COVID-19 Evidence Bulletin

23rd November 2022

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**clinical management**

**title:** Prevalence of Contraindications to Nirmatrelvir-Ritonavir Among Hospitalized Patients With COVID-19 at Risk for Progression to Severe Disease [Research Letter]

JAMA Network open | 15th november 2022

Introduction

The availability of outpatient treatment options for COVID-19, such as nirmatrelvir-ritonavir, remdesivir, molnupiravir, and monoclonal antibodies, raises hopes for reducing COVID-19–related morbidity and mortality. Among these options, nirmatrelvir-ritonavir (Paxlovid)…may be preferred for most high-risk patients because of the convenience of oral dosing and its high efficacy vs placebo in reducing hospitalization or death, as reported in a phase 2/3 trial…

However, there are circumstances in which nirmatrelvir-ritonavir should not be used, due to the effect of ritonavir. Ritonavir may elevate the concentrations of drugs highly dependent on hepatic cytochrome P-450 3A (CYP3A) metabolism, potentially resulting in serious reactions. Conversely, coadministration with potent CYP3A inducers can significantly reduce nirmatrelvir concentrations, potentially leading to the loss of virologic response. Furthermore, patients with severe kidney impairment and severe liver impairment were excluded from the clinical trials…These medical contraindications may be prevalent in patients with COVID-19 who are at high risk for progression to severe disease, as suggested by a recent study…

We examined the prevalence of contraindications to nirmatrelvir-ritonavir in patients hospitalized with COVID-19. We hypothesized that the rate would be high in these patients.

Methods

In this cohort study, we applied individual medical contraindications listed by the US Food and Drug Administration for nirmatrelvir-ritonavir to a large sample of patients hospitalized with COVID-19, ascertained by a positive reverse transcription–polymerase chain reaction test, in 36 greater Paris University hospitals from January 24, 2020, to November 30, 2021… No patients received nirmatrelvir-ritonavir. We examined the proportion of patients with contraindications to nirmatrelvir-ritonavir in this sample and in those who died within 28 days of hospital admission, who thereby would have needed therapy other than nirmatrelvir-ritonavir in the ambulatory setting. We also stratified the analysis by sex, age (≤65 y vs >65 y), and comorbidity based on International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) main chapters. Medical contraindications of nirmatrelvir-ritonavir and criteria used to approximate them are detailed…Analyses were performed using R software version 3.6.3. This study received approval from the institutional review board of the Assistance Publique–Hôpitaux de Paris clinical data warehouse. Patient consent was not applicable because this study did not contain factors necessitating it. The study was performed in accordance with STROBE reporting guidelines.

Results

Of 63 656 inpatients with COVID-19, 1131 patients (1.8%) were excluded because of missing data for sex or age. Of the 62 525 remaining patients (median [IQR] age, 52.8 [33.8-70.5] years, 31 561 [50.5%] women), 9136 (14.6%) had a medical contraindication to nirmatrelvir-ritonavir (Table 1), with higher rates in men (5568 [18.0%]) than in women (3577 [11.3%]), in older patients (5398 of 20 064 [26.9%]) than in younger ones (3738 of 42 461 [8.8%]), and in those with comorbidities (>37.0% for most comorbidities) than without comorbidities (1475 of 37 748 [3.9%]) (Table 2). Among 4861 patients who died, 2463 (50.7%) had a contraindication, with similar rates in men and women as well as older and younger patients but higher rates in patients with vs without comorbidities (Table 1 and Table 2). The most prevalent contraindications were severe kidney impairment and use of medications dependent on CYP3A for clearance.

Discussion

In this study, contradictions to nirmatrelvir-ritonavir were prevalent in individuals hospitalized with COVID-19, as previously suggested…These findings also alert researchers to the risk of confounding by contraindication in observational studies focused on nirmatrelvir-ritonavir, which may overestimate treatment efficacy if not excluding patients with contraindications to this treatment. In addition, some of the contraindicated medications listed here could be temporarily held in the context of using nirmatrelvir-ritonavir…

Study limitations include that even if not contraindicated, treatment may not have been given to some patients due to symptom duration of longer than 5 days or limited supply, and information about vaccination, race and ethnicity, and weight was unavailable. These findings support the need to anticipate supplies for alternative approved treatments and those that are under regulatory review (eg, SARS-CoV-2 main protease inhibitors), and for continued research on less expensive treatment options for low- and middle-income countries…

<https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2798450>

**title:** Covid-19: NICE rejects five treatments over uncertain evidence and price in draft guidance [News]

BMJ | 16th november 2022

NICE has recommended three drugs—nirmatrelvir plus ritonavir (Paxlovid), tocilizumab (RoActemra), and baricitinib (Olumiant)—for the treatment of covid-19 in adults, as part of draft guidance…

The review of the efficacy and cost effectiveness of drugs currently being used in the NHS to treat covid-19 considered treatments in the context of routine commissioning, rather than their use in exceptional circumstances, such as during a pandemic.

NICE has not recommended other covid-19 treatments, including casirivimab plus imdevimab (Ronapreve), molnupiravir (Lagevrio), remdesivir (Veklury), sotrovimab (Xevudy), and tixagevimab plus cilgavimab (Evusheld).

Currently, access to covid-19 drugs is guided by the UK wide clinical access policies agreed by the UK chief medical officers. Once the final NICE guidance is published, however, it will inform routine commissioning decisions for these treatments…

<https://www.bmj.com/content/379/bmj.o2759>

**title:** 6-month outcomes in patients with COVID-19 supported with extracorporeal membrane oxygenation (EuroECMO-COVID): a multicentre, prospective observational study

The Lancet Respiratory Medicine | 16th November 2022

Summary

Background

Extracorporeal membrane oxygenation (ECMO) has been widely used in patients with COVID-19, but uncertainty remains about the determinants of in-hospital mortality and data on post-discharge outcomes are scarce. The aims of this study were to investigate the variables associated with in-hospital outcomes in patients who received ECMO during the first wave of COVID-19 and to describe the status of patients 6 months after ECMO initiation.

Methods

EuroECMO-COVID is a prospective, multicentre, observational study developed by the European Extracorporeal Life Support Organization. This study was based on data from patients aged 16 years or older who received ECMO support for refractory COVID-19 during the first wave of the pandemic—from March 1 to Sept 13, 2020—at 133 centres in 21 countries. In-hospital mortality and mortality 6 months after ECMO initiation were the primary outcomes. Mixed-Cox proportional hazards models were used to investigate associations between patient and management-related variables (eg, patient demographics, comorbidities, pre-ECMO status, and ECMO characteristics and complications) and in-hospital deaths. Survival status at 6 months was established through patient contact or institutional charts review. This study is registered with ClinicalTrials.gov, NCT04366921, and is ongoing.

Findings

Between March 1 and Sept 13, 2020, 1215 patients (942 [78%] men and 267 [22%] women; median age 53 years [IQR 46–60]) were included in the study. Median ECMO duration was 15 days (IQR 8–27). 602 (50%) of 1215 patients died in hospital, and 852 (74%) patients had at least one complication. Multiorgan failure was the leading cause of death (192 [36%] of 528 patients who died with available data). In mixed-Cox analyses, age of 60 years or older, use of inotropes and vasopressors before ECMO initiation, chronic renal failure, and time from intubation to ECMO initiation of 4 days or more were associated with higher in-hospital mortality. 613 patients did not die in hospital, and 547 (95%) of 577 patients for whom data were available were alive at 6 months. 102 (24%) of 431 patients had returned to full-time work at 6 months, and 57 (13%) of 428 patients had returned to part-time work. At 6 months, respiratory rehabilitation was required in 88 (17%) of 522 patients with available data, and the most common residual symptoms included dyspnoea (185 [35%] of 523 patients) and cardiac (52 [10%] of 514 patients) or neurocognitive (66 [13%] of 512 patients) symptoms.

Interpretation

Patient's age, timing of cannulation (<4 days vs ≥4 days from intubation), and use of inotropes and vasopressors are essential factors to consider when analysing the outcomes of patients receiving ECMO for COVID-19. Despite post-discharge survival being favourable, persisting long-term symptoms suggest that dedicated post-ECMO follow-up programmes are required…

<https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(22)00403-9/fulltext>

**title:** Comparative effectiveness of sotrovimab and molnupiravir for prevention of severe covid-19 outcomes in patients in the community: observational cohort study with the OpenSAFELY platform

bmj | 16th november 2022

Abstract

Objective To compare the effectiveness of sotrovimab (a neutralising monoclonal antibody) with molnupiravir (an antiviral) in preventing severe outcomes of covid-19 in adult patients infected with SARS-CoV-2 in the community and at high risk of severe outcomes from covid-19.

