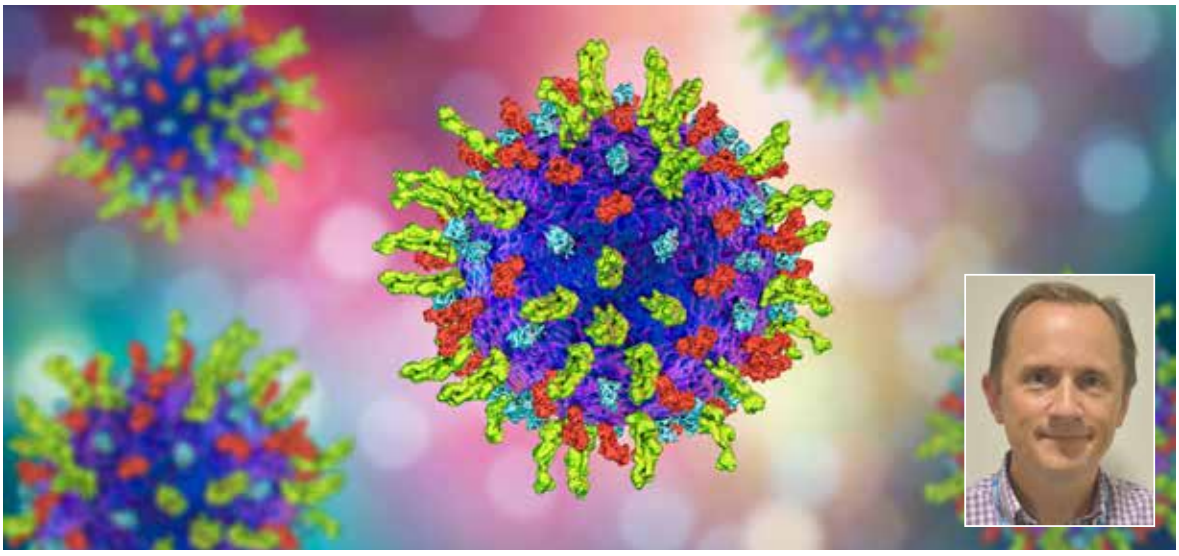
this week

PAXLOVID p 340 • **ASTRAZENICA ANTIBODY DRUG** p 341 • **PREGNANCY AND COVID** p 342



STEVE GSCHMEISSNER/SPL

Deaths may lead to new sepsis guidance

Clinical advice on how to treat new mothers with sepsis could change after two women died of a postpartum herpesvirus infection.

The Royal College of Obstetricians and Gynaecologists said viral infections must routinely be considered as a possible cause of postpartum infection.

The advice came after it emerged that Kimberley Sampson, 29, and Samantha Mulcahy, 32, had died from HSV-1, an infection caused by herpesvirus, 44 days apart at East Kent Hospitals University NHS Foundation Trust in 2018. In both cases clinical staff thought the women had bacterial sepsis.

The college said it could formally update its guidance on managing sepsis after pregnancy, pending the outcome of a full investigation into the deaths.

This week a BBC investigation revealed that one surgeon at the East Kent trust may have infected the two mothers while performing caesarean sections on them.

The trust said that it had not been possible to identify the source of either infection, and the women's families had been told that there was no link between the deaths.

However, documents obtained by the BBC showed that the trust had been told two weeks after the second death that "it does look like surgical contamination."

The royal college's president, Edward Morris, expressed "deepest sympathies" to the families of the women and said it was essential that their deaths were fully investigated. "Surgical infection appears to be a significant possibility in these deaths," he said. "Routine investigation and management of postpartum maternal sepsis should always consider viral sources of infection, and appropriate changes should be instituted to support earlier diagnosis and appropriate treatment."

He added, "While this is an extremely rare and complex situation, and it seems neither of these tragic deaths could have been foreseen nor prevented, it's incredibly disappointing that the families have had to challenge the trust and other health authorities to establish a potential link between the two cases.

"Each maternal death is a tragedy, and it's essential these deaths are fully investigated so we can understand the reasons behind them and make appropriate changes to guidelines and practice to prevent further deaths."

Gareth Iacobucci, *The BMJ*

Cite this as: *BMJ* 2021;375:n2881

Routine investigation of postpartum maternal sepis should always consider viral sources, said RCOG president Edward Morris (inset)

LATEST ONLINE

- Leading oncologist who overtreated patients is found to have impaired fitness to practise
- A record 100000 people in the US died from overdoses in 12 months of the pandemic
- Health and Care Bill fails to tackle workforce problems and risks outsourcing to private providers, BMA warns

SEVEN DAYS IN

Lords committee urges government to reverse cuts to children's centres

ANDREW FOX/ALAMY

A national network of family hubs should be at the core of a government strategy on child vulnerability, the House of Lords Public Services Committee has said. Over a million vulnerable children are now growing up with reduced life chances because of cuts to early years and youth support since 2010, with the risk of serious harm being disproportionately higher in the most deprived areas, it warned in a report. It said poor national coordination meant that many children fell through the gaps.

A recent government pledge to spend £492m on early help services over the next three years was welcome, the committee said, but came after a decade of underinvestment and would not repair the "creaking public services infrastructure" on which vulnerable children rely. The report calls for a return to levels of investment in early help services seen in 2010, when Sure Start centres started to be cut.

Spending on early intervention support in areas of England with the highest levels of child poverty fell by 53% between 2010 and 2019, the report said. Walsall, for example, which has some of the highest levels of deprivation anywhere in England saw early intervention spending fall by 81% over the decade.

Jacqui Wise, Kent Cite this as: *BMJ* 2021;375:n2851

Covid-19

Limit use of ivermectin to trials, says NICE

The drug ivermectin should be used to treat people with covid-19 only as part of a clinical trial, said NICE. In updating its guideline on managing covid-19 the agency noted a high degree of uncertainty about whether ivermectin was more effective than control in hospital or community settings. It also raised concerns about the quality of studies, uncertainty about the overall safety of ivermectin, and the possibility of rare serious adverse events. *The BMJ*'s living guideline made this recommendation on ivermectin on 31 March 2021 (*BMJ* 2020;370:m3379).

NHS seeks to clarify booster confusion

The NHS moved to tackle public confusion and misunderstanding over the difference between third primary doses of covid-19 vaccination and booster doses, as well as people's eligibility for the two. It published an explanatory document online outlining the difference between third primary doses—for which some severely immunosuppressed people are eligible—and boosters, which take place from six months after the primary course of two or three doses. Explanatory posters have also been produced for general practices.

England prepares to offer annual vaccine boosters

The NHS in England is preparing to offer an annual covid-19 booster vaccine programme if required, said the service's chief executive, Amanda Pritchard (above). She added that "further expansions" could be made to advice from the Joint Committee on Vaccination and Immunisation about which groups should receive booster vaccines. Officials are awaiting more data before deciding whether to recommend annual covid vaccine boosters in a similar way to annual winter flu vaccination.

US authorises Pfizer and Moderna as boosters

On 18 November the vaccine advisory committee of the US Centers for Disease Control and Prevention recommended booster doses of the Pfizer and Moderna covid vaccines for over 18s at least six months after completion of primary vaccination. The Food and Drug Administration had authorised both vaccines as a booster on the same day. Pfizer has said that its booster dose is 95% effective at preventing symptomatic infection in people who have no evidence of prior infection. Moderna did not submit any data on its booster, saying that it was still gathering evidence.

General practice

England's GP committee elects new chair

The BMA's General Practitioners Committee for England elected Farah Jameel (below) as its new chair. Jameel, a GP who is based in north London, is the first woman to chair the committee. She succeeds Richard Vautrey in the role and was elected after a vote at the committee's meeting on 18 November. Jameel was one of two candidates nominated for the post, along with a Stoke-on-Trent GP, Chandra Kanneganti. She has served on the committee's executive team since 2017 and has been a member of the committee since 2014.

Online consultations to undergo evaluation

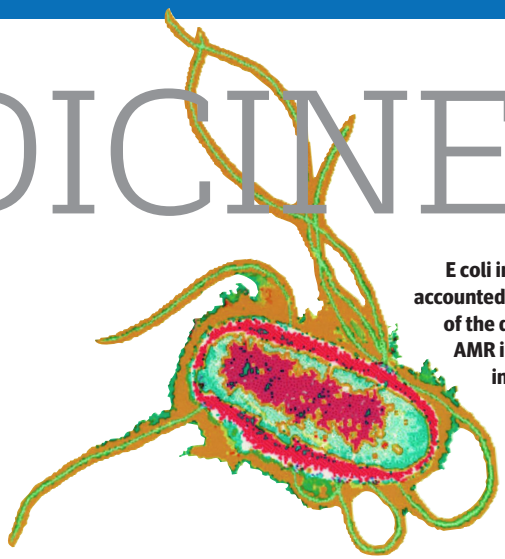
NHS England commissioned an independent evaluation of online consultations and digital tools in primary care in England. It will assess use of online systems to support patient access and triage, advantages and disadvantages of different modes of communication, lessons learnt from implementation in the pandemic, and the experiences of patients and staff. A few general practices are being asked to take part as case studies.

