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The New Necessary: How We Future-Proof for the Next Pandemic

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Foreword by Ara Darzi

In little over a year, the most lethal pandemic of the 21st century has spread to every quarter of the globe, claimed 2.5 million lives, caused terrible suffering, and wrecked families and economies. And it is not over yet.

We know the Covid-19 pandemic will be followed by another, and yet another. It is a question of when, not if. Indeed, the seeds of the next pandemic may already have been sown in the shape of a mutant strain of the existing SARS-CoV-2 virus – more deadly, more transmissible, more resistant.

Time is not on our side. We must prepare now. We have learned many lessons over the last year, from things we have got right and things we have got wrong. We must put plans for the future in place without delay.

We know that with the right measures, deaths can be avoided, illness and disability can be prevented and economies protected. But we must act now to be ready for the next pandemic.

Better surveillance to catch new viral strains, a maximum 100-day target for the preparation of new vaccines, faster production of therapeutic drugs, better testing, stockpiles of the right PPE and a gold standard data strategy are among the essential ingredients of a future pandemic plan.

We cannot wait for these developments. The need is urgent. It amounts to nothing less than a revolution in global public health and it will require global cooperation. The stakes could not be higher. With its presidency of the G7 group of nations in 2021, the UK has an unprecedented opportunity to take the lead. We must rise to the challenge.

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Introduction

Covid-19 has raged for over a year, its path littered with destruction. Lives lost, livelihoods destroyed, economies shaken. It has changed us in ways we may not even be able to comprehend. All of this, and still the challenge of the pandemic endures. With emerging strains of the virus and the race to vaccinate the world more like a marathon than a sprint, no immediate end appears in sight. While we're hopeful the economy will bounce back and life will return to some sort of normal, uncertainties and risks remain.

Two competing objectives have been at the forefront of government responses to date: How do we protect lives and simultaneously keep economies afloat? Measures have ranged from the blunt instrument of national lockdowns to living alongside the virus with the precision of test and trace – with countries often jumping from one to the other. There has been mixed success on achieving both.

Here in the UK, we have seen heroic efforts of many, particularly the NHS, in response. The vaccine rollout, which has so far covered close to 20 million people with first doses, is a national success story. Our testing capability has expanded dramatically, with over 600,000 people regularly tested on a daily basis. There is much to be proud of.

In this paper, we draw on these successes and identify gaps in response to focus on an emerging third objective.

How do we prepare for future pandemics?

This objective has taken on a more imminent importance. The next pandemic is likely not a new virus or plague, but a mutant strain of Covid-19 that is more deadly, more transmissible or resistant to antibodies. It could be all three.

Therefore, the most important lesson of the last year has been the need to prepare. As much of the world remains unvaccinated and a spate of recent mutations raise the risk of high transmissibility and potentially higher mortality, we have to face up to the realistic possibility of an even greater challenge than what has gone before. Shutting down borders and rolling out vaccines is not a long-term strategy. Instead, there needs to be a revolution within global public health. This has implications across testing, therapeutics, vaccines and PPE – and our ability to rapidly approve, manufacture and distribute innovations across each area. It requires a fundamental upgrade to data infrastructure and health surveillance.

We call this infrastructure **the new necessary**. It may be needed sooner than we think.

Work on it must start now.

Recommendations

This paper makes a series of recommendations across the short and medium term for the UK in order to better prepare the country for future pandemics – recognising that the next pandemic could be a new strain of Covid-19.

Leadership

- The UK, through its timely presidency of the G7, should lead the way on the development of new global health security infrastructure and coordination of the issues set out below.
- In addition to developing a new infrastructure for global health security, the UK should leverage and work with existing architecture where appropriate, for instance GAVI, the Vaccine Alliance; COVAX; the Coalition for Epidemic Preparedness Innovations (CEPI); and others.
- Consider creating the NIHP (National Institute for Health Protection) as a focused but nimble and high-quality organisation more akin to a national security service and keep traditional public health as a separate entity. The organisation must have resources and personnel to match this status, and should encompass the pandemic-preparedness elements of Public Health England.
- Commit significant funds to R&D on the key measures for pandemic preparedness, in order to build a pipeline of innovations and contribute to global research efforts.
- Work to address the market-failure challenge on financing products for pandemics.

Surveillance

- The UK should treat pre-pandemic preparedness as akin to a military operation, using the best military hardware and software to spot developments.
- When any threat or new strain is identified, there should be a rapid clinical characterisation, and immediate preparations to ensure there are adjustments to treatments, vaccines and other drugs.
- The UK must continue to sequence, collect and share data on mutations with the rest of the world and lead on setting up a global genomic surveillance database that operates in real time and identifies new strains or viruses, allowing action to be taken at source immediately.

Vaccines in 100 Days or Less

There must a be shared domestic and global aim for vaccine development to move to identification of threat to development and distribution of vaccines within a maximum of 100 days. The ambition should be to go even faster than this.

To achieve this ambition, the UK should:

- Conduct a comprehensive audit of bioreactor and mRNA production capacity; where there is a shortage, the government should develop support and incentives to repurpose existing infrastructure. This should start now for Covid-19, including with those companies not producing vaccines but which have capacity.
- Use the UK's competitive advantage in talent, location and regulation to compete with the incentives offered by the likes of South Korea, Singapore and Ireland to bring any necessary manufacturing capacity onshore.
- Develop "pop up" surge capacity through plastic single-use technologies (SUTs) – cost-efficient alternatives to stainless steel bioreactors.
- Incentivise and celebrate UK-based companies with manufacturing capacity who don't have their own proprietary vaccine to hand manufacture the vaccines of companies who do.

This ambitious aim cannot be achieved without global collaboration. The UK should play a leadership role and maximise the 16.7 million litres of global manufacturing capacity to develop vaccines and essential therapeutics, antibodies and antivirals in a pandemic.

Globally, we need:

- Leadership to address vaccine nationalism and ensure fair distribution. Countries should be encouraged to boost their own manufacturing and surge capacity, with oversupply a good problem to have, and feed into a mechanism that matches this supply with demand.
- Repurposing of manufacturing capacity in a pandemic. Only a small amount of the 16.7 million litres of manufacturing capacity for vaccines, therapeutics, antibodies and antivirals is being used for Covid-19. This should be repurposed, for example by encouraging companies with capacity who aren't making the vaccine to offer up their facilities.
- A plan to introduce more manufacturing capacity to Africa, Asia and Australasia – which, combined, have less than North America – should be developed.
- For future pandemics, risk should be taken out of the equation which can otherwise cause delays for manufacturers. Developed economies, including the UK, and internationally coordinated bodies should de-risk investments in developing vaccines through capital grants and advanced purchasing orders.

On vaccine trials and rollout, the UK should:

- Investigate the role of challenge trials in future pandemic preparedness planning and when it comes to variant vaccines to address new, dangerous strains. This should be globally coordinated.
- Be as efficient as possible in both manufacturing and administering so-called booster doses by utilising a single shot that delivers multiple vaccines. Share its proven expertise in vaccine rollouts with countries around the world and support them to develop blueprints of their own, recognising that rollout at scale in low- and middle-income countries (LMICs) is more difficult. It is important that, even while awaiting vaccine supply, countries use that time to prepare to roll out doses when they do become available.

Therapeutics, Antibodies and Antivirals

The UK should:

- Invest in large-scale, UK-based biologic manufacturing capacity.
- Increase funding into the development and manufacturing of therapeutics, antibodies and antivirals for future pandemics, ensuring a sufficient stockpile across each.
- Fast-track research into and stockpiling of antivirals for a potential "worst-case scenario" Covid strain, giving them the same focus and prioritisation as vaccines have received.
- Revisit the international aid commitment by providing additional funding for antivirals and diagnostic testing to be made available and earmarked for the countries unable to access sufficient vaccine supplies.
- Support efforts to further shorten the time required for clinical development by pushing for greater global coordination and data-sharing of clinical trials.
- Increase recruitment for trials by making future random control trials "opt-out" – so that everyone with a disease is automatically entered into the trials unless they object – once safety of drugs has been proved.

PPE

The UK should:

- Publish a clear strategy on what the frontline need of PPE will be in the circumstances of a more dangerous strain of the Covid virus.
- Set out clearly what the government plans to do to ensure N95 masks and other vital PPE supplies are available for key workers.

- Set out a clear roadmap for how the UK can ensure it has: 1) a six-month stockpile across all key PPE items, covering health and care workers, as well as frontline key workers; and 2) a plan for how to ensure the country can meet this supply in a continued crisis (this should include a mixture of pre-arranged agreements with companies overseas and the right UK manufacturing base).

Testing

The UK should:

- Invest in research and manufacturing capacity to deliver: 1) gold standard lab-based testing at scale (ELISA and PCR, for example); and 2) highly accurate rapid tests, which are affordable, to support mass testing.
- Incentivise the development and manufacturing of a rapid test able to detect virus even in incubation stage.
- A strategy that deploys the right tests in the right settings, ensuring we don't make the best the enemy of the good.
- Accelerate rollout of rapid diagnostics that detect contagious carriers of the virus and use a system of mass testing to identify and isolate carriers.
- Ensure that any mass testing system has sufficient incentives to promote 1) compliance with a positive result, and 2) regular testing at a very low cost to enable penetration.
- Link test data to a health passport and wider medical records.

Data

The UK needs:

- Cloud-based data storage and software, enabling health-care workers and medical devices to record data quickly and accurately.
- Real-time data reporting, analysis and insights to inform decision-making, from early warning of pressure points to algorithmic optimisation of vaccine rollouts.
- Best-in-class security, access controls and audit, encrypting all data as standard and ensuring personally identifiable data is never exposed without permission.
- A unique and persistent identifier for each citizen, enabling people to access their health data and prove their status to others, while at all times protecting their privacy.
- Better tools to pool data to expedite safety and efficacy trials, including for securing regulatory approval and large-scale post-treatment and post-vaccination surveys.

