comment: The recurrence rate in the overall study population was 8.7%, corresponding to a sustained clinical response rate at 8 weeks of 91.3%, which was durable over 24 weeks. Recurrence rates were low regardless of diagnostic approach or number of preceding CDI episodes. In contrast, CDI recurrence rates reported in the literature range from 20% to 36% in those with first recurrence to 40% or greater for 2 or more recurrences. [Clin Infect Dis. 2012;55(suppl 2):S154-S161] Limitations include the open-label design of this study, in which all patients received SER-109, limiting any conclusions on efficacy.

Screening for Clostridioides difficile colonization at admission to the hospital: a multicentre study Clin Microbiol Infect published online March 5, 2023

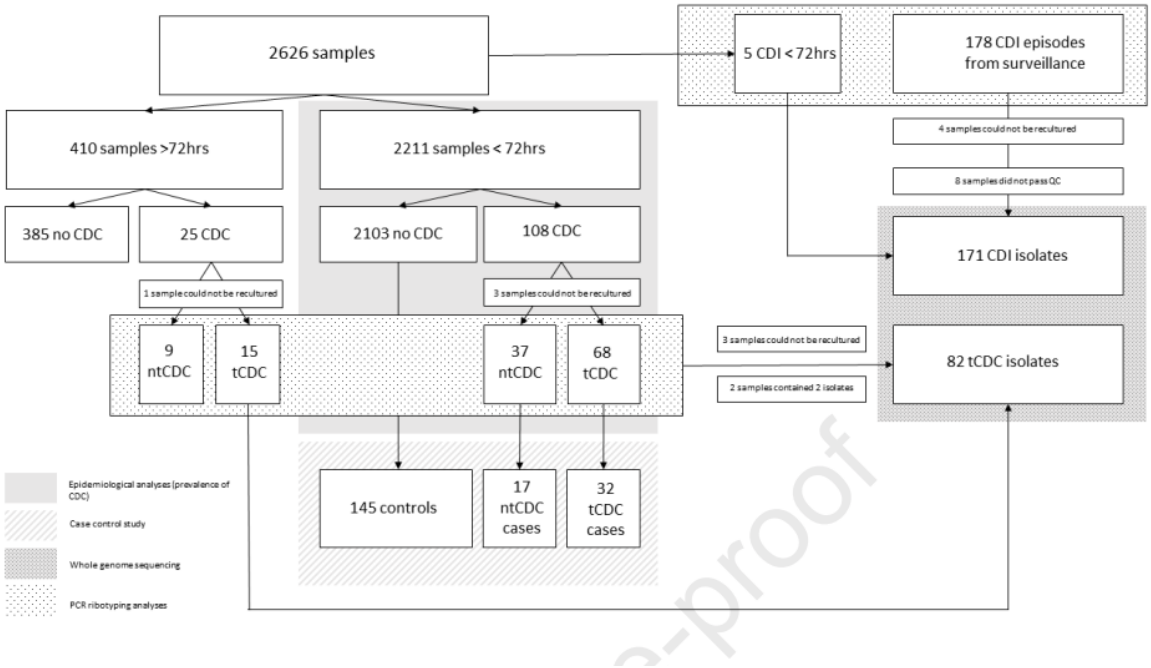
doi.org/10.1016/j.cmi.2023.02.022

The aim of the study was to determine the prevalence of C diff in the hospitals and investigate the value of a C. diff screening program for preventing colonized patients from progressing to CDI or transmitting C diff to other patients.

This is a multi-center study was performed in 4 hospitals. Newly admitted patients were screened for C diff. The risk to develop CDI during admission and one-year follow-up was assessed for colonized and non-colonized patients. C. difficile isolates from colonized patients were compared with isolates from incident CDI cases using core genome multi locus sequence typing (cgMLST) to determine if onwards transmission had occurred. . Patients with CDI at admission or CDI diagnosed within the first 72hrs of admission were excluded. Patients with a positive C. difficile culture but no diagnosis of CDI were considered C. difficile colonized (CDC).

The subset of CDC patients with a toxigenic strain in their stool cultures were considered toxigenic C. difficile colonized (tCDC). CDC patients were included as cases in the case control study. Stool culture for the presence of C. difficile was performed on a daily basis for new admissions. All identified isolates from (enrichment) culture were ribotyped by resolution capillary gel- based electrophoresis PCR-ribotyping. A multiplex PCR to detect toxin genes tcdA, tcdB, cdtA and cdtB was performed on cultured isolates. Strains positive for tcdA, tcdB or cdtA/cdtB were defined as toxigenic strains, all other strains were defined as non-toxigenic strains. Based on previous publications, ≤ 2 different alleles in the cgMLST were considered to be the same strain if the time frame of sampling was less than 124 days, and ≤ 3 different alleles if it was less than 1 year. Ward movement data of CDI and colonized patients were investigated if their isolates were genetically related.

CDC was present in 108 of 2,211 admissions (4.9%), while colonization with a toxigenic strain (tCDC) was present in 68 of 2,211 admissions (3.1%). Among the 108 colonized patients, 44 different PCR ribotypes (RTs) were found, but the "hypervirulent" RT027 was not detected. Of the 49 colonized patients and 145 control patients enrolled in a case-control study, none developed CDI within a month of admission or during 1-year follow up. Core genome multilocus sequence typing (MLST) identified six clusters with genetically related isolates from tCDC and CDI patients, but in these clusters only one possible transmission event from a tCDC to a CDI patient was identified by epidemiologic data.



Comment: In this endemic setting with a low prevalence of 'hypervirulent' strains screening for CDC at admission did not detect any CDC patients who progressed to symptomatic CDI and only one possible transmission event from a colonized patient to a CDI patient. Thus, screening on CDC at admission was not particularly useful. In addition, implementing screening was difficult.

While those tCDC patients that were detected did not have a high risk of progressing to CDI themselves and were not identified as an important direct source for incident hospitalized CDI cases," the investigators wrote: "Therefore, we think that we should focus on decreasing CDI susceptibility (e.g., by antimicrobial stewardship programs) and complying with general infection prevention measures to prevent spread from *C. difficile* and other nosocomial pathogens."

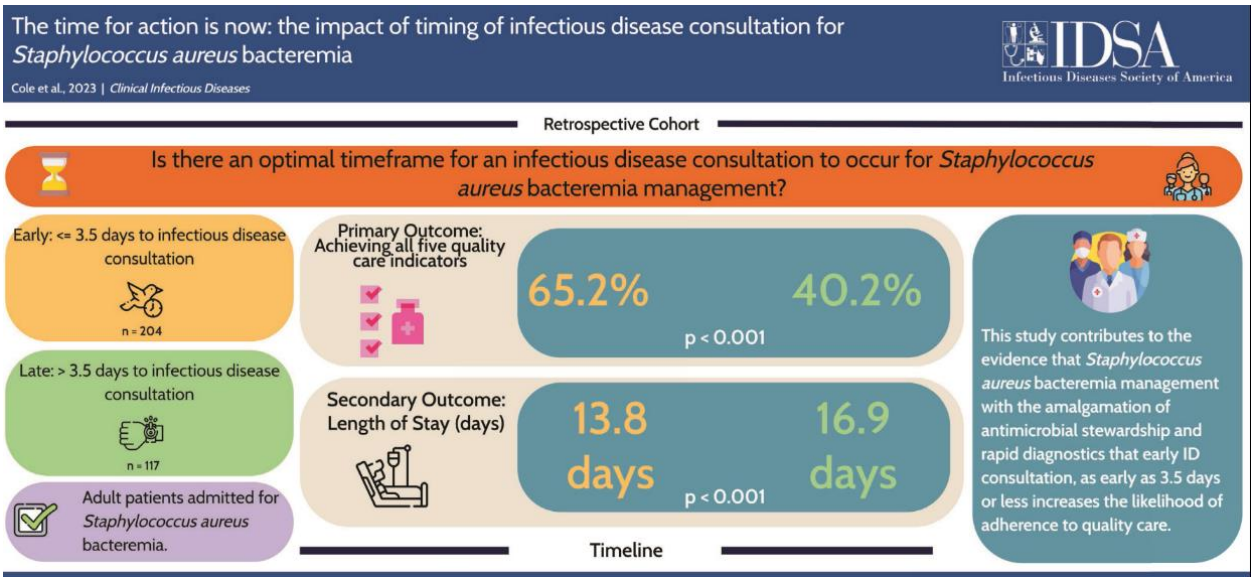
A few weaknesses: They may have missed a substantial amount of C. difficile introductions into the hospitals due to study design (screening was performed on only a few specific wards per hospital) and difficulties in study execution (stool samples were only received from half of 5200 consenting subject). Patients were only sampled once during the study. Consequently, they do not know how many patients were (a) transiently colonized, (b) persistent carriers, or (c) acquired colonization during admission, although this may affect both the risk for CDI progression and C. difficile transmission pressure. Environmental swabs were not taken during the study though colonized patients may contaminate the hospital environment with spores that can persist for long times. A direct transmission link can be missing when C. difficile acquisition occurs at a later moment from this contaminated hospital environment.

The time for action is now: the impact of timing of infectious disease consultation for Staphylococcus aureus bacteremia Clin Infect Dis published online March 3, 2023

This is a retrospective cohort study of adult patients admitted to the hospital from January 1, 2015 to January 1, 2020 with an initial episode of Staphylococcus aureus bacteremia (SAB) who received an ID consult (IDC) during the encounter were eligible for inclusion. A patient was excluded if they met any of the following criteria: age < 18 years old, relapse/reinfection of SAB from a previous encounter within one year prior, refusal of anti-staphylococcal antibiotic treatment, SARS-CoV-2 positive during the encounter for SAB, initiation of hospice care, transfer to another facility, or death within four days following collection of the initial positive blood culture. Included patients were stratified by time to IDC, defined as the time from collection of index positive blood culture to the placement of the IDC order. These patients were partitioned into two exposure groups (early and late) utilizing a machine learning algorithm (MLA). Rapid molecular testing was performed on the first positive blood culture with ASP intervention and IDC promotion 24 hours per day 7 days per week. The primary endpoint was a composite endpoint consisting of five quality care indicators including identification of the source of bacteremia in ≤ 4 days, follow-up blood cultures in ≤ 4 days, procurement of an echocardiogram in ≤ 4 days, use of parenteral (anti-MSSA or anti-MRSA agent) therapy, and appropriate recommended treatment duration. Secondary endpoints included all-cause in-hospital mortality, SAB recurrence within one year, length of stay, duration of bacteremia, early utilization of a β-lactam for MSSA bacteremia (within 48 hours of index culture positivity), and 30-day, 60-day, and 90-day readmission rates.

Using the Classification and Regression Trees algorithm, they identified a threshold value of 3.5 days to classify patients into either the early (≤ 3.5 days) or late (> 3.5 days) IDC exposure groups. Based on this partition, 63.6% (204/321) of patients were included in the early IDC group and 36.4% (117/321) in the late IDC group. Demographics and baseline characteristics were similar between IDC groups. Overall, 56.1% (180/321) achieved the composite endpoint. All five of the quality care indicators for the management of SAB were more frequently adhered to in the early IDC group (65.2% vs. 40.2%, P < .001), with an unadjusted odds ratio (OR) of

2.79 (95% CI, 1.75 – 4.46; P < .001). Among the individual components of the composite endpoint, identification of the source of SAB in ≤ 4 days (79.4% vs. 58.1%, P < .001) and use of appropriate empiric parenteral antibiotics (100% vs. 97.4%, P = .048) were significantly more likely to be achieved in the early group. Additionally, the median length of stay was shorter in the early group (13.8 days vs. 16.9 days, P < .001). Although there was no significant difference between 60-day and 90-day readmission rates, 30-day readmission was significantly lower in the early IDC group (19.1% vs. 32.5%, P = .007). Multivariable analysis identified early IDC in ≤ 3.5 days as an independent predictor for achieving the five quality care indicators (adjusted OR: 3.47, 95% CI 2.08 – 5.81; P < .001). Additionally, community-acquired SAB (adjusted OR: 2.69, 95% CI 1.27 – 5.68; P = .009) and source control procurement (adjusted OR: 4.12, 95% CI 2.45 – 6.93; P < .001) were identified as independent predictors for achieving the five quality care indicators.



Comment: This study supports existing evidence that early IDC, ASP, and rapid diagnostics as early as ≤ 3.5 days from index blood culture collection, increased the likelihood of adherence to a bundle of quality care indicators, decreased length of stay, and decreased 30-day readmission rate. The retrospective design and reliance on manual chart review may have resulted in data collection omissions. Curbside consultations are not well documented potentially excluding patients and misrepresenting the true effect of IDC on adherence to quality care indicators in SAB management. They do not discuss if TTE or TEE were used.

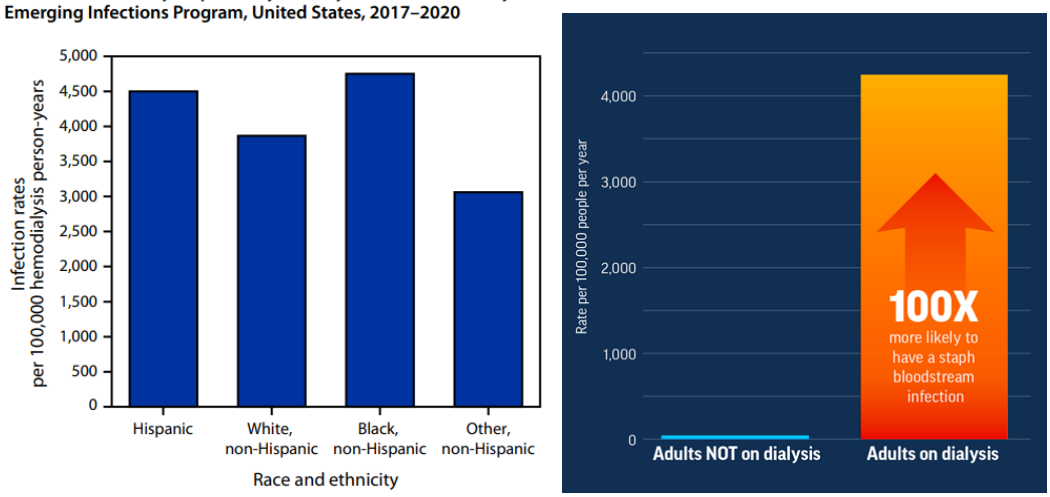
Vital Signs: Health Disparities in Hemodialysis-Associated Staphylococcus aureus Bloodstream Infections — United States, 2017–2020 MMWR 2023; 72:153-159

ESKD patients on dialysis are at increased risk for Staphylococcus aureus bloodstream infections (SAB), but racial, ethnic, and socioeconomic disparities associated with this outcome are not well described.