Design Observational cohort study with the OpenSAFELY platform.

Setting With the approval of NHS England, a real world cohort study was conducted with the OpenSAFELY-TPP platform (a secure, transparent, open source software platform for analysis of NHS electronic health records), and patient level electronic health record data were obtained from 24 million people registered with a general practice in England that uses TPP software. The primary care data were securely linked with data on SARS-CoV-2 infection and treatments, hospital admission, and death, over a period when both drug treatments were frequently prescribed in community settings.

Participants Adult patients with covid-19 in the community at high risk of severe outcomes from covid-19, treated with sotrovimab or molnupiravir from 16 December 2021.

Interventions Sotrovimab or molnupiravir given in the community by covid-19 medicine delivery units.

Main outcome measures Admission to hospital with covid-19 (ie, with covid-19 as the primary diagnosis) or death from covid-19 (ie, with covid-19 as the underlying or contributing cause of death) within 28 days of the start of treatment.

Results Between 16 December 2021 and 10 February 2022, 3331 and 2689 patients were treated with sotrovimab and molnupiravir, respectively, with no substantial differences in baseline characteristics. Mean age of all 6020 patients was 52 (standard deviation 16) years; 59% were women, 89% were white, and 88% had received three or more covid-19 vaccinations. Within 28 days of the start of treatment, 87 (1.4%) patients were admitted to hospital or died of infection from SARS-CoV-2 (32 treated with sotrovimab and 55 with molnupiravir). Cox proportional hazards models stratified by area showed that after adjusting for demographic information, high risk cohort categories, vaccination status, calendar time, body mass index, and other comorbidities, treatment with sotrovimab was associated with a substantially lower risk than treatment with molnupiravir (hazard ratio 0.54, 95% confidence interval 0.33 to 0.88, P=0.01). Consistent results were found from propensity score weighted Cox models (0.50, 0.31 to 0.81, P=0.005) and when restricted to people who were fully vaccinated (0.53, 0.31 to 0.90, P=0.02). No substantial effect modifications by other characteristics were detected (all P values for interaction >0.10). The findings were similar in an exploratory analysis of patients treated between 16 February and 1 May 2022 when omicron BA.2 was the predominant variant in England.

Conclusions In routine care of adult patients in England with covid-19 in the community, at high risk of severe outcomes from covid-19, those who received sotrovimab were at lower risk of severe outcomes of covid-19 than those treated with molnupiravir…

<https://www.bmj.com/content/379/bmj-2022-071932>

**title:** Angiotensin receptor blockers for the treatment of covid-19: pragmatic, adaptive, multicentre, phase 3, randomised controlled trial

bmj | 16th november 2022

Abstract

Objective To determine whether disrupting the renin angiotensin system with angiotensin receptor blockers will improve clinical outcomes in people with covid-19.

Design CLARITY was a pragmatic, adaptive, multicentre, phase 3, randomised controlled trial.

Setting 17 hospital sites in India and Australia.

Participants Participants were at least 18 years old, previously untreated with angiotensin receptor blockers, with a laboratory confirmed diagnosis of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection who had been admitted to hospital for management of covid-19.

Intervention Oral angiotensin receptor blockers (telmisartan in India) or placebo (1:1) for 28 days.

Main outcome measures The primary endpoint was covid-19 disease severity using a modified World Health Organization Clinical Progression Scale (WHO scale) at day 14. Secondary outcomes were WHO scale scores at day 28, mortality, intensive care unit admission, and respiratory failure. Analyses were evaluated on an ordinal scale in the intention-to-treat population.

Results Between 3 May 2020 and 13 November 2021, 2930 people were screened for eligibility, with 393 randomly assigned to angiotensin receptor blockers (of which 388 (98.7%) to telmisartan 40 mg/day) and 394 to the control group. 787 participants were randomised: 778 (98.9%) from India and nine (1.1%) from Australia. The median WHO scale score at day 14 was 1 (interquartile range 1-1) in 384 participants assigned angiotensin receptor blockers and 1 (1-1) in 382 participants assigned placebo (adjusted odds ratio 1.51 (95% credible interval 1.02 to 2.23), probability of an odds ratio of >1 (Pr(OR>1)=0.98). WHO scale scores at day 28 showed little evidence of difference between groups (1.02 (0.55 to 1.87), Pr(OR>1)=0.53). The trial was stopped when a prespecified futility rule was met.

Conclusions In patients admitted to hospital for covid-19, mostly with mild disease, not requiring oxygen, no evidence of benefit, based on disease severity score, was found for treatment with angiotensin receptor blockers, using predominantly 40 mg/day of telmisartan…

<https://www.bmj.com/content/379/bmj-2022-072175>

**title:** WHO Living Guidelines on antivirals for COVID-19 are evidence-based [Correspondence]

the lancet | 10th november 2022

Mary Wu and colleagues...suggest a change to WHO's COVID-19 treatment guidelines for monoclonal antibodies. These living guidelines were updated on Sept 16, 2022, with strong recommendations against the use of sotrovimab and casirivimab–imdevimab following the emergence of new SARS-CoV-2 variants and subvariants…We, as members of the WHO panel responsible for presenting the evidence to the Guideline Development Group (GDG), welcome this opportunity to elaborate on the evidence considered during the GDG meeting…

<https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(22)02306-6/fulltext>

**long-term effects**

**title:** Post–COVID-19 Symptoms 2 Years After SARS-CoV-2 Infection Among Hospitalized vs Nonhospitalized Patients

JAMA Network open | 15th november 2022

Importance: Identification of long-term post–COVID-19 symptoms among hospitalized and nonhospitalized patients is needed.

Objective: To compare the presence of post–COVID-19 symptoms 2 years after acute SARS-CoV-2 infection between hospitalized and nonhospitalized patients

Design, Setting and Participants: A cross-sectional cohort study was conducted at 2 urban hospitals and general practitioner centers from March 20 to April 30, 2020, among 360 hospitalized patients and 308 nonhospitalized patients with acute SARS-CoV-2 infection during the first wave of the pandemic. Follow-up was conducted 2 years later.

Main Outcomes and Measures: Participants were scheduled for a telephone interview 2 years after acute infection. The presence of post–COVID-19 symptoms was systematically assessed, with particular attention to symptoms starting after infection. Hospitalization and clinical data were collected from medical records. Between-group comparisons and multivariate logistic regressions were conducted.

Results: A total of 360 hospitalized patients (162 women [45.0%]; mean [SD] age, 60.7 [16.1] years) and 308 nonhospitalized patients (183 women [59.4%]; mean [SD] age, 56.7 [14.7] years) were included. Dyspnea was more prevalent at the onset of illness among hospitalized than among nonhospitalized patients (112 [31.1%] vs 36 [11.7%]; P < .001), whereas anosmia was more prevalent among nonhospitalized than among hospitalized patients (66 [21.4%] vs 36 [10.0%]; P = .003). Hospitalized patients were assessed at a mean (SD) of 23.8 (0.6) months after hospital discharge, and nonhospitalized patients were assessed at a mean (SD) of 23.4 (0.7) months after the onset of symptoms. The number of patients who exhibited at least 1 post–COVID-19 symptom 2 years after infection was 215 (59.7%) among hospitalized patients and 208 (67.5%) among nonhospitalized patients (P = .01). Among hospitalized and nonhospitalized patients, fatigue (161 [44.7%] vs 147 [47.7%]), pain (129 [35.8%] vs 92 [29.9%]), and memory loss (72 [20.0%] vs 49 [15.9%]) were the most prevalent post–COVID-19 symptoms 2 years after SARS-CoV-2 infection. No significant differences in post–COVID-19 symptoms were observed between hospitalized and nonhospitalized patients. The number of preexisting medical comorbidities was associated with post–COVID-19 fatigue (odds ratio [OR], 1.93; 95% CI, 1.09-3.42; P = .02) and dyspnea (OR, 1.91; 95% CI, 1.04-3.48; P = .03) among hospitalized patients. The number of preexisting medical comorbidities (OR, 3.75; 95% CI, 1.67-8.42; P = .001) and the number of symptoms at the onset of illness (OR, 3.84; 95% CI, 1.33-11.05; P = .01) were associated with post–COVID-19 fatigue among nonhospitalized patients. Conclusions and Relevance: This cross-sectional study suggested the presence of at least 1 post–COVID-19 symptom in 59.7% of hospitalized patients and 67.5% of nonhospitalized patients 2 years after infection. Small differences in symptoms at onset of COVID-19 were identified between hospitalized and nonhospitalized patients. Post–COVID-19 symptoms were similar between hospitalized and nonhospitalized patients; however, lack of inclusion of uninfected controls limits the ability to assess the association of SARS-CoV-2 infection with overall and specific post–COVID-19 symptoms 2 years after acute infection. Future studies should include uninfected control populations…

<https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2798446>

**infection control**

**title:** Safety of the fourth COVID-19 BNT162b2 mRNA (second booster) vaccine: a prospective and retrospective cohort study

the lancet respiratory medicine | 18th November 2022

Summary

Background

The effectiveness of the second BNT162b2 (Pfizer–BioNTech) mRNA COVID-19 booster vaccine dose (ie, fourth inoculation) is well established, but its safety has yet to be fully understood. The absence of sufficient vaccine safety information is one of the key contributors to vaccine hesitancy. In this study, we aimed to evaluate the safety profile of the second BNT162b2 mRNA COVID-19 booster vaccine using data from a retrospective cohort and a prospective cohort.

