this week

VALPROATE p 128 **HEPATITIS IN CHILDREN** p 130 **MONOCLONAL ANTIBODIES** p 132

JACK TAYLOR/GETTY IMAGES

"Shocking" life expectancy fall in poor areas

Men born in the poorest areas of the country are now expected to live almost 10 years less (73.5 years in the period 2018 to 2020) than those in the richest areas (83.2 years), and women eight years less (78.3 *v* 86.3), a "statistically significant" decrease from the period 2015 to 2017, show latest data from the Office for National Statistics.

The figures also show that girls born in the poorest areas of England live 19 years less in good health than those born in the wealthiest areas. In 2018-20 healthy life expectancy at birth for girls and women was 51.9 years in the most deprived areas and 70.7 years in the least deprived areas. The figures for boys and men were 52.3 and 70.5 years, respectively.

Michael Marmot, director of the UCL Institute of Health Equity, described the figures as shocking, saying they showed a continuing trend of worsening health inequalities. "They are telling us a great deal about how well society is functioning. If health is getting worse, then society's needs are not being met," he told *The BMJ*.

In February the government published its white paper on levelling up, which reiterated the ambition to improve healthy life expectancy by five years by 2035, while closing the gap between rich and poor people. However, the Health Foundation calculated that on current trends it will take 192 years to reach this target.

David Finch, assistant director at the Health Foundation, said, "Reducing these stark inequalities requires a fundamental shift towards a whole-government approach that actively improves the conditions needed to create good health, such as adequate incomes to cope with the rising cost of living, secure jobs, and decent housing.

"The upcoming disparities white paper presents a clear opportunity to move beyond the rhetoric and into action."

The new figures include the pandemic's first year but don't show the full effect of covid deaths on inequalities, said the ONS.

Figures for Wales showed similar trends, with female life expectancy at birth in the most deprived areas falling "significantly" from 79.1 in 2015-17 to 78.4 in 2018-20, although the drop for boys and men, from 74.3 to 74.1, was not statistically significant. Males in the most deprived areas were expected to spend 54.2 years on average in good health, compared with 67.6 in the least deprived areas. For females the respective figures were 53.3 and 70.2 years.

Jacqui Wise, Kent

Cite this as: *BMJ* 2022;377:o1056

The gap between people born in areas such as Jaywick, Essex, one of the UK's most deprived towns, and more prosperous places is growing

LATEST ONLINE

- Ohio doctor is acquitted of murdering 14 intensive care patients with fentanyl overdoses
- Non-invasive prenatal screening tests may give false results, warns US regulator
- Mix-and-match booster vaccination approach offers best protection, study reports

SEVEN DAYS IN

Valproate continues to be prescribed in hundreds of pregnancies, data show

STEVE PARSONS/PA

Affected mothers campaigning against the continued use of valproate in pregnancy in 2011

The epilepsy drug sodium valproate was prescribed to 247 patients in England during their pregnancy from April 2018 to September 2021 despite well known risks of birth defects, figures show. However, the number of patients given valproate during pregnancy has fallen in the past few years, from 86 in the year to September 2019 to 65 in 2020 and to 46 in 2021.

NHS Digital data showed that 23 patients started on valproate during pregnancy in the past three years. The risk of neurodevelopmental disorders in babies when the drug is taken during pregnancy is estimated to be 30-40%, in addition to an 11% risk of a congenital abnormality.

The anticonvulsant has been on the UK market since 1973, although evidence linking it with fetal malformation emerged decades ago, and its association with developmental delay came to light in the early 2000s.

Last week the *Sunday Times* reported that some patients were being given the drug without safety information leaflets or clear warnings on the packaging.

Alison Cave, chief safety officer at MHRA, told *The BMJ*, "If there are examples where this information has not been provided we would investigate this. Our safety work on sodium valproate is ongoing, and we will continue to review, adapt, and implement regulatory measures where appropriate that will enable the continued safe use of this medicine in individuals who can get pregnant, where there are no other viable options available."

Elisabeth Mahase, *The BMJ* Cite this as: *BMJ* 2022;377:o1013

Parkinson's disease

Smartwatch helps assess patients' needs

Patients with Parkinson's disease in England are being given smartwatches containing sensors, known as a Parkinson's KinetiGraph, to allow doctors to remotely assess their movement at home and adjust their medicines or request interventions such as physiotherapy. The scheme, funded by the NHS Transformation Digital Health Partnership Award, could be rolled out to the 120 000 patients with Parkinson's in England. The project lead, Camille Carroll, an associate professor in neurology at Plymouth University, said the smartwatch could reassure patients by providing a six month review while freeing up clinical capacity.

GMC

Good Medical Practice is out for consultation

Doctors would have a new duty to act, or help others to act, if they observed workplace bullying, harassment, or discrimination, under proposals outlined in a draft update of Good Medical Practice. They would also be asked to adopt a zero tolerance approach to sexual harassment. The ethics guide, last updated in 2013, also includes a proposed new rule on using social media, setting a duty for doctors not to use them to mislead and requiring them to "make reasonable checks" to avoid doing so. Doctors have until 20 July to respond to the 12 week consultation.

Abortion

Doctors in Scotland call for action on protesters

More than 70 consultants from Glasgow's Queen Elizabeth Hospital wrote to Scotland's women's minister, Maree Todd (below), asking for protest-free buffer zones to be established outside Scottish hospitals to end "intimidation and harassment" by anti-abortion protesters. The request followed protests by around 100 supporters of a group called 40 Days for Life outside the hospital. The consultants want Scotland to follow Northern Ireland, which has recently introduced draft legislation to create safe zones around hospitals.

Workforce

Abuse of GPs must be "wake-up call"

A UK-wide survey of almost 2000 members of the medical defence organisation MDDUS found that three quarters of 668 GP respondents said they had faced a rise in verbal abuse or aggression from patients in 2021, leading to increased stress. Half of the GPs said they were considering retiring early or leaving the profession—citing workload, mental health and wellbeing, and staff shortages. Chris Kenny, chief executive of MDDUS, said, "These findings should be a wake-up call for policy makers up and down the UK. Their decision making must factor in the clear connection between adequate funding and support for primary care services and health professionals, and patient safety."

Ministers' pledges to be evaluated

The government's progress against its pledges on the health and social care workforce will be analysed by an expert panel set up by the Health and Social Care Committee. Jane Dacre, the panel chair, said, "We've identified a recurrent theme—whether in maternity, cancer, or mental health services, progress is dependent on having the right number of skilled staff in the right place at the right time. Shortages have a real impact on the delivery of services and undermine achievements." She said the panel would focus on workforce numbers, skill mix, and wellbeing.

All medical graduates get a foundation place

The UK Foundation Programme Office has confirmed that all 787 medical graduates who were placed on the reserve list for training have been allocated a place to start in August. Kayode Oki, deputy chair of the BMA's Medical Students Committee (Education), blamed the need for a reserve list on the long term failure to plan for the medical workforce. "We will continue to lobby the government to provide the funding for foundation places much earlier in the cycle," he said.

MEDICINE

HRT

Javid promises "tsar" to tackle supply issues

England's health secretary, Sajid Javid, said he would appoint an "HRT tsar" to deal with reported shortages of some hormone replacement therapy products. Caroline Nokes, a Tory MP who chairs the women and equalities committee, told the Commons last week that pharmacies in her constituency had run out of HRT. Javid told the *Mail on Sunday* the role would be modelled on that carried out by Kate Bingham, as head of the covid vaccine taskforce, and he would meet suppliers to look at the situation.

Savid Javid said he will act on reports of HRT shortages

Overseas news

"Horrifying" practices are found in Iranian prisons

The World Medical Association called for an independent investigation into reports of denial of healthcare in Iranian prisons, which it said amounted to torture. Its president, Heidi Stensmyren, said Amnesty International had had reports of sick prisoners being left to die in substandard prison clinics or in isolation, prisoners forced to take psychotropic drugs, electric shock use, and sexual assault. "We demand immediate access to adequate medical care in prisons, as well as an independent and transparent investigation into deaths in custody," she said.

