COVID-19 weekly update

28th March 2022

**clinical management**

**Title:** Prone positioning of patients with moderate hypoxaemia due to covid-19: multicentre pragmatic randomised trial (COVID-PRONE)  
  
BMJ |23rd march 2022  
  
Objectives: To assess the effectiveness of prone positioning to reduce the risk of death or respiratory failure in non-critically ill patients admitted to hospital with covid-19. Design: Multicentre pragmatic randomised clinical trial. Setting 15 hospitals in Canada and the United States from May 2020 until May 2021. Participants Eligible patients had a laboratory confirmed or a clinically highly suspected diagnosis of covid-19, needed supplemental oxygen (up to 50% fraction of inspired oxygen), and were able to independently lie prone with verbal instruction. Of the 570 patients who were assessed for eligibility, 257 were randomised and 248 were included in the analysis. Intervention: Patients were randomised 1:1 to prone positioning (that is, instructing a patient to lie on their stomach while they are in bed) or standard of care (that is, no instruction to adopt prone position). Main outcome measures: The primary outcome was a composite of in-hospital death, mechanical ventilation, or worsening respiratory failure defined as needing at least 60% fraction of inspired oxygen for at least 24 hours. Secondary outcomes included the change in the ratio of oxygen saturation to fraction of inspired oxygen. Results: The trial was stopped early on the basis of futility for the pre-specified primary outcome. The median time from hospital admission until randomisation was 1 day, the median age of patients was 56 (interquartile range 45-65) years, 89 (36%) patients were female, and 222 (90%) were receiving oxygen via nasal prongs at the time of randomisation. The median time spent prone in the first 72 hours was 6 (1.5-12.8) hours in total for the prone arm compared with 0 (0-2) hours in the control arm. The risk of the primary outcome was similar between the prone group (18 (14%) events) and the standard care group (17 (14%) events) (odds ratio 0.92, 95% confidence interval 0.44 to 1.92). The change in the ratio of oxygen saturation to fraction of inspired oxygen after 72 hours was similar for patients randomised to prone positioning and standard of care.

Conclusion Among non-critically ill patients with hypoxaemia who were admitted to hospital with covid-19, a multifaceted intervention to increase prone positioning did not improve outcomes. However, wide confidence intervals preclude definitively ruling out benefit or harm. Adherence to prone positioning was poor, despite multiple efforts to increase it. Subsequent trials of prone positioning should aim to develop strategies to improve adherence to awake prone positioning.  
<https://www.bmj.com/content/376/bmj-2021-068585>

**title:** Awake prone positioning for patients with covid-19  
  
BMJ | 23rd march 2022  
  
It’s a matter of time

Awake prone positioning is thought to improve clinical outcomes in patients with covid-19 by modulating lung mechanics during progressive hypoxaemic respiratory failure. The intervention is attractive because of its perceived simplicity, with evidence of benefit in patients with acute respiratory distress syndrome who need invasive mechanical ventilation. However, data to inform its use in patients with covid-19, particularly those not requiring mechanical ventilation, are scarce. Randomised evidence from 2021 looked promising. In a meta-trial combining data from six open label superiority trials of patients requiring high flow nasal oxygen for covid-19, Ehrmann and colleagues found that awake prone positioning significantly reduced the risk of intubation or death compared with standard care (223 (40%) outcome events in the prone cohort versus 257 (46%) in the standard care cohort; relative risk 0.86, 95% confidence interval 0.75 to 0.98). Now a linked BMJ paper by Fralick and colleagues (doi:10.1136/bmj-2021-068585) reports findings from a new pragmatic randomised controlled trial of awake prone positioning in patients admitted to hospital with covid-19 across 15 North American centres (COVID-PRONE).6 A total of 257 participants requiring supplemental oxygen were assigned to prone positioning or standard care. The composite primary outcome was death, invasive mechanical ventilation, or worsening respiratory failure requiring at least 60% fraction of inspired oxygen. By contrast to previous findings, COVID-PRONE found no differences in the primary outcome between the intervention group (18 (14%) events) and the control group (17 (14%) events) (odds ratio 0.92, 95% confidence interval 0.44 to 1.92).

How can the discrepancy be explained? Firstly, participants in the meta-trial were managed awake and prone for a median of five hours daily, twice as long as participants in COVID-PRONE. Despite the authors’ best efforts (COVID-PRONE aimed for 16 hours a day prone and went through eight iterations to try to improve adherence), the median daily duration of prone positioning in the first 72 hours was 2.5 hours in the intervention group (with no proning at all beyond 72 hours) compared with 0 hours in the control group. Therefore, one of this trial’s key findings was that, in routine clinical settings, awake prone positioning is difficult for patients to tolerate for long enough to improve outcomes. In the meta-trial, the largest contributor to overall benefit was a Mexican sub-study, in which long durations of prone positioning were achieved (8.6 hours per day), resulting in a relative risk reduction of 22%.

Unlike sedated patients, awake patients with covid-19 are uncomfortable and in pain. Patient author DP was admitted to intensive care early in the pandemic and recalled breathing as though his lungs “were filled with shattered glass.” Combined with febrile episodes, fatigue, and the mental distress caused by an acute life threatening illness, lying face down for prolonged periods while awake can be extremely difficult. The Mexican sub-study of the meta-trial may have achieved better adherence and outcomes because an intensive care specialist was constantly available to encourage patients and clinical teams to persevere with prone positioning This resource would be unavailable in most standard healthcare settings. Even in an intensive care unit with one-to-one nursing, awake prone positioning can be poorly tolerated.

Secondly, differences in disease severity existed between participants in COVID-PRONE and previous trials. Only 4% of patients in COVID-PRONE required high flow nasal oxygen at baseline, whereas the meta-trial predominantly enrolled sicker patients already needing non-invasive respiratory support. Rates of mortality and intubation varied substantially between the trials—1% versus 22.2% and 4% versus 36.4%, respectively. These differences likely contribute to the discrepancies in the findings.

Duration of covid-19 infection is intrinsically linked to its severity, so both may be modifiers of the efficacy of prone positioning.8 In patients with early or mild disease, pulmonary physiology is probably insufficiently compromised for prone positioning to make a difference to outcomes through its effects on transpulmonary pressure distribution, lung compression, and ventilation-perfusion mismatching. During advanced, severe disease, however, prone positioning could help to reduce regional alveolar hyperinflation associated with raised positive end expiratory pressure, especially in patients requiring non-invasive respiratory support.

Fralick and colleagues’ new trial, together with previous trials, shows that both duration and timing of awake prone positioning are important determinants of its efficacy in patients with covid-19. Future studies must focus on finding optimal means of maintaining awake prone positioning in the care of severe, likely late stage covid-19. Patient and public involvement will be crucial to ensure that appropriate attention is paid to comfort and acceptability in the design and evaluation of complex interventions to enable awake prone positioning.

Awake prone positioning can still work, but timing and duration are fundamental determinants of efficacy as an intervention for progressive hypoxaemic respiratory failure in patients with covid-19.  
<https://www.bmj.com/content/376/bmj.o632>

**Title:** Tocilizumab plus dexamethasone versus dexamethasone in patients with moderate-to-severe COVID-19 pneumonia: A randomised clinical trial from the CORIMUNO-19 study group  
  
the lancet eclinical medicine | 24th march 2022   
  
Question: What is the effect of losartan on lung injury in hospitalized patients with COVID-19?  
In moderate-to-severe COVID-19 pneumonia, dexamethasone (DEX) and tocilizumab (TCZ) reduce the occurrence of death and ventilatory support. We investigated the efficacy and safety of DEX+TCZ in an open randomized clinical trial.

Methods: From July 24, 2020, through May 18, 2021, patients with moderate-to-severe COVID-19 pneumonia requiring oxygen (>3 L/min) were randomly assigned to receive DEX (10 mg/d 5 days tapering up to 10 days) alone or combined with TCZ (8 mg/kg IV) at day 1, possibly repeated with a fixed dose of 400 mg i.v. at day 3. The primary outcome was time from randomization to mechanical ventilation support or death up to day 14, analysed on an intent-to-treat basis using a Bayesian approach.

Findings: A total of 453 patients were randomized, 3 withdrew consent, 450 were analysed, of whom 226 and 224 patients were assigned to receive DEX or TCZ+DEX, respectively. At day 14, mechanical ventilation or death occurred in 32/226 (14%) and 27/224 (12%) in the DEX and TCZ+DEX arms, respectively (hazard ratio [HR] 0·85, 90% credible interval [CrI] 0·55 to 1·31). At day 14, the World health Organization (WHO) clinical progression scale (CPS) was significantly improved in the TCZ+DEX arm (OR 0·69, 95% CrI, 0·49 to 0.97). At day 28, the cumulative incidence of oxygen supply independency was 82% in the TCZ+DEX arms and 72% in the DEX arm (HR 1·36, 95% CI 1·11 to 1·67). On day 90, 24 deaths (11%) were observed in the DEX arm and 18 (8%) in the TCZ+DEX arm (HR 0·77, 95% CI 0·42–1·41). Serious adverse events were observed in 25% and 21% in DEX and TCZ+DEX arms, respectively.