Litigation

NHS litigation system "fails to deliver justice"

The NHS's litigation system is facing spiralling costs while failing to deliver justice or learn lessons when treatment goes wrong, parents and experts told a parliamentary investigation. Parents of three children who died as a result of botched care told the House of Commons health and social care committee of having struggled for years to find out what had gone wrong. The committee chair, Jeremy Hunt, said that the NHS had spent a "staggering" £10bn on clinical negligence cases last year.

MEDICINE



E coli infections accounted for most of the decline in AMR incidence in England

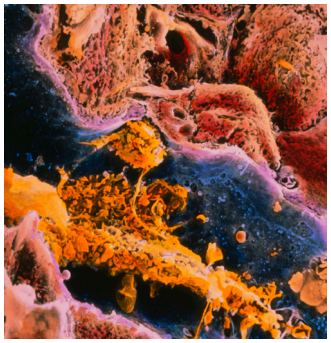
AMRs

Antibiotic resistant infections fell last year

The incidence of antibiotic resistant bloodstream infections fell in England in 2020 for the first time since 2016, although numbers remain higher than six years ago, data from the UK Health Security Agency showed. There were 55 384 antibiotic resistant bloodstream infections in 2020, down from 65 583 in 2019. Deaths attributable to antibiotic resistant bacteria also fell to 2228 last year, from 2596 the year before. The reduction in antibiotic resistance in 2020 was mainly driven by fewer *Escherichia coli* bloodstream infections, the report found.

Liver disease

Premature deaths rise by 10% in a year in England



The British Liver Trust called for urgent action to improve early detection of liver disease, such as cirrhosis (above), as data showed that premature deaths from the conditions rose in England from 9218 in 2019 to 10 127 in 2020. The charity called on the government to work with health services to improve early diagnosis by ensuring systematic pathways are commissioned and implemented in areas where they are currently absent and that these are evaluated regularly. It has launched an interactive map of survey results showing areas that don't have an effective pathway in place for the early detection of liver disease.

HIV and AIDS

NICE approves first long acting injectable treatment

NICE recommended cabotegravir with rilpivirine, the first long acting injectable treatment for adults with HIV-1 infection. In draft guidance it recommended that the injection should be given every two months when antiretroviral medicines have kept the virus at a low level (HIV-1 RNA ‹50 copies/mL), where there is no suspected viral resistance and no previous failure of other anti-HIV-1 medicines called non-nucleoside reverse transcriptase inhibitors and integrase inhibitors. An estimated 13 000 people in England will be eligible to be given cabotegravir with rilpivirine.

Smoking

Make England smoke free by 2030, say health leaders

More than 650 health activists urged the government to back amendments in the new Health and Care Bill to help England become smoke free by 2030. Two years ago the government made the pledge, including making smoked tobacco obsolete and having smokers quit or move to reduced risk products such as e-cigarettes. But it has still not published its new tobacco control plan to meet the goal, which it had planned to publish this year, or the post-implementation review of tobacco regulations that by law it was required to have done by May 2021.

Cite this as: *BMJ* 2021;375:n2871

FINED

Dudley Group NHS Foundation Trust has been fined more than **£2.5m** after pleading guilty to failing to provide safe care to two patients who died from sepsis despite repeated warnings about safety failings *[CQC]*

SIXTY SECONDS ON . . . **WINE, CHOCOLATE, AND COFFEE**

ARE WE ABOUT TO BE TOLD OFF FOR EXCESSIVE INTAKE?

Not this time. We're all aware that many studies over the years have told us why these things aren't or are good for our health in varying quantities. But one leading expert has taken a more systematic approach and produced an up-to-date summary of the evidence.

TELL ME STRAIGHT, DOC, WHAT SHOULD I AVOID?

"The answer is more complex than a simple yes or no," according to Thomas Lüscher, the recently departed editor of the *European Heart Journal*, who assessed the evidence in a recent editorial.

INDULGE US . . . WHAT DID HE FIND?

Broadly, that alcohol provides little if any health protection, while chocolate and coffee can have benefits, depending on the regularity and the volume at which they're consumed, and the type.

I NEED SPECIFICS. DARK CHOCOLATE AND DECAF COFFEE?

Tackling the question of whether these three items should be termed "forbidden joys," Lüscher wrote, "Wine is truly a joy, but at best neutral when consumed in moderation. Chocolate is a joy for our cardiovascular system, if consumed in dark, bitter form. And coffee? It wakes us up, less so, if you drink it regularly, and at the dose of up to four cups a day, might even be protective."

CASE CLOSED?

Perhaps not yet. Speaking to the *Guardian* about his findings, Lüscher said that despite the wealth of published evidence there is a lot we still don't know. "The optimal dose of chocolate, such as dark, bitter chocolate, is not known as this has not been properly investigated," he told the newspaper. "It is important that chocolate contains little sugar and fat, which are obviously not healthy. In particular, white chocolate is not healthy at all."

Gareth Iacobucci, *The BMJ*

Cite this as: *BMJ* 2021;375:n2868

Doctors will refuse to limit use of antiviral drug to unvaccinated patients, say ethicists

Leading ethicists have warned that doctors will revolt if the US drug regulator authorises an antiviral treatment for covid-19 for use only in people who have not been vaccinated. Pfizer has applied to the US Food and Drug Administration for emergency authorisation of its new antiviral PF-07321332 (to be marketed as Paxlovid), after early trial results indicated it could cut hospital admissions by 89% in recently infected adults at high risk of severe illness who were unvaccinated.

But the application for the treatment of unvaccinated people only could undermine US immunisation efforts, ethicists have warned, by rewarding people who ignored public health advice and penalising those who heeded it.

The final FDA authorisation may not reflect the application, Pfizer has noted, and could yet cover vaccinated people once trial data on that population are submitted.

Off-label prescribing will be strongly discouraged, but that won't perhaps stop some doctors from gaming the system
James Adams

Arthur Caplan, a professor of bioethics at New York University, told *The BMJ* that refusing a medicine to a vaccinated person with a breakthrough infection while giving it to a vaccine refuser in the next room was impossible to justify.

"No healthcare provider will comply," he said. "The goal of pandemic management is prevention, to prevent transmission. Any step that weakens efforts at prevention that lacks a scientific base is unethical in that it risks undermining support for prevention."

A Pfizer spokeswoman, Jerica Pitts, said that the company submitted data to the FDA as it became available and that it hoped to submit data from trials in two lower risk groups, containing many vaccinated participants, by the end of the year.

The trial in unvaccinated patients was stopped early because of strong results. A trial in low risk people did not start until early September.

Off-label use

James Adams, a medical ethicist and professor of emergency medicine at Northwestern University, Evanston, Illinois, said Pfizer "cannot really ask for any broader approval" until it had collected evidence of benefit in vaccinated people. But many doctors will not comply with a restriction on prescribing to the vaccinated, he predicted, and they may resort to off-label prescribing.

He said, "Speaking as a practising physician, I would look at the safety data and would consider prescribing the medication to vaccinated people who also might be at high risk. This will become very interesting. The government is bulk purchasing so might exercise control. I suspect that

Overcrowding in A&E caused over 4000 deaths last year

England had at least 4519 excess deaths in 2020-21 as a result of overcrowding and stays of 12 hours or longer in emergency departments, an analysis by the Royal College of Emergency Medicine has found.

The mortality figure was calculated from findings from the NHS's Getting It Right First Time (GIRFT) programme, which found that one in 67 patients staying in an emergency department for 12 hours came to excess harm, and hospital episode statistics (for 2020-21), which measure numbers of stays of 12 hours from time of arrival.

"Crowding kills"

Adrian Boyle, vice president (policy) of the Royal College of Emergency Medicine, expressed deep alarm at the figures. "To say this figure is shocking is an understatement. Quite simply, crowding kills. For many years we have issued warnings about the harm that dangerous crowding causes, but now we can see the number of excess deaths that have occurred as a result."