Surveillance data from the 2020 NHSN and the 2017–2020 Emerging Infections Program (EIP) were used to describe bloodstream infections (BSI) among patients on hemodialysis (hemodialysis patients) and were linked to population-based data sources to determine associations with race, ethnicity, and social determinants of health.

In 2020, 4,840 dialysis facilities reported 14,822 BSIs to NHSN; 34.2% were attributable to S. aureus. Among seven EIP sites, the SAB rate during 2017–2020 was 100 times higher among hemodialysis patients (4,248 of 100,000 person-years) than among adults not on hemodialysis (42 of 100,000 person-years). Unadjusted SAB rates were highest among non-Hispanic Black or African American (Black) and Hispanic or Latino (Hispanic) hemodialysis patients. Vascular access via central venous catheter was strongly associated with SAB (NHSN: adjusted rate ratio [aRR] = 6.2; 95% CI = 5.7–6.7 versus fistula; EIP: aRR = 4.3; 95% CI = 3.9–4.8 versus fistula or graft). Adjusting for EIP site of residence, sex, and vascular access type, SAB risk in EIP was highest in Hispanic patients (aRR = 1.4; 95% CI = 1.2–1.7 versus non-Hispanic White [White] patients), and patients aged 18–49 years (aRR = 1.7; 95% CI = 1.5–1.9 versus patients aged ≥65 years). Areas with higher poverty levels, crowding, and lower education levels accounted for disproportionately higher proportions of hemodialysis-associated SAB.

FIGURE 2. *Staphylococcus aureus* bloodstream infection rates* per 100,000 hemodialysis person-years, by race and ethnicity† — Emerging Infections Program, United States, 2017–2020

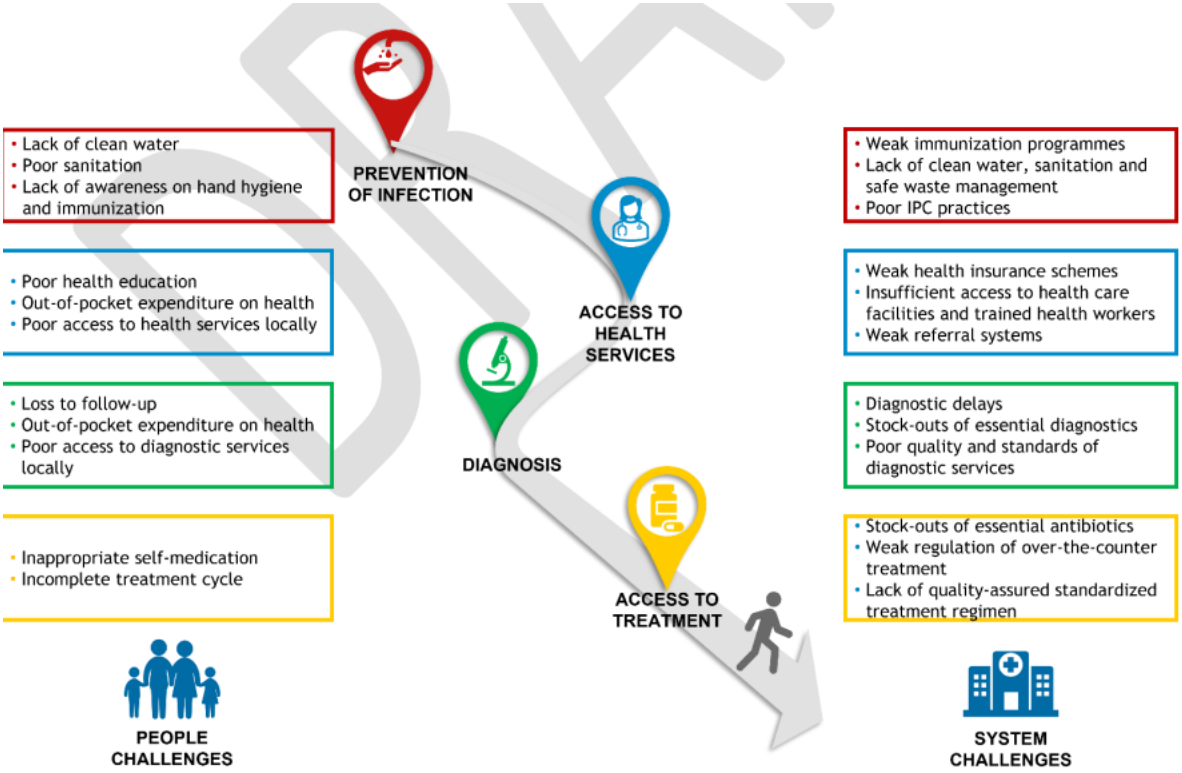


- **Comment:** Although vascular access type was the major risk factor for hemodialysis-associated SAB, race, ethnicity, and socioeconomic factors also affected infection rates and distribution, with Hispanic or Latino ethnicity as an independent risk factor. We need to prioritize prevention and optimized treatment of ESKD, identify and address barriers to lower-risk vascular access placement, and implement established best practices to prevent bloodstream infections. Increasing the use of vascular access types that are proven to be lower risk for infections, such as fistulas and grafts, for people starting and currently on dialysis is a critical step.

Draft WHO: People-centred framework for addressing antimicrobial resistance in the human health sector

The framework consists of 13 high-level interventions in the human healthcare sector that were developed through internal WHO consultations, multidisciplinary expert opinion, and review of existing evidence. The interventions span four pillars that are seen as critical to addressing AMR in healthcare settings: prevention of infections, access to essential health services, timely and accurate diagnosis, and appropriate and quality-assured treatment.

The interventions include implementing core infection prevention and control strategies in hospitals; ensuring an uninterrupted supply of antibiotics, vaccines, and diagnostics for AMR; improving laboratory and diagnostic infrastructure; and developing up-to-date, evidence-based infection treatment guidelines and antimicrobial stewardship programs. The target audience for the framework includes HCWs, ministry of health officials, and other experts and organizations working in the field of AMR at the national, regional, and global levels. WHO is also developing more detailed implementation guidance for each of the high-level interventions to be published by the end of 2023.

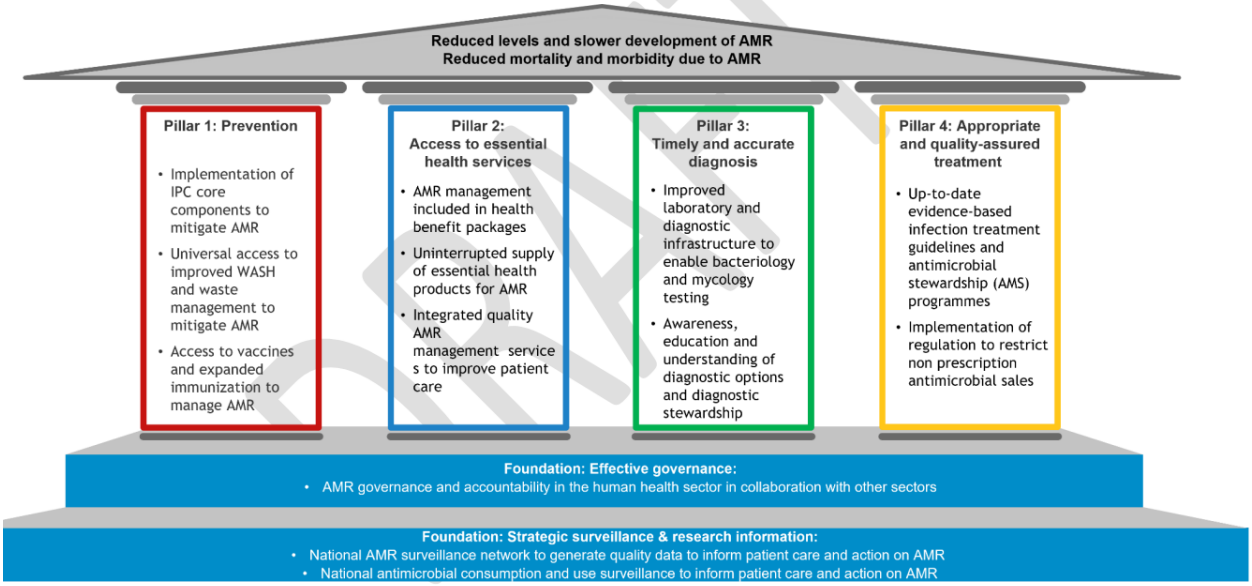


People-centered care is defined as “an approach to care that consciously adopts individuals’, carers’, families’ and communities’ perspectives as participants in, and beneficiaries of, trusted health systems that respond to their needs and preferences in humane and holistic ways,” organized around the health needs and expectations of people, rather than diseases.

Fig. 3. Steps for developing the people-centred framework

AMR: antimicrobial resistance; WHO: World Health Organization.

Comment: The framework seeks to provide a human face and to place people's perspectives and realities at the core of the AMR response, considering five key principles: (1) equity in access to health care; (2) quality of health care; (3) affordability of health products and services; (4) sustainability in the implementation of actions to address AMR; and (5) efficiency in the allocation of resources to achieve optimal health impact.



AMR: antimicrobial resistance; IPC: infection prevention and control; WASH: water, sanitation and hygiene.

Association of Proton Pump Inhibitor Use With Risk of Acquiring Drug-Resistant Enterobacterales. JAMA Network Open. 2023;6:e230470.

doi:10.1001/jamanetworkopen.2023.0470

To investigate the association between the use of PPIs and the risk of acquiring ESBL- or carbapenemase-producing Enterobacterales, investigators conducted a study involving 2,239 adult patients treated at two tertiary medical centers from December 31, 2018, to January 6, 2021. They conducted a nested case-control study to verify the association with PPIs and examine a possible dose-response association. They also looked at potential interactions with other microbiome-altering medications, such as antibiotics, laxatives, and immunosuppressant medications.

After identifying all the patients in the study who had positive results for ESBL- or carbapenemase-producing Enterobacterales during their hospitalization, the investigators randomly matched up to 5 patients who tested negative for those organisms to a control group. They then examined PPI use within 30 days before the index date in the two groups. The primary analysis adjusted for confounding factors such as sex, body mass index, presence of inflammatory bowel disease, Charlson Comorbidity Index score (which estimates risk of death based on underlying health conditions), and length of intensive care unit stay.

Among the 2,239 patients, 374 (51.6% male, mean age 61.1 years) were in the case group and 1,865 (51.0% male, mean age 60.9) were in the matched control group.

In the primary analysis, the adjusted incident rate ratio (aIRR) for acquiring ESBL- or carbapenemase-producing Enterobacterales with PPI use was 1.48 (95% confidence interval [CI], 1.15 to 1.91) at 30 days, with a higher risk among those with two daily PPI doses (aIRR, 1.75; 95% CI, 1.03 to 2.97). Use of H2RAs, which was much less common among patients, was not associated with an increased risk. Sensitivity analyses and the analysis of a pair-matched study with prospectively enrolled patients (aIRR, 2.96, 95% CI, 1.14 to 7.74) yielded similar results as the primary analysis, and the findings were consistent in subgroups and corroborated by a negative-control exposure analysis. The use of other microbiome-altering medications together with PPIs did not reveal additional risks, but antibiotics (aIRR, 2.78; 95% CI, 2.14 to 3.59) and laxatives (aIRR, 2.26; 95% CI, 1.73 to 2.92) were independently associated with more than a twofold increased risk of acquiring ESBL- or carbapenemase-producing Enterobacterales.

Comment: Mechanistically, reduction of gastric acidity may lead to increased gastric passage of pathogens or viable exogenous drug-resistant strains, delayed gastric emptying, increased bacterial translocation, and dysbiosis, resulting in intestinal colonization or infection. A recent systematic review and meta-analysis summarized the association of PPI use with the risk of colonization with ESBL- or carbapenemase-producing Enterobacterales. [JAMA Intern Med. 2020; 180:561-571] The present study further corroborates the risk associated with PPI use found in earlier studies included this meta-analysis. The variables captured in this study are also known to be associated with the likelihood of PPI use and may be surrogate markers of frequent exposure to antibiotics. The risk factors associated with acquisition of ESBL- or carbapenemase-producing Enterobacterales identified in the study population were consistent with well-known factors reported in previous studies30,38 and further strengthened the validity of these findings. Notably, laxatives yielded a higher risk than previously reported.39 Similar to antibiotics,40 it is possible that the positive association of laxatives with acquisition of ESBL- or carbapenemase-producing Enterobacterales is mediated via their disturbance of the microbiome.