Interpretation: Mechanical ventilation need and mortality were not improved with TCZ+DEX compared with DEX alone. The safety of both treatments was similar. However, given the wide confidence intervals for the estimate of effect, definitive interpretation cannot be drawn.  
<https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(22)00092-X/fulltext>

**Title:** COVID-19 Cases and Disease Severity in Pregnancy and Neonatal Positivity Associated With Delta (B.1.617.2) and Omicron (B.1.1.529) Variant Predominance  
  
JAMA| 24th march 2022  
  
The Omicron (B.1.1.529) variant of SARS-CoV-2 has spread rapidly but appears to cause less severe disease than the Delta (B.1.617.2) variant.[1](https://jamanetwork.com/journals/jama/fullarticle/2790609#jld220017r1) During pregnancy, Delta was associated with increased COVID-19 severity,[2](https://jamanetwork.com/journals/jama/fullarticle/2790609#jld220017r2) but infections and severity have not been examined during Omicron. We examined infections, illness severity, vaccinations, and early neonatal infections among obstetric patients during the pre-Delta, Delta, and Omicron epochs...

... As in nonpregnant people, Delta and Omicron variant predominance were associated with increased SARS-CoV-2 infections in pregnancy, with the majority occurring in unvaccinated individuals. Delta variant predominance was associated with increased illness severity and Omicron with decreased illness severity after adjusting for prior vaccination. The majority of early neonatal SARS-CoV-2 infections occurred among unvaccinated mothers with nonsevere COVID-19. Long-term risks of early neonatal SARS-CoV-2 infection are unknown, but maternal vaccination may be protective.

Limitations include the cases from a single institution and potentially missing data on vaccination or positive results of tests conducted outside the health care system. Rates of SARS-CoV-2 exposure and vaccinations among uninfected individuals were not available. Whether the decreased illness severity during Omicron is related to greater numbers of pregnant people previously infected or vaccinated or to intrinsic virological properties cannot be determined.  
<https://jamanetwork.com/journals/jama/fullarticle/2790609>

**title:** SARS-CoV-2 Placentitis and Intraparenchymal Thrombohematomas Among COVID-19 Infections in Pregnancy  
  
jama | 21st mARCH 2022

Background: The omicron variant (B.1.1.529) of SARS-CoV-2 has demonstrated partial vaccine   
Systematic meta-analysis did not find increased stillbirth risk during the early months of the SARS-CoV-2 pandemic but increased rates have been reported during the Delta wave. Pathology literature has documented diagnostic histopathologic features of SARS-CoV-2 placental infection: syncytiotrophoblast necrosis, increased perivillous fibrin, and intervillositis, with trophoblast infection confirmed by SARS-CoV-2 RNA in situ hybridization (RNA-ISH) or immunohistochemistry. SARS-CoV-2 placentitis causes severe placental damage, resulting in perinatal morbidity and mortality.3,5 Some variants of concern appear more perinatally virulent.5,6 We study placental pathology and perinatal outcomes in a series of SARS-CoV-2 placentitis cases before and during the Delta wave…

…We describe a severe form of SARS-CoV-2 placentitis with thrombohematomas occurring primarily in stillbirths from pregnancies complicated by SARS-CoV-2 infection during the 2021 pandemic wave. This pathology is distinctive and grossly identifiable, representing a change in the spectrum of SARS-CoV-2 pregnancy complications.1,2 The thrombohematomas are likely a result of severe viral placental damage. Our findings suggest a pathogenetic mechanism for the reported increased risk of stillbirth associated with SARS-CoV-2 infection in 2021.2,3 As maternal lakes were noted by ultrasound in 2 cases, further research is needed to understand if imaging may identify at-risk pregnancies.

Our study has several limitations, including (1) ascertainment bias due to inclusion of consultation cases and lack of universal SARS-CoV-2 screening at referring institutions, which limits assessment of the incidence of SARS-CoV-2 placentitis and stillbirth; (2) inability to obtain outcome data in several consultation cases; and (3) placental sonography was not reported after SARS-CoV-2 infection in most cases, and strain identification was limited.

Updated epidemiological studies evaluating pregnancy outcomes are required for corroboration of our findings. Follow-up studies of patients affected by SARS-CoV-2 placentitis are required for evaluation of long-term clinical outcomes.  
<https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2790175>

**title:** Perinatal Complications in Individuals in California With or Without SARS-CoV-2 Infection During Pregnancy  
  
jama internal medicine| 21st mARCH 2022

Background: The omicron variant (B.1.1.529) of SARS-CoV-2 has demonstrated partial vaccine   
Question What is the risk of perinatal complications associated with SARS-CoV-2 infection during pregnancy and what factors are associated with hospitalizations?

Findings In this cohort study of 43 886 pregnant individuals, SARS-CoV-2 infection during pregnancy was associated with an increased risk of severe maternal morbidity, preterm birth, and venous thromboembolism. Pregestational diabetes and Asian or Pacific Islander and Black race and ethnicity were associated with an increased risk of hospitalization.

Meaning This study found that SARS-CoV-2 infection may be associated with an increased risk of perinatal complications; this information can help inform treatment of the infection during pregnancy, aid patients in understanding the risks of these complications, and support the recommendation for vaccination of pregnant individuals and those planning conception.  
<https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2790318>

**title:** Effect of Antiplatelet Therapy on Survival and Organ Support–Free Days in Critically Ill Patients With COVID-19A Randomized Clinical Trial  
  
JAMA | 22nd mARCH 2022

Background: The omicron variant (B.1.1.529) of SARS-CoV-2 has demonstrated partial vaccine   
Question Does antiplatelet therapy administered to critically ill patients with COVID-19 improve organ support–free days (a composite end point of in-hospital mortality and duration of intensive care unit–based respiratory or cardiovascular support) up to day 21?

Findings In this bayesian randomized clinical trial that included 1557 patients, antiplatelet therapy with either aspirin or a P2Y12 inhibitor, compared with no antiplatelet therapy, resulted in a 95.7% posterior probability of futility with regard to the odds of improvement in organ support–free days within 21 days.

Meaning Among critically ill patients with COVID-19, there was a low likelihood that treatment with an antiplatelet agent provided improvement in organ support–free days within 21 days.  
<https://jamanetwork.com/journals/jama/fullarticle/2790488>

**title:** Thromboinflammation and Antithrombotics in COVID-19: Accumulating Evidence and Current Status  
  
the lancet | 16th mARCH 2022

…As Bernard Lown stated, “Do as much as possible for the patient, and as little as possible to the patient.” At this juncture in the global pandemic, all hospitalized patients with COVID-19 and low risk of bleeding should receive at least prophylactic-dose anticoagulation with a heparin anticoagulant, with consideration of therapeutic-dose heparin in some cases, but there is no proven efficacy supporting the addition of traditional antiplatelet therapies to prevent progressive thromboinflammatory complications of COVID-19. Nontraditional targeting of alternative platelet function pathways with agents like crizanlizumab, a P-selectin inhibitor (NCT04435184), or glenzocimab, a platelet glycoprotein VI inhibitor (NCT04659109), is under investigation. The clinical goal, however, should be to avoid thromboinflammation and hospitalization in the first place, an objective largely achievable through aggressive vaccination.  
<https://jamanetwork.com/journals/jama/fullarticle/2790489>

**title:** Association of Early Aspirin Use With In-Hospital Mortality in Patients With Moderate COVID-19  
  
JAMA network open | 24th mARCH 2022

Question Is early aspirin use in hospitalized patients with moderate COVID-19 associated with lower odds of in-hospital mortality?

Findings In a cohort study of 112 269 patients with moderate COVID-19, early aspirin use during the first day of hospitalization was associated with lower 28-day in-hospital mortality and pulmonary embolism incidence when compared with patients who did not receive early aspirin.

Meaning This study suggests that early aspirin use may be associated with lower odds of in-hospital mortality among hospitalized patients with moderate COVID-19; these findings warrant further study in a randomized clinical trial that includes diverse patients with cardiovascular comorbidities.  
<https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2790439>

**title:** Implementation of corticosteroids in treatment of COVID-19 in the ISARIC WHO Clinical Characterisation Protocol UK: prospective, cohort study  
  
the lancet digital health | 1st april 2022

Background. Dexamethasone was the first intervention proven to reduce mortality in patients with COVID-19 being treated in hospital. We aimed to evaluate the adoption of corticosteroids in the treatment of COVID-19 in the UK after the RECOVERY trial publication on June 16, 2020, and to identify discrepancies in care.