Methods

To evaluate the safety profile of the second booster vaccine, we analysed its short-term effects and compared them to those of the first booster by using data from, first, a retrospective cohort of 250 000 random members of the second-largest health-care organisation in Israel (Maccabi Healthcare Services) and, second, a prospective cohort (the PerMed study) of 4698 participants from all across Israel. Individuals who were aged 18 years or older who received the second BNT162b2 mRNA COVID-19 vaccine booster during the vaccination campaign, from Dec 30, 2021, to July 22, 2022, were eligible for inclusion in the retrospective cohort analysis. To be included in the PerMed study, participants needed to be 18 years or older, members of Maccabi Healthcare Services at the time of enrolment, using their own smartphone, and be able to give informed consent by themselves. Participants from the prospective cohort received smartwatches, downloaded a dedicated mobile application, and granted access to their medical records. The smartwatches continuously monitored several physiological measures, including heart rate. For analysis of the prospective cohort data, we used the Kruskal-Wallis test to compare heart rate levels observed before and after vaccination. The mobile application collected daily self-reported questionnaires on local and systemic reactions. Medical records of the retrospective cohort were accessed to examine the occurrence of 25 potential adverse events, and we evaluated the risk differences between 42 days in the periods before and after vaccination in a pairwise method using non-parametric percentile bootstrap.

Findings

The retrospective cohort included 94 169 participants who received the first booster and 17 814 who received the second booster. Comparing the 42 days before and after vaccination, the second booster was not associated with any of the 25 adverse events investigated, including myocardial infarction (risk difference, 2·25 events per 10 000 individuals [95% CI –3·93 to 8·98]) and Bell's Palsy (–1·68 events [–5·61 to 2·25]). None of the individuals was diagnosed with myocarditis or pericarditis following vaccination with the second booster. The prospective cohort included 1785 participants who received the first booster and 699 who received the second booster. We found no significant differences after inoculation with the first booster compared with the second booster (heart rate: day 2 [p=0·3], day 6 [p=0·89]; extent of self-reported reactions [p=0·06]). We found a significant increase in mean heart rate relative to that observed during the week before vaccination (baseline) levels during the first 3 days following the second booster (p<0·0001), peaking on day 2 (mean difference of 1·61 bpm [1·07 to 2·16] compared with baseline). Mean heart rate values returned to baseline levels by day 6 (–0·055 bpm [–0·56 to 0·45] compared with baseline).

Interpretation

Both our retrospective and prospective analyses support the safety of the second booster, with our findings reflecting physicians' diagnoses, patients' objective physiological measures, and patients' subjective reactions. We believe this study provides safety assurances to the global population who are eligible to receive an additional COVID-19 booster inoculation. These assurances can help increase the number of high-risk individuals who opt to receive this booster vaccine and thereby prevent severe outcomes associated with COVID-19…

<https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(22)00407-6/fulltext>

**title:** How Immune-Evasive Omicron Offspring and a Lack of Mitigation Measures Could Shape a COVID-19 Winter Wave

jama |16th november 2022

Wintertime and the living may not be easy—thanks to an ever-mutating SARS-CoV-2 and an ever-growing number of people who think that the pandemic is behind them.

While US COVID-19 cases, hospitalizations, and deaths neared pandemic lows this fall, the numbers were climbing in some European countries…

…as more immune-evasive Omicron subvariants continue to chip away at BA.5′s dominance. In the week ending October 29, BA.5′s estimated proportion of circulating SARS-CoV-2 variants in the US slipped just below 50% for the first time in months, according to the US Centers for Disease Control and Prevention (CDC). Two weeks later, BA.5 represented only 29.7% of circulating variants, with newer Omicron variants BQ.1 and BQ.1.1 accounting for a total of 44.2%, the CDC estimated.

Experts point to a combination of factors, some modifiable, some not, that could produce a third consecutive COVID-19–riddled winter in the US…

“One possibility is that we will do a little better than in some parts of the world, including Europe,” because the US has had a higher infection rate, providing at least some temporary immunity, Lipsitch added. He cautioned that “[t]he scale on which immunity from prior infection wanes is actually pretty hard to measure.”…

But in the US fewer than half the 227 million people who’d completed their primary COVID-19 vaccine series, or about 112 million, had received even 1 booster by November 1, according to the CDC.

But Plescia thinks the main problem might be that pandemic-weary people are simply tuning out the CDC and other federal agencies that are urging them to get the bivalent booster. “I don’t know how effective government messaging is anymore,” Plescia said…

The importance of COVID-19 vaccines and treatments “will be greatest if there’s a large winter surge, but they will bear fruit regardless under any possible scenario,” Lipsitch, who is also director of the Center for Communicable Disease Dynamics at the Harvard T.H. Chan School of Public Health, pointed out.

More Omicron Offspring

Omicron has been the most prolific SARS-CoV-2 variant so far. By November 12 of this year, 14 different Omicron subvariants had been detected in the US, although not all of them were still circulating, according to the CDC…

Concerns about Counts

Getting a handle on SARS-CoV-2 infection rates this winter will be more challenging than ever, given that most people who test—if they do test—use at-home rapid antigen assays and don’t report the results to public health agencies…

Immune evasion doesn’t necessarily correlate with more severe disease,…noting that the original Omicron variant was more immune evasive than previous variants but not more severe.

Still,…if COVID-19 cases increase, so will hospitalizations: “The vaccines are not perfectly protective.” Although vaccinated individuals have a lower risk of becoming seriously ill with COVID-19, their risk is not zero…

Back to Basics

One reason Plescia and other public health experts are counting so heavily on the bivalent boosters to curb serious COVID-19 illness this winter is because nonpharmaceutical interventions (NPIs) to stop the spread of SARS-CoV-2, such as social distancing and wearing face masks, have been all but abandoned in the US.

CDC Director Rochelle Walensky, MD, MPH, drew heat for not mentioning some of these NPIs in an October 21 tweet about protecting against respiratory infections. Get an updated COVID-19 booster and an annual flu shot, stay home if sick, and “practice good hand hygiene,” Walensky recommended…

However, she said, at this point in the pandemic, “we’re in this very odd place where we’re putting the onus of public health on the individual.”

Instead, public health leaders should be encouraging people to layer preventive measures, including getting vaccinated and wearing a mask in crowded indoor spaces, Amin said…

“I’m not advising people not to gather,” Rivers said. “That’s not on the table anymore.” But, she added, it wouldn’t hurt to crack open the windows a bit and run an air filter when company comes.

<https://jamanetwork.com/journals/jama/fullarticle/2798913>

**title:** Analysis of COVID-19 Vaccination Status Among Parents of Hospitalized Children Younger Than 5 Years With SARS-CoV-2 Infection During the Delta and Omicron Waves [Research Letter]

jama network open | 16th november 2022

Introduction

The appearance of the B.1.1.529 (Omicron) variant of SARS-CoV-2 in late December 2021 in France was associated with a rapidly increasing hospitalization rate among infants and children aged 0 to 5 years,…for whom COVID-19 vaccines were not licensed. The association between parents’ vaccination status and severe infection in young children remains unclear. The aim of this study was to analyze COVID-19 vaccination status among parents of hospitalized children younger than 5 years with SARS-CoV-2 infection during the Delta and Omicron waves.

Methods

This cohort study analyzed data from the COVID-19 Pediatric Observatory (PANDOR) study, a French national prospective surveillance study of hospitalized children with SARS-CoV-2 infection…All children younger than 5 years admitted between May 12, 2021, and February 14, 2022, with known information about parents’ COVID-19 vaccination status were included. The study was approved by the Institut national de la santé et de la recherche médicale ethics committee. All participants were provided written information, and oral consent was obtained. The study followed the STROBE reporting guideline.

