Production of dexamethasone must be rapidly ramped up to meet global demand, the World Health Organization has said.

The call came as Oxford University’s RECOVERY trial published its much anticipated preprint on the drug’s effect on covid-19. The investigators, who released headline findings last week, found that the drug cuts deaths in ventilated patients by one third and deaths in other admitted patients receiving oxygen by a fifth.

WHO’s director general, Tedros Adhanom Ghebreyesus, said, “The next challenge is to increase production and rapidly and equitably distribute dexamethasone worldwide, focusing on where it is needed most. Demand has already surged following the UK trial results.”

In the preprint paper published on 22 June, the study team reported that 454 of 2104 (21.6%) patients allocated to dexamethasone and 1065 of 4321 (24.6%) patients allocated to usual care died within 28 days (age adjusted rate ratio 0.83 (95% confidence interval 0.74 to 0.92)).

The randomised, controlled, and open label trial began in March and is investigating a number of potential covid-19 treatments at 176 NHS hospitals. In the dexamethasone arm patients were assigned in a ratio of 2:1 to a usual standard of care or to a usual standard of care plus dexamethasone 6 mg once daily for a maximum of 10 days (or until discharge if sooner). The preprint reported that dexamethasone reduced deaths in patients receiving invasive mechanical ventilation from 47% to 29% (0.65 (0.51 to 0.82)).

Of the ventilated patients, 94 of the 324 taking dexamethasone and 278 of the 683 receiving standard care died, a difference of around a third (0.65 (0.51 to 0.82)). Among patients receiving oxygen, 275 of the 1279 taking dexamethasone and 650 of the 2604 on standard care died (0.80 (0.70 to 0.92)).

However, in the group of patients receiving no respiratory support there was no significant difference in mortality: 85 of the 501 taking dexamethasone and 137 of the 1034 allocated to usual care died (1.22 (0.93 to 1.61)).

Carl Heneghan, director of the Centre for Evidence Based Medicine at Oxford University, said, “Given that this is a cheap, available drug, and given the size of the effect, it is clear there is strong evidence to make this treatment available to the right patients admitted to intensive care units.”

Elisabeth Mahase, The BMJ
Cite this as: BMJ 2020;369:m2512

WHO’s Tedros Adhanom Ghebreyesus said, “The next challenge is to rapidly and equitably distribute dexamethasone worldwide”
Health workers should be “highest priority” for covid vaccine, JCVI has advised

Frontline health and social care workers should be the first priority if a covid-19 vaccine became available, the Joint Committee on Vaccination and Immunisation recommends. The next priority group for vaccination should be people at increased risk of serious disease and death from infection because of age and risk factors such as underlying health conditions, says preliminary advice from the JCVI. It said work was continuing to identify which groups were most at risk and noted that “early signals have been identified of other potential risk factors including deprivation and ethnicity.” The JCVI said that frontline workers were at increased personal risk of exposure to infection and of transmitting it to susceptible and vulnerable patients. Vaccinating this group would also help to maintain resilience in the NHS and social care sector, it said.

The advice says that people at greatest risk of severe illness and death include adults over the age of 50 (with the risk increasing with age) and people with underlying comorbidities such as chronic heart, kidney, and pulmonary diseases, malignancy, obesity, and dementia. Also considered to be at greatest risk are people who were shielded, including those who have undergone solid organ transplantsations, those with severe respiratory conditions, and those on immunosuppression therapies.

Covid-19
UK’s pandemic alert level falls from 4 to 3
The UK’s coronavirus alert level was lowered from 4 to 3 after a recommendation from the Joint Biosecurity Centre. Under level 4, transmission is “high or rising exponentially,” whereas under level 3 the virus is in “general circulation.” In a joint statement the chief medical officers for England, Scotland, Wales, and Northern Ireland warned, “It does not mean the pandemic is over. The virus is still in general circulation, and localised outbreaks are likely to occur.”

Doctors “may quit” with poor post-covid support
The government must create a national plan to give doctors the mental wellbeing support they will need after the covid-19 pandemic, the Medical Protection Society warned. Without support and time to recuperate, many doctors may leave the profession or suffer in silence with psychological injuries, the defence body said. It called on the government to invest in local initiatives such as counselling services and to fund fast tracked research into the pandemic’s impact on doctors’ mental wellbeing.

Saliva test pilot scheme starts in Southampton
A new coronavirus saliva test will be trialled in Southampton, aiming to be accurate and more acceptable than the current swab test. The pilot scheme will involve 14 000 GPs, essential key workers, university staff, and their households. Participants will be asked to spit into a sample pot, which will be sent off or collected. The tests will be carried out weekly for four weeks. The trial also aims to find out whether routine testing at home could pick up cases of the virus earlier.

Leading scientist calls for UK coronavirus “tsar”
Peter Piot (below), director of the London School of Hygiene and Tropical Medicine, called on the prime minister to appoint a coronavirus tsar at cabinet level, with “authority to keep the country safe from covid-19 for the next few years.” Speaking on the BBC’s Andrew Marr Show, he said that the tsar should be able to work across all departments and organise future logistics for combating the spread of the virus. He said that he was optimistic about finding a new vaccine but that this was unlikely to be available before 2021.

Child health
Paediatricians urge plan for reopening schools
An open letter, signed by 1633 paediatricians and the Royal College of Paediatrics and Child Health, called on the UK government and the Northern Ireland Executive to publish a clear plan for getting children back to school. It also urged them to deliver recovery plans for young people. The letter, addressed to Boris Johnson, said the interruption to schooling “risks scarring the life chances of a generation of young people.”

Regulation
CQC will restart routine inspections in autumn
Routine inspections of healthcare providers that were suspended during the covid-19 crisis will restart in the autumn, the Care Quality Commission announced. The regulator said that it would also conduct inspections of higher risk providers over the summer. On 16 March all routine inspections of hospitals, GP surgeries, and care providers were stopped to allow services to focus on the covid-19 crisis. In the interim period the CQC has been checking up on providers remotely through its emergency support framework.

Second wave
Review UK’s preparedness
Health leaders urge
A group of medical, public health, and nursing leaders, including The BMJ’s editor in chief, Fiona Godlee, wrote an open letter to the government calling for a rapid cross party review of what needs to be done to prevent and prepare for a second wave of covid-19. The letter argues that an “immediate assessment of national preparedness” is required to give the public confidence that the virus can be contained. Policy areas needing attention include governance, procurement, coordination, the burden on ethnic minority people, and international collaboration.
MEDICINE

Drug development
UK launches scheme for new antibiotic research
The UK launched a subscription-style payment model to incentivise drug companies to invest in researching and developing new antibiotics in the face of growing antibiotic resistance. It will see drug companies receive upfront payment for their product, based on the value it provides to the NHS rather than how much it is used. The government has said that it is particularly interested in antibiotics that can provide treatment options for bloodstream infections, sepsis, and hospital-acquired pneumonia. The first two antibiotics will be selected and evaluated next year.

Clinical guidelines
NICE issues covid guidance on renal transplantation
Patients scheduled to receive a living donor kidney transplant and their donor must self-isolate for 14 days before the transplantation, along with household members, the National Institute for Health and Care Excellence recommended. If a patient needs dialysis in the meantime this must be done in a covid-19 secure environment. The new guidance said that patients with covid-19 should be temporarily removed from the waiting list until they recover.

