Boosting vaccines, injecting resilience and protecting liberty

By James Lawson and Matthew Lesh

EXECUTIVE SUMMARY

- The rapid rollout of vaccines against Covid-19 is protecting the vast majority of vulnerable people and the wider adult population, significantly reducing the virus's capacity to spread and kill, and accelerating the end of the pandemic.
- Covid-19 is becoming endemic with substantial ongoing community spread. The virus is also mutating, producing variants. There is uncertainty about our capacity to respond to a rise in cases over the winter months.
- We must learn to live with the virus while maintaining liberty. This can be enabled by boosting the UK's vaccine campaign and developing greater societal resilience against Covid-19 and future pandemics.
- The UK is enjoying a "vaccine dividend" which is disrupting the link between Covid-19 cases and deaths by as much as 90%, saving around 50,000 lives in the most recent wave of cases.
- It is imperative to ensure restrictions are withdrawn and not reintroduced by building sufficient resilience.
- The UK's vaccine campaign was a success but could have gone even faster. There are lessons to be learnt in multiple areas including around "war-effort" style distribution, use of spare doses, pacing, dosing schedules, reward mechanisms, new supplies, mix-and-matching doses, vaccine centre ventilation and safety, and countering misinformation.
 - There are about 2.1 million vulnerable ("Phase I") individuals who are entirely unvaccinated and 600,000 yet to have a second dose. There are 10.4 million adults who are entirely unvaccinated which, if they catch the virus, could result in 39,600 deaths and 148,000 hospital admissions.
 - There are many receptive to vaccines yet unvaccinated and growing evidence that there may be waning efficacy over time.
 - The UK is falling behind other countries that have vaccinated more people, such as France, and begun providing booster shots, such as Israel.
 - There is also a lack of transparency about forthcoming vaccine supply and efforts to update or procure next-generation vaccinations.

RECOMMENDATIONS

• If the Government wants to maximise the effectiveness of the vaccine campaign, protecting human life and increasing resilience, they should take the following steps:

- Redouble efforts to vaccinate those in the "Phase 1" vulnerable group who
 are due a second dose and/or completely unvaccinated, including using
 mobile vaccination units and home visits providing protection to those
 most likely to be hospitalised or die. This would make the most immediate
 contribution towards reducing hospitalisations and deaths, and building
 resilience.
- 2. Begin providing boosters, which are essential to maintain protection against waning antibody immunity, the Delta variant and future threats; prioritising the vulnerable but also offering a booster to the entire adult population.
- 3. Publish a detailed roadmap for Covid-19 vaccinations over the next five years, including an upcoming delivery schedule with plans for a backlog of boosters.
- 4. Update regulatory process to enable rapid approval of vaccine updates every time there is a new variant of concern, following the annual flu vaccine process.
- 5. Purchase a diverse range of new Covid-19 vaccines including updated Delta-variant specific vaccines and oral/nasal and "universal" vaccines.
- 6. Embrace "mix-and-match" doses, to enable greater supply flexibility and enhanced protection.
- 7. Offer vaccination to children aged over 12, with parental/guardian consent. This should be undertaken without coercion or implied restrictions, mirroring the rules of other vaccines offered to children and as a lower priority initiative than boosters for the vulnerable.
- 8. Counter misinformation to address vaccine hesitancy and enhance targeted marketing and distribution for those who are ready and willing to be vaccinated but have yet to make bookings.
- 9. Offer the flu vaccine across the entire population not just to those aged over 50 and vulnerable to build resilience against winter spikes in respiratory diseases, hospitalisations and deaths.
- 10. Permit pharmacies and private doctors to purchase, distribute and register vaccines from the international market, enabling more flexible boosters, greater vaccine choice and enhanced distribution capacity.
- 11. Support expanding human challenge trials to rapidly test updated and new vaccines.
- If the Government wants to avoid ongoing restrictions, protect liberty and increase broader societal resilience, it should take the following steps:
 - 12. Allow the 'Coronavirus Act' to automatically lapse and introduce new limited emergency mechanisms, including extensive parliamentary oversight, for future public health-related emergencies.
 - 13. Reject 'vaccine passports', a form of state-sanctioned discrimination that would effectively coerce some people into undertaking a medical procedure without informed consent (but maintain venue-customer and employee-employer freedom of contract).
 - 14. Establish an enhanced antibody testing capability, better informing individuals about their levels of protection and public health officials about overall societal resilience.
 - 15. Simplify travel restrictions further to encourage global economic activity, with better collaboration with airlines, a further easing of restrictions for the vaccinated, and a simplification of the "test to release" scheme.

- 16. Encourage, using guidance, ventilation through continued al fresco retail, hospitality, and leisure activity, use of outdoor heaters and better ventilation in schools as they reopen.
- 17. Encourage, using guidance, for vulnerable people to use masks with respirators, such as N95, KN95, FFP3, and FFP2, rather than less protective cloth or surgical masks.
- 18. Proactively invest in new and emerging treatments to tackle Covid-19, such as monoclonal antibody therapy drugs (i.e. Ronapreve, Sotrovimab, AstraZeneca's AZD7442), antiviral treatments (i.e. Pfizer's PF-07321332/Ritonavir), and other emerging drugs (i.e. fluvoxamine).
- If the Government wants to ensure medium to long term resilience against pandemics, it should take the following steps:
 - 19. Review medical regulatory processes to accelerate the assessment, approval, supply and distribution of new vaccines.
 - 20. Expand manufacturing and logistics capacity for rapid production of vaccine updates and new vaccines against future pandemics.
 - 21. Invest in vaccine platforms and proactively assess viral threats on an ongoing basis, developing fast-moving responses.

James Lawson is a Senior Fellow of the Adam Smith Institute. He is a business advisor, supporting executives to transform their operations through data, artificial intelligence, wider digital technologies and process improvement. He tweets @jl4w

Matthew Lesh is the Head of Research at the Adam Smith Institute. He tweets @ matthewlesh

Wider acknowledgements

The authors are also grateful for inputs from various supporting parties, including:

Jonathon Kitson is a Fellow of the Adam Smith Institute, independent researcher and forecaster. He has written on defence procurement, forecasting and vaccination strategy. He tweets @KitsonJ1.

Sarah Gall is a Data Scientist and former adviser to the Prime Minister of Australia. She produced figure 13. She tweets @sarahcgall_ and her GitHub page is github.com/sarahcgall

David Smith is an operational and process advisor. He supports organisations in transforming their businesses and embracing innovation and digital change.

This paper is written in a personal capacity and does not reflect the views of the authors' / contributors' employers or clients, past or present.

INTRODUCTION 5

The UK is over 15 months into the Covid-19 pandemic. To date, there have been over 130,000 confirmed deaths. Almost twice as many British civilians have died from Covid-19 than were killed in the entire Second World War.