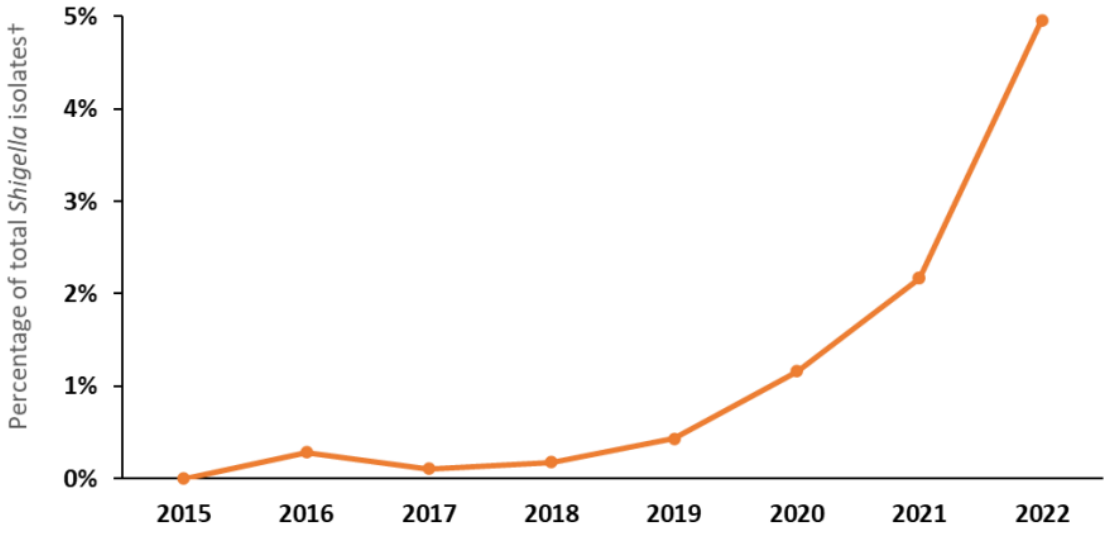
Despite their careful analyses, there still remains the possibility of unmeasured confounding. Their analyses were based on prevalent rather than incident use of PPIs, which could introduce prevalent-user bias. They used clinical cultures instead of screening cultures to assess the presence or absence of ESBL- and/or carbapenemase-producing strains, which could lead to misclassification of patients in the control group, in whom carriage would go undetected.

Regardless, these findings reinforce the need to promote judicious use of PPIs to mitigate the risk of acquiring drug resistant Enterobacterales among hospitalized patients.

Increase in Extensively Drug-Resistant Shigellosis in the United States HAN
February 24, 2023

CDC has been monitoring an increase in extensively drug-resistant (XDR) Shigella infections (shigellosis) reported through national surveillance systems. In 2022, about 5% of Shigella infections reported to CDC were caused by XDR strains, compared with 0% in 2015. Clinicians treating patients infected with XDR strains have limited antimicrobial treatment options. CDC defines XDR Shigella bacteria as strains that are resistant to all commonly recommended empiric and alternative antibiotics — azithromycin, ciprofloxacin, ceftriaxone, TMP-SMX, and ampicillin. Currently, there are no data from clinical studies of treatment of XDR Shigella to inform recommendations for the optimal antimicrobial treatment of these infections. As such, CDC does not have recommendations for optimal antimicrobial treatment of XDR Shigella infections. The isolates are mainly *S sonnei* (66%) and *S flexneri* (34%).

Figure: Percentage of *Shigella* isolates that showed an extensively drug resistant (XDR)* phenotype or genotype in the United States, by year, 2015–2022†



Comment: Shigella bacteria are easily transmissible. XDR Shigella strains can spread antimicrobial resistance genes to other enteric bacteria. The HAN alert comes on the heels of a reports about XDR *Shigella* outbreaks in Europe, and the United Kingdom. Many of these outbreaks have occurred among networks of men who have sex with men (MSM), with transmission occurring through sexual activity. Given these potentially serious public health concerns, CDC asks healthcare professionals to be vigilant about suspecting and reporting cases of XDR Shigella infection to their local or state health department and educating patients and communities at increased risk about prevention and transmission.

Mpox in people with advanced HIV infection: a global case series. Lancet published online February 21, 2023

doi.org/10.1016/ S0140-6736(23)00273-8

Starting on May 11, 2022, a network of clinicians from 19 countries evaluated 382 adult mpox patients who also had advanced HIV, including 27 of the 60 people globally who died by the end of the study on Jan 18, 2023. The current global mpox outbreak, which began in May 2022, has infected over 86,000 people in 110 countries. Ninety-six of them have died. The investigators report HIV patients have accounted for 38% to 50% of mpox cases.

Participants included 367 cisgender men, 4 cisgender women, and 10 transgender women. Median participant age was 35 years. At mpox diagnoses, 349 (91%) of 382 participants had HIV, 228 of 349 (65%) were adherent to ART, and 32 of 382 (8%) also had an additional infection related to their suppressed immune system. The median CD4 cell count (an indicator of immune function) was low, at 211 cells per millimeter cubed (cells/mm^3), with 22% of patients having CD4 cell counts of less than 100 cells/mm^3 and 25% with 100 to 200 cells/mm^3. Just over half of patients had an undetectable HIV viral load.

Severe complications were more common in patients with a CD4 count less than 100 cells/mm^3 than in those with more than 300 cells/mm^3 and included necrotizing skin lesions (54% vs 7%), lung dysfunction sometimes accompanied by nodules (29% *vs* 0%), and secondary infections and sepsis (44% *vs* 9%). A total of 107 patients (28%) were hospitalized, and 27 (25%) of them died. All deaths were among patients with CD4 counts of less than 200 cells/mm^3, and most occurred in those with a high HIV viral load. The clinicians suspected an inflammatory immune reaction to mpox in 21 (25%) of 85 people started or restarted on ART, 12 (57%) of whom died. Sixty-two of 382 patients (16%) received the Tpoxx smallpox/mpox drug (tecovirimat), and 7 (2%) were given other antivirals (cidofovir or brincidofovir). Three cases of tecovirimat resistance were identified. The article has several representative pictures to illustrate the severity of lesions.

Only 26 of the study participants (7%) had received the Jynneos mpox vaccine. Sixteen (4%) had been vaccinated before 2022, presumably for smallpox.

Comment: Those of us who have taken care of AIDS patients with mpox can confirm this is a much more difficult population to treat. Several have been treated with tecovirimat and either have a very slow response or recur after tecovirimat is stopped. Clinicians should also be aware that starting antiretroviral therapy in people with advanced HIV and mpox could contribute to deterioration and possible death, possibly as part of an immune reconstitution syndrome. Their data reinforces the importance of HIV and CD4 testing in mpox cases. The findings support the recommendations that all people at risk of mpox with HIV and a CD4 cell count of less than 200 cells per mm^3 should be prioritized for preventive mpox vaccination. see next review.

CDC Panel Recommends Jynneos vaccine for All Adults at Risk

The panel of outside experts voted unanimously on February 22nd in favor of use of two doses of the Jynneos vaccine, and finalizing the interim guidelines provided by CDC during the mpox outbreak in the United States. The recommendation of the committee is based on studies that showed vaccine effectiveness of 66%-83% for patients with full vaccination and 36%-86% for partial vaccination with no severe adverse effects. The intradermal injection is the preferred form of administration for adults during the outbreak but is also approved as a subcutaneous injection.

Comments: In the US, more than 29,000 cases of mpox were reported last year, including two deaths, according to the CDC. High risk persons such as HIV should be prioritized to receive the vaccine. We are still seeing low level transmission in the US.

Screening and Testing for Hepatitis B Virus Infection: CDC Recommendations — United States, 2023 MMWR 2023; 72(1);1–25

The CDC now recommends that adults should be tested for hepatitis B virus (HBV) at least once in their lifetime. An estimated 580,000 to 2.4 million individuals are living with HBV infection in the US, and two thirds may be unaware they are infected. Risk-based testing alone has not identified most persons living with chronic HBV infection and is considered difficult for providers to implement. Early diagnosis and treatment of chronic HBV infections reduces the risk for cirrhosis, liver cancer, and death.

The guidance now recommends using the triple panel (HBsAg, anti-HBs, total anti-HBc) for initial screening. Pregnant people should be screened ideally in the first trimester of each pregnancy, regardless of vaccination status or testing history. Pregnant people who have already received timely triple panel screening for hepatitis B and who have no new HBV exposures only need HBsAg screening, the guidelines state.

The document also added three groups at a higher risk for HBV infection: those incarcerated or formerly incarcerated, people with current or past hepatitis C virus infection, and people with current or past sexually transmitted infections and multiple sex partners. Those at higher risk for HBV should be screened periodically [more than once], based on shared decision-making between the provider and patient as well as individual risk and immune status.

Comment: In the US, the outcomes of chronic HBV infection has disproportionately affected Asian and Black persons; Asian people are 9 times and Black people are 2.5 times more likely to die from hepatitis B–related complications than non-Hispanic White persons.

Since 1988 the recommendation has been to annually screen for hepatitis B in pregnancy. This has resulted in a significant decrease in perinatal HBV infection through prophylaxis with hepatitis B vaccine and immune globulin. Universal hepatitis B screening of adults complements the 2022 ACIP recommendation for universal hepatitis B vaccination of adults

aged 19 to 59 years (in addition to adults >59 years with risk factors for HBV infection or who request vaccination) to protect the large unvaccinated adult population from hepatitis B. Although the new ACIP recommendation does not require adults to receive prevaccination hepatitis B testing, when feasible, the triple panel can save vaccination costs by identifying adults who do not need additional vaccine doses (i.e., people who test positive for HBsAg or total anti-HBc).

In summary, I believe the new CDC recommendations for universal screening of adults for HBV infection are a key step toward reducing chronic HBV–related morbidity and mortality in the US.

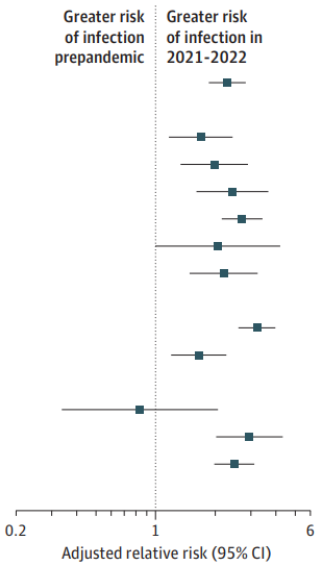
Household Transmission of Influenza A Viruses in 2021-2022. JAMA 2023; 329:482-489.

doi:10.1001/jama.2023.0064

This is a prospective study of influenza transmission in households in 2 states before the Covid-19 pandemic (2017-2020) and in 4 US states during the 2021-2022 influenza season. Primary cases were individuals with the earliest laboratory-confirmed influenza A(H3N2) virus infection in a household. Household contacts were people living with the primary cases who self-collected nasal swabs daily for influenza molecular testing and completed symptom diaries daily for 5 to 10 days after enrollment.

During the prepandemic seasons, 152 primary cases (median age, 13 years; 3.9% Black; 52.0% female) and 353 household contacts (median age, 33 years; 2.8% Black; 54.1% female) were included and during the 2021-2022 influenza season, 84 primary cases (median age, 10 years; 13.1% Black; 52.4% female) and 186 household contacts (median age, 28.5 years; 14.0% Black; 63.4% female) were included in the analysis. During the prepandemic influenza seasons, 20.1% (71/353) of household contacts were infected with influenza A(H3N2) viruses compared with 50.0% (93/186) of household contacts in 2021-2022. The adjusted relative risk of A(H3N2) virus infection in 2021-2022 was 2.31 (95% CI, 1.86-2.86) compared with prepandemic seasons.

	2021-2022 Influenza season		Pre-COVID-19 influenza seasons (2017-2018 and 2018-2019)		Adjusted relative risk of infection for 2021-2022 vs prepandemic seasons (95% CI)[a]
	No. of contacts	No. of infected contacts (%)	No. of contacts	No. of infected contacts (%)	
Overall	186	93 (50.0)	353	71 (20.1)	2.31 (1.86-2.86)
Age, y					
0-4	11	8 (72.7)	26	10 (38.5)	1.69 (1.17-2.46)
5-11	37	18 (48.6)	70	17 (24.3)	1.98 (1.34-2.94)
12-17	20	11 (55.0)	48	9 (18.8)	2.45 (1.61-3.72)
18-49	95	44 (46.3)	157	24 (15.3)	2.74 (2.16-3.48)
50-64	12	5 (41.7)	38	7 (18.4)	2.07 (1.00-4.28)
≥65	11	7 (63.6)	14	4 (28.6)	2.21 (1.49-3.29)
Current season influenza vaccination					
Unvaccinated	101	59 (58.4)	149	26 (17.4)	3.26 (2.63-4.04)
Vaccinated	85	34 (40.0)	204	45 (22.1)	1.66 (1.20-2.28)
Contact with primary case after symptom onset					
No time or <1 h	24	4 (16.7)	68	13 (19.1)	0.83 (0.34-2.07)
1-4 h	29	14 (48.3)	88	14 (15.9)	2.99 (2.03-4.40)
>4 h	133	75 (56.4)	197	44 (22.3)	2.50 (1.98-3.16)



Comment: In this study there was a significantly increased risk of household transmission of influenza A(H3N2) in 2021-2022 compared with prepandemic seasons. Additional research is needed to understand reasons for this association. There were substantial differences in age, race, and ethnicity of participants enrolled during the 2021-2022 influenza season compared with participants enrolled prior to the pandemic. It is possible that findings reported here are due to confounding related to these differences.

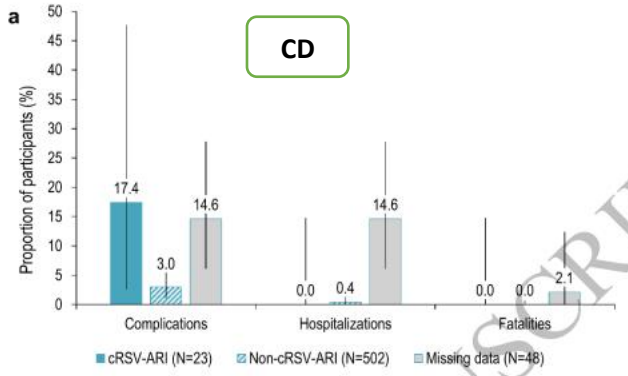
Respiratory syncytial virus disease burden in community-dwelling and long-term care facility older adults in Europe and the United States: A prospective study.