Training
Flexibility in medical pathway is announced
Health Education England announced plans to provide greater flexibility to trainees by extending its “out of programme pause” plan to include all specialties. This allows trainees to pause their training to work in the NHS or similar patient facing roles in the UK. It aims to support trainees’ wellbeing and give them the opportunity to gain competencies they may have missed during the covid-19 pandemic. The offer is available immediately and is open for applications for one year. See www.hee.nhs.uk/our-work/doctors-training/flexibility-medical-training-pathway.

Mental health
Inequality could be worse “for a generation”
The covid-19 pandemic could widen inequalities in mental health for a generation unless action is taken, the Centre for Mental Health warned. The charity said that the lockdown would put greater pressure on groups whose mental health was already poor before covid-19, such as women and children experiencing violence and abuse, as well as ethnic minorities. The charity’s report is backed by 12 mental health charities and the Royal College of Psychiatrists.

Drug companies will get upfront payments to create new antibiotics

SIXTY SECONDS ON… TWO METRE RULE

WE KNOW, KEEP TWO METRES APART
Not any more. While UK guidance for the past three months has been to stay at least 2 m apart from anyone outside of your household or support bubble, this week the prime minister announced a relaxation of the social distancing rule to a 1 m minimum.

HEY! DON’T STAND SO CLOSE TO ME
All right, no need to call the police. Actually, the World Health Organization has always recommended distancing of 1 m.

WHY’S THAT?
Well, some experts say there is little evidence to support the 2 m rule. Carl Heneghan and Tom Jefferson of the Centre for Evidence Based Medicine in Oxford recently highlighted that all of the 172 studies included in a Lancet review—which found evidence supporting distancing of 1 m or more—were “retrospective and suffer from biases that undermine the reliability of their findings.”

FREE HUGS ALL ROUND?
Not quite. Heneghan and Jefferson say that GP consultation data have shown that encouraging social distancing, as well as hand washing, can help reduce the transmission of infections. “Hand washing and encouragement are what we need, not formalised rules,” they say.

IS ANYONE AGAINST A RELAXATION?
The Independent Scientific Advisory Group for Emergencies (iSAGE) has urged caution, warning that a reduction will, in reality, result in the end of distancing entirely.

WHAT MIGHT THAT MEAN?
Member of iSAGE warn it will put those who cannot work from home, many of whom are from ethnic minority communities or are low paid workers, at most risk.

“Reducing distancing will make these populations less safe, running the danger of making already stark health inequalities much worse,” they said.

MAYBE A STEP BACK IS IN ORDER?
Yes, good plan.

Abi Rimmer, The BMJ
Cite this as: BMJ 2020;369:m2507
Local health teams trace eight times more contacts than centralised, national service

Local health protection teams have traced nearly eight times more contacts (77,642) than the national call centres and online service (9,997), latest figures show. The NHS Test and Trace system brings together the local health protection teams that handle complex cases, and the national call centre and online system—run by two private companies, Serco and Sitel.

The contracts are reportedly worth £108m, and some experts have said this money would have been better spent on resourcing and funding local public health teams, which were already in place and could have led the initiative.

The system began on 28 May, and until 10 June it had attempted to contact 14,045 people who had tested positive for covid-19, of whom 72.6% (10,192) were reached and asked to provide details of their recent close contacts. From this, 96,746 people were identified as close contacts and 87,639 were reached (90.6%).

However, the Office for National Statistics (ONS) reported that between 31 May and 13 June, 33,000 people tested positive for covid-19 in England. This suggests that potentially half of the cases are being missed by the contact tracing service.

Additionally, when the numbers of contacts identified by the system are broken down by who handled them, significantly more came from local health teams than from the national centres and website. According to the latest report (18 June), of 87,639 close contacts that were reached, only 9,997 were non-complex cases handled by the national teams. This means the remaining 77,642 were complex cases handled by local teams.

In a statement the Independent Scientific Advisory Group for Emergencies (ISAGE) said, “This raises serious questions about the efficiency and value for money of the contracts and highlights the vital role being played by the public health teams.”

“Chaotic and haphazard”
The group also pointed to “extensive data gaps” in the report. “This means we cannot tell how well the system is working. The actual number of daily and weekly cases in the community is unknown because testing has been chaotic and haphazard, and the methodology is now being revised. Because of this we don’t know how many cases have been missed and have not been transferred for contact tracing. ONS survey data suggest that there are many missing cases.”

Neither did the report show how

A survey found that 46% of the public said they did not have confidence in Serco to manage the track and tracing programme effectively.

UK drops contact tracing app for the Apple and Google model

The NHS has abandoned plans to develop its own centralised app for contact tracing in favour of developing a version based on Google and Apple technology.

The U-turn is an embarrassment for the government as the app was originally designed to be a key component of its test, track, and trace programme.

Ministers had wanted a centralised version of the technology in which anonymised data from people who reported covid-19 symptoms could be held on an NHS database. In the decentralised model, no data are held in a single official database. Last week Italy and Germany launched apps based on the Google-Apple model.

However, the NHS app, which has been tested in the Isle of Wight, recognised only 4% of Apple phones and 75% of Google’s Android devices. This is because the design of the iPhone operating system means that apps go to sleep when they are not being used and cannot be activated by Bluetooth.

The government said it had been testing both systems over the past month and found that the Apple-Google model recognised 99% of both Android phones and iPhones. This model does, however, have problems distinguishing between whether someone is one metre or three metres away.

“A new solution”
At the government’s daily pandemic briefing England’s health secretary, Matt Hancock, said, “As it stands, our app won’t work, because Apple won’t change their system. But it can measure distance. And their app can’t measure distance well enough to a standard we are satisfied with.” He added, “We will share our algorithm and the work we have done on distance calculation and combine that with their work, to deliver a new solution.”

Hancock would not put a date on when the new app would be launched, but it will not be until autumn at the earliest.

And then it may not involve contact tracing but be limited to enabling users to report symptoms, access advice, and order a test.

Hancock said, “In the meantime, the test and trace system, based on good old fashioned human contact tracing, is working well, identifying local outbreaks and helping us control the virus.”

The latest figures showed that a quarter of people who tested positive for covid-19 in the test and trace scheme’s second week could not be reached.

In a statement the Independent Scientific Advisory Group for Emergencies said it was “deeply concerned about

Our app won’t work, because Apple won’t change their system

Matt Hancock
The NHS app, which has been tested in the Isle of Wight, recognised only 4% of Apple phones and 75% of Google’s Android devices the current government contact tracing system, which is not fit for purpose.”

Chris Hopson, chief executive of NHS Providers, described the announcement about the app as disappointing. “This is a setback in delivering a world beating test and trace system, in which an effective app would play a valuable role.” He added, “This episode presents yet another example of the dangers of overpromising and underdelivering.”

