this week

COVID-19 INQUIRY page 45 • **THIRD WAVE** page 46 • **SEWELL RACE REPORT** page 48

JIM VARNEY/SPL

Colleges issue advice on vaccine symptoms

Three royal colleges have produced guidance for doctors seeing patients who have concerns about symptoms after receiving the Oxford-AstraZeneca vaccine.

The Royal College of Emergency Medicine, the Society for Acute Medicine, and the Royal College of Physicians say anyone who presents with symptoms suggestive of covid-19 vaccine induced thrombosis and thrombocytopenia (VITT) should have a full blood count to check platelet levels. Symptoms of concern include persistent or severe headaches, seizures or focal neurology; shortness of breath, persistent chest or abdominal pain; and swelling, redness, pallor, or cold lower limbs.

The guidance says VITT is unlikely if the platelet count is more than 150×10^9/L. But if it is below this level then a clotting and d-dimer test should be requested and VITT suspected if fibrinogen is low (d-dimer >2000). Patients with suspected VITT and headache symptoms should have cerebral venous imaging.

The British Society for Haematology said anyone with suspected VITT should be given intravenous immunoglobulin immediately and anticoagulation with non-heparin based treatments but that platelet transfusions should be avoided.

"This is an immune condition and there is no evidence that people with a prior history of thrombosis or known risk factors are more at risk. For most people, the risk of recurrent thrombosis from covid-19 infection is greater than the risk of this syndrome," it said.

The advice came after the *HSJ* reported that clinicians had concerns over a surge in anxious patients attending emergency departments. Investigations by EU and UK regulators into reports of unusual blood clots after receiving the vaccine concluded they were a "possible" and "extremely rare" side effect. Neither agency established a causal relation. However, the Joint Committee on Vaccination and Immunisation decided healthy adults under 30 should be offered an alternative where possible.

Katherine Henderson, RCEM president, said, "I saw 21 patients with concerns in an eight hour shift. It was important for us to have a strategy for managing those patients that didn't mean they were getting over-investigated but were getting reassurance. We also need to be aware that if somebody has significant symptoms it is always possible, given the rarity of VITT, that it is something else," she said.

Abi Rimmer, *The BMJ*

Cite this as: *BMJ* 2021;373:n960

Cerebral venous imaging is advised for patients whose blood tests point to suspected VITT and who have severe or persistent headache

LATEST ONLINE

- Radiologist who secretly filmed women in toilets on mobile phone is struck off
- Biden outlines plans to reduce US gun violence
- Chinese vaccines may need changes to improve their efficacy, says official

SEVEN DAYS IN

EMA launches investigation into four reports of blood clots after Janssen vaccine

The European Medicines Agency is investigating four cases of unusual blood clots with low platelets in people who have received the Janssen (Johnson & Johnson) covid vaccine. The news came as the CDC and FDA recommended use of the vaccine be paused in the US after six reports of a "rare and severe" type of blood clot among more than 6.8 million doses.

The EMA and the UK Medicines and Healthcare Products Regulatory Agency have investigated similar cases in people who had received the Oxford-AstraZeneca vaccine. No link has been found between this vaccine and blood clots, with the EMA concluding they were a "possible" side effect but "extremely rare." The EMA and MHRA said no restrictions were needed and that its benefits outweighed the risks. Like the AstraZeneca vaccine, Janssen's uses a viral vector platform.

The EMA's Pharmacovigilance Risk Assessment Committee said, "These reports point to a 'safety signal,' but it is not clear whether there is a causal association between vaccination with [Janssen's vaccine] and these conditions."

The EMA said it would decide whether regulatory action was needed once evaluation had concluded but said this "usually consists of an update to the product information."

Elisabeth Mahase, *The BMJ* Cite this as: *BMJ* 2021;373:n961

Covid-19

Incidence in England fell by 60% in two months

The rate of new SARS-CoV-2 infections in England fell by about 60% from February to March but has now levelled off, shows the 10th round of the React 1 study. The estimated R number is now 1, and infections are resulting in fewer admissions and deaths. Primary school children had the highest rate of infections at 0.41%, while over 65s had the lowest at 0.09%. Paul Elliott, director of React 1, said, "We need to continue to approach the situation with caution and keep sticking to the rules."

Neurological or psychiatric diagnoses are common

A third of people who have had covid-19 then have a neurological or psychiatric condition diagnosed within six months of infection—the first such diagnosis in 13% of patients—a study of 236 379 US patient records has found. Prevalence increased with severity of covid-19, with nearly half (46%) of people admitted to intensive care having a neurological or psychiatric condition diagnosed within six months (a first diagnosis for 26%), rising to 62% in patients who had had delirium (encephalopathy) during their covid-19 illness, the team reported in *Lancet Psychiatry*.

Italy's healthcare workers must have vaccine

Italy became Europe's first country to make vaccination against covid-19 mandatory for healthcare workers, as its government approved an emergency decree on 1 April to contain a third wave of the disease. Health professionals who refuse to have the vaccine will have the option to be transferred to duties that do not risk spreading the virus or to be suspended without pay for as much as a year. Italy has had over 3.5 million cases of covid-19 and 108 839 deaths (3%).

Bringing ethical thinking to pandemic policy making

The UK Pandemic Ethics Accelerator (ukpandemicethics.org), a collaboration between four universities and the Nuffield Council on Bioethics, was launched to bring ethical thinking to pandemic policy making. Principal investigator Ilina Singh (right), from Oxford University, said, "The pandemic has raised enormous challenges that require both world leading science and world leading ethics to address, to ensure public trust and accountability." The accelerator has engaged with the Cabinet Office's consultation on vaccine certification and will publish regular rapid reviews and other outputs.

Tracing is enhanced in south London

NHS Test and Trace is providing extra testing and genomic sequencing in parts of south London, predominantly in the boroughs of Wandsworth and Lambeth, where 44 confirmed and 30 probable cases of the variant first identified in South Africa have been found. All people with identified cases are isolating or have completed their isolation, and their contacts have been traced and asked to isolate. Everybody aged 11 years or over who lives or works in or travels through these boroughs is being advised to have a PCR test, whether or not they show symptoms.

Foreign workers

Some visas to be extended another year

A further 14 000 healthcare workers and their dependants whose visas were due to expire before 1 October are to have them extended for free for a year, the Home Office has said. The extension will include the Immigration Health Surcharge. NHS and private healthcare staff who need to renew their visas have to complete an online form, and their employers will be asked to confirm their eligibility.

Body image

Stop using BMI as measure of health, say MPs

MPs on the Women and Equalities Committee have called on the government to order a review of its obesity strategy after criticising its approach to eating disorders and poor body image as "potentially harmful" for the people it is meant to help. They also said that BMI, introduced to measure whole populations, should not be used to determine whether someone's weight is healthy. Calorie content on menus should also be scrapped, they said, and the use of altered images in advertising should be more strictly controlled.

MEDICINE

Lateral flow tests

Rapid testing rolled out to everyone in England

Free lateral flow tests are now available online for everyone to use at home, or to access through their workplace, or from their local authority or pharmacies, said the government, "to help prevent outbreaks and reclaim a more normal way of life." Ministers said more than 120 000 positive cases of covid-19 that would not have been found otherwise had been identified since the rollout. But critics described the approach as costly and unevaluated, warning that it may provide false reassurance.

Ministers say that freely available lateral flow tests will help prevent outbreaks of covid-19

Maternity services

Ten mental health hubs to open within months

Around 6000 women a year in England will gain access to 26 new hubs that will provide care and treatment for a range of mental health problems related to pregnancy and birth, such as post-traumatic stress disorder, severe fear of giving birth, and bereavement. The clinics, which were promised as part of the NHS long term plan, will also provide training to maternity services staff. Ten hubs will open within months, with all 26 operational by April 2021.

