Infectious Diseases Watch

March 7,2022

Ed Septimus, MD

General Infectious Diseases

Mortality Associated With Influenza and Respiratory Syncytial Virus in the US, 1999-2018

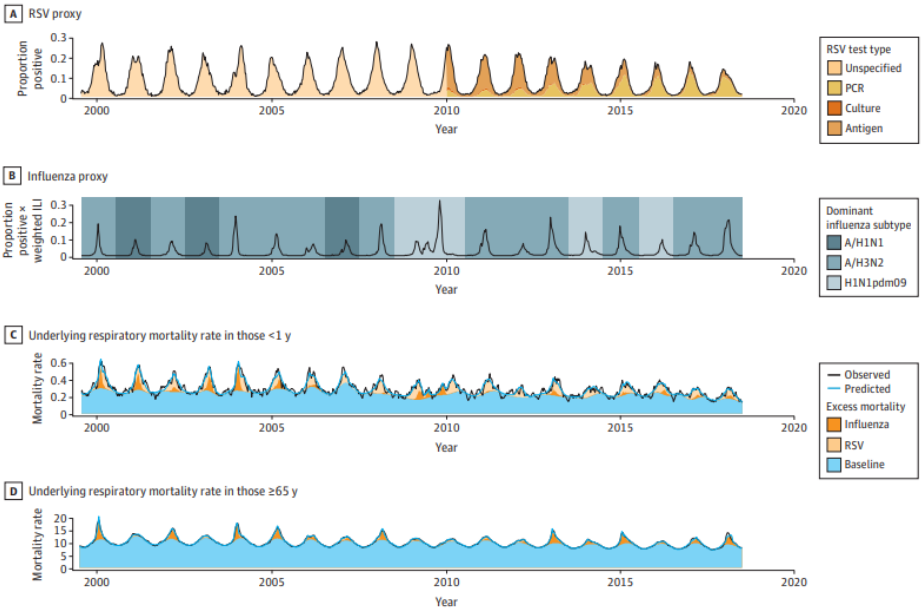
JAMA Netw Open published online February 28, 2022

doi:10.1001/jamanetworkopen.2022.0527

This is a cross-sectional study using data from 50.3 million US death certificates from 1999 to 2018 to create age-specific linear regression models and assess weekly mortality fluctuations above a seasonal baseline associated with RSV and influenza.

The study estimates a mean of 6549 underlying respiratory deaths associated with RSV each year (range, 5035-7645) and estimates a mean of 10,171 underlying respiratory deaths associated with influenza per year (range, 393 to 23,176), with greater interannual variation for influenza than for RSV. The highest mortality for both viruses was among individuals aged 65 years or older; RSV mortality was 5-fold higher than influenza mortality among children younger than 1 year of age. A lower proportion of influenza deaths occurred among those aged 65 years or older compared with earlier estimates (75.1% [95% CI, 67.4%-82.8%]). Influenza mortality was highest among those aged 65 years or older in seasons when A/H3N2 predominated (18,739 [95% CI, 16,616-21,336] deaths in 2017-2018) and among those aged 5 to 49 years when A/H1N1pdm2009 predominated (1683 [95% CI, 1583-1787] deaths in 2013-2014) and deaths in 2017-2018).

Figure 2. Weekly Time Series for Respiratory Syncytial Virus (RSV) and Influenza Surveillance Proxies and the Underlying Respiratory Mortality Rate per 100 000 Population in Children Younger Than 1 Year and Adults Aged 65 Years or Older



Comment: This study suggests that RSV poses a greater risk than influenza to infants, while both are associated with substantial mortality among elderly individuals. Influenza has large interannual variability, affecting different age groups depending on the circulating virus. The emergence of the influenza A/H1N1pdm2009 pandemic virus in 2009 shifted mortality toward youngrt adults, a trend still observed to date. Their model may be underestimating RSV mortality in recent years owing to changes in case ascertainment. Use of multiplex PCR panels increases the RSV testing pool to include individuals unlikely to have RSV, thus decreasing the weekly percentage of positive test results. The investigators did a sensitivity analysis which showed that there was little difference in mean estimates over the 20-year period. Although they do not have data by test type for influenza, increased use of PCR testing has likely improved influenza surveillance due to lower sensitivity of EIA. Unfortunately, they did not have access to age-specific viral surveillance data, and thus the same proxies had to be used for all age groups., Broad death categories may not be ideal for ascertaining RSV or influenza excess mortality. Lastly, they did not consider sex or race and ethnicity, which may be important for future work.

Etiology, Treatments, and Outcomes of Patients With Severe Community-Acquired Pneumonia in a Large U.S. Sample Crit Care Med published online February 2022

DOI: 10.1097/CCM.0000000000005498

This is a retrospective observational cohort study within the Premier database including 177 US hospitals The investigators set out to compare the clinical practice and outcomes in severe

community-acquired pneumonia (sCAP) patients to those in non-sCAP patients using guideline-defined criteria for sCAP for adults ≥18. (see below)

Validated definition includes either one major criterion or three or more minor criteria

Minor criteria
- Respiratory rate ⩾ 30 breaths/min
- Pa_{O2}/F_{IO2} ratio ⩽ 250
- Multilobar infiltrates
- Confusion/disorientation
- Uremia (blood urea nitrogen level ⩾ 20 mg/dl)
- Leukopenia* (white blood cell count < 4,000 cells/μl)
- Thrombocytopenia (platelet count < 100,000/μl)
- Hypothermia (core temperature < 36°C)
- Hypotension requiring aggressive fluid resuscitation

Major criteria
- Septic shock with need for vasopressors
- Respiratory failure requiring mechanical ventilation

Adult patients (≥ 18 yr old) with a principal diagnosis of pneumonia or a secondary diagnosis of pneumonia paired with a principal diagnosis of sepsis or respiratory failure were included. Patients with at least one guideline-defined major criterion for severe pneumonia were compared with patients with nonsevere disease. Among 154,799 patients with pneumonia, 21,805 (14.1%) met criteria for sCAP. They had higher organ failure scores (1.9 vs 0.63; $p < 0.001$) and inpatient mortality (22.0 vs 5.0%; $p < 0.001$), longer lengths of stay (8 vs 5 d; $p < 0.001$), and higher costs ($20,046 vs $7,543; $p < 0.001$) than those with nonsevere disease. Patients with sCAP had twice the rate of positive blood cultures (10.0% vs 4.5%; $p < 0.001$) and respiratory cultures (34.2 vs 21.1%; $p < 0.001$) and more often had isolates resistant to first-line community-acquired pneumonia antibiotics (10% of severe vs 3.1% of nonsevere; $p < 0.001$). Regardless of disease severity, *S. pneumoniae* was the most common pathogen recovered from blood cultures and *S. aureus* and *Pseudomonas* species were the most common pathogens recovered from the respiratory tract. Although few patients with sCAP had cultures positive for a resistant organism, 65% received vancomycin and 42.8% received piperacillin-tazobactam.