Jacqui Wise, London
Cite this as: BMJ 2020;369:m2472

Researchers question school closures

People under 20 are half as susceptible to covid-19 and far less likely to experience clinical symptoms than older age groups, a study published in Nature Medicine shows. The results suggest that interventions targeting children, such as school closures, are therefore likely to have limited impact in controlling spreads of covid-19. Researchers at the London School of Hygiene and Tropical Medicine applied an age structured mathematical model to epidemic data from Canada, China, Italy, Japan, Singapore, and South Korea to determine the level of susceptibility and clinical symptoms in various age groups. They found that, after contact with someone with covid-19, a person aged under 20 was roughly half as likely to become infected as someone over 20. Relative susceptibility to infection was 0.40 (95% credible interval 0.25 to 0.57) in children aged up to 9 years and 0.88 (0.70 to 0.99) in people aged 60-69.

A “sharp increase” in susceptibility is seen between the ages of 15 and 25, Nicholas Davies, evolutionary biologist and epidemiologist at the LSHTM, said at a press conference on 16 June. School closures are considered a key intervention for respiratory infection epidemics because of the high contact rates between children. To test how effective closures were likely to be against covid-19, the researchers modelled the impact of a three month closure on the course of epidemics of covid-19 and flu in three cities: Milan (median age 43 years), Birmingham (30), and Bulawayo (15).

School closures cut the peak incidence by 17-35% and delayed the peak by 10-89 days for influenza, compared with a 10-19% peak incidence decrease and a 1-6 day delay for covid-19. School closures were least effective in populations with lower median ages.

Ingrid Torjesen, London
Cite this as: BMJ 2020;369:m2439

Most ethnic minority doctors feel unsafe

Less than a third (29%) of black, Asian, and other ethnic minority doctors in the UK believe they are fully protected from covid-19 at work, whereas nearly half (46%) of their white colleagues do, shows a survey of around 7500 doctors.

The survey, carried out between 16 and 18 June, also showed that ethnic minority doctors were more likely to feel underdelivered in terms of resources. The government has instead put in a centralised, privatised system that has not been shown to work or been evaluated.

“If they had diverted all the money that they spent [on this system] to enable public health and local authorities and Public Health England, we would have had contact tracing off the ground much sooner, and we may have saved lives.”

The figures came as a survey of 1022 adults in the UK—commissioned by We Own It, which campaigns against the privatisation of public services—found that 46% said they did not have confidence in Serco to manage the track and tracing programme effectively. Only 27% said they did have confidence, while 28% said they didn’t know.

Elisabeth Mahase, The BMJ
Cite this as: BMJ 2020;369:m2486

The BMJ
Cite this as: BMJ 2020;369:m2506

Researchers question school closures

People under 20 are half as susceptible to covid-19 and far less likely to experience clinical symptoms than older age groups, a study published in Nature Medicine shows. The results suggest that interventions targeting children, such as school closures, are therefore likely to have limited impact in controlling spreads of covid-19. Researchers at the London School of Hygiene and Tropical Medicine applied an age structured mathematical model to epidemic data from Canada, China, Italy, Japan, Singapore, and South Korea to determine the level of susceptibility and clinical symptoms in various age groups. They found that, after contact with someone with covid-19, a person aged under 20 was roughly half as likely to become infected as someone over 20. Relative susceptibility to infection was 0.40 (95% credible interval 0.25 to 0.57) in children aged up to 9 years and 0.88 (0.70 to 0.99) in people aged 60-69.

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Many GPs think climate change is important, but they still see it as a peripheral matter that’s not core to their professional role or practice. With Greener Practice we’re trying to raise awareness that it is urgent and fundamental to our role, as we can’t have health without a healthy planet.

“It’s in the clinical realm we can have the biggest impact. When you say to GPs, ‘We need to be greener,’ a lot of the responses are around waste or consumables. Those are absolutely important, but they account for a very small proportion of the carbon footprint in general practice. The vast majority is in our clinical work.

“It’s important we look at alternatives to drugs, in situations where there is a good evidence base for lifestyle interventions. Social prescribing is another way of being greener, as is green prescribing: social prescribing with the added benefit of nature—things like gardening, conservation activities, and exercising in nature.

“There are also low carbon alternatives to prescribing. For example, in the UK we mainly prescribe metered dose inhalers that have a propellant in them that is 1000 to 3000 times more powerful than carbon dioxide.

As a result, they’re responsible for around a quarter of the GP prescribing carbon footprint. In many other parts of Europe they mainly use dry powder inhalers. We could safely switch. The vast majority of patients that would be completely safe, and it might even be more effective.

“I hope our website and the recent BMA policy document on sustainable general practice, which I helped develop, will be useful to GP colleagues.

“The covid-19 pandemic has made us transform. We now have an opportunity to transform our economy and put health and wellbeing at its centre. And you can’t do that without considering planetary health.”

For more information see www.greenerpractice.co.uk and the BMA’s policy document at bit.ly/17OPUKM

Abi Rimmer, The BMJ  Cite this as: BMJ 2020;369:m2483

NEWS ANALYSIS

Can vitamin D cut covid infection risk, review asks

Ingrid Torjesen finds out what the existing evidence shows

Public health agencies in England and Scotland are conducting urgent reviews into the potential for vitamin D to reduce the risk of contracting covid-19. Among the evidence being examined is a systematic review and meta-analysis published in The BMJ in 2017, which concluded that vitamin D supplementation cut the risk of acute respiratory infections. Since the start of the covid-19 pandemic the review has been viewed online more than 300 000 times and shared more times on social media than any other paper published in The BMJ in the past three years.

Public Health England has confirmed that the Scientific Advisory Committee on Nutrition will examine the findings of the paper as part of a wider review of the evidence on vitamin D supplementation and reduced risk of acute respiratory tract infections. At the same time NICE is producing a rapid evidence summary on vitamin D supplementation in the context of covid-19, and Public Health Scotland is conducting a similar evidence gathering exercise.

“Limited data”

“I suspect that they’re going to have problems drawing any definitive conclusion, simply because the data are limited,” said Adrian Martineau, professor of respiratory infection and immunity at Queen Mary University of London and one of the authors of The BMJ’s review. He said he knew of no laboratory studies that had looked specifically at the effect of vitamin D on immune responses to SARS-CoV-2.

Many such studies had investigated other respiratory viruses, however, and found that vitamin D metabolites augment innate antiviral immune responses while simultaneously reducing cytokine storms.

A meta-analysis in The BMJ that concluded vitamin D cut the risk of acute respiratory infections has been viewed over 300 000 times

Call for health checks to start at age 25 for some ethnic minority groups

The NHS could help prevent illness among ethnic minority groups and reduce their risk of contracting covid-19 by lowering the age at which the NHS health check begins for some patients, MPs have been told.

MPs on the women and equalities committee held an evidence session on 17 June for their inquiry into the effect of covid-19 on black and Asian people, who have been dying disproportionately. They asked medical and academic experts as well as ethnic minority representatives whether biological determinants were a primary factor in the difference in mortality and in which areas the government’s efforts would best be focused.

Biological factors

Kamlesh Khunti, professor of diabetes and vascular medicine at the University of Leicester, said, “The biological factors are well known. There are some modifiable and some non-modifiable factors. Having chronic diseases is definitely a modifiable factor. Primary prevention is key.

“We have an NHS health check which is for people aged 40 to 74. For people with BAME backgrounds, because they get these conditions earlier, we should extend that to age 25.”