To account for increasing numbers of parents vaccinated during the study period, we estimated hazard ratios (HRs) and 95% CIs for children who were hospitalized and had unvaccinated vs vaccinated parents by using a Cox proportional hazards regression model. The HRs are based on estimates of population prevalence of vaccination. From May 12, 2021, to February 14, 2022, the number of French adults aged 18 to 59 years who were vaccinated with 2 doses increased from 7% to 92%...Additional details are provided in the eMethods in the Supplement.

According to the spread of the different variants in France, we defined 2 periods: Delta (May 12 to December 12, 2021) and Omicron (December 20, 2021, to February 14, 2022). The week of December 13, 2021, was considered the washout period.

All statistical analyses were performed using Stata, version 16.1 (StataCorp LLC). A 2-sided P < .05 was considered significant.

Results

During the PANDOR study period, 599 children were admitted; for 208, their parents’ COVID-19 vaccination status was known. Of 163 children younger than 5 years (78%), 63 were admitted during the Delta period, 6 during the washout period, and 94 during the Omicron period (Table 1). For the association of SARS-CoV-2 hospitalizations in children younger than 5 years with vaccinated vs unvaccinated parents, the HRs were 0.03 (95% CI, 0.02-0.06) during the Delta period and 0.21 (95% CI, 0.14-0.33) during the Omicron period (Table 2).

Discussion

During both the Delta and Omicron periods, parents’ vaccination status was associated with a reduced risk of hospital admission for SARS-CoV-2 in children younger than 5 years. A study performed before the Omicron wave showed an association of parent vaccination with a reduced risk of SARS-CoV-2 infection in children, with lower odds ratios likely due to older children in the sample…The association between parent vaccination and reduced risk of admission for SARS-CoV-2 in children younger than 5 years suggests that parents played a major role in transmitting SARS-CoV-2 to their young children during both waves,…but the association between protection and vaccination seemed lower in the Omicron vs Delta period. The Omicron variant has been shown to be more transmissible, and the vaccine effectiveness against infection seems lower…

This study has some limitations. It was a retrospective analysis of a prospective observational study. The existence of siblings; source of infection in the household; dates of parents’ vaccination; and existence of a booster, which is a bias considering the change of vaccine effectiveness over time and across variants, were not recorded. Furthermore, environmental changes, lockdowns, and compliance with social distancing according to parent vaccination status were not evaluated. These results should not be extrapolated to other variants, such as the predominant variants BA.4 and BA.5. Nonetheless, these results reinforce recommendations for widespread vaccination of parents of young children…

<https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2798506>

**title:** Association of COVID-19 Vaccination With Influenza Vaccine History and Changes in Influenza Vaccination [Research Letter]

jama network open | 14th november 2022  
  
Introduction

Understanding willingness to receive new vaccines is critical for vaccine rollout and addressing vaccine hesitancy…Future COVID-19 and influenza vaccination may coincide, creating a need to understand the dynamics between ongoing vaccine adherence for familiar diseases and novel vaccine acceptance. We combine longitudinal data with a classification of individual influenza vaccination histories …to answer 2 questions: (1) how COVID-19 vaccination differs across historical influenza vaccination patterns, and (2) how influenza vaccination changed during the COVID-19 pandemic.

Methods

This survey study’s longitudinal survey data came from RAND’s American Life Panel (ALP), a probability-sampled panel of US adults. Walsh and colleagues…analyzed ALP self-reported vaccination across 6 influenza seasons spanning 2009 to 2017. Modeling individuals’ year-to-year tendency to repeat prior vaccination behaviors, panelists were classified as never, sometimes, or always influenza vaccinators…Subsequent influenza vaccination behavior (2019 to 2020) was assessed in May to June 2020 (N = 1643; 85% completion), which was largely prepandemic. COVID-19 vaccination, along with 2020 to 2021 and 2021 to 2022 influenza vaccination, was assessed in February to March 2022 (N = 2145; 68.8% completion). COVID-19 vaccination is operationalized as fully vaccinated (primary series, meaning single dose Janssen/Johnson & Johnson or 2 doses Pfizer/BioNTech or Moderna) vs not; boosters are not considered. Race and ethnicity were self-reported. An analytic sample of 1366 respondents have complete data. Sampling weights were applied for all analyses. Recruitment and retention are detailed in the eMethods of the Supplement. Online consent was obtained in accordance with study approval by RAND’s Human Subjects Protection Committee. Our approach followed the (AAPOR) reporting guideline. Two-sided P < .05 was considered statistically significant. Analyses were performed from June to September 2022.

Results

…Overall, the probability of full COVID-19 vaccination was 50% higher if the respondent reported getting the influenza vaccine in the 2021-2022 season (90.9% [858 of 944] vs 60.9% [440 of 723]; risk ratio [RR], 1.50; 95% CI, 1.40-1.59). Conversely, 2021-2022 influenza vaccination was 230% higher if the respondent reported getting a full initial COVID-19 vaccine (57.1% [585 of 1025] vs 17.3% [59 of 341]; RR, 3.30 [95% CI, 2.65-4.27]).

Table 2 focuses only on panelists classified as never influenza vaccinators through 2017. Those receiving the COVID-19 vaccine were significantly more likely to have switched from not receiving (in 2020) to receiving (in 2022) the influenza vaccine (OR, 12.82; 95% CI, 1.46-112.67). Both outcomes were more likely among more educated. Identifying as Democrat (vs Republican) was associated with COVID-19 vaccination (OR, 4.43; 95% CI, 1.51-12.97), but not associated with switching from no influenza vaccination to influenza vaccination.

Discussion

…COVID-19 vaccination was highest among those who historically always received the influenza vaccine, reinforcing studies showing shorter-term correlation between influenza and COVID-19 vaccination… Most strikingly, among individuals who historically never got the influenza vaccine, those receiving COVID-19 vaccine were substantially more likely to switch toward getting the influenza vaccine. This suggests that investing in vaccine acceptance has payoffs beyond the vaccine itself…

<https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2798391>

**title:** Four SARS-CoV-2 vaccine doses or hybrid immunity in patients on immunosuppressive therapies: a Norwegian cohort study

the lancet rheumatology|16th november 2022

Background

Summary

Data on response and safety of repeated vaccinations and hybrid immunity in patients with immune-mediated inflammatory diseases on immunosuppressive therapy is needed to further develop vaccination strategies in this vulnerable population. This study aimed to evaluate hybrid immunity and humoral immune response and safety of four SARS-CoV-2 vaccine doses in patients with immune-mediated inflammatory diseases on immunosuppressive therapy.

Methods

This prospective observational Norwegian study of vaccine response to COVID-19 (Nor-vaC) included adult patients aged 18 years and older with immune-mediated inflammatory diseases (rheumatoid arthritis, spondyloarthritis, psoriatic arthritis, Crohn's disease, or ulcerative colitis) on immunosuppressive therapy, who had received four SARS-CoV-2 vaccine doses (vaccine group) or three vaccine doses followed by COVID-19 (hybrid group), and healthy controls receiving three vaccine doses (control group). Patients were recruited from the Division of Rheumatology at Diakonhjemmet Hospital, Oslo, and the Department of Gastroenterology at Akershus University Hospital, Lørenskog. Patients who had COVID-19 before the third vaccine dose, and patients with allergies or intolerances to elements of the vaccine were excluded. Antibodies to the receptor-binding domain of SARS-CoV-2 spike protein (anti-RBD antibodies) were assessed 2–4 weeks following vaccination or COVID-19. This study is registered at Clinialtrials.gov, NCT04798625.

Findings

Between Nov 12, 2021, and April 19, 2022, 1458 participants with immune-mediated inflammatory diseases provided post-vaccination samples at 2–4 weeks following a third vaccine dose. After 544 participants were excluded, 715 (78%) of the remaining 914 participants received the fourth dose of the vaccine, and of these, 536 (75%) provided post-vaccination samples 2–4 weeks after their fourth vaccination (vaccine group). 199 (22%) of the 914 had COVID-19 after their third dose of the vaccine and of these, 167 (84%) provided samples (hybrid group). 256 of the eligible 703 patients had rheumatoid arthritis, 107 had spondyloarthritis, 115 had psoriatic arthritis, 130 had Crohn's disease, and 95 had ulcerative colitis). Median age was 56 years [IQR 45–65], 398 (57%) were women, and 305 (43%) were men. Patients in the vaccine group had higher anti-RBD antibody concentrations following the fourth vaccine dose (median 6192 BAU/ml [IQR 2878–11 243]) than after the third dose (median 5087 BAU/ml [1250–9081]; p< 0·0001), but lower antibody concentrations than the control group following the third dose (median 7595 BAU/ml [5916–12 001]; p< 0·0001). Antibody concentrations were higher in the patients in the hybrid group (23 548 BAU/ml [IQR 11 440–35 935]) than in the vaccine group (p<0·0001). No difference was found in antibody concentrations between the fourth dose of BNT162b2 (full-dose) and mRNA-1273 (half-dose). Patients and controls had a comparable safety profile after both three and four vaccine doses.