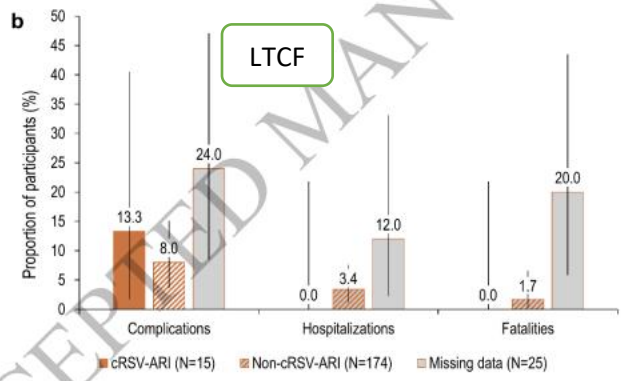
OFID published online March 1, 2023

doi.org/10.1093/ofid/ofad111

The investigators assessed the burden of confirmed RSV-acute respiratory infections (cRSV-ARI) in community-dwelling (CD) adults and those in long-term care facilities (LTCF). This is a prospective cohort study covering 2 RSV seasons (October 2019/March 2020, October 2020/June 2021). RSV-ARIs were identified through active surveillance, in medically stable CD-adults ≥50 years (Europe) or LTCF-adults ≥65 years (Europe/United States). RSV infection was PCR-confirmed from combined nasal/throat swabs.

Of 1981 adults enrolled, 1251 CD- and 664 LTCF-adults (season 1) and 1223 CD- and 494 LTCF-adults (season 2) were included in analyses. During season 1, overall incidence rates (IRs; cases/1000 person-years) and attack rates (ARs) for cRSV-ARI were 37.25 (95% confidence interval: 22.62–61.35) and 1.84% in CD-adults and 47.85 (22.58–101.4) and 2.26% in LTCF-adults. Complications occurred for 17.4% (CD) and 13.3% (LTCF) of cRSV-ARIs. No cRSV-ARIs led to hospitalization/death. Viral pathogens were co-detected in ≤17.4% of cRSV-ARIs.





Comment: RSV is an important cause of disease burden in CD- and LTCF-adults. Despite the observed low severity of cRSV-ARI, these results support the need for RSV prevention strategies among adults ≥50 years. The case definition (excluding infections with mild respiratory symptoms) may have led to an underestimation of RSV incidence. The relatively small sample size and healthier condition of the study population might explain the fact that RSV complications leading to hospitalization were not seen. However, a recent study has reported around 5.2 million confirmed RSV-ARI episodes, 470,000 related hospitalizations and 33,000 in-hospital deaths were estimated to occur in 2019, in a meta-analysis assessing the burden of RSV-ARI in adults ≥60 years of age from high-income. [Influenza Other Respir Viruses 2022:in press] See next review.

FDA advisors recommend first-ever RSV Vaccines for Adults February 28, 2023

A majority of the FDA's advisors said the safety and efficacy data supports using Pfizer's and GSK's RSV vaccine in adults ages 60 and older. But several FDA advisors said there could be a significant safety issue after two vaccine recipients out of about 20,000 developed Guillain-Barre syndrome. One recipient of the GSK vaccine also developed Guillain-Barré nine days after getting the vaccine. Two recipients of the GSK vaccine, both 71 and from South Africa, developed acute disseminated encephalomyelitis. FDA considers these cases possibly related. Other advisors were frustrated by a lack of efficacy data on people immunocompromised and nursing home residents. The vaccine was about 86% protective against lower respiratory tract illness with three or more symptoms, and 66.7% effective against the same condition with two or

more symptoms, according to an FDA review of Pfizer's data. The symptoms included wheezing, shortness of breath, rapid and shallow breathing as well as mucus production. The GSK vaccine was nearly 83 percent effective in lower respiratory tract illness in a study of about 25,000 patients — half on the vaccine and half on a placebo, according to data the company provided to the FDA. Both vaciines are protein based.

In the first vote Tuesday on Pfizer, seven FDA committee members said the safety data was adequate for an approval, while four said it was not, and one member abstained. In the second vote, seven committee members said the vaccine effectiveness data was adequate, while four said it was not, and one member abstained. After hours of deliberation over safety concerns, the FDA advisory panel on Wednesday by a vote of 10-2 to recommend approval of the GSK vaccine.

Comment: In adults ages 65 and older, RSV causes 6,000 to 10,000 deaths and 60,000 to 160,000 hospitalizations per year, according to the CDC. The risk of hospitalization increases with age, and adults ages 70 and older are more vulnerable. Among adults of all ages hospitalized with RSV, 19% require intensive care and 4% die, according to CDC data from three seasons. Mortality is the highest among seniors.

Concerned about the Guillain-Barre and acute disseminated encephalomyelitis cases will require a larger study population to determine whether there's an actual link to the vaccine. The vaccine was tested in a relatively healthy population in which hospitalizations were low, and some felt there was not any data on nursing home residents and people in poor health. It is unclear what the FDA's final decision will be, however, the FDA typically abides by advisory committee decisions and could grant formal approval within months. Both Pfizer and GSK said they would conduct continuing safety monitoring of the vaccines if they were approved by the FDA.

Physical interventions to interrupt or reduce the spread of respiratory viruses.

Cochrane Database of Systematic Reviews 2023, Issue 1. Art. No.: CD006207.

DOI: 10.1002/14651858.CD006207.pub6.

Viral epidemics or pandemics of acute respiratory infections (ARIs) pose a global threat. Examples are influenza (H1N1) caused by the H1N1pdm09 virus in 2009, severe acute respiratory syndrome (SARS) in 2003, and coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 in 2019. This is an update of a Cochrane Review last published in 2020. They include results from studies from the current COVID-19 pandemic. They included RCTs and cluster-RCTs investigating physical interventions (screening at entry ports, isolation, quarantine, physical distancing, personal protection, hand hygiene, face masks, glasses, and gargling) to prevent respiratory virus transmission.

They included 11 new RCTs and cluster-RCTs (610,872 participants) in this update, bringing the total number of RCTs to 78. Six of the new trials were conducted during the Covid-19 pandemic; two from Mexico, and one each from Denmark, Bangladesh, England, and Norway. They identified four ongoing studies, of which one is completed, but unreported, evaluating

masks concurrent with the Covid-19 pandemic. Many studies were conducted during non-epidemic influenza periods. Several were conducted during the 2009 H1N1 influenza pandemic, and others in epidemic influenza seasons up to 2016. Therefore, many studies were conducted in the context of lower respiratory viral circulation and transmission compared to Covid-19. The included studies were conducted in heterogeneous settings and adherence with interventions was low in many studies.

Medical/surgical masks compared to no masks.

They included 12 trials (10 cluster-RCTs) comparing medical/surgical masks versus no masks to prevent the spread of viral respiratory illness (two trials with healthcare workers and 10 in the community). Wearing masks in the community probably makes little or no difference to the outcome of influenza-like illness (ILI)/COVID-19 like illness compared to not wearing masks (risk ratio (RR) 0.95, 95% confidence interval (CI) 0.84 to 1.09; 9 trials, 276,917 participants; moderate-certainty evidence. Wearing masks in the community probably makes little or no difference to the outcome of laboratory-confirmed influenza/SARS-CoV-2 compared to not wearing masks (RR 1.01, 95% CI 0.72 to 1.42; 6 trials, 13,919 participants; moderate-certainty evidence).

N95/P2 respirators compared to medical/surgical masks.

They pooled trials comparing N95/P2 respirators with medical/surgical masks (four in healthcare settings and one in a household setting). They were very uncertain on the effects of N95/P2 respirators compared with medical/surgical masks on the outcome of clinical respiratory illness (RR 0.70, 95% CI 0.45 to 1.10; 3 trials, 7779 participants; very low-certainty evidence). N95/P2 respirators compared with medical/ surgical masks may be effective for ILI (RR 0.82, 95% CI 0.66 to 1.03; 5 trials, 8407 participants; low-certainty evidence). Evidence is limited by imprecision and heterogeneity for these subjective outcomes. The use of a N95/P2 respirators compared to medical/surgical masks probably makes little or no difference for the objective and more precise outcome of laboratory-confirmed influenza infection (RR 1.10, 95% CI 0.90 to 1.34; 5 trials, 8407 participants; moderate-certainty evidence). Restricting pooling to HCWs made no difference to the overall findings. Harms were poorly measured and reported, but discomfort wearing medical/surgical masks or N95/P2 respirators was mentioned in several studies (very low-certainty evidence).

Comment: The high risk of bias in these trials, variation in outcome measurement, and relatively low adherence with masking during the studies hampers drawing firm conclusions. To be clear, this analysis does not prove that high grade masks, properly worn, had no benefit at an individual level. For masks to be effective individuals must have the discipline to wear them correctly and consistently which is difficult in real world settings. The benefits of masking have been shown in healthcare and can be critical in preventing the spread of infection, but once again this depends on proper and consistent use. The Cochrane analysis pooled results from studies in communities around the world many which took place before 2016, with only two taking place during the Covid-19 pandemic. Their analysis concluded that in community settings (outside of healthcare) medical masks appeared to offer no additional protection compared with wearing no mask at all. In healthcare settings, they concluded that N95 respirators were no better than surgical masks in preventing transmission of respiratory diseases. However, the analysis recognized that adherence with mask wearing was a major problem, and that although studies took place during respiratory viral seasons, they may have not been able to detect

differences if local virus circulation was low. They did not monitor all aspects of mask and respirator use, such as observing whether participants were consistently and appropriately wearing masks. In fact, HCW frequently complained of discomfort wearing N95/P2 respirators in several studies reviewed. In addition, some of these studies were conducted within households as opposed to public or business locations. Some reviewers feel the Cochrane review incorrectly combined studies where people wore masks or respirators infrequently with those where they were worn all the time.

One just published study observed that medical/surgical masks were non-inferior to N95 respirators in a large study of 1009 healthcare workers in four countries providing direct care to Covid-19 patients reviewed in ID Watch earlier this year. [Ann Intern Med. doi:10.7326/M22-1966] They found among HCWs who provided routine care to patients with Covid-19, the overall estimates rule out a doubling in hazard of RT-PCR–confirmed Covid-19 for medical masks when compared with HRs of RT-PCR–confirmed Covid-19 for N95 respirators; however, some countries did observe a decrease risk with an-95 masks. There are a few weaknesses in this trial. The investigators authors defined equivalence as being less than “twice as bad.” Does this meet this definition of "equivalence?" Another major weakness was the intermittent use of respirators, which has been proved not to be effective. The only RCT to compare continuous and intermittent use of N95s showed that they protect HCWs only when they're worn continuously in the workplace. [Am J Respir Crit Care Med 2013; 187:960-6]

My colleagues in Boston observed increase nosocomial spread during Omicron. They mandated N-95 for all patient care to reduce spread from HCWs to patients. This was also at a time of high community activity in Boston at the time which impacted HCW infections. They postulate N-95 masks could prevent transmission to patients by better containing viral emissions from staff members with occult infections and prevent transmission from patients to staff by decreasing their viral exposure. They also instituted daily testing. The clusters rapidly abated after instituting universal N95 respirators and daily testing. [Clin Infect Dis 2022; 75: e296–e299]

So where does this leave us.-I think I would point out that in real world settings masks have marginal population-level benefits for the reason stated. On an individual basis if you are at high risk or caring for a high-risk patient then wearing a properly fitted high quality mask probably does provide some level of protection. In healthcare, if you have high community rates as they did in Boston wearing an N-95 mask for all patient care seems reasonable. If community rates are low, masks can probably be optional for routine patient care. If known Covid+ patients, then follow the CDC recommendations.

My bottom line is still to promote proper masking as an evidence-based mitigation strategy, especially considering emerging infectious diseases in healthcare settings. We also must assure the public that for masks to be effective they need to be properly fitted and worn at all times in areas with moderate to high transmission particularly indoor in crowded places especially with poor ventilation.

First At-Home Combination Test for Flu and Covid-19

The FDA issued an EUA for the first over-the-counter, at-home combination influenza and Covid-19 test on February 24, 2023, just two days after the company that makes the test announced that it had filed for bankruptcy protection. The single-use test works with a self-collected nasal swab and provides a result in about 30 minutes. The test is meant to be used by people 14 and older, or by an adult collecting a sample from someone age 2 or older.

The combination test correctly identified 99 percent of negative and 90 percent of positive influenza A samples, according to the FDA It also detected 100 percent of the negative and 88 percent of the positive Covid-19 samples. Testing continues for influenza B, which was not prevalent this year.

Comment: As you may guess, this is a molecular test, which means it detects and amplifies the genetic material of the viruses. Molecular tests are generally more sensitive than antigen tests, and an at-home molecular tests is expected to be more expensive than rapid antigen tests. Honestly speaking this new era testing is pretty exciting. It remained unclear when this combined test would be widely available for sale to consumers.

COVID-19

Covid-19 Impact: Three Year Anniversary

March 11th marks three years since the WHO declared Covid-19 a global pandemic. Below at updated statistics.

1. Cases**:** As of March 7, the WHO has confirmed 759,408,703 total cases. Of those, 102,247,392 — or 13.5 percent — were in the U.S.

2. Deaths: Since the pandemic's onset, there have been 6,866,434 deaths globally. The U.S. accounts for 16 percent of those deaths with a total of 1,111,342**.**

3. Hospitalizations**:** Since tracking began in August 2020, the CDC reports 6,020,879 Covid-19 patients have been hospitalized in the U.S.

4. Vaccinations: In the U.S., 230,142,115 people, or 69 percent of the US population, have received the primary series of the vaccine. However, only about 16 percent of the US population have received the bivalent booster. Globally, more than 5 billion people have been fully vaccinated, according to the WHO.