He said October 2021 saw an "unimaginable" 7059 stays of 12 hours from the time of decision to admit, the highest number ever recorded. "The number of 12 hour stays has risen drastically for six months and is very likely to rise again in the coming months," said Boyle. He said the predicted trajectory was supported by a recent report of the Association of Ambulance Chief Executives, which found that as many as 160 000 patients each year may be coming to harm as a result of delayed ambulance handovers.

The royal college has asked to meet England's health secretary, Sajid Javid, to discuss patient safety and the unprecedented pressures facing the urgent and emergency care system. It is also urging NHS trusts to safely expand capacity where possible and to focus on ensuring timely discharge of patients once their treatment was complete.

In the longer term, it urged the government to restore bed capacity to pre-pandemic levels, which would equate to an extra 7170 beds, to increase funding for social care to support patients when leaving hospital, and to publish a long term workforce plan to tackle shortages of emergency medicine consultants.

"The situation is unacceptable, unsustainable, and unsafe for patients and staff," Boyle said.

Gareth Iacobucci, *The BMJ*

Cite this as: *BMJ* 2021;375:n2835

OCTOBER 2021 saw an "unimaginable" 7059 stays of 12 hours from the time of decision to admit, the highest number ever recorded

PFIZER

off-label prescribing will be strongly discouraged, but that will not stop many doctors from loudly expressing opinions and, in some cases, perhaps even gaming the system to get access for high risk but vaccinated individuals."

Paxlovid could be authorised for unvaccinated people in a matter of weeks, but the company expects to make only enough to treat 180 000 people by the end of the year.

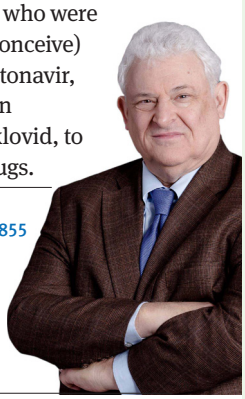
Another new covid antiviral with promising results, Merck's molnupiravir (Lagevrio), was studied in "at risk" people without differentiation on the basis of vaccination status, and its FDA application, submitted in October, is for use in all adults at risk.

The UK authorised molnupiravir on 4 November for use in adults with a positive covid test who have at least one risk factor for developing severe illness.

Many questions about both antivirals remain unanswered, because the results of these trials have been issued only in press releases. Safety concerns include molnupiravir's potential to affect human genes (its trial excluded women who were pregnant or likely to conceive) and the tendency of ritonavir, which must be given in combination with Paxlovid, to interact with other drugs.

Owen Dyer, Montreal

Cite this as: *BMJ* 2021;375:n2855



Any step that weakens efforts at prevention that lacks a scientific base is unethical in that it risks undermining support for prevention Arthur Caplan

AstraZeneca says its antibody drug is effective against severe covid-19

AstraZeneca's antibody treatment AZD7442 reduces the risk of developing symptomatic covid-19 when it is taken as a preventive measure, the company has said, and also reduces the risk of severe illness and death when taken shortly after symptoms start.

The injectable drug is currently being tested in two separate trials, which have reported that when taken as a prophylactic AZD7442 reduced the risk of symptomatic covid-19 by 83% and when taken three days after symptom onset it cut the risk of severe illness or death by 88%.

In both trials the drug was generally well tolerated, with no new safety issues identified in the six month analysis of the prevention trial. The findings, issued through a company press release, will be submitted to a peer reviewed medical journal for publication.

AZD7442 is a combination of two long acting antibodies, tixagevimab and cilgavimab, both derived from B cells donated by patients who had had SARS-CoV-2 infection. The antibodies were developed by Vanderbilt University Medical Center in Tennessee and licensed to AstraZeneca in June 2020.

The treatment is being produced with support from the US government. AstraZeneca has agreed to supply the US government with 700 000 doses, if the treatment is granted emergency use authorisation by the US Food and Drug Administration. AstraZeneca has submitted an application for AZD7442 as a prophylactic treatment for covid-19.

The UK had initially planned to purchase one million AZD7442 doses, but a deal has still not been agreed.

Elisabeth Mahase, *The BMJ*

Cite this as: *BMJ* 2021;375:n2860

Eleven Tory MPs and peers referred firms to "VIP lane"

A leaked document shows that 11 Conservative MPs and peers referred companies through the government's "VIP lane" for contracts for personal protective equipment. The document details 50 companies referred to the government's high priority list for contracts to supply PPE during the pandemic. About £1.6bn worth of contracts were awarded as a result of referrals from Tory politicians. No other political party successfully referred companies through this fast tracked route.

A National Audit Office report last year found that firms referred through the VIP lane had a 10 times greater rate of success in securing contracts than those whose bids went through normal channels.

Goggles deal

Michael Gove referred Mellor Designs, the firm of Tory donor David Mellor, to the VIP lane. The company was awarded six PPE contracts worth £16.4m. When the contracts were awarded Gove was minister at the Cabinet Office, which is responsible for government procurement. Mellor gave money to the Conservative party and to support Gove's party leadership bid in 2016. Transport secretary Grant Shapps is listed as referring the firm EyeSpace Eyewear for fast track treatment. It landed a £1.4m deal to provide goggles.

Angela Rayner, Labour's deputy leader, said, "It shows just how engulfed in corruption this government is that the minister in charge of procurement and ensuring that contracts are awarded to the best bidder and represent value for money for the taxpayer was helping his own donor to get VIP fast track access to contracts."

MATT HANCOCK REFERRED FOUR FIRMS THAT WERE SUBSEQUENTLY AWARDED PPE CONTRACTS

The document shows that the then health secretary for England, Matt Hancock, referred four firms subsequently awarded PPE contracts. The conservative backbench MPs Julian Lewis, Andrew Percy, Steve Brine, and Esther McVey and the conservative peer Paul Deighton referred one supplier each.

Jo Maugham, director of the Good Law Project, said, "We can at last see, in relation to the £12.5bn spent on PPE, the vast financial rewards you could reap if you had a minister looking out for your interests. There was no good reason, but obvious bad reasons, for the government to keep the public in the dark about these links."

Jacqui Wise, Kent

Cite this as: *BMJ* 2021;375:n2825

Give people a choice of treatment for depression, says NICE

People with depression should choose what treatment option is right for them, in discussion with their healthcare professional, draft guidance recommends.

In the first guideline for 12 years to focus on identifying, treating, and managing depression in adults, NICE advises that antidepressants should not be offered as the first line treatment for less severe depression "unless that is the person's preference." Patients with less severe depression should be able to choose from cognitive behavioural therapy, exercise, counselling, or psychotherapy. It advises that patients with more severe depression could choose from similar psychological interventions, as well as being able to choose an antidepressant as first line treatment.

The guidance puts much emphasis on shared decision making, with NICE creating a menu of treatment options to allow patients to pick the one that is right for them, in discussion with their healthcare practitioner. Nav Kapur, professor of psychiatry and population health at the University of Manchester and chair of the guideline committee, said, "We've emphasised the role of patient choice—suggesting that practitioners should offer people a choice of evidence based treatments and understanding that not every treatment will suit every person."

Practitioners should understand that not every treatment will suit everyone
Nav Kapur

The guideline recommends that people who are considering taking or stopping antidepressant drugs should discuss the benefits and risks with their healthcare professional, who should explain that withdrawal may take weeks or months to complete successfully, that it is usually necessary to reduce the dose in stages over time, and that most people stop antidepressants successfully.

Matt Smith-Lilley, lead on policy and engagement for mental health at the British Association for Counselling and Psychotherapy, said, "We've long campaigned for significant changes to these guidelines, including calling on NICE to recognise the substantial evidence base showing the effectiveness of counselling and psychotherapy for the treatment of depression."

He said many highly skilled counsellors and psychotherapists were currently underused and undervalued by commissioners, including the NHS. "The update to these guidelines must be backed by further investment in employment opportunities for counsellors and psychotherapists," he added.

Gareth Iacobucci, *The BMJ*
Cite this as: *BMJ* 2021;375:n2877

NEWS ANALYSIS

Covid and pregnancy: vaccine hesitancy and how to overcome it

What's the vaccine uptake among pregnant women?

Some 80 000 pregnant women in England had received two doses of the covid vaccine up to 31 October, a rise from 65 000 at the end of August, says the UK Health Security Agency. It's not possible to say what proportion this is of all pregnant women, as England doesn't collect data linking vaccinations, pregnancies, and births. But data from Public Health Scotland showed that only 15% (615/4069) of women who gave birth in August 2021 were fully vaccinated. Only 23% (165/704) of women aged 35-39 who delivered their baby in August 2021 had received two vaccine doses, against 71% of all adults aged 30-39 in the general population.