Interpretation

Vaccine boosters improve humoral immune responses and are safe in patients with immune-mediated inflammatory diseases on immunosuppressive therapy, and administration should be considered regularly in this patient group. Hybrid immunity with omicron induces a strong humoral response suggesting longer intervals between booster doses in this patient group…

<https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913(22)00330-7/fulltext>

**title:** Modelling the end of a Zero-COVID strategy using nirmatrelvir/ritonavir, vaccination and NPIs in Wallis and Futuna

The Lancet Regional Health – Western Pacific | 14th november 2022

Background

Summary

Ending Zero-COVID is challenging, particularly when vaccine coverage is low. Considering Wallis and Futuna, a French Zero-COVID territory affected by reluctance to vaccination, low immunity and high levels of comorbidities, we investigate how targeted use of nirmatrelvir/ritonavir (brand name Paxlovid) can complement vaccination and non-pharmaceutical interventions (NPIs), and mitigate the epidemic rebound expected when Zero-COVID ends.

Methods

We developed a discrete age-stratified compartmental model describing SARS-CoV-2 spread and healthcare impact once Wallis and Futuna reopens. It accounts for comorbidity risk groups (CRG), vaccine coverage (2 doses, 3 doses), the effectiveness of vaccines (recent or old injection), treatments and NPIs. In our baseline scenario, cases aged 65+ in intermediate/high CRG and 40+ in high CRG are eligible for treatment.

Findings

The epidemic is expected to start 13–20 days after reopening with a doubling time of 1.6-3.7 days. For medium transmission intensity (R0 = 5), 134 (115–156) hospital admissions are expected within 3 months, with no pharmaceutical measures. In our baseline scenario, admissions are reduced by 11%–21% if 50% of the target group receive treatment, with maximum impact when combined with NPIs and vaccination. The number of hospitalisations averted (HA) per patient treated (PT) is maximum when 65+ in high CRG are targeted (0.124 HA/PT), quickly followed by 65+ in intermediate/high CRG (0.097 HA/PT), and any 65+ (0.093 HA/PT). Expanding the target group increases both PT and HA, but marginal gains diminish.

Interpretation

Modelling suggests that test and treat may contribute to the mitigation of epidemic rebounds at the end of Zero-COVID, particularly in populations with low immunity and high levels of comorbidities…

<https://www.thelancet.com/journals/lanwpc/article/PIIS2666-6065(22)00249-8/fulltext>

**title:** Protection from previous natural infection compared with mRNA vaccination against SARS-CoV-2 infection and severe COVID-19 in Qatar: a retrospective cohort study

the lancet microbe | 11th november 2022

Background

Summary

Understanding protection conferred by natural SARS-CoV-2 infection versus COVID-19 vaccination is important for informing vaccine mandate decisions. We compared protection conferred by natural infection versus that from the BNT162b2 (Pfizer–BioNTech) and mRNA-1273 (Moderna) vaccines in Qatar.

Methods

We conducted two matched retrospective cohort studies that emulated target trials. Data were obtained from the national federated databases for COVID-19 vaccination, SARS-CoV-2 testing, and COVID-19-related hospitalisation and death between Feb 28, 2020 (pandemic onset in Qatar) and May 12, 2022. We matched individuals with a documented primary infection and no vaccination record (natural infection cohort) with individuals who had received two doses (primary series) of the same vaccine (BNT162b2-vaccinated or mRNA-1273-vaccinated cohorts) at the start of follow-up (90 days after the primary infection). Individuals were exact matched (1:1) by sex, 10-year age group, nationality, comorbidity count, and timing of primary infection or first-dose vaccination. Incidence of SARS-CoV-2 infection and COVID-19-related hospitalisation and death in the natural infection cohorts was compared with incidence in the vaccinated cohorts, using Cox proportional hazards regression models with adjustment for matching factors.

Findings

Between Jan 5, 2021 (date of second-dose vaccine roll-out) and May 12, 2022, 104 500 individuals vaccinated with BNT162b2 and 61 955 individuals vaccinated with mRNA-1273 were matched to unvaccinated individuals with a documented primary infection. During follow-up, 7123 SARS-CoV-2 infections were recorded in the BNT162b2-vaccinated cohort and 3583 reinfections were recorded in the matched natural infection cohort. 4282 SARS-CoV-2 infections were recorded in the mRNA-1273-vaccinated cohort and 2301 reinfections were recorded in the matched natural infection cohort. The overall adjusted hazard ratio (HR) for SARS-CoV-2 infection was 0·47 (95% CI 0·45–0·48) after previous natural infection versus BNT162b2 vaccination, and 0·51 (0·49–0·54) after previous natural infection versus mRNA-1273 vaccination. The overall adjusted HR for severe (acute care hospitalisations), critical (intensive care unit hospitalisations), or fatal COVID-19 cases was 0·24 (0·08–0·72) after previous natural infection versus BNT162b2 vaccination, and 0·24 (0·05–1·19) after previous natural infection versus mRNA-1273 vaccination. Severe, critical, or fatal COVID-19 was rare in both the natural infection and vaccinated cohorts.

Interpretation

Previous natural infection was associated with lower incidence of SARS-CoV-2 infection, regardless of the variant, than mRNA primary-series vaccination. Vaccination remains the safest and most optimal tool for protecting against infection and COVID-19-related hospitalisation and death, irrespective of previous infection status…

<https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247(22)00287-7/fulltext>

**title:** Effectiveness of the COVID-19 vaccines against hospitalisation with Omicron sub-lineages BA.4 and BA.5 in England [Comment]

The Lancet Regional Health – Europe| 10th november 2022

The Omicron sub-lineages BA.4 and BA.5, identified in South Africa in early 2022,…were first detected in England in April 2022…A case surge followed despite England having recently experienced waves with BA.1 and BA.2. BA.4 and BA.5 have identical spike proteins most similar to that of BA.2 but with additional mutations including the 69–70 deletion, L452R, F486V and wild-type amino acid at position Q493…Neutralisation assays have found BA.4 and BA.5 display increased evasion of antibodies from plasma of vaccinated or BA.1 infected individuals, as compared to BA.2…Recent data from Denmark and Portugal have found that the odds of being vaccinated did not differ amongst BA.5 and BA.2 cases…

We used a test-negative case–control (TNCC) study design to investigate VE against hospitalisation for BA.4, BA.5 and BA.2 during a period of co-circulation…

These data provide reassuring evidence of the protection conferred by the current vaccines against severe disease with BA.4 and BA.5; we found no difference in VE as compared to BA.2 and BNT162b2 and mRNA-1273 boosters provided similarly high levels of protection….

<https://www.thelancet.com/journals/lanepe/article/PIIS2666-7762(22)00233-2/fulltext>

**title:** Why hybrid immunity is so triggering [Editorial]

The Lancet Infectious Diseases| 10th november 2022

It is becoming clear that hybrid immunity, that is immunity provided by a combination of infection and vaccination, provides better protection against subsequent COVID-19 than either vaccination or infection alone – higher antibody levels, less frequent and less severe infection. However, the picture is complex due to a chequered pattern of immunity in the population. People differ not only in their history of infection timing and infecting variant, but also in the type of vaccine they received, how many doses and finally, how well their immune system responded.

<https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(22)00746-0/fulltext>

**rates & variants**

**title:** COVID-19 and Excess All-Cause Mortality in the US and 20 Comparison Countries, June 2021-March 2022 [Research Letter]

jama | 18th november 2022

The US experienced high COVID-19 death rates and higher excess all-cause mortality compared with peer countries during 2020…However, an important question is how cross-national differences in mortality shifted during 2021 and 2022 with both widespread availability of vaccination and new variants. We compared COVID-19 and excess all-cause mortality in the US, the 10 most- and least-vaccinated states, and 20 peer Organization for Economic Co-operation and Development (OECD) countries during the Delta and winter Omicron waves.

Methods

Using previous methodology, we compared the US overall, the 10 most- and least-vaccinated states, and the 20 OECD countries with 2021 population exceeding 5 million and greater than $25 000 per capita gross domestic product (Supplement 1)…US COVID-19 mortality, all-cause mortality, and vaccination data were obtained from the US Centers for Disease Control and Prevention…For other countries, COVID-19 mortality data were obtained from the World Health Organization, all-cause mortality data from OECD databases, and vaccination data from Our World in Data (Supplement 1)…Some mortality data from 2021 and 2022 were provisional.