The economic impact of government restrictions and voluntary responses means that despite a substantial revival, the economy is nearly one tenth smaller than its 2019 peak.² The impact on public finances has also been dramatic. Debt as a percentage of gross domestic product (GDP) jumped by 22 points (to 106% of GDP as of March 2021), as tax receipts fell and spending rose.³

Fortunately, vaccines are bringing an end to the pandemic closer. The rapid rollout of vaccines against Covid is protecting the vast majority of vulnerable people and the wider adult population, significantly reducing the virus's capacity to spread, hospitalise and kill.⁴

The Adam Smith Institute (ASI) contributed to the ideas behind the vaccine campaign in the paper, Worth a Shot: Accelerating Covid-19 vaccinations, published on 5 January, 2021. Back in December 2020 the UK was the first to approve the vaccine, but the rollout was painfully slow. Of the 22 recommendations the ASI made, over half were later trialled, partly adopted, or fully embraced helping to boost supply and distribution. The average daily vaccination rate increased ten-fold following the publication.

The progress in the vaccination campaign and the UK's resulting increased resilience is welcome. The success of vaccines has saved thousands of lives and fundamentally alters the cost benefit analysis of restrictions. The focus should now be on returning to normality.

Despite the removal of most restrictions, the threat from Covid-19 has not entirely disappeared. The virus continues to inflict pain in the United Kingdom, with tens of thousands of daily cases and over 700 deaths each week. Few in the UK favour an unattainable "zero Covid" strategy. Nevertheless, there is little clarity over how to reduce these deaths while fully restoring normality, especially given uncertainties over the future impact of future Covid-19 variants.

There is a risk not only posed by new variants but also waning and increased transmission as children return to school and the weather gets colder over the coming

¹ https://ourworldindata.org/explorers/coronavirus-data-explorer?zoomToSelection=true&ti me=2020-03-01..latest&facet=none&pickerSort=desc&pickerMetric=total_cases&hideControls=true& Metric=Confirmed+deaths&Interval=Cumulative&Relative+to+Population=false&Align+outbreaks=fals e&country=~GBR (Last accessed 10 August 2021)

² https://www.ons.gov.uk/economy/grossdomesticproductgdp/timeseries/abmi/qna (Last accessed 10 August 2021)

³ https://www.ons.gov.uk/economy/governmentpublicsectorandtaxes/publicspending/bulletins/ukgovernmentdebtanddeficitforeurostatmaast/march2021 (Last accessed 10 August 2021)

⁴ https://www.independent.co.uk/news/health/covid-uk-lockdown-delta-variant-winter-b1869259. html (Last accessed 10 August 2021)

months. This could combine with normal winter respiratory viruses, such as the flu, to put increased pressure onto the healthcare system.

A "normal" NHS winter crisis combined with rising Covid-19 cases and hospitalisations is already leading to discussion about further lockdowns, imposing extreme and potentially unnecessary costs on the public. Government scientists, ministers and Scottish First Minister Nicola Sturgeon have discussed reintroducing Covid-19 restrictions if not a lockdown.⁵

There is a complete lack of clarification from the Government about how they intend to address Covid-19 over the coming months let alone over the coming years. The decisions with respect to vaccine boosters, for example, appear to have been dangerously delayed despite evidence of waning immunity.

The costs of the pandemic, both in terms of deaths and unprecedented restrictions of liberty make it essential to build societal resistance against Covid-19 (in all its forms) and future pandemics. The central goal must be to protect the public's health while removing the temptation or necessity of ever reentering lockdown for any virus. This paper explores how we can live with the virus, restoring our liberties, by further expansion of our vaccine campaign and developing greater societal resilience.

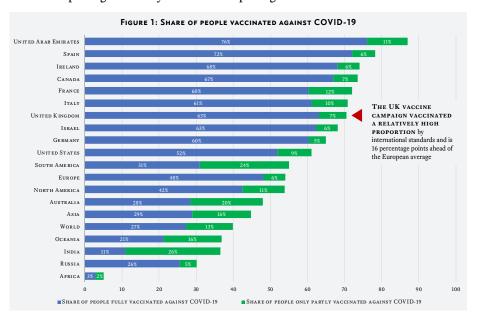
⁵ https://www.thenational.scot/news/19541828.nicola-sturgeon-update-fm-hold-briefing-circuit-breaker-lockdown-considered/ (Last accessed 10 September 2021) https://inews.co.uk/news/covid-lockdown-government-plans-october-firebreak-restrictions-hospital-admissions-1185533 (Last accessed 10 September 2021)

SITUATION REPORT: GREAT PROGRESS BUT RISKS AHEAD

THE VACCINE CAMPAIGN HAS BEEN A GENERAL SUCCESS, PROVIDING SIGNIFICANT PROTECTION AGAINST COVID-19

The UK's vaccine campaign is perceived to be a resounding success across the political spectrum. Nearly 90% of adults have now received at least one dose of a vaccine. Eighty percent of adults are fully vaccinated (with two doses)⁶.

The UK has vaccinated a relatively high proportion of its total population by international standards (see Figure 1), and is 16 percentage points ahead of the European average. The UK also vaccinated earlier than other countries, allowing for the sooner reopening of society without reimposing restrictions.

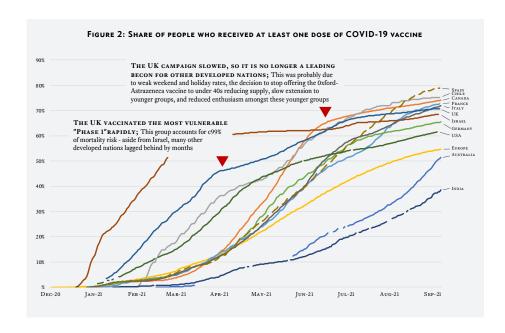


The chart shows the breakdown of vaccinations by those that have been partly or fully vaccinated (where a person is fully vaccinated if they have received a single-dose vaccine or two doses of a two-dose vaccine). Source: 1 September extract of official data collated by Our World in Data

That said, despite starting first, as the pace of the vaccine has slowed since April (see Figure 2), other developed nations have caught up or even overtaken the UK. Now several EU nations (including Belgium, Denmark, France, Finland, Italy, Ireland, Spain, Portugal and Malta) have overtaken the UK in terms of vaccinated percentages across their overall populations. Others like Sweden and Germany could also overtake the UK based on current trends. The most recent trends reflect policy decisions (which are explored further below), with Spain having the highest share (in Figure 2) as they have prioritised vaccinating children, while Israel now has a lower share than the UK, having prioritised booster vaccines for the vulnerable.