UN condemns attacks in Central African Republic

From 1 January to 15 April the UN recorded 43 incidents affecting humanitarian organisations working in the Central African Republic, with 11 aid workers injured. More than half of the country's population of around five million people depend on humanitarian assistance. Denise Brown, UN coordinator in the country, said, "Every time humanitarians come under attack, the lives of thousands of vulnerable people are at risk."

Mental health

Pregnant patients miss out on support

From January to December 2021 just 40 411 new and expectant mothers in England had contact with perinatal mental health services, far short of the NHS target to treat at least 57 000 women this financial year, showed research by the Royal College of Psychiatrists. Perinatal services in England received 93 494 referrals for mental health assessments last year, said the college, which is calling for a covid-19 recovery plan for mental health, additional funding for services, and more psychiatric community facilities.

Eating disorder hospital in York is judged unsafe

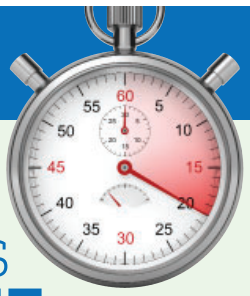
Schoen Clinic York, a specialist eating disorder hospital, was placed in special measures after a CQC inspection found that patients were "at risk of physical and psychological harm due to unsafe and unacceptable food provision." The hospital, run by Newbridge Care Systems, has been rated inadequate. It was found to have a "closed culture" that prevented staff from raising concerns without fear of reprisal.

Cite this as: *BMJ* 2022;377:o1048

FEMALE AUTHORS

It will take **725** years for the proportion of NEJM original articles with a female first author to reach **50%** if the current rate of increase (0.03%) continues

[Journal of Racial and Ethnic Health Disparities]



SIXTY SECONDS ON . . . SALT FIGHTING CHOPSTICKS

IS THIS A NEW SUPERHERO?

You could say that. In an attempt to reduce the amount of salt people put on their food, Japanese researchers have developed chopsticks that use electrical stimulation to trick the tastebuds into thinking that food is saltier than it is.

AN A-SALT ON THE SENSES?

So it seems. In a small study involving 36 people, researchers reported that the chopsticks enhanced the taste of salt approximately 1.5 times. In the trial, participants were given a 0.56% salt gel and a 0.8% salt gel to taste. Initially, they named the 0.8% gel as being saltier. After trying the 0.56% gel with the chopsticks, however, they reported it was saltier than the 0.8% gel.

COULD I USE A FORK?

The researchers certainly think so. They said that their invention could be used to adapt other everyday utensils.

WILL THIS CAUSE THE FOOD INDUSTRY TO GRIND TO A HALT?

Actually, the project is a collaboration between Miyashita Laboratory at Meiji University, Japan, and the food and beverage company Kirin, which has said it's committed to developing new ways to support disease prevention while also giving consumers tasty food. In Japan, the average daily salt intake is 10.9 g for men and 9.3 g for women, which is far higher than the less than 5 g per day recommended by the World Health Organization. Both WHO and the Japanese health ministry have set targets to reduce salt intake.

TAKE THE FINDINGS WITH A PINCH OF SALT?

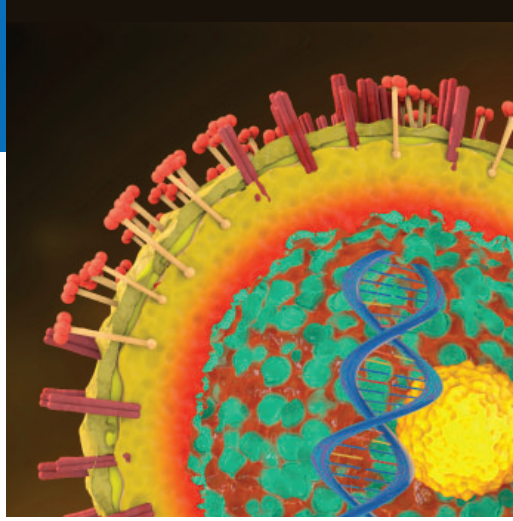
So far just one small trial has been performed, and the results have been provided only through a press release, so it doesn't look like you'll find these salt fighting chopsticks in shops any time soon. Miyashita Laboratory is probably worth keeping an eye on, however. In something straight out of Willy Wonka's factory, they've also developed a lickable TV screen that emulates the flavours of the food being shown.

Elisabeth Mahase, *The BMJ*

Cite this as: *BMJ* 2022;377:o1038

BRIEFING

What's behind the outbreaks of hepatitis in children?



More than 100 idiopathic cases have been reported around the world. **Elisabeth Mahase** looks at what we know so far

How many children have been affected?
The World Health Organization has so far reported 169 cases of acute hepatitis of unknown origin from 11 countries in Europe and the US, as of 21 April 2022.

In the UK, where the rise was first noted at the start of 2022, 114 cases have been confirmed, followed by 13 in Spain, 12 in Israel, nine in the US, six in Denmark, five in Ireland, four in the Netherlands and in Italy, two in Norway and in France, and one in Romania and in Belgium. Ages of the affected children range from 1 month to 16 years.

Japan's health ministry reported on 25 April its first possible case.

Is this higher than normal?
It seems to be. Will Irving, professor of virology at the University of Nottingham, told *The BMJ* that there had always been a background but low incidence of severe hepatitis in young children without a known cause but that now the numbers had risen five- to 10-fold. These cases are referred to as non-A-E hepatitis because, although the patients are known to have hepatitis, all the markers for the usual suspects—hepatitis A, B, C, and E—are negative.

Irving said, "Normally a paediatric haematologist in, say, Birmingham, at one of the big UK centres, might see one or two cases a month. For many years we've wondered whether there was another virus that's causing non-A-E hepatitis. There's always a background level there, but now Birmingham has seen 40 cases in three months."

How serious is the illness?
Most children seem to be recovering well. However, WHO has confirmed that at least one child has died, while 17 children (around 10% of the total known cases) have needed a liver transplant.

Simon Taylor-Robinson, consultant hepatologist at Imperial College London, said, "Treatment is usually supportive, with hydration and management of temperature, because the problem normally resolves. The liver has an amazing ability to regenerate itself after an insult. Generally, within a few days or weeks, things settle back down with this supportive treatment.

"If blood tests are significantly abnormal, treatment would be in a specialised hospital, as in rare cases the liver injury can require more specialised medical intervention."

Why is it happening?
While there is no certain cause, the current hypothesis relates to adenovirus type 41, because many of the children have tested positive for this virus. Adenovirus 41 is known to infect children and cause symptoms such as diarrhoea, vomiting, and fever, although it has not previously been linked to hepatitis.

In its latest report the UK Health Security Agency said it believed there was a "cofactor affecting young children which is rendering normal adenovirus infections more severe or causing them to trigger immunopathology." The report listed possible cofactors, including susceptibility arising from lack of prior exposure during the pandemic; a prior or coinfection with covid or another infection; or a toxin, drug, or environmental exposure.

The agency listed other possible causes that did not fit as well with the current evidence. These included a novel variant of adenovirus, with or without a contribution from a cofactor as listed above; a drug, toxin, or environmental exposure; a novel pathogen either acting alone or as a coinfection; or a new variant of SARS-CoV-2.