Each location’s COVID-19 mortality rate per capita was calculated over 2 periods: (1) Delta from June 27, 2021 (week 26), to December 25, 2021 (week 51), and (2) Omicron from December 26, 2021 (week 52), to March 26, 2022 (week 12). We estimated excess all-cause mortality by comparing mortality in each period with mortality in 2015-2019, fitting underlying trends using prepandemic, out-of-sample validation (Supplement 1)…

For each period, we calculated the difference in US deaths if mortality rates of other locations were realized. We used regression models to statistically compare rates across locations (Supplement 1), with significance set at P < .005 for 2-sided tests to account for multiple testing. Analyses were conducted in R version 4.0.2 (R Foundation for Statistical Computing). The study was deemed not human subjects research by the Brown University institutional review board.

Results

The US reported 370 298 COVID-19 deaths (112 per 100 000) during the Delta and Omicron waves (61/100 000 and 51/100 000, respectively). COVID-19 deaths per capita in the US overall and in both state subgroups significantly exceeded those of all peer countries during the study period (Table 1). However, there were significantly fewer COVID-19 deaths in the top 10 states by vaccination uptake (73% coverage) at 75 deaths/100 000 compared with the bottom 10 (52% coverage) at 146 per 100 000 (P < .001).

US excess all-cause mortality exceeded COVID-19 mortality at 145/100 000 and exceeded peer countries in all periods, as did excess all-cause mortality in the least-vaccinated states (Table 2). However, the 10 most-vaccinated states had excess all-cause mortality comparable with or less than that of several peer countries over Delta and Omicron combined (eg, Denmark, Germany, the Netherlands, Austria, Italy, Finland). While excess all-cause mortality in the top 10 states significantly exceeded that of many comparators during Omicron, excess all-cause mortality was significantly less than COVID-19 mortality for the top 10 states during this wave (29 vs 47 per 100 000, P < .001).

From June 27, 2021, to March 26, 2022, the US would have averted 122 304 deaths if COVID-19 mortality matched that of the 10 most-vaccinated states and 266 700 deaths if US excess all-cause mortality rate matched that of the 10 most-vaccinated states. If the US matched the rates of other peer countries, averted deaths would have been substantially higher in most cases (range, 154 622-357 899 for COVID-19 mortality; 209 924-465 747 for all-cause mortality).

Discussion

The US continued to experience significantly higher COVID-19 and excess all-cause mortality compared with peer countries during 2021 and early 2022, a difference accounting for 150 000 to 470 000 deaths. This difference was muted in the 10 states with highest vaccination coverage; remaining gaps may be explained by greater vaccination uptake in peer countries, better vaccination targeting to older age groups, and differences in health and social infrastructure.

This study also highlights the value of excess mortality in understanding effects of COVID-19. Excess all-cause mortality began to fall below COVID-19 mortality in several countries and highly vaccinated states during Omicron, perhaps owing to reductions in non–COVID-19 deaths. However, cross-location differences may also reflect differences in COVID-19 death coding.

Limitations include use of some provisional mortality estimates and lack of adjustment by age and comorbidities. Nevertheless, unadjusted estimates remain important, because a country’s response to COVID-19 should reflect risks in its population rather than a hypothetical standardized population.

These findings highlight that the US continued to lag peer countries in COVID-19 and excess all-cause mortality, albeit with lower mortality in highly vaccinated states…

<https://jamanetwork.com/journals/jama/fullarticle/2798990>

**public health & health inequalities**

**title:** Rates of Routine Cancer Screening and Diagnosis Before vs After the COVID-19 Pandemic [Research Letter]

JAMA Oncology | 17th november 2022

The COVID-19 pandemic triggered substantial disruptions to health care delivery in the US due to stay-at-home orders and patient fears about visiting health care facilities…Thus, many forms of health care use, including cancer screenings, sharply decreased in early 2020…Although the temporary pause in preventive screening was clinically reasonable and situationally appropriate, long-term delays or avoidance will have adverse implications for population-level cancer-related morbidity and mortality. Studies suggest that cancer screening rebounded through summer 2020; however, more than 2 years after the start of the pandemic, long-term consequences for preventive cancer screening and diagnosis are unknown…

The aim of this study was to examine patterns in breast, cervical, and colorectal cancer screening and diagnosis before and after the pandemic.

Methods

This cross-sectional study used the Trilliant Health all-payer claims and encounters database, which includes inpatient, outpatient, and prescription drug claims from all 50 states and the District of Columbia. We analyzed calendar year quarterly medical claims from January 2017 to December 2021. Patients aged 21 to 85 years were included (guideline-concordant target populations for the included screening procedures). For breast and cervical cancer, only women were included. Using Current Procedural Terminology codes, we calculated the quarterly number of individuals, per 100 000 eligible beneficiaries, who received screening for breast cancer (mammography), cervical cancer (Papanicolaou test and human papillomavirus screening), and colorectal cancer (colonoscopy, stool testing, stool DNA, computed tomography colonography, or sigmoidoscopy)…As a secondary outcome, we assessed the annual prevalence rate for each cancer type. Percentage changes in screening tests and diagnoses were compared. In accordance with the National Human Research Protections Advisory Committee Guidelines, this study was exempt from review and informed consent because the data were deidentified. We followed the STROBE reporting guideline.

Results

The analysis included 306 million unique individuals with a mean (SD) age of 51.5 (17.2) years; 167 558 961 were female (54.6%) and 139 438 790 were male (45.4%) individuals, and the mean (SD) Charlson Comorbidity Index score was 0.7 (1.7) (0 indicates no comorbid conditions). For breast cancer, the median (IQR) quarterly rate of prepandemic screening mammography was 8216 (8116-8407) per 100 000 beneficiaries, which declined to 4951 in quarter (Q) 2 of 2020—a 40% decrease (Figure 1). Screening mammography rebounded to prepandemic levels by Q3 and Q4 of 2020 but declined to a median (IQR) rate of 7374 (7127-7577) per 100 000 beneficiaries in 2021, with quarterly deficits ranging from 6% to 17%. For cervical cancer, the median (IQR) quarterly rate of prepandemic screening was 5602 (5462-5851) per 100 000 beneficiaries. The rate of cervical cancer screening fell to 3563 in Q2 of 2020—a 36% decline. By Q3 of 2020, cervical cancer screening rebounded toward the prepandemic median, then progressively declined from 4853 in Q4 of 2020 to 4246 in Q4 of 2021. Colorectal cancer screening decreased from a prepandemic median (IQR) of 3162 (3126-3202) per 100 000 beneficiaries to 1746 in Q2 of 2020—a 45% difference. From Q3 of 2020 to Q4 of 2021, quarterly colorectal cancer screening ranged from 2590 to 2861 per 100 000 beneficiaries, 82% to 90% of the prepandemic median. Consistent with the reported reductions in cancer screening, prevalence rates declined by 6.0% to 7.1% between 2019 and 2020 and an additional 4.8% to 6.1% between 2020 and 2021 (Figure 2).

Discussion

In this cross-sectional study, population-based screening and diagnosis remained below prepandemic levels for the 3 cancer types. The findings suggest that screening quickly rebounded after the initial stages of the pandemic; however, the longer follow-up time reveals that gaps in preventive cancer screening returned and worsened…A strength of the study was using a nationally representative, all-payer data set. A limitation of the study was that the reason for each test was not examined (eg, screening vs problem or diagnostic reason). The pattern we found suggests a substantial proportion of forgone care through 2021. To mitigate long-term consequences, multiple stakeholders will need to consider novel strategies and dedicate appropriate resources to increase guideline-concordant cancer screening…

<https://jamanetwork.com/journals/jamaoncology/fullarticle/2798851>

**title:** Increased Delay in Diagnosis, But Not Treatment, Among Patients With Oral Cancer During the COVID-19 Pandemic [Research Letter]

JAMA Otolaryngology | 17th november 2022

Delays in the diagnosis and treatment of patients with cancer are associated with poor outcomes. Although essential health care services such as surgical and medical oncology were generally not suspended during the COVID-19 pandemic worldwide, mandatory quarantine and other lockdown measures may have led to unintended detrimental effects on early cancer detection and treatment. Recent work…has pointed to the fragility of cancer surgery systems globally, with an estimated 1 in 7 patients who were in regions with full lockdowns not undergoing planned surgery or experiencing longer preoperative delays.