Type of Test	Nonsevere		Severe	
	Test (%)	Positive Test (Row %)	Test (%)	Positive Test (Row %)
Blood culture	122,402 (92.0)	5,460 (4.5)	20,641 (94.7)	2,055 (10.0)
Respiratory culture	34,108 (25.6)	7,212 (21.1)	11,770 (54.0)	4,029 (34.2)
Influenza test	28,532 (21.5)	471 (1.7)	4,539 (20.8)	153 (3.4)
UAT for *Streptococcus*	20,264 (15.2)	1,365 (6.7)	3,621 (16.6)	340 (9.4)
UAT for *Legionella*	27,429 (20.6)	403 (1.5)	5,069 (23.2)	77 (1.5)
Nasal swab for *Staphylococcus*	7,586 (5.7)	1,391 (18.3)	3,674 (16.8)	725 (19.7)
PCR for *Legionella*	95 (0.07)	1 (1.1)	40 (0.18)	1 (2.5)
PCR for *Chlamydia*	2,023 (1.5)	2 (0.10)	505 (2.3)	0 (0.0)
PCR for *Mycoplasma*	2,183 (1.6)	15 (0.69)	559 (2.6)	0 (0.0)

Organism	Nonsevere			Severe		
	Blood Culture ($n = 122,402$)	Respiratory Culture ($n = 34,108$)	Overall ($n = 125,089$)	Blood Culture ($n = 20,641$)	Respiratory Culture ($n = 11,770$)	Overall ($n = 21,230$)
	Count (column %)					
Methicillin-sensitive *Staphylococcus aureus*	709 (0.58)	1,681 (4.9)	2,312 (1.8)	326 (1.6)	1,068 (9.1)	1,279 (6.0)
Methicillin-resistant *S. aureus*	509 (0.42)	1,386 (4.1)	1,823 (1.5)	224 (1.1)	829 (7.0)	961 (4.5)
Streptococcus pneumoniae	1,801 (1.5)	1,091 (3.2)	2,810 (2.2)	489 (2.4)	520 (4.4)	916 (4.3)
Escherichia coli	1,162 (0.95)	515 (1.5)	1,672 (1.3)	426 (2.1)	353 (3.0)	739 (3.5)
Pseudomonas species	211 (0.17)	1,655 (4.9)	1,844 (1.5)	114 (0.55)	720 (6.1)	786 (3.7)
Klebsiella species	378 (0.31)	691 (2.0)	1,054 (0.84)	166 (0.80)	454 (3.9)	591 (2.8)
Other bacteria	502 (0.41)	641 (1.9)	1,134 (0.91)	217 (1.1)	379 (3.2)	577 (2.7)
Haemophilus influenzae	114 (0.09)	266 (0.78)	379 (0.30)	56 (0.27)	147 (1.2)	195 (0.92)
Proteus mirabilis	168 (0.14)	172 (0.50)	338 (0.27)	112 (0.54)	134 (1.1)	239 (1.1)
Serratia species	20 (0.02)	148 (0.43)	165 (0.13)	18 (0.09)	96 (0.82)	108 (0.51)
Any bacteria resistant to ceftriaxone + macrolide	948 (0.77)	1,948 (5.7)	2,828 (2.3)	477 (2.3)	1,188 (10.1)	1,545 (7.3)
Any bacteria resistant to ceftriaxone + quinolone	497 (0.41)	942 (2.8)	1,396 (1.1)	254 (1.2)	693 (5.9)	883 (4.2)
Any bacteria resistant to quinolone alone	909 (0.74)	1,319 (3.9)	2,173 (1.7)	479 (2.3)	932 (7.9)	1,316 (6.2)
Any bacteria resistant to any community-acquired pneumonia therapy option	1,534 (1.3)	2,461 (7.2)	3,891 (3.1)	795 (3.9)	1,524 (12.9)	2,131 (10.0)

Comment: Despite nearly 100% blood culture sampling, the yield of these was only 10% in sCAP and 4.5% in nonsevere. As prior studies have demonstrated only a minority of patients with CAP have a positive culture from either blood or sputum. In this article only ~ 1/3 had a positive culture from either blood or respiratory. Among those patients who had positive cultures, patients with sCAP had higher rates of positivity overall but the organisms differed by source of the culture, with *S. aureus* accounting for the greatest percentage of positive

respiratory cultures and *S. pneumoniae* accounting for a higher percentage among positive blood cultures. The prevalence of resistance to first-line CAP regimens was 13.1%, largely because of resistance among respiratory samples, which often cannot be used to distinguish between true infection and colonization. Despite low rates of resistance, patients with sCAP had double the rate of treatment with broad-spectrum antibiotics including piperacillin-tazobactam and cefepime, and 65% of sCAP patients received vancomycin. To further complicate the discussion, because pneumonia is usually a clinical diagnosis, it is possible that some of the patients could have had an alternative cause for their symptoms such as CHF etc. Recent studies suggest viral infection accounts for 24–40% of CAP [Eur Respir Rev 2016; 25:178-188], but very few patients in this study underwent viral testing. Increase utilization of viral testing and new syndromic molecular panels for CAP could reduce unnecessary antibiotics. This article and others continue to report a relatively low rates of culture positivity even among patients with severe disease. In an interesting article from 2020, investigators studied 120 patients hospitalized for CAP who provided a high-quality sputum specimen using Gram stain, quantitative sputum culture, bacterial speciation by MALDI-TOF, and viral multiplex PCR. Thresholds for diagnosis of bacterial infection were $\geq 10^5$ cfu/mL sputum for RBPs (recognized bacterial pathogens such as *S. pneumoniae*, *H. influenzae*, and *S. aureus*) and $\geq 10^6$ cfu/mL for NRF (normal respiratory flora). Recognized bacterial pathogens were found in 68 of 120 (56.7%) patients; 14 (20.1%) of these had a coinfecting respiratory virus. NRF was found in 31 (25.8%) patients; 10 (32.2%) had a coinfecting respiratory virus. They concluded NRF, with or without viral coinfection, appear to have caused ~25% of cases of CAP and may have played a contributory role. By obtaining high quality sputum specimens, they were able to identify the etiology of CAP in >90% of patients. [OFID 2020; DOI: 10.1093/ofid/ofaa307] The findings in the current article supports the need for obtaining better sputum samples and using new advanced diagnostic tools that could provide rapid information on the microbial etiology of pneumonia. See next article

Impact of *Streptococcus pneumoniae* Urinary Antigen Testing in Patients With Community-Acquired Pneumonia Admitted Within a Large Academic Health System OFID published online January 2022

doi.org/10.1093/ofid/ofab522

This is a retrospective study of adults hospitalized in 2019 who had PUAT performed. The purpose of the study was to examine the use of pneumococcal urinary antigen testing (PUAT) for patients with CAP as an antimicrobial stewardship tool. They standardized their order sets to include universal PUAT for CAP. They compared incidence and timing of de-escalation in PUAT- positive vs -negative groups and described patients' outcomes.

A third-generation cephalosporin, ceftriaxone, with cefpodoxime as oral switch, plus azithromycin was recommended as the empiric treatment of choice during the study period. Initial de-escalation was assessed within the first 3 DOT and defined as (1) a change in the antimicrobial regimen to a narrower spectrum agent (i.e., de-escalation of antipseudomonal coverage), (2) discontinuation of MRSA coverage, or (3) discontinuation of atypical coverage. Of note, ED patients who trigger sepsis alert criteria (i.e., presence of both infection and a systemic inflammatory response) are promptly initiated with broad-spectrum (often anti-MRSA

and antipseudomonal) coverage per the sepsis protocol. Traditionally, at their institution, piperacillin-tazobactam is considered the workhorse antipseudomonal agent.

They were able to evaluate 910 patients, 121 (13.3%) of whom were PUAT positive. No difference in baseline characteristics, including severity of illness, was observed between groups. Initial de-escalation occurred in 82.9% and 81.2% of PUAT-positive and -negative patients, respectively (*P* = .749). Median time to de-escalation was shorter in the PUAT-positive group (1 [interquartile range {IQR}, 0–2] day vs 1 [IQR, 1–2] day, *P* = .01). Within 24 hours of PUAT, more patients in the PUAT-positive group had atypical coverage discontinued (61.3% vs 47.2%, *P* = .026) without difference in MRSA agent discontinuation or antipseudomonal de-escalation. Among the PUAT-positive group, unadjusted analysis demonstrated shorter median length of stay in patients who were de-escalated compared to those who were not (6 [IQR, 4–10] vs 8 [IQR, 7–12] days, *P* = .0005), without difference in the incidence of *C difficile*, in-hospital mortality, or 30-day infection-related readmission. Clinical characteristics and baseline severity of illness including PSI class 5 determination, median PSI score, and need for initial ICU admission did not differ between patients who were de-escalated and those which required escalation or were not de-escalated, indicating that baseline severity of illness was balanced.