- Better tools to manage the logistics for mass testing and mass vaccinations, including allocating and distributing supplies and certifying that they are authentic.
- Internationally agreed data standards and definitions, so that countries are aligned on how to identify and respond to new threats in a timely and targeted manner.

The Next Pandemic: New Mutations, New Strains

The virus mutates – as all viruses do – and Covid-19's mutations have included some that are much more transmissible and may not be fully covered by existing vaccines. Mutations can form new strains, and it is possible that a new strain arises which is not susceptible to any vaccine. This puts us in a position where we need to be prepared to combat the virus with tools other than a vaccine in a worst-case scenario. We need to have the capacity to add antivirals and other biologics to our tool kit.

Normally we are told that as a virus mutates, mortality reduces, either because hosts die or the virus becomes weaker. Covid-19 is now somewhere in the middle which – in today's interconnected, largely unvaccinated world – is a problem. New strains appear to have higher mortality rates and, if allowed to spread, could do significant damage compared to the original SARS-CoV-2.

SARS-CoV-2: The "Wild-Type", Mutations and Strains

The genetic makeup of Covid-19 has evolved since researchers first began to study it last year. It will continue to change as the virus spreads throughout the population. The originally sequenced virus, identified in Wuhan in January 2020, is called the "wild type" SARS-CoV-2. Wild-type viruses are the naturally occurring, non-mutated strain of a virus. [1]

But a virus's genetic makeup changes, or mutates, as it spreads. Covid-19 currently undergoes changes to its genetic sequencing at a rate of one to two changes per month. [2] These changes are called mutations.

These mutations of the wild-type SARS-CoV-2 then create "strains", which are distinguishable by one or more mutations from other strains. Strains can elicit different responses from the human immune system or vary in their transmission characteristics. [3]

Covid-19 Mutations

Not all mutations are significant – only certain types of mutations can make a virus more dangerous to people. [4] However, some of the new Covid-19 strains appear to be more transmissible and respond differently to antibodies. This is when mutations can become potentially dangerous. Current key mutations include:

- **N501Y:** Speeds up transmission

- **E484K:** May reduce the virus's vulnerability to antibodies (based on early evidence, more research required)
- **K417N:** May reduce the virus's vulnerability to antibodies (based on early evidence, more research required)
- **K417T**: Not enough data to say definitively, research is ongoing

Emerging Covid-19 Strains

The moment any new strain is identified, there should be a rapid characterisation of the new mutation and immediate preparations to ensure there are adjustments to treatments, vaccines and other drugs. The UK is a global leader in sequencing Covid-19 and has carried out more than half of the sequencing of new strains of the virus that have been submitted to a global database. [5]

Experts believe that polymerase chain reaction (PCR) and lateral flow tests (LFTs) will continue to be able to identify Covid-19 infections in the same way with all current emerging strains. This is because the parts of the virus that the tests use to identify positive cases are likely to remain the same regardless of the strain. [6]

Once we exit the lockdown first imposed in January – and with cases reduced – the UK should commit to sequencing every positive sample of Covid-19.

Table 1 – Notable Covid-19 strains so far

Strain name	Common name	Mutations	Increases severity of virus?	Resistant to existing vaccines?
B1.1.7, 20I/501Y.V1 or VOC 202012/0	Kent/UK strain	**N501Y** (increases transmissibility) P681H 69/70 deletion	**No**	**No**

B.1.35 1 or 20H/ 501Y.V2	South Africa strain	**N501Y** (increases transmissibility) **E484K** (reduces antibody recognition) **K417N** (reduces antibody recognition)	**No**	Vaccines less effective
P.1 or 20J/501Y.V3	Brazil strain	**N501Y** (increases transmissibility) **E484K** (reduces antibody recognition) **K417T** (unknown)	Not yet clear	Not yet clear

Eradication in the Short to Medium Term Is Not an Option

No country has been able to eradicate Covid-19 except by total isolation – which as a policy is neither sustainable nor economically viable. Even China, South Korea and New Zealand, despite the most stringent curbs, have been unable to eliminate the virus completely; furthermore, for economic reasons, isolation can't continue indefinitely.

In the long term, there could be advancements in therapeutics or vaccines that do allow us to eradicate Covid-19 in its entirety, but in the short to medium term, it's clear that, ultimately, virus anywhere leads over time to virus everywhere. If it is still circulating in Africa or South America, it will in the end come our way.

Anywhere Is Everywhere: Global Collaboration

Right now, nationalism in vaccine acquisition is following the same pattern as the early rush for PPE, with countries doing all they can to protect their own. But no one country can outmanoeuvre Covid-19 on its own, and every country is affected by the state of the fight globally.

What is necessary is that major high-income countries like Britain build the capability to be able to look after themselves and, at the same time, rebuild international coalitions to form interdependent manufacturing chains. The objective should be to boost the scale and capacity of developing new innovations.

With this new capacity, the world must adopt a completely new approach to global health that recognises that the present public health infrastructure has failed and that the market alone cannot be the arbitrator of choosing which demand to meet with limited supply. The weaknesses nationally and internationally are manifest and are not correctable without a plan involving a partnership between the public and private sectors and between governments.

The UK, through its timely presidency of the G7, should lead the way on the development of new health security infrastructure. This could include an agreed global and/or national "code of conduct" for pandemics, to ensure concerted responses independent of political affiliation. Plugging into and guiding existing institutions, including the WHO, GAVI and CEPI, this would fill the health security gap – especially when it comes to identifying pandemics at source and bringing together key stakeholders across policy, science, logistics and manufacturing to coordinate resources. It is critical this has the buy-in of both developed and developing countries.

The National Institute for Health Protection

The commitment by the UK government to actively work to build resilience in the health system for any future pandemics is to be welcomed, and the National Institute for Health Protection (NIHP) could be an exemplar of best practice around the world. It is scheduled to go live in April 2021. [7] According to official documentation, this new organisation will be responsible for "monitoring, identifying and ensuring [UK] readiness to respond to public health hazards" and goes on to describe the operational setup of the organisation as combining "...the health protection capabilities of PHE with NHS Test and Trace, including the UK-wide Joint Biosecurity Centre (JBC)." The government will transfer staff and systems into the new organisation over the following months.

It's important this new organisation is positioned as part of the UK's security infrastructure, attracting the resources and decision-making capacity that goes with such status – as opposed to simply being a bigger, better Public Health England (PHE). The latter served an important role in the UK pre-pandemic, including running a number of public-health campaigns, such as on the cessation of smoking. It's critical that this does not become mixed up with the obvious gap that the NIHP is there to fill: the identification and prevention of potential pandemics. Equally, the NIHP must be fleet of foot and avoid creating unnecessary bureaucracy. As such, the government should seriously consider creating the NIHP as a separate organisation drawing in the pandemic and serious infection elements of PHE – such as its lab, R&D and epidemiology capacity – but plugged into the security services, and keep traditional

public health prevention campaigns separate entity. Regardless of its structure, the body will need strong, empowered leadership from day one.

Surveillance and Sequencing: Stopping Pandemics Before They Begin

Surveillance

It is critical that we have military-grade surveillance that can identify the moment when a potential pandemic-inducing virus first enters circulation. Certain behaviours – such as visiting hospital or purchasing symptom-treating drugs – will increase when a virus arrives, and these should trigger early-warning measures within government. Early carriers can then be tested and, if necessary, isolated, as well as having any new, unidentified virus tracked. This would give rise to a number of the measures set out in this paper.

Surveillance also gives researchers more time to develop new treatments, public health organisations space to prepare responses, and individuals the opportunity to minimise their exposure to sources of disease risk. [8] Surveillance requires a combination of data and hardware. In the last year, we have seen examples of best practice around the world and a number of promising innovations that will enable this critical first step. These include:

- **FluSight in the US**: Since 2013, the "Predict the Influenza Season Challenge" by the Centres for Disease Control and Prevention (CDC) has encouraged outside academic and private industry researchers to forecast the timing, peak and intensity of the flu season. The CDC's FluSight programme also uses public health and clinical laboratories to test specimens to understand what influenza virus types, subtypes and lineages are circulating and the age groups affected in real time. Outpatient facilities and hospitals report influenza-like illnesses to a central surveillance network to keep track of potential outbreaks. State and territorial health departments report the estimated level of geographic spread of influenza activity in their jurisdictions each week through the State and Territorial Epidemiologists Report. [9]

- **Wastewater surveillance:** Wastewater, or sewage, includes water from household and building use (i.e., toilets, showers, sinks) that can contain human faecal waste, as well as water from non-household sources (e.g., rainwater and industrial use). Wastewater testing has been successfully used as a method for early detection of other diseases, such as polio, and can act as an indicator that is independent of health-care-seeking behaviours and access to clinical testing. Covid-19 can be shed in the faeces of individuals with both symptomatic and asymptomatic infection, capturing data on both types of infection. In most developed economies, a large majority of the population is served by sewage systems, making this type of surveillance widely representative of many communities. [10]

- **Australia's Vital Intelligence Project:** The Vital Intelligence Project is a health and respiratory monitoring platform using new and existing camera networks as well as unmanned aerial vehicles (UAVs) and remotely piloted aircraft systems (RPAS) for the detection of infectious and respiratory conditions. Sensors fitted in the drones record body temperature, pulse rate, respiratory rate and other biomarkers to look for abnormalities within groups such as crowds, workforces, airlines, cruise ships, border crosses, and within potential at-risk groups, such as seniors in care facilities. This type of surveillance is being explored in the hopes that critical interventions can be deployed sooner and with greater effectiveness. [11]

- **Microsoft's Project Premonition:** It is estimated that 60 to 75 per cent of emerging infectious diseases are caused by pathogens that jump from animals to people. These pathogens move through the environment in complex ways and are difficult to monitor. Because of that, Microsoft is exploring the use of robotics and genomics to identify new viruses before they become full-blown pandemics. Microsoft's "robotic smart traps" continuously monitor the environment for certain insects, such as mosquitoes, which transmit pathogens and collect blood samples from other animals. The company's "cloud-scale genomic analyses" attempt to identify all the species of organisms and viruses in environmental samples to spot new transmission patterns. [12]
- **South Korea:** In light of the country's relative success containing the spread of Covid-19 during the first wave in early 2020, South Korea has been widely cited for its successful use of technology-driven surveillance techniques. This surveillance was used primarily for contact-tracing purposes, using mobile-phone data, CCTV footage, and electronic transaction data to provide extensive data on peoples' movements. Although the technology used in South Korea is widely available in most countries, this type of surveillance requires political willingness to repurpose and there is a significant privacy trade-off. [13]

Sequencing

Since the beginning of the pandemic, scientists have monitored SARS-CoV-2 and watched it evolve in real time more closely than any other virus in history. The virus mutates and many of the genomes sequenced today differ about 20 points from the earliest genome sequences in China in January 2020. [14] The ability to rapidly respond to emerging mutations and accelerate vaccine or biologic enhancements where necessary will be essential in fighting this pandemic and the next one.