Regulation

Trust faces criminal charges over sepsis deaths

The Care Quality Commission is bringing a criminal prosecution against Dudley Group NHS Trust, in which two patients died after alleged exposure to "significant risk of avoidable harm." The charges relate to care given to a mother of six, Natalie Billingham, 33, and 14 year old Kaysie-Jane Robinson, who both died of sepsis. Lawyers for the trust appeared before Dudley magistrates on 7 April for a brief initial hearing. The trust has to enter pleas at a hearing on 2 July.

Call for end to GMC's power to appeal tribunal

Thirteen healthcare organisations are calling on the government to act to remove the GMC's power to appeal against decisions by medical practitioner tribunals. The government agreed in 2018 that the power, which duplicates similar powers held by the Professional Standards Authority, should be scrapped and is consulting on legislation to abolish it. But healthcare bodies have told Matt Hancock, health secretary for England, that the move is urgent and should be made now, by including it in the health and social care bill.

Liverpool University

Staff vote for strike action over job cuts

The University and College Union said that 84% of its members from the University of Liverpool who voted in a ballot over job cuts supported strike action and 90% backed action short of a strike. The university's restructuring plans could axe 47 jobs in its Faculty of Health and Life Sciences. The union is in dispute with the university over the metrics being used to select candidates for redundancy.

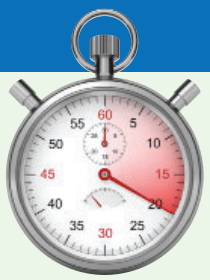
Cite this as: *BMJ* 2021;373:n951

ELECTIVE CARE

Four million fewer people completed elective treatment in 2020 compared with 2019, down from 16 million to 12 million *[The Health Foundation]*

CORRECTION

In the 3-10 April issue of *The BMJ* (page 3) we mistakenly used an image of a vial of GnRH stimulant instead of a GnRH analogue to illustrate an item in Seven Days in Medicine on the use of puberty blockers for gender dysphoria



SIXTY SECONDS ON . . . COVID INQUIRY

SURELY IT'S NOT THE RIGHT TIME?

That's what Boris Johnson said last July when he committed to an independent inquiry. It would be "an irresponsible diversion" during the pandemic, he recently reiterated.

BUT THE PUBLIC WANTS ANSWERS

So polling suggests, but formal inquiries take years. Calls for a quick review, from medical journals, the BMA, royal colleges, and bereaved families, have gone unheeded.

WHAT ABOUT LEARNING LESSONS NOW?

Quite. The informal People's Covid Inquiry, convened by the Keep Our NHS Public campaign, is filling the gap, receiving testimony from experts, key workers, and the public at fortnightly hearings. A panellist, Neena Modi, professor of neonatal medicine, told *The BMJ*, "If ever there was a time to ask questions, it has got to be now."

IS THIS JUST ABOUT BLAME, THOUGH?

No. Michael Mansfield, the inquiry's chair and a human rights barrister, told *The BMJ* the "focus is the present predicament" and "the rebuild of public health." The inquiry aims to publish recommendations, establish accountability, and bring justice. "We endeavour to ask the questions everyone wants answers to," he said.

ABOUT PPE SUPPLY, FOR INSTANCE?

"A complete dereliction of duty" is how palliative care consultant Rachel Clarke described failures to supply hospices, at the latest hearing. "We kept calling the allegedly 24 hour hotline, and there was no response."

DAMNING STUFF

That's not the half of it. Jacky Davis, panellist and consultant radiologist, said, "Tens of thousands of people died unnecessarily because of government mistakes."

WILL MINISTERS GIVE EVIDENCE?

Alas, the government hasn't replied to the inquiry's invitation, unlike *BMJ* columnist Helen Salisbury, health inequalities expert Michael Marmot, and former children's laureate Michael Rosen, to name a few.

CAN I WATCH AND CONTRIBUTE?

Yes. Submit questions and testimony at www.peoplescovidinquiry.com.

Richard Hurley, *The BMJ*

Cite this as: *BMJ* 2021;373:n952

Government faces legal action over rapid tests contract

The non-profit organisation the Good Law Project has been given the go ahead to mount a High Court challenge to the government's decision to award contracts to Abingdon Health to produce rapid antibody tests for covid-19.

The Department of Health and Social Care for England bought a million lateral flow test kits from the UK Rapid Testing Consortium, a group of manufacturers led by Abingdon Health and assembled by John Bell (below), regius professor of medicine at Oxford University and the government's life sciences adviser.

The contract, which was awarded without competitive tender, included a provision for the government to buy more kits if the test was approved for home use by the Medicines and Healthcare Products Regulatory Agency by a specified date. But the approval was not forthcoming, and England's health secretary, Matt Hancock, announced in January that the government was moving to a different procurement strategy.

A study by Public Health England, published in November in *The BMJ*, estimated that the accuracy of the AbC-19 rapid tests in real world conditions was less than had been thought and that around one in five key workers testing positive would be false positives.

Mrs Justice O'Farrell ruled on 3 March that the Good Law Project could challenge the decisions in awarding the contracts but on one ground only: that the award breached the government's equal treatment obligations. Now Mr Justice Waksman, after hearing both sides, has considerably widened the scope of the challenge. His decision means that the Good Law Project can argue that:

- there was apparent bias in the award, given that Bell was on "both sides of the contract" as government legal adviser and a major figure in the UK Rapid Testing Consortium
- the contract led to unlawful state aid, and
- the government acted irrationally when awarding the contracts.

In a statement the health department said, "Meeting the urgent challenges created by this global pandemic required the combined efforts and expertise of the public and private sector. We have been clear from the outset that public authorities must achieve value for taxpayers."

Clare Dyer, *The BMJ* Cite this as: *BMJ* 2021;373:n965

Warning of summer rise in covid infections and deaths

The later stages of the government's roadmap out of lockdown are "highly likely" to cause a surge of covid-19 infections, hospital admissions, and deaths this summer, indicates modelling by three groups of scientists considered by the Scientific Advisory Group for Emergencies (SAGE).

SPI-M-O, SAGE's Scientific Pandemic Influenza Group on Modelling (Operational) subgroup, reviewed modelling from Imperial College London, the University of Warwick, and the London School of Hygiene and Tropical Medicine. It concluded that any resurgence in hospital admissions and deaths after reopening non-essential retail, hairdressers, gyms, and outdoor hospitality from 12 April was "highly unlikely to put unsustainable pressure on the NHS."

But the return of indoor socialising, the reopening of indoor hospitality, including cinemas, theatres, and concert halls (stage 3), from 17 May, and the removal of remaining social distancing rules with full unlocking (stage 4) from 21 June were "highly likely" to lead to a further resurgence in admissions and deaths, says the SPI-M-O paper. The scale, shape, and timing of that potential third wave were "highly uncertain," it added.

"Growing exponentially"

The predictions emerged as WHO warned that the global pandemic was still "growing exponentially," with an average of more than 4.4 million new cases of covid-19 every week over the past two months.

Despite a 9% rise in cases and 5% in deaths last week, however, more countries were easing their

Budesonide cuts recovery time in patients not in hospital, study finds

Inhaled budesonide can shorten the time it takes for people not admitted to hospital to recover from covid-19 by three days, a trial in people over 50 at greater risk of covid-19 and people aged over 65 has found.

As part of the Principle trial, 961 people were randomly assigned to receive inhaled budesonide at home and were compared with 1819 patients randomly assigned to the usual standard of NHS care alone.

The interim analysis involved 751 people in the budesonide group (800 µg twice a day for 14 days) and 1028 in the usual care group who were SARS-CoV-2 positive. It found the median time to self-reported recovery for people taking budesonide was 3.011 days shorter than with usual care (95% Bayesian credible interval 1.134 to 5.410 days), with a high probability (0.999) of being superior to usual care.

Around a third (32%) of people taking budesonide recovered in the first 14 days after randomisation and remained well until 28 days, compared with 22% in the usual care group.

The researchers reported that, of those who had completed all 28 days of study, 8.5% in the budesonide group and 10.3% in the usual care group were admitted to hospital with covid-19.

