this week

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£100bn Moonshot test scheme revealed

The government has drawn up plans to carry out 10 million covid-19 tests a day by early next year as part of a £100bn expansion of its national testing programme, documents leaked to *The BMJ* show.

Funding for Operation Moonshot will almost match what is spent on the NHS in England each year (£130bn) to create a mass testing regime "to support economic activity and a return to normal life." The current capacity is 350 000 tests a day.

The leaked documents reveal a heavy reliance on the private sector to achieve the goal and give details of "letters of comfort" that have been signed with companies to reach three million tests a day by December.

Critics are concerned that the programme ignores the current problems with testing and appears to have been devised with little input from scientists or local health experts.

Under the plan, testing will be rolled out to workplaces, entertainment venues, GP surgeries, pharmacies, and schools to improve access. Digital immunity passports will also be launched to allow people who test negative to return to work and travel.

The memo says that implementing mass testing is a "top priority" for Boris Johnson. "This is described by the prime minister as our only hope for avoiding a second national lockdown before a vaccine, something the country cannot afford," it says.

Martin McKee, professor of European public health at the London School of Hygiene and Tropical Medicine, said, "The plan disregards the enormous problems with the existing testing and tracing programmes." He added, "It focuses on only one part of the problem, testing, and says nothing about what will happen to those found positive, a particular concern given the low proportion of those who isolate.

"What parliamentary scrutiny will there be of a programme that would cost almost as much as the annual budget for the NHS?"

Devi Sridhar, professor of global public health at Edinburgh University, said, "I'm concerned about the reliance on the private sector. There is a case for giving the extra billions to the NHS and asking it to deliver."

A Department of Health and Social Care spokesman said, "We are increasing capacity to 500 000 tests a day by the end of October, and the ability to get rapid, on-the-spot results will significantly increase our ability to stop the spread, and for our economy to recover."

Gareth Iacobucci, Rebecca Coombes, *The BMJ*

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Boris Johnson at a press conference last week after Operation Moonshot was leaked to The BMJ

LATEST ONLINE

- Covid-19: Doctors working outside their expertise are unlikely to face GMC charges
- Reports from the BMA's virtual annual representative meeting
- NHS funds medicinal cannabis for first time since the law changed in 2018

Operation Moonshot Memos prompt questions over cost, evidence, and the private sector's role

The £100bn plan to carry out 10 million covid-19 tests a day by early next year as part of an expanded national testing programme raises many concerns. **Gareth Iacobucci** examines the leaked documents

I wish the government were much more focused on getting our current system working effectively
Chris Ham

This is yet another standalone initiative, developed without any apparent involvement of those on the ground
Martin McKee

What is Operation Moonshot?
It refers to the government's plan to deliver a mass population testing programme for covid-19 by early 2021, with the aim to test the whole UK population each week.

A confidential briefing memo sent to Scotland's first minister and cabinet secretaries, seen by *The BMJ*, reveals plans to grow the UK's testing capacity from the current 350 000 tests a day to up to 10 million by early 2021, costing "over £100bn to deliver."

The plans are dependent on a huge upscaling in diagnostic capacity and the use of as yet unvalidated technologies (p 340). They envisage a prominent role for the private sector in planning and delivery.

What is the desired outcome?
The government's aim is to "utilise the full range of testing approaches and technologies to help reduce the R rate, keep the economy open and enable a return to normal life." The Whitehall memo makes it clear that the prime minister views mass testing as the UK's "only hope for avoiding a second national lockdown before a vaccine, something the country cannot afford."

Many suspect that the desire for positive headlines is also driving this particular agenda.

What's new about the strategy?
The current advice is that only people with covid symptoms should have a test. Moonshot moves way beyond this by planning to test the whole population "where testing enables economic or other vital activity and builds societal confidence."

With the current test and trace system struggling to operate effectively, and people still being asked to travel hundreds of kilometres to get a standard polymerase chain reaction (PCR) swab test, there are concerns that the government is running before it can walk. Chris Ham, former chief executive of the King's Fund, said, "I wish the government were much more focused on getting our current system working effectively, particularly given the increases in positive cases, because we are at a very critical moment now."

How did they arrive at £100bn?
The documents do not explain how the £100bn cost was calculated. Ministers have refused to be drawn since *The BMJ* first published the details on 9 September but have not denied that it was used in internal correspondence. To put the number in context, £100bn is almost a year's budget for the NHS in England (£130bn) and more than double the UK's annual defence budget (£41bn).

The documents say that the government's Scientific Advisory Group for Emergencies (SAGE) is modelling the potential effect of a mass testing programme on the R number, while the Treasury is doing the same for the economy.

Nigel Edwards, chief executive of the Nuffield Trust, said he was stunned by the figure being quoted, which he said could fund 150 new NHS hospitals. "It seems an astonishingly large amount of money to be talked about without a proper assessment of the costs and benefits," he said.

Who is leading the programme?
A presentation prepared by the consultancy firm Boston Consulting Group, seen by *The BMJ*, reveals a heavy reliance on the accountancy and consultancy firm Deloitte to manage and oversee the plans, alongside other firms such as PA Consulting.

The presentation is packed with jargon heavy flow diagrams and metaphorical references such as "Moonshot headquarters" and "Mission HQ." The lack of clinical and system-wide input has drawn criticism from experts.

Martin McKee, professor of European public health at the London School of Hygiene and Tropical Medicine, said, "This is yet another standalone initiative, developed without any apparent involvement of those on the ground or acknowledgement of existing structures. Worse, it envisages a major role for Deloitte, a company that has presided over many of these problems."

Since the start of the pandemic Deloitte has played a prominent role in building and managing logistics at drive-through testing facilities and in introducing home testing. But it faced

"STRATEGIC PARTNERS"

Supply
- GSK
- Smith & Nephew
- Thermofisher
- QuantuMDx
- Optigene

Digital
- X-Lab Systems
- Ordnance Survey
- NHS Login
- Gov.Verify
- Equifax/Experian

Logistics and warehousing
- Boots and Sainsbury's
- DHL
- Kuehne+Nagel
- G4S
- Serco

Workforce
- Universities
- Society of Microbiologists
- British Society of Immunology

Laboratories
- AstraZeneca

Channels and distribution
- Engineering & Logistics Staff Corps (British Army)
- CILT (Chartered Institute of Logistics and Transport)
- CIM (Chartered Institute of Marketing)
- Job Centres

MALCOLM WILLETT

criticism in April after reports that GPs were left without access to many thousands of their patients' covid-19 test results carried out at its centres.

How will capacity be scaled up?
The documents show the plan is to effectively build a new diagnostics industry to hugely increase capacity. They indicate that "letters of comfort are in place with companies to reach 3 million tests per day by December."

Potential partners listed include drug companies such as GSK on the supply side and AstraZeneca for increasing laboratory capacity. Boots, Sainsbury's, DHL, Kuehne+Nagel, G4S, and Serco are earmarked for logistics and warehousing (box, left). Some experts have expressed alarm at the sums of public money that could be channelled into private firms.

Anthony Costello, a former director of maternal and child health at the World Health Organization and professor at University College London, described the plans as "waste/corruption on a cosmic scale."

How will it be staffed?
The documents state that the government will work with universities, the Society of Microbiologists, and the British Society of Immunology to grow the diagnostic workforce. There are also plans to offer covid-19 tests at general practices and pharmacies to boost access, as part of what the government calls a "huge new operational infrastructure."

The documents say, "This will include a new warehousing and an expanded logistics network, and a new workforce with the appropriate skills and expertise to deliver, administer and process our new testing technology in every corner of the UK."

But there is little detail, and Edwards said that recruitment on this scale and pace sounded "deeply implausible." He said, "If half of the cost is on testing and the other half is on staff (as in the NHS), we could be talking about employing 1.6 million people."