Scientists were able to gain an early understanding and characterisation of the virus because of the extensive sequencing that took place right from the start of the pandemic. Early sharing of the virus's genetic data led to the rapid development of diagnostics and the consistent sequencing that followed played a key role in the rate at which vaccines were produced. [15]

Globally, almost 490,000 SARS-CoV-2 genomes have been sequenced. Of those genomes, more than half (250,673) were sequenced in the UK by the COG UK Consortium and the Wellcome Sanger

Institute. This continuous sequencing combined with epidemiological data is providing real-time insights into emerging new variants and their genetic makeup. [16]

To maintain its standing as a global leader in genomic sequencing, the UK must continue to sequence, collect and share data on new mutations with the rest of the world and lead on these discussions. An effective global genomic surveillance system or database that operates in real time needs to be a global concern as it is an essential tool when dealing with Covid-19 and any future pandemics. [17] Virus anywhere is virus everywhere, so a globally accessible database of genomic surveillance will help keep this virus under control and potentially stop the next pandemic from spreading as quickly and going as far as Covid-19.

Table 2 – The percentage of cases sequenced [18]

Country	Reported cases	Samples sequenced	Percentage of cases sequenced
Australia	28,238	16,537	58.6%
New Zealand	2,128	1,034	48.6%
Taiwan	776	137	17.7%
Denmark	144,047	16,790	11.7%
Iceland	5,683	601	10.6%
Gambia	3,791	360	9.5%

Vietnam	1,421	113	8%
UK	2,116,609	157,439	7.4%
Thailand	5,762	343	6%
Japan	207,001	9,599	4.6%

Vaccines: A Local and Global Solution

It is impossible to fully disaggregate and isolate the responsibilities of the UK when it comes to the development, manufacture and distribution of vaccines. It is such a global, interconnected industry. However, given the UK's ambitions to play a leading role and the success of the UK's domestic rollout of Covid-19 vaccines, it is important to set out what needs to happen locally and globally for the next pandemic. Actions in both categories can be united by a single aim:

Vaccines should take weeks – working to an ambition of 100 days from a threat being discovered – to be developed and distributed.

This is far from impossible especially for known variants. Even in the early days of the Covid-19 pandemic, the SARS-CoV-2 genome was known and widely shared, and within days viable vaccine candidates had been produced. [19] A quick look at reporting around this time – and the decisions taken by CEPI on which vaccines to invest in – show there was gathering consensus on the companies and vaccines that would be most effective. In future pandemics, we need to turn this insight into strategy, only backing a few vaccines that we know will work and doing all we can to repurpose (and celebrate the repurposing of) manufacturing capacity from others to maximise production. This should not be at the cost of preclinical studies.

As set out below, this will require an increase in bioreactor capacity and fast-turnaround repurposing of existing capacity – including in the UK. Above all else, it will need global leadership and coordination.

Vaccines: Supply and Manufacturing in the UK

The UK has proved itself a global leader on the rollout of vaccines, but the reality is that we must go further and faster in future pandemics. Globally, excellent vaccine rollout should not be the exception but the norm, reducing the threat of viruses mutating elsewhere and then spreading throughout the UK.

Covid-19 has led to a transformational moment in vaccine technologies. As detailed below, it has taken almost a year for reputable vaccines to be developed, tested and approved, however it will likely take many years more for them to be available at sufficient scale globally.

Looking ahead, the overarching objective must be to reduce the time it takes from a threat being identified and sequenced to a vaccine being distributed to weeks rather than months.

The ambition of CEPI that has since been adopted by Prime Minister Boris Johnson [20] is for a vaccine to be developed within 100 days. This should be the lower limit of our ambition. With the right measures in place, we believe a vaccine can be produced at scale in a very short of space of time. This requires the UK to do four things:

- Boost vaccine manufacturing and surge capacity and speed in the UK.
- Reduce research, development and approval times for future vaccines, especially those responding to a new mutant strain.
- Contribute to a globally coordinated effort that ensures vaccines reach everyone.
- Invest R&D dollars in novel vaccine formats that can rapidly be deployed and altered in response to emerging threats.

Table 3 – Timeline for UK-approved Covid-19 Vaccines

Vaccine	Research started	Clinical trials began	Phase III trial results announced	Received regulatory approval in UK	Rollout began
Pfizer/BioNTech	17 March 2020 [21]	5 May 2020	18 November 2020	2 December 2020	8 December 2020
	Time taken from start to rollout:				
	< 1 year, using existing research from 2018				
Oxford University/ AstraZeneca	10 January 2020	24 April 2020	23 November 2020	30 December 2020	4 January 2021
	Time taken from start to rollout:				

Vaccine	Research started	Clinical trials began	Phase III trial results announced	Received regulatory approval in UK	Rollout began
	Almost 1 year (for approval and rollout)				
Moderna	Vaccine designed by 13 January 2021	March 16 2020	16 November 2020	8 January 2021	Estimated spring 2021
	Time taken from start to rollout: 1 year for approval, timeline for rollout in UK TBD				

Although the table above indicates that research and development began on specific dates, in most cases there was pre-existing research that scientists were able to repurpose to address the Covid-19 virus. For many years researchers have been studying related coronaviruses, which cause SARS (severe acute respiratory syndrome) and MERS (Middle East respiratory syndrome), research efforts that have now paid off significantly. [22] Investment in upstream research for vaccines can help accelerate the development of vaccines by allowing research to continue and be well funded.

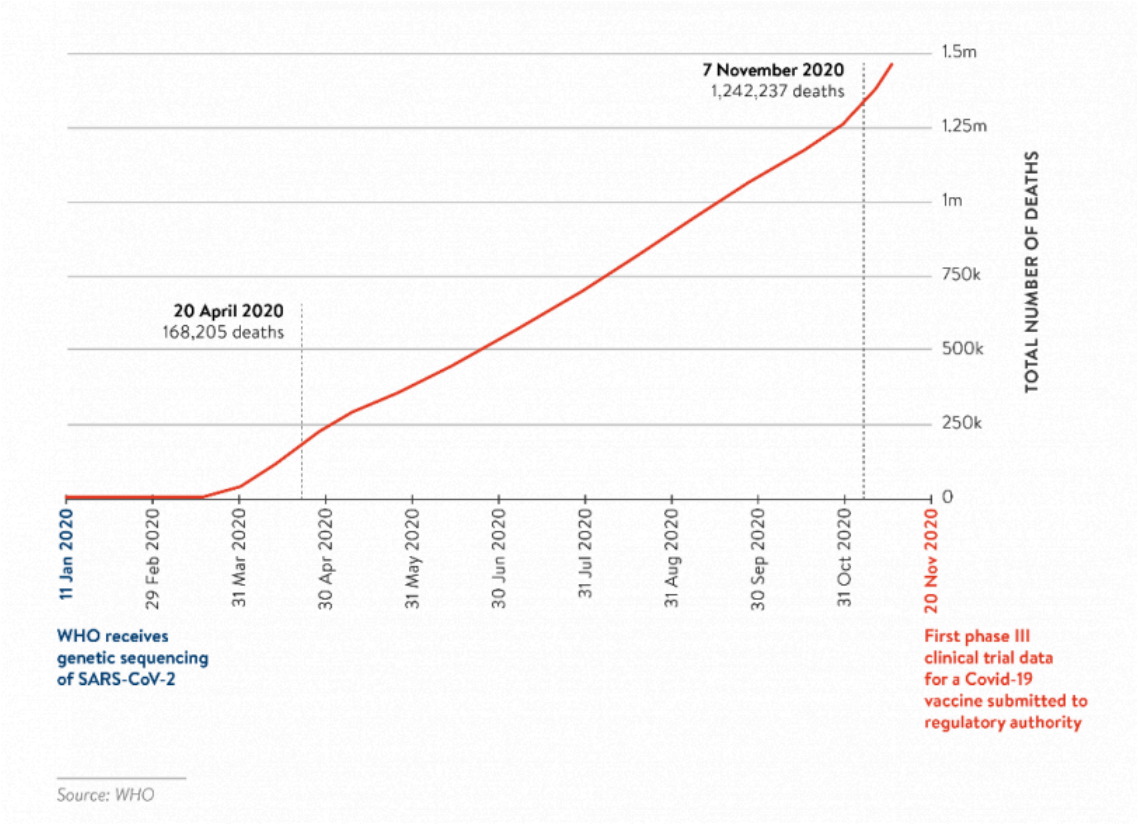
As can be seen from the diagram below, if the vaccine had been developed and approved within 100 days, rather than the approximate 300 days it took, global deaths could have been reduced by more than 1 million. In the UK, where vaccines are proving to be 94 per cent effective, [23] an earlier vaccine would have avoided 93,244 deaths. [24] Innovations in research and the use of challenge trials means 100 days is a realistic target for future pandemic.

The government should set 100 days as the maximum time it will take to go from disease identification to rollout of a vaccine – the ambition should be weeks when it comes to known variants.