5. Long Covid-19: The after-effects of a COVID-19 infection for some are debilitating. Researchers estimate about 10 percent of cases result in long Covid-19, and as many as 79 percent who experience the condition report it became a factor which limited them in their daily lives. It is estimated that 65 million worldwide have suffered from long Covid-19 since the pandemic began.

6. Variants**:** The evolution of the SARS-CoV-2 virus has given rise to five variants of concern throughout the pandemic: alpha, beta, delta, gamma and omicron. Omicron subvariant XBB 1.5 has now become the dominant strain in the US.

Comment: These numbers are sobering. Fortunately, we are in a different phase of the pandemic with high community immunity through vaccination and/or natural immunity. This past winter did not see the surge we had experienced in past years. However, we still have too many deaths especially in the elderly. In addition, trust has eroded in public health, and we have lost public health workers and we cannot encourage enough residents to choose infectious diseases as a specialty. If we are to rebuild trust in public health, we must start to work with each other and not against each other. We must create a safe space for constructive conversation. Instead of demonizing those we disagree with, we need to approach one another with compassion and engage in productive dialogue. On the positive side we have many more tools to combat this virus and absent the emergence of a new virulent variant, I hope the worst is behind us and we can begin to get back to the "new norm."

Lab Leak Most Likely Origin of Covid-19 Pandemic WSJ February 26, 2023

The US Energy Department has concluded that the Covid-19 pandemic most likely arose from a laboratory leak, according to a classified intelligence report recently provided to the White House and key members of Congress. The Energy Department previously was undecided on how the virus emerged.

The Energy Department's conclusion is the result of new intelligence and is significant because the agency has considerable scientific expertise and oversees a network of US national laboratories, some of which conduct advanced biological research. According to the WSJ, the FBI previously came to the conclusion that the pandemic was likely the result of a lab leak in 2021 with "moderate confidence" and still holds to this view. While the Energy Department and the FBI each say an unintended lab leak is most likely, they arrived at this conclusions for different reasons. The CIA and another agency that officials would not name remain undecided between the lab-leak and natural-transmission theories.

Comment: The new report highlights how different parts of the intelligence community have arrived at disparate judgments about the pandemic's origin. The Energy Department now joins the FBI in saying the virus likely spread via a mishap at a Wuhan laboratory. An outbreak at a seafood market in Wuhan had initially been thought to be the source of the virus, but some scientists and Chinese public-health officials now see it as an example of community spread and not the place where the first human infection occurred. Despite the agencies' differing analyses, the update reaffirmed an existing consensus that Covid-19 was not the result of a Chinese biological-weapons program. It should be pointed out, the conclusion was "low confidence." Four other agencies, along with a national intelligence panel, still judge that it was likely the result of a natural transmission, and two are undecided. This seems to fall somewhere between *not sure* and *who knows*! How did we get here-the most obvious answer: early in the pandemic was the need in urgent situations to make recommendations with imperfect data.

Wastewater-based monitoring of SARS-CoV-2 at UK airports and its potential role in international public health surveillance PLOS Global Public Health PLOS Glob Public Health 2023; 3: e0001346.

doi.org/10.1371/journal. pgph.0001346

In this study, the investigators monitored sewage in samples from terminals (n = 150) and aircraft (n = 32) at three major international airports in the UK for 1–3 weeks in March 2022. As the raw samples were more turbid than typical municipal wastewater, they used beef extract treatment followed by polyethylene glycol (PEG) precipitation to concentrate viruses, followed by RT-qPCR for the detection of SARS-CoV-2 and a fecal indicator virus, crAssphage. crAssphage can be used as a tool to monitor fecal contamination patterns. [Emerg Infect Dis 2020; 26:1731-1739]

All samples taken from sewers at the arrival terminals of Heathrow and Bristol airports, and 85% of samples taken from sites at Edinburgh airport, were positive for SARS-CoV-2. This suggests a high COVID-19 prevalence among passengers and/or airport staff members. Samples derived from aircraft also showed 93% SARS-CoV-2 positivity. No difference in viral prevalence was found before and after Covid-19 travel restrictions were lifted.

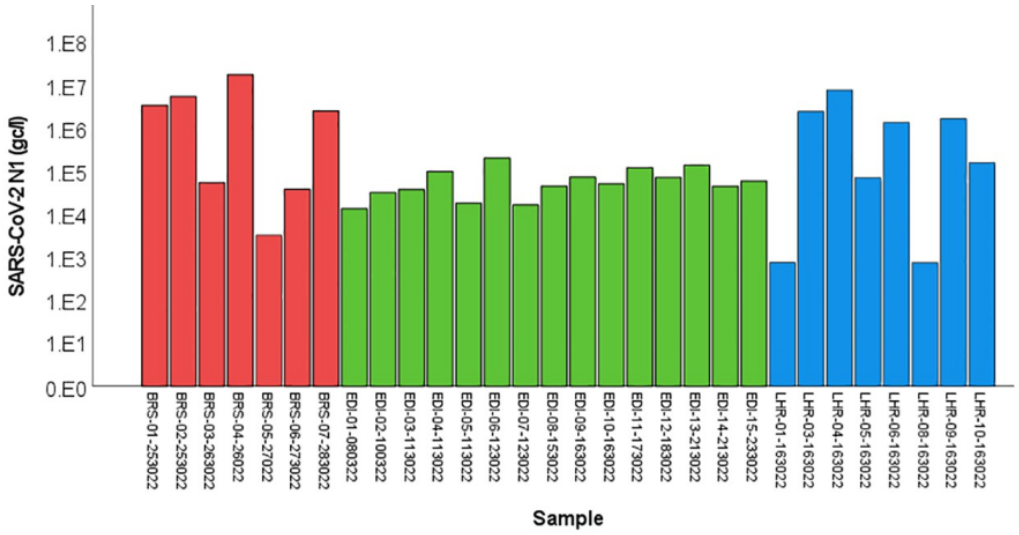


Fig 4. SARS-CoV-2 RNA concentration in samples taken from vacuum trucks at Bristol (BRS–red bars), at Edinburgh (EDI–green bars) and at Heathrow (LHR–blue bars) airports.

Comment: The results suggest that wastewater is a useful tool for monitoring the global transfer rate of human pathogens and other disease-causing agents across international borders and should form part of wider international efforts to monitor and contain the spread of future disease outbreaks. Wastewater may capture both inbound and outbound passengers as well as office staff working in the same terminal. Nonetheless, the regular sampling of airport and aircraft wastewater can be useful as targeted monitoring system for emerging diseases and other agents (e.g., anti-microbial resistance genes) that have not yet become endemic in many areas around the globe. See next two articles.

Aircraft Wastewater Surveillance for Early Detection of SARS-CoV-2 Variants — John F. Kennedy International Airport, New York City, August–September 2022
MMWR 2023; 72:210-211

They collected about a quart of wastewater from each of 88 incoming flights from the United Kingdom, the Netherlands, and France. Aircraft wastewater samples were collected from selected flights arriving at John F. Kennedy International Airport in New York City. Wastewater (approximately 0.25 gal [1 L]) was collected from each plane during normal maintenance using a device that attaches to the lavatory service panel port and the lavatory service truck hose. After concentration with affinity-capture magnetic nanoparticles, wastewater samples were tested for SARS-CoV-2 by RT-PCR). Samples with cycle thresholds <40 underwent whole genome sequencing.

Sixty-five samples (81%) were positive, with the same proportion among the three originating countries. Investigators sequenced 27 SARS-CoV-2 genomes from 25 samples and identified various Omicron substrains (United Kingdom, 12 BA.5 and 1 BA.4.6; France, 8 BA.5; and Netherlands, 5 BA.5 and 1 BA.2.75).

Comment: The investigators admit to the inability to differentiate travelers with connecting flights, and potential carryover of SARS-CoV-2 RNA between flights unrelated to travelers. However, wastewater surveillance can be used not only to monitor SARS-CoV-2 variants entering the US but can also provide a complementary early warning system for not only the detection of SARS-CoV-2 variants but other pathogens of public health concern.

Effect of Predeparture Testing on Postarrival SARS-CoV-2–Positive Test Results Among International Travelers — CDC Traveler-Based Genomic Surveillance Program, Four U.S. Airports, March–September 2022. MMWR 2023; 72:206-209

The investigators remind us that, from December 6, 2021, to June 11, 2022, the US required passengers on all inbound international flights to provide either a negative result from a COVID-19 test within 1 day of departure or provide proof of a SARS-CoV-2 infection within the previous 90 days. While the CDC no longer requires it, the agency still recommends predeparture testing.

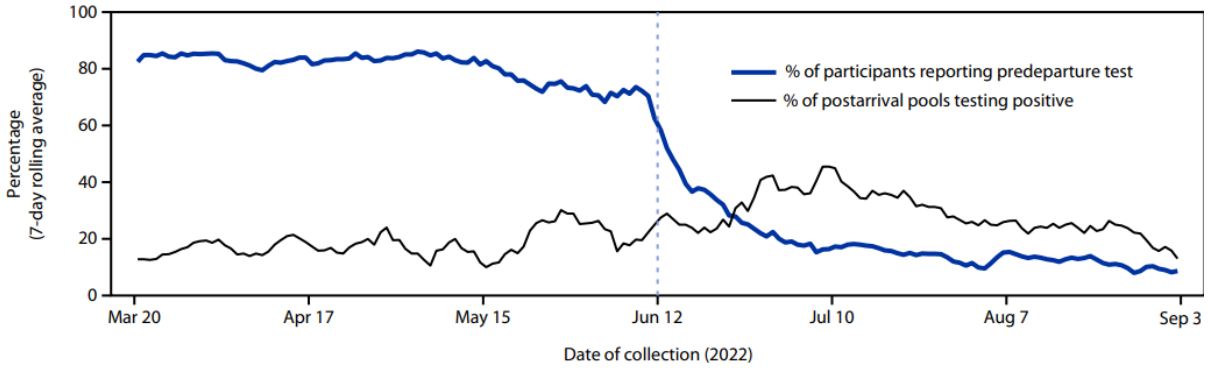
In this report, participating passengers arrived at one of four US airports in two 12-week periods during and after the predeparture testing requirement who volunteered to participate provided a postarrival lower nasal swab sample in the airport (The airports were located in New Jersey, New York, Georgia, and California.

From March 20, 2022 to September 3, 2022, 28,056 travelers from 24 countries were tested for Covid-19 using RT-PCR, for a total of 3,049 samples. From March 20th to June 11th, fully 13,190 (79.1%) of 16,668 volunteers in the CDC's Traveler-based Genomic Surveillance program reported undergoing predeparture testing, declining to 1,786 of 11,123 (16.1%) from June 12th to September 3rd.

A total of 22.7% of 3,049 pooled samples were positive for SARS-CoV-2, rising 56%—from 17.9% (291 of 1,622) in the early period to 28.0% (400 of 1,427) in the latter period. The increase was seen across countries, airports, incidence rates, pool size, age, and sex.

After adjustment, the pooled nasal swab specimens obtained during the requirement were 52% less likely to be positive for SARS-CoV-2 than those collected after the requirement was lifted, (adjusted odds ratio [aOR], 0.48).

FIGURE 1. Percentages (7-day rolling average) of participants reporting a predeparture SARS-CoV-2 test* and pools† testing positive SARS-CoV-2§ during postarrival testing — Traveler-based Genomic Surveillance Program, United States, March 20–September 3, 2022



Comments: Predeparture testing may reduce potential SARS-CoV-2 transmission risk during or after travel by reducing the number of infectious travelers. Reducing the number of persons traveling while infected with SARS-CoV-2 through predeparture testing also could reduce air travel–associated transmission in airports, aircraft, and destination communities. CDC continues to recommend testing before and after international travel. Along with other strategies, including isolation of persons with confirmed or suspected Covid-19 and masking, testing before international travel may be an important element of a multipronged Covid-19 prevention strategy. The incidence data were matched with pooled test results based on a flight's country of origin, and it is possible that participants began their itinerary in a different country and later connected to the U.S.-bound flight. In addition, as testing rates decline globally, reported incidence data might not fully reflect actual Covid-19 risk in a given country. There is no mention of vaccination, masking, or variant.

Viral burden rebound in hospitalised patients with COVID-19 receiving oral antivirals in Hong Kong: a population-wide retrospective cohort study Lancet Infect Dis published online February 13, 2023

doi.org/10.1016/ S1473-3099(22)00873-8

The investigators did a retrospective cohort study of hospitalized patients with a confirmed diagnosis of Covid-19 in Hong Kong for an observation period from February 26 to July 3, 2022 (during the omicron BA.2.2 variant wave). Adult patients (age ≥18 years) admitted 3 days before or after a positive Covid-19 test were selected from medical records held by the Hospital Authority of Hong Kong. They included patients with non-oxygen-dependent Covid-19 at baseline receiving either molnupiravir (800 mg twice a day for 5 days), nirmatrelvir–ritonavir

(nirmatrelvir 300 mg with ritonavir 100 mg twice a day for 5 days), or no oral antiviral treatment (control group). Viral burden rebound was defined as a reduction in cycle threshold (Ct) value (≥3) on quantitative RT-PCR test between two consecutive measurements, with such decrease sustained in an immediately subsequent Ct measurement (for those patients with ≥3 Ct measurements). Logistic regression models were used to identify prognostic factors for viral burden rebound, and to assess associations between viral burden rebound and a composite clinical outcome of mortality, intensive care unit admission, and invasive mechanical ventilation initiation, stratified by treatment group.