These plans show waste on a cosmic scale
Anthony Costello

What are other countries doing?
China and South Korea initially deployed testing on a wide scale to try to reduce the spread of covid-19, and the US and India are now testing widely. Denmark, with a population of six million, announced on 18 May that it would offer mass testing, including to people without symptoms. France has also tried population testing. But none of these countries has rolled out testing on the same whole population scale as the UK is proposing.

Devi Sridhar, professor and chair of global public health at the University of Edinburgh, said a commitment to wider testing can cause problems if capacity becomes stretched. "We don't want to make the same mistakes as France, where there is broader testing being offered and it is being used by lots of 'worried well,' leading to queues and delays in results," she said.

Is there evidence for mass testing?
Experts fear Moonshot has had little involvement from scientists, clinicians, or experts in screening. Jon Deeks, professor of biostatistics at the University of Birmingham and leader of the Cochrane Collaboration's covid-19 test evaluation activities, said, "The document lacks insight into how screening works, particularly the need to balance the harms you can create through false positives against the benefits from true positives."

The plans rely on as yet unvalidated tests, and Deeks warned of a "risk of this backfiring." He said, "Even if you have a test which is 99% specific, so only 1% of people get a false positive result, if you then test 60 million people we will be classifying a group the size of the population of Sheffield as wrongly having covid." If these people and their close contacts had to isolate, this, Deeks noted, would create "substantial economic harm and massive need for further testing."

What does SAGE say?
In a consensus statement dated 31 August the advisers struck a cautious note. It said, "Careful consideration should be given to ensure that any mass testing programme provides additional benefit over investing equivalent resources into improving the speed and coverage of NHS Test and Trace for symptomatic cases."

It added that "mass testing can only lead to decreased transmission if individuals with a positive test rapidly undertake effective isolation."

Is the plan achievable?
Experts are highly sceptical. Edwards said, "My strong suspicion is this will end up like the airport on the island or the garden bridge [promised by Johnson when he was London mayor but not delivered]. Quite a lot of effort will be expended, but I will be quite surprised if it survives a more rigorous look at the economics."

McKee was equally sceptical, saying the plans bore the hallmark of a government "whose ambition far exceeds its ability to deliver."

Gareth Iacobucci, *The BMJ*

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Moonshot's "mission analysis" from the leaked documents

Mission	Objective	Test setting	Geography
Mass test general population to contain spread and build societal confidence	Pilot LAMP test in Greater Manchester (see p 340)	Train stations; additional settings to be agreed	Salford
Test asymptomatic NHS employees regularly to ensure NHS can operate effectively	Deliver a pilot for asymptomatic testing in NHS and other settings; build body of evidence	Hospitals; laboratories (Lighthouse, NHS)	Southampton, Basingstoke, Manchester
Test target institutions (such as schools and universities) regularly using a risk based model to enable safe return to normal life	a) Lateral flow testing	Schools or universities (TBC)	UK
	b) Cohort pooling	Schools (TBC)	UK
	c) ePCR	TBC	UK
Develop an agile and comprehensive testing capability, beyond current approach, to identify and contain outbreaks	Develop use of mobile and quick turnaround technologies	Closed institutions; open institutions; community gatherings and local community	UK
Enable private sector organisations to deliver testing safely and effectively, including to facilitate economic activity or protect their workforces	TBC	Employers; point of entry to venues	UK

CLIVE BRUNSKILL/GETTYIMAGES

Operation Moonshot Plan relies on technology that does not exist

Delivering mass testing on the scale and level of ambition set by prime minister Boris Johnson will probably require "testing technology that currently does not exist," say leaked documents revealed by *The BMJ*.

The Operation Moonshot plans, which could see the government spend over £100bn to ensure 10 million covid-19 tests a day, show it's likely that new testing technology would need to be developed, validated, procured, and made operational within months to meet the early 2021 deadline.

Jon Deeks, professor of biostatistics at the University of Birmingham and leader of the Cochrane Collaboration's covid-19 test evaluation activities, has described the plan as a "nice dream."

He told *The BMJ*, "This is not the way we should be tackling something when people are dying right now: thinking about things we have not got. We should be thinking about the things we have got and we know work. Backing a horse that hasn't yet been born is a really bad strategy."

The Moonshot documents list several tests being considered for rollout across the UK, despite some having lower sensitivity than polymerase chain reaction (PCR) tests. These would be used "for screening/enabling purposes, with PCR used to confirm positive results or in situations where accuracy is needed for highest risk individuals," say the documents.

There is not much publicly available evidence for the use of these tests on SARS-CoV-2

What do we know about the tests?

The listed tests are reverse transcriptase (RT) PCR, Endpoint PCR, LamPORE, Direct LAMP, lateral flow antigen tests, and whole genome sequencing. However, there is not much publicly available evidence for the use of these tests on SARS-CoV-2. What is accessible is mainly from non-peer reviewed preprints of research carried out by the manufacturers.

For example, in the case of RT-PCR a preprint paper from the company DnaNudge claimed that its point-of-care test, which involves nasopharyngeal swabs, had an average sensitivity of 94.4% (95% confidence interval 86% to 98%) and an overall specificity of 100%. It concluded that the test was "specific and rapid" and could detect SARS-CoV-2 "without laboratory handling or sample pre-processing."

A study assessing LamPORE (also available as a preprint), carried out by its manufacturer, Oxford Nanopore Technologies, claimed that the test was "rapid, sensitive, and highly scalable." It reported that results could be obtained from 12 samples in about an hour, when starting with extracted RNA, and from 96 samples in less than two hours. It also said the test correctly identified 79 of 80 positive samples.

However, Deeks pointed to inaccuracies in the documents concerning the tests. He said, "I have spoken to the person doing the DnaNudge evaluation, and he said they have not done it on saliva—they have only done it on swab [samples]. So why has that list got saliva on it?"

Also, Deeks said that, despite LamPORE being listed as taking 90 minutes, it actually needs 6.5 hours to run. "The 90 minutes is the middle bit. That does not include plating up the samples, doing the DNA extraction, and things like that. So from sample to result it's about 6.5 hours."

He added, "No publicly available data for a lot of the tests [are available] . . . It's not good science. If these were drugs, the government would have had to register these studies on the Clinical Trials Register, with the protocol, and to publish the results."

Potential harms

Deeks's main concern was that the "whole of this programme has been built without thinking about the harms it could do."

He said, "The mathematical laws as to what happens when you start

Potential technologies for expanding testing as listed in Moonshot documents

Technology	Time from test to result	Potential sample	Key characteristics
qrt-PCR	2-24 hours	Swab Saliva	High sensitivity (>90%); high cost (£40 per test)
Endpoint PCR	<24 hours	Swab Saliva	Low cost (£2-5 per test); high sensitivity (>90%); high volume
LamPORE	90 minutes	Swab Saliva	High sensitivity; moderate cost; near-patient options
Direct LAMP	20-60 minutes	Swab Saliva	Higher cost (£10-20 per test); rapid results; lower sensitivity (80-100%)
Lateral flow antigen tests	10-30 minutes	Saliva (Swab)	Higher cost (£5-30 per test); rapid results; lower sensitivity (80-100%)
Whole genome sequencing	2-24 hours	Swab Saliva	Higher cost (£20 per test)

CLIVE BRUNSKILL/GETTYIMAGES

WHAT IS HAPPENING IN GREATER MANCHESTER?

The Moonshot documents emphasise that trialling new models for delivering testing in local areas will be "critical." This includes a large trial in Salford, Greater Manchester, where the prevalence of covid-19 is currently higher than in most of the UK.

The Salford City Council website says that the trial involves weekly testing of the saliva of people who do not have covid-19 to "identify any positive cases early and allow those who know they are coronavirus free to go about their normal lives."

The test being used is the LAMP test, and though the council has said it will be rolled out in phases across the area, it gives no dates for when this will happen.