Methods. We did an audit of clinical implementation of corticosteroids in a prospective, observational, cohort study in 237 UK acute care hospitals between March 16, 2020, and April 14, 2021, restricted to patients aged 18 years or older with proven or high likelihood of COVID-19, who received supplementary oxygen. The primary outcome was administration of dexamethasone, prednisolone, hydrocortisone, or methylprednisolone. This study is registered with ISRCTN, ISRCTN66726260.

Findings. Between June 17, 2020, and April 14, 2021, 47 795 (75·2%) of 63 525 of patients on supplementary oxygen received corticosteroids, higher among patients requiring critical care than in those who received ward care (11 185 [86·6%] of 12 909 vs 36 415 [72·4%] of 50 278). Patients 50 years or older were significantly less likely to receive corticosteroids than those younger than 50 years (adjusted odds ratio 0·79 [95% CI 0·70–0·89], p=0·0001, for 70–79 years; 0·52 [0·46–0·58], p<0·0001, for >80 years), independent of patient demographics and illness severity. 84 (54·2%) of 155 pregnant women received corticosteroids. Rates of corticosteroid administration increased from 27·5% in the week before June 16, 2020, to 75–80% in January, 2021.

Interpretation. Implementation of corticosteroids into clinical practice in the UK for patients with COVID-19 has been successful, but not universal. Patients older than 70 years, independent of illness severity, chronic neurological disease, and dementia, were less likely to receive corticosteroids than those who were younger, as were pregnant women. This could reflect appropriate clinical decision making, but the possibility of inequitable access to life-saving care should be considered.  
<https://www.thelancet.com/journals/landig/article/PIIS2589-7500(22)00018-8/fulltext>

**title:** SARS-CoV-2 co-infection with influenza viruses, respiratory syncytial virus, or adenoviruses  
  
the lancet | 25th mARCH 2022

Measures to reduce transmission of SARS-CoV-2 have also been effective in reducing the transmission of other endemic respiratory viruses. As many countries decrease the use of such measures we expect that SARS-CoV-2 will circulate with other respiratory viruses, increasing the probability of co-infections. The clinical outcome of respiratory viral co-infections with SARS-CoV-2 is unknown.

We examined clinical outcomes of co-infection with influenza viruses, respiratory syncytial virus, or adenoviruses in 212 466 adults with SARS-CoV-2 infection who were admitted to hospital in the UK between Feb 6, 2020, and Dec 8, 2021, using the International Severe Acute Respiratory and Emerging Infection Consortium–WHO Clinical Characterisation Protocol…  
  
…As public health restrictions are lifted, respiratory virus co-infections are more likely to occur during future winters. The marked increase in risk among patients with co-infection has several implications for policy. First, our results provide further support for vaccination against both SARS-CoV-2 and influenza viruses. Second, they suggest that testing for influenza viruses is important in hospital inpatients with COVID-19 to identify patients at risk and a cohort of patients who might have different responses to immunomodulatory and antiviral therapy.  
<https://www.thelancet.com/journals/landig/article/PIIS2589-7500(22)00018-8/fulltext>

**title:** Host-targeting oral antiviral drugs to prevent pandemics  
  
the lancet | 25th mARCH 2022

Background: The omicron variant (B.1.1.529) of SARS-CoV-2 has demonstrated partial vaccine   
Support for using ER glucosidase I as a broad-spectrum antiviral target comes from a study that identified two siblings with a deficiency of ER glucosidase l, which is targeted by the single high-dose approach. Despite significant hypogammaglobulinaemia, the children had no history of viral disease and were not able to generate immune responses to live viral vaccines. The investigators concluded that there is a strong potential benefit of using inhibitors of glucosidase l as a means of controlling viral infections, especially those that pose a threat of rapid global spreading. But there is no need for complete inhibition of glucosidase I for therapeutic benefit. We believe that the gravity of the pandemic urgently demands us to try so-called off the beaten track host-targeting antivirals rather than only the current direct acting antiviral approaches. The use of host-targeting antivirals is supported by encouraging animal and human toxicity data and could provide a broad-spectrum oral antiviral that is mutation-proof. We believe that the higher single-dose regimen (at most, two single doses) should be recommended for global ease of use. We want to initially clinically use the generically available potent iminosugar, MON-DNJ (NCT0269629), used in the above high-dose approach studies, for which some phase 1 data are available. The less potent, but generically approved, orally available iminosugar miglustat could be used at a single high dose to target coronaviruses and influenza as proof of principle. HIV patients have been given high doses of miglustat in a combination trial. The safety of miglustat at lower concentrations is well documented in its routine use in Gaucher's disease for over 20 years. All currently available data make a clinical trial of this novel concept feasible and hence an imperative for promoting public health. This could be a transformational approach. Broad-spectrum, safe orally available antivirals are desperately needed worldwide, not only to help terminate this pandemic but to prevent the next one. This approach urgently needs support to further evaluate its promise to fill a major unmet need.  
<https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(22)00454-8/fulltext>

**title:** The multifaceted protease-anti-protease imbalance in COVID-19  
  
the lancet ebio medicine | 24th mARCH 2022

Background: The omicron variant (B.1.1.529) of SARS-CoV-2 has demonstrated partial vaccine   
In this issue of eBioMedicine, Dr. McElvaney and colleagues report altered protease/anti-protease balance in moderate to severe COVID-19 ARDS by the disease processes as well as therapies targeting IL-6 signaling. The authors use relevant clinical samples (plasma, tracheal aspirate, and lungs) of COVID-19 subjects to measure alpha-1 antitrypsin (AAT) level and its activity against the protease neutrophil elastase (NE) before and after tocilizumab, an IL-6 receptor antagonist used in COVID-19 treatment.  
<https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(22)00157-8/fulltext>

**title:** The intersecting pandemics of tuberculosis and COVID-19: population-level and patient-level impact, clinical presentation, and corrective interventions  
  
the lancet respiratory medicine| 23rd mARCH 2022

Background: The omicron variant (B.1.1.529) of SARS-CoV-2 has demonstrated partial vaccine   
The global tuberculosis burden remains substantial, with more than 10 million people newly ill per year. Nevertheless, tuberculosis incidence has slowly declined over the past decade, and mortality has decreased by almost a third in tandem. This positive trend was abruptly reversed by the COVID-19 pandemic, which in many parts of the world has resulted in a substantial reduction in tuberculosis testing and case notifications, with an associated increase in mortality, taking global tuberculosis control back by roughly 10 years. Here, we consider points of intersection between the tuberculosis and COVID-19 pandemics, identifying wide-ranging approaches that could be taken to reverse the devastating effects of COVID-19 on tuberculosis control. We review the impact of COVID-19 at the population level on tuberculosis case detection, morbidity and mortality, and the patient-level impact, including susceptibility to disease, clinical presentation, diagnosis, management, and prognosis. We propose strategies to reverse or mitigate the deleterious effects of COVID-19 and restore tuberculosis services. Finally, we highlight research priorities and major challenges and controversies that need to be addressed to restore and advance the global response to tuberculosis…  
<https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(22)00092-3/fulltext>

**title:** Ritonavir and COVID-19: pragmatic guidance is important  
  
the lancet | 22nd mARCH 2022

Background: The omicron variant (B.1.1.529) of SARS-CoV-2 has demonstrated partial vaccine   
We thank Joseph Heskin and colleagues for highlighting the crucial issue of drug–drug interactions (DDIs) with ritonavir, the pharmacoenhancer or booster co-formulated with the novel SARS-CoV-2 protease inhibitor, PF-07321332 (Paxlovid, Pfizer [New York, NY, USA]). Since Paxlovid will be primarily administered to non-hospitalised individuals and prescribed by clinicians who might not routinely manage complex interactions or have access to their full medication list, an awareness of the DDI potential and clear pathways to support safe decision making are essential, ideally led by pharmacists who have speciality knowledge in this area. If managed appropriately, DDI should, in most cases, not necessitate a change in antiviral management…  
<https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(22)00280-X/fulltext>

**title:** Immunoglobulin G1 Fc glycosylation as an early hallmark of severe COVID-19  
  
Background. Immunoglobulin G1 (IgG1) effector functions are impacted by the structure of fragment crystallizable (Fc) tail-linked N-glycans. Low fucosylation levels on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike (S) protein-specific IgG1 has been described as a hallmark of severe coronavirus disease 2019 (COVID-19) and may lead to activation of macrophages via immune complexes thereby promoting inflammatory responses, altogether suggesting involvement of IgG1 Fc glycosylation modulated immune mechanisms in COVID-19. Methods: In this prospective, observational single center cohort study, IgG1 Fc glycosylation was analyzed by liquid chromatography-mass spectrometry following affinity capturing from serial plasma samples of 159 SARS-CoV-2 infected hospitalized patients. Findings: At baseline close to disease onset, anti-S IgG1 glycosylation was highly skewed when compared to total plasma IgG1. A rapid, general reduction in glycosylation skewing was observed during the disease course. Low anti-S IgG1 galactosylation and sialylation as well as high bisection were early hallmarks of disease severity, whilst high galactosylation and sialylation and low bisection were found in patients with low disease severity. In line with these observations, anti-S IgG1 glycosylation correlated with various inflammatory markers.