	All Patients (N = 910)		
Antimicrobial	Positive PUAT (n = 121[a])	Negative PUAT (n = 789)	*P* Value
Azithromycin	81 (66.9)	579 (73.4)	.171
Doxycycline	43 (35.5)	216 (27.4)	.081
Vancomycin	61 (50.4)	366 (46.4)	.466
Piperacillin-tazobactam	52 (43.0)	295 (37.4)	.281
Cefepime	7 (5.8)	80 (10.1)	.177
Aztreonam	5 (4.1)	25 (3.21)	.780
Amikacin	3 (2.5)	45 (5.7)	.383
Fluoroquinolone	4 (3.3)	12 (1.5)	.698
Linezolid	6 (5.0)	5 (0.6)	.001
Ceftriaxone	89 (73.6)	573 (72.6)	.917
Ampicillin-sulbactam	3 (2.5)	31 (3.9)	.599
Meropenem	8 (6.6)	18 (2.3)	.018
Atypical coverage[b]	103 (85.1)	722 (91.5)	.038
MRSA coverage[c]	64 (52.9)	368 (46.6)	.236
Pseudomonas aeruginosa coverage	61 (50.4)	368 (46.6)	.499

Comment: There was earlier de-escalation in the PUAT-positive group. This seems to be due primarily to discontinuation of atypical rather than anti-MRSA or antipseudomonal coverage. In many ways this is disappointing, since a positive PUAT should also trigger de-escalation of anti MRSA and antipseudomonal agents. In addition, this also highlights the impact of the SEP-1 measure on initial antibiotic selection. As the article above also highlights MRSA and pseudomonas are uncommon causes of CAP including sCAP.

COVID-19

COVID-19 News

White House rolls out next COVID-19 plan March 2, 2022

1. "Test to treat." The administration will launch a nationwide "test-to-treat" initiative to minimize the time between a positive test result and treatment. Pharmacy-based clinics will be operationalized to serve as "one-stop" test-to-treat locations, in which Americans who receive a positive COVID-19 test result are rapidly seen by a provider and receive antiviral therapy, all in one visit. The plan notes that hundreds of one-stop sites will be made available nationwide in March. [Need to have criteria who is eligible for antiviral therapy and coordinate with the patient's physician. Given drug interactions will pharmacist have a complete list of medications, and will pharmacy have a recent creatinine if adjustment is needed? So, on paper sounds good but we need safeguards in place to do it safely. We also need a reliable supply chain]

2. Improved COVID-19 tracking. The administration is seeking additional funding from Congress to improve data infrastructure at the federal, state and local level to be better prepared to rapidly respond to emerging threats and new COVID-19 variants. This includes better surveillance through genomic sequencing and wastewater surveillance. The amount of funding was not specified in the plan. "The administration will continue to prioritize modernizing our state and local public health data systems to move from siloed and outdated public health data systems to connected, resilient, adaptable, and sustainable 'response-ready' systems," the plan states. [This is badly needed, and many states have already received Covid funding to upgrade data systems]

3. Universal vaccine**.** The administration plans to accelerate research and development toward a single COVID-19 vaccine to protect against the virus and all of its new variants, which will require additional funding from Congress. [this is a long-term goal]

4. Vaccines for young children. Once COVID-19 vaccines are authorized by the FDA and recommended by the CDC for America's youngest children, the administration says it will make them available "at thousands of pediatric and primary care sites across the country," as well as children's hospitals and health systems. [need to do a better job at convincing parents to vaccinate their children]

5. Prioritization of immunocompromised Americans. The plan acknowledges the challenges immunocompromised Americans face in navigating COVID-19 risks. The administration notes that they will be prioritized for access to antiviral treatments, and the CDC will prioritize communication with individuals who are moderately or severely immunocompromised to ensure they understand how and when their vaccine protection may be waning over time. "If an additional shot is needed, the administration will conduct outreach so people who are immunocompromised understand how to stay protected against COVID-19 and ensure that they

can receive additional shots at a convenient time," the plan notes. [need to link these patients to testing and therapeutics if appropriate -see #1]

6. Hospital capacity. The administration has worked with FEMA to mobilize planning teams that will work with every state and territory to assess hospital needs ahead of surges and begin expanding hospital bed capacity. Additionally, the administration notes it has strengthened its medical response corps for non-military medical personnel to support communities that need assistance.

7. Long COVID-19 research**.** The administration aims to pioneer a national research agenda to advance scientific understanding of long COVID-19, in which several governmental agencies (including HHS, the Department of Veterans Affairs and the Defense Department) will create a comprehensive plan to foster research and data-sharing across the government and in collaboration with academic and industry partners. [agree]

8. Free masks. Pointing to its January 2022 move in which President Biden deployed "hundreds of millions of high-quality masks to the American public for free," the preparedness plan notes that the administration will continue to distribute more high-quality masks for adults and children, although the quantity or timeline was not made clear. [this is fine, but need guidance when and who should wear masks]

Comment: Overall this is a good start with a few reservations. I have made comments in brackets. I would have added the need to improve communication and messaging to regain confidence in our public agencies. We need to fundamentally transform the CDC and where possible separate Washington DC from Atlanta, meaning separate the science from the politics. Another challenge, to accomplish this plan, Congress with need to allocate significant additional funding which is badly needed as we invest in building a robust public health system to be ready for the next emerging infectious disease. It is not if, but when.

The COVID-19 Treatment Guidelines Panel's Statement on the Role of Bebtelovimab for the Treatment of High-Risk, Nonhospitalized Patients With Mild to Moderate COVID-19 NIH Guidelines March 2, 2022

Preferred Therapies

For nonhospitalized patients with mild to moderate COVID-19 who are at high risk of progressing to severe disease, the Panel recommends using 1 of the following therapies (listed in order of preference): This is unchanged.

- Nirmatrelvir 300 mg with ritonavir 100 mg (Paxlovid) orally twice daily for 5 days, initiated as soon as possible and within 5 days of symptom onset in those aged ≥12 years and weighing ≥40 kg (AIIa)**.**
- Sotrovimab 500 mg as a single intravenous (IV) infusion, administered as soon as possible and **within 7 days of symptom** onset in those aged ≥12 years and weighing ≥40 kg (AIIa)**.**
- Remdesivir 200 mg **I**V on Day 1, followed by remdesivir 100 mg IV once daily on Days 2 and 3, initiated as soon as possible and within 7 days of symptom onset in those aged ≥12 years and weighing ≥40 kg (BIIa)**.**

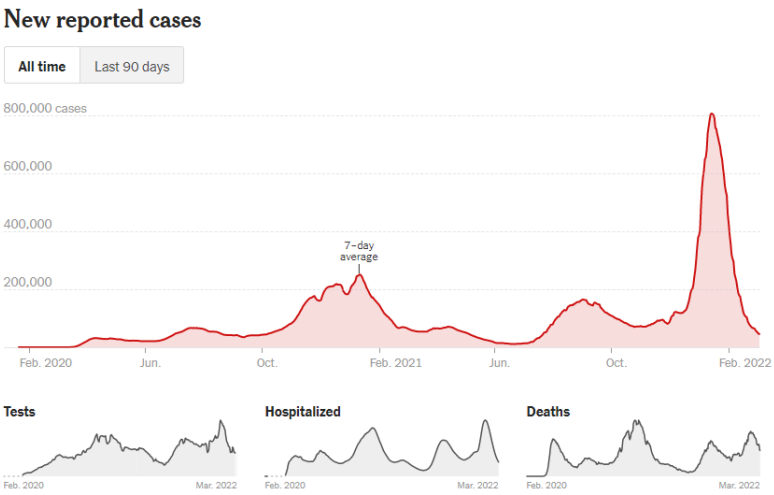
Alternative Therapies

If none of the preferred therapies for high-risk, nonhospitalized patients are available, feasible to deliver, or clinically appropriate (e.g., due to drug-drug interactions, concerns related to renal or hepatic function), the Panel recommends using 1 of the following therapies (listed in alphabetical order):