Zania Stamataki, associate professor in viral immunology at Birmingham University,

Some groups of terminally ill patients are twice as likely to die by suicide, data show

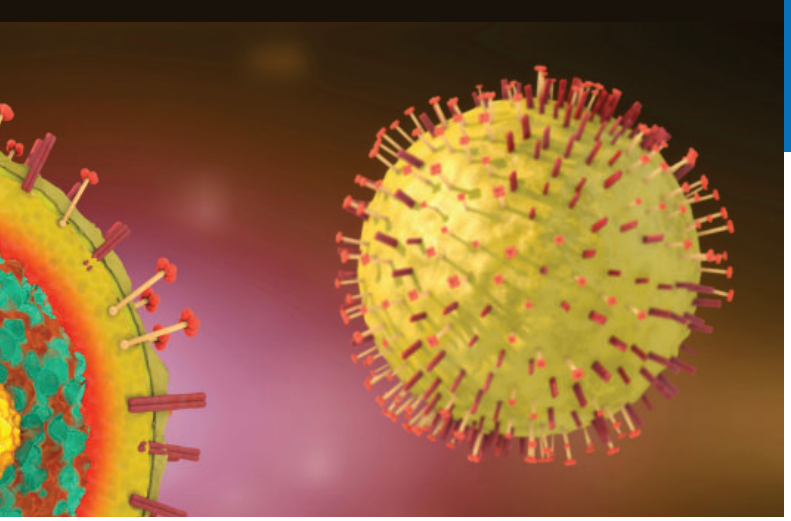
Patients with some serious health conditions are twice as likely as the general population to kill themselves, an analysis published by the Office for National Statistics shows.

The findings "illustrate the dangers of this country's ban on assisted dying and add to growing evidence that the laws that govern how we die in this country lack compassion and are in urgent need of reform," Jacky Davis, a consultant radiologist and chair of Healthcare Professionals for Assisted Dying, told *The BMJ*.

Gordon Macdonald, chief executive of Care Not Killing, a pressure group opposed to assisted suicide, said, "There is a clear link between a terminal diagnosis and treatable clinical depression. Much more work needs to be done to support dying and vulnerable people by providing them with universal access to treatment for physical and psychological needs."

Last April, Matt Hancock, then England's secretary of state for health, asked the ONS for data on suicide among terminally ill people to inform the debate on the UK ban on assisted dying.

The agency analysed hospital episode statistics for England between 1 January 2017 and 31 March 2020. Of 17 195 suicides, 455 (2.6%) involved patients with chronic obstructive pulmonary disease, 465 (2.7%) had chronic ischaemic heart conditions, and 58 (0.3%) had severe cancers (liver cell carcinoma; oesophagus; mesothelioma; and malignant neoplasm of bronchus and lung, pancreas, and meninges).



It is conceivable that whatever was causing the odd case before is now simply circulating more widely
Will Irving

said, "The rising incidence of children with sudden onset hepatitis is unusual and worrying. If an adenovirus is to blame, this could be a new variant that may cause liver injury in children with naive or immature immune systems. But we need to know more.

"Alternatively, if adenovirus is the culprit for hepatitis in children who are otherwise well, we ought to look for other infections and environmental causes that could exacerbate adenoviral inflammation."

Might the pandemic have played a role?

Irving said the pandemic could have had an effect, notably through the reduction in social mixing and virus spreading. "It is conceivable that whatever it was that was causing the odd case before is now, like all of the other viruses, simply circulating more widely because of the effects of lockdown and then the release from lockdown.

"That's an alternative hypothesis: that there's always been a non-native virus that we haven't yet identified and that it's simply circulating at greater levels than it used to," he told *The BMJ*.

Elisabeth Mahase, *The BMJ*
Cite this as: *BMJ* 2022;377:o1067

More needs to be done to support dying people
Gordon Macdonald

Suicide rates increased sharply after diagnosis of severe disease but the increase slowed over time. Among matched controls suicide rates increased steadily over time.

Dignity in Dying, which campaigns for the law to allow dying people to be prescribed life ending drugs on request, has estimated that there are 3000 to 6500 suicide attempts among terminally ill people each year. About 50 Britons a year travel to Switzerland for assisted suicide.

Sarah Wootton, its chief executive, said, "Those who block reform on assisted dying are defending a law that puts vulnerable people at risk and fails to provide adequate choice or protection—the very basics of good end-of-life care. The data must act as a clarion call for parliament to examine the full impact of the current law."

The BMJ supports legalisation of assisted dying.

Richard Hurley, *The BMJ*
Cite this as: *BMJ* 2022;377:o1014

NHS relaxes covid infection prevention and controls

The NHS has relaxed infection prevention and control (IPC) requirements for hospitals and general practices as it seeks to free up capacity to tackle the huge treatment backlog.

Revised guidance from NHS England and NHS Improvement published last week says providers will no longer have to adhere to routine physical distancing measures but should carry out risk assessments to determine when some precautions such as personal protective equipment are required in specific settings.

Isolation precautions for inpatients with covid are also being relaxed. Isolation periods can fall from 10 to 7 days if patients have two negative lateral flow tests 24 hours apart as well as showing clinical improvement, and inpatients who are contacts of cases no longer have to isolate if they are asymptomatic.

In a letter to service leaders, NHS England said the revised guidance "takes into account the UK Health Security Agency's latest assessment of the scientific evidence." Providers should plan to return "to pre-pandemic physical distancing in all areas, including in emergency departments and ambulances, as well as all primary care, inpatient, and outpatient settings," the letter said. They should also be "returning to pre-pandemic cleaning protocols outside of covid-19 areas, with enhanced cleaning only required in areas where patients with suspected or known infection are being managed," it added.

All patients, visitors, and staff "should continue to practise good hand and respiratory hygiene," including the use of face masks, and current triaging arrangements outlined in IPC guidance will still apply, it said.

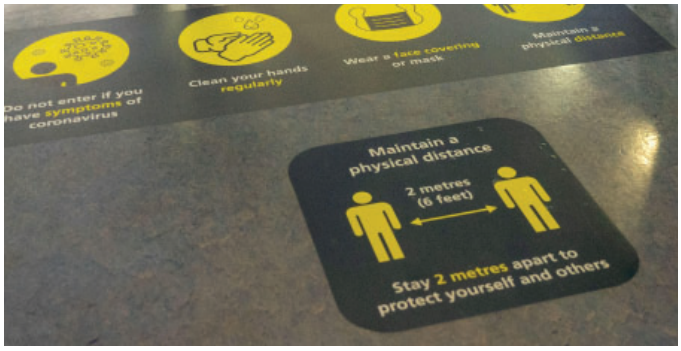
Free up capacity

Layla McCay, director of policy at the NHS Confederation, said the revisions would free up much needed capacity. "Health leaders have had to walk a tricky tightrope of following strict guidance that has kept transmission to a minimum while ensuring they stay on track to deliver ambitious targets to recover the elective backlog," she said. "On balance, they will welcome this update."

But Tom Lawton, a critical care consultant and member of the campaign group FreshAirNHS, who has carried out research into hospital acquired covid, said he was concerned by the relaxations, particularly given reports that some hospitals have stopped testing asymptomatic patients.

He told *The BMJ*, "My worry is that the numbers of hospital acquired infections will go up, but we won't know about it. Not having the resources to properly isolate patients is not a reason for not testing."

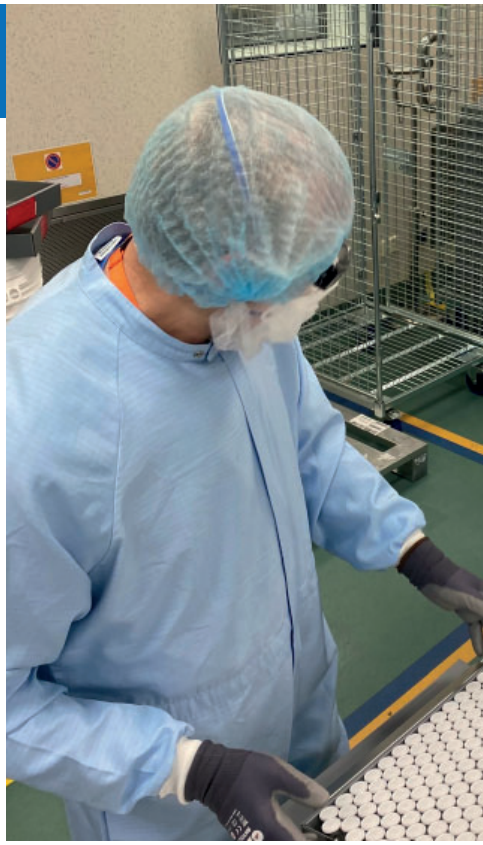
Gareth Iacobucci, *The BMJ*
Cite this as: *BMJ* 2022;377:o1029



NEWS ANALYSIS

Has the spread of omicron BA.2 made antibody treatments redundant?