Since fewer people than expected were admitted to hospital in the trial, however, and because covid cases and admissions were dropping, the researchers said it was not clear whether budesonide reduced admissions.

The government said budesonide was "not currently being recommended as standard of care but can be considered (off-label) on a case-by-case basis for symptomatic covid-19 positive patients aged 65 and over, or aged 50 or over with comorbidities."

Elisabeth Mahase, *The BMJ*
Cite this as: *BMJ* 2021;373:n957

restrictions, which could prolong the crisis. WHO emphasised that social distancing, mask wearing, and hand hygiene were still essential to control the spread of the virus.

In the modelling study of the UK situation, the third wave is expected to be smaller than the second wave seen in January, with a peak occurring in summer or autumn. But the most pessimistic scenarios, modelled by scientists at the London School of Hygiene and Tropical Medicine, predict admissions and deaths at a similar scale to January.

Vaccine efficacy

LSHTM's scientists assumed higher virus transmission after all restrictions are lifted and used lower but plausible vaccine efficacy. They assumed the AstraZeneca vaccine would reduce transmission by only 31%, while the teams at Imperial College London and the University of Warwick based their calculations on 50-75% reduced transmission.

Warwick's modelling suggested that most deaths and hospital admissions in a post-roadmap third wave would involve people who had received two vaccine doses, even without vaccine protection waning or a new variant that escapes vaccines. High levels of uptake in the age groups most at risk would mean that immunisation failures accounted for more serious illness than in unvaccinated people, the team said.

The models assume that the effectiveness of vaccines remains high and immunity does not wane, and they do not consider the effect of new variants of concern, against which existing vaccines may be less effective.

The R rate in England is currently estimated to be 0.8-1.0, up from 0.6-0.8 before schools reopened. It is too early for the estimated R rate to fully reflect the impact of schools reopening or lockdown easing at the end of March, says SPI-M-O, which is not confident that R now remains below 1 in any NHS England region.

As lockdown measures are eased further under the roadmap, the R rate is expected to rise substantially, and scientists at Imperial College say it could exceed 4 when restrictions are fully lifted at the end of June.

As there is considerable uncertainty about the level of control that can be achieved at each step of the roadmap, SPI-M-O says it remains critically important to evaluate the effect of each step before taking the next.

KEVIN J FROST / ALAMY

WHO warned that despite rises of 9% in cases and 5% in deaths last week, more countries were easing their restrictions, which could prolong the crisis

Ingrid Torjesen, London

Cite this as: *BMJ* 2021;373:n923

"Vaccine passports" must not add to workload, says RCGP

Any introduction of covid status certification or "vaccine passports" must have zero impact on GPs' workload, the Royal College of General Practitioners has said.

In evidence given to the government about a possible covid status certification scheme, the college expressed concern that involving GPs would intensify workload pressures.

Status certification

The government called for evidence on covid status certification as part of its review into whether a scheme might be used to reopen businesses and reduce social restrictions.

Certification would use testing and vaccination data to confirm people had "a lower chance of transmitting covid-19 to others." It would be available to vaccinated and unvaccinated people who have been tested.

Alternative solutions for people not digitally enabled, and for those requiring proof of exemption, must also be developed
Royal College of GPs

The government said that certification could be used in settings such as theatres and nightclubs, and mass gatherings such as festivals and sports events, to help manage risks where large numbers of people are brought together. People would be certificated if they had either an up-to-date vaccine status; a negative lateral flow or PCR test, taken at a test site on the day of their admission to a venue or the day before; or proof of natural immunity to covid-19.

The RCGP said that while it had no objections in principle to a vaccine certificate or "passport," the process must not add to GPs' workload so they can focus fully on patient care.

In a statement the college said, "We understand that initial planning for certification aims to use the NHS Digital data processing services dataset, which is positive in terms of having no impact on primary care IT. However, alternative solutions for those not digitally enabled, and for those requiring proof of exemption, must also be developed to ensure there is no addition to GP workload."

The college added that, because general practice was often patients' first point of contact, easy alternative routes must be in place for the certification process, such as a national helpline. It believed that certification should primarily be used to enable safe international travel, because its use in the UK could create inequalities among certain patient groups where vaccine uptake was lower.

Pilot scheme

Pilots of the certification scheme will be run across a range of events, including the World Snooker Championship at the Crucible Theatre in Sheffield and the Circus nightclub in Liverpool, with the aim of admitting a maximum crowd of 20 000 to Wembley Stadium for the FA Cup final on 15 May. A second phase of pilot schemes will take place from the end of May.

Abi Rimmer, *The BMJ*

Cite this as: *BMJ* 2021;373:n919

NEWS ANALYSIS

What did the Sewell race commission say on health?

The government commissioned review that found "no evidence of systemic or institutional racism" in the UK has been heavily criticised. **Gareth Iacobucci** examines what it contained on health and ethnicity

In its much criticised report, the Commission on Race and Ethnic Disparities included a detailed chapter on health disparities. The commission, chaired by Tony Sewell, said that obtaining consistent ethnicity data across health conditions was challenging but that it had based its findings on the available evidence.

What do the data on life expectancy show?

The report concluded that ethnic minority groups have better outcomes than the white population. It cited data from Scotland showing that life expectancy is generally higher in the larger ethnic minority populations than in the white Scottish group, particularly among people in Indian, Pakistani, and Chinese ethnic groups, and despite higher levels of deprivation.

England's life expectancy data are not published, but the report noted that in 2019 age standardised mortality rates were 26% lower in black and South Asian people than in white people, despite higher deprivation.

What did the report say about disparities in covid-19?

The commission highlighted reports from the government's race disparity unit, which concluded that most of the increased risk of infection and death from covid-19 among people from ethnic minorities was explained by socioeconomic factors and that inequalities in outcomes "are driven by risk of infection, as opposed to ethnicity alone being a risk factor."

Shockingly high covid mortality rates can be attributed to living conditions that are the result of longstanding inequalities and structural racism
Michael Marmot

But writing in the *Guardian* Michael Marmot, global expert on inequalities, argued this ignored the role racism plays, as highlighted in his 2020 report. He said the "shockingly high" covid-19 death rates among black, Bangladeshi, Pakistani, and Indian people in Britain "can be attributed to living in deprived areas, crowded housing, and being more exposed to the virus at work and at home," and that "these conditions are themselves the result of longstanding inequalities."

AMER GHAZZAL/SHUTTERSTOCK

What else did it say on socioeconomic disparities?

The commission noted that Marmot's landmark 2010 review on health inequalities found variations by ethnicity but "did not answer why the social determinants of health are unequally distributed between different racial and ethnic groups."

The commission added, "Some ethnic minority groups have higher life expectancies and lower risks of many cancers than the white majority population, despite higher levels of deprivation. These factors are complex, but this is no way an overall negative picture for ethnic minority groups."

However, Marmot said his work had been quoted selectively, with no "explicit reference to race/inequality in two reports from our institute last year." He said that in 2010 he had thought that most ethnic differences in health could be explained by socioeconomic characteristics, but he changed his view after chairing the Commission of the Pan American Health Organization on Equity and Health Inequalities in the Americas. "It highlighted the effects of colonialism and structural racism, and emphasised the overwhelming need to deal with such racism in combating the social determinants of health inequalities," said Marmot.

Mala Rao, director of Imperial College London's Ethnicity and Health Unit and adviser to NHS England's Workforce Race Equality Strategy, said the "denial of structural and institutional racism as an explanatory driver of health and socioeconomic inequalities is deeply troubling."

Were specific diseases examined?

Yes. The commission reported that white people had the highest incidence of all cancers but that incidence and survival rates varied between different ethnic groups. Limited data on survival show that, among ethnic minority groups (not including white minorities), survival is generally better or the same for lung, prostate, and colorectal cancers, with mixed evidence for breast cancer.