Interpretation: Association of low galactosylation, sialylation as well as high bisection with disease severity and inflammatory markers suggests that further studies are needed to understand how anti-S IgG1 glycosylation may contribute to disease mechanism and to evaluate its biomarker potential.  
<https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(22)00141-4/fulltext>

**title:** Comparison of Trials Using Ivermectin for COVID-19 Between Regions With High and Low Prevalence of Strongyloidiasis: A Meta-analysis  
  
jama network open | 21st mARCH 2022

Question Does prevalence of strongyloidiasis interact with the relative risk (RR) of mortality in ivermectin trials for the treatment of COVID-19?

Findings In this meta-analysis of 12 randomized clinical trials involving 3901 patients, favorable mortality results were limited to trials in high-prevalence regions, with no evidence that ivermectin had a mortality benefit in low-prevalence regions. Meta-regression found an association between the regional prevalence of strongyloidiasis and risk of mortality, with a decrease in RR of 39% for each 5% increase in strongyloidiasis prevalence.

Meaning Evidence supports that strongyloidiasis prevalence interacts with the RR of mortality in ivermectin trial results; no evidence was found to suggest ivermectin has any role in preventing mortality in patients with COVID-19 in regions where strongyloidiasis is not endemic.  
<https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2790173>

**covid rates & variants**

**title:** Covid-19: What do we know about the delta omicron recombinant variant?  
  
bmj | 24th mARCH 2022

A combination of the delta (AY.4) and BA.1 omicron variants has been named by the World Health Organization as the BA.1 x AY.4 recombinant. First detected in France in January 2022, it has since picked up the nickname “deltacron”1—Elisabeth Mahase finds out more…  
<https://www.bmj.com/content/376/bmj.o792>

**title:** Helen Salisbury: The persistence of covid  
  
BMJ| 22nd mARCH 2022  
  
With wave after wave of SARS-CoV-2 variants, COVID-19 patients filled the worlds' hospitals and   
Figures from the Office for National Statistics for the week ending 12 March showed that one in 20 people in England had covid-19, one in 25 in Wales, and one in 14 in Scotland and Northern Ireland.1

Unsurprisingly, this level of infection is putting pressure on general practice as we scramble to arrange cover for absent colleagues. Many people who are triple jabbed and have managed to dodge the virus for two years are finally succumbing. The majority will be back at work after 10 days or so—I’ve yet to meet anyone who’s had a negative lateral flow test on day 5 or 6. For most it will be no more than an unpleasant one or two weeks, laced with guilt about letting their colleagues down. But for some it will be a prelude to many months of fatigue, breathlessness, reduced exercise tolerance, and cognitive impairment…  
<https://www.bmj.com/content/376/bmj.o740>

**long-term effects:**

**title:** SARS-CoV-2-specific antibody and T-cell responses 1 year after infection in people recovered from COVID-19: a longitudinal cohort study  
  
the lancet microbe | 23rd mARCH 2022  
  
…SARS-CoV-2-specific neutralising antibody and T-cell responses were retained 12 months after initial infection. Neutralising antibodies to the D614G, beta, and delta viral strains were reduced compared with those for the original strain, and were diminished in general. Memory T-cell responses to the original strain were not disrupted by new variants. This study suggests that cross-reactive SARS-CoV-2-specific T-cell responses could be particularly important in the protection against severe disease caused by variants of concern whereas neutralising antibody responses seem to reduce over time.  
<https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247(22)00036-2/fulltext>

**title:** Risks and burdens of incident diabetes in long COVID: a cohort study  
  
the lancet diabetes & endocrinology | 21th mARCH 2022  
  
Question: Is the Delta variant (B.1.617.2) more transmissible than previous strains of SARS-CoV-2   
There is growing evidence suggesting that beyond the acute phase of SARS-CoV-2 infection, people with COVID-19 could experience a wide range of post-acute sequelae, including diabetes. However, the risks and burdens of diabetes in the post-acute phase of the disease have not yet been comprehensively characterised. To address this knowledge gap, we aimed to examine the post-acute risk and burden of incident diabetes in people who survived the first 30 days of SARS-CoV-2 infection…  
  
…In the post-acute phase, we report increased risks and 12-month burdens of incident diabetes and antihyperglycaemic use in people with COVID-19 compared with a contemporary control group of people who were enrolled during the same period and had not contracted SARS-CoV-2, and a historical control group from a pre-pandemic era. Post-acute COVID-19 care should involve identification and management of diabetes.  
<https://www.thelancet.com/journals/landia/article/PIIS2213-8587(22)00044-4/fulltext>

**title:** Rising diabetes diagnosis in long COVID  
  
the lancet diabetes & endocrinology | 21th mARCH 2022   
  
… The data presented by Xie and Al-Aly3 have major implications for clinical policy and public health. If COVID-19 is indeed a risk factor for diabetes in the post-acute phase of infection, screening and management of dysglycaemia should be an integral part of clinical guidelines for COVID-19 diagnosis and follow-up. The long-term implications of SARS-CoV-2 infection increasing diabetes risk are profound. The rates of type 2 diabetes, and associated non-communicable diseases, are already growing, as shown on the diabetes atlas by the International Diabetes Federation. With large and growing numbers of people worldwide infected with SARS-CoV-2 (434 154 739 cumulative cases by Feb 28, 2022) any COVID-19-related increases in diabetes incidence could lead to unprecedented cases of diabetes worldwide—wreaking havoc on already over-stretched and under-resourced clinical and public health systems globally, with devastating tolls in terms of deaths and suffering.

The potential connection between COVID-19 and diabetes highlights that infectious diseases (eg, SARS-CoV-2) and chronic diseases (eg, diabetes) cannot be viewed in siloes. When we emerge out of the pandemic, the much-neglected non-communicable diseases, such as type 2 diabetes, will continue their relentless trajectory, possibly in an accelerated manner, as the leading burdens of global health.  
<https://www.thelancet.com/journals/landia/article/PIIS2213-8587(22)00078-X/fulltext>

**title:** Even Mild COVID-19 May Change the Brain  
  
JAMA | 23rd mARCH 2022  
  
A large study comparing brain scans from the same individuals before and after SARS-CoV-2 infection suggests that brain changes could be a lingering outcome of even mild COVID-19. Writing in Nature, researchers at Oxford University’s Wellcome Centre for Integrative Neuroimaging reported that several months after study participants had SARS-CoV-2 infections, they had more gray matter loss and tissue abnormalities, mainly in the areas of the brain associated with smell, and more brain size shrinkage than participants who hadn’t been infected with the virus…  
  
…The Clinical Takeaway: Josephson said the study puts into context concerns about ongoing infections, including those that are mild. But he cautioned that despite the study’s cognitive findings, the clinical significance of the COVID-19 group’s additional brain changes is not clear.

It’s also too soon to know if the changes are reversible. The timeframe between SARS-CoV-2 infection and the second round of imaging was relatively short. “Whether this is a temporary effect, perhaps related to anosmia or inflammation, or an effect that is more long lasting and could be associated with the cognitive and other neurologic and psychiatric changes described in some with long COVID remains an ongoing area of study,” noted Josephson, who is a professor and chair of the Department of Neurology at the University of California, San Francisco.

A recent report in JAMA Neurology suggests that the cognitive changes observed among some patients with COVID-19 might endure, particularly for those with more severe disease. Investigators found a higher incidence of cognitive impairment among older adults in Wuhan, China, a year after COVID-19 hospitalization compared with their spouses who hadn’t been infected, even after adjusting for age, sex, educational level, body mass index, and comorbidities.

On the other hand, in a written FAQ provided to media, Douaud suggested that the damage observed in her team’s study might improve in due course: “Since the abnormal changes we see in the brain of the infected participants might be related to their loss of smell, it is possible that recovering their smell might lead to these brain abnormalities becoming less marked over time. Similarly, it is likely that the harmful effects of the virus (whether direct, or indirect via inflammation or immune reaction) decrease over time after infection.” She cited small previous studies indicating that issues detected on functional brain imaging may in part improve more than 6 months after SARS-CoV-2 infection. The bottom line for now, in Josephson’s view: “Making sure we are vigilant and attentive to patients’ cognitive concerns post-COVID remains extremely important.”