More targeted help for people from ethnic minority groups was needed in primary care, Khunti added, saying, “We’ve had a lockdown
dampening down inflammation, a major problem in covid-19.

“This combination of actions makes vitamin D an interesting candidate both as a potential tool in covid-19 prevention and as an adjunct to other therapies for people who already have the disease,” said Martineau.

**Reverse causality**
He said a few observational studies had linked low vitamin D status to adverse outcomes in covid-19 but said these were limited by the potential for confounding to explain the associations. Reverse causality could also be operating, he added. “Inflammation itself can disturb vitamin D metabolism and actually render somebody deficient, as we have recently shown in patients with asthma and chronic obstructive pulmonary disease.”

PHE updated its advice on vitamin D supplementation in April when it recommended that everyone should consider taking a daily 10 μg supplement because lockdown meant that people might not get enough of the vitamin from sunlight. It added that at that time there was not enough evidence to recommend vitamin D supplements specifically for reducing the risk of covid-19. Public Health Scotland gave similar advice in June.

Both PHE and the Scottish agency especially recommend supplementation for people with dark skin who require more sun exposure to make sufficient vitamin D. There have also been suggestions that a deficiency may explain why people of black and Asian backgrounds experience more adverse outcomes from covid-19.

“It’s an interesting hypothesis,” Martineau said. “It’s unlikely ethnic disparities will be explained by a single factor. My hunch is that socioeconomic and structural factors will be more contributory than biological ones. Nevertheless, the vitamin D story is worthy of exploration.”

**Recruiting participants**
A national longitudinal study, called COVIDENCE UK, is looking to recruit 12 000 people. Participants will complete an initial online questionnaire collecting information on determinants of vitamin D status and other putative risk factors. This information will be linked to notifications of incident covid-19 captured through monthly online follow-up, linked to routinely collected health outcome data held by NHS Digital. A randomised controlled trial over the winter is then planned, looking at the potential for different supplementation strategies.

Martineau appealed to BMJ readers to sign up. “Healthcare professionals are at heightened risk of covid-19; it’s vital they are well represented in our study so we can identify modifiable risk factors as soon as possible. Already 9000 people are taking part, many of them NHS colleagues.”

Regardless of any impact on covid-19, if everyone took a 10 μg daily vitamin D supplement it would have a real benefit for musculoskeletal health, Martineau added. “Our unpublished preliminary data indicate that two in three participants are not taking supplemental vitamin D, and they are likely to represent a more health conscious subgroup of the population.

“One of the questions our trial will look at is whether providing supplements free of charge improves uptake,” he said.

**WE KNOW**

that 63% of healthcare workers who have died were from a BAME background

Chaand Nagpaul, BMA of council of the BMA, said it had asked the government to investigate why the first 10 doctors to die from covid-19 were all from an ethnic minority background. “The impact on healthcare workers has been severe,” said Nagpaul. “We now know that 63% of healthcare workers who have died were from a BAME background.

“From the outset, the BMA was calling for mitigations in terms of risk assessments and looking at ethnicity as a risk factor in its own right.”

The MPs asked to what extent the disproportionate death rate from covid-19 was because of the nature of the virus itself, comorbidities, or socioeconomic factors. Nagpaul said, “The matter of race and ethnicity is interlinked with many other risk factors and inequalities.

“We know, for example, that you’ve got twice as much likelihood of dying if you come from a deprived community compared with a more affluent one, and we also know that there’s twice as many BAME people who live in deprived areas. “There probably are race inequalities that have led to a greater proportion of BAME people with low wages, working in those key roles, that could not allow them the same protection as those who were able to work at home.”

Adrian O’Dowd, London
Cite this as: BMJ 2020;369:m2462
Footballers from West Ham United and Wolverhampton Wanderers and match officials take part in a minute’s silence on 20 June to commemorate the people in the UK who have died in the covid-19 pandemic. The recorded number of deaths from covid-19 was then 42 589.

England’s Premier League season restarted three days earlier with teams playing games postponed during lockdown being behind closed doors, as social distancing laws prohibit fans inside venues.

Alison Shepherd, The BMJ
Cite this as: BMJ 2020;369:m2504
IN MEMORY OF THOSE WE HAVE SADLY LOST
The number of deaths from covid-19 in the UK is among the highest reported internationally. This covid-19 related mortality surge comes on the heels of a historical legacy of stalling improvements in life expectancy in the UK. A clear understanding of what’s driving mortality is critical, to inform evidence based policies and interventions for tackling both covid-19 and other causes of death.

In three months, SARS-CoV-2 has claimed at least 46 000 lives in England and Wales, and is now a leading cause of death, overtaking the annual death toll from major conditions such as lung cancer and stroke. The death toll from covid-19 is still rising, and even these grim statistics don’t fully capture the effect of covid-19 since deaths from other causes also increased (by over 12 000) during the same period.

**Excess deaths**

An analysis by the Office for National Statistics (ONS) of non-covid deaths and excess deaths over the 2015-19 average provides strong evidence that covid-19 deaths are under-recorded in death certification.

Concerns about under-reporting of covid-19 deaths, and the need to capture the indirect death toll (for example, caused by people not receiving healthcare for other conditions), have led to the widespread use of “excess” deaths as a measure of the overall effect of the pandemic.

Compared with the 2015-19 average, there were 58 000 excess deaths in England and Wales from 5 March to 29 May 2020. A caveat to this measure is that the choice of baseline affects the number of excess deaths. For example, a baseline of 2015-19 results in 8% fewer excess deaths than a baseline of 2019. The ONS acknowledges that its analysis—which uses 2015-19 as a comparator—could therefore underestimate the true scale of excess deaths.

Excess deaths can be a useful measure of the overall effect of the covid-19 pandemic but are of limited practical value in informing how the NHS and other public services should respond. Accurate estimates of cause specific morbidity and mortality are also essential, to help target public health surveillance and to inform control strategies and health service planning.

Influenza provides a good parallel: like covid-19, influenza causes substantial morbidity and hospital admissions but influenza related deaths are substantially under-recorded—for some of the same reasons that apply to covid-19. To try and overcome this problem, authorities such as Public Health England and the US Centres for Disease Control estimate rates of influenza related deaths using alternative approaches that combine both mortality and surveillance data.

Equally robust, coordinated systems of mortality surveillance should be implemented nationally and internationally for covid-19, a deadlier virus than influenza. This entails UK public health agencies working with relevant national and international agencies, using their combined skills and expertise and building on existing systems for disease and mortality surveillance.

The timely availability of accurate mortality data is also critical for informing a swift response to rapidly changing disease patterns. The ONS’s speedy analysis of covid related mortality, including secondary analyses of inequalities and other causes of death, is commendable and compares favourably with the lengthier process of data release in many other countries. However, the underlying data must be improved. In particular, the feasibility of recording ethnicity on death certificates (adopted by Scotland in 2012) should be revisited as a priority given the evidence about ethnic differences in morbidity and mortality, now so greatly amplified in relation to covid-19.

**Poor performance**

Even before covid-19, the UK’s life expectancy was lower than in other western European countries and showed the least improvement between 2011 and 2018. Its relatively high mortality in 2020 from all causes risks a further slide down life expectancy league tables. Female life expectancy in particular, already among the lowest compared with European peers, is likely to slide even further behind, given the ONS finding that the increase in deaths has disproportionately affected older women.