Methods

We retrospectively assessed the delays in patients diagnosed with oral squamous cell carcinoma (OSCC) in a tertiary care University Hospital in Naples, Italy, during a 2-year period. The study was approved by the institutional review board of the University of Campania, and written informed consent was given by participants. Seventy (34 women) newly diagnosed patients with histopathologically confirmed OSCC were stratified into 2 groups: patients attending the Maxillofacial Surgery Unit of the University of Campania “Luigi Vanvitelli” before and during COVID-19 pandemic, respectively. The time elapsed between self-reported onset of symptoms and the first specialist consult was considered as patient delay (D1) and the time between the first consultation and diagnosis was considered as professional delay (D2). The total diagnostic delay (DD) was calculated as D1 + D2. The duration between the final diagnosis and the beginning of the proposed treatment was referred to as treatment delay (D3). Effect size was assessed as small (d = 0.2), medium (d = 0.5), and large (d = 0.8) based on benchmarks suggested by Cohen…

Results

The mean (SD) DD detected in the whole cohort spanning 2019 and 2020 was 136.47 (71.34) days (median, 131; range, 21-367 days). Subgroup analysis per year showed that longer diagnostic delay was observed in 2020 compared with 2019 (Table). Compared with the prepandemic year, patients diagnosed with OSCC in 2020 experienced an additional delay of 35.57 days (95% CI, 5.6-65.54) for D1, 21.43 days (95% CI, 4.43-38.43) for D2, and 57 days (95% CI, 25.62–88.38) for DD. Cohen d showed a medium effect size for D1 (d = 0.57) and D2 (d = 0.60), and a large effect for overall DD (d = 0.91). There was a slight decrease in the mean (SD) D3 in 2020 compared with 2019 (20.00 [14.50] vs 26.82 [31.76] days), and this difference was classified as a small difference (d = 0.27). Overall, treatment options included surgery (41 [58.6%]), radiotherapy (6 [8.6%]), chemotherapy (1 [1.4%]), combined chemotherapy and radiation treatment (12 [17.1%]), whereas 10 patients (14.3%) were lost to follow-up after diagnosis or refused the proposed treatment plan.

In a sensitivity analysis, tight lockdown measures (March 2020-May 2020) were not associated with a significant increase in delay for any variable compared with the whole 2020 (Mann-Whitney test). When compared with 2019 and after controlling for age, sex, and stage of tumor, patients in 2020 experienced a mean (SD) 55.11 (15.92) (95% CI, 23.30-86.92) additional days of diagnostic delay.

Discussion

In Italy, lockdown restrictions and COVID-19 collateral effects on health care were severe…Movement restrictions and limited access to primary care may have negatively affected patient-related delay in our cohort. Importantly, practitioner delays are widely dependent on regional health care policies and internal organizational structure and, as such, should be amenable to targeted interventions in response to emerging circumstances. Our findings show that while professional diagnostic delay (D2) was significantly increased in 2020, treatment delay was not. In general, patients attend outpatient service for diagnostic procedures, and once surgery is scheduled, they are admitted for inpatient care. This suggests that inpatient service for OSCC was not disrupted during COVID-19 in this single university hospital. A limitation of this study stems from the limited external validity of the data. Furthermore, multiple social and health care–related changes occurring during the COVID-19 pandemic and not specifically considered in this study may have contributed to the increased delay observed in our research.

Because evidence of the collateral effects of pandemic lockdowns has salient implications in terms of local health policies, awareness of patterns and delays in the diagnosis and treatment of patients with OSCC may inform future decisions involving a restricted access to health care in South Italy and worldwide…

<https://jamanetwork.com/journals/jamaotolaryngology/fullarticle/2798897>

**title:** Global impact of COVID-19 on childhood tuberculosis: an analysis of notification data

the lancet – global health | December 2022

Summary

Background

There is concern that the COVID-19 pandemic has damaged global childhood tuberculosis management. Quantifying changes in childhood tuberculosis notifications could support more targeted interventions to restore childhood tuberculosis services. We aimed to use time-series modelling to evaluate the impact of COVID-19 on child tuberculosis notifications.

Methods

Annual tuberculosis case notification data reported to WHO by 215 countries were used to calculate annual notification counts for the years 2014–20, stratified by age groups (0–4, 5–14, and ≥15 years) and sex. We used time-series modelling to predict notification counts for 2020, and calculated differences between these predictions and observed notifications in 2020 for each of the six WHO regions and at the country level for 30 countries with high tuberculosis burden. We assessed associations between these differences and the COVID-19 stringency index, a measure of COVID-19 social impact.

Findings

From 2014 to 2019, annual tuberculosis notification counts increased across all age groups and WHO regions. More males than females in the 0–4 years age group and ≥15 years age group had notifications in all years from 2014 to 2020 and in all WHO regions. In the 5–14 years age group, more females than males were notified globally in all years, although some WHO regions had higher notifications from males than females. In 2020, global notifications were 35·4% lower than predicted (95% prediction interval –30·3 to –39·9; 142 525 observed vs 220 794 predicted notifications [95% prediction interval 204 509 to 237 078]) for children aged 0–4 years, 27·7% lower (–23·4 to –31·5; 256 398 vs 354 578 [334 724 to 374 431]) in children aged 5–14 years, and 18·8% lower (–15·4 to –21·9; 5 391 753 vs 6 639 547 [6 375 086 to 6 904 007]) for people aged 15 years or older. Among those aged 5–14 years, the reduction in observed relative to predicted notifications for 2020 was greater in males (–30·9% [–24·8 to –36·1]) than females (–24·5% [–18·1 to –29·9]). Among 28 countries with high tuberculosis burden, no association was observed between the stringency of COVID-19 restrictions and the relative difference in observed versus predicted notifications.

Interpretation

Our findings suggest that COVID-19 has substantially affected childhood tuberculosis services, with the youngest children most affected. Although children have mostly had fewer severe health consequences from COVID-19 than have adults, they have been disproportionately affected by the effects of the pandemic on tuberculosis care. Observed sex differences suggest that targeted interventions might be required. As countries rebuild health systems following the COVID-19 pandemic, it is crucial that childhood tuberculosis services are placed centrally within national strategic plans…

<https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(22)00414-4/fulltext>

**mental health**

**title:** Symptoms of Anxiety and Depression Among Adolescents Before vs During COVID-19–Related School Closures in China [Research letter]

JAMA Network Open | 14th november 2022   
  
Introduction

Chinese schools focus on examination-centered pedagogy, with high levels of academic stress among adolescents…Investigation of the association with adverse mental status is lacking. From February to April 2020, all Chinese adolescents attended online classes at home during the COVID-19 pandemic lockdown. We compared the psychological status of adolescents at school and at home using baseline psychological data of adolescents while they were studying in school. We hypothesized that school attendance was associated with negative mental health outcomes.

Methods

In this cohort study, we surveyed 5 representative middle schools in China with similar shutdowns, policies, and levels of circulating virus. We adopted an overall sampling method and conducted 2 rounds of surveys of all students from November 22, 2019, to January 4, 2020 (round 1) and from March 21 to 31, 2020, during lockdown (round 2). All adolescents were in grades 7 (aged 13 years), 8 (aged 14 years), and 9 (aged 15 years). The protocol was approved by the Ethics in Human Research Committee of the Third Affiliated Hospital of Beijing University of Chinese Medicine. Written informed consent was obtained from parents and guardians. This study followed the STROBE reporting guideline.

Depression and anxiety symptoms were measured using the 9-item Patient Health Questionnaire (range, 0-27, with higher scores indicating more symptoms) and 7-item Generalized Anxiety Disorder Scale (GAD-7; range, 0-21, with higher scores indicating more symptoms)… Cutoff scores were set at 10. For statistical analysis, we used SAS software, version 9.2 (SAS Institute Inc), with significance set at 2-sided P = .05. Data were analyzed from April 17 to July 18, 2021. We adjusted the effect of nonresponse using the ratio and regression estimation.

Results

Respondents returned 13 637 valid questionnaires in round 1 and 10 216 in round 2. Adolescents were older in round 2 (mean [SD] age, 14.33 [1.12] vs 13.77 [1.02] years) (P < .001). There was no difference in sex distribution between round 1 (51.28% boys and 48.72% girls) vs round 2 (51.11% boys and 48.89% girls) (P = .79) (Table). The adolescents in round 1 reported a higher rate of depression (odds ratio, 1.36 [95% CI, 1.30-1.42]; P < .001) and anxiety (odds ratio, 1.61 [95% CI,1.51-1.71]; P < .001) symptoms compared with round 2.