Pakistani women and Bangladeshi men have the highest risks of cardiovascular disease (CVD) incidence; CVD prevalence and incidence are lower in black African and black Caribbean ethnic groups, while men and women from the Chinese ethnic group have lower CVD incidence than white people, it said.

Rates of ischaemic heart disease, hypertension, and diabetes are higher in the South Asian population, and the black population had more hypertension and diabetes but lower ischaemic heart disease than the white group. Black people have a 1.5-2.5 times greater risk of having a stroke than white people, and the risk is also 1.5 times greater in South Asian people, particularly those from Pakistani and Bangladeshi ethic groups, than in white people.

People from the Chinese ethnic group have a lower risk of stroke than white people. Prevalence of type 2 diabetes (when diagnosed biochemically) is three to six times higher in South Asian and black ethnic groups than in white people.

What did it say about obesity?

In England, when compared

with white people, black adults have a consistently higher risk of obesity; adults and children from the Chinese ethnic group have a consistently lower risk; and no consistent patterns were seen in South Asian adults or children, relative to white people.

And lifestyle factors?

In 2019 the prevalence of smoking among adults in England was 13.9%, but white and mixed ethnicity adults were above this average, and Asian, black, and Chinese adults were below it. White British men and women are the most likely to drink alcohol at hazardous, harmful, or dependent levels, while Asian men and women are the least likely. White adults are most likely to be active, while people of Asian ethnicity are least likely.

Were genetics and ethnic disparities examined?

The report acknowledges "clear ethnic differences in risk" for diseases such as cancer, diabetes, and obesity, but it concludes that genetics make only a "modest" contribution, aside from some exceptions such as the higher incidence of prostate cancer in black populations.

What about mental health?

The commission recognised advice from experts that "mental ill health has little to do with genetic predisposition but rather is to do with adverse social circumstances, including racism and hardship." It cited the finding in Simon Wessely's 2018 mental health review that black people were eight times more likely to be subjected to community treatment orders than white people and were four times more likely to be detained. But it added, "Such disparity is often taken as evidence of racism. However, it must be benchmarked against disparity in the prevalence of mental illness," citing evidence showing significantly higher risks of diagnosed schizophrenia among ethnic minorities.

Marmot said, "It is surprising that the authors are so ready to dismiss structural racism when they quote, 'experts advise us that mental ill health has little to do with genetic predisposition but rather is to do with adverse social circumstances, including racism and hardship.' The debate is more than semantic."

The Royal College of Psychiatrists was also critical.

Are barriers to accessing healthcare mentioned?

The commission noted that majorities of all ethnic groups reported positive experiences of access. It observed a relative lack of satisfaction with GP services among British Asian people but added, "The overall picture suggests racism and discrimination are not widespread, as black groups are more or less equal in their satisfaction to white groups."

It also highlighted evidence that black and Asian people with mental health needs were less likely to be receiving treatment, but it "does not believe that the evidence it reviewed offers support to claims of discrimination within psychiatry."

What about the huge disparity in maternal mortality?

The commission emphasised that maternal deaths were rare in the UK, but it noted that poor outcomes were higher in mothers and babies from black and Asian ethnic groups.

It advised that more research should be "one of the highest priorities" for the new Office for Health Disparities.

Do we need a new Office for Health Disparities?

The report argues the office's remit should be to "properly target health disparities in the UK, focusing on research, communications and expertise," working across government. Its brief will be broader than that of the NHS Race and Health Observatory, established last year.

Were there any other recommendations?

The report noted staff's "lack of trust" in the ability of Care Quality Commission inspections to understand and consider race disparities. It recommended a review of the CQC's approach to scoring employee diversity and inclusion. It also recommended a review of the causes of disparate pay in NHS England and how to tackle them.

Gareth Iacobucci, *The BMJ*

Cite this as: *BMJ* 2021;373:n943

Concern over chronic primary pain guidance

Doctors in pain management have raised concerns about NICE's guidance on treating chronic primary pain, which they said does not reflect clinical practice or current evidence.

Patients could be left in "despair," said the British Pain Society, because of the recommendation that the only drugs doctors should prescribe are certain antidepressants. Commonly prescribed drugs, including paracetamol, NSAIDS, benzodiazepines, and opioids, should not be used, said NICE, and instead patients should be offered exercise programmes, therapy, and acupuncture. The society, an alliance of more than 1200 clinicians, emphasised that the "blanket and inexpert withdrawal of medication in such a vulnerable group of patients could easily lead to despair and unintended harm."

John Hughes, dean of the Royal College of Anaesthetists' Faculty of Pain Medicine, warned the guidance risked the decommissioning of specialist services, which, once gone, "we will never get back."

The NICE guideline committee said it had dealt with all issues raised during the consultation and that explanations were set out in guideline documents.

Zosia Kmietowicz, *The BMJ*

Cite this as: *BMJ* 2021;373:n942

"Doctors should register financial interests"

EXCLUSIVE Nearly 90% of doctors' organisations agree the UK should have a mandatory and public register of doctors' interests, a survey by *The BMJ* has found.

Last year the Independent Medicines and Medical Devices Safety Review, chaired by Julia Cumberlege (left), called for the GMC to expand its register to include a list of financial and non-pecuniary interests for all doctors. One of the key conclusions of the review, which investigated harmful side effects caused by the pregnancy test Primodos, the anti-epileptic drug sodium valproate, and surgical mesh, was that patients had a right to know if their doctor had financial or other links with pharmaceutical or medical device companies.

The BMJ wrote to six faculties, 14 royal medical colleges, and the Academy of Medical Royal Colleges about such a register. It received a 71% response rate. Of the responses, 13 (87%) agreed there should be a mandatory and public register of doctors' interests. The Faculty of Intensive Care Medicine agreed but only if substantial investments were declared and the cost was not passed to members.

Abi Rimmer, *The BMJ*

Cite this as: *BMJ* 2021;373:n933

THE BIG PICTURE

Wall of hearts memorial plea

Bereaved families are asking the prime minister to allow the National Covid Memorial Wall, opposite the Houses of Parliament in London, to remain as a national commemoration after more than 1000 people have painted 150 000 hearts to represent the UK's pandemic death toll.

Covid-19 Bereaved Families for Justice, which coordinated the memorial's creation, is inviting people to walk the 500 m wall and reflect on the nation's loss. Members of the public can also add a dedication to a lost loved one by writing a name into a heart.

More hearts will be added as the death toll grows, said Matt Fowler, cofounder of the group. "Memorials begin when they're completed. So this isn't an end, it's a beginning," he added.

Alison Shepherd, *The BMJ*

Cite this as: *BMJ* 2021;373:n947

WILL ROSE

EDITORIAL

Covid-19 has redefined airborne transmission

Improving indoor ventilation and air quality will help us all to stay safe

Over a year into the covid-19 pandemic, we are still debating the role and importance of aerosol transmission for SARS-CoV-2, which receives only a cursory mention in some infection control guidelines.[1 2]

The confusion has emanated from traditional terminology introduced during the last century. This created poorly defined divisions between "droplet," "airborne," and "droplet nuclei" transmission, leading to misunderstandings over the physical behaviour of these particles.[3] Essentially, if you can inhale particles—regardless of their size or name—you are breathing in aerosols. Although this can happen at long range, it is more likely when close to someone, as the aerosols between two people are much more concentrated at short range, rather like being close to someone who is smoking.[4]

Particles laden with virus

People infected with SARS-CoV-2 produce many small respiratory particles laden with virus as they exhale. Some of these will be inhaled almost immediately by those within a typical conversational "short range" distance (<1 m), while the remainder disperse over longer distances to be inhaled by others further away (>2 m). Traditionalists will refer to the larger short range particles as droplets and the smaller long range particles as droplet nuclei, but they are all aerosols because they can be inhaled directly from the air.[5]

Why does it matter? For current infection control purposes, most of the time it doesn't. Wearing masks, keeping your distance, and reducing indoor occupancy all impede the usual routes of transmission, whether through direct contact with surfaces or droplets, or from inhaling aerosols. One crucial difference, however, is the need for added emphasis on ventilation because the tiniest suspended particles can remain airborne for hours, and these constitute an important route of transmission.