Although the UK’s mortality trends relative to other countries will partly depend on how the pandemic plays out in the UK and elsewhere, 2020 has not been an auspicious start to turning the tide. We must ensure our monitoring and surveillance systems are comprehensive, reliable, and timely enough to drive much needed improvements in covid-19 mortality, all cause mortality, and life expectancy.
Covid-19 and ethnic minorities

The government’s latest report falls seriously short on commitment

The government can no longer distance itself from its responsibilities to the ethnic minority population and workforce

Demands to address the health inequalities facing ethnic minorities date back at least two decades. Yet it has taken a global pandemic for those demands to be taken seriously. The question now is what can be done and how quickly?

After widespread criticism of an inadequate initial report, and following accusations of deliberate delay or suppression, the government has finally released Public Health England’s full report on ethnic disparities in covid-19. It includes a consultation with over 4000 stakeholders, a rapid review, and a brief set of recommendations.

The report is clear that there is a problem. Deaths from covid-19 among people from ethnic minorities are two to four times higher than in the white majority population. The rapid review and the stakeholder consultation suggest that these differences may be partly explained by comorbidities, overcrowded housing, income inequality, and occupational risk, although no original or secondary data are presented to provide a definitive answer. The themes of delayed access and the role of racism and distrust emerge strongly from stakeholder interviews.

PHE’s resulting recommendations are sensible and largely uncontroversial (box), but they are not new and fail to direct a clear programme of action. The proposals lack detail and provide no time frames for delivery or methods of implementation. Crucially, nobody is held responsible or accountable. The report does not say which systems and structures will enable the actions to be delivered.

PHE and others previously identified that wider socioeconomic inequalities and deprivation underpin ethnic disparities in covid-19 outcomes. Inequalities were exacerbated in recent years by changes to the labour market, social security system, and immigration policy. Low quality or insecure work appears to increase exposure and risks from covid-19. It is therefore disappointing to see only one recommendation on these deeply rooted wider determinants of health. The recommendations are silent on the critical issues of employment security, adequate safety nets, and the causes of occupational segregation. Similarly, nothing is said about a longstanding need to reduce household overcrowding, a key candidate for covid-19 transmission.

Social housing restrictions on local authorities impair adequate housing provision for larger and multigenerational households. Interaction between immigration policy and the health risks for ethnic minorities, whether through avoiding seeking care or being unable to take leave from work, is another area that requires sharper focus.

Five actions

We urge the government to take five immediate steps. Firstly, mandatory collection of ethnicity data must be prioritised, and the new NHS Race and Health Observatory can be a catalyst. Comprehensive data collection across multiple administrative sources, including death records, will be the foundation for further research into explanatory factors for covid-19 disparities. For example, a better understanding of intrahousehold transmission will have implications for the causal role of larger and multigenerational households.

Disaggregating ethnic groups is vital since exposure, survival, and risk factors vary by group. Comorbidities are more influential in Bangladeshi men, while black Africans, who face the highest age adjusted death rates, are more likely to work in the social care sector than their white majority peers.

The government can no longer distance itself from its responsibilities to the ethnic minority population and workforce

Public Health England’s core recommendations

• Mandate ethnicity data collection and recording
• Support community participatory research
• Improve healthcare access, experience, and outcome
• Accelerate culturally tailored occupational risk assessment
• Fund and implement culturally tailored covid-19 messaging
• Accelerate culturally tailored chronic disease efforts
• Ensure covid-19 recovery reduces inequality caused by wider health determinants

Secondly, culturally tailored occupational risk assessment for covid-19 is urgently required and should be delivered with clear messaging. Thirdly, priority covid-19 testing for all public facing jobs, already implemented by some NHS trusts, should become standard practice. Fourthly, explicit ownership of the recommendations and accountability for their implementation at ministerial level is essential to achieve the level of detailed thought and action needed to reduce the dangers that covid-19 poses to ethnic minority populations. Finally, the government and public health organisations must make an open and tangible commitment to working together to end health inequalities for ethnic minorities.

The current ethnic and socioeconomic disparities in covid-19 cannot be separated from social determinants of health, particularly deprivation, and widening health inequalities. Covid-19 does discriminate on the basis of inequalities, and the government can no longer distance itself from its responsibilities to the ethnic minority population and workforce.

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WHAT ARE ANTIBODY TESTS?

Studies have shown that patients who have survived covid-19 have antibodies associated with the disease in their blood. Tests can thus be designed to detect those antibodies and indicate whether someone has been infected by the virus in the past. However, such tests aren’t always accurate, and antibodies can gradually disappear from the blood over time.

Antibody tests are different from the standard polymerase chain reaction (PCR) tests for covid-19, which detect the presence of viral RNA in, for example, fluid from a patient’s nose or throat. PCR tests can reveal whether someone currently has the virus, but the whole process, including collecting and running samples, means that it can take a day or two to deliver a result (which also makes it expensive—each sample costing around £40-£120). In principle, antibody tests are a lot faster and cheaper: some can give results in less than 30 minutes with prices around £8 a sample, although these may not be the most accurate type.

HOW DO THE TESTS WORK?

An ideal antibody test is like Cinderella’s glass slipper—only one foot will fit. When testing for covid-19, small antigen proteins from the SARS-CoV-2 virus are coated on to a plate. These are then exposed to a blood sample from a patient, and an enzyme and chemical reagent are applied.

If the specific antibodies that target the SARS-CoV-2 virus are present in the blood sample, they will attach to the viral antigens on the plate. The enzyme then sticks to the antibody, which subsequently activates the chemical reagent, causing a colour change or giving off a luminescence that indicates a positive result (in some lab based tests, measuring the amount of light can quantify how many antibodies are present).

These tests can be performed in laboratories, but simpler versions can also be packaged in self-testing kits for people to use at home, using a finger prick to take a blood sample. One big difference is that lab based tests can quantify the number of antibodies in a sample, while self-testing kits merely provide a positive or negative result.

HOW ACCURATE ARE THE LAB TESTS?

There are two key measures of an antibody test’s quality: its sensitivity and specificity. Highly sensitive tests can accurately detect whether people have antibodies present in their blood. If a test is described as highly specific, this means that it’s specific to a particular type of antibody and can also reliably detect people who do not have covid-19 antibodies. The presence of some types of antibodies can give an indication of when a person may have been infected.

So far, the quality of antibody tests for covid-19 vary in quality, but several offer sensitivity and specificity near to or even at 100%, say their manufacturers. Very occasionally, an antibody test may give a false positive result (suggesting that people have covid-19 antibodies when in fact they do not) because of cross reactivity with coronaviruses other than SARS-CoV-2, for example.

No test can always be 100% accurate. Lab test kits made by the drug companies Roche and Abbott were evaluated by Public Health England in a series of experiments using samples from confirmed covid-19 patients. Public Health England found that the Abbott test was 93.4% sensitive and 100% specific for samples collected two weeks after the patient first showed symptoms. The Roche tests were 87% sensitive and 100% specific. The lower the sensitivity, the higher the likelihood of false negative results.