- Bebtelovimab 175 mg as a single IV infusion, administered as soon as possible and **within 7 days of symptom** onset in those aged ≥12 years and weighing ≥40 kg, ONLY if none of the preferred therapies are available, feasible to deliver, or clinically appropriate (CIII). The assessment of the clinical efficacy of bebtelovimab is limited to 1 small, Phase 2, randomized, placebo-controlled trial in patients at low risk of disease progression and 1 small randomized controlled trial.
- Molnupiravir 800 mg orally twice daily for 5 days, initiated as soon as possible and **within 5 days of symptom onset** in those aged ≥18 years, ONLY if none of the preferred therapies are available, feasible to deliver, or clinically appropriate (CIIa)**.**

Comment: I think the NIH has it right. We need more data on the efficacy of bebtelovimab. Another important change has been shortening the eligibility to within 7 days on symptoms from 10 days for MCA.

COVID-19 by the Numbers



	DAILY AVG. ON MAR. 5	14-DAY CHANGE	TOTAL REPORTED
Cases	45,819	-57%	79,166,521
Tests	1,063,433	-2%	—
Hospitalized	40,695	-43%	—
In I.C.U.s	7,556	-44%	—
Deaths	1,539	-32%	957,215

Comment: Trends are clear in the last 2-3 weeks with rapidly declining cases, hospitalization, ICU admissions, and deaths. The question now is what will our COVID-19 future look like? The short and honest answer is we do not know yet.

Manufacturer and Test Name (Links to Instructions for Use)	Test Type	Who can use this test: Symptoms	Who can use this test: Age	Other Details
Abbott Diagnostics Scarborough, Inc.: BinaxNOW COVID-19 Ag Card Home Test (/media/144575/download)	Antigen	• People with symptoms that began within the last 7 days • People without symptoms. The test is to be performed two times over three days (serial testing)	• Age 15 years and older • Age 2 years and older when collected by an adult	• Nasal swab • Requires supervision of a telehealth proctor and a smartphone or computer • Results in 15 minutes
Abbott Diagnostics Scarborough, Inc.: BinaxNOW COVID-19 Antigen Self Test (/media/147255/download)	Antigen	• People with symptoms that began within the last 7 days • People without symptoms. The test is to be performed two times over three days (serial testing)	• Age 15 years and older • Age 2 years and older when collected by an adult	• Nasal swab • Smartphone optional • Results in 15 minutes
Access Bio, Inc.: CareStart COVID-19 Antigen Home Test (/media/152188/download)	Antigen	• People with symptoms that began within the last 7 days • People without symptoms. The test is to be performed two times over three days (serial testing)	• Age 14 years and older • Age 2 years and older when collected by an adult	• Nasal swab • Smartphone optional • Alternate brand name: On/go COVID-19 Antigen Self-Test • Results in 10 minutes

Manufacturer and Test Name (Links to Instructions for Use)	Test Type	Who can use this test: Symptoms	Who can use this test: Age	Other Details
ACON Laboratories, Inc: Flowflex COVID-19 Antigen Home Test (/media/152699/download)	Antigen	• People with symptoms that began within the last 7 days • People without symptoms. The test is to be performed two times over three days (serial testing)	• Age 14 years and older • Age 2 years and older when collected by an adult	• Nasal swab • Smartphone optional • Alternate brand name: On/Go One COVID-19 Antigen Home Test • Results in 15 minutes
Becton, Dickinson and Company (BD): BD Veritor At-Home COVID-19 Test (/media/151763/download)	Antigen	• People with symptoms that began within the last 7 days • People without symptoms. The test is to be performed two times over three days (serial testing)	• Age 14 years and older • Age 2 years and older when collected by an adult	• Nasal swab • Requires a smartphone • Results in 15 minutes
Celltrion USA, Inc.: Celltrion DiaTrust COVID-19 Ag Home Test (/media/153421/download)	Antigen	• People with symptoms that began within the last 7 days • People without symptoms. The test is to be performed two times over three days (serial testing)	• Age 14 years and older	• Mid-turbinate nasal swab • Smartphone optional • Results in 15 minutes
Cue Health Inc.: Cue COVID-19 Test for Home and Over The Counter (OTC) Use (/media/146471/download)	Molecular	• People with or without symptoms	• Age 18 years and older • Age 2 years and older when collected by an adult	• Nasal swab • Requires a Cue Cartridge Reader (sold separately) • Requires a smartphone • Results in 20 minutes

Manufacturer and Test Name (Links to Instructions for Use)	Test Type	Who can use this test: Symptoms	Who can use this test: Age	Other Details
Detect, Inc.: Detect Covid-19 Test (/media/153746/download)	Molecular	• People suspected of COVID-19 • People without symptoms. The test is to be performed two times over three days (serial testing)	• Age 14 years and older • Age 2 years and older when collected by an adult	• Nasal swab • Requires a Detect Hub (sold separately) • Requires a smartphone • Results in 60 minutes
Ellume Limited: Ellume COVID-19 Home Test (/media/144593/download)	Antigen	• People with or without symptoms	• Age 16 years and older • Age 2 years and older when collected by an adult	• Mid-turbinate nasal swab • Requires a Smartphone • Results in 15 minutes
iHealth Labs, Inc.: iHealth COVID-19 Antigen Rapid Test (/media/153924/download)	Antigen	• People with symptoms that began within the last 7 days • People without symptoms. The test is to be performed two times over three days (serial testing)	• Age 15 years and older • Age 2 years and older when collected by an adult	• Nasal swab • Smartphone optional • Results in 15 minutes

Manufacturer and Test Name (Links to Instructions for Use)	Test Type	Who can use this test: Symptoms	Who can use this test: Age	Other Details
InBios International Inc: SCoV-2 Ag Detect Rapid Self-Test (/media/154337/download)	Antigen	• People with symptoms that began within the last 5 days • People without symptoms. The test is to be performed two times over three days (serial testing)	• Age 14 years and older • Age 2 years and older when collected by an adult	• Nasal swab • Results in 20 minutes
Lucira Health, Inc: Lucira CHECK-IT COVID-19 Test Kit (/media/147495/download)	Molecular	• People with or without symptoms	• Age 14 years and older • Age 2 years and older when collected by an adult	• Nasal swab • Smartphone optional • Results in 30 minutes
Maxim Biomedical, Inc.: MaximBio ClearDetect COVID-19 Antigen Home Test (/media/155635/download)	Antigen	• People with symptoms that began within the last 5 days • People without symptoms. The test is to be performed two times over three days (serial testing)	• Age 14 years and older • Age 2 years and older when collected by an adult	• Nasal swab • Results in 15 minutes