A statement on the website says, "It is proposed that there will be an initial two-week period to test the 'proof of concept.' This would enable us to test end-to-end the reliability of the different elements of what is a complex practical process. The 'proof of concept' testing will take place with smaller groups of our community and enable us to ensure each of these elements is working well before then rolling out a Salford-wide programme."

screening mass populations are not in the right direction in terms of the harms that will be done. The key thing is specificity, and the documents do not mention specificity or false positives, which is how you get harm. If you start using tests in 60 million people, even if they are 99% specific you will end up giving false positives to hundreds of thousands of people."

Deeks warned that using less reliable tests to enable people to attend events such as football matches would be "dangerous," as it could give people false confidence and see them ease protective measures such as social distancing.

However, he was positive about expanding testing, provided that it was done correctly. "Some of these tests have potential to improve how well we can do test and trace. If they can improve the capacity and speed, that would be very useful. We just need to be very clear as to where they are going to go and what their purpose is," he said.

Backing a horse that hasn't yet been born is a really bad strategy
Jon Deeks

Elisabeth Mahase, *The BMJ*

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"IF YOU USE tests in 60 million people, even if they are 99% specific you will end up giving false positive results to hundreds of thousands of people" Jon Deeks

GP surgeries could be used to improve access to covid-19 tests

General practices and pharmacies could be used to make covid-19 testing more available to the public, according to the leaked Operation Moonshot documents.

They state that a "huge new operational infrastructure" would be needed to process results and to "develop novel methods of allowing people to access testing." This would include the use of "familiar locations" such as GP surgeries and pharmacies, as well as other local venues.

"A new workforce with the appropriate skills and expertise to deliver, administer and process our new testing technology in every corner of the UK" would also be needed, said the documents.

Several GPs told *The BMJ* they were keen to be included in plans to control the pandemic. Jackie Applebee, a GP in London, said local public health services, including general practices, were frustrated at being excluded from testing, tracing, and supporting patients affected by covid.

"In general practice we don't know which patients have had covid-19 because we are not aware of test results, and we see patients who find it hard to get a test because they don't have a car," she said.

"Local health bodies have felt excluded when, in fact, local systems are best placed to get on top of the pandemic. The money going to Serco, Deloitte, and others would be better spent on NHS public health and primary care services."

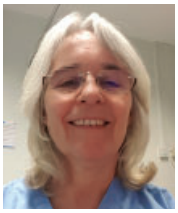
However, Jane Wilcock, a GP in Salford, pointed out that not all GP premises could safely offer testing. "We have been enormously successful at not passing on covid-19 to patients in the community, and we don't want this to change. But it is essential there is local testing available where it is possible to have a separate pyrexia room," she said.

"Also, when you're not well it is not always possible to travel a long way for a test, so having this available locally would be beneficial."

Primary care networks, which Oxford GP Joe McManners admitted had fallen off the radar during the pandemic, have been set up partly to integrate health systems and should, he said, be well placed to enable GPs to work together to decide which general practices in a local area could act as testing sites.

Using these networks would ensure all England's localities had an accessible testing site, assuming staffing and funding issues were resolved, said Azeem Majeed, head of primary care at Imperial College London. Improving access to tests will be particularly important in the winter, when other viruses are circulating, said Majeed. "A saliva test would be a big step forward," he said.

We see patients who find it hard to get a test because they don't have a car
Jackie Applebee



When you're not well it is not always possible to travel a long way for a test
Jane Wilcock

Primary care networks should be well placed to enable GPs to work together
Joe McManners

Elisabeth Mahase, *The BMJ*

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SEVEN DAYS IN

Scotland launches contact tracing app, with England and Wales to follow

Scotland has launched a contact tracing app for covid-19 that is based on the same Apple and Google toolkit used across Ireland since July.

A day after the Scottish government's announcement, the Department of Health and Social Care for England said an app will be available in England and Wales on 24 September. Its launch was delayed while NHSX, the NHS's technology unit, tried to develop a system in which anonymised data could be held on an NHS database.

The Protect Scotland app was downloaded nearly 600 000 times in the two days after its launch. First minister Nicola Sturgeon (left) said, "The more people who download and use the app, the more effective it can be in helping to make connections that may otherwise have been missed. This will allow people to self-isolate quickly if they are exposed to the virus."

All the apps use Bluetooth to alert users if they have been in contact with someone who has tested positive and advises them to self-isolate. They do not store identity details or location but use encrypted codes between smartphones to tell users they have spent at least 15 minutes within 2 m of someone who has tested positive.

Jacqui Wise, London Cite this as: *BMJ* 2020;370:m3566

Covid-19

Drug companies vow not to rush vaccine

The heads of AstraZeneca, BioNTech, GlaxoSmithKline, Johnson & Johnson, Merck, Moderna, Novavax, Pfizer, and Sanofi, which are all working towards a covid-19 vaccine, issued a joint statement promising to "only submit [a vaccine] for approval or emergency use authorisation after demonstrating safety and efficacy through a phase 3 clinical study" and "to always make the safety and well-being of vaccinated individuals our top priority." The statement followed a letter from seven drug industry CEOs last week urging that "political considerations should be put aside" in covid-19 drug and vaccine development and that clinical data should be publicly disclosed.

US "should end Gilead's monopoly" on remdesivir

The US government should end the shortage of the antiviral drug remdesivir by eliminating Gilead's monopoly, said a report from Public Citizen, a consumer interest pressure group. Remdesivir, an unapproved investigational drug used in patients with severe covid-19, is being rationed in the US. Doctors and politicians called on the Trump administration to use existing laws to increase supplies of the drug by allowing other companies to make generic versions of the drug and to permit imports of generic versions from foreign manufacturers.

London hospital "must improve infection control"

Hillingdon Hospital NHS Foundation Trust, which was hit by a covid-19 outbreak in July that required 70 staff to self-isolate, has been ordered to take stringent measures to control infection. An investigation found that a nurse with covid-19 had unwittingly infected 16 others during a training session on 30 June, described by one doctor as a "super-spreading event." The Care Quality Commission, which carried out an unannounced inspection on 4-5 August, has used its urgent enforcement powers to place conditions on the trust's registration to protect patients and staff.

Private hospitals commit to training juniors

Private healthcare providers committed to training junior doctors while they are working at their hospitals to help tackle the NHS backlog caused by the pandemic. The NHS has been using operating theatres and clinical facilities in the independent sector to tackle the backlog of elective procedures caused by covid-19. Cliff Shearman, vice president of the Royal College of Surgeons of England, said, "It's only right that NHS funded treatment should help train the NHS workforce of the future."

Infection risk is lowest in intensive care staff

A study of 545 staff who worked at University Hospitals Birmingham NHS Foundation Trust at the height of the pandemic found that cleaners (34%; 10/29) were most likely to test positive for antibodies to SARS-CoV-2, followed by clinicians working in acute medicine (33%; 10/30) or general internal medicine (30%; 30/99). The lowest seroprevalence was seen among staff working in intensive care (15%; 9/61), emergency medicine (13%; 2/15), and general surgery (13%; 3/23), in findings reported in *Thorax*. Workers from ethnic minority backgrounds were nearly twice as likely to have already had the infection as white staff.

Lucentis

Companies are fined £412m for unfair marketing

France's Competition Authority fined the Swiss drug companies Novartis and Roche €444m (£412m) for abusing their dominant market position to steer eye doctors towards the wet macular degeneration treatment Lucentis (ranibizumab), which they sell jointly, at the expense of the cancer drug Avastin (bevacizumab), which is often used off label in its place and costs 30 times less. Novartis, which was found to have "unjustifiably exaggerated" Avastin's risks, will pay about 85% of the fine and plans to appeal. Roche said that it was studying its options. In 2014, Italian authorities fined the two companies €180m over similar allegations.