Why is the uptake so low?

Pat O'Brien, consultant obstetrician and vice president of the Royal College of Obstetricians and Gynaecologists, believes that there are two main drivers. "The first is the natural and understandable reluctance of pregnant women to take anything unusual or new during pregnancy because of fear that it might harm their baby," he told *The BMJ*.

The second is the Joint Committee on Vaccination and Immunisation's initial advice that it was better for pregnant women to avoid the vaccine unless they were at high risk of serious disease, because of a lack of evidence on safety. This advice changed as new evidence emerged, and the JCVI advised in April 2021 that all pregnant women should be offered the vaccine.

O'Brien rejects accusations of mixed messages. "We have more information about the safety of the vaccine in pregnancy, and we have increasingly gained evidence that covid infection is potentially worse in pregnant women than it is in non-pregnant people of the same age," he said. "The huge difference with covid is that this information usually accumulates over a decade, whereas here it has been compressed into 18 months."

What are the effects on the women of low uptake?

Unvaccinated pregnant women have a substantially higher risk of needing hospital treatment for covid than those who are vaccinated. From 1 February to 30 September 2021, 98% of the 1714 pregnant women admitted to hospital with symptomatic covid were unvaccinated, the UK Obstetric Surveillance Study reported. In the third wave of the pandemic, in July to September 2021, 13 women who were pregnant or recently pregnant died—more than in the first wave (nine women) or the second wave (11).

Marian Knight, professor of maternal and child population health at the University of Oxford's National Perinatal Epidemiology Unit and a coauthor of the study, told *The BMJ* that the results provided "clear evidence of the protection of vaccines." Data indicate that the delta variant of SARS-CoV-2 has a more

severe effect in pregnancy. Knight said recent data from the Intensive Care National Audit and Research Centre show that in the most recent wave of infection almost a third of women of reproductive age who were admitted to intensive care were either pregnant or recently pregnant, compared with around 12% in pre-pandemic times.

Knight, who also co-leads the MBRRACE-UK maternal mortality surveillance programme, attributes the deaths of pregnant women to low vaccination rates, the delta variant, and inequitable treatment. "Even though it's very clear in the RCOG guidelines that women should be treated, there is still a very risk averse culture that weighs fetal risk over maternal benefit," she said.

Will admissions and deaths fall as more women are vaccinated?

Experts hope so, but they warn of several barriers. Knight identified the need to tackle "unfounded rumours" about the effect of the vaccine on fertility and menstruation.

"All the evidence shows that there is no impact of vaccination on fertility, so it's a really important message that if you are planning pregnancy you get vaccinated," she said. "One would hope that within a year, if uptake among women of reproductive age has matched the rest of the population, I'm not having to count women dying. At the moment, I'm counting women dying every week."

O'Brien said it was equally important for the JCVI and the government to ensure booster doses are offered to all pregnant women. "Many women becoming pregnant now have had both doses over six months ago," he said. "The majority are under the age of 40, so right now those pregnant women are not included for a booster dose."

What's the effect on babies of low vaccination rates in pregnancy?

A recent study found that pregnant women who tested positive for covid-19 at the time of birth were more likely to have pre-eclampsia or to need an emergency caesarean and were twice as likely to have a stillbirth. Since the start of the pandemic about one in five pregnant women admitted to hospital with symptomatic covid have had a premature baby.

Experts are concerned that the positive effects of vaccination on fetal health have not been widely emphasised or understood. Knight said, "Being born preterm can have lifelong consequences," adding that preterm births were potentially happening slightly earlier in women who were infected with the delta variant.

How can the NHS increase uptake?

Making it as easy as possible for pregnant women to get vaccinated is vital, the experts say. Knight highlighted that in the initial phase of the vaccine rollout even women who wanted to be vaccinated sometimes had difficulty accessing it. She said that areas where antenatal clinics had offered vaccination, such as in Manchester, uptake rates exceeded 60%.

"Offering vaccination at antenatal clinics when women are able to have the conversations around their own individual needs with their midwives and doctors, then and there, will help," she said. O'Brien suggested that pharmacies could also be used in the longer term. "Doing everything you can to make it convenient is key," he said.

What should clinicians be doing?

Knight said, "There is an onus on us to be fully apprised of the benefit-risk equation so that we can have those conversations." She also highlighted the importance of repeat messaging, given the developing evidence. "Women may need several conversations to understand and enable them to make a fully informed choice," she said. "It's really important to have those conversations every time women see health professionals."

O'Brien said that clinicians should also be emphasising that the benefits of the vaccine far outweigh any risks to babies. "It protects you against increased risk of serious infection, but it also protects the baby from that additional risk of being born prematurely, which can potentially be serious for the baby as well," he said.

What else could have made a difference?

Knight cites a *BMJ* editorial she cowrote in August 2020, which argued that excluding women from vaccine trials would leave clinicians in the position of recommending vaccination to pregnant women without evidence of efficacy or safety. "Sadly, that is the position we've got into," she said. "Because of difficulty in interpreting the messaging around vaccination in pregnancy in the early days when there was no evidence . . . that was interpreted as a lack of support [for vaccination].

"So, we've had extreme vaccine hesitancy among pregnant women and confusion among health professionals as to what they should be advising."

O'Brien agrees, arguing that a tranche of the cohort of pregnant women at lower risk could have been included in the initial trials. "Systematically excluding pregnant women from trials has had a large detrimental effect," he said.

I hope that in a year, if uptake matches the rest of the population, I'm not having to count women dying. At the moment I'm counting women dying every week Marian Knight

We have increasingly gained evidence that covid infection is potentially worse in pregnant women than it is in non-pregnant people of the same age Pat O'Brien

FROM 1 February to 30 September 2021 98% of the 1714 pregnant women admitted to hospital with symptomatic covid were unvaccinated

Gareth Iacobucci, *The BMJ*

Cite this as: *BMJ* 2021;375:n2862

Data from Public Health Scotland showed that only 15% (615/4069) of women who gave birth in August 2021 were fully vaccinated. Only 23% (165/704) of women aged 35-39 who delivered their baby in August 2021 had received two vaccine doses, compared with 71% of all adults aged 30-39 in the general population

THE BIG PICTURE

Covid's hidden front line

Sanitation workers have been largely forgotten during the pandemic, the charity WaterAid says. While many have continued to work in hospitals and quarantine centres throughout the pandemic, few have received extra training or support from their employers, and PPE has often been scarce or unfit for purpose. WaterAid is calling on government bodies, employers, and the public to protect, respect, support, and invest in these essential staff.

Elisabeth Mahase, *The BMJ*

Cite this as: *BMJ* 2021;375:n2875

1. Iliyasu Abbas, pit latrine and septic tank emptier, Kano state, Nigeria
2. Julius Chisengo, faecal sludge transporter, Dar es Salaam, Tanzania
3. Kona Nagmoni Lata, street sweeper, Dhaka City, Bangladesh
4. Julius Chisengo
5. Aminu Usaini, sanitation worker, Kano state, Nigeria

IMAGES BY NELSON OWOICHO, SAM VOX, AND HABIBUL HAQUE

EDITORIAL

Life expectancy by ethnic group in England

A complex picture emerges from latest ONS analysis

The disproportionate effect of covid-19 on ethnic minority populations led to a welcome and overdue focus on ethnic disparities in health.[1] Their higher covid-19 mortality was widely viewed as having exacerbated pre-existing health inequalities, particularly for Black and South Asian people.[1 2] Although previous evidence had shown a more mixed pattern of ethnic differences in health outcomes,[3 4] our knowledge and understanding have been limited by a lack of nationally representative data on mortality by ethnic group. The first Office for National Statistics (ONS) estimates of life expectancy and cause-specific mortality by ethnicity based on census data are therefore timely.[5 6]

These show that for the prepandemic period 2012-19, the White ethnic group had lower life expectancy and higher overall mortality than all ethnic minority groups except the Mixed group. For individual causes of death, the picture was more varied, with ethnic minority groups generally having lower mortality than the White group for half of the 30 leading causes of death (responsible for about 80% of all deaths). Potential reasons for this include the healthy migrant effect—particularly for more recent migrants—and lower rates of tobacco and alcohol use in certain ethnic minority groups.[7 8]

Although labelled as experimental statistics, the methods used by ONS linking census records to patient registers and death records are not new. ONS used the same data linkage and similar methods for their covid-19 mortality analyses, which have been so critical to our understanding of ethnic disparities in outcomes.[9] Similar methods were also used to estimate life expectancy and cause-specific mortality by ethnic group in Scotland.[10-12]

Ethnic differences in health outcomes are complex and go in both directions

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The latest analyses have some unavoidable limitations, including the differential likelihood of data linkage and loss to follow-up by ethnic group, which the ONS corrected for. For every ethnic group, the analysis achieved around 90% linkage between the census and the patient register; these records then linked to 88% of all deaths occurring during the study period.[5 13] Previous work based on ONS longitudinal study data suggests that these biases reduce the mortality advantage for ethnic minorities but do not reverse it.[14]

However, the ONS analyses also have unique advantages. Ethnicity recorded in the census is self-assigned and complete, whereas ethnicity coding in healthcare records may not be.[15] The whole population sample used by the ONS (over 50 million people with over 7 million from ethnic minorities) is much larger than previous studies, enabling analysis of cause-specific mortality by individual ethnic groups.