Regulators in the US and UK are reviewing their authorisations for monoclonal antibody treatments just months after they were issued. **Elisabeth Mahase** asks what the future holds for this class of biologicals



The US Food and Drug Administration has removed its authorisation for the SARS-CoV-2 monoclonal antibody treatment sotrovimab because of concerns that it is ineffective against the omicron subvariant BA.2, which is now dominant in the US.

The UK's MHRA authorised sotrovimab for high risk over 12s with mild to moderate covid-19 last December after reporting that a single dose, given as an intravenous infusion over 30 minutes, reduced the risk of hospital admission and death by 79% in high risk adults with symptomatic covid. The regulator has told *The BMJ* that it is also now reviewing the treatment to see if the "benefit-risk balance remains favourable."

Laura Squire, the MHRA's chief officer for healthcare access and quality, said, "We are in contact with the FDA and are looking closely at the data supporting their decision."

Developed by GlaxoSmithKline and Vir Biotechnology, sotrovimab is a single monoclonal antibody that works by binding to the SARS-CoV-2 spike protein, thereby preventing the virus from attaching to and entering human cells.

The drug was first authorised by the FDA in May 2021, and the agency announced on 5 April 2022 that "the authorised dose of sotrovimab is unlikely to be effective against the BA.2 subvariant . . . Sotrovimab is not authorised in any US state or territory at this time."

This is not the first time that authorisation for a covid-19 monoclonal antibody treatment has been affected by the spread of omicron. In January the FDA announced that, because of the high frequency of BA.1, both REGEN-COV (casirivimab and imdevimab) and the combination treatment of bamlanivimab and etesevimab were "not currently authorised for use in any US region because of markedly reduced activity against the omicron variant."

Researchers are trying to surmount these evasive strategies by targeting parts of spike conserved across mutants
Danny Altmann

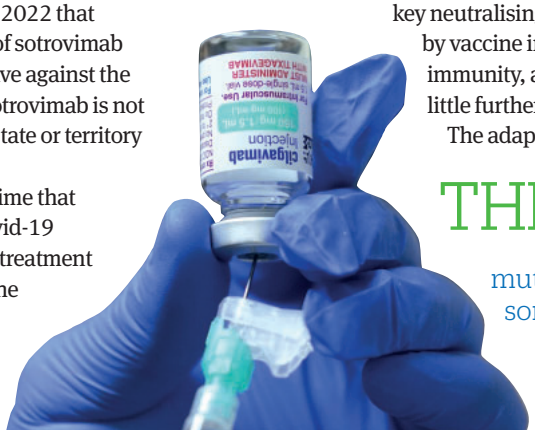
Why don't these antibody treatments work against omicron?

Antibody treatments generally target and bind to the spike protein of SARS-CoV-2, an area of the virus highly susceptible to mutations. The BA.1 variant has 37 such spike mutations, while BA.2 has 31, rendering some antibody treatments ineffective because they struggle to bind to and neutralise the virus.

Danny Altmann, an immunologist at Imperial College London, said that, while the focus on neutralising antibodies against specific parts of the SARS-CoV-2 spike had enabled several vaccines and treatments to be developed quickly, it also meant the resulting protection strategy was vulnerable to new mutations and variants.

"We were all shocked last November, when we first saw the way in which the BA.1 mutations had taken out virtually all of the key neutralising epitopes targeted by vaccine induced antibody immunity, and BA.2 takes this a little further still," he said.

The adaptability of the virus has forced drug developers to rethink their strategy. Altmann says that researchers are now using "predictions from structural biology and monoclonal antibody technology" to develop broadly neutralising antibodies that can "surmount these evasive strategies, targeting parts of spike conserved across mutants."



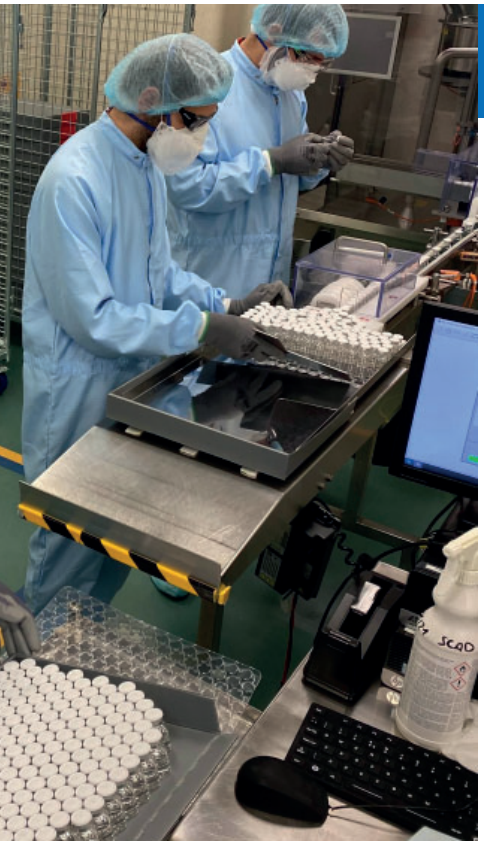
THE BA.1 variant has 37 spike protein mutations, while BA.2 has 31, rendering some antibody treatments ineffective

Do any antibody treatments still work?

Eli Lilly's bebtelovimab has been shown to work against both BA.1 and BA.2. Authorised by the FDA in February, the treatment is for mild to moderate covid-19 in high risk people aged over 12.

In a statement the FDA said it was "carefully monitoring circulating viral variants and their sensitivity to authorised monoclonal antibodies, including bebtelovimab. Laboratory testing showed that bebtelovimab retains activity against both the omicron variant [BA.1] and the BA.2 omicron subvariant."

However, since bebtelovimab has not been evaluated in placebo controlled trials involving patients at high risk of progressing to severe covid-19, the FDA has said that it should be used only "when the



preferred treatment options are not available, feasible to use, or clinically appropriate."

Eli Lilly did not respond to queries from *The BMJ* as to why bebtelovimab remained effective against the BA.1 and BA.2 omicron variants.

What about Evusheld?

Despite being authorised by the MHRA on 17 March, Evusheld (tixagevimab and cilgavimab) has not yet reached patients in the UK. The treatment was approved to prevent covid in people unlikely to mount an immune response from vaccination or for whom vaccination is not recommended, such as those who are immunocompromised or have blood cancer.

AstraZeneca, Evusheld's maker, reported in late March that the pre-exposure prophylactic retained "potent neutralising activity" against BA.1 and BA.2 in preclinical studies and that in infected mice it "significantly reduced the viral burden and limited inflammation in the lungs."

However, the UK Health Security Agency does not seem convinced. A Department of Health and Social Care spokesperson told *The BMJ* that the agency is "carrying out further testing on the treatment's effectiveness against the omicron variant [BA.2]" and those results "will inform decisions on next steps, including procurement."

Elisabeth Mahase, *The BMJ*

Cite this as: *BMJ* 2022;377:o1009

"Only a quarter of patients admitted to hospital feel recovered a year on"

Only around one in four people who had covid-19 reported feeling fully recovered within a year of being discharged from hospital, a study has found.

The research, presented at the 2022 European Congress of Clinical Microbiology and Infectious Diseases held in Lisbon, included 2320 patients discharged from NHS hospitals from March 2020 to April 2021. They were assessed at five months and at one year after discharge, with 807 (32.7%) seen at both visits.

The study found the proportion of patients reporting full recovery was practically unchanged between the two visits: 26% at five months (501 of 1965) and 29% at one year (232 of 804). Recovery was assessed through patient reported outcome measures, physical performance, and organ function. Blood samples were taken at five months to check for the presence of inflammatory proteins.

Factors associated with being less likely to report full recovery at one year were being female (odds ratio 0.68 (95% confidence interval 0.46 to 0.99)), being obese (0.50 (0.34 to 0.74)), and having had invasive mechanical ventilation (0.42 (0.23 to 0.76)).