Viral rebound occurred in 16 of 242 (6.6%) of patients given nirmatrelvir–ritonavir, 27 of 563 (4.8%) of molnupiravir recipients, and 170 of 3,787 (4.5%) of untreated participants. Impaired immune status was a risk factor for viral rebound, regardless of treatment status (nirmatrelvir–ritonavir odds ratio [OR], 7.37; molnupiravir OR, 3.05; control, 2.21). Among molnupiravir recipients, increased odds of rebound were linked to age 18 to 65 years (OR, 2.68) and concomitant corticosteroids (OR, 3.11). Viral rebound was not tied to increased probability of death, ICU admission, or mechanical ventilation (nirmatrelvir–ritonavir adjusted OR [aOR], 1.90; molnupiravir aOR, 1.05; no treatment aOR, 1.27). Risk factors for rebound among nirmatrelvir–ritonavir recipients included age 18 to 65 years (OR, 3.09), greater chronic condition burden (OR, 6.02), and simultaneous receipt of corticosteroids (OR, 7.51). Surprisingly, the odds of viral burden rebound in patients receiving nirmatrelvir–ritonavir were significantly reduced in individuals who were not fully vaccinated (defined as those who had received less than two doses of Pfizer or less than three doses of CoronaVac).

Comment: Based on this study of hospitalized Covid-19 patients, the investigators conclude that viral rebound was not common, and was observed with or without oral antiviral use. Increased odds of rebound were apparent in specific patient subgroups: aged 18–65 years (vs >65 years), those with high comorbidity burden, and those concomitantly taking corticosteroids, while the odds were lower in those who had not been fully vaccinated. Viral burden rebound did not appear to be associated with adverse serious clinical outcomes, and thus oral antivirals should continue to be offered to COVID-19 patients at risk of severe or fatal outcomes. A limitation of the study was that no sequencing was performed, making it difficult to differentiate between relapse with the same strain and recurrence of reinfection by a different strain than the one responsible for the initial infection episode. Bottom line, this study supports the importance of continuing to offer antivirals to individuals with Covid-19 who are at increased risk of progression to severe Covid-19. Further studies are needed to better define the causes of viral rebound in patients with Covid-19.

Association of COVID-19 Vaccination With Risk for Incident Diabetes After COVID-19 Infection JAMA Network Open. 2023;6(2):e2255965.

doi:10.1001/jamanetworkopen.2022.55965

The current study included 23,709 adult patients (54% of whom were female) with at least one COVID-19 infection treated within the Cedars-Sinai Health System between the beginning of the pandemic through June 2022. The average age was 47 years and diagnostic data were pulled from ICD-9 and ICD-10 codes. A total of 14,856 patients were unvaccinated prior to infection and 8,853 were vaccinated.

Unvaccinated individuals saw a 78% increased chance of developing diabetes within 90 days of infection (OR 1.78, 95% CI 1.35-2.37, *P*<0.001), while no significant association was observed in vaccinated individuals (OR 1.07, 95% CI 0.64-1.77).

During the study time frame, incidence of new-onset type 2 diabetes was 2.1% overall: 2.7% of the unvaccinated group and 1% of the vaccinated group.

Kwan's group noted, however, that although the diabetes risk was higher among the unvaccinated individuals, "suggesting a benefit of vaccination," the interaction term between vaccination status and diabetes diagnosis didn't reach statistical significance (OR 0.59, 95% CI 0.34-1.06, *P*=0.08). No interaction was observed for age, sex, or preexisting cardiovascular risk factors, including hypertension or hyperlipidemia.

"Although further studies are needed to validate this hypothesis, we remain steadfast in our belief that COVID-19 vaccination remains an important tool in protecting against COVID-19 and the still-uncertain risks that people may experience during the post-infection period," he added.

To account for temporal confounders stemming from disruptions in healthcare use during the pandemic, the researchers used a new benchmark diagnosis -- such as urinary tract infection and gastroesophageal reflux -- as the comparator to represent a marker of healthcare engagement unrelated to COVID-19. Models were adjusted for sex, timing of index infection, and pre-infection vaccination status.

COVID-19 infection didn't appear to increase the risk for other cardiometabolic conditions compared with a benchmark diagnosis, however, specifically in regard to new-onset hypertension (OR 1.06, 95% CI 0.88-1.28) and hyperlipidemia (OR 0.91, 95% CI 0.73-1.15).

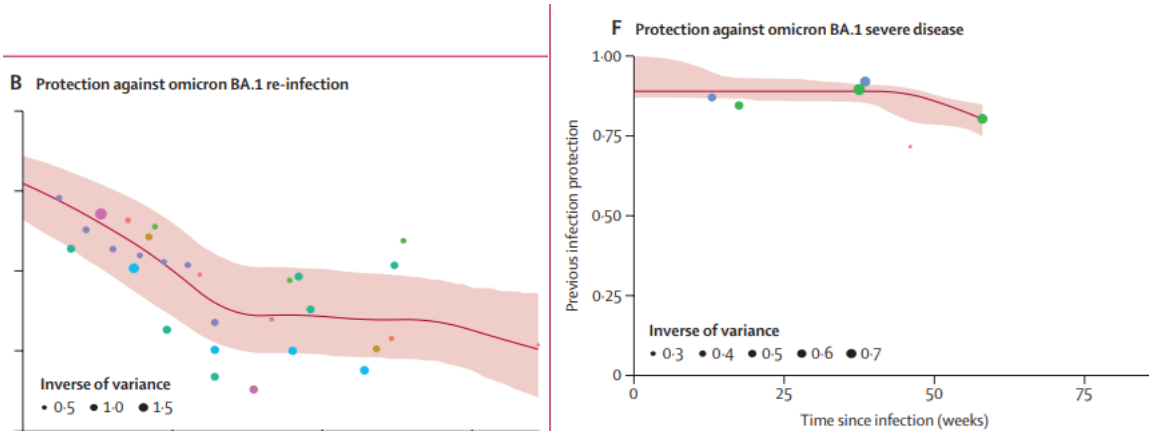
Comment: Our results validate early findings revealing a risk of developing type 2 diabetes after a Covid-19 infection and indicate that this risk has, unfortunately, persisted through the Omicron era. The association remained even after accounting for temporal confounders. These results also suggest that Covid-19 vaccination prior to infection may provide a protective effect against diabetes risk. Mechanisms contributing to postinfection diabetes risk remain unclear, although persistent inflammation contributing to insulin resistance is a proposed mechanism.

Past SARS-CoV-2 infection protection against re-infection: a systematic review and meta-analysis Lancet published online February 16, 2023

doi.org/10.1016/ S0140-6736(22)02465-5

This is a systematic review and meta-analysis. They identified, reviewed, and extracted from the scientific literature retrospective and prospective cohort studies and test-negative case-control studies published from inception up to September 31, 2022, that estimated the reduction in risk of Covid-19 among individuals with a past SARS-CoV-2 infection in comparison to those without a previous infection. They performed a meta-analysis on the effectiveness of past infection by outcome (infection, symptomatic disease, and severe disease), variant, and time since infection. They ran a Bayesian meta-regression to estimate the pooled estimates of protection. Risk-of-bias assessment was evaluated using the National Institutes of Health quality-assessment tools. The systematic review was PRISMA compliant.

They identified a total of 65 studies from 19 different countries. Their meta-analyses showed that protection from past infection and any symptomatic disease was high for ancestral, alpha, beta, and delta variants, but was substantially lower for the omicron BA.1 variant. Pooled effectiveness against re-infection by the omicron BA.1 variant was 45·3% (95% uncertainty interval [UI] 17·3–76·1) and 44·0% (26·5–65·0) against omicron BA.1 symptomatic disease. Mean pooled effectiveness was greater than 78% against severe disease (hospitalization and death) for all variants, including omicron BA.1. Protection from re-infection from ancestral, alpha, and delta variants declined over time but remained at 78·6% (49·8–93·6) at 40 weeks. Protection against re-infection by the omicron BA.1 variant declined more rapidly and was estimated at 36·1% (24·4–51·3) at 40 weeks. On the other hand, protection against severe disease remained high for all variants, with 90·2% (69·7–97·5) for ancestral, alpha, and delta variants, and 88·9% (84·7–90·9) for omicron BA.1 at 40 weeks.



Comment: These findings confirm that past infection affords significantly reduced protection against re-infection by the omicron BA.1 variant compared to previous variants, highlighting the high immune escape features of this variant. The finding that the level of protection from past infection by variant and over time is equivalent to that provided by two-dose mRNA vaccines has important implications for guidance regarding the timing of vaccine doses, including boosters. In addition, this review confirms protection from severe disease was high for all variants. The immunity conferred by natural infection should be weighed alongside protection from vaccination when assessing future disease burden from Covid-19, providing guidance on when individuals should be vaccinated on the basis of immune status and risk. Over our lifetime we are frequently reinfected with viruses that cause respiratory illnesses, including other coronaviruses. These infections also generate B and T white response that prevent serious illness even after neutralizing antibodies wane. I recall the Barrington Declaration [review in the Covid-19 Daily Briefing in 2020] in the fall of 2020 which called for a new strategy with a focus on protecting the elderly and vulnerable while letting those at low risk for severe illness "live their lives normally to build up immunity to the virus through natural infection." The aim was to minimize deaths and social harm until we reach "herd immunity." I felt at the time that the Declaration went too far based on our level of knowledge at the time. While the goal of herd immunity has proved elusive as the virus mutated, the declaration's central premise was probably correct: "As immunity builds in the population, the risk of infection to all—including the vulnerable—falls." This is what has happened over the past three years. Vaccines helped mitigate severe illness while people developed natural and hybrid immunity. The CDC has nonetheless dug in and refused to provide exemptions from vaccine mandates for those with natural immunity, as many European countries did.

Bottom line, I continue to articulate the need to consider natural infection in our vaccination policy and to underscore the current vaccines are not “sterilizing” vaccines (like measles) and will not protect against mild infection but are very good to protect against severe disease. The current Lancet article showed at 10-month immunity after Covid-19 infection remained high against severe disease for all variants. Prior articles reviewed in ID Watch also demonstrate that hybrid immunity outperforms vaccination alone. See next review.

Rethinking next-generation vaccines for coronaviruses, influenza viruses, and other respiratory viruses Cell Host & Microbe published online January 11, 2023

doi.org/10.1016/j.chom.2022.11.016

Viruses that replicate in the human respiratory mucosa without infecting systemically, including influenza A, SARS-CoV-2, endemic coronaviruses, RSV, and many other ‘‘common cold’’ viruses, cause significant mortality and morbidity and are important public health concerns. Because these viruses generally do not elicit complete and durable protective immunity by themselves, they have not to date been effectively controlled by licensed or experimental vaccines.” This review examines challenges that have slowed the development of effective mucosal respiratory vaccines, emphasizing that all of these viruses replicate extremely rapidly in the surface epithelium and are quickly transmitted to other hosts, within a narrow window of time before immune responses are fully deployed. This is a well written and detailed review by the NIH.

Key Points

1. Natural infections with mucosal respiratory viruses may not be fully controlled by human immune responses because the human immune system has evolved to tolerate them during very short intervals of mucosal viral replication.
2. Since mucosal and systemic immunity only partially protects against infection with mucosal respiratory viruses, we must take advantage of alternative host immune mechanisms.
3. Immune correlates of protection against mucosal respiratory viruses are incompletely understood, vary between viral strains and subtypes, with viral drift, and they exhibit inter-individual variation.
4. Vaccine-related questions of route of administration, antigen configuration, adjuventation, and association with adjunctive therapy are of great importance for current research.
5. Vaccinated hosts and host risk groups are many and heterogeneous.
6. Public health considerations relating to next-generation respiratory vaccines must contribute to shaping vaccine design, including vaccine schedule, role of boosting, frequency of vaccination and duration/completeness of protection, side effects, and public acceptance.

Table 1. Epidemiologic and immunologic parameters of selected human respiratory viruses and vaccines used to control them

Virus	Incubation period[a]	Marked viremia	Infection elicits long-term protective immunity	Re-infections are rare	Vaccines elicit long-term protective immunity	Vaccine type
Measles (to prodrome)	≈10 days	yes	yes	yes	yes	replicating
Mumps	≈16 days	yes	yes	yes	yes	replicating
Rubella	≈16 days	yes	yes	yes	yes	replicating
Smallpox[b]	≈12 days	yes	yes	yes	yes	replicating
VZV[c]	≈14 days	yes	yes	yes	yes	replicating
Endemic coronaviruses	≈5 days	no	no	no	no	none
Influenza virus	≈2 days	no	no	no	no	replicating, other
Parainfluenzaviruses	≈4 days	no	no	no	no	none
RSV	≈5 days	no	no	no	no	none
SARS-CoV-2	≈4 days	no[d]	no	no	no	non-replicating

[a]Viral incubation periods, especially shorter incubation periods, typically have very broad ranges; these estimates are taken from cross-sections of the literature.
[b]Smallpox was eradicated from natural circulation in 1978.
[c]Varicella-zoster virus (VZV) recrudescence (referred to as zoster, zona, or "shingles") results from release of latent viruses from ganglia; second exogenous respiratory infections in normal persons are rare.
[d]Although SARS-CoV-2 antigens have been detected in multiple tissues, the virus does not appear to be associated with significant "free" viremia, as evidenced by difficulty in culturing infectious virions from blood or tissues, and by weak elicitation of broad and durable protective systemic immunity.

Comment: The authors correctly conclude **"**past unsuccessful attempts to elicit solid protection against mucosal respiratory viruses and to control the deadly outbreaks and pandemics they cause have been a scientific and public health failure that must be urgently addressed." They outline the complexities in detail on the challenges to developing next-generation respiratory vaccines (see key points). I know we have the technology and the know how to create the next generation of vaccines.

Assessment of COVID-19 as the Underlying Cause of Death Among Children and Young People Aged 0 to 19 Years in the US JAMA Network Open. 2023; 6:e2253590.

doi:10.1001/jamanetworkopen.2022.53590

Although children account for only 0.1% of COVID-19 deaths, almost 1500 who were younger than 18 years have died since the pandemic's beginning, significantly more than the number of deaths due to influenza.