Looking Ahead: The findings should be replicated in different populations before being considered definitive. Expect additional analyses from Douaud’s group, too. The team hopes to scan the UK Biobank COVID-19 Repeat Imaging study participants for a third time in a year or two.

How best to manage patients’ cognitive symptoms remains an area of robust study, according to Josephson. The current analysis, he said, “also emphasizes just how important it is to continue to work to understand the mechanisms of these neurological symptoms and whether vaccination or severity of illness modifies them.”

Some of the altered brain regions identified in the study also have memory-related functions. Although there were no signs of memory impairment, if the damage persists, there could be implications for later memory problems or even dementia. Down the line, insight should come from the Alzheimer’s Association and researchers from more than 30 countries, who have formed an international consortium to study SARS-CoV-2 infection’s effects on the central nervous system in the short- and long-term.  
<https://jamanetwork.com/journals/jama/fullarticle/2790595>

**title:** Neuropsychiatric and Cognitive Outcomes in Patients 6 Months After COVID-19 Requiring Hospitalization Compared With Matched Control Patients Hospitalized for Non–COVID-19 Illness  
  
jama psychiatry | 23rd mARCH 2022  
  
Question Do neuropsychiatric and cognitive sequalae after hospitalization for COVID-19 differ from sequalae after hospitalization for non–COVID-19 illness of comparable severity?

Findings In this case-control study of 85 COVID-19 survivors and 61 control patients with non–COVID-19 illness matched for age, sex, and intensive care unit admission status, cognitive impairment was significantly worse in COVID-19 survivors 6 months after symptom onset; however, the absolute difference in cognitive impairment was small. The overall burden of neuropsychiatric and neurologic diagnoses and symptoms appeared similar in cases and controls.

Meaning In this study, long-term mental health complications in patients who had COVID-19 were significant but seemed not to be unique to COVID-19 because similar complications were observed among individuals hospitalized for non–COVID-19 illness of comparable severity; this highlights the importance of including well-matched control groups when investigating post–COVID-19 sequalae.  
<https://jamanetwork.com/journals/jamapsychiatry/fullarticle/2790554>

**infection control**

**title:** Airborne transmission: Are CO2 monitors a long term solution or “pandemic hack?”

BMJ| 23rd march 2022  
  
As more people have acknowledged the airborne transmission of SARS-CoV-2, CO2 monitors have emerged as a cost effective way to tell how well ventilated a space is. Chris Baraniuk asks what the evidence is and if they should be adopted more widely…  
<https://www.bmj.com/content/376/bmj.o736>

**title:** Covid-19: They think it’s all over—it depends how you look at the world

bmj | 24th march 2022  
  
Covid-19: They think it’s all over—it depends how you look at the world  
  
McKee and van Schalkwyk are right to raise broader questions about the management of the pandemic. As we are told to live with covid-19 with the proud boast that we have the least restrictions in Europe, I want to provide a different perspective. I’m a public health consultant with tetraplegia caused by injury. In the first phases of the pandemic, I lived in something close to terror. The soundtrack of 2020 for me was sirens from the nearby hospital. As the prevalence fell, my fear slipped away, and it felt like normal life had returned. Vaccination added a further layer of security, notwithstanding its reducing effectiveness over time. As case numbers remain high, however, even if I don’t feel the same fear, I feel more at risk, and my world is closing in again; it is worse still for people who are immunocompromised…  
<https://www.bmj.com/content/376/bmj.o762>

**title:** Covid-19: Who will be eligible for free testing from 1 April?  
  
bmj| 25th March 2022

With free covid testing ending in England for most of the public on 1 April, Gareth Iacobucci looks at what this means for staff and at-risk patients. What’s changing in England from 1 April?

The government’s Living with Covid document published in February, set out plans to end all covid-19 restrictions in England and move to a strategy where vaccines and treatments are the “first line of defence.” A key plank of this strategy is that, from 1 April, the government will no longer provide free universal symptomatic and asymptomatic covid testing for the general public. Its justifications are the higher levels of immunity in the population and the need to rein in the “very significant cost to the taxpayer” of providing universal free testing.  
  
Ministers have said that “individuals who are most at risk from the virus” will still be able to access free symptomatic testing, but they have yet to set out further details…  
<https://www.bmj.com/content/376/bmj.o807>

**title:** Covid-19: Moderna will ask for authorisation for vaccine for infants and children

BMJ| 25th march 2022  
  
Moderna said it would ask the US Food and Drug Administration (FDA) for emergency use authorisation for its vaccine for children aged from 6 months to 6 years of age on 23 March 2022. Moderna also said it would ask the FDA for emergency use authorisation of its vaccine for children aged 6 to 12. The vaccine is already approved for children aged 6 to 12 in Australia, Canada, and Europe. It said it was also updating its submission to the FDA for approval of the vaccine for children aged 12 to 17. The company is also preparing to evaluate a booster dose for all paediatric populations. Moderna chief executive Stephane Bancel said, “We remain committed to helping to end the covid-19 pandemic for children of all ages.” . At present only the Pfizer BioNTech vaccine is approved for children aged 5 to 18…  
<https://www.bmj.com/content/376/bmj.o798>

**title:** WAS LOCKDOWN NECESSARY?

BMJ | 23rD march 2022  
  
Two years on from the UK's first covid lockdown, Kit Yates looks at whether it could have been avoided

On 23 March 2020 at 8 pm prime minister Boris Johnson came onto our TV screens to address the nation about the escalation of the covid situation in the UK. “From this evening I must give the British people a very simple instruction,” he said. “You must stay at home.” It was the beginning of the UK’s first lockdown. Two years on from that surreal Monday evening, more than 185 000 people in the UK have died from covid-19 hundreds of thousands of people continue to struggle with the burden of long covid hospitals have frequently been unable to provide the expected quality of care, and the NHS has just struggled through the worst winter on record.

Despite this long lasting and ongoing impact, some people’s memories of the early days of the pandemic seem shorter than others. We are hearing from some sections of the media that that first lockdown was unnecessary—that the worst impacts of that first wave of the pandemic could have been mitigated, while simultaneously avoiding the damage done by lockdown…  
<https://www.bmj.com/content/376/bmj.o776>

**title:** Effectiveness of BNT162b2 against COVID-19 in adolescents  
  
The Lancet Infectious Diseases| 21st March 2022  
  
…To date, this study is the only vaccine effectiveness evaluation against the omicron variant in adolescents after one and two mRNA vaccine doses. In adults from the UK, a similar high vaccine effectiveness against symptomatic disease was observed for both the delta (91%) and omicron (66%) variants 2–4 weeks after two BNT162b2 doses given 8–12 weeks apart which was similar to data from South Africa reporting vaccine effectiveness of 70% against the omicron variant 2 weeks or more after the second vaccine dose. The rapid waning of protection after the first and second BNT162b2 dose against symptomatic disease with the omicron variant, the now dominant variant in the UK and worldwide, indicates that the current adolescent immunisation programme as a stand-alone intervention is unlikely to sustain suppression of infections in the medium-to-long term. If the aim of the programme is to reduce infections, then regular boosters will likely be needed.  
<https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(22)00177-3/fulltext>

**title:** Association of COVID-19 Vaccination in Pregnancy With Adverse Peripartum Outcomes

JAMA| 24th march 2022  
  
Question Is COVID-19 vaccination during pregnancy associated with adverse peripartum outcomes?

Findings In this population-based retrospective cohort study of 97 590 individuals in Ontario, Canada, COVID-19 vaccination during pregnancy, compared with vaccination after pregnancy and with no vaccination, was not significantly associated with increased risk of postpartum hemorrhage, chorioamnionitis, cesarean delivery, admission to neonatal intensive care unit, or low newborn 5-minute Apgar score.

Meaning COVID-19 vaccination during pregnancy was not significantly associated with an increased risk of adverse peripartum outcomes.  
<https://jamanetwork.com/journals/jama/fullarticle/2790607>

**title:** Association of SARS-CoV-2 Vaccination During Pregnancy With Pregnancy Outcomes

JAMA| 24th march 2022  
  
Questions Is SARS-CoV-2 vaccination during pregnancy associated with adverse pregnancy outcomes?

Findings In this population-based retrospective cohort study that included 157 521 deliveries in Sweden and Norway, SARS-CoV-2 vaccination during pregnancy, compared with no SARS-CoV-2 vaccination during pregnancy, was not significantly associated with risk of preterm birth (adjusted hazard ratio [aHR], 0.98), stillbirth (aHR, 0.86), small for gestational age (adjusted odds ratio [aOR], 0.97), low Apgar score (aOR, 0.97), or neonatal care admission (aOR, 0.97).