Symptom severity

The research paper, published in *Lancet Respiratory Medicine*, is part of the Post-Hospitalisation Covid-19 study, a national consortium led by Leicester University and University Hospitals of Leicester NHS Trust.

An earlier paper from the same group identified four clusters of symptom severity at five months, which the latest study confirmed at the one year mark. Just over 1600 patients had sufficient data to allocate them to a cluster, with 319 (20%) having very severe physical and mental health impairment, 493 (30%) having severe physical and mental health impairment, 179 (11%) having moderate physical health impairment with cognitive impairment, and 645 (39%) having mild mental and physical health impairment.

The researchers found that being obese, reduced exercise capacity, more symptoms, and increased levels of the inflammatory biomarker C reactive protein were associated with the more severe clusters. Levels of the inflammatory biomarker interleukin 6 (IL 6) were also found to be higher in the "very severe" and the "moderate with cognitive impairment" clusters than in the "mild" cluster.

Louise Wain, a study author, epidemiologist, and GSK/British Lung Foundation chair in respiratory research at the university, said, "No specific therapeutics exist for long covid, and our data highlight that effective interventions are urgently required. Our findings of persistent systemic inflammation, particularly in those in the very severe and moderate with cognitive impairment clusters, suggest that these groups might respond to anti-inflammatory strategies.

> THE STUDY FINDINGS SUGGEST THAT SOME PATIENTS MIGHT RESPOND TO ANTI-INFLAMMATORY STRATEGIES
> Louise Wain

"The finding also suggests the need for complex interventions that target both physical and mental health impairments to alleviate symptoms. However, specific therapeutic approaches to manage post-traumatic stress disorder might also be needed."

A paper describing the longest known covid infection—a patient who tested positive for 505 days before dying—was also presented at the conference. The previous longest confirmed case was believed to be 335 days.

Elisabeth Mahase, *The BMJ*

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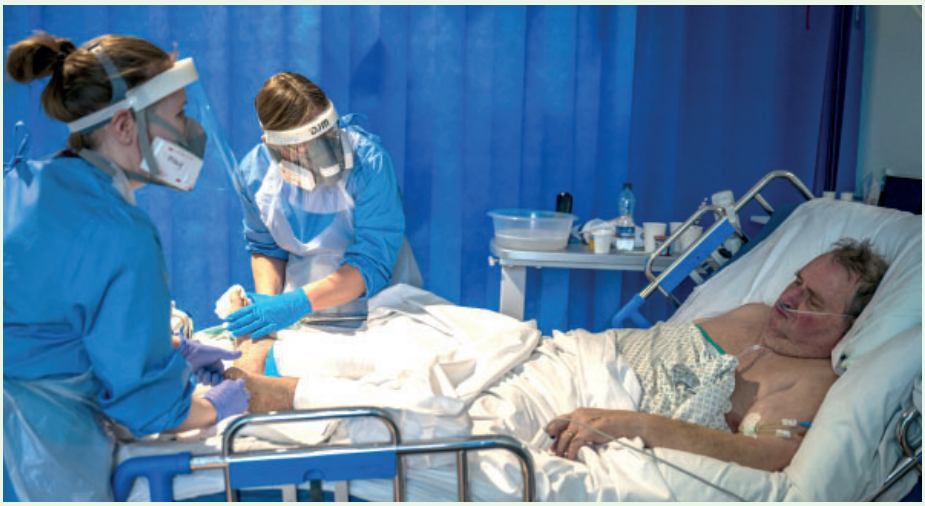

LYNSEY ADDARIO/GETTY

THE BIG PICTURE

Africa's lifesaving medical drones

Africa's vast and difficult terrain makes the delivery of healthcare to its many remote communities challenging. But thanks to international collaboration several countries are pioneering a drone service that could benefit the whole continent.

In Tanzania drones are being used to spray a silicone based liquid that spreads across large expanses of stagnant water on the island of Zanzibar where malaria carrying mosquitoes lay their eggs. In the southern region of Cheju, Eduardo Rodriguez (left, main image) who works for the Chinese drone manufacturer DJI, trains Khadija Ali Abdulla from the State University of Zanzibar in how to fly the drones.

Meanwhile, Rwanda was the first country in the world to use drones to deliver blood and essential medicines to rural hospitals. The breakthrough came after an agreement between the government and the US manufacturer Zipline, which maintains the drones (below) in two centres in the east African state. One in Muhanga has 14 drones serving 21 hospitals in western Rwanda and has so far delivered more than 20 000 units of blood.

Alison Shepherd, *The BMJ*

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EDITORIAL

Unethical studies of ivermectin for covid-19

Flawed research means we still do not know if this drug is safe or effective

ROBERTO ALMEIDA AVELEDO/ZUMA/SHUTTERSTOCK

Early in the covid-19 pandemic ethicists warned researchers against "pandemic research exceptionalism"—lowering ethical standards because of the urgency of the crisis.[2] Despite these warnings, there have been many examples of researchers doing exactly that.[3] There is no better illustration of such exceptionalism than the research into ivermectin for covid-19.

Ivermectin is used to treat a range of parasitic diseases. On the basis of in vitro activity against SARS-CoV-2,[4] the drug was tested as a possible treatment and prevention for covid-19. Initial randomised trials and systematic reviews suggested large benefits from the drug, including reduced hospital admissions and improved survival rates.[5,6] It turns out that many of the results were—literally—too good to be true.[7]

An analysis of 26 major trials of ivermectin for covid-19 found that over one third had "serious errors or signs of potential fraud."[7] One prominent meta-analysis that suggested a large survival benefit from the drug was retracted.[6] The authors did a re-analysis and found that the effect of ivermectin on survival that they had shown in their retracted study "was dependent on the inclusion of studies with a high risk of bias or potential medical fraud."[8] The editor of the *American Journal of Therapeutics* published an expression of concern about another high profile meta-analysis, noting suspicious data in several of the included studies and concluding that "exclusion of the suspicious data appears to invalidate the findings regarding ivermectin's potential to decrease the mortality of covid-19 infection."[9]

Two recent ethics scandals have cast a further shadow over ivermectin research. First, a report of an experimental study in Mexico City that gave almost 200 000 ivermectin based medical kits to residents with covid-19 was retracted from the preprint server SocArXiv,[10] because the experiment was conducted "without proper consent or appropriate ethical protections."[11] Second, in jail in Arkansas, USA, four incarcerated men developed severe side effects after a physician gave them high dose ivermectin as experimental covid-19 treatment without their knowledge.[10] The four men are suing the jail.

Urgency is never an excuse for poorly designed studies, ethical misconduct, or the violation of human rights

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Lack of consent was not the only ethical violation in these two scandals. The research participants were exposed to a risk of drug side effects without knowing they had been given ivermectin. In Mexico, the failure to give information to the participants infringed on a human right established in Mexico's constitution: the right to access information.[12] The Arkansas case raises additional concerns as it involved incarcerated people, who risk coercion and exploitation when they are enrolled in clinical research.

It is still unclear whether ivermectin is safe or has any benefit in the treatment or prevention of covid-19.[13] The flawed and potentially fraudulent research represents a huge missed opportunity to answer an important research question.

Abandon research exceptionalism

The pressure to act quickly in a global health emergency can lead researchers to cause harm or add to already existing injustices. But the answer is not to abandon research during crises, which could itself lead to "inadequate, ineffective, or even harmful care."[14] The answer is to abandon research exceptionalism.