MEDICINE

Public health

Food and drink companies "exploit pandemic"

Companies trading in alcohol, tobacco, junk foods, gambling, infant milk formula, and fossil fuels are "leveraging" the coronavirus crisis to boost their brands, often to the detriment of public health and sustainability goals, showed research from the NCD Alliance and the SPECTRUM consortium of researchers. For example, in Brazil the brewer Karsten adapted its logo to resemble a pair of lungs with the slogan, "Good beer is like air: you can't live without it," while encouraging three steps to survive: "Isolate, use sanitiser, and drink beer for fun." The research authors called for a tough response from governments and regulators.

E-cigarettes are safer but not without risks

Electronic cigarettes are significantly less harmful than tobacco but are not risk-free, concluded the Committee on Toxicity of Chemicals in Food, Consumer Products, and the Environment. If smokers switched completely to e-cigarettes harm would be cut, but some risks would fall more than others, its report said. For example, a "considerable reduction in risk of lung cancer would be anticipated," but the risk reduction would be much less for other conditions such as asthma.

Contraception

Make some pills available over counter, say MPs

The progestogen-only pill (POP) should be made available over the counter in pharmacies

Karsten, a Brazilian brewer, adapted its logo during the covid crisis

without a prescription because cuts to services are making it harder for women to access contraception, said the All Party Parliamentary Group on Sexual and Reproductive Health. Postpartum contraception in all maternity settings should also be funded, it said, and a national digital contraception service should be developed to help women get the contraceptives they need. Such a service would "protect contraceptive provision in the event of another 'lockdown,' even out inequalities in remote access , and streamline care pathways for women," the group's report advised.

Climate crisis

"Include emission targets" in economic recovery

Government action to help the economy recover from the pandemic should also aim to achieve net zero carbon emissions, said the Climate Assembly UK, which comprises 108 members of the public commissioned by six House of Commons select committees. The assembly would most like the government to limit investment in high carbon industries, rethink and invest in infrastructure, support low carbon industries, make the most of opportunities created by moving to net zero emissions, and deal with covid-19 and the climate crisis together where possible.

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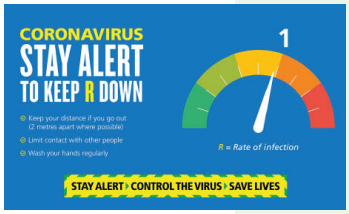
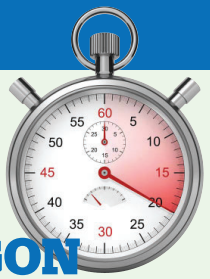
MMR UPTAKE

Counts of vaccinations in children aged 12 to 18 months in England were almost 20% lower in the first few weeks after lockdown than in the same period in 2019, although they have now returned to near normal levels (−3.3%)

[Public Health England]



SIXTY SECONDS ON . . . JARGON



IT'S EVERYWHERE

You're telling me. Terms that used to be the preserve of scientists are suddenly being bandied around by politicians on television, brought up over a coffee with friends, or appearing in the family WhatsApp group. Flattening the curve to the R number and contact tracing have all entered the general lexicon since SARS-CoV-2 emerged.

BUT THEY MAKE ME SOUND CLEVER

Uhm. While it's good that everyone is involved in the debate, and some terms can be helpful, problems arise when they aren't used correctly or properly explained.

ARE WE NOT ALL ON THE SAME PAGE?

Not always, says public health consultant Angela Raffle. False positive and negative top her list of words that should be banned from general use. "They mean different things to different people. When talking with the general public we cannot be sure they have the same shared understanding."

CAN YOU PUT THAT IN CONTEXT?

Exactly. Raffles says that when these terms are used without any context it creates confusion. For example, a false positive can mean someone who tests positive for covid-19, but what they have actually got are viral fragments from an infection they had a long time ago, meaning they're not infectious or a new case. However, to someone working in a laboratory a false positive would mean a test that is done incorrectly and therefore indicates the virus is present when it is not.

IT'S TESTING OUR PATIENTS

You can say that again. Pillar 1 and pillar 2 testing are more examples of confusing terms. They were first used to loosely separate out hospital based (pillar 1) and community based (pillar 2) testing. "It's jargon. I want to know which are the tests done diagnostically because someone had symptoms, which are done as safety checks before operations, which are done for employment purposes, and which are done because they are contacts of cases. When you are muddling all those together it does not give you the information you need," argues Raffle.

SO, FEW OF US REALLY KNOW WHAT WE'RE TALKING ABOUT?

That's right. But try telling that to politicians.

Elisabeth Mahase, *The BMJ*

Cite this as: *BMJ* 2020;370:m3567

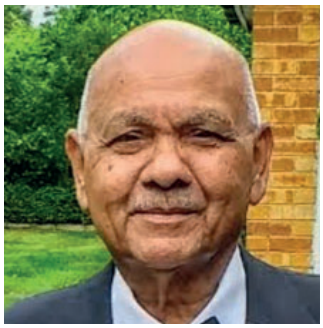

Edmond Adedeji


Saad Al-Dubbaisi


Krishan Gopal Arora


Medhat Sobhy Atalla


Abdul Chowdhury


Mohinder Dhatt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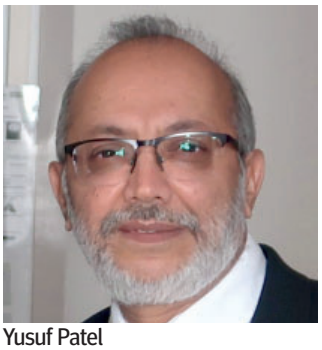
Sadeq Elhowsh


Kamlesh Kumar Masson


Karamat Ullah Mirza


Poornima Nair


Yusuf Patel


Jitendra Rathod


Manjeet Singh Riyat


Alfa Saadu


Anton Sebastianpillai


Furqan Siddiqi


Erwin Spannagl


Adil El Tayar


Peter Khin Tun

THE BIG PICTURE

Remembering the UK doctors who have died from covid-19


Fayaz Ayache


Syed Zishan Haider


Thaung Htaik


Nasir Khan


Rudresh Pathak


Mamoona Rana


Vishna Rasiah


Abdorreza Sedghi


Tariq Shafi


Mohamed Sami Mahmood Shousha


Craig Wakeham


David Wood


Habib Zaidi

Many healthcare workers have lost their lives to covid-19 in the line of duty. The BMA has been collecting the names of doctors in the UK who were reported to have died while working during the pandemic, and *The BMJ* has created a memorial page to honour their lives (bmj.com/covid-memorial).

The list highlights the devastating toll on doctors from ethnic minority backgrounds, including many migrant workers on whom the NHS depends.

Fiona Godlee, *The BMJ's* editor in chief, said, "The web page honours doctors who have lost their lives working for the good of others under the most difficult of circumstances in this covid-19 pandemic. Each name represents an irreplaceable gap in a family and a workplace.

"No one should have to risk their lives or health because of their work, and we honour those who have paid this ultimate sacrifice. In doing so we commit to all efforts that will bring this pandemic to an end and that will ensure the safety and wellbeing of everyone working on the front line of healthcare."

Chaand Nagpaul, chair of the BMA council, said, "The death of a fellow doctor is always tragic, but to lose so many at the hands of the virus is devastating.

"We offer our profound sorrow and heartfelt condolences to the families, friends, and colleagues of these committed clinicians who cared for patients in the most challenging of times, battling against this highly infectious and deadly virus.

"They are the GPs and hospital doctors who treat us when we are sick, and they are our friends and colleagues, who dedicated their lives to the pursuit of helping people get better.

"We owe them our gratitude, our respect, and a pledge that we will remember them."

Juliet Dobson, editor, bmj.com

EDITORIAL

Are scientists underestimating seroprevalence of SARS-CoV-2?

Current antibody tests fail to identify people who had mild infections

Testing for severe acute respiratory coronavirus 2 (SARS-CoV-2), which causes covid-19, is complex and politically sensitive. Seroprevalence studies use antibodies as markers of pathogen exposure to estimate the proportion of the population that has been infected.