Meaning In this population-based study conducted in Sweden and Norway, vaccination against SARS-CoV-2 during pregnancy was not associated with an increased risk of adverse pregnancy outcomes.  
<https://jamanetwork.com/journals/jama/fullarticle/2790608>

**title:** COVID-19 mRNA Vaccines During Pregnancy: New Evidence to Help Address Vaccine Hesitancy [editorial]

JAMA| 24th march 2022

In this issue of JAMA, 2 population-based observational retrospective studies evaluating outcomes in more than 250 000 pregnancies from 3 countries together provide the strongest evidence to date regarding the safety of COVID-19 vaccines in pregnancy…  
<https://jamanetwork.com/journals/jama/fullarticle/2790610>

**title:** Safety and Efficacy of a Third Dose of BNT162b2 Covid-19 Vaccine

new england journal of medicine | 23rd march 2022  
  
Active immunization with the BNT162b2 vaccine (Pfizer–BioNTech) has been a critical mitigation tool against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection during the coronavirus disease 2019 (Covid-19) pandemic. In light of reports of waning protection occurring 6 months after the primary two-dose vaccine series, data are needed on the safety and efficacy of offering a third (booster) dose in persons 16 years of age or older.

Methods: In this ongoing, placebo-controlled, randomized, phase 3 trial, we assigned participants who had received two 30-μg doses of the BNT162b2 vaccine at least 6 months earlier to be injected with a third dose of the BNT162b2 vaccine or with placebo. We assessed vaccine safety and efficacy against Covid-19 starting 7 days after the third dose.

Results: A total of 5081 participants received a third BNT162b2 dose and 5044 received placebo. The median interval between dose 2 and dose 3 was 10.8 months in the vaccine group and 10.7 months in the placebo group; the median follow-up was 2.5 months. Local and systemic reactogenicity events from the third dose were generally of low grade. No new safety signals were identified, and no cases of myocarditis or pericarditis were reported. Among the participants without evidence of previous SARS-CoV-2 infection who could be evaluated, Covid-19 with onset at least 7 days after dose 3 was observed in 6 participants in the vaccine group and in 123 participants in the placebo group, which corresponded to a relative vaccine efficacy of 95.3% (95% confidence interval, 89.5 to 98.3).

Conclusions: A third dose of the BNT162b2 vaccine administered a median of 10.8 months after the second dose provided 95.3% efficacy against Covid-19 as compared with two doses of the BNT162b2 vaccine during a median follow-up of 2.5 months.  
<https://www.nejm.org/doi/full/10.1056/NEJMoa2200674?query=featured_coronavirus>

**title:** Neutralization Profile after Recovery from SARS-CoV-2 Omicron Infection [letter]

new england journal of medicine|23rd march 2022  
  
…Despite certain limitations of this study, including the small sample size and retrospective study design (Table S7), our data support the hypothesis that the omicron BA.1 variant is an extremely potent immune-escape variant that shows little cross-reactivity with the earlier variants. Therefore, unvaccinated persons who are infected with the omicron BA.1 variant only (without previous SARS-CoV-2 infection) might not be sufficiently protected against infection with a SARS-CoV-2 variant other than omicron BA.1; for full protection, vaccination is warranted.  
<https://www.nejm.org/doi/full/10.1056/NEJMc2201607?query=featured_coronavirus>

**title:** Reporting and data sharing level for COVID-19 vaccine trials: A cross-sectional study

the lancet ebiomedicine|24th march 2022  
  
Background: The results and data availability of vaccine trials directly affect the decisions of healthcare providers, the public, and policymakers as to whether the vaccine should be applied. However, the reporting and data sharing level of COVID-19 vaccine studies are not clear. Methods: A cross-sectional study was conducted. A systematic search up to 9 May 2021 in 12 databases and an updated search to 6 July 2021 were conducted in the Cochrane Living Systematic Review and Network Meta-Analysis database to identify COVID-19 vaccine trials. The basic characteristics of included trials were summarized. The reporting level was assessed according to the CONSORT checklist. The data sharing level was assessed by open science practices. Types of incomplete reporting including protocol deviation, lack of primary outcomes clarity, and the omission of harms were analyzed.

Findings: Finally, thirty-six COVID-19 vaccine articles reporting on 40 randomized controlled trials were included in this analysis. Based on the CONSORT checklist, the mean reporting score was 29.7 [95% confidence interval 28.7, 30.7]. Thirty-one articles (31/36, 86.1%) had data sharing statements, twenty-five articles (25/36, 69.4%) provided access to the source data. Twenty-seven articles (27/36, 75.0%) had protocol deviation, lack of primary outcomes clarity, or the omission of harms.

Interpretation: The reporting and data sharing level of COVID-19 vaccine trials were not optimal. We hope that the reporting and data sharing of future trials will be improved. We recommend establishing a comprehensive, accurate data sharing system for future vaccine trials.  
<https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(22)00146-3/fulltext>

**title:** Sputnik V protection from COVID-19 in people living with HIV under antiretroviral therapy

the lancet eclinical medicine| 23rd march 2022  
  
Background: HIV-infection is known to aggravate the course of many infectious diseases, including COVID-19. International guidance recommends vaccination of HIV+ individuals against SARS-CoV-2. There is a paucity of data on epidemiological efficacy assessment of COVID-19 vaccines among HIV+. This paper provides a preliminary assessment of Sputnik V vaccine effectiveness in HIV+ patients on antiretroviral therapy (ART). Methods: We performed a retrospective cohort study to assess the effectiveness of the standard Sputnik V vaccination regimen in 24,423 HIV+ Moscow residents during spring - summer 2021, that included dominance of delta variant, with estimation of hospitalization and severe illness rates in vaccinated and unvaccinated patients. Data were extracted from the Moscow anti-COVID-19 vaccination and COVID-19 incidence Registries.

Findings: The data obtained indicate that Sputnik V epidemiological efficiency in the entire cohort of HIV+ on ART was 76·33%; in HIV+ with CD4+ ≥ 350 cells/µl, vaccine efficiency was 79·42%, avoiding hospitalization in 90·12% cases and protecting from the development of moderate or severe disease in 97·06%. For delta variant in this group the efficiency was 65·35%, avoiding the need for hospitalization in 75·77% cases and protecting from the development of moderate or severe disease in 93·05% of patients. There was a trend, although not statistically significant, of declining vaccine efficiency in immune-compromised individuals (CD4+ < 350 cells/µl).   
  
Interpretation: The study suggested epidemiological efficiency of immunization with Sputnik V in HIV+ ART-treated patients for the original and delta SARS-CoV-2 variants.  
<https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(22)00090-6/fulltext>

**title:** Outdoor mass gathering events and SARS-CoV-2 infection in Catalonia (North-East Spain)

the lancet regional health| 22nd march 2022  
  
…In summary, Suñer et al.’s work showcased an intelligent use of health registry data to evaluate the relationship between mass gathering events and SARS-CoV-2 infection. Future research could build upon this study by employing electronic health records, insurance claims data, and geographic information systems to track the health impact of public gatherings. Such studies will expedite epidemiologic analyses, characterize the effectiveness of preventive measures implemented in each event, and provide real-time decision support regarding reopening in the era of novel variants.  
<https://www.thelancet.com/journals/lanepe/article/PIIS2666-7762(22)00043-6/fulltext>

**title:** Effectiveness of COVID-19 vaccines in older adults in Colombia: a retrospective, population-based study of the ESPERANZA cohort  
  
the lancet healthy longevity | 21st march 2022   
  
…All vaccines analysed in this study were effective at preventing hospitalisation and death from COVID-19 in fully vaccinated older adults, which is a promising result for the national vaccination programme against COVID-19 in Colombia and in countries where these biologics have been applied. Efforts should be improved to increase coverage among older adults. In addition, given that we observed that the effectiveness of vaccines declined with increasing age, a booster dose is also justified, which should be prioritised for older adults…  
<https://www.thelancet.com/journals/lanhl/article/PIIS2666-7568(22)00035-6/fulltext>

**title:** Assessing the effectiveness of COVID-19 vaccines in older people in Latin America

the lancet healthy longevity | 21st march 2022   
  
…International, national, and regional health authorities must keep working on population access to and education on basic hygiene and sanitation, as well as the safety, efficacy, and effectiveness of COVID-19 vaccines. Despite the overwhelming evidence for the effectiveness of vaccines, vaccination coverage is far from 100%, even in high-income countries. There is large room for improvement, in which public health scientists and practitioners could have a key role.

Evidence-based information is crucial for disseminating correct health messages to enhance public trust and interest to adhere to vaccine schedules and boosters especially in high-risk populations such as older people.