SARS-CoV-2 transmits mostly between people at close range through inhalation

If we accept that someone in an indoor environment can inhale enough virus to cause infection when more than 2 m away from the original source—even after the original source has left—then air replacement or air cleaning mechanisms become much more important.[6 7] This means opening windows or installing or upgrading heating, ventilation, and air conditioning systems, as outlined in a recent WHO document.[8] People are much more likely to become infected in a room with windows that can't be opened or lacking any ventilation system.

Masks usually impede large droplets from landing on covered areas of the face, and most are at least partially effective against inhalation of aerosols. However, both high filtration efficiency and a good fit are needed to enhance protection against aerosols because tiny airborne particles can find their way around any gaps between mask and face.[9 10]

If the virus is transmitted only through larger particles (droplets) that fall to the ground within a metre or so after exhalation, then mask fit would be less of a concern. As it is, healthcare workers wearing surgical masks have become infected without being involved in aerosol generating procedures.[11-13] As airborne spread of SARS-CoV-2 is fully recognised, our understanding of activities that generate aerosols will require further definition. Aerosol scientists have shown that even talking and breathing are aerosol generating procedures.[14-16]

It is now clear that SARS-CoV-2 transmits mostly between people at close range through inhalation. This does not mean that transmission through contact with surfaces or that the longer range airborne route does not occur, but these routes of transmission are less important during brief everyday interactions over the usual 1 m conversational distance. In close range situations, people are much more likely to be exposed to the virus by inhaling it than by having it fly through the air in large droplets to land on their eyes, nostrils, or lips.[17]

Better ventilation

Improved indoor air quality through better ventilation will bring other benefits, including reduced sick leave for other respiratory viruses and even environmentally related complaints such as allergies and sick building syndrome.[21 22] Less absenteeism—with its adverse effect on productivity—could save companies significant costs,[23] which would offset the expense of upgrading their ventilation systems. Newer systems, including air cleaning and filtration technologies, are becoming ever more efficient.[24]

Covid-19 may well become seasonal, and we will have to live with it as we do with influenza.[25] Improving indoor ventilation and air quality, particularly in healthcare, work, and educational environments, will help all of us to stay safe, now and in the future.

Julian W Tang, consultant, University of Leicester
julian.tang@uhl-tr.nhs.uk
Linsey C Marr, professor, Civil and Environmental Engineering, Virginia Tech, US
Yuguo Li, professor, University of Hong Kong
Stephanie J Dancer, consultant, Edinburgh Napier University and NHS Lanarkshire, Edinburgh

Cite this as: *BMJ* 2021;373:n913
Find the full version with references at http://dx.doi.org/10.1136/bmj.n913

EDITORIAL

Covid-19 passport has many challenges

Governments should proceed with great caution through this minefield

With millions of people receiving covid-19 vaccines globally, some countries have already started planning the implementation of "vaccine passports"—accessible certificates confirming covid-19 vaccination linked to the identity of the holder. The purpose of vaccine passports, governments argue, is to allow people to travel, attend large gatherings, access public venues, and return to work without compromising personal safety and public health.[1] There remain, however, considerable practical and ethical challenges to their implementation.

Vaccine passports are not only permissible under international health regulations, they already exist. They incentivise vaccination,[3] an international public good with many positive benefits[4] including individual and population immunity.

Least infringement

The public health principle of least infringement states that to achieve a public health goal, policy makers should implement the option that least impairs individual liberties.[5] While lockdowns may be required, the continued restriction of the civil liberties of those who are immune and pose minimal risk of spreading infection may be unethical, as lack of freedom of movement is one of the most common adverse impacts of the pandemic on people's lives.[3 6] Additionally, vaccine passports could help prevent other health and socioeconomic harms caused by lockdowns, thereby accruing individual and collective health, economic, and social benefits.

The AstraZeneca vaccine may reduce transmission by up to 67% while the Pfizer BioNTech vaccine is 85% effective in preventing asymptomatic and symptomatic infections after the second dose,[7 8] generating indirect benefits that extend to unvaccinated individuals through a reduction of SARS-CoV-2 circulation. Given that there are currently more than 200 vaccine trials under way, however, establishing the characteristics of each vaccine for the purpose of passport renewal would be challenging.

The practical and ethical challenges to the implementation of vaccine passports are considerable

Vaccine passports need to be internationally standardised and must have verifiable credentials that safeguard against problems such as forgery and loss of privacy. WHO does not currently endorse covid-19 vaccine or immunity passports because of these concerns.[9] It has, however, initiated a Smart Vaccination Certificate Working Group to establish key specifications and standards for effective and interoperable digital solutions for covid-19 vaccination.

Ethical concerns remain about the societal divide that these passports could cause. The Nuffield Council on Bioethics states that such passports could enable coercive and stigmatising workplaces, thereby compounding current structural disadvantages.[10] Vaccine passports must be available and accessible to all to prevent exacerbating existing societal inequalities and worsening the health divide. Vaccines are scarce and access remains unequal, both globally and within countries. Covid-19 vaccines are also contraindicated in some people with serious health conditions and allergies.[11] People facing vaccination access problems will be unable to obtain vaccine passports. Pregnant women are at an increased risk of severe covid-19 illness[12]; however, as clinical trials did not include pregnant women, the uncertain risk of vaccination during pregnancy may also lead to understandable hesitancy in this group. Ethnic minorities are also more likely to be vaccine hesitant.[13]

Moral failure

With most vaccine doses delivered in high income countries, WHO warned that the world is on the brink of a catastrophic moral failure.[14] Nearly 25% of the world's population may not have access to a vaccine until at least 2022.[15] This will widen the global north-south divide and create a situation where people from high income countries are able to travel, but not those from low income countries.

As vaccine passports would probably be digital and require access to private medical records, there are important questions around internet access, costs of acquiring and maintaining the passports, privacy, and data protection that must be tackled. Many consider adequate internet access a fundamental human right[16]; as large numbers of people do not have smartphones or stable internet connections, their exclusion breaches their rights to equality, particularly for those in low and middle income countries. Whether it is legal for workplaces, airlines, and entertainment venues to access vaccination data remains controversial, as this can perpetuate a form of elitism.[17] Furthermore, ensuring patient sensitive data are not used for other purposes is essential.

If they are to be rolled out, the benefits of vaccine passports should not be dispersed unequally, and societies globally must strive to ensure that they are available to all.

Tasnime Osama, honorary clinical research fellow in primary care and public health, Imperial College London tasnime.osama15@imperial.ac.uk

Mohammad S Razai, academic clinical fellow in primary care, St George's University of London

Azeem Majeed, professor of primary care and public health, Imperial College London

Cite this as: *BMJ* 2021;373:n861

Find the full version with references at http://dx.doi.org/10.1136/bmj.n861

DATA BRIEFING

UK deaths in 2020: how do they compare with previous years?

John Appleby turns to historical records for a long view of deaths last year

The pandemic caused huge loss of life last year. The attribution of deaths to covid-19 will have changed within countries over the course of the pandemic, partly as a result of changes in testing and under-recording of covid-19 as a cause early on in the pandemic[1]; there is also variation between countries because of differences in the practice of recording deaths.

Globally, an estimated 1.83 million people died from confirmed covid-19 in 2020.[2] In England and Wales, the number of deaths with covid-19 mentioned on the death certificate in 2020 was 80 830[3]—an average of 221 a day.[3]

How does 2020 compare with previous years? Provisional figures from the Office for National Statistics (ONS) show 608 002 registered deaths in England and Wales in 2020.[4] This was the second highest number of deaths in a year since 1838. The most deaths in the past 183 years occurred in 1918—a year also notable for a pandemic (fig 1).

These figures exclude deaths not registered in England and Wales, which means the huge loss of military lives in the two world wars (about 888 000 over the four years of the first world war and 384 000 over the six years of the second world war[5]) are largely excluded.