Considerable variation has been observed in the results of SARS-CoV-2 seroprevalence studies.[1] A recent survey in Spain suggested that a small fraction of the population was seropositive, despite the country being severely affected by the virus.[2]

Seroepidemiological studies may underestimate the true seroprevalence of SARS-CoV-2 for several reasons. Accuracy demands the use of an assay sensitive enough to reliably detect antibody responses to mild infection across different post-exposure scenarios. The selection of target antigen is critical, with recent data showing that the trimeric spike glycoprotein offers superior detection to the nucleocapsid in people with low level antibody responses.[4] Of the 24 serological diagnostic tests that the FDA initially authorised for emergency use, six consider only the nucleocapsid, including high throughput tests in widespread use.

The nature of the pandemic means that tests have been evaluated mostly on people who experienced severe covid-19 symptoms.[5] Recent evidence describes a clear link between the magnitude of serological responses and severity of illness.[4 6] This implies that unless assay performance is also assessed in mild and convalescent cases, the threshold for a positive result may be too high, resulting in missed community cases.

Tests have been evaluated mostly on people who experienced severe covid-19 symptoms

Stephen Burgess, statistician, School of Clinical Medicine, University of Cambridge
sb452@medschl.cam.ac.uk

Mark J Ponsford, clinical immunologist, Immunodeficiency Centre of Wales, University Hospital Wales, Cardiff

Dipender Gill, clinician scientist, St George's, University of London

Other problems with test calibration include the effect of demographic factors such as age, sex, and ethnicity on antibody responses and hence assay results,[7] and the effect of timing, since early testing before seroconversion may result in false negative results. Preliminary reports showing rapid decline in virus specific IgG levels suggest that testing too late may also miss cases.[8]

Test performance is also influenced by the choice of antibody. Of the FDA authorised tests, most detect only IgG and IgM antibodies, the dominant components of the bloodborne antibody response. But IgA also has an important role in the immune response to respiratory tract infections and seems immunologically relevant in covid-19, particularly in asymptomatic people.[9 10]

Look for IgA

SARS-CoV-2 enters cells by interacting with host proteins expressed in the respiratory tract, cornea, and gastrointestinal tract.[11] IgA is the predominant immunoglobulin expressed at these mucosal surfaces,[12] and IgA responses with neutralising capability are described for several viral pathogens.[9 10 13] IgA antibodies specific to SARS-CoV-2 have now been detected in various biological specimens, including serum, saliva, and breast milk.[4 14 15]

Serum IgA antibody responses may be detectable earlier than IgG and IgM responses[16 17] and can persist for at least 38 days in hospital patients recovering from covid-19.[18] This is consistent with a recent Cochrane review, which found that IgA based serological testing had greater sensitivity than other methods.[5] A recent seroprevalence survey of 1473 residents (79% of the local population) in Ischgl, Austria, using a combined IgG and IgA approach found SARS-CoV-2 antibodies in 42.4% of those tested, far higher than rates in previous population based surveys of other infection hotspots.[19] Similarly, IgA antibodies were detected in 11% of 1862 people sampled from the general population in Luxembourg, whereas IgG antibodies were found in only 1.9%.[20]

Finally, mucosal and bloodborne immune responses may provide complementary information crucial for accurate assessment of viral exposure in both individuals and populations. In a cross sectional study of UK healthcare workers, combined IgG, IgA, and IgM testing for SARS-Cov-2 spike protein in saliva samples identified 15% of participants as positive despite a negative serum test result.[4]

In conclusion, current seroprevalence studies may fail to detect people who have had mild covid-19. Standardised approaches are required so seroprevalence estimates are comparable. Specific consideration should be given to the selection of the SARS-CoV-2 antigen in diagnostic assays, calibration of assay thresholds, the breadth of the antibody response, and the role of mucosal antibody responses. Application of these principles in future seroprevalence surveys may offer more accurate insight into the population dynamics of covid-19 and help inform epidemiological modelling strategies and public health policy.

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EDITORIAL

UK's record on pandemic deaths

Recent changes in definition can't disguise the country's poor international ranking

The grim daily count of covid-19 deaths in the UK is nearing single digits.[1] But evidence of the UK's higher overall death toll during the first wave of the pandemic relative to comparable countries is unequivocal.

England had the highest excess all-cause mortality rate among 23 European countries in the first five months of 2020 compared with 2015-19, followed by Spain and Scotland, with mortality being spread throughout the country in contrast to the more localised patterns in Europe.[2] England also had the second (after Spain) highest peak of excess all cause mortality and the slowest fall to normal levels—so the longest period of excess deaths.

Recent changes to the definition of a covid-19 death in England (from all deaths after a positive test to deaths within 28 days) have reduced the UK's official covid-19 death toll by 16%.[1 3] But the change doesn't alter the UK's poor ranking among European peers. Excess mortality rates based on death certification data[2] circumvent differences in how covid-19 deaths are counted and also include deaths from the wider effects of the pandemic.

The overall death rate for England from 1 January to 31 July was the highest since 2009. The year got off to a good start, with a mild influenza season and almost 5000 fewer deaths in England and Wales up to early March 2020 than the 2015-19 average.[1 6 7] But in the ensuing five months, there were over 58 000 more deaths than the 2015-19 average, of which almost 52 000 (89%) were related to covid-19.[1] Almost half (44%) of all excess deaths occurred in care homes.

Almost half (44%) of all excess deaths occurred in care homes

Total deaths returned to near normal levels some weeks ago, as they did in other European countries, then they fell below normal. In the eight weeks to 7 August there were about 1700 (2%) fewer all cause deaths in England and Wales than the 2015-19 average (figure).[1] This welcome respite has a darker side, however, as it suggests many of the earlier deaths had been premature, for which ONS analyses provide further corroboration.[7]

Hidden covid-19 deaths

Early indications suggest that many of the excess deaths not related to covid-19 since March were not the result of reduced care for serious non-covid conditions. For example, the sharp surge in total and non-covid deaths followed by a return to near normal levels mirrors the trajectory of covid-19 deaths,[1] whereas the effect of reduced healthcare would have been more persistent.

Furthermore, excess non-covid deaths occurred predominantly among frail older adults, many in care homes, and included a sharp rise in deaths from dementia and ill defined conditions, suggesting that many such deaths were related to undiagnosed covid-19.[6 7 8]

Comparisons with 2015-19 also suggest a substantial and continuing "displacement" of non-covid deaths from hospitals to private homes and, earlier in the pandemic, to care homes.[1 7] This could have contributed to a greater proportion of deaths occurring in other settings with lower rates of testing.[6]

Even so, lives have undoubtedly been lost as substantially fewer people received healthcare for life threatening conditions during this period.[7 9 10] Such deaths could mount over time as the NHS struggles to cope with the backlog of deferred care alongside winter pressures and a possible resurgence of covid-19. Although other countries also face these challenges, the UK is less well equipped to deal with them, with overstretched health and social care services that historically have been under-resourced and understaffed compared with other high performing health systems.[11 12]

Among many brutal realities of the pandemic has been a clear amplification of existing socioeconomic and ethnic inequalities, both in the UK[13-16] and beyond.[17]

The lessons of the first wave of covid-19 must inform policy decisions for tackling any resurgence. While controlling the pandemic is clearly a priority, it's also imperative to take the long view as many of the risk factors for dying from covid-19—such as cardiovascular disease, diabetes, obesity, and deprivation—are also leading contributors to the lacklustre mortality improvements and widening inequalities prevailing in the UK before the pandemic.