Such exceptionalism is not needed to run fast, informative trials during a pandemic. The Recovery trial, for example, was a collaborative triumph that allowed clinicians quickly and efficiently to discard ineffective treatments such as lopinavir-ritonavir while adopting effective ones such as dexamethasone.[14,15] The trial started in March 2020 and released its first results in June 2020, finding an effective treatment for covid just 10 weeks after enrolling the first participant while maintaining high ethical standards.[16]

The Nuffield Council on Bioethics has recommended several ways to conduct ethical research even under crisis conditions.[17] These include research teams developing study protocols with input from the local community. Research funders should require inclusive community engagement plans in all proposals and should collaborate with governments, national research institutions, and multilateral agencies at the start of an emergency to agree research priorities. Research ethics committees must consider "whether the proposed consent processes are the most appropriate and sensitive that they can be in the circumstances."[17]

The urgency of a pandemic is never an excuse for poorly designed studies, ethical misconduct, or the violation of human rights.

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EDITORIAL

Sexual violence in Ukraine

A devastating war crime with far reaching consequences

On 24 February 2022, Russia launched a military invasion of Ukraine. Reports of sexual violence against women and girls began to emerge less than two months later. Multiple perpetrator rape, sexual assault at gunpoint, and rape in front of children have been reported to non-governmental and human rights organisations in Russian controlled areas.[1]

The use of sexual violence against civilians during armed conflict is widespread and is now recognised as a war crime by the International Criminal Court. Yet, the reasons why men commit conflict related sexual violence vary. Most rapes committed by armed groups in the Democratic Republic of Congo (DRC), for example, were intended to terrorise civilians to gain control over land and other resources.[2] By contrast, the rape and sexual slavery of Tutsi women during the Rwandan genocide in 1994 was a means of stripping an entire ethnic group of its humanity.[3] In former Yugoslavia, sexual violence by the Serbian authorities was part of a government sanctioned strategy to destroy the lives and reproductive abilities of Bosnian Muslim women.[4] The underlying motivations for the sexual violence against Ukrainian women and children will eventually become clear.

Sexual violence has long term consequences. Women and girls' experiences of sexual violence are associated with a significant rise in the rate of severe mental health problems, including post-traumatic stress disorder, depression, and thoughts of suicide.[5] Sexual violence also increases the likelihood that women and girls will experience other forms of violence later in life, including intimate partner violence,[6] in ways that further exacerbate their poor mental health.[7]

Less well recognised is the potential for conflict related sexual violence to destroy communities, cultural identities, and social networks in Ukraine and elsewhere. Nearly 30 years after the Rwandan genocide, unwanted pregnancies from conflict related sexual violence has led to widespread loss of identity, fraught relationships with families, and the stigmatisation of an entire generation.[8] A large qualitative study of community perceptions of sexual violence after a decade of conflict in the DRC highlighted the extensive isolation and shame experienced by survivors.[9] In these ways, conflict related sexual violence has the power to undermine the stability of entire societies.

AVPICS/ALAMY

Conflict related sexual violence has the power to undermine the stability of entire societies

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Accountability and punishment

Although ensuring systems of accountability and punishment for perpetrators is the key to prevention and social change in the long term, a swift and effective international response to the survivors of sexual violence in Ukraine is critical now. But what should be done?

Identifying survivors of conflict related sexual violence among Ukrainian refugees is challenging. Women and girls in most settings are reluctant to report their experiences for several reasons including stigma,[10] fear of social isolation,[9] and simply not wanting to relive the trauma through its telling.[11] Men, boys, and lesbian, gay, bisexual, trans, and intersex (LGBTI) populations also experience conflict related sexual violence, which often goes unrecognised.[12] Approaching refugees with a survivor centred approach that is inherently non-discriminatory and considers the diverse needs of people who have experienced multiple traumatic events is therefore essential.[13]

Once survivors have been identified, the task of providing individualised mental health support becomes somewhat easier. A recent review of psychological interventions for survivors of gender based violence in humanitarian settings showed the potential for cognitive behavioural therapies (common elements treatment approach and interpersonal psychotherapy), mindfulness therapeutic approaches, and exposure oriented interventions (eye movement desensitisation and reprocessing and narrative exposure therapy).[14]

But treating individuals does little to tackle the broader issues of stigma and loss of community identity that can arise from conflict related sexual violence. A recent systematic review of interventions to reduce sexual violence in humanitarian settings points to the potential of community based strategies to increase the economic empowerment of women survivors and challenge the gendered social norms that contribute to stigmatisation and exclusion.[15] But we are still a long way from being able to implement such strategies in Ukraine.

In the meantime, there is much that can be done. Providing fast track visas to Ukrainian refugees is an obvious starting point.[16] Better evidence on how to prevent conflict related sexual violence is also urgently needed.[17] For both of these to happen, however, researchers, funders, and policy leaders need to move beyond thinking of sexual violence as a problem for the mental health of a small number of individuals. This is a problem that affects whole societies, and there is simply far more at stake for Ukraine.

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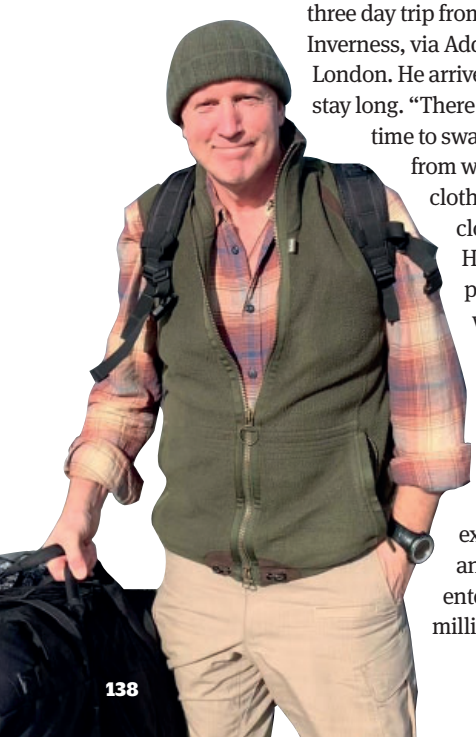
OVERSEAS AID

The British doctors offering their skills to war torn Ukraine

More than 11 million Ukrainians have been forced from their homes as a result of Russia's invasion. **Chris Stokel-Walker** speaks to some of the medics who have travelled from the UK to provide their expertise in and around the country



Andy Kent, an orthopaedic trauma surgeon, travelled from Yemen to Poland, via his home in Inverness in a few days last year

Andy Kent was in Yemen on 1 March 2022, working with local doctors to try to treat patients, when he received a call asking him to travel to Ukraine. Kent, an orthopaedic trauma surgeon based at Raigmore Hospital in Inverness, has worked for the past decade with UK-Med, a frontline medical aid charity. Russia's invasion of Ukraine prompted fears that medical support would be needed to treat patients who were caught up in the fighting or fleeing for their lives.

Kent accepted, and he began the three day trip from Yemen back to Inverness, via Addis Ababa and London. He arrived home but couldn't stay long. "There was literally just time to swap out my clothing from warm weather clothing to cold weather clothing," he says. He was on the next plane to Poland, where he met up with colleagues from UK-Med at the border and crossed into Ukraine.

It was an eye opening experience. As Kent and his colleagues entered Ukraine, millions streamed in the opposite direction. For the 7.1 million Ukrainians who have been forced to flee their homes for elsewhere in Ukraine as a result of war, as well as the 4.5 million who have left the country entirely, getting treatment for ailments has taken a back seat to survival. But it's still needed.

Ukraine's medical system has held up admirably and is the envy of many countries, say UK doctors who have travelled to Ukraine and its neighbouring nations. "They are excellent," says Paul Ransom, consultant in emergency medicine at Brighton and Sussex University Hospitals NHS Trust, who is currently in eastern Ukraine with UK-Med. Ukraine has 7.46 hospital beds per 1000 people, nearly three times the UK's number. And their medical professionals are well trained. "They've had eight years already with the hostilities in the Donbas, and they've got very good, well trained surgeons and a pretty good ambulance service," says Ransom.

Reluctance to share information

However, nothing can truly prepare you for an armed invasion. Freda Newlands, an emergency medicine doctor at Dumfries and Galloway Royal Infirmary, who is also working with UK-Med, says, "Although the health service is standing up very, very well under the circumstances, they agreed they could do with a little bit of help with primary health and looking after the chronic medicine of people who moved [within Ukraine]."