Since 1838 the population of England and Wales has grown nearly fourfold, from 15.2 million to 59.8 million. We would expect more deaths in a larger population. But even taking into account population changes, deaths per 100 000 population were higher in 2020 than in any year since 2003 (fig 2). Comparing year-on-year changes in crude death rate shows just how out of line 2020 is with historical trends. On this measure 2020 had the fifth highest increase (13.8%) historically (fig 3).

The number of deaths with covid-19 mentioned on the death certificate was 80 830—an average of 221 a day

But it's not just the size of the population that has increased over the years. The proportion of older people has also grown. And as with a larger population we would expect the number of deaths to increase as the population ages. The ONS provides age standardised mortality rates per 100 000 back to 1942, which take account of changes in the age structure of the population.

These show huge improvements in death rates since the second world war, with age standardised mortality rates more than halving between 1942 and 2019 (fig 4). But last year bucked the almost straight downward trend to record the highest death rate since 2008 and the highest year-on-year increase since 1943 (fig 5).

While covid-19 vaccines, improved treatment, and immunity by infection have started to reduce deaths this year, the pandemic is by no means over. Globally, covid-19 deaths in 2021 up to 24 February were 2.8 million, over 50% more than in the whole of 2020.[2] And in just the first 10 weeks of this year (to the week ending 12 March), covid-19 deaths had increased by 67% over last year's total, to 134 597 in England and Wales.[3 6]

John Appleby, director of research and chief economist, Nuffield Trust, London
john.appleby@nuffieldtrust.org.uk
Cite this as: *BMJ* 2021;373:n896


In 2020 England and Wales recorded the second highest number of deaths in a year since 1838

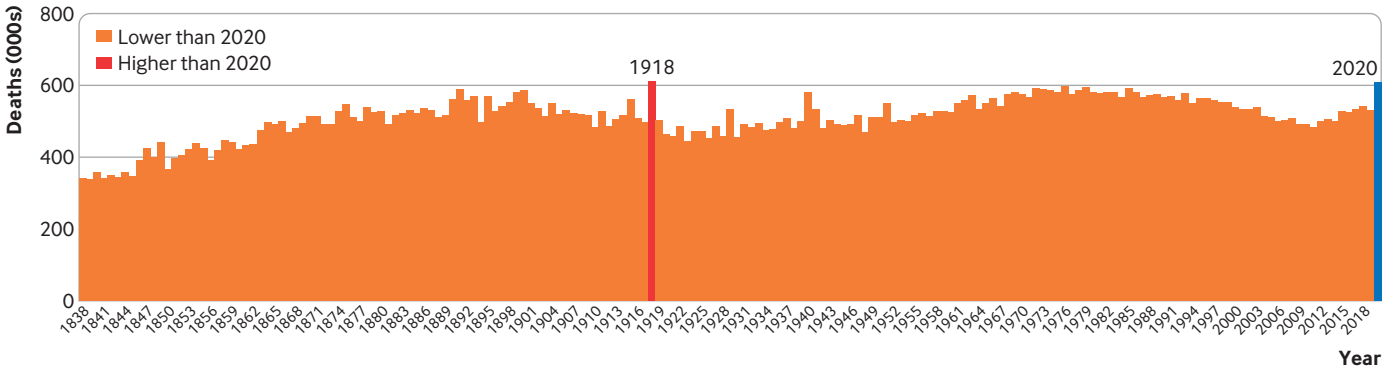


Fig 1 | Total deaths in England and Wales, 1838-2020[4]

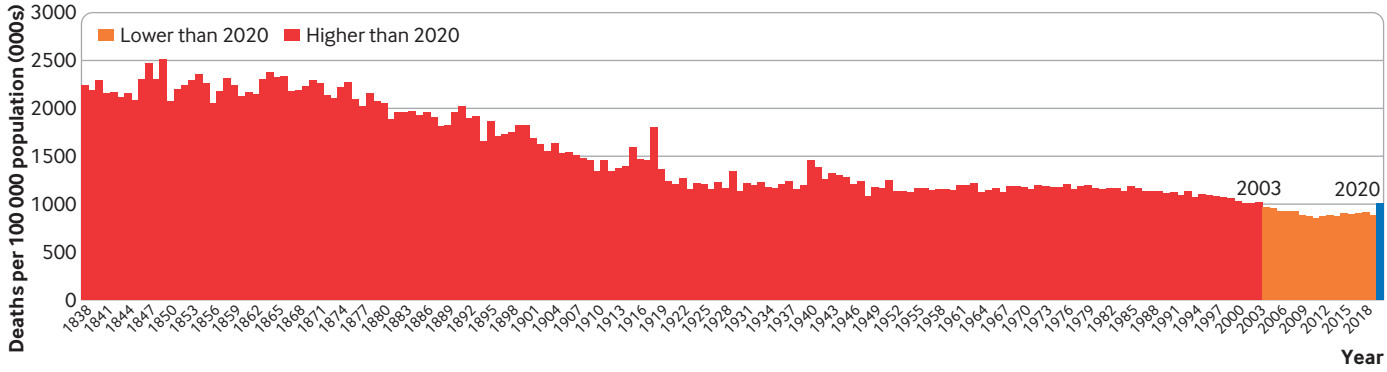


Fig 2 | Deaths per 100 000 population in England and Wales, 1838-2020[4]

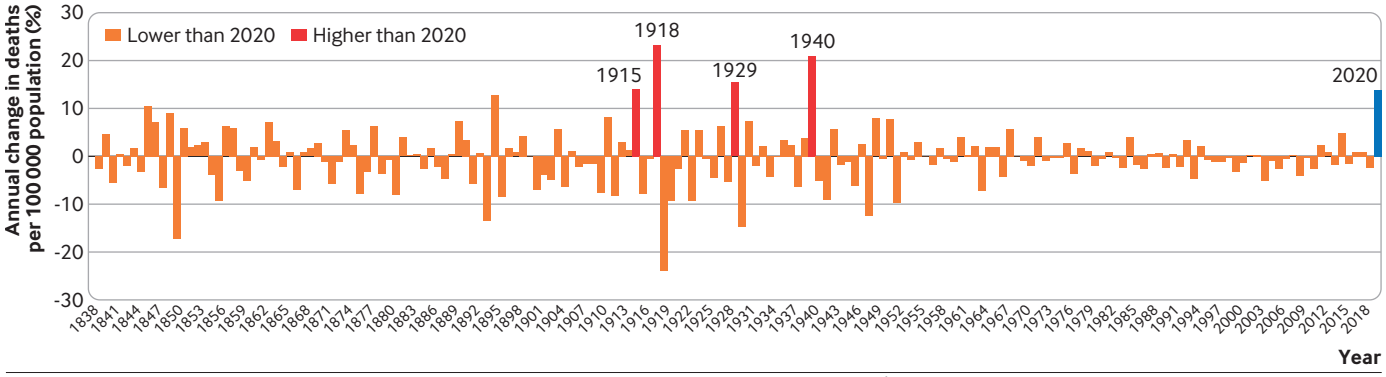


Fig 3 | Year-on-year percentage changes in deaths per 100 000 population, England and Wales 1839-2020[4]

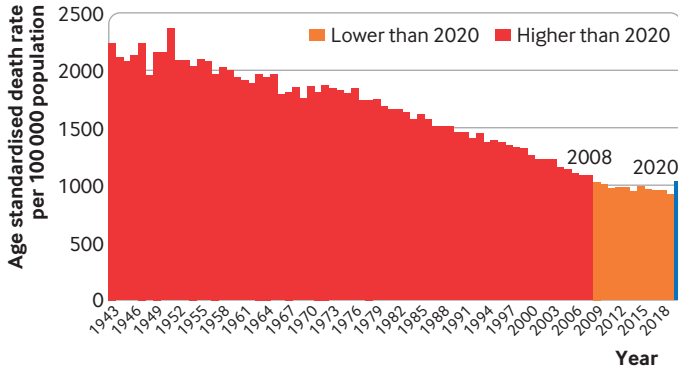


Fig 4 | Age standardised mortality rates per 100 000 in England and Wales, 1942-2020[4]