Veena S Raleigh, senior fellow, King's Fund, London
v.raleigh@kingsfund.org.uk

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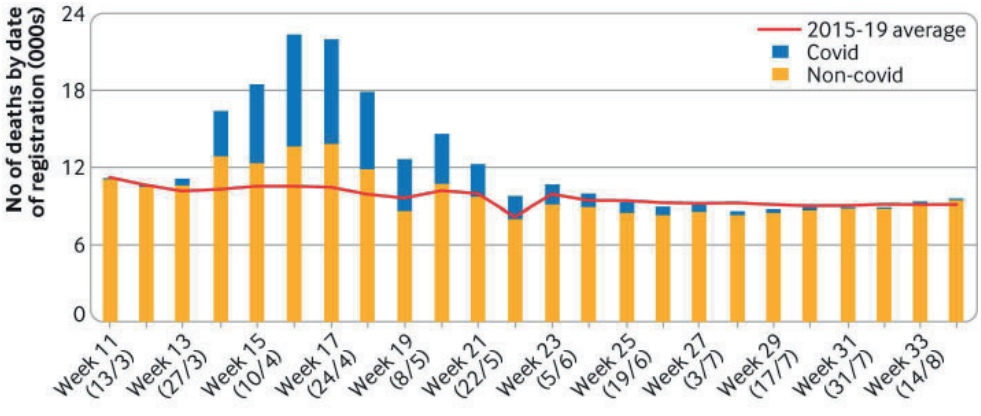
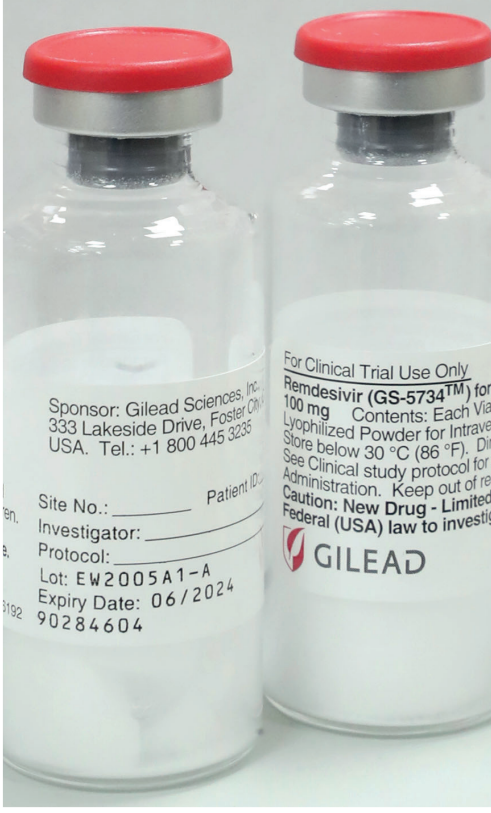


Weekly deaths in England and Wales: week ending 13 March to week ending 21 August 2021

HEAD TO HEAD

Should doctors recommend covid-19 treatments and vaccines when full data are not publicly available?



yes

The usual "essential" of full data transparency before prescription should become a "nice to have" in this urgent, fraught emergency

Raymond M Johnson, associate professor of medicine (infectious diseases), Yale School of Medicine, New Haven, Connecticut Raymond.Johnson@yale.edu

In normal circumstances, insisting on full data transparency and limiting decision making to published data alone is rightly paramount. But a pandemic is far from normal, and to insist on normal practice adds delay to interventions that could cost lives. A pandemic gives us little choice other than unpublished manuscripts (preprints) to guide therapeutic decision making. They should be used, thoughtfully.

Of course, physicians would prefer to prescribe treatments and vaccines that have been thoroughly tested and scrutinised in peer reviewed, randomly controlled trials with full data transparency. But this isn't always possible, when we don't know how much data collection is enough and we lack the understanding of a disease to know how to interpret the findings. The usual "essential" of full data transparency before prescription should become a "nice to have" or an "as much as possible" in the urgent, fraught emergency circumstances we find ourselves in.

Preprint data and adaptive trials

Beyond surge capacity, our medical systems need prepositioned, randomised, adaptive cascading trials to evaluate treatments. Quality preprints can identify therapeutics, or inform study arms, during adaptive clinical trials. This applies especially to repurposed or off-label drug use where prescribing them on the basis of unpublished data has a lower threshold than adopting newer treatments or vaccines, because the treatment and its effects and side effects are to some extent known, and the infected patients are acutely and specifically at risk for harm.

Hypothetically, back in March, the first iteration of a covid-19 randomised trial could have included standard of care versus hydroxychloroquine (HQ)[2] versus lopinavir/ritonavir,[3] on the basis of published SARS-CoV-2 in vitro and MERS case-control data. In April, when a 150 subject randomised control trial preprint was released showing no HQ virologic or clinical benefit,[4] hypothetical investigators could have closed the hydroxychloroquine arm and substituted steroids based on experience in China.[5] When lopinavir/ritonavir was subsequently found ineffective,[6] the lopinavir/ritonavir arm could have closed and an alternative arm opened, such as convalescent plasma.

Unlike conventional clinical trials, adaptive cascading trials are not intended to answer a prespecified question to garner approval and publication; they are intended to rapidly optimise medical treatment during a pandemic.

Adaptive clinical trials are not a new idea,[7] but, formulated through existing health bureaucracies reliant on publication and peer review, they are likely ineffective. Public health agencies are the antithesis of nimble and adaptable.

Academic medical centres can contribute to pandemic responses by scrutinising primary published data and preprints to design and perform adaptive clinical trials. Therapeutics can evolve during pandemics, or we can use what we have and hope to do better next time.

RECOVERY trial

We have one real life example already. The RECOVERY trial is an adaptive clinical trial that argues for using unpublished data to shape medical practice during a pandemic. The trial structure incorporates several critical features for research in such a situation. First, it identified a limited number of treatment arms to allow definitive comparisons between them. Second, it intentionally focused on clinical outcomes, rather than mechanistic investigations, to reach clinical efficacy endpoints. An independent data monitoring committee analyses the interim data to identify benefit and harm early, to "adapt" the trial as it moves forward.

RECOVERY was designed to close and add treatment arms over time. Unpublished data were released as a press release (though this is not without its problems), and then as a preprint,[11] showing a mortality benefit for steroid treatment in covid-19 patients developing hypoxemia.

Because RECOVERY is a high quality trial its unpublished data should be guiding decisions now. Because pandemics are temporally and geographically dynamic, limiting decision making to full published data adds a delay that adversely affects the design of adaptive trials and, potentially, pandemic outcomes.

The critical part in using unpublished data is content review and ensuring as much as possible that preprint data contain key information—the protocol, summary data tables, and the statistical analysis used. Qualified parties should review preprints, pharmacodynamics, and toxicities to assess biologic plausibility and risk before incorporating therapeutics into adaptive trials or practice. Thus, unpublished results can deliver crucial interventions without sacrificing integrity.

With knowledge of the new coronavirus less than a year old, treatment remains fraught with uncertainty. Preprint data and adaptive clinical trials are imperfect but can guide active decision making in life-or-death situations, says **Raymond M Johnson**. But **Peter Doshi** and **David Healy** argue that without complete transparency, products should not be endorsed as being based on science

no

This is about a chain of trust that stems from knowing that judgments have been scrutinised and challenged

Peter Doshi, associate professor, Department of Pharmaceutical Health Services Research, University of Maryland School of Pharmacy, Baltimore, Maryland pdoshi@rx.umaryland.edu

David Healy, professor, Department of Family Medicine, McMaster University, Hamilton, Ontario

The trust we place in licensed medicines is a strong reason for insisting on full data transparency and reporting, even in a pandemic. Few would disagree with the importance of transparency, but even during normal times it remains a challenge—so, why demand it during a pandemic? The reason is that data transparency builds the foundation for information we can trust. Data secrecy, by contrast, creates risks too large to take.