Manufacturer and Test Name (Links to Instructions for Use)	Test Type	Who can use this test: Symptoms	Who can use this test: Age	Other Details
OraSure Technologies, Inc.: InteliSwab COVID-19 Rapid Test (/media/149912/download)	Antigen	• People with symptoms that began within the last 7 days • People without symptoms. The test is to be performed two times over three days (serial testing)	• Age 18 years and older • Age 2 years and older when collected by an adult	• Nasal swab • Smartphone optional • Results in 30 minutes
Quidel Corporation: QuickVue At-Home OTC COVID-19 Test (/media/147250/download)	Antigen	• People with symptoms that began within the last 6 days • People without symptoms. The test is to be performed two times over three days (serial testing)	• Age 14 years and older • Age 2 years and older when collected by an adult	• Nasal swab • Results in 10 minutes
SD Biosensor, Inc.: COVID-19 At-Home Test (/media/155126/download)	Antigen	• People with symptoms that began within the last 6 days • People without symptoms. The test is to be performed two times over three days (serial testing)	• Age 14 years and older • Age 2 years and older when collected by an adult	• Nasal swab • Results in 20 minutes

Manufacturer and Test Name (Links to Instructions for Use)	Test Type	Who can use this test: Symptoms	Who can use this test: Age	Other Details
Siemens Healthineer: CLINITEST Rapid COVID-19 Antigen Self-Test (/media/155176/download)	Antigen	• People with symptoms that began within the last 7 days • People without symptoms. The test is to be performed two times over three days (serial testing)	• Age 14 years and older • Age 2 years and older when collected by an adult	• Nasal swab • Results in 15 minutes

Comment: Sorry for long list, but I thought this would be a good reference since there are many counterfeit and insensitive tests out on the market. This reference also outlines who is eligible, when to test, and if they have symptoms or not. All the tests recommend serial testing in asymptomatic individuals.

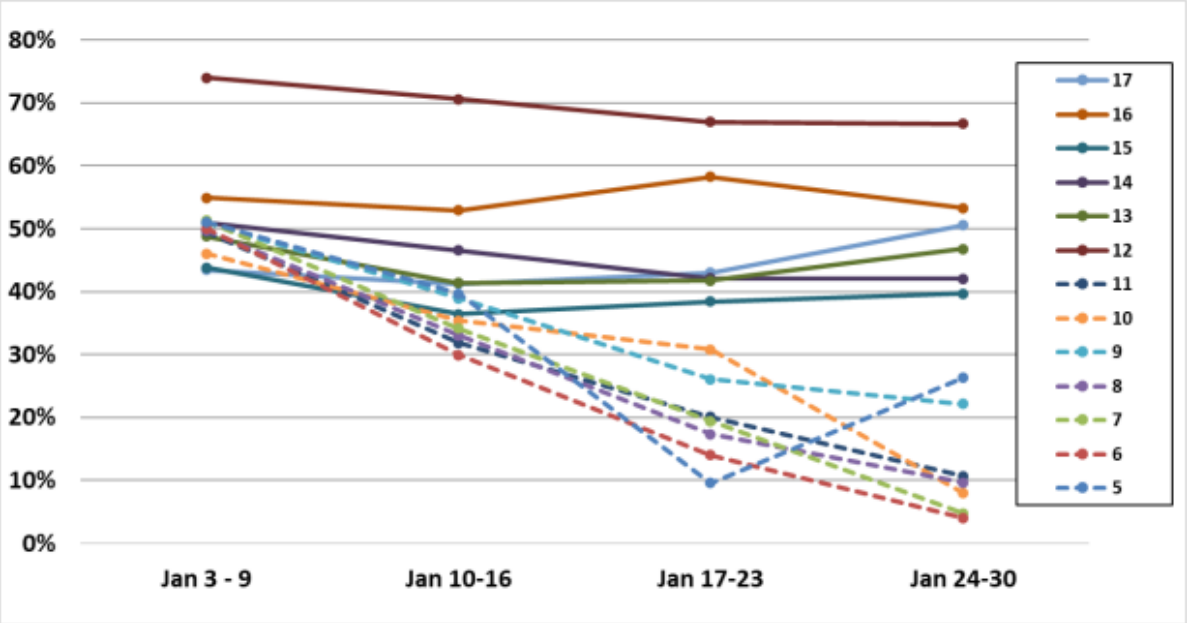
Journal Review

Effectiveness of the BNT162b2 vaccine among children 5-11 and 12-17 years in New York after the Emergence of the Omicron Variant medRxiv posted February 28, 2022

doi.org/10.1101/2022.02.25.22271454

From December 13, 2021, to January 30, 2022, among 852,384 fully vaccinated children 12-17 years and 365,502 children 5-11 years, VE against cases declined from 66% (95% CI: 64%, 67%) to 51% (95% CI: 48%, 54%) for those 12-17 years and from 68% (95% CI: 63%, 72%) to 12% (95% CI: 6%, 16%) for those 5-11 years. During the January 24-30 week, VE for children 11 years was 11% (95%CI -3%, 23%) and for those age 12 was 67% (95% CI: 62%, 71%). VE against hospitalization declined from 85% (95% CI: 63%, 95%) to 73% (95% CI: 53%, 87%) for children 12-17 years, and from 100% (95% CI: -189%, 100%) to 48% (95% CI: -12%, 75%) for those 5-11 years. Among children newly fully vaccinated December 13, 2021 to January 2, 2022, VE against cases within two weeks of full vaccination for children 12-17 years was 76% (95% CI: 71%, 81%) and by 28-34 days it was 56% (95% CI: 43%, 63%). For children 5-11, VE against cases declined from 65% (95% CI: 62%, 68%) to 12% (95% CI: 8%, 16%) by 28-34 days. However, the study data showed that COVID-19 vaccines reduce the risk of more severe illness and hospitalization for children 5-11.

Figure 1: Vaccine Effectiveness against Infection, by Week and Year of Age



Comment: The biological difference between the two ages is likely to be minimal, but while 12-year-old children got 30 micrograms of the vaccine — the same dose given to adults — children who were 11 received only 10 micrograms. Only about 25% children aged 5 to 11 years has received two doses of the vaccine. The data is generally consistent with the UK showing that vaccine effectiveness against symptomatic infection in adolescents aged 12 to 17 years drops to 23 percent after two months. [med Rxiv February 18, 2022, doi.org/10.1101/2021.12.10.21267408] However, vaccination of children 5-11 years was protective against severe disease and is recommended. Vaccination has also been shown to decrease viral shedding compared to unvaccinated. [N Engl J Med 2021; 385:2489-2491] Vaccine effectiveness was lowest among children 12 and older who were vaccinated at least five months earlier but had not received a booster shot; for them, the study found "no significant protection" during Omicron. But protection for children with a third dose was 81% during Omicron. New CDC vaccine effectiveness studies and surveillance data show that COVID-19 vaccination in eligible children and adolescents continues to offer protection against severe COVID-19 disease, including during Omicron. Additional data by the CDC, tracking rates of COVID-19 cases and deaths across 29 jurisdictions, also found the disease appeared less frequently among vaccinated children during the Omicron wave. See next article

Effectiveness of COVID-19 Pfizer-BioNTech BNT162b2 mRNA Vaccination in Preventing COVID-19–Associated Emergency Department and Urgent Care Encounters and Hospitalizations Among Nonimmunocompromised Children and Adolescents Aged 5–17 Years — VISION Network, 10 States, April 2021–January 2022 MMWR published March 1, 2022

In partnership with CDC, the VISION Network examined 39,217 emergency department (ED) and urgent care (UC) encounters and 1,699 hospitalizations among persons aged 5–17 years with COVID-19–like illness across 10 states during April 9, 2021– January 29, 2022, to estimate VE using a case-control test negative design.