Consistent evidence

The results are consistent with previous evidence of ethnic differences in disease incidence and prevalence, including, for example, a higher risk of cardiovascular disease and diabetes and lower risk of many cancers and chronic respiratory disease in South Asian groups. The analyses were also sensitive enough to detect differential mortality for uncommon causes of death, including HIV and tuberculosis.[6]

ONS findings for the prepandemic period are also consistent with other analyses showing lower mortality among ethnic minority groups than in the White group,[16 17] and the fact that "all cancers" are now the leading cause of death in England where rates are highest in the White group.[5]

ONS analyses for 2020, however, show that covid-19 has reduced the mortality advantage of some ethnic groups and reversed it in the Bangladeshi and Pakistani groups as well as Black Caribbean males.[18] The difference in outcome between covid-19 and other major causes of death is perhaps unsurprising given differences in key risk factors. The higher covid-19 mortality in some ethnic minorities is primarily because of a higher risk of infection driven by a higher likelihood of living in densely populated urban areas; in larger and multigenerational households (especially among older Bangladeshi and Pakistani adults); and to work in public facing roles such as health and social care.[19 20]

In conclusion, despite a widely held perception of uniform ethnic minority disadvantage, ONS data show that ethnic differences in health outcomes are more complex and go in both directions,

The new Office for Health Improvement and Disparities provides an ideal opportunity to do this, as well as tackling the large and longstanding health inequalities associated with deprivation and geography. A cross-government strategy, with the NHS and public health services working together, to reduce these inequalities is now required. The covid-19 pandemic has shown the agility with which government and public services can respond. Similar action is now required to reduce the gross health inequalities that have blighted our society for too long.

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EDITORIAL

Elder abuse in the UK

Out of the shadows and onto the agenda

Elder abuse is a major public health problem, facing one in six older people globally (defined as aged 60 and older).[1 2] Older people with dementia are at much higher risk,[3] and the disease is predicted to affect over a million people in the UK by 2025.[4]

In 2021, a report by the House of Lords described abuse of older people, particularly those with dementia, as complex, poorly measured, and hidden.[5] Physical abuse includes violence, but psychological and financial abuse is recorded as the most common form of harm, including manipulation of older people to obtain assets through marriage, wills, and abuse of lasting powers of attorney.[6] Controlling and coercive behaviour by perpetrators and social isolation of victims make elder abuse difficult to detect or tackle.[7] The UK General Medical Council recommends that health professionals should be familiar with different types of abuse in order to identify patients at risk, noting that many abuses are now criminal offences.[8]

UK policy changes—and challenges

UK legislation has changed substantially in the past decade, including the introduction of new domestic abuse crimes.[1 2] The Forced Marriage Unit was established in 2005 to protect victims coerced into marriage, and the Office of the Public Guardian was established in 2007 to protect people from abuse of powers of attorney. In health and social care, adult safeguarding guidance and multiagency safeguarding teams now exist.[8]

We do not yet know whether these changes have led to more action against abuse because basic data on the scale of elder abuse in the UK are lacking, creating "systematic invisibility."[13]

Health professionals would welcome more training—and support—on how to detect, record, and report suspected abuse

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In the year to March 2020 alone, police recorded 758 941 domestic abuse related crimes in England and Wales, including 24 856 offences of coercive control. The proportion of domestic abuse cases declined by age for women and increased for men, but the data are not disaggregated further.[15] Most domestic abuse cases are closed by police with no further action.[16]

The Forced Marriage Unit recorded 11 519 reports of forced marriages between 2012 and 2020. We calculate that 9% (1048 cases) involved people with learning difficulties or mental incapacity, and 20% of victims were male.[17] Reports of forced marriages of older people have increased over the past five years.[17] To date, only four prosecutions have been brought for forced marriage, none involving older people or those with limited mental capacity.[18]

Between 2015 and 2021 the Office of the Public Guardian investigated around 12 000 cases of potential abuse of power of attorney.[19] Again, the majority ended in no action.

Two more proposed changes to UK law risk substantially increasing financial abuse of older people: the Law Commission proposes to "modernise" marriage law;[21] and the Ministry of Justice proposes "modernising" lasting powers of attorney.[22] Both proposals aim to make procedures simpler and easier. Although both include limited safeguards, lawyers and experts argue that these are unlikely to prevent vulnerable individuals, particularly older people with failing capacity, being coerced into either marriage or powers of attorney.[23 24]

Role of health professionals

Health professionals have a vital role in protecting vulnerable older people from abuse. General practitioners and practice teams are often the professionals in closest contact with older patients, and may be the only contact for those who are socially isolated. Primary care is therefore an important space for identifying and recording elder abuse.[25] Health professionals can also support marriage registrars who become concerned about possible coercion in a marriage process and support solicitors concerned about coercion in the context of powers of attorney or wills.[26] They can also back MPs lobbying for change.

When protecting vulnerable older adults, health professionals must weigh up the ethical imperative to maintain patient-doctor confidentiality against a duty to escalate concerns to third parties—in patients' best interests—if abuse is witnessed or suspected.[27 28] Furthermore, guidance needs to be developed urgently on the new duties for health professionals to cooperate, enshrined in the 2021 Domestic Abuse Act.[29] Given the increasing risks of elder abuse in the UK and the rapidly changing legislative environment, health professionals, especially in primary care, would welcome more training—and support—on how to detect, record, and report suspected abuse, so the appropriate action can be taken.

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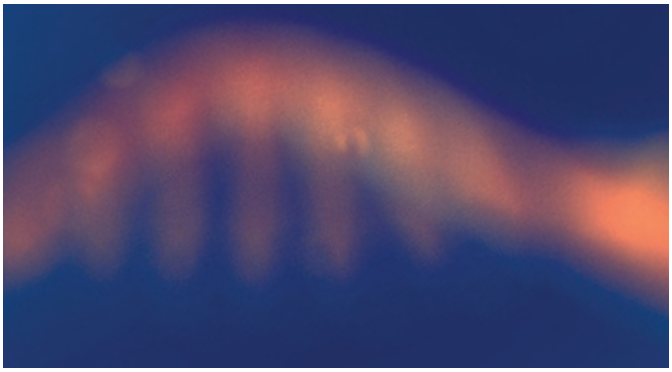
FEATURE

mRNA vaccines: hope beneath the hype

mRNA vaccines have proved themselves as the most effective covid-19 vaccines, and their makers are now seeking to help conditions from cancer to HIV. **Andy Extance** investigates their promise and limitations



The next decade will "see a revolution in mRNA therapeutics," says Paul Burton, chief medical officer at Moderna in the United States. Along with Germany based BioNTech, Moderna has already shown, by changing the course of the covid-19 pandemic, how powerful medicines based on messenger ribonucleic acid (mRNA) can be (box 1). The companies had originally planned to use their technology for other conditions, particularly cancer. After more than 10 years spent developing the technology, they're now set to use their covid-19 success as a springboard to achieve their original goals.

Moderna has several therapeutic targets in its sights: from heart failure and faster, more effective influenza shots to the mosquito-borne viral disease chikungunya. BioNTech, meanwhile, hopes to have a malaria vaccine ready by the end of 2022. "This is a platform that I think can bring huge value to patients globally, in all sorts of different diseases," Burton says. Researchers elsewhere agree that mRNA treatments are promising, while warning that they're not a total panacea.

The pandemic allowed mRNA technology to come of age
Robin Shattock

Coming of age in the pandemic

Moderna has "learned tremendously" from covid-19, Burton says. "We're well positioned to bring that now to bear on this next wave of therapeutics," he says. "This is just the beginning. The number of diseases that are amenable to treatment with this platform is remarkable."