⁶ https://coronavirus.data.gov.uk/details/vaccinations#card-latest_reported_vaccination_uptake (Last accessed 9 August, 2021)

⁷ https://www.theguardian.com/world/2021/aug/06/six-eu-states-overtake-uk-covid-vaccination-britain-rollout-slows (Last accessed 9 August, 2021)



The chart shows the share of people who have received at least one dose of a Covid-19 vaccine, divided by the total population of the country (including children). Data Source: 8 September extract of official data collated by Our World in Data

Nevertheless, the UK's vaccination progress has completely changed the core dynamic of the pandemic. Previously Covid-19 could cause mass hospitalisations and deaths as it spread through an unexposed population. Now the "Phase 1" vulnerable group (aged 50+ or with pre-existing conditions) who account for almost all (approx. 99%) mortality risk have been offered both vaccines, with an average takeup of around 90%. This leaves a much smaller vulnerable population lacking protection.

The UK's vaccines — from Oxford/AstraZeneca, Pfizer/BioNTech, and Moderna — all provide substantial protection against Covid-19. These vaccines emerged from trials showing over 95% efficacy against severe cases resulting in hospitalisation or death, and indeed severe cases altogether.⁸ This has been validated since in real world studies, with Scottish data showing Oxford/AstraZeneca's vaccine reduced hospitalisation by 94% after just one dose.¹⁰

While the emergence of variants poses a renewed challenge, Israeli data suggests vaccines reduce the risk of death by more than 85% regardless.¹¹ Variants can be

⁸ See studies (Last accessed 9 August, 2021) Oxford/AstraZeneca: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7894131/, https://www.astrazeneca.com/content/astraz/media-centre/press-releases/2021/azd1222-us-phase-iii-primary-analysis-confirms-safety-and-efficacy.html. Pfizer: https://www.ema.europa.eu/en/documents/assessment-report/comirnaty-epar-public-assessment-report_en.pdf https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=908ecbe7-2f1b-42dd-94bf-f917ec3c5af8. Moderna: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=e0651c7a-2fe2-459d-a766-0d59e919f058

⁹ The most commonly quoted figures are efficacy against "mild or moderate" or "symptomatic" symptoms where Oxford/AstraZeneca, Pfizer/BioNTech, and Moderna achieved 89%, 95% and 94% efficacy results respectively, but these are less insightful for understanding resilience.

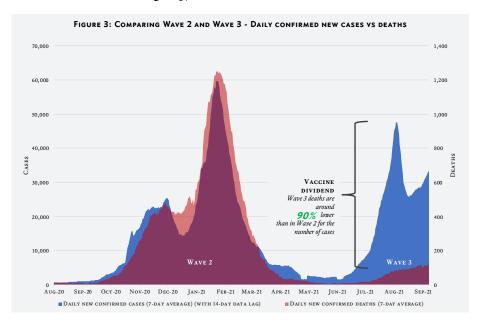
¹⁰ https://www.astrazeneca.com/media-centre/articles/2021/first-real-world-study-of-covid-19-vaccine-astrazeneca-demonstrates-94-reduction-in-hospitalisations.html (Last accessed 9 August, 2021)

¹¹ https://www.bmj.com/content/374/bmj.n1960 (Last accessed 9 August, 2021)

more or less infectious (transmissible between people) and virulent (harmful to an infected person) than the original virus. Respiratory diseases often evolve to become more infectious but less virulent — though this is by no means guaranteed and there are counterexamples. The Delta variant is 40% to 60% more infectious (transmissible) than the Alpha variant. There is also some evidence that it is more likely to lead to hospitalisations for unvaccinated individuals compared to the Alpha or original virus. Alpha or original virus.

DESPITE THE EMERGENCE OF THE DELTA VARIANCE, THE UK IS EXPERIENCING A "VACCINE DIVIDEND" BREAKING THE LINK BETWEEN COVID-19 CASES AND DEATHS BY AS MUCH AS 90%, EQUIVALENT TO AS MANY AS FIFTY THOUSAND LIVES SAVED

The impact of the vaccine campaign is no longer just a promise based on theory or trials but borne out by the UK's real life data. Despite the Delta variant becoming prevalent in the UK, incomplete vaccination of the vulnerable and a dramatic rise in confirmed cases to over 60,000 daily cases, deaths remained low compared to previous waves (see Figure 3). Indeed, there is a huge "vaccine dividend", with "Wave 3" (post-June 2021) deaths being around 90% lower than in "Wave 2" for the number of cases suffered (which uncoincidentally mirrors the vaccinated share of the Phase 1 vulnerable group).



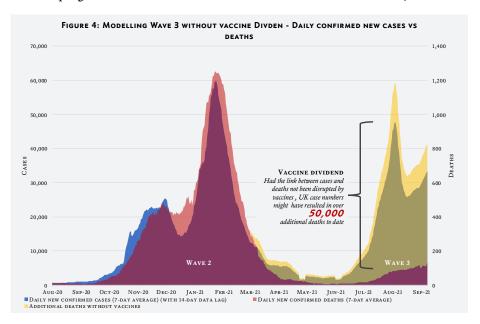
The chart overlays Covid-19 cases and deaths over the period 1 August 2020 to 7 September 2021. It uses a rolling 7-day average of the number of daily confirmed Covid-19 cases, and deaths. Note: A 14-day lag has been applied to the case data, to align it with deaths. This enables a better case to case comparison, as there has typically been a lag between a confirmed case and a resulting death. Forecasters making policy decisions based on case numbers will project these forward based on case fatality ratios to estimate upcoming deaths. Data Source: 8 September extract of official data collated by Our World in Data

¹² https://theconversation.com/will-coronavirus-really-evolve-to-become-less-deadly-153817

¹³ https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/993321/S1267_SPI-M-O_Consensus_Statement.pdf (Last accessed 10 September 2021)

¹⁴ https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)01358-1/fulltext (Last accessed 10 September 2021)

Vaccinating the population (Phase 1 vulnerable group in particular), has thus disrupted the link between Covid-19 cases and deaths. While other improvements (e.g. better hospital treatments and increased natural immunity) have also contributed to a fall in the infection fatality rate, vaccines can safely be credited as the primary source of defence in Wave 3. Modelling Wave 3 without vaccines shows that had the link not been disrupted, UK case numbers (1 March - 7 September 2021) might have resulted in over 50,000 additional deaths to date. Public Health England modelling looking at age groups suggested that by March 2021 (proceeding Wave 3 estimate), an estimated 10,400 deaths were averted as a result of the vaccination programme. This means vaccines have saved at least over 60,000 lives.