The first critical risk is that of an exaggerated estimate of a product's benefits when relying on scientific publications alone, not the underlying data. When the underlying clinical study reports for oseltamivir were finally made public they revealed that the data collection on lower respiratory tract complications relied on patients' self-reporting, which makes sense for some outcome measures, such as pain, but not pneumonia. The result was a complete loss of confidence in the quality of data collected for the key performance assumption underpinning global stockpiling.[12]

The second critical risk is underestimating a product's side effects. A year after novel vaccines were manufactured and rolled out on expedited timelines to tackle the threat of 2009 H1N1 swine flu, post-marketing reports of narcolepsy emerged in some Pandemrix vaccine recipients. But it would take a further seven years—and a lawsuit—to unearth internal pharmacovigilance reports by the manufacturer, which had suggested that problems with the vaccine's safety had been produced in real time during the pandemic.[13]

Copious evidence already shows that adverse event data collected in trials are under-reported in journal publications.[14] Moreover, serious adverse events may disappear if classified under rubrics such as "intercurrent illness" or "new medical histories," which do not require serious adverse event reports—as has happened in vaccine and treatment trials.[15,16]

Only publicly available full datasets will allow for a thorough assessment of side effects.

But the benefits of transparency go beyond a truer understanding of product safety and efficacy: earning public trust, for a start. Jobbing doctors and patients alike reasonably expect any licensed covid-19 treatment or vaccine to work as advertised. This is about a chain of trust: only open data can allow other researchers with the ability to analyse it to do so, generating the trust that stems from knowing that judgments have been scrutinised and challenged.

Data transparency also creates the optimal environment for products—there will be many covid-19 products, to be sure—to compete on the strength of their evidence base, not on the strength of promotion and buzz.

No legitimate barriers

Finally, it must be recognised that there are no legitimate barriers to data transparency during the covid-19 pandemic. Companies can have little basis for claiming commercial confidentiality, as most products with any prospect of market entry have already been guaranteed massive profits through advance government purchases. There should also be no concern about patient privacy: guarantees to patients and trial participants regarding the privacy of their data should be honored, and such patient level data can and should be duly de-identified.

Nor should data release cost us valuable time. While it does take time to prepare data for sharing, the core work involves de-identification, and the trial specific methods can be determined in advance while trials are ongoing, for easy release when data collection is complete.

Before any treatment or vaccine is made widely available, study protocols should be in the public domain, along with statistical analysis plans, clinical study reports, patient level data, and copies of the correspondence with regulators and other key stakeholders.

Data transparency is not a "nice to have." Claims made without access to the data—whether appearing in peer reviewed publications or in preprints without peer review—are not scientific claims. Products can be marketed without access to the data, but doctors and professional societies should publicly state that, without complete data transparency, they will refuse to endorse covid-19 products as being based on science.

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COVID-19

Do many people have a pre-existing immunity to covid-19?

It has been commonly accepted that the human population had no protective response to SARS-CoV-2 before it emerged last year, but is that actually the case? **Peter Doshi** reports

Even in local areas that have experienced some of the greatest rises in excess deaths during the covid-19 pandemic, serological surveys since the peak indicate that at most only around a fifth of people have antibodies to SARS-CoV-2: 23% in New York, 18% in London, 11% in Madrid. Among the general population the numbers are substantially lower, with many national surveys reporting in single digits.

With public health responses around the world predicated on the assumption that the virus entered the human population with no pre-existing immunity before the pandemic, serosurvey data are leading many to conclude that the virus has, as Mike Ryan, WHO's head of emergencies, put it, "a long way to burn."

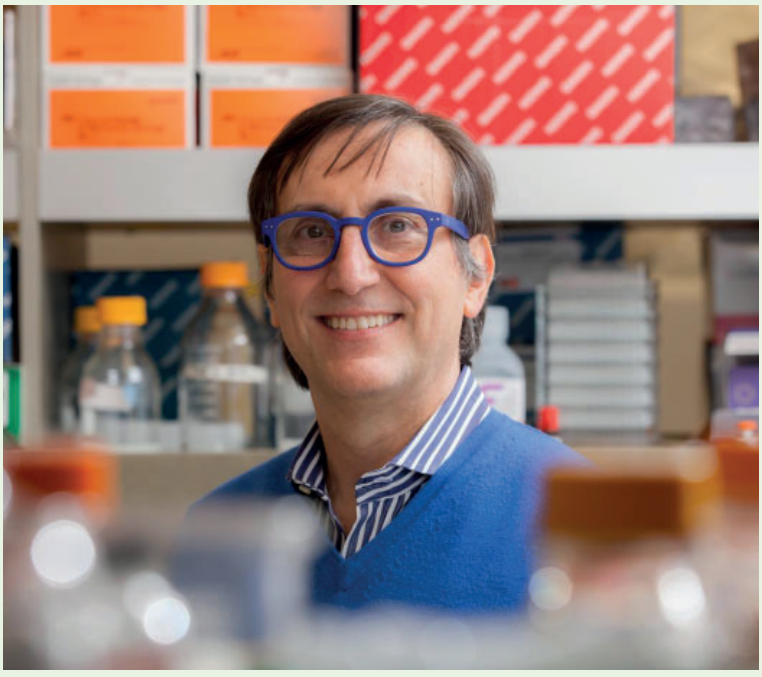
In a study of donor blood specimens obtained in the US between 2015 and 2018, 50% displayed various forms of T cell reactivity to SARS-CoV-2. A similar study that used specimens from The Netherlands reported T cell reactivity in two of 10 people who had not been exposed to the virus.

In Germany reactive T cells were detected in a third of SARS-CoV-2 seronegative healthy donors (23 of 68). In Singapore a team analysed specimens taken from people with no contact or personal history of SARS or covid-19; 12 of 26 specimens taken before July 2019 showed reactivity to SARS-CoV-2, as did seven of 11 from people who were seronegative against the virus. Reactivity was also discovered in the UK and Sweden.

Though these studies are small and do not yet provide precise estimates of pre-existing immunological responses to SARS-CoV-2, they are hard to dismiss, coming from different laboratories in different continents and with several being published in *Cell* and *Science*. Researchers are also confident that they have made solid inroads into ascertaining the origins of the immune responses.

"Our hypothesis, of course, was that it's so called common cold coronaviruses, because they're closely related," said Daniela Weiskopf, senior author of a paper in *Science* that confirmed this hypothesis. "We have really shown that this is a true immune memory and it is derived in part from common cold viruses."

Taken together, this growing body of research may force pandemic planners to revisit some of their foundational assumptions about how to measure population susceptibility and monitor the extent of epidemic spread.



Swine flu deja vu

In late 2009, months after the World Health Organization declared the H1N1 "swine flu" virus to be a global pandemic, Alessandro Sette (left) was part of a team working to explain why the so-called "novel" virus did not seem to be causing more severe infections than seasonal influenza.

Their answer was pre-existing immunological responses in the adult population—B cells and, in particular, T cells which "are known to blunt disease severity." Other studies came to the same conclusion: those with pre-existing reactive T cells had suffered less severe H1N1 disease.

In addition, a study carried out during the 2009 outbreak by the US CDC reported 33% of those over 60 years old had cross-reactive antibodies to the 2009 H1N1 virus, leading the CDC to conclude "some degree of preexisting immunity" to the new H1N1 strains existed, especially among adults over age 60.

The data forced a change in views at WHO and CDC, from an assumption prior to 2009 that most people "will have no immunity to the pandemic virus" to one that acknowledged "the vulnerability of a population to a pandemic virus is related in part to the level of pre-existing immunity to the virus." But by 2020, it seems that lesson had been forgotten.

This is a true immune memory derived from common cold viruses
Daniela Weiskopf

Many people got infected and didn't create antibodies
Marcus Buggert

Population immunity: underestimated?

Seroprevalence surveys measuring antibodies have been the preferred method for gauging the proportion of people in a given population who have been infected by SARS-CoV-2 (and have some degree of immunity to it).

That only a minority of people, even in the hardest hit areas, display antibodies against SARS-CoV-2 has led most public health planners to assume the pandemic is far from over. In New York City, where just over a fifth of people surveyed had antibodies, the health department concluded that "as this remains below herd immunity thresholds, monitoring, testing, and contact tracing remain essential public health strategies." Whatever that threshold number is, "we're nowhere near close to it," said WHO's Ryan in late July.