Back in 1987 Robert Malone, a graduate student at the Salk Institute for Biological Studies in La Jolla, California, first showed that mixing mRNA with fatty droplets could get cells to make proteins. For years afterwards, many researchers struggled to find the right biochemical strategy to exploit mRNA's potential in a drug or vaccine, while others saw mRNA as too expensive and unstable (box 2).

The pandemic "allowed the technology to come of age," says Robin Shattock, professor of mucosal infection and immunity at Imperial College London. "It's had quite a long and chequered approach to getting to something that works. But, now it's there, that will cause a huge amount of investment and further technological advances."

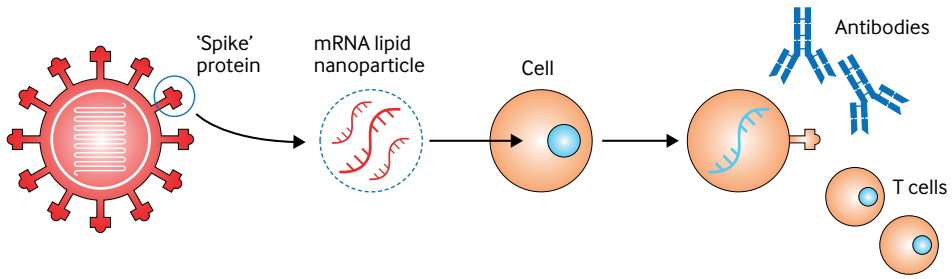
"Immunologically, mRNA enables very, very good vaccines," says Akiko Iwasaki, professor of immunobiology, epidemiology, and molecular, cellular, and developmental biology at Yale University. "When the phase III [covid-19 mRNA vaccine] trial data were coming out, I was very excited about the incredible efficacy." Both BioNTech and Moderna's vaccines have attained efficacy levels above 90% in preventing covid-19. That ranks close to the most successful existing vaccines, such as those for hepatitis A, for which efficacy nears 100%.

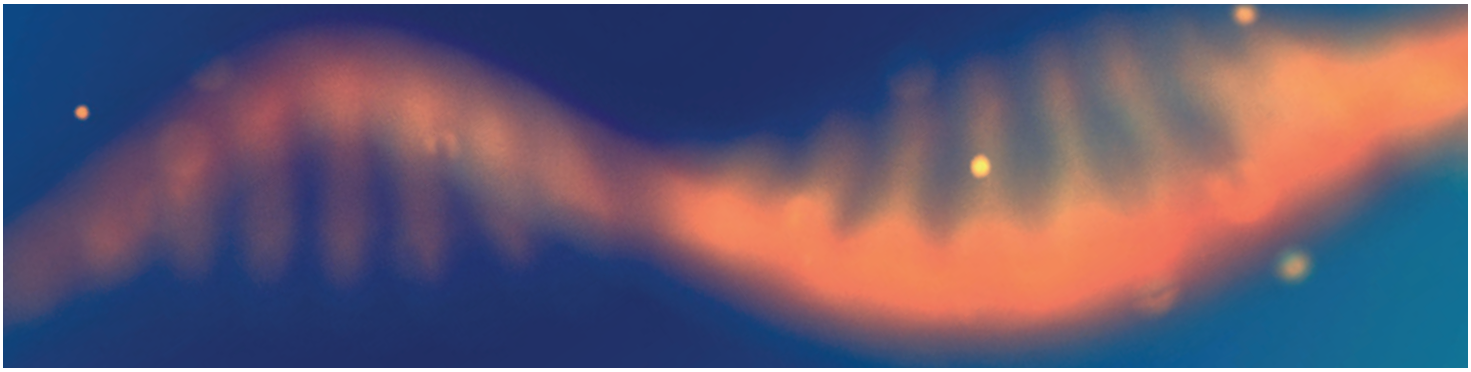
Box 1 | How mRNA covid-19 vaccines work

Until 2020, most vaccines used either disabled forms of bacteria or viruses or protein molecules that form part of the shell that wraps around the genetic material at their centre.

Covid-19 vaccines from Moderna and BioNTech instead deliver messenger RNA (mRNA) directly to cells. These encode an antigen—namely the spike protein from the outer coating of SARS-CoV-2 that lets the virus grab onto our cells. The human cell's own machinery then makes the antigen from the mRNA template and the resulting protein provokes an adaptive immune response. Thus, the body learns to identify, target, and destroy that protein, including live virus particles.

As Moderna's Paul Burton puts it, they "use your body's cellular machinery to translate that messenger RNA into a protein that is perfectly designed for human beings." Dealing directly with the genetic sequence makes vaccines much faster to develop than traditional methods.





Box 2 | Vital mRNA innovations

Foreign mRNA would usually be detected and destroyed by the body's immune system before it could be turned into protein. In 2005, University of Pennsylvania researchers Drew Weissman and Katalin Karikó swapped one of the four bases comprising the letters of the RNA genetic code, uridine, for an alternative, called pseudouridine. The mRNA made using pseudouridine was able to evade the immune system's detection, paving the way for mRNA treatments.

mRNA is also naturally broken down in cells. To maintain its viability for longer while it does its job, the mRNA is encased in fatty lipid molecules, forming tiny nanoparticle balls. "It's a platform technology that we can reproducibly use," Moderna's Paul Burton told *The BMJ*. "The fidelity is extremely high."

Covid-19 was a better proving ground for mRNA vaccines than other conditions
Paul Hunter

Covid-19 was a better proving ground for mRNA vaccines than other conditions, says Paul Hunter, professor in medicine at the University of East Anglia. "Coronaviruses were always going to be an easy target for a vaccine," he says. That's because the SARS-CoV-2 virus's spike protein is an obvious target for antibodies to block.

The relative ease of developing mRNA vaccines may improve prospects for diseases for which it is currently not economically viable to develop vaccines. Hunter concedes that mRNA vaccines still face the very large costs of testing vaccines in clinical trials, and he says that not all viruses are as easy to target as SARS-CoV-2.

Becoming first choice

The speed with which companies can develop mRNA vaccines means that this technology will also be "a first choice platform to test other pathogens," says Iwasaki. It took Moderna seven weeks to produce its covid-19 vaccine and send it off for testing. By contrast, it can be at least three months before flu vaccines made using traditional approaches can be tested.

That speed, however, combined with mRNA vaccines' novelty, has contributed to some people's hesitancy about receiving them. "That's a major hurdle," Iwasaki told *The BMJ*, although she believes that those with conditions like cancer might be less hesitant if mRNA therapy proves to be effective, particularly when treatment options are limited.

Personalised cancer vaccines will be an especially important area for driving investment, Shattock says. This is the area that both Moderna and BioNTech were founded to investigate. The approach here involves identifying proteins specific to a patient's tumour and then making a vaccine specifically targeting them. Burton says that Moderna's cancer vaccines, currently in phase II clinical trials, can contain more than 30 different mRNA sequences for different personalised antigens. The company's technology is now advanced enough that this is no more challenging than the single sequence covid-19 vaccine, he added.

Vaccines with multiple mRNA sequences could help other conditions, like cytomegalovirus, which can cause birth defects and organ transplant complications. Cytomegalovirus's outer coat comprises six proteins. "That's very difficult to generate a vaccine against using standard technology," Burton says. Cytomegalovirus is the therapeutic area in which Moderna is furthest advanced after covid-19, having started phase III clinical trials in October 2021. Without the accelerated development timelines regulators brought in for the pandemic, phase III trials for vaccines typically take two to four years to complete.

The mRNA vaccine platform offers high fidelity that could also benefit flu vaccines, where traditional inactivated virus vaccines often suffer from mutations that make them less effective. In addition, vaccine production could start later, because mRNA vaccines can be manufactured more rapidly, enabling more informed decisions about what strains to include.

These two advantages might improve the 40-60% protection against infection that existing flu vaccines offer. But to bring mRNA flu vaccines to market they must match or beat the protection offered by existing vaccines at an affordable price. That is a different challenge to the one that faced manufacturers developing vaccines against covid-19, where there were no existing treatments.

Moderna started conducting phase I trials for a flu mRNA vaccine in 2015, using two strains (H10N8 and H7N0) for which there were no other

The relative ease of developing mRNA vaccines may improve prospects for diseases for which it is currently not economically viable to develop vaccines

vaccines. The Moderna vaccines generated immune responses, validating the mRNA approach, but immunity was short lived. In July 2021, it launched a 180 person phase I/II trial of a flu vaccine containing four mRNA sequences targeting four different strains, expected to run through early 2022.