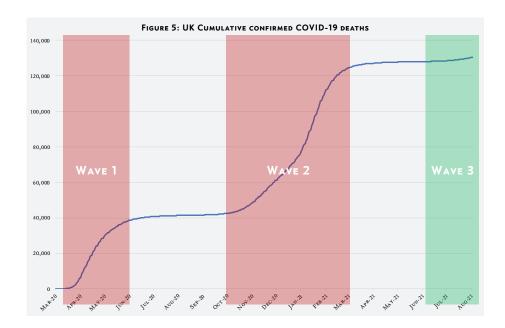


The chart builds on Figure 3 using the same underlying data but adding a theoretical projection of additional deaths without vaccines. This projection is modelled by applying the average case fatality ratio seen at the peak of Wave 2 (between 1 December 2020 and 28 February 2021 before the vaccine campaign took off in earnest or had time to build resilience) and applying after March 2021. It is not a dynamic projection and does not factor in how policies might now be more restrictive without the vaccines nor the impact of the Delta variant which could have increased the case fatality ratio without vaccines. Data Source: 8 September extract of official data collated by Our World in Data

THE HEAVY COSTS OF THE PANDEMIC BOTH IN TERMS OF DEATHS AND UNPRECEDENTED RESTRICTIONS OF LIBERTY NECESSITATE BUILDING SOCIETAL RESISTANCE AGAINST COVID-19

Despite this substantial progress, there is much cause for caution. The cumulative confirmed death toll of Covid-19 now stands at over 133,500 (see figure 5). While the majority of these lives were lost in the first two waves of the pandemic (with around 40,000 and 80,000 deaths respectively), the Government will need to ensure the UK avoids a repeat during the current phase or subsequent outbreaks of variants — or new pandemics.

¹⁵ https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/977249/PHE_COVID-19_vaccine_impact_on_mortality_March.pdf (Last accessed 10 August 2021)



The chart shows the cumulative number of UK confirmed Covid-19 deaths. Limited testing early in the crisis, as well as challenges in attribution of the cause of death (e.g. when a patient catches Covid-19 in hospital) means the data may not provide an accurate reflection of the true number of deaths. Nonetheless, this provides one of the clearest metrics of the impact of Covid-19 and is well corroborated by excess death calculations. Data Source: 7 August extract of official data collated by Our World in Data

Beyond the immediate death toll, policymakers should seek to avoid further restrictions and lockdowns. The UK has exercised emergency coercive powers over its citizens on a scale without precedent. The population has been placed under effective house arrest and with much economic and social activity prohibited for many months at a time. This was authorised often by ministerial decree with limited parliamentary debate or oversight.

Moreover, blurred lines between guidance and law led to unclear rules and uneven legal enforcement. The overall state response amounts to the most significant interference with personal freedom in all our lifetimes. This is to say nothing of the secondary impacts of such restrictions, which extend from school closures to bankrupted businesses, mental health issues and worsening wider health outcomes. Such powers, regardless of whether or not they were justified in the unprecedented circumstances, should in principle not be used lightly (or for too long). The goal should be to avoid such restrictions.

As around 90% of the vulnerable have now been fully vaccinated, the bulk of initial resilience that can be achieved is in place. It is an appropriate time to consider how the UK restores fundamental liberties, without allowing state interference and control to be ratcheted up, preventing us from returning to normality even once the pandemic is over.

As a historical point of comparison, while the Second World War ended in May 1945, rationing only formally ended in 1954, and various controls over dairy and cheese production were only fully removed with the abolition of the Milk Market-

ing Board in 1994. The continuation of restrictions caused substantial economic damage in the United Kingdom, particularly compared to West Germany or the United States of America which removed wartime restrictions, cut taxes and dismantled government intervention.¹⁶

THE GOVERNMENT HAS A RESPONSIBILITY TO ENSURE THAT IT UNDOES ITS RESTRICTIONS FULLY, BUILDING SUFFICIENT RESILIENCE TO AVOID THE NEED OR TEMPTATION TO REIMPOSE THEM IN FUTURE.

Covid-19 has set an extraordinary and previously unimaginable precedent about the acceptability of extreme state interventions in the face of risks to public health. This represents a substantial movement of the 'Overton Window'.¹⁷ It is not outside the realm of possibility that there will be demands for similar, lockdown-style interventions, in scenarios that just a few years ago would have been outlandish.

Prior to Covid-19, UK deaths from flu typically ranged between 10,000 and 25,000 per year. In the winter of 2019 there were an estimated 28,300 excess winter deaths, with respiratory diseases cited as the leading cause. Historically this would not have prompted a Covid-19-style policy or societal response, but this would now be plausible using the precedents set.

Any future demands for lockdowns and restrictions against Covid-19 or other viruses should require full parliamentary scrutiny, with more thorough review of forecasting processes and assumptions. The cost-benefit analysis of restrictions has altered significantly given our knowledge of the virus, the resilience established, and the steep costs of intervention.

The grounds or thresholds that could trigger Covid-19-style restrictions in future remain undefined. The expectations for government(s) and the impetus to intervene with significant restrictions in future are exacerbated by poorly defined "goalposts", inconsistent government communication, limited past cost-benefit analysis and regular policy changes (see Figure 6).

The Government implemented "Eat Out to Help Out" over August 2020 to encourage people to go out, only to then implement tiered restrictions just over a month after it concluded. The Government began easing the second lockdown on 2 December, only to then introduce a Tier 4 effective lockdown 19 days later in London (and nationally after 25 days), and the third full lockdown on 6 January 2021.

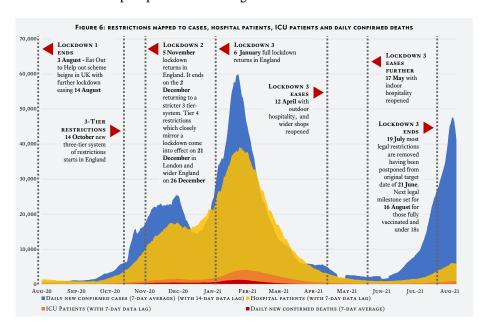
After the vaccine campaign success, the Government recognised that lockdowns were no longer necessary. It also concluded that it would be best to ease restrictions

¹⁶ https://www.cps.org.uk/research/history-repeating-the-lessons-of-the-postwar-recovery/ (Last accessed 10 September 2021)

¹⁷ The Overton Window is the range of policies deemed politically acceptable by the mainstream population, or window of discourse

¹⁸ https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/excesswintermortalityinenglandandwales/2019to2020provisionaland2018to2019final (Last accessed 10 August, 2021)

in the summer when there is less pressure on the NHS. However, it postponed part of its unlocking plan from 21 June to 19 July under the stated aim of vaccinating more of the population (despite having already offered vaccines to all the 'Phase 1 vulnerable group' and a subsequent collapse in the vaccination rate). The apparent Wave 3 peak in early August came just a few weeks after the removal of restrictions and at a much lower level than forecast by the Government. The policy approach has varied and the past provides limited guidance for the future.