We randomly selected 202 nonrespondents in round 2 and ensured they could complete the questionnaire online. No significant nonrespondent bias was found in round 2. In round 2, rates were 14.86% (95% CI, 14.17%-15.55%) for depression and 7.44% (95% CI, 6.93%-7.95%) for anxiety. After adjusting for the effect of nonresponse, the rates were 14.26% (95% CI, 13.60%-14.92%) and 8.28% (95% CI, 7.71%-8.85%), respectively.

Discussion

Chinese education focuses on obtaining high scores in College Entrance Examination through repeated examinations, and academic stress may cause depression and anxiety…To obtain better academic performance, 63.9% of Chinese adolescents sacrifice sleep and attend extracurricular classes, and 51.0% of adolescents do not get optimal sleep… Sleep deprivation among adolescents may also contribute to anxiety and depression… Social interactions (eg, social anxiety) and peer-related stressors may also play roles in mental health. Thus, after lockdown, the removal from school and extracurricular activities and more sleep and access to peers via social media may help reduce adolescents’ stress.

However, some factors of lockdown may be associated with worsened mental health, such as disengagement from face-to-face peer contact and potential exposure to parental distress, financial pressure, and domestic violence. Although we did not consider these variables, the prevalence of depression and anxiety at round 2 was lower than at round 1. The psychological impact of schooling on adolescents may be greater than that of these variables.

The findings of this cohort study suggest that the school environment is associated with psychological stress, alleviated after leaving school…

<https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2798392?resultClick=1>

**title:** COVID-19-related financial strain and adolescent mental health

the lancet | 15th november 2022

Summary

Background

The COVID-19 pandemic and associated responses have induced a host of crises worldwide, including an economic recession and a global mental health crisis. The specific effects of recession on youth mental health are understudied. We aimed to examine the mechanisms by which pandemic-related financial strain may affect mental health in a diverse sample of American adolescents.

Methods

We analyzed data from the Adolescent Brain Cognitive Development Study (ABCD Study®), a large, longitudinal study of diverse US adolescents which collected data before and during the pandemic (N = 9,720, mean age 12.9 years, 18.2% Black). Linear mixed-effects models tested associations of financial strain (parent-reported household wage loss and youth-reported financial stress) with depressive symptomatology over time, covarying for multiple confounders including pre-pandemic socioeconomic status and psychopathology, and pandemic-related environmental factors. Longitudinal mediation analyses examined potential mechanisms leading from wage loss to youth mental health.

Findings

Financial strain was highly prevalent, especially among low-income participants, with >70% of the total sample reporting lost wages. Both wage loss and subjective financial stress were associated with depressive symptomatology over time (Estimate = 0.04, P = 0.014; Estimate = 0.17, P < 0.001; respectively). The association between financial stress and depressive symptomatology was robust to the addition of multiple environmental confounders (Estimate = 0.16, P < 0.001). Both family-level (family conflict) and individual-level (financial stress) factors mediated the relationship between wage loss and depressive symptomatology.

Interpretation

The financial effects of COVID-19 (and worldwide responses to it) have taken a significant toll on youth mental health. In families that lost wages, youth-reported financial stress and familial factors mediated the relationship between wage loss and mental health over time. Findings highlight financial stress as a key driver of youth mental health burden and identify familial factors as critical targets for intervention to mitigate mental health risks in periods of economic crises…

<https://www.thelancet.com/journals/lanam/article/PIIS2667-193X(22)00208-3/fulltext>

**recovery**

**title:** US CDC begins agency-wide changes after pandemic failures [Report]

the lancet | 19th November 2022

An independent review made several recommendations for improving the public health agency…

The US Centers for Disease Control and Prevention (CDC) is on a mission to reorganise and modernise itself, so that its mistakes during the pandemic will not happen again. The aim is to make the nation's leading disease detective more nimble and accountable, and fortify its role as public health protector. But although some changes have been made, progress will be limited without support from the US Congress…

<https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(22)02354-6/fulltext>

**title:** Offline: COVID-19—the lessons that science forgot [Comment]

the lancet | 9th november 2022

Remember the pandemic? Barely. Economist Impact, a policy research team within The Economist Group, supported by The Lancet's publisher Elsevier, last week launched Confidence in Research—a report exploring attitudes of scientists to the practice and communication of science during the pandemic. Based on a survey of over 3000 researchers worldwide, Economist Impact identified important actions that should be considered if mistakes are not to be repeated during future health emergencies…

<https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(22)02358-3/fulltext>

**title:** Human rights and the COVID-19 pandemic: a retrospective and prospective analysis

the lancet | 17th november 2022

Summary

When the history of the COVID-19 pandemic is written, the failure of many states to live up to their human rights obligations should be a central narrative. The pandemic began with Wuhan officials in China suppressing information, silencing whistleblowers, and violating the freedom of expression and the right to health. Since then, COVID-19's effects have been profoundly unequal, both nationally and globally. These inequalities have emphatically highlighted how far countries are from meeting the supreme human rights command of non-discrimination, from achieving the highest attainable standard of health that is equally the right of all people everywhere, and from taking the human rights obligation of international assistance and cooperation seriously. We propose embedding human rights and equity within a transformed global health architecture as the necessary response to COVID-19's rights violations. This means vastly more funding from high-income countries to support low-income and middle-income countries in rights-based recoveries, plus implementing measures to ensure equitable distribution of COVID-19 medical technologies. We also emphasise structured approaches to funding and equitable distribution going forward, which includes embedding human rights into a new pandemic treaty. Above all, new legal instruments and mechanisms, from a right to health treaty to a fund for civil society right to health advocacy, are required so that the narratives of future health emergencies—and people's daily lives—are ones of equality and human rights…

<https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(22)01278-8/fulltext>

**workforce wellbeing**

**title:** The challenges of doing paediatric research during the first year of the covid-19 pandemic [Opinion]

bmj| 15th november 2022

…In response, paediatricians from multiple subspecialties quickly started doing research within a new, challenging environment. Existing and new regional research networks joined their efforts and created innovative global consortiums to investigate the spectrum of paediatric covid-19, spontaneously modelling a new paradigm of paediatric international research. These authors share their personal and scientific insights as clinicians, citizens, and researchers…

A nuanced analysis of the year would help us to reflect on the choices and sacrifices we made. Public opinion and policy makers must be made aware of the sacrifices, disappointments, frustrations, challenges, suffering, and renunciations experienced by those healthcare professionals who try to include research as their standard of care while taking care of patients—even during a pandemic. Policy makers need to ensure academic freedom and respect, by avoiding erosions in civility and achieving gender and race equality in the research and healthcare environment. Every crisis is an opportunity…

<https://www.bmj.com/content/379/bmj.o2750>

**health management**

**title:** Covid-19: Funding for pandemic preparedness being “sucked away” by war in Ukraine [News]

bmj | 14th november 2022

A funding gap of around ₤10.5bn (€12bn; $12.4bn) for pandemic preparedness in developing countries has emerged as governments in richer countries divert finance to military aid for Ukraine and other urgent domestic priorities, a conference on development finance has been told…

The UK had reduced its funding for development aid from 0.7% of GDP to 0.5%, and commitments from other countries were “falling away,”…

Peter Baker, assistant director of the Centre for Global Development, said that there was a need for global monitoring of covid-19 and stockpiling of vaccines but there was an urgent need to improve primary healthcare in many countries and that the “bulk of the funding needs to go to locally led campaigns.”…

<https://www.bmj.com/content/379/bmj.o2748>

**i****nternational perspectives**

**title:** Covid-19: China eases rules amid rise in cases [News]

bmj | 15th november 2022

…Despite a new rise in cases—on 10 November more than 10 500 new cases were recorded, the highest daily total since April—the government has slightly eased its strict zero tolerance policy on covid. Quarantine for close contacts has been cut from seven days in a state facility to five days, and three days at home, and officials will also stop recording secondary contacts, so many people will avoid having to quarantine at all…

<https://www.bmj.com/content/379/bmj.o2743>

We

[TRFT Library & Knowledge Service](https://www.trftlibraryknowledge.com/) aim to bring together the latest guidelines, research and news on Covid-19 through our [Covid-19 portal](https://www.trftlibraryknowledge.com/coronavirus.html). For daily updates on Covid-19 visit our '[Latest Health](https://trfthealthweeklydigest.wordpress.com/)' newsfeed, or use the hashtag [#covid19rftlks](https://twitter.com/hashtag/covid19rftlks?src=hashtag_click) to see our latest tweets on Covid-19 research, guidelines and news.

We also produce a range of subject-specific news feeds to ensure our clinical and professional teams stay up to date with developments in their work areas. Please visit our [website](http://www.trftlibraryknowledge.com/) for more information

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