Only a global approach that secures access to vaccines for all who need them presents a meaningful pathway to an effective resolution of this catastrophe. The solutions have been developed in record time, with not only one, but multiple effective vaccines. These vaccines now need to be distributed to all that need them. Adequate distribution, education, and information are key factors and represent some of the essential learnings that have been extracted from the current crisis. These learnings need to be implemented to avert and better respond to future pandemics.  
<https://www.thelancet.com/journals/lanhl/article/PIIS2666-7568(22)00073-3/fulltext>

**title:** Estimated COVID-19 Cases and Hospitalizations Averted by Case Investigation and Contact Tracing in the US

jama network open | 25th march 2022  
  
Question What are the estimated numbers of COVID-19 cases and hospitalizations averted by case investigation and contact tracing (CICT) programs in the US?

Findings This decision analytical model study used CICT program data from 23 jurisdictions and estimated that CICT programs averted 1.11 to 1.36 million cases and 27 231 to 33 527 hospitalizations over 60 days during the 2020 to 2021 winter peak of the pandemic. The upper estimate assumes that all interviewed cases and monitored contacts complied with isolation and quarantine guidelines, whereas the lower estimate assumes that fractions of interviewed cases and monitored or notified contacts did so.

Meaning These findings suggest that CICT programs likely played a critical role in curtailing the pandemic.  
<https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2790518>

**workforce well-being**

**title:** Burnout: set up watchdog to protect NHS staff, says wellbeing champion

BMJ | 24th march 2022  
  
NHS leaders have expressed concern after the latest figures showed that staff absences in hospitals   
A regulator that sets standards on staff wellbeing and holds the NHS to account should be established to help protect doctors from burnout, a champion of physicians’ wellbeing has said. The proposal was one of several put forward by Clare Gerada, president of the Royal College of General Practitioners, who recently stepped down as medical director of the confidential mental health support service NHS Practitioner Health. She was speaking on 22 March to MPs on the House of Commons health and social care committee about how the covid-19 pandemic had increased the number of doctors struggling with mental health problems, particularly in general practice…  
<https://www.bmj.com/content/376/bmj.o780.full>

**title:** NHS Disabled Staff Experiences During Covid-19

NHS employers | 21st march 2022  
  
This report outlines the working experiences of NHS disabled staff during the first wave of the pandemic, access the key findings and recommendations.  
<https://kingsfund.blogs.com/health_management/2022/03/nhs-disabled-staff-experiences-during-covid-19.html>

**recovery:**

**title:** Covid-19: Public inquiry must include effects on children, say experts

BMJ | 24th march 2022   
  
A recent World Health Organization (WHO) report examines how 19 countries worked to mitigate   
The government’s upcoming covid-19 public inquiry must include the effect of the pandemic on children and young people, a group of leading doctors and scientists have said. The draft terms of reference for the inquiry were published on 15 March but made no specific mention of children or young people other than a single reference to “restrictions on attendance at places of education.” “There is no doubt that school closures and broader lockdowns harmed children,” said the letter to the Times signed by 50 people including Russell Viner, former president of the Royal College of Paediatrics and Child Health, and Andrew James, president of the Royal College of Psychiatrists. “Educational losses have been most marked in children from deprived families and in vulnerable children.”…  
<https://www.bmj.com/content/376/bmj.o777>

**title:** BMA expresses gratitude and grief for doctors who died from covid

BMJ| 23rd march 2022

Question How has the rate of potentially preventable hospitalizations (ambulatory care–sensitive   
Chaand Nagpaul (centre), BMA council chair, this week addressed the guests at a BMA memorial service for doctors who have lost their lives to covid-19. In recalling the past two turbulent years he said, “It is a cruel tragedy that, in saving the lives of tens of thousands of patients, so many doctors lost their own.”

The service on 16 March also saw the unveiling of the memorial sculpture (right) created by Richard Tannenbaum to “convey the sense of continuity of care that the NHS has provided . . . and that we the public are inextricably linked with those NHS workers who lost their lives in caring for us.” It stands in the courtyard of BMA House in central London…  
<https://www.bmj.com/content/376/bmj.o752>

**title:** Is the UK's covid inquiry at risk of forgetting about children and young people?

BMJ| 24th march 2022

Many countries are declaring an end to this phase of the covid-19 pandemic, yet the underlying   
Almost the only thing that people seem to agree on about the SARS-CoV-2 pandemic and its management is that we need to learn lessons for future crises. As such, in the UK, there are high expectations of the upcoming public inquiry, chaired by Heather Hallett. But did those drawing up the draft terms of reference, published recently, forget about children? Hallett has a golden opportunity to examine who in government was responsible for childrens’ rights and needs, and to consider how children and adolescents have been affected by our pandemic response.

The (albeit short) Terms of Reference do not include the words child, childhood, babies, toddlers, school, childcare, college, or for that matter, play, interaction, or socialisation.1 During periods of lockdown and restrictions over the past two years, children have had their opportunities to interact, socialise, and play with other children or people outside their household severely limited. The covid inquiry now needs to consider whether these responses were proportionate to the risk faced by children from SARS-CoV-2 or to a broader goal of protecting society…  
<https://www.bmj.com/content/376/bmj.o785>

**title:** David Oliver: Can the recovery plan for elective care in England deliver?

BMJ | 23rd march 2022

This report concludes that the pandemic has shown that our current understanding of resilience and   
Even before the covid-19 pandemic hit the UK in 2020, waiting lists for elective outpatient appointments, investigations, and procedures were growing. Covid has rapidly increased already long waiting times. Across the four UK nations we now face longer waits and more patients on lists than in decades, including more than six million in England.1 There’s also concern that millions of patients are potentially missing from lists, who would ordinarily have been booked in pre-pandemic times.

In response, NHS England, with a strong push for action from ministers, last month published the Delivery Plan for Tackling the Covid-19 Backlog of Elective Care.3 The plan is ambitious and rich in targets. Overall, it states the need for an increase in activity of 30% above pre-pandemic levels by 2024-25 to reduce waiting times. But how will this be achieved? A 30% rise is a steep increase, especially with a depleted and tired workforce. No sooner had the plan been published than the NHS started to see a resurgence in acute covid admissions after the government had lifted all protection measures.

The recovery plan aims to create dozens of diagnostic and surgical hubs, physically separate from main hospital sites that are susceptible to acute demand surges, to include and co-opt additional private sector capacity. An elephant in the room is that the UK, and England in particular, has among the lowest general hospital and intensive care bed capacity per head among developed countries, with hospitals routinely full.

The plan also calls for a redesign of outpatient care delivery and a move away from wasteful practices such as routine follow-ups in stable patients, cancellations, or “no shows,” as well as from low value physical appointments, where perhaps referral wasn’t required or where telephone or online advice would have been more efficient.

More emphasis is placed on patient involvement and self-direction, more direct access to clinical staff for direct consultation, more explicit prioritisation of cases, and greater use of digital technology such as booking apps. Some targeted funding streams have been set up to aid this improvement and innovation, although much of the money announced was already budgeted for.

The stumbling block with all of this is the “who?” We don’t yet have an NHS workforce plan. The health secretary has already made clear in a speech that any increase in clinical workforce numbers will need to come from existing funds.7 Huge vacancy numbers already exist across a range of clinical disciplines….  
<https://www.bmj.com/content/376/bmj.o724>

**title:** Virtual Wards And Covid-19: An Explainer

nuffield trust | 21st march 2022

'Virtual wards' have existed for a number of years, but Covid-19 has led to further research and pilot schemes exploring their use. How have they been used during the pandemic and what does the future hold? This explainer provides some answers.  
<https://kingsfund.blogs.com/health_management/2022/03/virtual-wards-and-covid-19-an-explainer.html>

**title:** Coronavirus Act 2020 Two Years On

House of Commons Public Administration and Constitutional Affairs Committee | 21st march 2022

Interventions intended to interrupt transmission of SARS-CoV-2 led to a striking fall in the incidence   
This report sets out concerns about Parliament’s lack of ability to scrutinise and amend emergency provisions in the Coronavirus Act over the last two years and draws out the lessons that can be learned in legislating for future emergencies.  
<https://kingsfund.blogs.com/health_management/2022/03/coronavirus-act-2020-two-years-on.html>

**title:** Government Preparedness For The Covid-19 Pandemic: Lessons For Government On Risk

House of Commons Public Accounts Committee | 23rd march 2022

This report concludes that the UK government was underprepared for a pandemic like Covid-19 and also failed to learn from both simulation exercises and actual incidents. It also expresses concerns about the government approach to risk management and says it must introduce robust central leadership, accountability and oversight for cross-cutting risks.  
<https://kingsfund.blogs.com/health_management/2022/03/government-preparedness-for-the-covid-19-pandemic-lessons-for-government-on-risk.html>