Based on usual vaccine development timelines, a commercial mRNA based flu vaccine is likely to be on the market in four to seven years. Moderna's is the leading candidate, but BioNTech's covid-19 vaccine partner Pfizer is developing a flu vaccine independently under the two companies' collaboration agreement, which is now in phase I testing. Sanofi is also developing an mRNA based flu vaccine, and GSK is partnering with CureVac on both flu and second generation covid-19 mRNA vaccines.

Meanwhile, Moderna has vaccines for chikungunya, Epstein-Barr virus, metapneumovirus, Zika, and respiratory syncytial virus in development. The company is also exploring delivering multiple mRNA sequences to vaccinate against several viruses at once. And it is also working on what would be the world's first HIV vaccine, which the company is preparing for testing in humans.

Iwasaki emphasises the size of the challenge here. HIV mutates rapidly, changing its proteins' shapes and making it difficult to target. Even mRNA might be unable to overcome that. Existing mRNA technology might also be unable to protect against the herpes virus, which has also never had a working vaccine. "For those types of pathogens, we may need additional tweaks to make the vaccines more effective," Iwasaki told *The BMJ*. She notes, for example, the need for vaccines to generate "the right type of immunity in the right type of tissue." For SARS-CoV-2, mRNA vaccines stimulate the immune system to produce circulating memory T cells and B cells. Herpes vaccination could benefit from resident memory T cells forming in genital mucosal tissues. "This kind of localised mucosal immunity can be developed, but not with the current technology," Iwasaki says.

This technology will be a first choice platform to test other pathogens
Akiko Iwasaki

The ability to make complex antigens in large amounts opens up so many diseases
Paul Burton

Equity

Even if mRNA vaccines can treat some of the conditions with the greatest unmet need, many of these diseases are most common in developing countries. To reach those regions, companies like BioNTech and Moderna will have to share manufacturing know-how with local factories, Iwasaki says.

With the pandemic ongoing, and booster jabs now in the conversation, covid-19 looks to be the workhorse of the mRNA vaccine industry for the near future. To make its covid-19 vaccine more widely available, Moderna works with organisations like the World Health Organization backed Covax initiative. Moderna has also lowered the vaccine dose in its boosting shots, which, says Burton, "will free up maybe a billion doses in 2022 that can be deployed around the world."

Asked whether the cost of mRNA vaccines is a barrier to access in developing countries, Burton says that mRNA covid-19 vaccines had provided good value. But Moderna has so far declined to share its technology blueprint to allow companies in other countries to make the vaccine domestically, instead reportedly planning a $500m manufacturing facility of its own in Africa. Meanwhile, WHO and its Covax partners are working with a South African consortium to establish a covid-19 mRNA vaccine technology transfer hub. And in October 2021, BioNTech signed an agreement with the Rwandan government and Institut Pasteur de Dakar in Senegal to build an mRNA production facility starting in mid-2022.

A major challenge to expanding manufacturing capability is that mRNA vaccines must be kept very cold to remain stable. And even though storage temperatures for covid-19 vaccines have increased from −70°C to −20°C, availability of suitable freezers remains a barrier, Iwasaki says.

Stability is a particular problem for covid-19 vaccines because they have long mRNA sequences to encode the spike protein, which contains 1273 amino acid building blocks. Burton told *The BMJ* that this will be less of a problem in other conditions, allowing storage at higher temperatures. "If you can shorten that, it stabilises the whole particle," he says. Burton added that Moderna is developing its lipid nanoparticle technology to increase storage temperatures even further.

Robin Shattock thinks that mRNA medicines will ultimately become more available because the capacity to make them will increase in different parts of the world. Experts say that the technology is easier to establish from scratch than traditional vaccine manufacturing, which requires large vats of cell culture that can be subject to variations in yield and vulnerable to various hiccups.

Traditional vaccines need a big factory to make the protein or the virus, which takes a long time. One bottleneck is making modifications like adding glucose residues, says Burton, which our bodies do much faster. "The amazing thing about mRNA is it goes into the cell, uses your body's cellular machinery to translate into a protein, and then it's naturally modified. The ability to make complex antigens in large amounts, it opens up so many diseases."

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CORONAVIRUS

Covid-19: Why China is sticking to "zero tolerance" public health measures

China's covid strategy has been to identify and interrupt community transmission through swift containment measures, sometimes for whole cities. And, despite already vaccinating over 75% of the population, it seems to be sticking to this approach. **Andrew Silver** asks why

YANG MIN/COSTFOTO/SIPA/ALAMY

CHEONG KAM KA/XINHUA/ALAMY

Medical workers take swab samples from residents for COVID-19 testing in south China

Maintenance of containment has greatly reduced the impact of covid-19 lives lost and socioeconomic progress, wrote researchers—including George Gao, head of China's Center for Disease Control and Prevention (CDC)—in a Nature Medicine paper in April.

When people test positive for covid-19 in China they have to isolate, and authorities must implement targeted movement restrictions and PCR testing in geographical areas, working quickly to trace contacts who may have been exposed so that they too can be isolated. Authorities that don't act quickly enough and people who don't comply with covid-19 regulations face punishment.

Covid-19 measures led to the closure of Shanghai Disneyland, and testing was required before the guests already inside were allowed to leave. The government has also built a 5000 room quarantine facility on the outskirts of Guangzhou to house domestic and international travellers for at least two weeks of quarantine.

In their paper, Gao and colleagues wrote that public health measures for covid-19 could change with the introduction of vaccines in and outside of China.

"PCR testing strategies will be adjusted to fit the changing epidemiological situation in China—probably one in which few or fewer non-pharmaceutical interventions will be needed for effective epidemic control," the authors wrote.

"Throughout 2020, PCR testing served the public well, helping to make and keep China nearly free of SARS-CoV-2 and providing socioeconomic space and time for vaccine development and long term prevention and control of covid-19."

Today, however, China has already fully vaccinated over one billion of a total

XINHUA/LU HANXIN/ALAMY

International Health Station in Baiyun District, Guangzhou City in the south of China

population of around 1.4 billion people, and some are wondering why measures haven't changed. "Suppression strategies are not 'solutions' to covid-19 but rather ways to buy time—and fairly costly ones," says Thomas Hale, a public policy researcher at Oxford University, UK, who leads a project that tracks government responses to covid-19 worldwide. "China has now vaccinated a large share of its population, so the question is, what is the value of buying more time?"

Immunity

Reuters has reported that Ruili, a border town and international transit hub in southwestern China, has had multiple outbreaks and disruptions, leading to a rare outburst against covid-19 restrictions from a former vice mayor, who wrote on social media that "the long term closure of the town has formed a deadlock in the town's development."

Some say that China—a country ranked 177th for press freedom in 2021 by Reporters Without Borders—may be balancing a number of factors, including public perception of the government and economic effects of SARS-CoV-2. "They want people to see them as being very confident and good at governance, and containing an outbreak is a very observable thing," says Sean Sylvia, a health and development economist at the University of North Carolina at Chapel Hill, USA. "You're not going to have a lot of people reporting on people facing economic hardship."

By 5 November about 76% of China's population were fully vaccinated, said a calculation by Reuters based on data announced by China's National Health Commission. Only domestically developed covid-19 vaccines are approved for emergency use in the country. These use more traditional and easier to deploy technology, such as an inactivated virus, rather than mRNA vaccines, which have more complex supply chains. Sylvia and others think that shortcomings with vaccines or the vaccination rate could be delaying a change in China's covid tactics.

China may reach 85% fully vaccinated by early next year
George Gao

They want people to see them as being very confident and good at governance
Sean Sylvia

The main reasons people haven't been vaccinated are concerns about efficacy or safety
Wang Weibing

Few publicly available studies have reported the efficacy of China's vaccines, including those from two leading brands, Sinopharm and Sinovac, which are also exported abroad and which, alongside Pfizer-BioNTech, are the most widely used covid-19 vaccines in the world in terms of doses delivered. The available studies indicate lower efficacy levels than those of mRNA vaccines such as Pfizer-BioNTech's (World Health Organization data suggested 51% effectiveness at preventing symptomatic disease with Sinovac's CoronaVac and 79% with Sinopharm, compared with over 90% with Pfizer) and antibody levels that last three to six months.

Wang Weibing, an epidemiologist at Fudan University in Shanghai, says that the main reasons people in China haven't been vaccinated are concerns about efficacy or safety. Some others can't be vaccinated because of underlying conditions.

The Sinovac and Sinopharm vaccines are approved by the European Medicines Agency and WHO, which emphasise that the drugs provide protection against severe disease and hospital admission. "The demand to get vaccinated is rather strong at our centres," says Charles Poon, medical director of Raffles Medical China North Zone in Beijing. But he adds that "there is also quite a lot of interest and a waiting queue" for the Pfizer-BioNTech vaccine. The *Wall Street Journal* has reported that health officials delayed approval of the Pfizer-BioNTech vaccine because of concerns that it would hurt confidence in locally developed vaccines.