WHAT ABOUT SELF-TESTING?

Self-test kits are more of a wild west. In April, the UK government purchased two million finger prick self-test kits from two Chinese companies at a cost of £16m. In May, however, researchers from the University of Oxford found the kits to be insufficiently accurate. The tests were never used—half a million of them are sitting in storage—and the government is reportedly seeking a refund.

Self-testing kits display only a positive or negative result, with no further details. Home tests that involve a finger prick are designed with a certain threshold of antigen reagent activity that will then show a positive or negative result. Depending on how the manufacturer set up the test, people could get a negative result even though they do have a small number of covid-19 antibodies in their blood—just not enough to get over the test kit’s threshold and trigger the “positive” indicator.

People could get a negative result even with a small number of covid-19 antibodies in their blood—just not enough to get over the test kit’s threshold and trigger the “positive” indicator.
their blood—just not enough to get over the test kit’s threshold and trigger the “positive” indicator. Furthermore, accurately placing a drop of blood into the test cartridge on some tests requires care, and it may not always be done correctly.

Eleanor Riley, professor of immunology and infectious disease at the University of Edinburgh, says that it doesn’t matter how many times you do one of these tests: very low levels of antibodies won’t get picked up. Just as home pregnancy tests aren’t infallible, self-test kits for covid-19 should never be used as definitive indicators of whether someone has had the virus, she says.

A positive result should be seen as a prompt for further testing and confirmation, and a negative result doesn’t mean that the person has never had the virus.

WHAT ANTIBODY TESTS ARE BEING USED AROUND THE WORLD?

Crucially, no internationally accepted standard exists for covid-19 antibody tests, leaving governments to evaluate tests using their own criteria. This is a big problem, says Lawrence Young, professor of molecular oncology at the University of Warwick, as it means that no one can use a standard set of tests.

In the US, around a dozen antibody tests have been approved for use by the Food and Drug Administration, including those supplied by Roche and Abbott. Abbott has shipped more than 11 million antibody lab tests to healthcare organisations in the US so far.

The Roche and Abbott tests are also being used in other countries including Germany, Italy, and, as mentioned, the UK, which has purchased 10 million lab antibody tests manufactured by these two companies. The UK is also developing its own finger-prick tests through a consortium, with the aim of eventually distributing them to the public.

Meanwhile, the UK’s Medicines and Healthcare Products Regulatory Agency has taken action to prevent the sale of other commercial home testing kits that were previously available in the country. Such tests have not been validated, and any results from them should not be considered reliable, the UK agency has said. Australia recently found that one million finger-prick tests purchased by the government from two companies based in the US and China weren’t accurate enough to be used.

Antibody tests continue to form part of several countries’ strategies, particularly as governments look to ease lockdown measures and raise their test and trace capacity. Singapore has used antibody tests to aid contact tracing and surveillance efforts. Japan has said that it will complement PCR testing with antibody tests, citing their faster application and results and acknowledging the risk of false outcomes.

Furthermore, antibody tests can be useful for modelling how far covid-19 has spread in the community, particularly given the confusion over asymptomatic transmission. A study of antibody prevalence in 885 people in England recently suggested that about 7% of the population had been infected with SARS-CoV-2. Researchers in Germany found antibody evidence suggesting that 16% of its population had been infected with covid-19 so far.

Japan has launched a pilot scheme to ascertain the extent of covid infections in three prefectures, including Tokyo, using antibody tests. And in Wuhan, China, authorities have tested 9.9 million people using a mix of PCR and antibody tests to find out how widely the new coronavirus has spread in the place where it first emerged back in December.

DOES A POSITIVE ANTIBODY TEST RESULT MEAN THAT I AM IMMUNE?

This is the question on most people’s minds, but they shouldn’t get their hopes up, says Simon Clarke, associate professor in cellular microbiology at the University of Reading. “There’s been far too much said about immunity passports and [the suggestion that] ‘If you’ve got antibodies, you’re immune,’” he says.

Scientists still don’t know what an ideal immune system response to covid-19 looks like. Antibodies may be very important, but so may the response of T cells, for example. It’s possible that merely having antibodies isn’t enough to prevent reinfection by the virus. And antibodies may also gradually disappear from someone’s system over time—perhaps after a few months or years—potentially leaving that person vulnerable to SARS-CoV-2 again. Our immunity to the seasonal flu tends to last for about a year, but it’s still unknown whether covid-19 will be the same, longer, or shorter.

And, as we’ve heard, the accuracy of antibody tests is still under review in many cases. People may get a false positive result showing that they have antibodies and may relax their attitude towards handwashing and social distancing. “People are interested in these tests because they want certainty,” says Riley. “The problem with the individual tests is they cannot give them that.”
COVID-19

Why the government is wrong about antibody tests being a game changer

Boris Johnson has described antibody testing as “game-changing” in the pandemic. But experts have concerns over test reliability, and what results will mean for individuals or the UK. Stephen Armstrong reports

On 21 May England’s health and social care secretary, Matt Hancock, called reliable SARS-CoV-2 antibody testing on a large scale “an important milestone” in developing “immunity passports.” Such documents would, said Hancock, differentiate between people who had recovered from covid-19 and those still vulnerable to infection, freeing many from social distancing and giving people who have the antibodies assurances of what they could safely do.

On 10 June, however, the head of the NHS Test and Trace programme, Dido Harding, said not enough was known about the level of protection that coronavirus antibodies provided. “I know we all want it to be true that if we have antibodies it will then mean we are free to do things others are not,” she told a press briefing. “But at the moment . . . if we have an antibody test what it tells you is you have antibodies.”

And a letter to The BMJ (see p 479) from a group of senior clinical academics and physicians publicly questions the antibody testing strategy, just as the first systematic review of studies on covid-19 antibody tests is set to be published. Jon Deeks, professor of biostatistics at Birmingham University and The BMJ’s chief statistician, who led the Cochrane review, said the analysis shows “we don’t have much data [on the tests] and we can’t trust any of it.”

The meaning of accuracy

The Cochrane review, an advance copy of which The BMJ has seen, concludes that the data supporting existing antibody tests are so vague that it’s impossible to know how accurate the tests are, especially for people with mild or no symptoms or after symptoms have gone.

Test accuracy, says Matt Keeling, professor of populations and disease at the University of Warwick, is measured in sensitivity and specificity. High sensitivity means that if you’ve previously been infected with SARS-CoV-2 the test will correctly identify this, while high specificity means that if you haven’t been infected the test will correctly identify that. “This is important, as any [people with] false positives could incorrectly assume they have had the virus and therefore are a lower risk,” he explains.

At the time of writing two of the world’s leading suppliers of covid-19 antibody tests are the drug companies Abbott and Roche. In May the UK government purchased 10 million kits from the two companies after validation from Public Health England (PHE) that they worked. Media reports at the time stated that the Abbott and Roche tests boasted 99% and 100% specificity, respectively, but these figures came from the companies themselves and were based on those PHE’s initial studies rather than peer reviewed research.