Researchers examined national population-level, cross-sectional data from 2019 through 2022, utilizing CDC and other sources to identify and compare the underlying causes of U.S. deaths among individuals younger than 19 years. In all, 821 deaths (1.0/100,000 population) were attributable to Covid-19 during the study period (August 2021 through July 2022), when Delta and Omicron were circulating. Children younger than 1 year had the highest Covid-19 death rate (4.3/100,000). In 2019, prior to the pandemic, the leading cause of death in individuals younger than 19 years was a perinatal condition, followed by accidents, congenital malformations, assault, suicide, malignancy, heart disease, and influenza and pneumonia. Overall, for those younger than 19, Covid-19 was within the top 10 causes of death, accounting for 2% of all causes. Covid-19 was the leading infectious cause of death for children during the study period, ranking above influenza and pneumonia, sepsis, and intestinal infections.

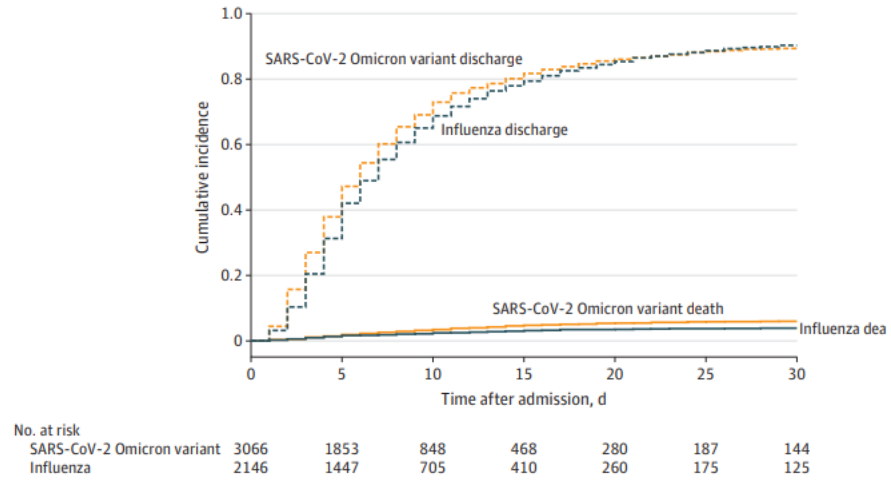
Comment: Although children are a much lower risk for death due to Covid-19, when compared with other causes of pediatric deaths (both disease and non-disease related) the mortality due to Covid-19 can be better put into perspective. Covid-19 is now considered a vaccine-preventable disease, however, only 43% of children have been vaccinated. Covid-19 is now a top 10 cause of death. We need to do better at increasing vaccination rates in children. Like adult vaccination it may not prevent infection, but it will prevent serious disease and deaths from Covid-19.

Hospital Outcomes of Community-Acquired SARS-CoV-2 Omicron Variant Infection Compared With Influenza Infection in Switzerland. JAMA Network Open. 2023;6:e2255599.

doi:10.1001/jamanetworkopen.2022.55599

This cohort study was based on a national COVID-19 and influenza registry. Hospitalized patients aged 18 years and older with community-acquired SARS-CoV-2 Omicron variant infection who were admitted between January 15 and March 15, 2022 (when B.1.1.529 Omicron predominance was >95%), and hospitalized patients with influenza A or B infection from January 1, 2018, to March 15, 2022, where included. Patients without a study outcome by August 30, 2022, were censored. The study was conducted at 15 hospitals in Switzerland.

Patients with the SARS-CoV-2 Omicron variant were younger (median [IQR] age, 71 [53-82] years) than those with influenza (median [IQR] age, 74 [59-83] years; P < .001). Overall, 214 patients with the SARS-CoV-2 Omicron variant (7.0%) died during hospitalization vs 95 patients with influenza (4.4%; P < .001). The final adjusted subdistribution hazard ratio (sdHR) for in-hospital death for SARS-CoV-2 Omicron variant vs influenza was 1.54 (95% CI, 1.18-2.01; P = .002). Overall, 250 patients with the SARS-CoV-2 Omicron variant (8.6%) vs 169 patients with influenza (8.3%) were admitted to the ICU (P = .79). After adjustment, the SARS-CoV-2 Omicron variant was not significantly associated with increased ICU admission vs influenza (sdHR, 1.08; 95% CI, 0.88-1.32; P = .50).



Comment: In this cohort study of 5,212 patients hospitalized with the SARS-CoV-2 Omicron variant or influenza A or B in Switzerland, the SARS-CoV-2 Omicron variant was associated

with an approximately 1.5-fold higher risk of in-hospital all-cause mortality up to day 30 compared with influenza. There was very limited information on the vaccination type (mRNA vs live-attenuated vs protein based) for patients with the SARS-CoV-2 Omicron variant; therefore, this variable could not be considered in analysis. Not all centers completed follow-up information, resulting in a small proportion of missing outcomes and subsequent exclusions. They cannot exclude residual confounding, as information on influenza vaccination, preexisting immunity as well as further potential unidentified confounding variables were largely missing.

Symptom and Viral Rebound in Untreated SARS-CoV-2 Infection. Ann Intern Med

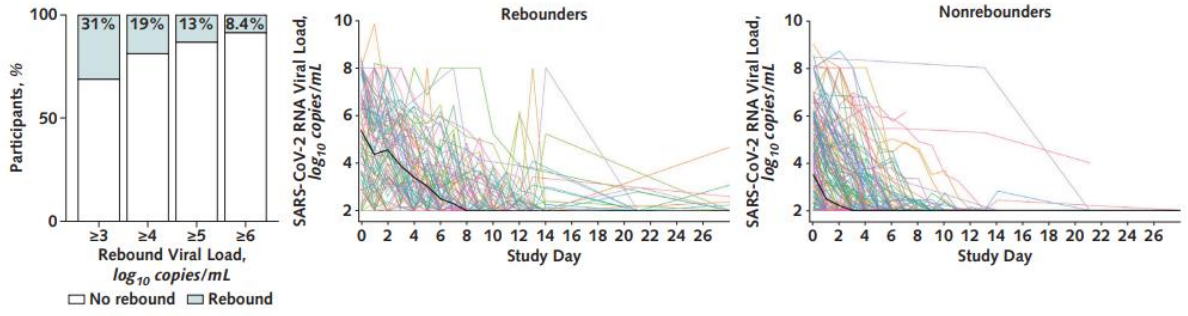
Published online February 21, 2023

doi:10.7326/M22-2381

This is a retrospective analysis of participants in the randomized, placebo-controlled trial. [ACTIV-2/ A5401] (Adaptive Platform Treatment Trial for Outpatients With COVID-19) 563 participants receiving placebo were included. Participants recorded the severity of 13 symptoms daily between days 0 and 28. Nasal swabs were collected for SARS-CoV-2 RNA testing on days 0 to 14, 21, and 28. Symptom rebound was defined as a 4-point increase in total symptom score after improvement any time after study entry. Viral rebound was defined as an increase of at least 0.5 log10 RNA copies/mL from the immediately preceding time point to a viral load of 3.0 log10 copies/mL or higher. High-level viral rebound was defined as an increase of at least 0.5 log10 RNA copies/mL to a viral load of 5.0 log10 copies/mL or higher.

Symptom rebound was identified in 26% of participants at a median of 11 days after initial symptom onset. Viral rebound was detected in 31% and high-level viral rebound in 13% of participants. Most symptom and viral rebound events were transient, because 89% of symptom rebound and 95% of viral rebound events occurred at only a single time point before improving. The combination of symptom and high-level viral rebound was observed in 3% of participants. Most were unvaccinated and infected with pre-Omicron variants.

Figure 2. Description of AN SARS-CoV-2 RNA rebound after study enrollment (primary analysis definition).



AN = anterior nasal. **Left.** Bar graph shows percentage of participants having AN SARS-CoV-2 RNA rebound ≥0.5 $\log_{10}$ copies/mL at any follow-up time point after study enrollment. The frequencies of viral rebound were assessed with a minimum rebound viral load of ≥3.0, ≥4.0, ≥5.0, or ≥6.0 $\log_{10}$ RNA copies/mL. **Center and right.** These graphs show AN SARS-CoV-2 RNA in $\log_{10}$ copies/mL by study day in rebounders and nonrebounders, respectively. The thick black lines show median AN SARS-CoV-2 RNA copies/mL for each day. The *y*-axes show AN SARS-CoV-2 RNA in $\log_{10}$ copies/mL, whereas the *x*-axes denote study day.

Comment: To help improve the understanding of the natural course of Covid-19, the investigators analyzed the symptom and viral rebound dynamics of participants receiving placebo in the RCT ACTIV-2/A5401 trial for outpatients. Overall, they found that viral or

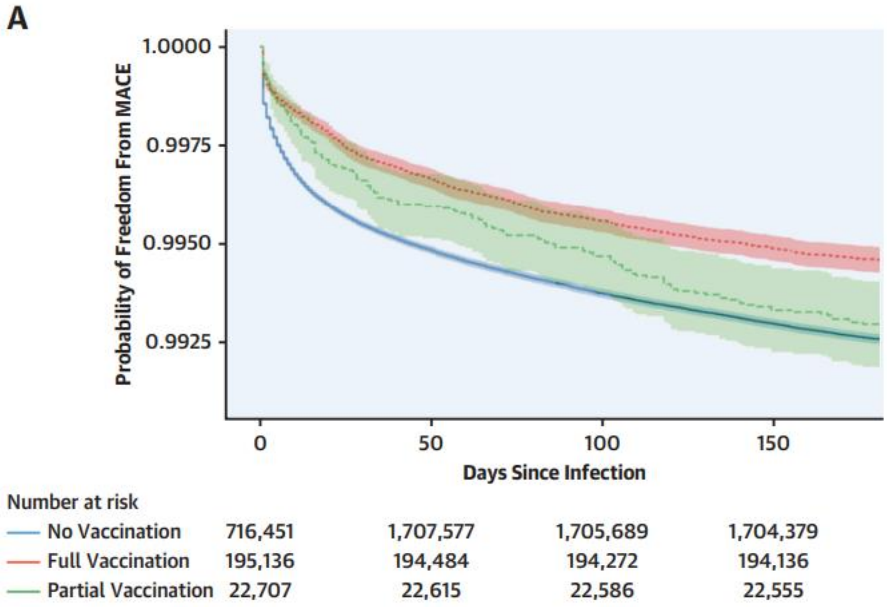
symptom rebound after initial improvement was relatively common, with 1 in 4 participants having symptom rebound and almost 1 in 3 having viral rebound during their infection, as assessed by daily symptom and nasal virus sampling. However, both symptom and viral rebound were short, lasting only 1 day in most participants. This is in contrast to the more prolonged symptom and viral rebound after nirmatrelvir–ritonavir treatment in previous case reports [N Engl J Med. 2022;387:1045-1047]. Symptom or viral relapse in the absence of antiviral treatment is common, but the combination of symptom and viral rebound is rare. They also identified characteristics associated with the occurrence of symptom rebound, including female sex, having risk factors for severe disease, and having higher levels of nasal SARS-CoV-2 RNA shedding and symptom scores at study enrollment. Their observations could be affected by the underlying study population because the ACTIV-2/A5401 study enrolled a largely unvaccinated population infected with pre-Omicron variants. However, recently published studies have reported that neither vaccination nor Omicron variants substantially alter viral kinetics. [Infect Control Hosp Epidemiol. 2022:doi:10.1017/ice.2022.124] These results provide insight into the natural kinetics of viral rebound and symptom relapses during Covid-19, which is important in the interpretation of studies reporting rebound after nirmatrelvir– ritonavir or other antiviral treatment.

Impact of Vaccination on Major Adverse Cardiovascular Events in Patients With COVID-19 Infection J Am College of Cardiol published online February 20, 2023

doi.org/10.1016/j.jacc.2022.12.006

SARS-CoV-2 infection increases the risk of major adverse cardiac events (MACE) and long-term cardiovascular sequelae after recovery. However, the association of vaccination on cardiovascular outcomes following infection has not been fully elucidated in the US. The investigators wanted to further study the association between vaccination and MACE among patients with prior SARS-CoV-2 infection. Using data from the National COVID Cohort Collaborative (N3C), they included patients aged 18 to 90 years who were initially infected with SARS-CoV-2 between March 1, 2020, and February 1, 2022. Starting from the first day following initial infection, the follow-up time was 180 days. They considered mRNA vaccines by Pfizer and Moderna and viral vector vaccines by J&J. Individuals were classified as fully vaccinated if they received ≥2 mRNA vaccines or 1 J&J vaccine ≥14 days before SARS-CoV-2 infection and as partially vaccinated if they received only 1 mRNA vaccine or their second mRNA or 1 J&J vaccine within 14 days of infection.

A total of 195,136 (10.1%) patients were fully vaccinated, 22,707 (1.2%) were partially vaccinated, and 1,716,451 (88.7%) were not vaccinated. Overall, MACE was observed among 13,948 patients (0.7%): 12,733 cases occurred among nonvaccinated patients (0.7% of these patients), 160 in partially vaccinated patients (0.7%), and 1,055 in fully vaccinated patients (0.5%). Patients with and without MACE had significant differences in comorbidities including previous MACE (29.1% vs 0.9%; $P < 0.001$), type II diabetes (33.9% vs 7.5%; $P < 0.001$), hyperlipidemia (50.7% vs 14.4%; $P < 0.001$), ischemic heart disease (40.6% vs 3.9%; $P < 0.001$), liver disease (4.0% vs 0.8%; $P < 0.001$), and obesity (29.4% vs 16.4%; $P < 0.001$). Cox proportional hazards model showed full (aHR of 0.59; 95% CI: 0.55-0.63) and partial (aHR of 0.76; 95% CI: 0.65-0.89) vaccination were associated with reduced risk of MACE . Median time from last vaccination to MACE is 212 days (IQR: 133-293 days). Risk of MACE significantly increased with male sex; age, notably among patients ≥66 years of age; and comorbidities, especially previous MACE.