Accelerating vaccine development does not mean that the safety of trials or vaccines will be compromised. Shortening the timeframe for development and approval can be achieved in several ways, for example the capacity of the Medicines & Healthcare products Regulatory Agency (MHRA) can be

boosted to reduce review time or resources for clinical trials be increased so more patients can be recruited quicker. It is also important to note that once vaccines have been developed, even less time and resources will be necessary for "top-ups" or boosters to address virus variants.

Figure 1 – Difference in global deaths if a vaccine had been approved within 100 days v 300



Vaccines in 100 Days or Less: The UK Picture

How Many Vaccines Do We Need in the UK Each Year?

Understanding the demand for vaccines is difficult as it depends on the threat in front of us. Taking Covid-19 as an example, the UK has more than enough. With contracts out for 407 million doses of seven of the most promising vaccines – three of which have been approved for use – the UK could vaccinate the entire population three times over and still have leftover doses. Kate Bingham and the Vaccine Taskforce have done a remarkable job in securing this supply.

However, ordering vaccines is just the first step. The four additional vaccines the UK ordered still must complete clinical trials and receive approval from the MHRA. Once approval is granted, these companies still need to ensure they have the manufacturing capacity to get the vaccines out as quickly as possible.

With almost 54.1 million people in the UK over age 16, [25] the current age requirement for Covid-19 vaccines, **the UK will need a little over 108 million doses if each person requires two doses.**

For future pandemics, the demand of government will evolve beyond *ordering* enough vaccines to being able to *produce* enough vaccines. This raises significant questions over the UK's own manufacturing capacity. More needs to be done to bring sufficient capacity onshore and, at the same time, support a worldwide repurposing of manufacturing capacity during a time of crisis.

Manufacturing Capacity in the UK

The UK government has invested in vaccine manufacturing and "fill and finish" facilities to increase domestic capacity, for example, by partnering with biotech company Valneva in Livingston, West Lothian, securing capacity with Thermo Fisher in Swindon and Wockhardt in Wrexham, to carry out fill and finish, and through investments in the Centre of Process Innovation in Darlington for developing facilities for vaccine production using new RNA-based technology. [26]

The Wrexham plant has the capability to fill and finish about 300 million doses of the Oxford University/AstraZeneca vaccine a year. [27] Once its vaccine is approved, Valneva's West Lothian facility is reportedly due to produce up to 200 million doses of inactivated whole virus vaccines in 2021. [28]

In addition to individual plants, the UK government has invested in the Cell and Gene Therapy Catapult Manufacturing Innovation Centre in Braintree, Essex, that will have the capacity to produce millions of doses per month of a range of vaccine types; the centre is due to open in December 2021.

The government allocated an additional £93 million to expand and accelerate construction of the Vaccines Manufacturing and Innovation Centre that will mass produce vaccines. [29] The Centre is currently under construction in Oxfordshire and is due to open in the summer of 2021. [30]

These advancements are to be welcomed, but we need to acknowledge that at the beginning of the pandemic the UK had little or no onshore vaccine manufacturing capacity. It had to be created over the first nine months of 2020. We should never allow ourselves to be exposed to biological threats because we have not established onshore manufacturing capability. We would also call upon the UK to use its competitive advantage in talent, place and regulation to compete with the incentives offered by the likes of South Korea, Singapore and Ireland to manufacturers.

A Bioreactor Capacity Audit in the UK

Bioreactors are used in industrial processes to produce therapeutics, vaccines and antibodies. For example, with the AstraZeneca vaccine, bioreactors are used to grow a mass of human cells that are

eventually deliberately infected by the modified, harmless virus. This virus, which reproduces inside the reactor, is the active ingredient of the AstraZeneca vaccine. This phase of the process takes about four to six weeks. [31]

The bioreactors producing the AstraZeneca vaccine are operated by three outside contractors – Oxford Biomedica in Oxfordshire, Cobra in Staffordshire and Halix in the Netherlands. A single reactor can produce several million doses of vaccine, however scaling up this process can be difficult and expensive [32] and there is significant variance in yield between different sites.

It is unclear how much bioreactor capacity there is in the UK, and the government should commission an urgent audit to understand what we have and what it is being used for. Capacity should then be earmarked for surge manufacturing during a pandemic, with coordination from government. Where a bioreactor is manufacturing non-essential therapeutics or vaccines, this should be repurposed to produce pre-identified vaccines. This should draw upon the latest single-use technology, meaning repurposing takes weeks not months (see below).

Based on conversations we have had with experts, we understand that a likely estimate of global bioreactor capacity being used to manufacture Covid-19 vaccines is just 25 per cent.

Increasing Bioreactor Capacity

Following an audit of the UK's capacity, the government should ensure that there is sufficient onshore bioreactor capacity to produce essential vaccines and therapeutics for its adult population during a pandemic. If additional capacity is needed, capital grants should be made available to facilitate the establishment of new bioreactors.

Repurposing UK Bioreactor Capacity in Weeks, Not Months

Repurposing bioreactors is possible, but it involves shutting down one production line and then restarting another – a technology transfer that also requires time and money, but less than building a new site from scratch. The costs to do this are in the tens to hundreds of millions and, according to industry experts, timescales range from six weeks to six months.

Despite these challenges, the government should undertake a comprehensive audit of bioreactor capacity and develop support and incentives to repurpose existing infrastructure. This work should start now.

To encourage global coordination on this front, the UK should lead the conversation on establishing ethical guidelines relating to treatment options and various types of trials, including challenge trials.

Vaccines: Global Supply and Manufacturing

How Many Vaccines Do We Need Globally Each Year?

There are 7.8 billion people in the world, about 5.52 billion of whom are over age 16. [33] If everyone in the world needs two doses, more than 11 billion doses are needed. Researchers at University College London (UCL) estimate that the world will need between **7 billion and 14 billion doses,** depending on dosage per vaccine and boosters required. [34]

Global Manufacturing Capacity: A Lot, Unevenly Distributed

A study from Rader and Langer shows that around the world there is approximately 16.7 million litres of manufacturing capacity, and a fifth of this belongs to contract manufacturing organisations – those outside of pharma companies – while the remaining 78 per cent is in-house. [35] This is unevenly distributed, with North America alone having more than Asia and the rest of the world (excluding Europe).

A survey of manufacturers conducted by CEPI from April to June 2020 estimated that within this capacity, 2 billion to 4 billion doses of Covid-19 vaccines could be produced globally by the end of 2021 without disrupting existing vaccine supplies. [36] However, there are models that predict that it may be 2023 or later before enough vaccines are produced to cover the global population. [37]

The 2 billion doses of COVAX vaccines set to be delivered by the end of the year are significant but not nearly enough to vaccinate the more than 6 billion individuals currently living in LMICs, especially if vaccines continue to require two doses per person.

Two key considerations with manufacturing are ensuring 1) sufficient surge capacity, and 2) making the production processes as efficient as possible so the yields are higher in every individual plant. Covid-19 has made it clear that there is insufficient surge capacity in the UK, but just how much surge capacity is needed is unclear.

1. **Surge capacity: Repurposing some of the 16.7 million litres of manufacturing capacity**

Experts suggest that only 25 per cent of capacity around the world is being used to produce Covid-19 vaccines. In a pandemic, there has to be better global coordination to repurpose this – a transition which can takes months. This bioreactor capacity will contribute vital capacity to building antiviral biologics and antibodies, not only to producing vaccines.

This will mean some disruption to the production of other biologics, but it will be offset if bioreactor capacity is increased more broadly. The disruption can also be minimised through the use of single-use bioreactors – essentially large plastic bags that sit within a container and can be disposed of quickly, reducing the sterilisation time.

Efforts should also be made to incentivise non-vaccine-producing pharmaceutical and biologic companies to repurpose their manufacturing capacity. Already, we have seen Sanofi agree to manufacture both the Johnson & Johnson and Pfizer/BioNTech vaccine, [38] and this could develop further. GlaxoSmithKline (GSK), Merck and others in this space who haven't followed suit should be encouraged to do so.

2. **Making production processes as efficient as possible**

Experts and those involved in manufacturing have informed us that even between manufacturing plants *making the same vaccine,* there can be a difference in yield of up to four times, due to varying manufacturing processes. Leadership is important in this regard and, during a pandemic, more should be done to enable to the cross-sharing of best practice and approaches – ensuring that incentive to do so trumps any desire to maintain secrecy in order to preserve competitive advantage.

Distribution Must Be Global

COVAX was created to ensure that all countries around the world have equitable access to safe and effective Covid-19 vaccines as soon as possible. COVAX is co-led by Gavi, CEPI and the World Health Organisation (WHO); it was launched in April 2020. [39]

COVAX is aiming to buy enough Covid-19 vaccines to immunise the 20 per cent of people most vulnerable to the virus worldwide and vaccinate 2 billion people by the end of 2021. To achieve this, high- and middle-income countries pay into the fund and receive a share of the procured vaccines, and poorer countries receive vaccines free of charge. Of the 7.8 billion people on Earth, over 6 billion people live in LMICs. [40]

COVAX's first vaccine distribution forecast published in the beginning of February said that it would aim to deliver more than 330 million vaccine doses in the first half of 2021. [41] On average, those doses would cover around 3.3 per cent of the total populations of 145 participating countries.

The mechanisms of support for the developing world like COVAX must have the funding and authority to be equal in line with wealthier nations, not last in line. Many health experts have stressed that vaccines need to be shared more equitably or it could be years before Covid-19 is brought under control at the global level. [42] The longer Covid-19 is left uncontrolled in unvaccinated or under-vaccinated regions, the more likely it is for the virus to mutate into strains that existing vaccines do not protect against. [43]

Ultimately, something that has been sorely absent in the last 12 months – global leadership – is needed to address vaccine nationalism and ensure fair distribution. Countries should be encouraged to boost their own manufacturing and surge capacity – with oversupply a good problem to have – and feed into a mechanism that matches this supply with demand. Before then, the UK should share its proven expertise in vaccine rollouts with countries around the world and support them to develop blueprints of their own – it's important that, even before vaccine supply becomes available, countries use the available time to prepare for rollout.