Similar to figures 3 and 4 the chart overlays Covid-19 cases and deaths over the period 1 August 2020 to 7 August 2021. However, it uses a single scale rather than dual scale. It uses a rolling 7-day average of the number of daily confirmed Covid-19 cases, and deaths. This is then overlaid with the total number of hospital and ICU patients on that day.

Note: A 14-day lag has been applied to the case data, and a 7-day lag has been applied to the hospital/ICU data to align it with deaths. Again, this is to better align fatal cases (and their subsequent hospitalisation) to deaths. A timeline of key events in terms of restrctions and lockdowns has been added enabling decisions to be considered in context of prior and subsequent cases, hospitalisations and deaths. Data Source: 7 August extract of official data collated by Our World in Data

If any conclusions can be drawn from past lockdowns, it is that they were primarily implemented when the Government's forecasts suggested the NHS would be overwhelmed. This was correlated with exponential increases in confirmed cases, as measured by the R number (or reproduction rate), as well as consideration for the virulence of Covid-19 and resulting case-fatality ratio.19 As cases, hospitalisation, and ICU patients rose, "Protect the NHS" provided the clearest guide to the Government's tolerance level.

Regardless of other factors, the scenario of NHS over-saturation is deemed as unacceptable for the Government because it implies a high degree of negligence and culpability. An overwhelmed NHS would provide patients with substandard treat-

¹⁹ R represents the number of people that one infected person will on average pass a virus onto

ment resulting in more deaths than if the same number of cases had been more spread out. By comparison, deaths that occur annually from flu and multiple other causes are an established reality and more politically acceptable.

THE HIGH COST OF THE PANDEMIC — TO OUR HEALTH, ECONOMY AND LIBERTIES — MAKES IT IMPERATIVE TO BUILD SOCIETAL RESISTANCE AGAINST COVID-19 AND FUTURE PANDEMICS.

Societal resilience is essential as the UK enters its next phase in the pandemic and threats continue to evolve. The Government needs to plan with a long-term mindset to handle Covid-19, other respiratory diseases and new viruses in general for the coming decades. Covid-19 has already produced multiple variants, with the World Health Organisation labelling four of these as "of concern" and four as "of interest".²⁰

While the vaccines do provide substantial protection against the dominant Delta variant and slow its spread, they are far from perfect or as effective as they were against the Alpha variant. Moreover, the levels of antibodies against Covid-19's spike protein have been shown to decline significantly over time, indicating lower protection.^{21 22} A recent Israeli study indicated that protection against the virus begins to diminish from two months after vaccination, and the reduction in viral load as a result of vaccination entirely disappears after six months, in the context of the Delta variant.²³ (There is still likely to be continued protection against hospitalisation and death over a longer period of time, though likely to be at a reduced level.)

With both the threat posed by the virus and our defences against it changing, the Government will need to revisit and augment its vaccination programme, while improving its ability to respond to future virus epidemics without such severe interference and disruption to society.

²⁰ https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/ (Last accessed 10 August, 2021)

²¹ https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)01642-1/fulltext (Last accessed 10 August, 2021); https://www.reuters.com/world/middle-east/israel-sees-drop-pfizer-vaccine-protection-against-infections-still-strong-2021-07-05/ (Last accessed 10 September 2021)

²² However, the paper also notes that "the clinical implications of waning antibody levels post vaccination are not yet clear, and it remains crucial to establish S-antibody thresholds associated with protection against clinical outcomes"

²³ https://www.medrxiv.org/content/10.1101/2021.08.29.21262798v1 (Last accessed 10 September 2021)

AUGMENTING THE VACCINE CAMPAIGN: LEARNING FROM THE CAMPAIGN SO FAR

While the vaccine campaign has been a success and changed the dynamics of the pandemic, there are lessons to be learnt. It could have gone even faster.

In international terms, the UK was the first to begin vaccinating and is well ahead of other European countries and narrowly ahead of the United States. Nevertheless, the first month of the campaign was unremarkable, initially vaccinating at such a slow rate that the Phase 1 vulnerable group would have only received one dose by late 2022.²⁴ Israel began its campaign vaccinating at a rate as much as 10-times faster than the UK per head.²⁵ With the cost of the pandemic estimated at billions weekly, this slow ramp-up demonstrated the importance of constant evaluation and optimisation.

Dismayed by these results and the Government's unambitious target of one million doses per week, the ASI produced, *Worth a Shot: Accelerating Covid-19 vaccinations*. ²⁶ This paper recommended 22 measures to accelerate the supply and distribution of vaccines, and challenged the UK to target 6 million doses per week. Over half of the recommendations were later trialled, partly adopted, or fully embraced.



The chart shows the daily Covid-19 vaccine doses administered using a rolling 7-day average, both in terms of doses administered, and as a share of the population. The data is overlaid with different targets. Data Source: 7 August extract of official data collated by Our World in Data

While the vaccine campaign subsequently accelerated as much as ten-fold, it never reached the ASI's target and left open several opportunities for further acceleration using a full "war effort" style approach (See Figure 7). The claim that further

²⁴ https://www.adamsmith.org/research/worth-a-shot (Last accessed 10 August, 2021)

²⁵ Ibid

²⁶ Ibid

acceleration wasn't possible due to supply constraints does not hold up to scrutiny as supplies never ran out, meaning by definition, that this was not the ultimate bottleneck even if it was an important constraint. Indeed, some areas of the UK, like Wales, managed to vaccinate faster than others, implying that there was unused supply that could have been used to accelerate across the country. Moreover, more could have been done to bring forward and expand the range of supplies and a "mix-and-match" approach would have enabled further flexibility.

After crossing the 500,000 daily doses threshold, and even the occasional day that made the ASI's 6 million weekly doses target look feasible (e.g. March 20 recorded 873,784 doses administered in a single day), the campaign stopped accelerating from end-March.²⁷ Indeed, a significant slowdown since mid-May has enabled other countries to catch up if not overtake (see Figure 2). The UK can no longer claim to be the envy of Europe. Suboptimal elements of the campaign have included:

- Never fully embracing "war effort" measures to expand distribution, like mobile vaccination centres for remote and immobile communities, widespread drive-in centres and extended (or even 24/7) services.
- The weekend reduction in the number of appointments and vaccinations. Public holidays, a unique opportunity to vaccinate workers without disruption, typically led to dramatic falls in vaccine distribution and even forced some centres to close.
- Vaccine centres did not operate reserve lists and were hesitant in giving away spare doses at the end of a shift to those outside the target group, even if this meant wastage (particularly Pfizer/BioNTech), although many haphazardly used spare doses anyway and this approach has since become more flexible.
- Slow and inconsistent pacing of the campaign and extending its scope to younger cohorts as the campaign matured beyond the Phase 1 vulnerable group.
- Placing greater focus on maintaining precise dosing schedules to the letter than on the overall speed of coverage.
- Not adopting prizes and idea crowdsourcing to reward best practices and generate new opportunities for acceleration.
- Supplies from Moderna arrived later than initially promised, while failing to approve the vaccine faster (e.g. by treating the US Food & Drug Administration's approval as equivalent, or preparing more proactively for its arrival).
- Neglecting "mix-and-match" doses, despite evidence that this could boost protection while easing supply chain challenges (as explored further below).
- Insufficient emphasis on ventilation and vaccination centre safety while retaining antiquated guidance focusing on hand washing, potentially discouraging nervous patients and most likely acting as a driver for a rise in cases among the vulnerable.
- Insufficient countering of anti-vax misinformation or hostile (potentially state-sponsored) propaganda, with limited proactive education and nurturing of those who have yet to adopt the vaccine this is particularly crucial for the Phase 1 vulnerable group who account for around 99% of mortality risk, and yet where 10% remain unvaccinated altogether.