Many internally displaced people had a need for mental health and psychological support, as well as more prosaic treatment such as monitoring blood pressure, diabetes, asthma, and other chronic diseases that were "slipping through the net because they hadn't been monitored, or they didn't have their medication, or they missed follow-up appointments because of being on the move," says Newlands.

The visiting doctors have been compelled to move from staying in children's orphanages to rented apartments, and they initially struggled to convince some Ukrainian doctors to discuss how they could be supported. Kent says, "Ukraine had gone under martial law, which meant that all the hospitals essentially were under military control.

"There was a reluctance for them to talk about their plans for military casualties, and they were definitely not willing to talk about the number of casualties they were hearing about in the east of the country."

Connections and collegiality were eventually brokered and built, such that UK doctors are helping to offer training and support to Ukraine's existing infrastructure. Doctors including Ransom and Kent have

From far left: Paul Ransom conducts CBRN training sessions with local doctors; Freda Newlands assesses a Ukrainian patient; Roman Clegg, a Ukrainian born doctor, with boxes of supplies organised by his charity, British-Ukrainian Aid

also been asked to provide "CBRN" training, which equips medics to handle patients who have been subjected to chemical, biological, radiological, or nuclear attacks—a grim reminder of the reality of Russian offensive capabilities.

Mixed motivations

All of the doctors who travelled to Ukraine had their own reasons for making the journey. Newlands didn't become a doctor until she was 48, and her motivation was always to do something humanitarian through her work. "A lot of my friends here in the UK feel that they don't have a skill they can help with necessarily, and they feel frustrated," she says. "I'm lucky enough to have a skill I can transfer and to have the time to be able to do it."

For Ransom, who's recently gone part time with NHS work, his circumstances coincided with concern for a country he'd previously visited. "I've been here before," he says. "I know the country. And I've got really fond of some of the towns I've been to before. When it's a place you know that's at risk like this, it brings home the human cost."

Kent's motivation is a desire to help based on his 20 years in the army, knowing what could happen in a conflict. The fact that it meant him missing a family holiday to the United States is no matter. "I felt that my leave would be better used in Ukraine than in Washington DC," he says.

For some doctors, the Russian invasion has hit closer to home. Roman Clegg, a Ukrainian born doctor who works at University College London Hospital, has parents living in the western city of Lviv. When Russian troops crossed the border in February he and other British doctors of Ukrainian heritage set up a charity, British-Ukrainian Aid, to send medical supplies. From a depot in Essex from which they collected equipment including burn dressings and antibiotics, Clegg and his colleagues travelled to the Ukraine-Poland border.

Clegg is a former president of the Ukraine Medical Association, and when the war began he started receiving phone calls offering help and donations. "We had to face the challenge and start facilitating all these efforts, channelling them to the proper channels," he says.

He and his colleagues who travelled to the border began treating patients for the first few weeks of the war. "There was nothing acute like trauma but a lot of exacerbation of chronic conditions," he explains. "Someone off insulin for a few days waiting in the queue on a train, asthma dissipation, heart disease."

While the humanitarian crisis is just beginning, the expected huge flow of injured and sick people has yet to come. Clegg says that the Ukrainian doctors he speaks to are discouraging volunteers from showing up at the border or in Ukraine, as so many would-be patients have fled the country. Instead, his efforts in the near future may be directed to building a field hospital to support the existing healthcare system.

The medical situation is comparatively calm, at least for now. While Russia claims to be stepping down offensive operations in the country and evidence shows that its soldiers are beating a hasty retreat, having failed in their goal of capturing the country, they are causing chaos as they leave, massacring people in cities such as Bucha. And there's no guarantee that hostilities will cease entirely—on top of which the country has to rebuild, including its health service, which has been targeted.

"The number one priority is to say thank you to all the medical community, who have been absolutely outstanding," says Clegg. "Second, we're grateful for foreign assistance and help. We just want people to be mindful that help will be needed for quite some time."

Ukraine's medical system has held up admirably and is the envy of many countries

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THE BMJ INTERVIEW

WHO chief scientist optimistic for a pan-coronavirus vaccine in two years

Soumya Swaminathan tells **Mun-Keat Looi** she's worried about the relaxation of covid testing around the world, and its impact on global surveillance, and the "two track pandemic"

It's a challenging time to be a scientist, let alone the first ever chief scientist at the World Health Organization, a relatively new role. Barely nine months into her tenure Soumya Swaminathan was faced with a once in a century global health emergency and an entirely new virus that would change the face of science and medicine dramatically.

"It is incredible what we've learnt about this virus in just over two years," she tells *The BMJ*, "we haven't learnt as much about some other pathogens in decades of research."

She speaks with awe at the speed at which diagnostics, vaccines, and drugs have been developed and is optimistic that a pan-coronavirus vaccine could arrive much sooner than many might expect. She expresses her admiration for large platform clinical trials, including WHO's own Solidarity and the UK's Recovery trial. "They've provided such valuable information about how to treat patients. That really brought mortality down significantly."

But there are plenty of scientific gaps remaining and Swaminathan has choice words about the "two track pandemic," the way governments have adapted to the changing scientific evidence, and the relaxation of testing as deaths have plummeted.

"We're concerned that many countries have reduced testing and therefore we're not getting a good handle on the stage of the pandemic. This is important because we need to be able to be vigilant and pick up a new variant as soon as it emerges and take appropriate action."

What do you wish we'd known at the start of the pandemic?

I wish we'd had better preparedness in terms of surveillance—in terms of really understanding what those non-pharmaceutical interventions are that are most effective—because at the beginning of any pandemic you do not have the vaccines and the drugs so you have to rely on public health measures like wearing a mask, physical distancing, ventilation, and so on.

A better understanding of things like airborne transmission, for example, right at the beginning of the pandemic [would have been helpful] but also non-pharmaceutical interventions and how they affect people in different socioeconomic conditions—looking more at the social and behavioural sciences, understanding people's behaviour and how to change it. We need to focus on these areas, so we're better prepared for the next pandemic.

Sometimes, you do things pre-emptively because it's a serious situation—you don't wait for all the data

Recent data point to the fact that the one factor which had the most impact on how a country managed the pandemic and the toll that it took on its population was trust—trust of people in government and trust in each other. That's telling because many of the interventions are based on science. Sometimes, you do things pre-emptively because it's a serious situation—you don't wait for all the data and evidence. That's a lesson that we should learn—we should be able to take pre-emptive action. Especially if it's a low risk intervention like wearing a mask, which is just common sense, even though there weren't any clinical trials on it at the beginning.

How do you think governments have coped, or not, with gaps in the science?

The governments that did well did a few things right. First, they listened to public health experts.

Second, decision making, from a political science perspective, involves not just the pure science behind something but many other interests and conflicts of interest that arise, as well as the impacts on economies, the ethics of certain decisions, and so on. Governments that set up multidisciplinary groups that tried to tackle all these different aspects—taking into account the science behind the virus and the interventions, but also looking at all of these different aspects—made the best decisions.

The governments that did well communicated regularly and transparently. They were open with the data they used to explain to the public what the decisions were based on when they were tightening restrictions or when they were loosening restrictions—explaining the rationale. Those were the governments that took their populations on board and kept

BIOGRAPHY

Born in Chennai, Soumya Swaminathan earnt her medical degree at the Armed Forces Medical College in Pune and her doctorate in paediatrics from All India Institute of Medical Sciences in New Delhi. In 1989 she completed a postdoctoral medical fellowship in neonatology and paediatric pulmonology at the Children's Hospital Los Angeles at the Keck School of Medicine of the University of Southern California.

Her research career focused on tuberculosis and HIV before she served as secretary to the government of India for health research and as director general of the Indian Council of Medical Research from 2015 to 2017—during which time she built research capacity in Indian medical schools and forged partnerships between low and middle income countries in the health sciences.

From 2009 to 2011 she was coordinator of Unicef, UN Development Programme, World Bank, and WHO Special Programme for Research and Training in Tropical Diseases in Geneva, and was appointed the first WHO chief scientist in March 2019.

the lines of communication open, prioritising the welfare of people.