Comment: The investigators found full vaccination was associated with decreased risk of myocardial infarction and ischemic stroke after Covid-19. Limitations include unmeasured confounding variables and inability to factor in vaccines beyond those distributed in the US. They also did not consider SARS-CoV-2 reinfections following index illness, because patients may present with positive tests for varying periods. They could not account for different SARS-CoV-2 variants over time. Lastly vaccination rates were very low.

Effectiveness of bivalent mRNA booster vaccination against SARS-CoV-2 Omicron infection, the Netherlands, September to December 2022 Eurosurveill published online February 16, 2023

doi.org/10.2807/1560-7917.ES.2023.28.7.2300087

National Institute for Public Health and Environment, Bilthoven, the Netherlands used data from 32,542 participants of an ongoing prospective cohort study (VASCO) among community-dwelling Dutch adults aged 18–85 years who are followed with 3-monthly questionnaires and 6-monthly serum samples. Only participants who had received primary vaccination and one or two monovalent booster vaccinations before the start of the bivalent booster program (September 19, 2022) were included. Follow-up started on September 26, 2022 (1 week after the start of the bivalent booster vaccination program), or 3 months after the last monovalent vaccination or last prior infection (occurring before September 26, 2022), whichever came last.

The study involved 12,988 participants aged 18–59 years who had previously received a primary vaccination series and one monovalent booster vaccination and 19,554 participants aged 60–85 years who had previously received a primary vaccination series and one (n = 8,963) or two (n = 10,591) monovalent booster vaccinations. Of these individuals, 5,504 (42.4%) 18–59-year-olds and 11,900 (60.9%) 60–85-year-olds received a bivalent vaccine after September 19, 2022. Prior SARS-CoV-2 infection was present in 9,605 (74.0%) of 18–59-year-olds and 10,898 (55.7%) of the 60–85-year-olds. During the study period, 3,005 SARS-CoV-2 infections, based on a positive SARS-CoV-2 PCR or (self-administered) antigen test, were reported by the participants.

Cox proportional hazard models with calendar time as underlying time scale and bivalent vaccination as time-varying exposure were used to estimate effectiveness of bivalent vaccination relative to receiving the primary vaccination series and one or two monovalent booster vaccinations. Estimates were adjusted for age group, sex, education level and presence of a medical risk condition.

Among 18–59-year-olds who received primary vaccination and one monovalent booster, the overall relative effectiveness of bivalent vaccination against infection was 31% (95% confidence interval [CI] 18 to 42). Among participants with prior Omicron infection, the relative effectiveness of a bivalent booster appeared lower (20%; 95% CI −7 to 40) than participants with no prior infection (32%; 95% CI 14 to 47) or prior pre-Omicron infection (44%; 95% CI 13 to 64), although CIs largely overlapped. Among 60–85-year-olds who received primary vaccination and one or two monovalent booster vaccinations, overall relative effectiveness was 14% (95% CI 3 to 24). Among participants with prior Omicron infection this was 6% (95% CI −30 to 31). Estimates among 60–85-year-olds were similar to the main estimate across different stratified analyses and sensitivity analyses.

In participants aged 18–59 years, compared with those without bivalent vaccination and without prior infection, relative effectiveness of bivalent vaccination among participants without prior infection (37%; 95% CI 21 to 50), which was similar to relative protection from a prior pre-Omicron infection and no bivalent vaccination (34%; 95% CI 21 to 44). Meanwhile, relative protection from a prior Omicron infection with or without bivalent vaccination was substantially higher (80–83%). Similarly, participants aged 60–85 years showed higher relative protection from prior Omicron infection with (82%; 95% CI 76 to 86) or without bivalent vaccination (82%; 95% CI 79 to 85) than from bivalent vaccination without prior infection (14%; 95% CI: 1 to 25) or prior pre-Omicron infection without bivalent vaccination (43%; 95% CI 32 to 52).

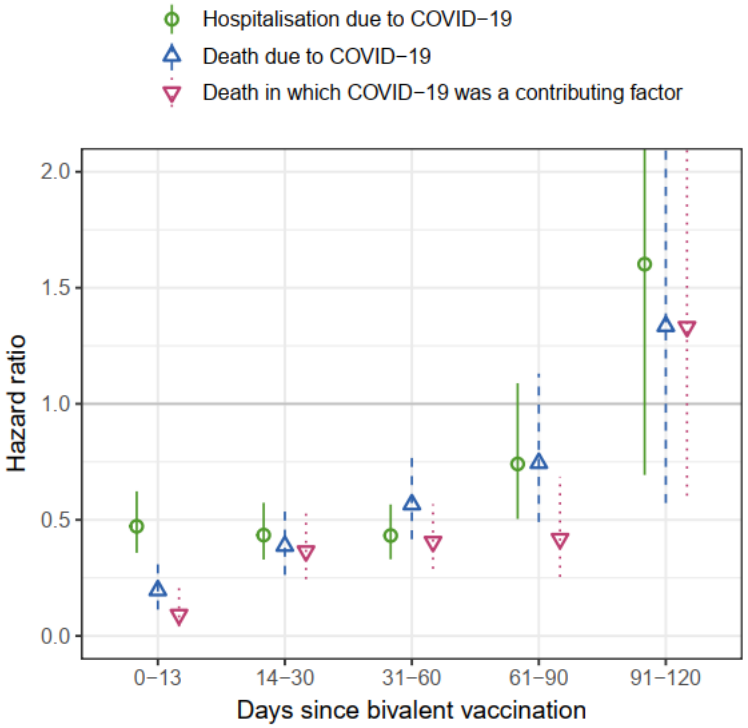
Comment: The bivalent booster vaccination campaign has shown benefit in reducing Covid-19 hospitalizations, which is especially important for those at increased risk, including elderly people and those with a medical risk condition. However, they found limited added protection of bivalent vaccination in preventing SARS-CoV-2 Omicron infection among persons who received primary vaccination and one or two monovalent booster vaccinations. Especially in persons with prior Omicron infection, the added benefit seems small," the authors concluded.

Bivalent booster effectiveness against severe COVID-19 2 outcomes in Finland, September 2022 – January 2023 MedRvix posted online March 5, 2023

doi.org/10.1101/2023.03.02.23286561

The investigators used a Finnish register-based cohort to compare the risk of severe Covid-19 outcomes among those who received bivalent vaccination (exposed) between 1 September 2022 and 31 January 2023 to those who did not (unexposed). The study cohorts included 1,197,700 elderly aged 65–120 years and 444,683 chronically-ill individuals aged 18–64 years. During the study 627,378 (52%) elderly and 66,871 (15%) chronically ill were vaccinated with a bivalent booster; approximately a third of them received Pfizer BA.1 while the other two thirds received Pfizer BA.4-5. The median time since bivalent vaccination by the end of follow-up was 75 days (interquartile range 61–85 days) and 73 days (interquartile range 54–88 days) among the elderly and chronically ill, respectively. To control for confounding, all analyses were adjusted for a set of potential confounders; a negative control outcome was used to assess the presence of residual confounding.

Among elderly aged 65–120 years, bivalent vaccination reduced the risk of hospitalization and death due to Covid-19. Among the elderly the hazard ratios comparing exposed and unexposed ranged from 0.36 to 0.43 during the first 14–30 days since bivalent vaccination but signs of waning were observed as soon as two months after vaccination. Among the chronically ill aged 18–64 years bivalent vaccination did not reduce the risk of severe Covid-19 outcomes.



Comment: There was a similar Israeli study conducted among people aged 65 years or more which reported slightly higher BA.4-5 bivalent booster effectiveness against severe Covid-19 outcomes. [SSRN Journal (2022) doi:10.2139/ssrn.4314067] In a UK analysis including individuals aged 50 years or more, the BA.1 bivalent booster effectiveness against hospitalization due to Covid-19 was similar to the results in this paper, but no waning was observed after ten weeks since bivalent vaccination. [Public Health England. COVID-19 vaccine surveillance report: week 5. (2023] Among the chronically ill they did not observe bivalent vaccination to reduce the risk of severe Covid-19 outcomes, although previous studies have found a benefit among working-age adults, but only a small proportion of the cohort received a bivalent booster. There is no mention of circulating variants. Despite some shortcomings studies do favor bivalent booster for the elderly. These results are important for further developing Covid-19 vaccination program worldwide.

Effects of remdesivir in patients hospitalised with COVID-19: a systematic review and individual patient data meta-analysis of randomised controlled trials Lancet Respir Med published online February 21, 2023

doi.org/10.1016/ S2213-2600(22)00528-8

For this systematic review and meta-analysis, researchers searched PubMed, Embase, the Cochrane COVID-19 trial registry, ClinicalTrials.gov, the International Clinical Trials Registry Platform, and preprint servers from January 1, 2020, until April 11, 2022, for RCTs of remdesivir in adult patients hospitalized with Covid-19 and contacted the authors of eligible trials to request individual patient data. The primary outcome was all-cause mortality at day 28 after randomization.

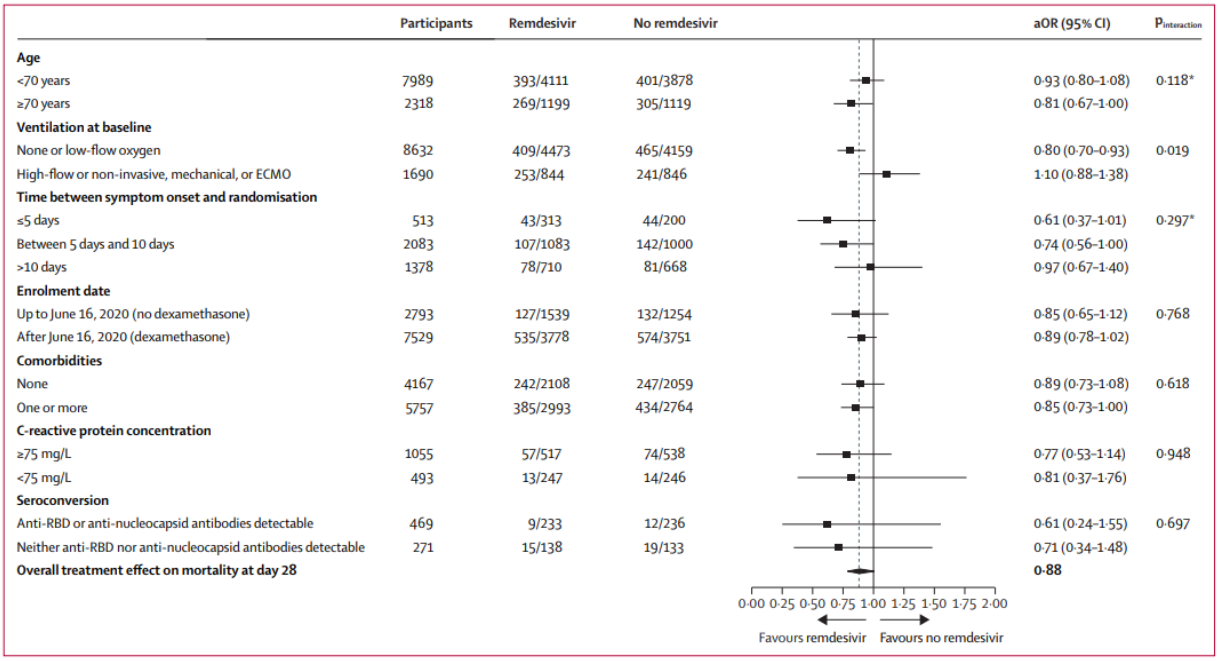
The search identified 857 records, yielding 9 RCTs eligible for inclusion. Of these 9 eligible RCTs, individual data were provided for 8, covering 10,480 patients hospitalized with Covid-19 (99% of such patients included in such RCTs worldwide) recruited between February 6, 2020, and April 1, 2021. The 10,480 patients included in the individual patient data meta-analysis had a median age of 58 years, with the majority being male (6,610, 63.1%) and more than half (5,845, 58.1%) had at least one comorbidity.

Patients were randomly assigned after a median symptom duration of 9 days; 1,729 (16.5%) patients received non-invasive or mechanical ventilation at baseline and 7,620 (72.7%) patients were enrolled after June 16, 2020, when dexamethasone became part of usual care for the treatment of patients with severe COVID-19. Baseline characteristics were similar between randomized groups.

Overall, 662 (12.5%) of 5,317 patients in the remdesivir group died by day 28 compared with 706 (14.1%) of 5,005 patients in the no-remdesivir group (adjusted odds ratio [aOR] 0.88, 95% confidence interval [CI] 0.78–1.00, $P = 0.045$). Meanwhile, the number of patients either requiring new mechanical ventilation or dying up to day 28 was lower in the remdesivir group (988 [18.5%] of 5,346 patients) than in the no-remdesivir group (1,123 [22.3%] of 5,034 patients; aOR 0.81, 95% CI 0.73–0.90, $P < 0.0001$), and the number of mechanical-ventilation-free days

was higher in the remdesivir group (adjusted incidence rate ratio 1.05, 95% CI 1.04–1.07, *P* < 0.0001; individual patient data available from six trials only).

Additionally, patients receiving remdesivir had better clinical status on an ordinal scale — i.e., less respiratory support at day 28 (aOR 0.87, 95% CI 0.80–0.96, *P* = 0.0037) and at day 14 (aOR 0.88, 0.81–0.95, *P* = 0.0015) than patients in the no-remdesivir group.



Comment: Patients treated in hospital for Covid-19 who are receiving no or conventional oxygen support have significant survival benefits from remdesivir. For patients requiring more respiratory support, evidence is inconclusive and treatment should therefore be individualized. The effect size of remdesivir in patients with more respiratory support or acquired immunity and the cost-effectiveness of remdesivir remain to be further elucidated. This evaluation was underpowered to evaluate patients who were ventilated when receiving remdesivir, but other studies have not shown benefit with remdesivir. The findings do align with several aspects of the NIH guidelines. Remdesivir is recommended for patients treated in hospital for Covid-19 who require only conventional oxygen and not for patients who are receiving mechanical ventilation or ECMO.