Roche’s marketing material claims a sensitivity of 100% 14 days after the confirmation a patient has had covid-19 through a PCR test that detected the presence of the virus. Abbott claims 100% accuracy 17 days after symptom onset. The PHE studies evaluating the kits use date of symptom onset. The discrepancy between the times used makes it difficult to compare the two test kits, yet alone standardise them for use by the NHS.
The accuracy of a test relates to whether it makes errors: people with the disease wrongly getting negative results, and people without the disease wrongly getting positive results. “Saying a test is 100% accurate implies to the public that neither of these two types of error occurs,” says Deeks. “The reports from PHE make it clear that this statement is misleading.”

A Roche Diagnostics UK spokesman told The BMJ, “Our test is designed to be used as an aid to identify who has previously been exposed to the virus and has been through a rigorous regulated process. This is based on extensive testing and validation, including the measurement of over 5400 samples. We are rolling out antibody tests to the NHS as part of the crucial next step in understanding the spread of this virus, and providing greater confidence and reassurance as we move into the next phase of our response to this pandemic.”

**Testing the testers**

However, it’s not just the tests that are uncertain. Even the studies evaluating the tests have problems, as the Cochrane review found. Standards for reporting diagnostic accuracy studies have been around for a decade, says Deeks, yet none of the 54 studies the Cochrane review saw fit those. “We cannot properly tell anything about the research until the researchers start following those guidelines.”

For instance, PHE’s report on Roche’s test has changed since the original study was posted online. Roche’s controversial claim to 100% accuracy was based on a subgroup of patients who had the longest time between the start of symptoms and being tested for antibodies and had originally consisted of just eight patients tested after six to seven weeks.

But the report The BMJ accessed online at the time of writing includes patients without symptoms, boosting the number of patients to 10 and reducing the accuracy to a score of nine out of 10. A PHE spokesperson said that this update was due to two samples being incorrectly labelled as missing interval data and that this had been noted in the document control section of the report.

More importantly, the assessments of the tests were based on samples and not patients—and almost certainly some patients will have contributed multiple samples that will make the results look more precise than they actually are, says Deeks.

“Where will these tests be used? That’s where you do the study,” he says. “The samples [used in evaluating these tests] are probably from the patients in hospitals, who will be the most severely affected, and their antibody response is not that of people with mild symptoms or those who are asymptomatic.”

Because the origin and severity of disease in the samples are not known, it is not possible to check whether they are representative of the typical patient groups receiving an antibody test in real life. And patients without covid-19 but with similar respiratory illnesses were not included, so it’s difficult to tell whether false positives might arise from such people. Moreover, as the studies were undertaken in expert PHE laboratories, the performance of the tests when used in practice may not be as good.

According to Sheila Bird from Edinburgh University’s College of Medicine and Veterinary Medicine there are several problems with PHE’s evaluation of the Roche and Abbott tests, including quality of samples and the absence of data on age and sex, sample sizes, and use of repeat samples.

PHE acknowledged that a small number of samples were repeat samples from different points in the patient’s disease. It said that samples reflected the general population. “Our evaluations have been completed in record time using the samples and tests that were available to us. We are confident the volume of samples and methodology was of a high standard,” its spokesperson said.

“Any laboratory using these tests is still required to complete their own evaluation to ensure the tests perform as described—our work is designed to reduce the amount of local work required. Our evaluation work is ongoing and, as more tests become available, we will continue to refine our approach.”

**Purpose unclear**

The big question is: what will these tests actually be used for? “What people really want to know from these tests is: am I safe from infection?” says Al Edwards, associate professor in biomedical technology at Reading University.

“These tests, at the moment, can’t answer that.”

Neither the Abbott nor the Roche test detects antibodies against
SARS-CoV-2’s outer “spike protein,” which studies have indicated are most important for neutralising the virus. Both tests detect antibodies for a different protein termed N.

Moreover, although antibody tests can measure the concentration of antibody in the blood, it is not yet known what level is related to protection. The measles vaccine offers lifetime immunity, but the most effective cholera vaccine, Dukoral, provides antibodies that protect for only five years.

In fact, there is currently no evidence that covid-19 antibodies confer immunity at all—and it’s conceivable they won’t, says Edwards. Immunity passports may never come to fruition.

In a statement to The BMJ, the Department of Health and Social Care for England said, “We do not currently know how long an antibody response to the virus lasts, nor whether having antibodies means a person cannot transmit it to others.” But it reiterated that antibody testing “will play an increasingly important role as we move into the next phase of our response to this pandemic.”

It further said, “Antibody testing is helping us learn about the level and length of immunity following infection and how the virus is spreading across the country,” adding that PHE is currently running the SIREN study of 10 000 healthcare workers to establish whether antibodies indicate any kind of immunity to covid-19.

Epidemiological studies such as SIREN could well make use of antibody tests. Wider testing could measure the spread of the disease across the country, identifying vulnerable population groups and geographical regions. The Chinese city of Wuhan, for instance, used antibody tests to check its population of around 10 million as it eased out of lockdown. But the authors of the letter to The BMJ believe that this is not in the UK government’s plans.

Will Irving, professor of virology at the University of Nottingham and a signatory to the letter, said using antibody tests for epidemiological surveys was possible but would need the structure of a formal epidemiological study, taking into account geography, ethnicity, age, and sex. “This is not the same as simply testing a random set of volunteers who wish to know their antibody status,” he said.

**Wasted money?**

So what do we know about the available covid-19 antibody tests? They are not a good indicator of current infection or for telling people to isolate, says Andrew Preston, reader in microbial pathogenesis at the University of Bath. They are much more accurate if used 14 days after symptoms arise, but currently people with symptoms are told to self-isolate for 14 days anyway, making taking a test moot.

The UK government has already spent £1.6m buying antibody tests from China that proved inaccurate, many of which now lie in storage. When it ordered 10 million of the Roche and Abbott tests, financial details of the deal were not disclosed. If the Abbott test is supplied at cost, however, there is evidence to indicate that the NHS will spend £79 per test.

The demand for an expensive, fast turnaround on uncertain tests—NHS trusts required to offer tests at short notice, building up to thousands of samples a day—is arguably a waste of public money, given that the tests are neither clinically urgent nor a public health priority.

Irving told The BMJ, “The government has been focusing on arbitrary, meaningless targets, such as numbers of tests per day, without any regard for the clinical value of those tests, whether or not the tests are actually carried out, or whether the results are returned in a timely fashion to someone who knows the patient and is able to interpret those results.”

The capacity target of 200 000 tests by the end of May included antibody testing as well as PCR antigen tests. By 31 May it had carried out 23 000 antibody tests, and as at 2 June testing capacity included 40 000 antibody tests. But, says Irving, “Focusing simply on numbers of tests done, without any consideration of the quality of those tests results, is contrary to the basic principles of pathology testing.

“I think the government bought the tests because they were caught out in not having the reagents or the tests for virus testing early on,” says Preston. “The idea of buying antibody tests to create immunity passports looked attractive, but using them like that is some way off.”

“If they’re not being used for full epidemiological studies, I think their main function will be in deciding who to vaccinate, assuming the vaccine comes. That will be useful—but I’m not sure it’s a game changer.”