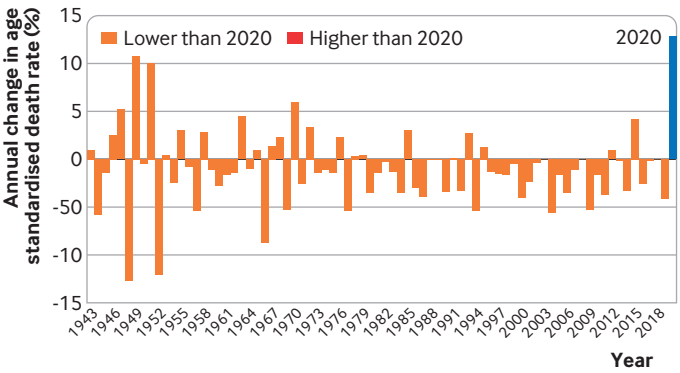


Fig 5 | Percentage year-on-year changes in age standardised mortality rates per 100 000 in England and Wales, 1943-2020[4]

COVID-19

How AstraZeneca lost the vaccine PR war

The negative headlines show no signs of abating for the pharma giant. **Jacqui Wise** reports on how miscommunication and politics created a nightmare for the firm and the world's vaccination effort

Hailed as a "vaccine for the world" with its low price and easy storage requirements, AstraZeneca's vaccine candidate has faced a string of setbacks this year with questions over effectiveness, possible side effects, and long running disputes about supplies.

It's not clear why the Anglo-Swedish company and its vaccine have been singled out for so much criticism, but poor communication seems to be at the heart of the problem. Martin McKee, professor of European public health at the London School of Hygiene & Tropical Medicine, said, "This is a company that has taken an innovative product to market in record time but has mishandled communications at every step. Trust and confidence are so important for vaccines—you can't divorce the two."

Blood clots

AstraZeneca's latest crisis is possibly also its biggest so far. Its vaccine has been linked to thrombosis, as well as a rare type of blood clot in the brain called cerebral venous sinus thrombosis (CVST), with a number of episodes in younger women.

The vaccine was authorised for use in Europe at the end of January and started to be used more widely in February. On 7 March Austrian authorities announced they were investigating a death that was possibly vaccine related. A few days later Denmark and Norway were investigating reports of blood clots and a death after vaccination. On 15 March Germany suspended its use of the vaccine, followed swiftly by several other countries.

The European Medicines Agency (EMA) and the World Health Organization say that the vaccine's benefits outweigh any risks: the EMA undertook an in-depth review of the issue and, while acknowledging a "possible" link to blood clots that should be listed as "very rare" side effects, on 7 April it confirmed that the "overall benefit-risk remains positive" for the vaccine's continued use. The cause of the clots is still unknown, with research ongoing.

In the UK, which has ordered 100 million doses of the vaccine, the Joint Committee on Vaccination and Immunisation (JCVI) advised on 7 April that people aged under 30 should be offered alternative vaccines where available—even though the Medicines and Healthcare Products Regulatory Agency (MHRA), which conducted the UK review of the evidence, emphasised that it was "not recommending new age restrictions in AstraZeneca vaccine use."

The MHRA said that, up to 31 March, 79 thrombosis events with low platelets had been reported from over 20 million doses of the vaccine administered. Among these reported cases, 19 people have died. The overall risk of these blood clots is about four people in every million who receive the vaccine.

At the time of writing, Australia, Belgium, and France have restricted the vaccine to people aged over 55, while Italy and Spain limited its use to over 60s after the EMA's announcement. Scandinavian countries had already paused their rollouts of the vaccine, while Canadian provinces had suspended its use in under 55s on 30 March. Several German states have also suspended its use in people under 60.

Ines Hassan, senior policy researcher with the Global Health Governance Programme at the University of Edinburgh, sees a positive in the way the issue is being investigated. She said, "The scrutiny from regulators and pharmacovigilance experts shows the system and safety monitoring procedures are working as they should."

What's not helpful is how it's been communicated. Whether from different regulators, government officials, academics, or the media, Hassan told *The BMJ*, "It is clear that the mixed messaging from these different stakeholders has caused confusion among the general public, and it has already led to increased vaccine hesitancy in some parts of Europe among other regions."

McKee said that, although the MHRA and the JCVI have different roles, it's "extremely regrettable" that one is advising

ASTRAZENECA'S SIX MONTH NIGHTMARE

2020

9 Sep Phase III trials are paused after a single event of unexplained illness

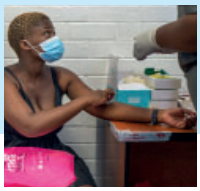
30 Dec Argentina and UK approve AstraZeneca vaccine for emergency use

2021

25 Jan German newspaper Handelsblatt claims that the vaccine has only 8% efficacy in elderly people

29 Jan European Medicines Agency (EMA) approves AstraZeneca vaccine. French president, Emmanuel Macron (above), claims that it is "quasi-ineffective" in people aged over 65

9 Feb South Africa halts rollout of AstraZeneca vaccine after study shows disappointing results against the 501 variant



7 March Austrian authorities announce investigation of a potentially vaccine related death

10 March EMA press release suggests no specific issue with batch used in Austria

15 March Germany suspends use of AstraZeneca vaccine, pending investigation of three deaths and four other incidents

18 March EMA said that benefits still outweigh risks

Trust and confidence are so important for vaccines—you can't divorce the two
Martin McKee, LSHTM

One big lesson is that transparency is essential, especially with regulators and the general public
Ines Hassan, University of Edinburgh

no age restrictions while the other proposes that people under 30 should be offered an alternative. Those aged from 30 to, for example, 50 will wonder why the UK guidance, even if contradictory, differs from that in other countries. He adds, " I have previously criticised messaging about the AstraZeneca vaccine. Sadly, it seems that we have learnt little."

In the US

Adding salt to the wound, AstraZeneca had simultaneously but separately faced criticism in the US. In a 22 March press release the company announced the long awaited results of a key US trial, one that it hoped would finally win emergency use approval for the vaccine from the US Food and Drug Administration. The FDA has been cautious around the AstraZeneca vaccine: it has yet to issue approval for its use despite approving vaccines from Pfizer, Moderna, and Johnson and Johnson (Janssen) and nearly four months since the UK approved it.

In the March announcement AstraZeneca said the results showed a 79% efficacy in preventing symptomatic disease. Hours later, however, the US National Institutes of Health (NIH) took the unusual step of issuing a midnight statement saying that its Data and Safety Monitoring Board had "expressed concern that AstraZeneca may have included outdated information from that trial, which may have provided an incomplete view of the efficacy data."

AstraZeneca said the agreed cut-off point for data was 17 February, as publicised in its initial release. In response to the NIH, within 48 hours it added more recent data and revised the efficacy down to 76%. The US chief medical adviser, Anthony Fauci, called this an "unforced error" on AstraZeneca's part. Speaking on *Good Morning America*, he said, "It was not necessary—if you look at it, the data really are quite good, but when they put it into the press release it wasn't completely accurate."

McKee said that it is "completely unprecedented that a data monitoring committee would say that what you said in a press release was not accurate. It's so basic that you don't issue contradictory information. What on earth was going on there that they didn't check?"

However, Peter English, a retired consultant in communicable disease control who is former editor of *Vaccines in Practice* magazine and immediate past chair of the BMA's Public Health Medicine Committee, has sympathy for the company. "It seems like it was an attack on the company and not founded on science," he said. "AstraZeneca had stated in advance in their protocol the time period, so [they] couldn't cherry pick the data. If they had done it other way round they would rightly have been criticised."