Among children aged 5–11 years, VE against laboratory-confirmed COVID-19–associated ED and UC encounters 14–67 days after dose 2 was 46%. Among adolescents aged 12–15 and 16–17 years, VE 14–149 days after dose 2 was 83% and 76%, respectively; VE ≥150 days after dose 2 was 38% and 46%, respectively. Among adolescents aged 16–17 years, VE increased to 86% ≥7 days after dose 3 (booster dose). VE against COVID-19–associated ED and UC encounters was substantially lower during the Omicron predominant period than the Delta predominant period among adolescents aged 12–17 years, with no significant protection ≥150 days after dose 2 during Omicron predominance. However, a 2-dose VE against COVID-19–associated hospitalization was still 73%–94%. Furthermore, in adolescents aged 16–17 years, VE during the Omicron predominant period increased to 81% ≥7 days after a third booster dose.

Comment: The findings must be interpreted with caution. The CDC study did not exclude unvaccinated adolescents who had some immunity from a prior infection, which may have made vaccination seem less effective than it was. The data on hospitalizations, a more reliable proxy for severe disease than emergency room and urgent care visits was limited.

Several studies have shown that even though vaccine efficacy against infection wanes over time, the immune response [T and B cells] remains highly protective against sever disease and death, even against the Omicron variant. However, vaccine uptake among young children has been slow; fewer than one in four children aged 5 to 11 are now fully vaccinated. More than half of adolescents 12 to 17 have been fully vaccinated, with two shots, but only 12 percent have received a third booster dose. The CDC. recommends booster shots for all Americans aged 12 and older. Pfizer is evaluating the benefit of a third dose in younger children.

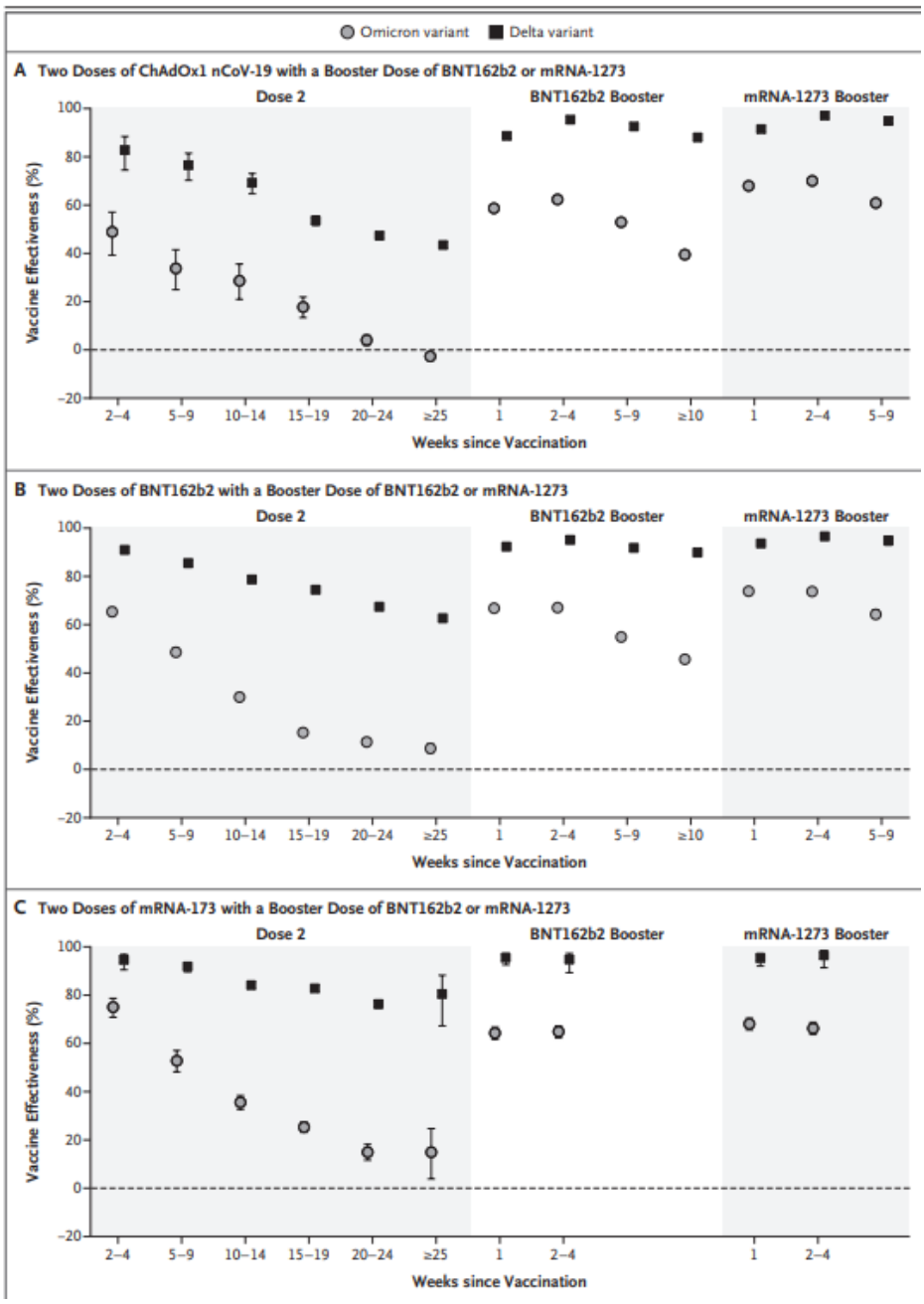
Covid-19 Vaccine Effectiveness against the Omicron (B.1.1.529) Variant N Engl J Med published online March 2, 2022

DOI: 10.1056/NEJMoa2119451

They used a test-negative case–control design to estimate vaccine effectiveness (VE) against symptomatic disease caused by the omicron and delta variants in the UK. Vaccine effectiveness was calculated after primary immunization with two doses of Pfizer, AstraZeneca, or Moderna vaccine and after a booster dose of Pfizer, AstraZeneca, or Moderna.

Between November 27, 2021, and January 12, 2022, a total of 886,774 eligible individuals infected with the omicron variant, 204,154 eligible individuals infected with the delta variant, and 1,572,621 eligible test-negative controls were identified. At all-time points investigated and for all combinations of primary course and booster vaccines, VE against symptomatic disease was higher for the delta variant than for the omicron variant. No effect against the omicron variant was noted from 20 weeks after two AstraZeneca doses, whereas VE after two Pfizer doses was 65.5% (95% confidence interval [CI], 63.9 to 67.0) at 2 to 4 weeks, dropping to 8.8% (95% CI, 7.0 to 10.5) at 25 or more weeks. Among AstraZeneca primary course recipients, VE increased to 62.4% (95% CI, 61.8 to 63.0) at 2 to 4 weeks after a Pfizer booster before decreasing to

39.6% (95% CI, 38.0 to 41.1) at 10 or more weeks. Among Pfizer primary course recipients, VE increased to 67.2% (95% CI, 66.5 to 67.8) at 2 to 4 weeks after a Pfizer booster before declining to 45.7% (95% CI, 44.7 to 46.7) at 10 or more weeks. VE after an AstraZeneca primary course increased to 70.1% (95% CI, 69.5 to 70.7) at 2 to 4 weeks after a Moderna booster and decreased to 60.9% (95% CI, 59.7 to 62.1) at 5 to 9 weeks. After a Pfizer primary course, the Moderna booster increased VE to 73.9% (95% CI, 73.1 to 74.6) at 2 to 4 weeks; VE fell to 64.4% (95% CI, 62.6 to 66.1) at 5 to 9 weeks.