Perhaps the most contentious element of the UK's campaign has been the handling of the Oxford/AstraZeneca vaccine, from early clashes with the EU, through to discouraging its use among younger patients over blood clot side effect concerns. Critics of the Oxford/AstraZeneca vaccine also pointed to mRNA vaccines achieving higher efficacy rates in their clinical trials.

Initially, on 7 April 2021, under-30s were offered an alternative, and then on 7 May under-40s. The Joint Committee on Vaccination and Immunisation (JCVI) advised "a preference... to receive an alternative to the Oxford/AstraZeneca vaccine – where available and only if this does not cause substantial delays in being vaccinated". So in theory, under-40s could still opt in to receive the Oxford/AstraZeneca if they wanted a vaccine faster given the arguably tiny risks involved. In practice, this amounted to a highly discouraging message against opting in, and there was no practical mechanism to opt in easily, especially when booking online. By contrast, in Australia, under-40s have been given the option to book an Oxford/AstraZeneca appointment online and discuss their situation at the appointment to ensure informed consent.

This had real consequences: using the available Oxford/AstraZeneca doses could have meant opening vaccination up to younger cohorts earlier, meaning less community transmission of the virus, fewer hospitalisations and deaths. Instead, there were substantial surges in case numbers among unvaccinated younger people throughout the summer, some of which led to spread to older cohorts, contributing to the current rate of hospitalisations and deaths.

A recent study, based on six months of vaccinations in Catalonia for over a million people, suggests this change in policy was an overreaction.²⁸ The data showed vaccinations do very slightly increase the risk of blood clots. Despite the past focus on Oxford/AstraZeneca, the researchers conclude that its safety profile is "broadly similar" to that of Pfizer/BioNTech.²⁹ Most importantly, the risk of the same blood clot types is much higher from an actual infection of Covid-19.³⁰

The study examined three types of blood clots, venous thromboembolism (VTE), arterial thromboembolism (ATE) and thrombosis with thrombocytopenia syndrome (TTS). The risk of VTE is slightly higher for a Pfizer/BioNTech dose (a 1.29-fold increase) compared to an Oxford/AstraZeneca dose (a 1.15-fold increase). By contrast, the risk of VTE increases 8.04-fold after diagnosis of Covid-19. For TTS, the risk increase was again lower for Oxford/AstraZeneca (1.35 and 1.03 for Pfizer/BioNTech and Oxford/AstraZeneca respectively), especially when compared to catching Covid-19 (3.52). The ATE incidents were not elevated compared to the norm after vaccinations.

Another recent study also challenges the assumption that Oxford/AstraZeneca is inferior to the mRNA vaccines. Real-word comparisons from Bahrain showed it

²⁸ https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3886421 (Last accessed 10 August, 2021)

²⁹ Ibid

³⁰ Ibid

reduced the impact of Covid-19 to a 1.52% hospitalisation rate and 0.03% death rate, compared to 1.99% and 0.15% for Pfizer/BioNTech respectively, or 13.22% and 1.32% for the unvaccinated respectively. 31

^{31 &}quot;Covishield" referenced in the paper is the Serum Institute of India's brand name for the Oxford/AstraZeneca vaccine

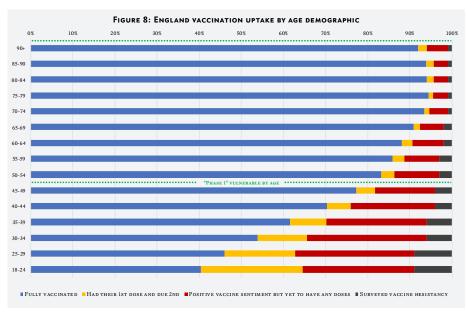
This section presents key recommendations, including the need for booster vaccinations, rapidly updating existing vaccines to reflect new variants, potential mixing of vaccines, and extending vaccination to the young, alongside placing a renewed focus on those in vulnerable segments who have yet to be vaccinated.

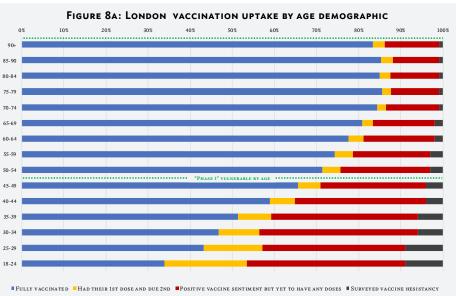
FURTHER FOCUS ON THE "PHASE 1" VULNERABLE POPULATIONS WOULD MAKE THE MOST MEANINGFUL CONTRIBUTION TOWARDS REDUCING HOSPITALISATIONS AND DEATHS AND BUILDING SOCIETAL RESILIENCE

According to the JCVI, the Phase 1 group of those aged over 50, in care homes, and with pre-existing conditions represent around 99% of preventable mortality from Covid-19.³² The rapid offer and rollout of vaccines to this group was the primary enabler to end the third lockdown and ease its restrictions, in the knowledge that hospitalisation and deaths would not return to prior peaks. Broadening and deepening protection within this group is the surest way to build societal resilience to Covid-19 and avoid the temptation or need to reimpose restrictions. The use of boosters covered above is important, but the more critical gap is in the significant numbers of Phase I persons who have yet to receive their 2nd dose or even any doses at all.

A significant portion of the "Phase 1" vulnerable group remains at risk from Covid-19 despite positive sentiment towards taking the vaccine (as shown in Figure 8 below in yellow and red). There are some who are hesitant to take the vaccine and will not consent to its use, and they should retain the right to make that decision. But the truly 'antivax' group are a small minority.