Vaccine Regulation and Rollout

Challenge Trials

On 17 February the UK announced the approval of the world's first human challenge trials. The Human Challenge study is being delivered by a partnership between the UK government's Vaccines Taskforce, Imperial College London, the Royal Free London NHS Foundation Trust and the company hVIVO. [44]

Human challenge trials are able to quickly determine a vaccine's efficiency as researchers infect healthy, immunised patients with small doses of the virus and monitor their immune systems' responses. As it stands, vaccine candidates in challenge trials must have already passed safety trials and are given to patients in a controlled environment that is monitored 24/7. [45]

We understand the reluctance to make challenge trials the norm but appreciate their speed and efficacy. Random control trials will always have a scientific advantage and remain the most effective means of determining whether a vaccine works or not – and to what extent – but we would urge the government to investigate the role of challenge trials in future pandemic preparedness planning and when it comes to variant vaccines to address new, dangerous strains. This should be globally coordinated.

Rolling Platform Trials

Rolling platform trials, or adaptive trials, are constantly running and therefore are always prepared in the case of a pandemic. The benefits of these types of trials are abundant, including the ability to answer research questions when sufficient data have accrued rather than when a pre-specified sample size is reached, multiple questions can be evaluated simultaneously, new questions can be substituted into the trial as initial questions are answered, and patients are more likely to receive the treatment that is most likely to be effective for them. [46] An example of this type of trial is the REMAP-CAP which is currently evaluating community acquired pneumonia.

Vaccine Trials and Regulation

According to the WHO, there are around 200 Covid-19 vaccines in some phase of development around the world as of December 2020. [47] Under normal circumstances it takes between ten and 15 years to develop, manufacture, approve and bring a vaccine to market. The longest phase of this process is

generally the clinical trial period which can take years to complete. [48] However, in response to the Covid-19 pandemic, researchers were able to expedite this process without compromising the safety of participants during trials.

During the clinical trials for the AstraZeneca vaccine, phase II and III clinical trials were run in parallel on the basis of the phase I safety data. This saved months, if not years, of waiting before researchers were able to determine if the vaccine was effective. Although it could be argued that this strategy could marginally increase the risk to the volunteers in the phase III trial (when compared to traditional linear trials where full phase II data would be analysed before phase III begins), this risk is small and volunteers are required to fully understand and consent to this risk.

Phase III of clinical trials tend to be the longest phase as they require statistically significant data to prove that participants are protected from the virus being targeted. This phase requires volunteers to be exposed to the virus, which can take time when case rates are low. This part of the process was sped up by extending the trials to high-incidence areas at the time, such as Brazil.

The development of vaccines is not only time-consuming and costly, but it also poses a significant risk to manufacturers. According to research from UCL, [49] a company taking a vaccine from their lab to the market can expect a success rate of about 6 per cent. [50] With that level of risk combined with the high price tag that comes with vaccine development, it is not surprising that nearly 80 per cent of global vaccine sales come from just five large multinational corporations. All of these corporations are based in high-income countries and are able to manage risk across large product portfolios. [51]

For future pandemics, this risk should be taken out of the equation. Developed economies, including the UK, and internationally coordinated bodies should de-risk investments in developing vaccines through capital grants and advanced purchasing orders.

> **One Shot, Multiple Vaccines**
>
> As more strains appear, it is likely we'll need more vaccines. Already AstraZeneca has committed to developing a new variant vaccine for the South Africa strain. To be as efficient as possible in both manufacturing and administering so-called booster doses, a single shot that delivers multiple vaccines should be pursued. This happens already for pneumococcal vaccines.
>
> There are emerging vaccines that can do this, but they are still in an early stage. For example, there is an antibody that works on multiple strains by striking the heart of the conserved epitope of the spike protein and one vaccine that can carry up to eight strains. Support should be given to fast-track the development of this technology.
>
> **The Danger Theory – Two Doses of Different Vaccines**

Thought should be given to the Danger Theory, introduced by Polly Matzinger in the 1990s. This theory claims that an immune response is triggered by "danger signals," or "alarm signals," released by the body's own cells, not because of presence of "non-self" (i.e., genetically foreign entities). [52] Although this theory, like most others, is debated, if this is true it is worth considering mixing vaccine shots. If the immune system is forced to respond to more danger signals, it will produce a stronger immune response.

Look at a 6-in-1 Vaccine in the UK

The 6-in-1 vaccine is one of the first vaccines babies in the UK receive. The vaccine protects against six serious childhood diseases – diphtheria, hepatitis B, Hib (Haemophilus influenzae type b), polio, tetanus and whooping cough – all in a single jab that is administered three times. [53]

Therapeutics, Antibodies and Antivirals

Supply

Access to critical biologics is now a national security issue, especially in light of Brexit and given that future pandemics will emerge that require such medicines. Data from the CPHI Annual report underscore the trends in biologics supply and demand that will require strategic engagement between governments, drug companies and manufacturers in order to ensure stable supply. While short-term pressures are beginning to ease, the landscape from 2024 on reveals that manufacturing capacity will be a problem, driven by "the progress of Alzheimer's drugs, PDL/PDL-1 checkpoint inhibitors and COVID-19 therapeutics currently in late-stage development".

There is a significant gap between reactor capacity that is coming onstream and what is required to meet future demand.

The UK has limited domestic large-scale manufacturing capacity as a result of the lack of incentives to encourage companies to set up manufacturing sites domestically, as well as a historically fragmented approach to this increasingly important area. FujiFilm Dyosynth Biotechnologies and Lonza Biologics – which were both members of the BIA Antibody Taskforce during its early phase but are not currently – have small-scale manufacturing capability, which is insufficient to produce what is needed. The closest capacity is in the Republic of Ireland, but accessing it requires significant advance notice to reserve the facilities.

There are a number of actions that the government could undertake, which include:

1. Assuming the financial risk for companies that are willing to take on the role of contract manufacturer for Covid-19 therapeutics and antibodies.
2. Paying for access to manufacturing space by guaranteeing production.
3. Paying a premium to purchase and stockpile antibodies and essential therapeutics, and potentially to licence them.

These are necessary stopgap measures. What is required is immediate investment in large-scale biologic manufacturing capacity, which is now a matter of national security. The UK's exit from the European Union increases the urgency for domestic-capacity expansion and creates higher hurdles from a regulatory perspective.

Such collective-action challenges lend themselves to government intervention in the form of coordination and financial support, which is part of what the American government did by relaxing laws on antitrust activity to enable industry coordination, as well as with Operation Warp Speed, which invested in expanding manufacturing capacity for credible vaccine candidates.

A dedicated forum for government regulators and manufacturers would make sure that the necessary moves happen in an orderly way. This would also ensure cooperation to quickly yet rigorously review and fast-track approval so that these life-saving drugs could be made available as quickly as possible.

Trials in the UK Should Be "Opt-Out" Not "Opt-In"

Within the UK, there are three significant clinical trials for Covid-19 treatments: REMAP-CAP, RECOVERY and PRINCIPLE. The RECOVERY trial has been hailed as an example of how clinical trials for Covid-19 treatments should be carried out. Credit is deserved, and yet the current pandemic demands more. There should be more transparency around the kinds of drugs that are under consideration for trialling, with the criteria for which ones are selected made clearer. Moreover, where there are drugs that show especially promising results in other trials, they should be fast-tracked into UK trials. Those that treat hospitalised patients should be placed in RECOVERY while drugs to treat non-hospitalised patients should be trialled in PRINCIPLE. An additional arm (in PRINCIPLE) that focuses on people under age 50 with Covid-19 should be added and include those without underlying conditions. It is critical to have drugs that keep people from being hospitalised.

Moving forward, once safety has been proved, clinical trials should be "opt-out" in any future pandemic – meaning all hospitalised patients should be enrolled automatically – thereby increasing the number of people who will receive either a placebo or the drug itself.

In addition to rapid triaging and agreement on trials, more government support should be dedicated to small-scale but promising work. It would be akin to the research and development category that the Labour government under Tony Blair used to allocate additional university research funding.

The UK's centralised health system provides a key advantage in conducting these trials. Recruiting patients who are not hospitalised can be particularly challenging, as doing so requires strong coordination across relevant institutions. A person who tests positive for Covid-19 must be quickly identified and recruited for trial participation. Those conducting the trial need ready access to networks of hospitals and testing centres for this to happen seamlessly, making countries with centralised health services best positioned to carry out such trials. The UK's NHS is part of what make the RECOVERY trial so valuable.

We must work towards better global coordination of clinical trials.

What is needed is centralised coordination of the full life cycle of Covid-19 treatment development activities. Such a coordinating function – which could be linked to the WHO's SOLIDARITY trial – should have two components. The first would aggregate and disseminate data collected from national drug regulatory bodies. In addition to creating a central repository of data on clinical trials, it would help to shore up the drug supply chain. It would include data on:

- upcoming clinical trials with costs, data, and information on whether public or philanthropic money is supporting the trials
- approvals for emergency/limited use of investigational and unregistered interventions
- real-time reporting of drugs shortages and/or their active pharmaceutical ingredients (APIs) by both regulators and drug companies
- other relevant data that may indicate potential problems, as an early-warning system

Second, this coordinating function should merge duplicate trials – allowing for a series of larger trials with better, more substantial data. The UK should play a leadership role in conducting these global trials and build off the success of the RCT trials over the last year. Any candidates that are shown to be safe and have some level of effectiveness must then be fast-tracked for approval and given the same treatment as vaccines in terms of repurposing manufacturing capacity and rapid distribution.

There are more than 200 trials of new or repurposed drugs – almost all will fail due to inability to recruit patients.

Therapeutics Currently Being Used

There has been some progress on the development and authorisation of treatments for Covid-19 patients. The most widely used of these is dexamethasone, which is approved for use in the UK, the US and Japan and has been clinically shown to reduce death among those on ventilators or receiving supplemental oxygen. This is the main treatment for Covid-19 in many LMICs.