Comment: Primary immunization with two doses of AstraZeneca or Pfizer vaccine provided limited protection against symptomatic disease caused by the omicron variant. A Pfizer or Moderna booster after either the AstraZeneca or Pfizer primary course substantially increased protection, but that protection waned over time. The populations that have received different vaccines as a primary course are different. For example, AstraZeneca was the main vaccine used early in the program in care homes and among persons in clinical risk groups. Furthermore, mRNA vaccines were the main vaccines used in persons younger than 40 years of age after the reported association between AstraZeneca and vaccine-induced thrombotic thrombocytopenia. Although adjustments were made for age and clinical risk factors, these age differences may explain some of the differences in the findings for the primary course — for example, the high VE against Omicron 2 to 9 weeks after the second dose of Pfizer is likely to be primarily among recently vaccinated young adults and teenagers. The investigators were not able to determine VE against severe illness using their test-negative, case-control study design, because the number of severe Omicron cases leading to hospitalization was too small and the natural lag between infections and poor outcomes was too long.

Major Update 2: Remdesivir for Adults With COVID-19: A Living Systematic Review and Meta-analysis for the American College of Physicians Practice Points

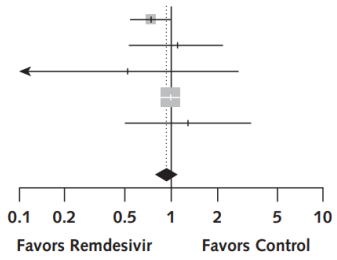
Ann Intern Med published online March 1, 2022

doi:10.7326/M21-4784

Since the last update (search date 9 August 2021), 1 new RCT and 1 new subtrial comparing a 10-day course of remdesivir with control (placebo or standard care) were identified. This review summarizes and updates the evidence on the cumulative 5 RCTs and 2 subtrials for this comparison. This update confirms a 10-day course of remdesivir, compared with control, probably results in little to no mortality reduction (5 RCTs). Updated results also confirm that remdesivir probably results in a moderate increase in the proportion of patients recovered by day 29 (4 RCTs) and may reduce time to clinical improvement (2 RCTs) and hospital length of stay (4 RCTs). New RCTs, by increasing the strength of evidence, lead to an updated conclusion that remdesivir probably results in a small reduction in the proportion of patients receiving ventilation or extracorporeal membrane oxygenation at specific follow-up times (4 RCTs).

Figure 1. Mortality for remdesivir 10-day course versus control (placebo or standard care).

Study, Year (Reference)	Control	Remdesivir Events, *n*	Remdesivir Total, *n*	Control Events, *n*	Control Total, *n*	RR (95% CI)
Beigel et al [ACTT-1], 2020 (4)	Placebo	59	541	77	521	0.74 (0.54–1.01)
Wang et al, 2020 (5)	Placebo	22	158	10	78	1.09 (0.54–2.18)
Spinner et al [SIMPLE-2], 2020 (7)	Usual care	2	193	4	200	0.52 (0.10–2.80)
Pan et al [Solidarity], 2021 (8)	Usual care	301	2743	303	2708	0.98 (0.84–1.14)
Abd-Elsalam et al, 2021 (16)	Usual care	9	100	7	100	1.29 (0.50–3.32)
Random-effects model		393	3735	401	3607	0.94 (0.79–1.12)
Heterogeneity: $I^2 = 0\%$						



Comment: In hospitalized adults with COVID-19, the findings confirm that remdesivir probably results in little to no difference in mortality and increases the proportion of patients recovered. Remdesivir may also reduce time to clinical improvement. Overall early remdesivir in patients on low amount of oxygen combined with steroids seems to result in the best outcomes. More recently remdesivir has been shown to reduce progression for high-risk outpatients with mild to moderate Covid-19.

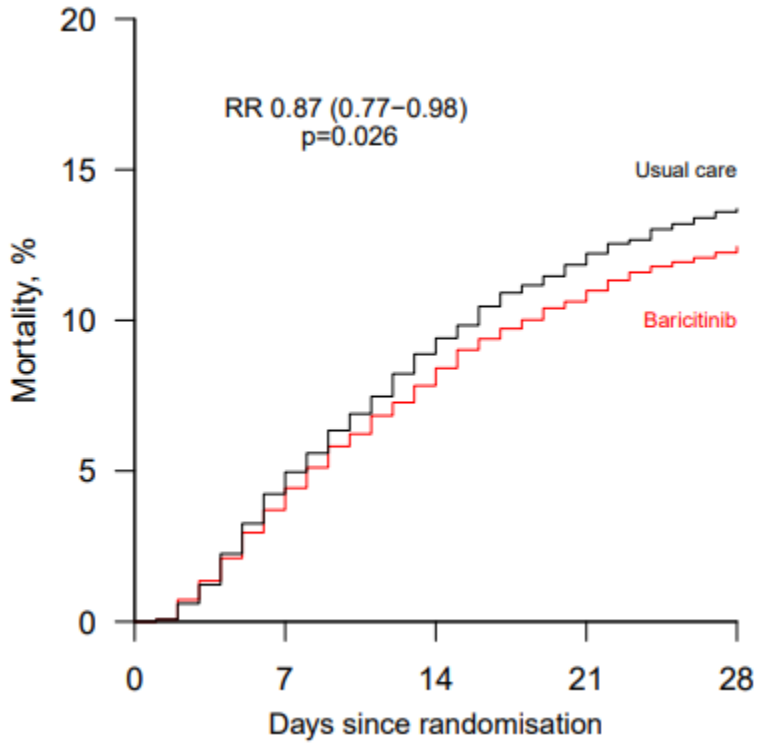
Baricitinib in patients admitted to hospital with 4 COVID-19 (RECOVERY): a randomised, controlled, 5 open-label, platform trial and updated meta-analysis

medRxiv posted March 3, 2022

doi.org/10.1101/2022.03.02.22271623

This is a randomized, controlled, open-label platform trial (Randomised Evaluation of COVID-19 Therapy [RECOVERY]), is assessing multiple possible treatments in patients hospitalized for COVID-19. Eligible and consenting patients were randomly allocated (1:1) to either usual standard of care alone (usual care group) or usual care plus baricitinib 4 mg once daily by mouth for 10 days or until discharge if sooner (baricitinib group). The primary outcome was 28-day mortality assessed in the intention-to-treat population. A meta-analysis was also conducted that included the results from the RECOVERY trial and all previous randomized controlled trials of baricitinib or other JAK inhibitor in patients hospitalized with COVID-19.

8156 patients were randomly allocated to receive usual care plus baricitinib versus usual care alone. At randomization, 95% of patients were receiving corticosteroids and 23% receiving tocilizumab (with planned use within the next 24 hours recorded for a further 9%). Overall, 513 (12%) of 4148 patients allocated to baricitinib versus 546 (14%) of 4008 patients allocated to usual care died within 28 days (age-adjusted rate ratio 0.87; 95% CI 0.77-0.98; p=0.026). This 13% proportional reduction in mortality was somewhat smaller than that seen in a meta-analysis of 8 previous trials of a JAK inhibitor (involving 3732 patients and 425 deaths) in which allocation to a JAK inhibitor was associated with a 43% proportional reduction in mortality (rate ratio 0.57; 95% CI 0.45-0.72). Including the results from RECOVERY into an updated meta-analysis of all 9 completed trials (involving 11,888 randomized patients and 1484 deaths) allocation to baricitinib or other JAK inhibitor was associated with a 20% proportional reduction in mortality (rate ratio 0.80; 95% CI 0.71-0.89; p<0.001).