One thing that has been missing is a global view, especially when it comes to trade and travel. While all leaders want to protect their citizens, and they're duty bound to do it, one also must look at the impact of one's actions on people in other countries.

What would you say are the biggest remaining gaps in the science of covid-19?
We still don't completely understand the behaviour of the virus in different populations. We know that morbidity and mortality are correlated with older age. But at the same time, we have to understand that the data that are coming from different countries in different parts of the world are very uneven. And many countries don't have the same type of diagnostics or genomic capacities (see box, p 142). So, we still don't understand why and how the waves of this virus are coming through different populations with different periodicity in different countries.

Long covid, we still are learning about: the longer term sequelae of this virus and why, early on, we knew that some people who recovered from infection, particularly those who were more severely ill, had symptoms that persisted for quite some time. Now we're seeing that in large population based studies, incidence of diseases like diabetes and cardiovascular diseases are around two or three times higher in people who had even mild covid. Clearly that's something this virus is doing. It's not affecting only the respiratory tract, it's affecting multiple systems, multiple organs in the body. There have been worrying reports about the impacts on the brain and cognitive function. It may be setting up an autoimmune response, or there may be some kind of viral reservoir with ongoing inflammation—there are many hypotheses, which need further research to unravel. This seems to be very different from other respiratory viruses that we've dealt with.

On the research and development side, developing a pan-coronavirus vaccine that can cover the variants of SARS-CoV-2 and perhaps even go beyond and be effective against other coronaviruses would be the holy grail. And it appears to be scientifically quite feasible to develop one in the next couple of years—that's partly because of the huge amount of research that's gone into SARS-CoV-2. And also the understanding of immunology as well as on the virus itself. So we're in a good position to be optimistic about a pan-coronavirus vaccine.

FABRICE COFFRINI/AFP/GETTY IMAGES

Governments that did well communicated regularly and transparently. They were open with the data they used

What do people, even experts, still misunderstand about the covid science?
Immunity after natural infection and the duration of immunity. And that whether or not people have been infected, they need to be vaccinated. And what a full vaccination schedule looks like.

Also, the fact that this virus—different from previous coronaviruses—can be transmitted by people who are asymptomatic. You don't necessarily have to be sick—you can be well and still be spreading it, which is why continuing to wear masks, especially if you are in a crowded or poorly ventilated place, is so important, even after mask mandates are lifted.

Some east Asian countries did this following SARS in 2003. It is not stigmatising to wear a mask in public and every time you have a respiratory infection, or you're not feeling well, or you are in a very crowded place, you wear a mask and that's just part of normal behaviour. I hope that this behaviour becomes common in other parts of the world, because we can also reduce incidence of diseases like influenza and respiratory syncytial virus, which we have really seen less of over the past two years because of the precautions we've been taking. That's just a sensible way of dealing with respiratory infections, which does not seem to be widely understood.

Has the scientific effort for non-covid health emergencies suffered?
Yes—many researchers stopped doing what they were doing if they were working on other pathogens and tried to help with the covid response. Everything else did take a backseat and we need to pick that back up.

Similarly, we've seen essential health service disruption. WHO has been doing surveys across its member states and has found that over 90% of countries are reporting disruptions in at least one essential health service. Many are reporting disruptions across many services, particularly immunisation, maternal and child health, and cancer treatment.

But we have gained an understanding of the various tools that have been put to good use, the scientific tools and the discoveries that have been made. For example, the longitudinal studies that have been performed at population level, but also things like the adaptive trials platform that had been tried for many diseases at a very small scale and previously barely made it into phase 1 trials. Then, all of a sudden, billions of people around the world have had

THE WORLD MUST BUILD A GENOMIC INFRASTRUCTURE

In March, WHO released a genomic surveillance strategy calling on countries to invest in genomics capacity—not just to track future variants of SARS-CoV-2, but also to be able to detect and understand the epidemiology of other common diseases such as dengue fever or tuberculosis.

"Also, to understand drug resistance," says Swaminathan, "for example, we know antimicrobial resistance is a big problem, but we don't have good data from many countries." She emphasises the need to invest not just in hardware but also infrastructure, training, and the workforce, "the experts, the bioinformatics, and the analytical expertise."

"Using the power of genomics and sequencing—the cost of which is coming down and is becoming more accessible—better to understand local epidemiology will enable countries to use it for their own decision making and policy making. But we will also then have platforms where the data is shared rapidly and freely so that there's understanding at the global level of pathogen spread and evolution."

Covid-19 has shown how "once we have the genomic sequence, we can very quickly develop diagnostics as well as vaccines," she says, "But, at this point in time, a third of countries around the world still don't have access to genomics, so there's a big gap. We need global efforts in terms of investments from philanthropists and other global agencies—health agencies as well as national investment."

covid vaccines tested using it, which opens up the possibility of using that same platform for other diseases.

This is the opportunity we have today, and something that WHO, along with partners like the Coalition for Epidemic Preparedness Innovations and others, are investing in: to use the technologies developed in the pandemic to develop vaccines for other pathogens, which may not cause pandemics but certainly cause outbreaks year after year, like Ebola, Lassa fever, Marburg virus, dengue, and haemorrhagic fever, Then, of course, the big ones like tuberculosis and malaria, for which we still don't have good vaccines. The science that's been done during the past two years now provides an opportunity for us to answer some of these other questions.

Has the framework for vaccine evaluation, globally, become stronger?

Clinical research has advanced a lot, including things like frameworks for evaluating drugs, either repurposed or new drugs, as well as for new vaccines for diseases and in many areas. One framework is on designing and the conduct of clinical trials from the traditional double blind randomised controlled trials to thinking about adaptive trial designs—where you could have multiple vaccines or multiple drugs [tested at the same time and compared with a] common control or placebo—and also thinking about what happens in a situation like we're in today when large parts of the world, perhaps people already have antibodies to this virus [and therefore may not be eligible for a trial]. How do you then evaluate new vaccines? Perhaps by using immunobridging studies, by setting up the gold standard, or by defining the assays and the benchmarks so you could continue to develop better and new vaccines.

Scientific tools and processes have been so nimble, so adaptable, and so collaborative

Our understanding now, both of the tools that we have and the scientific processes, has evolved and so has the regulatory system. They've been so nimble, so adaptable, and so collaborative. Regulatory agencies from around the world have come together and agreed on some common standards, and that's accelerated the speed at which people get access to these products. These are all very positive lessons we've learnt and hopefully will continue to use.

How will the pandemic end?

We're not expecting that this virus is going to be eliminated or eradicated. It's going to stay with us, clearly. It's spread too widely and, unfortunately, infects many animal species.

The best case scenario is that with increasing levels of population immunity, both because of exposure to the virus and because of vaccination, by the end of 2022 the severity of the disease declines even though people may still be getting infected. The worst case scenario is that the next variant is not only more transmissible but more virulent than omicron and is able to evade the immune responses that we've generated thanks to vaccination. And then basically, we start over again.

The in-between scenario is the virus becomes endemic, you get waves of infection and you may then see an increasing number of deaths as well. This could occur at different times in different countries, and it would depend on how quickly immunity wanes and how many susceptible people there are in the population—not just the elderly and those with underlying illnesses and who are immunocompromised, but new birth cohorts who don't have immunity.

SARS-CoV-2 will most likely evolve and variants will emerge. We must be watchful. We have to continue surveillance, including genomic. We have to keep our tool kit—and not just vaccines—ready to use. Right now, the drugs are not available in many parts of the world. We need the diagnostics, and to make sure we have the personal protective equipment, the oxygen, and so on to treat people when needed and not go back to the shortages that we had at the beginning.

We are confident of quickly adapting vaccines and taking them through the regulatory process through immunobridging studies and being able to roll them out fairly quickly. But it means constantly being on top of this pandemic, not just believing we have come to the end and relaxing all measures.

Mun-Keat Looi, International Features Editor, *The BMJ*

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