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**Immune passports are some way off**

Andrew Preston, Bath University

**The government has focused on arbitrary, meaningless targets**

Will Irving, Nottingham University

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A home SARS-CoV-2 IgG antibody test kit. Blood from a finger prick is sent back to an Abbott lab for analysis.
We are writing to express concerns over aspects of the establishment of SARS-CoV-2 antibody testing in England. NHS England and NHS Improvement wrote to NHS trusts and pathology networks on 25 May, asking them to offer antibody testing at short notice and ramp up capacity to thousands of samples a day.1,2

We have three concerns about the request. First, there is no specific clinical indication for the test on an individual basis. Second, the test’s performance has not yet been assessed to the standard typically required of a novel test. And third, the resource implications are not considered.

We support the rapid provision of diagnostic tests. It is essential, however, that quality systems, which have evolved over many years and are the foundation for delivering the right result of the right test to the right person at the right time, are not circumvented.

No clinical indication

In usual clinical practice, antibody testing fulfils several purposes. In acute illness, an IgM antibody response can be used to diagnose an infectious cause. The presence of IgG antibodies can provide evidence of prior infection or vaccination and likely immunity to future infection for some viruses, such as measles or hepatitis A. For other viruses, such as measles, IgG antibodies can provide evidence of prior spread of infection.

The concept of “immune passports,” allowing healthcare workers or others to work, has not been established. Those with a positive antibody test should still consider themselves at risk and follow infection control policies designed to prevent nosocomial spread and risk of infection. There is, therefore, no benefit to healthcare organisations or to others in knowing the status of employees at present.

Unproved performance

No reference standard has been defined for SARS-CoV-2 antibody tests. Access to “true positive” and “true negative” samples is difficult, even in large teaching hospitals. Laboratories across the country will have found it hard to achieve standard verification in a matter of days, not least because different platforms will be used for this test from manufacturers including Abbott, Roche, Siemens, Ortho, and Diasorin. Currently, there are no openly available data to compare the performance of these platforms.

Public Health England (PHE) has published verification data, but concerns remain about its breadth. Those who are at highest risk of death are elderly people, those from black and minority ethnic groups, and immunocompromised people. There are no data showing the tests’ performance in these groups. The correct route to generating valid test performance data is well designed prospective clinical studies. The assay is being rolled out at an unprecedented pace and scale without adequate assessment, potentially compromising public trust in pathology services.

NHS England requires the result to be available in 24 hours. Given that routine testing of patients is neither clinically urgent nor does it meet a clear public health need, this push to introduce a non-evidence based test for uncertain gains risks inefficient use of scarce resources.

NHS England and NHS Improvement state that patient consent should be documented in their notes. Patient consent should always be obtained, but the need for it to be explicitly documented is not consistent with routine antibody testing and reflects the uncertain utility and performance of the test. Hard pressed GPs are being expected to provide a phlebotomy service and patient counselling. Given the uncertainties, both the pre-test counselling and discussion of results are likely to be difficult and time consuming.

Conclusion

Monitoring the epidemic is important. The only current justification for large scale SARS-CoV-2 IgG antibody testing is for research purposes, including public health surveillance to inform epidemiology. This should be done through carefully designed studies with clear objectives, sampling frames, inclusion criteria, and consent procedures. Without this framework, it will be difficult to interpret results, and their applicability will be uncertain.

The Royal College of Pathologists has set out seven principles for testing.3 Drawing on these, and on sound principles for testing of healthy asymptomatic people,4 we would like to see a carefully developed and clearly articulated strategy for serological testing, with clear scientific or clinical aims as part of a unified covid-19 response strategy with coordination across NHS England and NHS Improvement, PHE, and the Scientific Advisory Group for Emergencies.

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Feature, p 476
Commercial influence and covid-19

Greater independence in producing healthcare evidence is more important than ever

Although the covid-19 pandemic has provoked the best of human compassion, the hallmarks of unhealthy commercial influence have also emerged. This week, The BMJ published the initial list of signatories to our call for action to reduce commercial influence in how healthcare evidence is produced and used (www.bmj.com/commercial-influence-call-to-action). Signatories include professors, patient advocates, clinicians, and researchers who want to see product evaluation, medical education, and clinical practice much freer from commercial interests.

Previous BMJ investigations have highlighted systemic weaknesses in the regulation of drugs, devices, and tests, and the experience with covid-19 may prove another powerful example of this problem. For example, the UK government used “commercial confidentiality” to justify concealing the names of nine covid-19 antibody tests that had been found to be insufficiently accurate.

Antibody tests do not need to work well to be approved in Europe; nor is independent evaluation required.

Regulation in the US is usually more stringent but has been relaxed during the pandemic to facilitate approval of tests for covid-19.

Early release

Equally concerning is the release of partial or preliminary findings before peer review—often through commercial press releases—that is distorting public perceptions, ongoing evaluations efforts, and political responses to the pandemic.

Remdesivir is a key example. The antiviral drug, made by US company Gilead, was unapproved at the start of the pandemic, but in early April the New England Journal of Medicine published a small descriptive study of a compassionate use scheme for patients with covid-19. Gilead funded the study, a third of the authors were Gilead employees, and Gilead’s press release reported “clinical improvement in 68% of patients in this limited dataset.”

Despite being a non-randomised, uncontrolled, company funded study of just 53 patients, media headlines described “hopeful” signs and reported “two thirds” of patients showing improvement.

Two weeks later, the Lancet published a randomised placebo controlled trial of remdesivir from China, finding no statistically significant clinical benefit in the primary outcome of time to clinical improvement.

On the same day as the lacklustre Lancet findings were published, two other events helped sustain global hype about remdesivir. First, an upbeat media release by Gilead promoted preliminary results from another company funded study.

Second, Anthony Fauci, a member of President Trump’s coronavirus task force, unexpectedly announced preliminary findings from a publicly funded trial being run in the US. Adding to Trump’s previous promotion of remdesivir as a potential “game-changer,” Fauci told the world the trial’s results suggested the drug could become the “standard of care” for covid-19, before any peer reviewed data were available for scrutiny.

A month later, the published paper showed a difference of four fewer days in time to recovery among those taking remdesivir, compared with placebo, but no significant reduction in deaths. The primary outcome had been changed during the trial, and, following a data safety monitoring board recommendation and Fauci’s public announcement in April, treating physicians were allowed to switch trial participants from placebo to remdesivir, bringing an early end to masking for some participants.

The published report also disclosed that Gilead supplied the drug for the trial, one of the trial investigators was a Gilead employee, and six other authors declared financial ties to Gilead. Finally, an additional note disclosed that employees of Gilead “participated in discussion about protocol development and in weekly protocol team calls,” a level of engagement suggesting this drug trial could not be regarded as independent from the manufacturer.

Commercial drivers

Whatever the evidence ultimately shows about remdesivir’s benefits and harms, commercial influence once again seems to be driving overly positive perceptions of a still unproved drug. These concerns underscore the critical importance of rigorous and independent evaluation of tests and treatments. Even during a pandemic, speed should not be allowed to undermine the basic standards of trustworthy evidence.

The BMJ thanks all those who have signed the call for more independence from commercial interests in medical research, education, and practice, and encourages others to consider adding their signatures (https://www.bmj.com/commercial-influence).

During this fast moving and lethal pandemic, independent and trustworthy evidence, interventions, and guidance are more important than ever.

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