Comment: In patients hospitalized for COVID-19, baricitinib significantly reduced the risk of death but the size of benefit was smaller than that suggested by previous trials. The total randomized evidence to date suggests that JAK inhibitors (mostly baricitinib) reduce mortality in patients hospitalized for COVID-19 by about 20%. In addition, in RECOVERY, there was no significant excess in death or infection due to non-COVID-19 causes and no excess of thrombosis, or other safety outcomes. The benefits of baricitinib on 28-day mortality were consistent across all subgroups, including by age, sex, ethnicity, C-reactive protein, and level of respiratory support received (although over 90% participants were either on simple oxygen or receiving non-invasive mechanical ventilation). In January 2022, the WHO updated their COVID-19 therapeutics guidelines to include a strong recommendation for the use of baricitinib as an alternative to an IL-6 receptor inhibitor, in combination with corticosteroids, in patients with severe or critical COVID-19. This is similar to the NIH guidelines. This was a randomized open label trial which meant participants and local hospital staff were aware of the assigned treatment, however, the outcomes were clear and were ascertained without bias through linkage to routine health records and consistent with other trials.

Surveillance of SARS-CoV-2 in the environment and animal samples of the Huanan Seafood Market Res Square posted February 25, 2022

doi.org/10.21203/rs.3.rs-1370392/v1

The origins of SARS-CoV-2 remain unclear. The investigators have reported that a certain number of the early case clusters had contact with Huanan Seafood Market. Therefore, the surveillance of SARS-CoV-2 within the market is of vital interest. The investigators presented

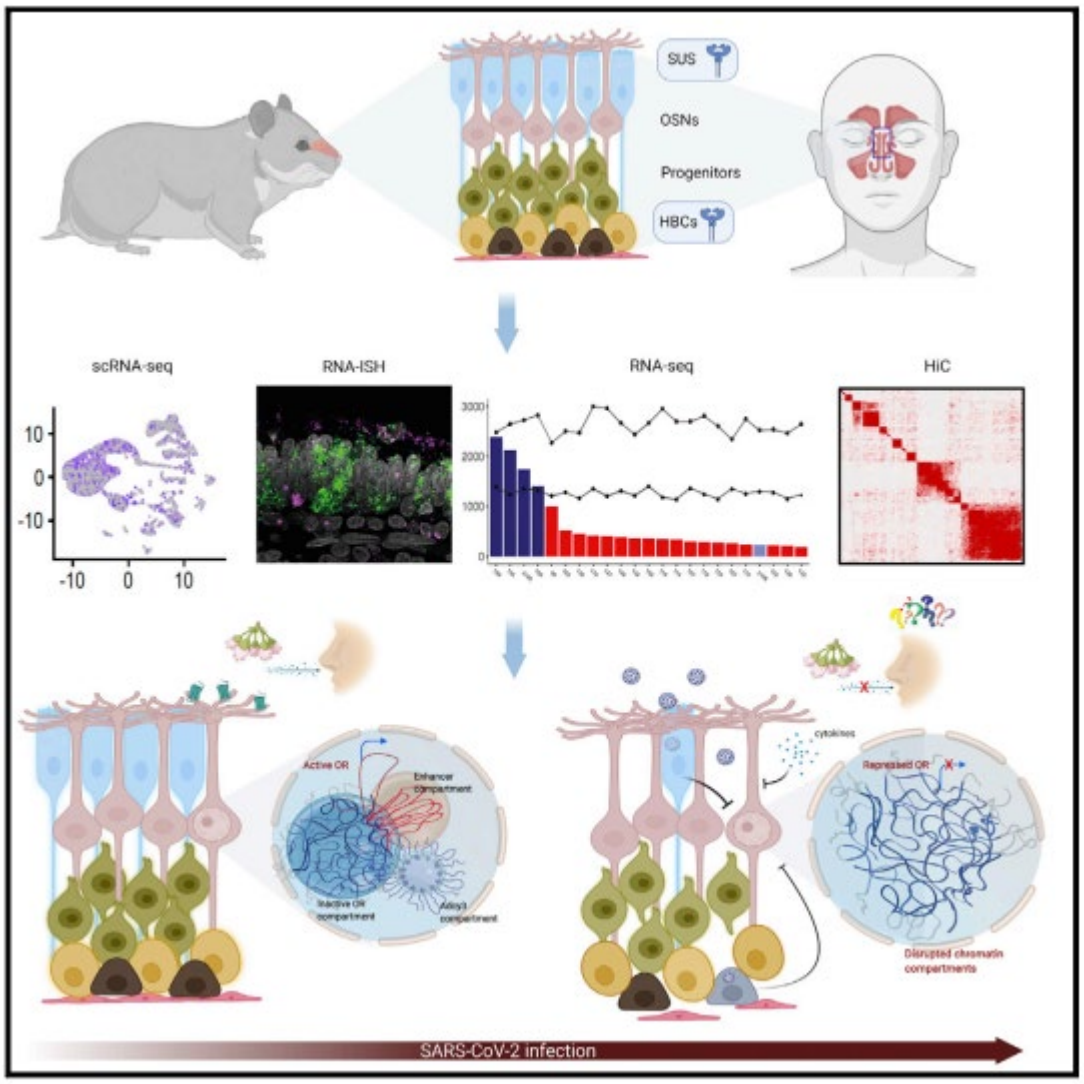
the SARS-CoV-2 detection results of 1380 samples collected from the environment and the animals within the market in early 2020. By SARS-CoV-2-specific RT-PCR, 73 environmental samples tested positive for SARS-CoV-2 and three live viruses were successfully isolated. The viruses from the market shared nucleotide identity of 99.980% to 99.993% with the human isolate HCoV/Wuhan/IVDC-HB-01(ancestral strain). In contrast, no virus was detected in the animal swabs covering 18 species of animals in the market. The SARS-COV-2 nucleic acids in the positive environmental samples showed significant correlation of abundance of *Homo sapiens* with SARS-CoV-2. Therefore, the SARS-CoV-2 sequences from environmental samples were highly similar to the clinical strains obtained during the early stage of the COVID-19 outbreak.

Comment: in summary, this study provided evidence of the prevalence of SARS-CoV-2 in the Huanan Seafood Market during the early stage of COVID-19 outbreak. Of interest, live SARS-CoV-2 viruses was only found in environmental samples with no SARS-CoV-2 being detected in the animal samples from the market. Clearly, more work involving international coordination is needed to investigate the real origins of SARS-CoV-2. Another possibility is that this pattern might be evidence that the market boosted the epidemic after the virus started spreading in humans somewhere else. This report is from the National Institute for Viral Disease Control and Prevention, Chinese Center for Disease Control and Prevention.

Non-cell-autonomous disruption of nuclear architecture as a potential cause of COVID-19- induced anosmia Cell published online February 1, 2022

doi.org/10.1016/j.cell.2022.01.024

Neurological and cognitive defects are among the least understood symptoms of COVID-19 patients, with olfactory dysfunction being their most common sensory deficit. Here, the investigators show that both in humans and hamsters, SARS-CoV-2 infection causes widespread downregulation of olfactory receptors (ORs) and of their signaling components. This non-cell-autonomous effect is preceded by a dramatic reorganization of the neuronal nuclear architecture, which results in dissipation of genomic compartments harboring OR genes. Analysis of human OE (olfactory epithelium) autopsies confirmed that SARS-CoV-2 infection correlates with significant decrease of OR (olfactory receptors) and OR signaling gene transcription and reduction of interchromosomal OR contacts.



Comment: The investigators provide a molecular explanation for SARS-CoV-2-induced anosmia and a mechanism by which this virus can alter the identity and function of cells that lack entry receptors. The authors believe the most likely explanation for COVID-19-induced anosmia is the non-cell-autonomous, widespread, and persistent downregulation of OR and OR signaling genes. They did not identify the circulating molecule(s) that induce reorganization of OSN (olfactory sensory neurons) nuclear architecture and the OSN signaling pathway responsible for it. Therefore, currently, they can only speculate that similar mechanisms apply to other neuronal populations, a concept that they did not explore. Furthermore, they did not establish that the reported downregulation in OR and OR signaling genes is responsible for COVID-19-induced anosmia, but instead they inferred this from the phenotypes of knockout mice.