Other treatments currently being used in different countries include:

- Veklury (remdesivir), which has regulatory approval in Australia and Japan and can be used for all hospitalised patients in the US. It is currently administered intravenously but Gilead, the company producing the drug, is working on an inhaled form that could be administered on an outpatient basis and used in LMICs. Support for remdesivir is not universal, as the WHO has recommended against it and some studies suggest there is insufficient evidence that it reduces death.
- Avigan (favipiravir) is potentially able to remove the virus from the airways and –although this is yet to be shown in a large randomised clinical trial – it has been approved to treat Covid-19 in China, Italy, Kenya, Russia, Saudi Arabia and Thailand. There is still ambiguity about the effectiveness of

the drug on patients with moderate to severe symptoms and trials are ongoing in North America.

- Added to this list recently were tocilizumab (an anti-inflammatory treatment given by injection) and sarilumab. The UK government-funded REMAP-CAP clinical trial showed that the risk of death is reduced by 24 per cent when given to patients within 24 hours of entering intensive care. Most of the data come from when the drugs were given in combination with a corticosteroid, such as dexamethasone. Tocilizumub and sarilumab will be made available for use immediately.

- A new treatment being developed at Tel Aviv's Ichilov Medical Center that has recently completed phase I trials appears to have helped numerous moderate-to-serious cases of Covid-19. All 30 patients in the trial recovered, 29 of whom recovered within three to five days. The medicine fights the cytokine storm, the potentially lethal immune overreaction to the coronavirus infection that is likely responsible for many of the deaths associated with the disease. The protein is inhaled once a day for five days and helps calm the immune system and curb the "storm". The treatment is now progressing to further trials. [54]

The European Medicines Agency (EMA) has made some progress in the authorisation of therapeutics, including granting conditional marketing authorisation for Veklury to treat adolescents and adults with Covid-19 who need supplemental oxygen. In September, the regulator gave authorisation for dexamethasone to be used for patients aged 12 and over who are hospitalised with Covid-19 and in need of respiratory assistance.

Antibody Treatments

Antibody treatments will still be needed even once vaccines are in widespread use. They work in various ways: by targeting different parts of the coronavirus and by providing protection. They hold the potential to prevent Covid-19 infection if administered before the onset of symptoms, or before exposure to the virus, especially in high-risk populations. They also appear to be effective as a therapy for people who become sick. As such, they can serve as a bridge to a vaccine with a role to play after immunisation campaigns have been carried out. Below are examples of notable antibody treatments that are being trialled, but this list is not exhaustive.

- Lilly's LY-Co555: In January results from a phase III trial conducted by the NIH's National Institute of Allergy and Infectious Diseases (NIAID) showed that LY-Co555 reduced the risk of developing symptomatic Covid-19 by 57 per cent among residents and staffers of long-term care facilities. [55] This trial is important to note as it was designed to evaluate a vulnerable population and addressed the challenges of running a clinical trial in long-term-care facilities, a setting which normally does not conduct trials. [56] This innovation alone makes the trial noteworthy given the reality that many elderly people are unsuitable candidates for vaccines, but it is important to note this does not work on new Covid-19 variants.

- AstraZeneca's AZD7442: A combination of two long-acting antibodies (LAAB) derived from convalescent patients after SARS-CoV-2 infection designed to remain effective for between six and 12 months after a single dose is administered. It is expected to reduce the risk of resistance developed by the virus. [57]

- GlaxoSmithKline/Vir Biotechnology's VIR-7831: A dual-action monoclonal antibody that was selected for clinical development based on its potential to block viral entry into healthy cells and clear infected cells, providing a high barrier to resistance. [58]

- South Korea's Celltrion Group's CT-P59: A monoclonal antibody treatment candidate that could be used to prevent illness from Covid-19. The phase III trial results published in January 2021 showed that CT-P59 is an effective treatment for patients with mild to moderate cases of Covid-19, especially for those aged 50 and over. Recovery time also lessened and viral load decreased quickly and significantly through the seventh day of treatment. [59]

- Kiniksa Pharmaceuticals: The company announced data from early-stage clinical trials of its monoclonal antibody, mavrilimumab, in patients with severe Covid-19 pneumonia and hyperinflammation. Early results are promising, and phase II trial data is expected by the second quarter of this year. [60]

- Adagio Therapeutics has developed monoclonal antibodies that bind to, neutralise, and protect against the original SARS-CoV-2 virus as well as the new variants currently in circulation. Broad neutralising activity has been demonstrated in the lead monoclonal antibody, ADG-2, which was selected and engineered for breadth, potency, ease of use, durability (half-life extended) and efficiency of production. ADG-2 is a promising candidate for the prevention and treatment of Covid-19 and potentially future respiratory illnesses caused by SARS-related-CoVs. [61]

The development of Covid-19 antibody treatments demonstrates how the pandemic has generated cooperation among competitors. Our first paper on therapeutics highlighted the leadership of Takeda in "conceiv[ing] and spearhead[ing] the CoVIg-19 Plasma Alliance, a collaboration that includes plasma companies with the support of global organisations outside the industry, [working on its] anti-Covid-19 Hyperimmune Globulin (CoVig-19) medicine." [62] Now Lilly, Vir and GSK are collaborating to evaluate "a combination of two Covid-19 therapies in low-risk patients with mild to moderate Covid-19 … This unique collaboration marks the first time that monoclonal antibodies from separate companies will be brought together to explore potential outcomes." [63]

The lack of manufacturing capacity that has plagued Covid-19 treatments such as monoclonal antibodies (MAbs) must be addressed so that each region has reliable production of these life-saving biologics. This is important for both meeting current needs as well as being prepared for future pandemics. MAbs must be administered in infusion centres, which many health systems in LMICs lack. As a result, it is challenging to make them accessible. However, this may change as a result of a relatively new

partnership between Merck KGaA, non-profit scientific research organisation IAVI and India's Serum Institute, who are working together to develop mAbs for Covid-19. A main goal of this collaboration is to ensure equitable access to promising treatments for LMICs. [64]

Antivirals

The worst-case scenario for Covid-19 is that a new strain arises which has a mutation that creates a strong bind with the body's ACE2 receptors (angiotensin-converting enzyme 2 is an enzyme attached to the cell membranes of cells located in the lungs, arteries, heart, kidney and intestines). In practice, this would mean a strain that is resistant to antibodies – and therefore vaccines. In this situation, we would need to turn towards antivirals – medication that would stop the virus from multiplying within the body.

This has been the direction of travel for strains so far – notable variants have a stronger ACE2 bind and we've seen a consequential reduction in vaccine efficacy. It is incumbent upon our government and others to give antivirals the same focus and attention as vaccines. They may be our only option at some point in the future.

Some antiviral drugs for Covid-19 are worth noting. It is important that we secure supplies of those proven to be safe and effective:

- Colchicine (an anti-inflammatory oral medication used to treat gout) may emerge as an effective oral treatment, particularly for treating non-hospitalised patients. The UK's RECOVERY trial is in the process of testing the effectiveness of colchicine in patients hospitalised with Covid-19. This drug has particular relevance for LMICs as it is readily available at pharmacies, is inexpensive, and is easily administered outside of hospitals.
- There is considerable enthusiasm for the insufficiently tested ivermectin, which is an inexpensive drug that can be purchased over the counter. Early, non-peer-reviewed studies suggested that the drug may have antiviral properties, which has led to an explosion in its use to treat Covid-19, particularly in Latin America. The use of the drug outside of clinical trials has made rigorous testing challenging. However, data have been released from a small trial that show promising results.
- Interferon beta (IFN-beta) is also emerging as a promising antiviral. The UK's University of Southampton and the company Synairgen are partnering on the development. What makes the drug unique is the oral-inhalation approach. In December, the company announced that it was beginning phase III trials for the drug in the UK and 19 other countries, and that the US FDA had granted the drug fast-track status and approved it for US studies.

There are a range of other antivirals also being trialled across the world, and it is vital that these are prioritised and given the necessary funding.

Small Molecule Antivirals

Most antiviral drugs are small-molecule inhibitors that target different stages of the viral life cycle by interacting with virus or host proteins critical for virus replication. This is what defeated HIV and we have precedent of their value in flu and hepatitis C. Work is needed to invigorate research in this area.

The government should commit to an antiviral strategy, ensuring there are sufficient stockpiles of these and a clear plan to roll them out at scale in case of a large outbreak of a new strain that's resistant to antibodies.

Key Recommendations for Therapeutics, Antibodies and Antivirals

Effective treatments are desperately needed for all stages of the disease: drugs that will keep people out of hospitals; drugs that will shorten hospital stays; and drugs that will prevent hospitalised people from moving into critical care and intensive care.

The UK government can take the following steps to ensure that this happens:

1. Invest in large-scale, UK-based biologic manufacturing capacity.
2. Increase funding into the development and manufacturing of therapeutics, antibodies and antivirals for future pandemics, ensuring a sufficient stockpile across each.
3. Fast-track research into and stockpiling of antivirals for potential "worst-case scenario" Covid strain, giving them the same focus and prioritisation as vaccines have been given. This should include small molecule antivirals.
4. Revisit the international aid commitment by providing additional funding for antivirals and diagnostic testing to be made available and earmarked for the countries unable to access sufficient vaccine supplies.
5. Support efforts to further shorten the time required for clinical development by pushing for greater global coordination and data-sharing of clinical trials.
6. Increase recruitment for trials by making future random control trials "opt-out" once safety of drugs has been proved.

Testing

Over the course of the Covid-19 pandemic we have discovered many tools for how to respond to the virus. One ever-present element of the response has been diagnostic testing. Testing remains, and will remain, a central plank in responding to this and future pandemics. It is the critical tool in helping us avoid widespread blunt measures like lockdowns, and instead specifically target those who have the virus.