³² Joint Committee on Vaccination and Immunisation: advice on priority groups for COVID-19 vaccination, 30 December 2020 - GOV.UK (www.gov.uk) (Last accessed 10 September 2021)





The charts show the proportion of people in England and London who have been fully vaccinated (where a person has received two doses of a two-dose vaccine) compared against those who have only had one dose (and are thus due a second dose) and the proportion who surveyed as vaccine hesitant. The gap in red is those who displayed positive vaccine sentiment but have yet to receive any vaccine doses. Vaccine hesitancy includes those who, according to surveys: have been offered a vaccine but declined the offer; are very or fairly unlikely to have the vaccine if offered; are neither likely nor unlikely to have the vaccine if offered; are neither likely nor unlikely to have the vaccine as offered; and the August ONS survey data extract³⁴

There are about 2.1 million vulnerable ("Phase 1") individuals who are entirely unvaccinated and 600,000 yet to have a second dose. Overall, there are 10.4 million adults who are entirely unvaccinated. This would result, if this entire population catches the virus as it circulates through the community, in approximately 39,600

 $[\]textbf{33} \ \, \text{https://coronavirus.data.gov.uk/details/vaccinations?areaType=nation\&areaName=England (Last accessed 31 August, 2021)}$

³⁴ https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/healthandwellbeing/bulletins/coronavirusandvaccinehesitancygreatbritain/9august2021 (Last accessed 31 August, 2021)

deaths and 148,000 hospital admissions.³⁵ Of those deaths and hospital admissions, 84% (33,200 and 124,000) would be expected to be in the Phase 1 priority group.

The vaccination of all Phase I individuals would require 3.3 million doses in England and nearly four million across the UK. Since the case fatality ratio for unvaccinated patients in this group is significantly higher than in other segments of the population and they accounted for 99% of mortality before vaccinations, any doses delivered to this group would deliver the greatest return on investment.

Failing to focus on those Phase 1 individuals who are ready and willing to be vaccinated and most vulnerable, but who have yet to be vaccinated for whatever reason, risks the vaccine campaign becoming negligent in meeting its core objectives. It is preferable to vaccinate another "Phase 1" vulnerable individual ahead of a 20-year-old, even if both events are positive. Vaccinating someone in "Phase I" group is five times more likely to prevent a death then someone who is younger, thereby five times more effort should be made to vaccinate each "Phase 1" individual over a younger person.³⁶

Recommendation 1: Redouble efforts to vaccinate those in the "Phase 1" vulnerable group who are due a second dose and/or completely unvaccinated, including using mobile vaccination units and home visits — providing protection to those most likely to be hospitalised or die. This would make the most immediate contribution towards reducing hospitalisations and deaths, and building resilience.

BOOSTERS ARE NEEDED TO MAINTAIN PROTECTION AGAINST WANING IMMUNITY, THE DELTA VARIANT AND FUTURE THREATS - ISRAEL AGAIN PROVIDES THE LEADING PRECEDENT

Boosters represent an obvious and desirable extension of the current vaccine campaign and are already a confirmed part of the Government's strategy (potentially in September).³⁷³⁸ In late March 2021, a further 60 million doses of Pfizer/BioN-Tech were secured for autumn 2021, with a further 35 million doses since ordered for autumn 2022.³⁹⁴⁰ Boosters could be integrated as part of a "mix-and-match" strategy (described in the next section) to provide additional protection, particularly against variants.

³⁵ This calculation is based Covid-19 infection fatality ratio across different age groups determined by Imperial College's Covid-19 response team, UK Government data on unvaccinated people and hospital admissions and deaths, and ONS' mid-2020 population estimates, see https://www.imperial.ac.uk/media/imperial-college/medicine/mrc-qida/2020-10-29-COVID19-Report-34.pdf

³⁶ This is a calculation based upon the number of unvaccinated individuals across age groups that are susceptible to death if they all became infected with Covid-19 as it circles through the population, as per the previous citation. Of the 39,600 deaths among unvaccinated people, 33,200 are aged 50 or over and 6,400 are aged under 50. 33,200/6,400=5.19

³⁷ https://www.england.nhs.uk/coronavirus/wp-content/uploads/sites/52/2021/07/C1327-covid-19-vaccination-autumn-winter-phase-3-planning.pdf (Last accessed 30 August, 2021)

³⁸ https://www.gov.uk/government/news/most-vulnerable-could-be-offered-booster-covid-19-vaccines-from-september (Last accessed 30 August, 2021)

³⁹ https://www.gov.uk/government/news/uk-secures-extra-60-million-pfizerbiontech-covid-19-vaccines(Last accessed 10 August, 2021)

⁴⁰ https://www.thetimes.co.uk/article/booster-doses-for-next-year-cost-lbn-after-pfizer-puts-price-up-f07s70m69 (Last accessed 30 August, 2021)

Boosters are not just a luxury. They are a requirement for maintaining resilience as protection from existing vaccination looks likely to decline over time. ⁴¹ The vaccines are believed to maintain a good level of antibody protection for 6 months, as should a past infection. ⁴² ⁴³ However, a sample of 605 adults found that after 10 weeks antibody levels plummeted five-fold for AstraZeneca and two-fold for Pfizer/BioNTech. Another study demonstrated a similar reduction in antibodies, by 40% in each month after the second dose, for those who received the Pfizer/BioNTech vaccine. ⁴⁴

It is likely that individuals will have a longer lasting, and perhaps even strengthening, memory T cells and B cells that will provide ongoing protection against severe disease, hospitalisation and death.⁴⁵ Nevertheless, the lack of ongoing antibody protection means individuals will be more likely to experience reinfection, if exposed to the virus, thus increasing ongoing circulation. This will put pressure onto the healthcare system and risks increasing the level of deaths as the virus reaches unvaccinated individuals or those who have a weak immune response to the vaccine.

The UK is already falling behind in its booster campaign, with Israel again providing a guiding light (see Figure 9). Israel started its booster campaign on July 30th and has already covered nearly 30% of its entire population, motivated by the spread of the Delta variant.

The latest Israeli data suggests the focus on boosters has been a highly effective strategy, reducing both the risk of infection and severe illness. The combination of waning immunity and the Delta variant reduced the headline efficacy of vaccines (in terms of preventing symptomatic cases) from around 90% to just 50%, hence the continued spread of Covid-19, even if the prior vaccines still fundamentally reduce the risk of hospitalisation and death. The boosters restored protection to a level "similar to the original "fresh" vaccine efficacy reported against the Alpha strain". As

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1007573/S1332_How_long_will_vaccines_continue_to_protect_against_COVID-19.pdf (Last accessed 30 August, 2021);

https://www.gov.uk/government/publications/jcvi-interim-advice-on-a-potential-coronavirus-covid-19-booster-vaccine-programme-for-winter-2021-to-2022/jcvi-interim-advice-potential-covid-19-booster-vaccine-programme-winter-2021-to-2022 (Last accessed 30 August, 2021)

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00675-9/fulltext (Last accessed 30 August, 2021)

https://www.medrxiv.org/content/10.1101/2021.08.19.21262111v1.full (Last accessed 10 September 2021)