**title:** Investigation Into The Government’s Contracts With Randox Laboratories Ltd

National audit office | 25th march 2022

At the start of the Covid-19 pandemic, the government needed to act rapidly to create high-volume testing capacity in the UK. As part of these efforts, the government awarded contracts for testing services which included some to Randox Laboratories Ltd. Concerns have been raised in Parliament regarding the transparency and management of these contracts. The report concludes that government did not document key decisions adequately when awarding a contract.  
<https://kingsfund.blogs.com/health_management/2022/03/investigation-into-the-governments-contracts-with-randox-laboratories-ltd-1.html>

**HEALTH INEQUALITIES & public health**

**title:** Strengthening public mental health during and after the acute phase of the COVID-19 pandemic

the lancet |24th march 2022  
  
The evolving nature of the COVID-19 pandemic with its incumbent stresses and the emergence of highly transmissible SARS-CoV-2 variants continue to challenge human resilience worldwide. In March, 2022, WHO reiterated the substantial impact of the pandemic on mental health and wellbeing globally; in the first year of the pandemic, there was a 25% increase in anxiety and depression globally and young people are at increased risk of suicide and self-harm injuries. There are also uncertainties about the long-term prognosis of people who recovered from COVID-19 its long-term effects on the general population and the pressure of the pandemic on health-care systems in the future. Joint actions from governments, the global health community, social and private sectors, and key stakeholder groups are required to address the neuropsychiatric and long-term strength and asset-building needs associated with the pandemic…  
<https://www.thelancet.com/journals/lanpub/article/PIIS2468-2667(22)00042-1/fulltext>

**title:** It is not too late to achieve global covid-19 vaccine equity  
  
BMJ | 24th MARCH 2022  
  
Gavin Yamey and colleagues say that a new, urgent push for global vaccine equity could help avert suffering and deaths, protect economies, and prevent new virus variants

During the covid-19 pandemic, we have seen the best of international collective action and its limits. Global scientific cooperation drove the development of safe, highly effective covid-19 vaccines in under one year.1 Yet we have also witnessed global vaccine inequity in which low and middle income countries have “limited supply and limited vaccine brand options.” With the omicron wave dissipating, several well vaccinated high income nations with stockpiles of covid-19 vaccines are rushing to declare the pandemic over, reminding us of how things unfolded with tuberculosis, malaria, and HIV/AIDS in the past. But the pandemic is not over and 2.8 billion people remain completely unvaccinated. Now is the time to recommit to, and further invest in, equitable and effective country led vaccination campaigns. In this paper, we briefly examine how global vaccine inequity arose, lay out a renewed case for urgently ramping up our commitment to vaccine equity, and propose principles to ensure no one is left behind in the quest to vaccinate the world.  
<https://www.bmj.com/content/376/bmj-2022-070650>

**title:** Ending the covid-19 pandemic means helping countries to catch-up with vaccination, not giving up

BMJ | 24th march 2022  
  
Like covid-19, complacency can be contagious. Seth Berkley argues that during a pandemic complacency can be very dangerous.

The governments of predominantly wealthy nations with high vaccination coverage are beginning to relax their covid-19 restrictions and response with an almost audible sigh of relief as societies reopen and life appears to return to normal. However, relaxing restrictions now is without question a gamble and risks sending a message that the pandemic is over. There are 2.8 billion people around the world still unvaccinated, and there is a constant threat of new variants triggering fresh resurgences. We are still very much in a state of global crisis; this pandemic is likely far from over.

The gamble could pay off if global leaders don’t take their eye off the ball. Ending the covid-19 pandemic globally must continue to be a priority, alongside other pressing global crises, such as the looming global recession, the energy crisis and now the devastating conflict in Ukraine. If global leaders fail to finish the job they will reinforce the misleading message that covid-19 is no longer a threat to dozens of countries still struggling with low vaccination coverage. At a time when vaccine doses are finally beginning to flow freely to these countries, that could spell disaster…  
<https://www.bmj.com/content/376/bmj.o786>

**title:** Strategies to Promote Equity in COVID-19 Antiviral Treatment

JAMA health forum | 25th march 2022  
  
The SARS-CoV-2 pandemic has had a disproportionate effect on Black and Indigenous people, racial and ethnic minorities, and other historically marginalized groups.1 Two antiviral oral drugs, Paxlovid (Pfizer; nirmatrelvir copackaged with ritonavir) and molnupiravir have received emergency use authorization when taken within 5 days for symptomatic, high-risk COVID-19 infection. Paxlovid and molnupiravir reduce hospitalization by 89% and 31%, respectively.2 These drugs complement COVID-19 infusion therapeutics, eg, remdesivir and sotrovimab.2

To date, inequities have emerged in receipt of COVID-19 vaccines and monoclonal antibody (mAb) treatment.3,4 Prescription of oral antiviral drugs among primary care and other clinicians could improve access to marginalized populations by avoiding the logistic challenges associated with time-sensitive appointments at infusion centers. If equitably deployed, these new treatments could mitigate COVID-19–related inequities in hospitalizations and deaths in racial and ethnic minority communities.

Ethical principles (ie, maximize benefit, equal concern, and mitigate health inequities) and procedural fairness and transparency developed for allocation of COVID-19 vaccines are relevant to COVID-19 therapeutics.1 Operationalization of these principles involves unique challenges. These include fluctuations in patient demand based on COVID-19 surges and public awareness of therapeutic options, and time-sensitive COVID-19 testing and treatment windows, in addition to fluctuations in production and supply of therapeutics. Operationalization of these ethical principles is further hindered by current US Department of Health and Human Services (HHS) policy that allocates therapeutics to states based on population size rather than need,5 with states in turn establishing their distribution policies and public awareness campaigns.  
<https://jamanetwork.com/journals/jama-health-forum/fullarticle/2790540>

**title:** Challenges of the COVID-19 Pandemic Among Individuals With Autism Spectrum Disorder

jama psychiatry | 25th march 2022  
  
With the persistence of COVID-19 caused by the novel coronavirus SARS-CoV-2, researchers and clinicians worldwide have advanced in their efforts to identify vulnerable groups who are at risk of developing a severe course of illness. Nonetheless, knowledge regarding COVID-19 severe morbidity and mortality risk among individuals with autism spectrum disorder (ASD) has been relatively limited thus far. Early suggestions for routes to overcome the challenges faced by individuals with ASD have acknowledged several factors that may lead to increased risk of COVID-19 infection and hospitalization among these patients, highlighting the need to ensure they receive the same standard of care in light of potential health care barriers.1 In this Viewpoint, we aim to discuss whether progress has been made with regard to the evaluation of the potential risk of severe COVID-19 illness among individuals with ASD and to summarize current knowledge regarding the uptake of vaccinations as a proxy of standard of care in this vulnerable population…  
<https://jamanetwork.com/journals/jamapsychiatry/fullarticle/2790551>

**international perspectives**

**title:** The US shouldn't settle for its current number of covid deaths or vaccination rates

BMJ| 22nd march 2022  
  
The US is moving into a new phase of the covid-19 pandemic. Some are calling this the endemic phase but I would urge us to consider what this word means and if we are there yet. Endemic does not mean that a disease has reached a mild level of infectiousness, harmless symptoms, or even low numbers of new cases. Endemic infections are those that are at predictable levels or expected prevalence.1 And, while not formally in the definition of endemic, it commonly includes the concept that we accept the level of infection, and any ensuing harms, as tolerable.

As we monitor the spread of the omicron subvariant BA.2 in the US, the number of people in hospital with covid-19 has dropped to below 30 0002 and daily cases are continuing to decline.3 Still, our more than 969 000 deaths3 from covid-19 in the US should make us all pause and consider how well this country has responded to this pandemic and how we should measure success.  
<https://www.bmj.com/content/376/bmj.o763>

**title:** Vaccination against all odds in Brazil

the lancet child & adolescent hEALTH | 21ST march 2022  
  
In a country internationally praised for its effective immunisation logistics, Brazil is lagging when it comes to vaccinating its younger population against COVID-19. A shortage of doses, the proliferation of fake news, the surge of the Omicron variant, and the lack of a strong vaccination campaign by the federal Government have slowed down the pace of vaccination of 5–11 year olds. But despite the obstacles, parents are still lining up to vaccinate their children, say experts.

According to Renato Kfouri, immunologist and director of the Brazilian Society of Immunization, “many regions of the country suffered with a lack of vaccines [for children] during the first 2 weeks of the campaign [Jan 15–30, 2021]. Many children have not been vaccinated not because they reject the vaccine, but rather because they haven't had the chance to get the vaccine”. Kfouri told The Lancet Child & Adolescent Health that São Paulo, which primarily uses CoronaVac (produced by Brazil's Butantan Institute), was able to vaccinate almost 60% of those aged 5–11 years, but places like Rio de Janeiro, which rely on Pfizer, have had to halt vaccination at least twice…  
<https://www.thelancet.com/journals/lanchi/article/PIIS2352-4642(22)00094-3/fulltext>

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