A year into dealing with Covid-19 we have a far better understanding of how this diagnostic capacity needs to be structured. These lessons need to be learned urgently to ensure future pandemics, and particularly the risk of more resistant strains of Covid-19, can be responded to in a targeted way that avoids the dramatic economic impact we have seen this time around.

A New Approach to Testing Is Needed

To be ready for future pandemics, we need to be able to have the capacity to test every part of the country at speed, using accurate rapid tests.

Such an approach will require the following elements:

- Incentivising the development and manufacturing of a rapid test that is able to detect virus even in incubation stage.
- Capability to deliver gold standard lab-based testing at scale – PCR and ELISA, for example.
- A strategy that deploys the right tests in the right settings, ensuring we don't make the best the enemy of the good.
- Accelerated rollout of rapid diagnostics, which, while they may be less accurate, detect almost all contagious carriers of the virus and can be scaled more easily.
- Sufficient incentives built into any mass-testing system that ensure: 1) compliance with a positive result, and 2) regular testing.
- A link between test data and a health passport.

This would mean the UK having the capacity to conduct, quickly, large-scale lab-based testing to provide gold standard accuracy for those who need to know with certainty whether they have the virus or not (frontline medical staff, for example). In addition, the UK would have the capability to mass produce rapid tests for regular population-level testing to identify contagious carriers.

This would sit alongside the right support to encourage the emergence of new types of tests like breathalysers.

Such a capability would mean the UK would be able, in the absence of full vaccination of the population, to continue to live alongside a virus, avoiding full lockdowns.

How Do We Deliver This New Approach?

Moving the country to this level of preparedness on testing requires a step change in our approach. We believe it requires specific action across the following areas:

1. **Manufacturing**
2. **Validation**
3. **Deployment strategy**
4. **Usage strategy**

The steps required on each of these are set out below.

Manufacturing

While major testing suppliers are largely based overseas, the UK does have a growing ecosystem of small- and medium-size testing manufacturers like SureScreen and Thriva. We have previously written about a number of these companies. Their experiences point to a step change the UK needs to make in supporting our domestic testing suppliers. Preparing for the next pandemic on testing manufacture will involve:

- Regular and ongoing interaction with UK testing innovators.
- Ensuring a level playing field for UK suppliers.
- Providing access to funding and patient samples to help the UK's ecosystem of suppliers produce new tests and scale at speed.
- Setting up a framework to be able to make advanced orders of tests to support development.
- Support for pre-purchase of reagents and other materials to ensure UK firms can ramp up production.
- Galvanising the ecosystem of suppliers around future innovations that could be game-changers in a future pandemic.

Validation

In our view, one of the key issues that has held back the deployment of tests is the complex validation process for tests. The current system includes trials by PHE and then validation by the MHRA. This has led to delays and a lack of focus on what the end goal is with testing.

To be better prepared to deal with the next pandemic the following steps are needed on validation:

- **End goal:** A clear brief on what is needed, such as accurate enough rapid tests as soon as possible.
- **Standalone validation unit:** A standalone, nimble and well-resourced unit responsible for validation and approval. This should sit outside the MHRA and PHE and report to a Minister (of Testing).
- **Transparency:** Clear requirements on the required accuracy of tests, which should ensure it links to the brief of what is needed (and not stopping good enough tests from coming onstream in the search for the perfect test). There should also be transparency on the validation process.
- **Resources:** Better resources to interact more closely and more regularly with testing manufacturers on the validation process.
- **Fast-track process:** A streamlined, fast-track validation system to allow credible tests to be brought onstream quickly in the event of a future crisis, learning lessons from the FDA's Emergency Use Authorisation process in the US.

Deployment Strategy

The government needs a clear strategy for testing. This has been absent throughout the crisis in the UK. Critically this strategy needs to match the right tests with the right need. A basic outline is suggested below:

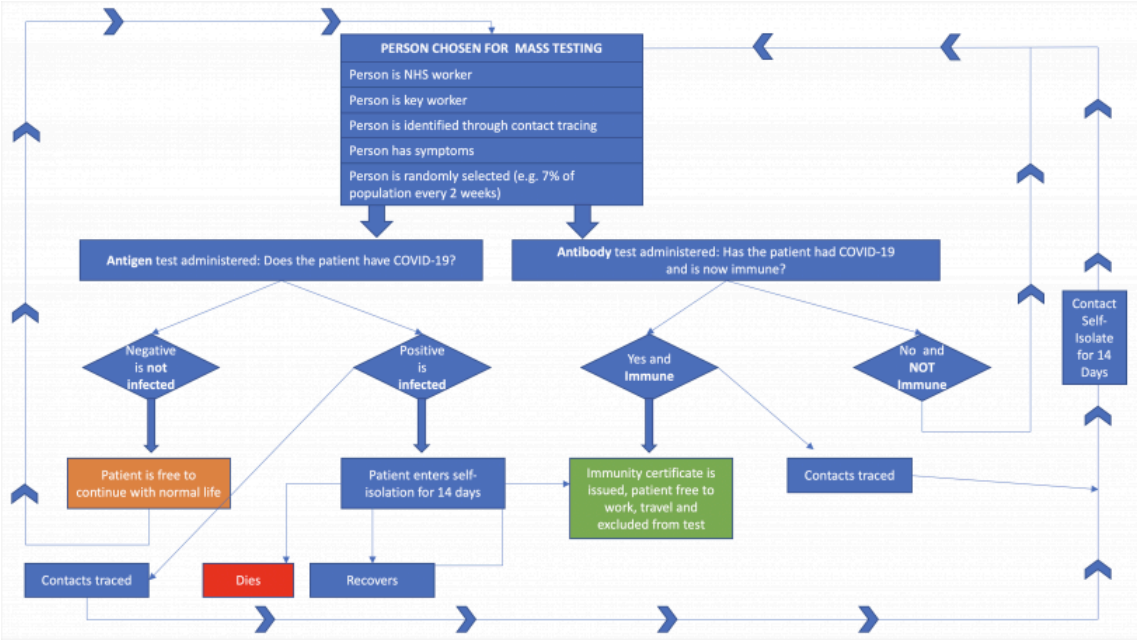
Lab-based tests: Slower but more accurate

Used for definitive confirmation of positive rapid test results, as well as for testing NHS and care home workers.

Rapid tests: Faster but less accurate

Used to test large groups on a regular basis, such as at universities and key workers.

Figure 2 – A framework for mass testing



Source: TBI

Usage Strategy

It is not only vital that we deploy the right tests for the right purpose but also that we ensure they are used and results followed up on.

According to Baroness Dido Harding, head of NHS Test and Trace, between 20 per cent and 40 per cent of those contacted after a positive Covid-19 test are not fully self-isolating. This means 20,000 people per day are not isolating when they should be.

The whole testing regime fails if those who are testing positive do not isolate. To fix this a number of steps are required:

- Covid ID to enable people to show their current testing status.
- Freedom from lockdown restrictions for those able to show they have received a recent negative test.
- Imaginative policy-thinking on how to encourage regular testing, for instance through financial incentives.

PPE

At the beginning of the crisis, the UK was on the back foot in terms of its preparedness with PPE.

This left the country having to play catchup from early on in our response to Covid-19. After an initial review of all the PPE needed, the Department of Health & Social Care (DHSC) ended up ordering 14.6 billion items of PPE by the end of May. [65]

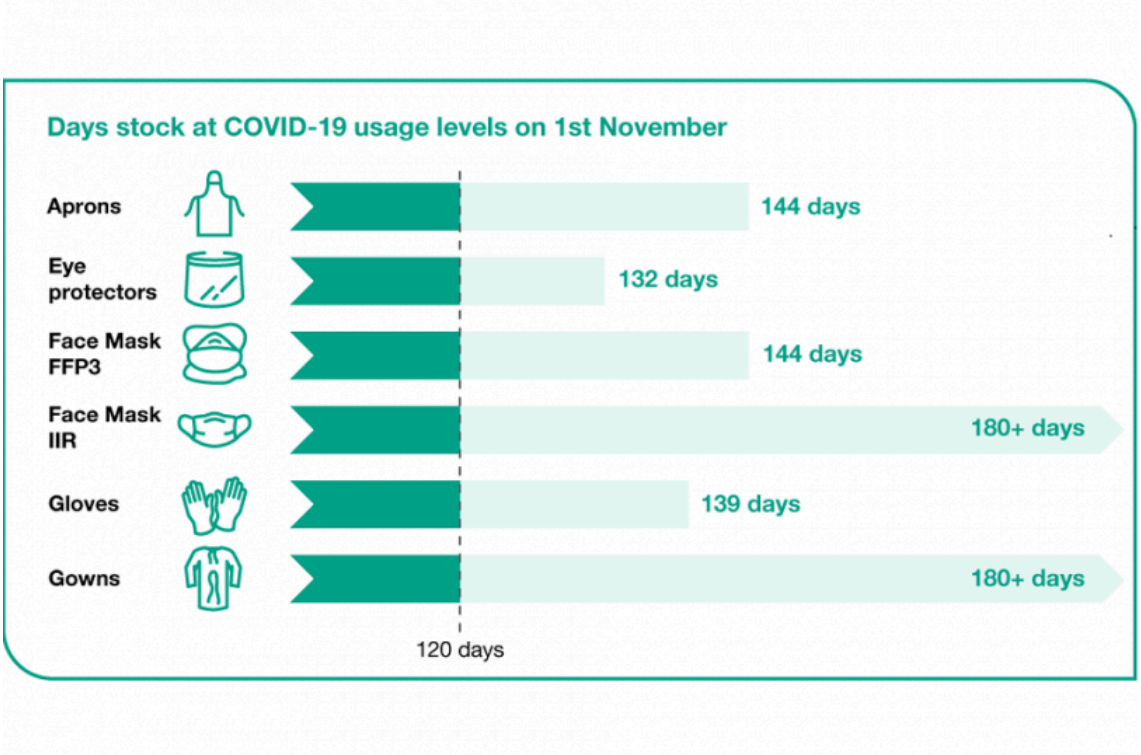
The PPE pipeline was severely stretched, leading to shortages at the front line. The National Audit Office (NAO) states in a report from November 2020 that 126 deaths and 8,152 diagnosed cases of Covid-19 were linked to occupational exposure.