Sylvia says, "The Chinese government realises that there's a lot of hesitancy in China and that the vaccine is not particularly effective or is [not] as effective as they hoped, which is why the other containment policies become more important."

Although he is not privy to deliberations, adds Sylvia, if the vaccines available were considered effective enough and the vaccination coverage was higher, it would be rational for China's policy to change. "Say you had maximum take-up of the vaccine and it was effective and everything—it would make less

CHEN XINBO/XINHUA/ALAMY

People queue at a COVID-19 vaccination site of Jingcheng Hospital

LAOMA/ALAMY

Testing temperature in Canton in February 2020

sense to invest as much in strict containment," he said.

An epidemiologist at a university in Beijing has told *The BMJ* under anonymity that they think some public health measures could change once 80-85% of people have been fully vaccinated and have received a booster shot. The CDC's Gao has said in a TV interview that China may reach 85% by early next year. Gao had also accepted an interview request from *The BMJ*, but his personal assistant at the Chinese Academy of Sciences' Institute of Microbiology asked to reschedule a phone interview set for 30 September and did not offer an alternative arrangement or reply to follow-up requests for alternative dates. Gao had not responded to an emailed list of questions for this article by the time of publication.

Chinese authorities currently recommend booster shots to select groups six months after vaccination because of waning protection, and 37.97 million people in China had received a booster shot as of 5 November, the National Health Commission said. But Nancy Qian, a professor studying China at Northwestern University's Kellogg School of Management, USA, says that rolling out an annual booster to the population is not a simple task.

Qian wrote on Bloomberg, "Most countries, including China, are not accustomed to offering annual flu vaccinations. Administering a round of new boosters every year is much more expensive and logistically difficult than delivering basic vaccines—say, for measles—that only need to be injected a few times during a person's life."

Administering yearly boosters is more expensive and logistically difficult than basic vaccines
Nancy Qian

Australia and New Zealand's geography helped their covid measures
Bonny Ling

The denser the population, the higher likelihood of transmission to potential hosts
Ian Lipkin

Outbreak risk

China is the fourth largest country in the world—behind Russia, Canada, and the US—and has a higher population density than all three: 153 people per km^2 in China, compared with 9 per km^2 in Russia, 4 per km^2 in Canada, and 36 per km^2 in the US. "The denser the population, the higher the likelihood of transmission to potential hosts," says Ian Lipkin, an epidemiologist at Columbia University in New York, who was a special adviser to China's science and technology minister during the 2003 SARS outbreak.

Outbreaks could stem from cases arriving from outside the country, similarly to what happened in countries entirely surrounded by water such as Australia and New Zealand. Earlier this year researchers estimated that of every 100 000 travellers to Australia and New Zealand, five would transmit SARS-CoV-2 to a border or health worker or to someone in the community with a link to quarantine and isolation systems.

"If we look at Australia and New Zealand, their geography helped their covid control measures, but nothing is foolproof," says Bonny Ling, an independent researcher in the UK who studies human rights and migration in the Asia-Pacific region.

There may also be non-human risks from inside China's borders. The origins of SARS-CoV-2 remain a controversial enigma, but David Hayman, an epidemiologist at Massey University in New Zealand and member of WHO's original SARS-CoV-2 origins investigation team, says that, because we don't know how the people in Wuhan were infected, it's not known whether the virus is still circulating in a wild bat or other animal host. "It is not possible to say that another SARS-CoV-2 outbreak from an animal source couldn't happen again, including inside China," he says.

China claims that it's able to extinguish outbreaks, but not all public health experts are sure. "I have no reason to believe in their reports on epidemics," says Vasily Vlassov, an epidemiologist at National Research University's Higher School of Economics in Moscow. He says that if waterlocked Australia and New Zealand couldn't do it, why would China, with its long land borders?

One problem with controlling covid-19 is that regular surveillance would be needed, as even people with no or mild symptoms can transmit SARS-CoV-2. Chen Chien-jen, an epidemiologist at Academia Sinica's Genomics Research Center in Taipei, served as health minister for Taiwan during the 2003 SARS outbreak and says that China would need to test everyone for covid-19 every week if it wanted to identify all cases. "Otherwise, how can you identify a virus in the population?" says Chen. This could be particularly challenging in rural areas.

Oxford University's Hale says that governments should continuously evaluate the costs and benefits of covid-19 approaches and should not be inflexible. He adds, "If China waits until covid-19 is widely suppressed around the world to relax its stance, it may—sadly—be waiting a very long time indeed."

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MEDICINE IN THE MEDIA

Headlines play down the gravity of covid-19 in children

Media coverage has been criticised for minimising the effect of covid-19 on children, implying that the lives of those with underlying health conditions are somehow less important than the lives of healthy individuals. **Jacqui Wise** reports

"Only six healthy children died of covid in a year, but lockdowns fuel youth health timebomb," read the headline in the *Telegraph*. A later version removed "only" from the headline, but the words "only" and "just" were still used repeatedly in the main body of the article.

The piece prompted an angry reaction, with many commentators saying the coverage sounded like eugenics. "An abhorrent, dystopian headline," wrote Gavin Yamey, professor of global health and public policy at Duke University, on Twitter. Martin McKee, professor of European public health at the London School of Hygiene and Tropical Medicine, told *The BMJ*: "The reporting has been especially shocking. Parents of children with underlying health conditions have seen it as implying that those lives are somehow less valued. The authors need to challenge this disgraceful interpretation."

The *Telegraph* was reporting the results of a study published in *Nature Medicine*, which reviewed deaths of children and young people under 18 years old with a positive SARS-CoV-2 test that occurred between March 2020 and February 2021. A total of 3105 children and young people died in England in this time period, 61 of whom were positive for SARS-CoV-2. A panel of three experts concluded that 25 deaths were caused by SARS-CoV-2 infection, including three from paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. They concluded that 41% of all children who died with covid-19 died from it.

Six of the 25 children and young people who died seemed to have no underlying health conditions. The paper says that 76% of those who died had chronic conditions, 64% had multiple morbidities, and 60% had life limiting conditions. Neurological conditions were the most cited comorbidity, which includes learning disabilities and mental health conditions.

Tom Lawton, consultant in critical care and anaesthesia at Bradford Teaching Hospitals, told *The BMJ*: "The authors try to unpick the issues of deaths 'with' versus 'from' covid-19 during the first part of the pandemic, but in doing so have fuelled the fire of minimising childhood deaths. They calculate a death rate using the whole population, even those children who were never infected. This could be compared to stating that cyanide is not dangerous because nobody died from cyanide poisoning in 2020."

He added: "The interpretation of the study as suggesting that the lives of children with comorbidities are somehow worth less than those without is not the fault of the authors, but the paper does not avoid minimisation tropes."

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Interpretation

The analysis covers the period when the predominant SARS-CoV-2 variants were wild type and alpha, before the delta wave had started.

"The findings from the paper are outdated and no longer hold," says Deepti Gurdasani, senior lecturer at Queen Mary University London. "This is clear when we look at the up-to-date data, where it appears that 70% of all deaths in 0-19 year olds 'with' covid-19 are from covid-19 as per ONS [Office for National Statistics] death certification (by contrast with the 40% reported in the paper)."

She adds that the number of deaths in children has vastly increased in the past few months since the spread of the delta variant. The ONS says that there had been 68 covid-19 deaths in 0-19 year olds in England and Wales up to the end of October. Gurdasani estimates from Public Health England data that there have now been around 101 deaths in children.

Christina Pagel, professor of operational research at University College London, says that she doesn't doubt the numbers in the study. On Twitter she said: "Yes children are much less likely to die from covid than adults. But tragically it can still happen. We should not be taking the *Nature Medicine* paper as licence to let covid infect children freely."

McKee also points out that the paper only looks at deaths, the most extreme outcome of covid-19, and that decisions on schools must consider the large burden of morbidity, including large numbers of hospital admissions. "But the fundamental problem is the implication that because fewer children die from covid-19 than other causes we somehow need to worry less about it, even though there are many things we could do to reduce the risk."

Study author Russell Viner told *The BMJ*: "I recognise that there are multiple different perspectives on data, and I would not seek to control or comment on those, aside from asking journalists to report our data accurately." Viner, professor of child and adolescent health at University College London, said: "Any death of a child is a dreadful event and one too many, more so if there were no known other medical conditions where parents were likely aware that these were likely or potentially life-limiting."

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