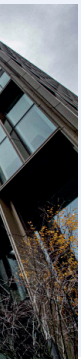
He told *The BMJ*, "It was incredibly irresponsible of the NIH [to issue that statement], as it implied there was something terrible going on—which we found out a few days later wasn't the case. It brought the vaccine into disrepute based on nothing. This harms confidence in all covid vaccines and in vaccines overall."

Early troubles

Part of the problem may be that AstraZeneca isn't a traditional vaccine manufacturer. McKee told *The BMJ*, "A number of commentators have raised questions about the experience of the board in communicating some of the challenging messages around vaccines."

Oxford University, which developed the vaccine, originally intended to partner with the US company Merck, but the UK government—which had invested £65.5m in the vaccine's development—insisted on a UK based company. (GlaxoSmithKline reportedly turned down a partnership, as it had its own candidates in development.)

Andrew Pollard, the Oxford vaccine group's chief scientist, was delighted that the Anglo-Swedish company agreed to undertake the drug's production at cost and at volume, making it "a vaccine for the world." But it seems that no good deed goes unpunished, and AstraZeneca's learning curve has been steep.



22 March
AstraZeneca announces US trial results claiming 79% efficacy

23 March
US National Institutes of Health's Data and Safety Monitoring Board expresses concern that AstraZeneca may have included outdated information from the trial. AstraZeneca issues new data and revises the figure to 76% on 25 March

30 March
Canada suspends use of AstraZeneca vaccine in under 55s

31 March
German states suspend use of AstraZeneca vaccine in under 60s

6 April
UK Medicines and Healthcare Products Regulatory Agency (MHRA) pauses a trial of the vaccine in children and teenagers pending investigation of the blood clot link. Marco Cavaleri (above), EMA head of vaccines, told an Italian newspaper that "it is clear there is a link with the vaccine [and blood clots] . . . but we still do not know what causes this reaction." EMA distances itself from the comments

7 April
EMA investigation concludes that "unusual blood clots with low blood platelets should be listed as very rare side effects" for the vaccine but that "overall benefits of the vaccine in preventing covid-19 outweigh the risks of side effects." MHRA advises that alternative vaccines should be offered to under 30s where available

MHRA
Regulating Medicines and Medical Devices

8 April
Australia, Belgium, France, and Italy announce restrictions on use of the vaccine

In September 2020, phase III clinical trials of the vaccine in Brazil, South Africa, the UK, and the US were temporarily paused because of unexplained neurological symptoms in one of the volunteers. After investigating the incident the MHRA gave the go-ahead to restart UK trials within days, but the FDA maintained the US suspension for six weeks, apparently unhappy that it hadn't been told of the problem quickly enough. This seems to have sparked the general caution in the FDA's approach to evaluation.

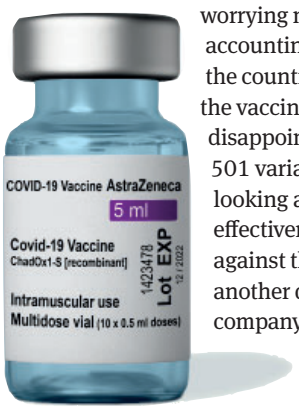
Then, on 23 November, AstraZeneca was criticised for the way it announced the vaccine's efficacy. It had combined the results of different trials and had, critics said, missed out key details. Rather than coming up with a single figure for efficacy like other vaccine manufacturers—Pfizer and Moderna had just a week earlier announced higher than expected efficacies of 91% and 95%, respectively—AstraZeneca announced an overall 62% efficacy and another of 90% in people who had originally received a half dose (this followed a dosing error in one arm of the phase III trial, which fortuitously led to better results). The higher number was later reinterpreted as due to a longer gap between doses.

Media reports criticised how AstraZeneca had communicated the information about its trials. "There have been contradictions between statements given to investors, press releases, and internal documents," said McKee. A scientific paper can't be sent out for peer review if it has market sensitive information such that a reviewer or editor could potentially exploit the market position. Preprint publications can face delays, which make it difficult to coordinate with market communications. McKee said that this may be why AstraZeneca relied on press releases—"but, that said, they should be consistent [with their information], and they haven't always been so."

Nevertheless, on 30 December the UK and Argentina became the first countries to approve the shot. The year ended with AstraZeneca marking its first vaccine success but with the shine somewhat taken off. And there was more to come.

Annus horribilis?

On 25 January the German newspaper *Handelsblatt* claimed the vaccine had only 8% efficacy in over 65s. The report turned out to be baseless—but not before damage had been done to public confidence in the vaccine across the continent.



The company has been caught up in geopolitics
Kate Bingham, UK Vaccine Taskforce

A few days later the EMA approved the vaccine for all age groups in the EU, but that same day the French president, Emmanuel Macron, claimed it was "quasi-ineffective" for over 65s. After Macron's comments Germany and France initially prevented the vaccine's use in over 65s. Confusion over which age groups should have the vaccine has contributed, unsurprisingly, to a lack of confidence. More than half of people surveyed in France, Germany, and Spain thought that the shot was unsafe in a YouGov poll published on 22 March.

The timing couldn't have been worse. It came just as AstraZeneca faced a political crisis with the EU around missing vaccine deliveries. The company had agreed to deliver as many as 120 million doses to the EU by the end of March, but yield problems and other issues prompted it to tell the EU that it could supply only 30 million doses (subsequently increased to 40 million). The EU, in the grip of a rising third wave of infections, did not take this well.

Although other vaccines have also had supply problems, AstraZeneca seems to have become a political football between the EU and the recently Brexit-ed UK. The European Commission's president, Ursula von der Leyen, threatened to block AstraZeneca from exporting doses of vaccine to the UK, and the Belgian MEP Philippe Lamberts accused the company of dishonesty and arrogance, saying that it had "over-promised and under-delivered." At the time of writing the dispute is ongoing, alongside the new blood clot issue.

To cap it all, AstraZeneca suffered another blow in February when South Africa—grappling with rising infections and a worrying new variant of the virus accounting for 90% of the cases in the country—halted the rollout of the vaccine after a study showed disappointing results against the 501 variant. With countries now looking at new variants and the effectiveness of existing vaccines against them, the decision was another disappointment for the company.

Kate Bingham, former head of the UK's Vaccine Taskforce, called AstraZeneca "heroes" for the way the company picked up the vaccine and worked out how to test, manufacture, and distribute it at low cost around the world. Speaking to the *Financial Times*, she said that the company had become caught up in geopolitics.

Hassan emphasised that AstraZeneca has not fallen short on meeting regulatory requirements: it submitted the necessary data as expected, including when it recently submitted interim analysis findings to the FDA.

However, communication about trial design early in development, and later about the number of patients with covid-19 symptoms from its primary analysis, could perhaps have been handled better, she said.

Tricky balance

"One big lesson is that transparency is essential, especially with regulators and the general public," said Hassan, while acknowledging that overcommunicating without causing unnecessary alarm is a tricky balance to strike. She adds that the responsibility to communicate safety issues is not the manufacturer's alone—it's the responsibility of regulators, policy makers, public health academics, and the media, among others.

Peter English questions why the one vaccine being sold at cost price is the one that's been the most vilified. "The amount of bad press they have got is not based on the science," he said. "It seems completely disproportionate or unfounded. It looks like a lot of them are attacks on AstraZeneca itself and seem to have an ulterior motive. It almost feels like there is a deliberate misinformation campaign."

But the consequences of AstraZeneca's problems go far beyond one company's reputation and profits. Its vaccine is an indispensable part of WHO's plan to roll out two billion doses to 92 nations by the end of the year, through the Covax initiative. The UK's order of 100 million doses places AstraZeneca at the heart of its vaccination programme.

And many commentators worry that crumbling confidence in the vaccine may spill over to others, as the world is already grappling with vaccine hesitancy as an obstacle to wider coverage and an end to the pandemic. As McKee said, "When you lose trust it's really difficult to regain it."

Jacqui Wise, freelance journalist, London
jacquiyoung1@gmail.com

Cite this as: *BMJ* 2021;373:n921