It is a vital component in our preparations for future pandemics that we ensure the country has access to the right amounts of the right PPE.

The Government Plan

In September the DHSC published a new strategy on PPE. It set out an ambition to create a strategic stockpile, equivalent to four months' stock of key products.

Figure 3 – Graphic from the UK government PPE strategy showing UK stockpile as of 1 Nov 2020



Source: https://www.gov.uk/government/publications/personal-protective-equipment-ppe-strategy-stabilise-and-build-resilience/personal-protective-equipment-ppe-strategy-stabilise-and-build-resilience

Alongside this, the government began a review to determine the "nature, composition and volume of a future pandemic stockpile". [66]

In its strategy paper, the DHSC set out its plan covering supply, distribution, UK manufacturing and user needs. We welcome these steps but believe the country needs to go further and faster.

Table 4 – Government PPE plan

	Pre Covid-19	Emergency response	Stabilise and build resilience September 2020 to March 2021
Supply	NHS supply chain	Demand model established	Demand model refined

	Wholesalers Pandemic Influenza Preparedness Programme stockpile in place for pandemic influenza	175 new global suppliers identified and contracted with Stockpile depleted In April, the National Supply Disruption Response hotline received on average 592 calls a day	National Supply Disruption Response hotline receives on average less than 50 calls a day Four-month stockpile in place for all products by November Commission advice on new stockpile
Distribution	Distributed to 226 NHS trusts	Distributed to 58,000 different settings Local resilience forums Mobilised surge capacity across the public and private sector	PPE portal A blueprint for rapid mobilisation for other pandemic responses
UK manufacturing	Less than 1% of PPE manufactured in the UK	Signed contracts with UK manufacturers Disposable PPE by default	Reviewing future requirements to sustain this high level of UK PPE manufacture Reusable by design PPE where possible UK-based supply is anticipated to meet on average 70% of forecasted demand in December

		for all categories of PPE excluding gloves
User needs	Difficulties with PPE fit reported and compatibility with working practices	FFP3 fit-testing pilot Reflecting user need and preferences in PPE provision UK manufacturing uniquely placed to engage directly with users Shift towards more innovative and sustainable PPE [67]

What Is Needed to Be Fully Prepared?

Unless the whole world is vaccinated quickly, we continue to run the risk of new strains of the virus emerging that are resistant to our current vaccines.

For this reason, and as outlined above, we need to be prepared that the next pandemic could be a new, more dangerous strain of the current Covid-9 pandemic.

To be fully prepared, the UK needs to take the following steps:

- Publish a clear strategy on what the frontline need of PPE will be in the circumstances of a more dangerous strain of the Covid virus.
- Set out clearly what the government plans to do to ensure N95 masks and other vital PPE supplies are available for key workers.
- Set out a clear roadmap for how the UK can ensure it has: 1) a six-month stockpile of all key PPE items, covering health and care workers, as well as frontline key workers; 2) a plan for how to ensure the country can meet this supply in a continued crisis, which should include a mixture of pre-arranged agreements with companies overseas and the right UK manufacturing base. (As an example of this type of arrangement we spoke with a major mask manufacturer who suggested the government could support a domestic mask company to purchase an international supplier to

upgrade our supply. A specific example suggested would be for a UK company, with support from the government, to buy the Irish mask manufacturer IREMA and then purchase the major US supplier Prestige Ameritech. This would bring together IREMA's mask-making capability and Ameritech's respirator manufacturing.)

Data: Avoiding, Containing and Countering Risks

The use of fragmented and outdated data infrastructure throughout the current pandemic has meant we have likely seen a higher death toll than we would have with a more sophisticated system. We must treat pre-pandemic preparedness as akin to a military operation, using the best military hardware and software to spot developments**.** Data is key to understanding who has the virus, where and how it spreads, and the rollout and performance of different types of vaccines, therapeutics and testing. This is all critical to providing insight that informs decision-making.

Yet countries all over the world have struggled to match the speed and intelligence of the virus with sophisticated data systems. In many countries, the number of tests executed has been low, track and trace has been poorly executed, and outdated systems have meant we have struggled to keep an accurate account of the virus in real-time.

Data, knowledge and understanding are key not only to beat the current pandemic but also to prepare for the next. The ever-increasing risk of new mutations could render our current protocols, treatments and vaccines ineffective; we need to use data to help us prepare to adapt treatments and vaccines for future threats. Radical reform of global health data infrastructure must be a key priority.

There are three key components to this:

1. Avoiding Risks: Health Surveillance

Countries must gather a more complete picture of the threat the world faces and the environment they are operating in. We failed to contain the virus when it first originated as countries' inability to test most of the people falling ill meant that official tallies of the number of people infected were a poor guide to how bad the situation really was. Although some countries have succeeded at contact tracing [68] and were able to more effectively break the chain of transmission, most countries have struggled to coordinate both manual and automated approaches.

Quickly identifying any new threat, where it originates and how it could spread is essential to avoid a virus getting out of hand. To do this, we must implement surveillance systems which allow early tracking and discovery of disease and new mutations, as well as mass-testing regimes. We must collect, secure, aggregate and report on health data in near real-time and in machine-readable formats.

2. Containing Risks: Proof Infrastructure

It's increasingly clear that even countries that have managed to keep cases low may not be able to protect themselves from failures elsewhere. South Korea was praised for its initial handling of the crisis but today finds itself exposed to more infectious variants originating overseas.

We must therefore ensure we have the right infrastructure to contain risks. Secure, portable health data is a precondition for getting life back to normal now and will be necessary to prepare to contain future threats. In a post-pandemic world, a requirement for proof of test and vaccination status will be essential to keep cities and global travel open. We must implement a unique and persistent identifier for each citizen, enabling people to access their health data and prove their status to others, while at all times protecting their privacy.

Getting the design, governance and protections for new proof infrastructure right will be key.

3. Countering Risks: Accelerated Vaccine, Diagnostics and Therapeutics Design, Delivery and Distribution

Once a threat is already out of hand, we must do everything in our power to counter it through effective diagnostics, therapeutics and vaccines. Clinicians have so far learned by necessity how to better treat Covid-19, but we are still learning which therapeutics work best in different circumstances. The power of modern science has also been evident in the pace of vaccine development. Advances in messenger RNA (mRNA) technology enabled the Moderna and Pfizer vaccines to be designed in a matter of days after the virus was sequenced. [69] But it is right to ask how we can go faster in the future.

Greater pooling of trial data and agreed data standards could enable more widespread passporting of approvals from one country to another, [70] and the potential for challenge trials as a faster route to obtaining data required for regulatory approvals merits further consideration. [71]

Rolling vaccines out on a global scale requires making important decisions about allocation and distribution. With better international data on supply chains, absorptive capacity and the cost of delay in different scenarios, leaders might be better able to cut through disputes about which supplies go to which countries, in what order and at what times. [72] Within countries, a more data-driven approach to prioritisation would help avoid doses sitting on shelves any longer than necessary.

As we have set out previously, achieving the necessary step change in data and situational awareness to avoid, contain and counter risks will require:

1. Cloud-based data storage and software, enabling health-care workers and medical devices to record

data quickly and accurately.

2. Real-time data reporting, analysis and insights to inform decision-making, from early warning of pressure points to algorithmic optimisation of vaccine rollouts.
3. Best-in-class security, access controls and audit, encrypting all data as standard and ensuring personally identifiable data is never exposed without permission.
4. A unique and persistent identifier for each citizen, enabling them to access their health data and prove their status to others, while at all times protecting their privacy.
5. Better tools to pool data to expedite safety and efficacy trials, including for securing regulatory approval and large-scale post-treatment and post-vaccination surveys.
6. Better tools to manage the logistics for mass testing and mass vaccinations, including allocating and distributing supplies and certifying that they are authentic.
7. Internationally agreed data standards and definitions, so that countries are aligned on how to identify and respond to new threats in a timely and targeted manner.

Conclusion

Covid-19 has been an all-encompassing crisis like no other. All parts of society and all aspects of our lives have been touched by it. It has required a level of response by government not seen since the Second World War. Many aspects of that response have had to be developed in real time, particularly as our understanding of the virus has evolved. We have learned – in certain cases, the hard way – what is most effective and what is needed to respond to a pandemic of this kind. This knowledge should not be lost.

The next pandemic is a question of when, not if. It may even be a case of the world having to respond to even deadlier versions of the current Covid-19 virus. We cannot afford to play catchup again.

This document seeks to draw together the key lessons we have learned from the response to Covid-19 and apply them to the UK as it looks to finesse its pandemic preparedness. In particular, it focuses on the types of capabilities that will be needed to allow us to respond more speedily and at greater scale next time.

As we have set out, we believe the UK needs, urgently, to put in place the following steps:

- An improved surveillance system that draws on best practice from around to world and adopts the latest in military-grade hardware to identify and sequence viral strains sooner.
- A faster timeline to prepare vaccines, with the infrastructure needed to deliver at scale.
- The ability to produce effective therapeutics, antibodies and antivirals at greater scale, faster.
- A clear strategy and capability on testing, ensuring we have the right tests, at the right scale, for the right purposes.
- A comprehensive plan on PPE to ensure we have not only the right stockpile but also access to the right equipment on an ongoing basis during a future pandemic.
- Gold standard capabilities on data capture, storage and access so that we are able to fight the next virus with the best possible knowledge and information on it.

This document should serve as a checklist against a series of recommendations, set out upfront. It is consciously organisation agnostic, but we are drawn to the creation of the National Institute for Health Protection (NIHP) which will launch in April 2021. If this organisation is treated as a new, vital piece of security infrastructure and given the personnel and resource to match, it should become the focal point for the UK's pandemic preparedness effort. Properly empowered and willing to play an active role globally, the NIHP can deliver against everything set out in this paper.

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