But memory T cells are known for their ability to affect the clinical severity and susceptibility to future infection, and the T cell studies documenting pre-existing reactivity to SARS-CoV-2 in 20-50% of people suggest that antibodies are not the full story.

"Maybe we were a little naive to take measurements such as serology testing to look at how many people were infected with the virus," the Karolinska Institute immunologist Marcus Buggert told *The BMJ*. "Maybe there is more immunity out there."

The research offers a powerful reminder that very little in immunology is cut and dried. Physiological responses may have fewer sharp distinctions than in the popular imagination: exposure does not necessarily lead to infection, infection does not necessarily lead to disease, and disease does not necessarily produce detectable antibodies. And within the body, the roles of various immune system components are complex and interconnected. B cells produce antibodies, but B cells are regulated by T cells, and while T cells and antibodies both respond to viruses in the body, T cells do so on infected cells, whereas antibodies help prevent cells from being infected.

Unexpected twist of the curve

Buggert's home country has been at the forefront of the herd immunity debate, with Sweden's light touch strategy against the virus resulting in much scrutiny and scepticism. The epidemic in Sweden does seem to be declining, Buggert says. Something must have happened, he says, particularly considering that social distancing was "always poorly followed, and it has only become worse."

Understanding this "something" is a core question for Sunetra Gupta, an Oxford University epidemiologist who developed a way to calculate herd immunity thresholds that incorporates a variable for pre-existing innate resistance and cross protection. Her

Calculating the herd immunity threshold

In theory, outbreaks of contagious disease follow a certain trajectory. In a population lacking immunity, new infections grow rapidly. At some point, an inflection in this growth should occur, and the incidence will begin to fall.

The 1970s gave rise to a theory that defined this inflection point as the herd immunity threshold (HIT), and offered a simple formula for estimating its size: HIT = 1 – (1/R0) (where R0 is the disease's basic reproduction number, or the average number of secondary cases generated by an infectious individual among susceptible people). This calculation has guided—and continues to guide—many vaccination campaigns, often used to define target vaccination levels.

The formula rests on two assumptions—that, in a given population, immunity is distributed evenly and members mix at random. While vaccines may be deliverable in a near random fashion, from the earliest days, questions were raised about the random mixing assumption. Apart from certain small closed populations such as "orphanages, boarding schools or companies of military recruits," truly random mixing is the exception not the rule.

Nearly 50 years later, Gabriela Gomes, an infectious disease modeller at University of Strathclyde, is reviving concerns that the theory's basic assumptions do not hold. Her team says that not only do people not mix randomly, infections (and subsequent immunity) do not happen randomly either. "More susceptible and more connected individuals have a higher propensity to be infected and thus are likely to become immune earlier. Due to this selective immunisation by natural infection, heterogeneous populations require less infections to cross their herd immunity threshold," they wrote.

Gabriela Gomes, University of Strathclyde

While most experts have taken the R0 for SARS-CoV-2 (generally estimated between 2 and 3) and concluded that at least 50% of people need to be immune before HIT is reached, Gomes and colleagues calculate the threshold at 10 to 20%.

Ulrich Keil, professor emeritus of epidemiology from University of Muenster says the notion of randomly distributed immunity is "a very naive" that ignores the large disparities in health among populations and "also ignores completely that social conditions might be more important than the virus itself." He adds, "Tuberculosis here is the best example. We all know that the immune system is very much dependent on the living conditions of a person and this depends very much on education and social conditions."

Researchers led by Sunetra Gupta at University of Oxford have arrived at similar conclusions by considering the issue of pre-existing immunity. When a population has people with a pre-existing immunity, as T cell research indicates may be the case, the herd immunity threshold based on a R0 of 2.5 can be reduced from 60% of a population getting infected to 10%, depending on the quantity and distribution of immunity, according to their calculations.

group argues that herd immunity thresholds "may be greatly reduced if a fraction of the population is unable to transmit the virus."

"The conventional wisdom is that lockdown occurred as the epidemic curve was rising," Gupta explains, "So once you remove lockdown that curve should continue to rise." But that is not happening in places like New York, London, and Stockholm. The question is why.

Possible answers are many, Gupta says. One is that social distancing is in place, and people are keeping the spread down. Another possibility is that a lot of people are immune because of T cell responses or something else. "Whatever it is, if there is a significant fraction of the population that is not permissive to the infection, then that all makes sense, given how infectious SARS-CoV-2 is."

Buggert's study in Sweden seems to support this position. Investigating close family members of patients with confirmed covid-19, he found T cell responses in those who were seronegative or asymptomatic. While around 60% of family members produced antibodies, 90% had T cell responses. (Other studies have reported similar results.) "So many people got infected and didn't create antibodies," concludes Buggert.

Deeper discussion

T cell studies have received scant media attention, in contrast to research on antibodies, which seem to dominate the news (probably, says Buggert, because they are easier, faster, and cheaper to study than T cells). Two recent studies reported that naturally acquired antibodies to SARS-CoV-2 begin to wane after just 2-3 months, fuelling speculation in the lay press about repeat infections.

But T cell studies allow for a substantially different, more optimistic, interpretation. In the Singapore study, for example, SARS-CoV-1 reactive T cells were found in SARS patients 17 years after infection. "Our findings also raise the possibility that long lasting T cells generated after infection with related viruses may be able to protect against, or modify the pathology caused by, infection with SARS-CoV-2," the investigators wrote.

There is a significant fraction of the population that is not permissive to the infection
Sunetra Gupta

T cell studies may also help shed light on other mysteries of covid-19, such as why children have been surprisingly spared the brunt of the pandemic, why it affects people differently, and the high rate of asymptomatic infections in children and young adults.

The immunologists I spoke to agreed that T cells could be a key factor that explains why places like New York, London, and Stockholm seem to have experienced a wave of infections and no subsequent resurgence. This would be because protective levels of immunity, not measurable through serology alone but instead the result of a combination of pre-existing and newly formed immune responses, could now exist in the population, preventing an epidemic rise in new infections.

But they were all quick to note that this is speculation. Formally, the clinical implications of the pre-existing T cell reactivity remain an open question. "People say you don't have proof, and they're right," says Buggert, adding that the historical blood donor specimens in his study were all anonymised, precluding longitudinal follow-up.

There is the notion that perhaps T cell responses are detrimental and predispose to more severe disease. "I don't see that as a likely possibility," says Alessandro Sette, an immunologist from La Jolla Institute for Immunology in California, while emphasising that we need to acknowledge the possibility. "It's also possible that this absolutely makes no difference. The cross reactivity is too small or weak to affect the virus. The other outcome is that this does make a difference, that it makes you respond better."

Weiskopf adds, "Right now, I think everything is a possibility; we just don't know. The reason we're optimistic is we have seen with other viruses where [the T cell response] actually helps you." One example is swine flu, where research has shown that people with pre-existing reactive T cells had clinically milder disease.

Acquiring the evidence

Weiskopf and Sette say that compelling evidence could come through a properly designed prospective study that followed a cohort of people who were enrolled before exposure to SARS-CoV-2, comparing the clinical course of those with and without pre-existing T cell responses.

Understanding the protective value of pre-existing SARS-CoV-2 T cell reactivity is "identical to the situation on vaccines," says Antonio Bertoletti, professor of infectious disease at Duke-NUS Medical School in Singapore. "Through vaccination we aim to stimulate antibodies and T cell production, and we hope that such induction of immunity will protect… but we need a phase III clinical study to really demonstrate the effect."

"At the start of the pandemic, a key mantra was that we needed the game changer of antibody data to understand who had been infected and how many were protected," two immunologists from Imperial College London wrote in a mid-July commentary in *Science Immunology*. "As we have learned more about this challenging infection, it is time to admit that we really need the T cell data too."

Peter Doshi, associate editor, *The BMJ*
pdoshi@bmj.com
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