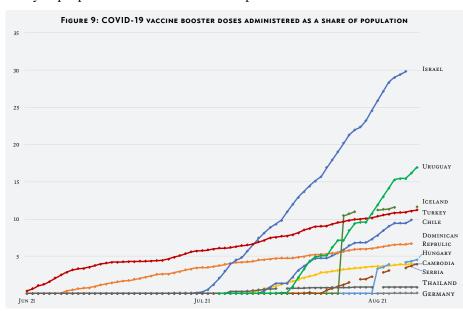
https://www.biorxiv.org/content/10.1101/2021.08.23.457229v1 (Last accessed 10 September 2021)

https://www.medrxiv.org/content/10.1101/2021.08.06.21261707v3 (Last accessed 31 August, 2021)

https://www.medrxiv.org/content/10.1101/2021.08.11.21261885v1 (Last accessed 31 August, 2021)

https://www.gov.il/BlobFolder/reports/vaccine-efficacy-safety-follow-up-committee/he/files_publications corona booster-27082021.pdf (Last accessed 31 August, 2021)

A study by Israeli health provider Maccabi, which covers around one-quarter of the population found a booster to be 86% effective in preventing cases among people aged over 60 compared to those who had just two jabs. ⁴⁹ Meanwhile, an Israeli health ministry study found that the protection from infection after a third dose was four times higher, and protection from serious illness and hospitalisation to be five to six times higher, than after two doses. ⁵⁰ Another Israeli study found that a third booster jab reduces viral loads among breakthrough cases, likely to reduce the ability of people who have had a booster to pass on the virus. ⁵¹



The chart shows the cumulative total Covid-19 vaccine boosters administered. Data Source: 8 September extract of official data collated by Our World in Data

THE UK'S BOOSTER STRATEGY LACKS SCOPE, AND SHOULD TO BE EXTENDED TO THE ENTIRE ADULT POPULATION

The initial booster focus rightly mirrors the original roll out by targeting the most vulnerable, starting firstly with over-70s, care home residents and the immunosuppressed, and then extending to over-50s and over at-risk groups. However, there is no plan to extend boosters to the remaining adult population and the dates of the booster campaign remain unconfirmed (as of publication). This is substantially behind elsewhere in the world. It could leave many vulnerable if cases increase over the coming winter months.

Failing to offer boosters to the whole adult population — and delaying them for those groups more at risk — would prove 'penny-wise and pound-foolish' when immunity eventually declines across the population. Similarly, excessive delay in providing boosters to higher-risk groups would threaten to increase risk in the segment of the population most likely to need hospitalisation and at risk of a fatal outcome. The only consistent policy that maintains societal resilience is to offer

⁴⁹ https://www.reuters.com/business/healthcare-pharmaceuticals/third-pfizer-dose-86-effective-over-60s-israeli-hmo-says-2021-08-18/ (Last accessed 10 September 2021)

⁵⁰ https://www.reuters.com/world/middle-east/israel-finds-covid-19-vaccine-booster-significantly-lowers-infection-risk-2021-08-22/ (Last accessed 10 September 2021)

⁵¹ https://www.medrxiv.org/content/10.1101/2021.08.29.21262798v1 (Last accessed 10 September 2021)

the boosters to all, albeit after prioritising the vulnerable — and to get on with this process, rather than lagging even EU peers.

The most legitimate criticism against providing boosters in the United Kingdom relate to the need to provide vaccines more equitably across the world, with many billions yet to be vaccinated, particularly in developing countries. ⁵² However, boosters and global distribution should not be seen as an 'either/or' proposition. Over the coming months billions more doses of various vaccines will become available. Pfizer expects to produce 3 billion doses by the end of 2021. ⁵³ AstraZeneca will also deliver around 3 billion, and Moderna between 800 million to 1 billion, by the end of 2021. ⁵⁴ The top five vaccine producers, including Pfizer, Moderna, AstraZeneca, J&J expect to produce 12.9 billion jabs by the end of 2022. ⁵⁵ This indicates extremely strong forthcoming supplies that will provide enough vaccines to both provide for developing countries and boosters in developed countries. The central goal will be to ensure no doses are wasted, as a result of logistics or under ambitious booster plans, that could have helped save lives.

Recommendation 2: Begin providing boosters, which are essential to maintain protection against waning antibody immunity, the Delta variant and future threats; prioritising the vulnerable but also offering a booster to the entire adult population.

Recommendation 3: Publish a detailed roadmap for Covid-19 vaccinations over the next five years, including an upcoming delivery schedule with plans for a backlog of boosters.

UPDATE THE REGULATORY PROCESS TO ENSURE RAPID APPROVAL, AND PLENTIFUL PROCUREMENT, OF COVID-19 VACCINES UPDATED TO TACKLE THE DELTA VARIANT AND FUTURE MUTATIONS

The danger of vaccine-resistant mutations will continue to grow while community transmission continues. The Delta variant has proven remarkably effective at spreading, even through the vaccinated population. The danger of mutations is increased by the fact that nine in ten people in poor countries will not receive a Covid-19 vaccine this year.⁵⁶

Thankfully, virus variants undermining vaccines is not a new challenge. Influenza constantly mutates, requiring global monitoring and an annual vaccine update — a process that dates back to the 1950s. ⁵⁷ Twice a year — in February for the Northern Hemisphere's winter and September for the Southern Hampshire — the World Health Organisation convenes a meeting to assess which influenza strains are most

⁵² https://www.theguardian.com/society/2021/sep/10/dame-sarah-gilbert-uk-covid-booster-jabs-unnecessary-for-all (Last accessed 10 September 2021)

⁵³ https://www.biopharma-reporter.com/Article/2021/08/10/Pfizer-and-BioNTech-COVID-19-vaccine-capacity-to-hit-4-billion-doses-in-2022

⁵⁴ https://investors.modernatx.com/news-releases/news-release-details/moderna-announces-additional-investments-increase-global-supply (Last accessed 10 September 2021)

⁵⁵ https://www.fiercepharma.com/manufacturing/moderna-j-j-and-astrazeneca-planning-big-covid-19-production-upgrades-catalent-eyes-a (Last accessed 10 September 2021)

⁵⁶ https://www.amnesty.org/en/latest/news/2020/12/campaigners-warn-that-9-out-of-10-people-in-poor-countries-are-set-to-miss-out-on-covid-19-vaccine-next-year/ (Last accessed 10 August, 2021)

⁵⁷ https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5139605/ (Last accessed 10 August, 2021)

likely to spread and cause illness. They recommend a flu vaccine that typically includes two influenza A (H1N1 and H3N2) and one or two influenza B strains.

Manufacturers then update their vaccines to reflect the latest strains. The flu vaccine is typically manufactured using fertilized hens' eggs to incubate the virus, which is then extracted, inactivated and purified. Importantly, regulators, knowing that existing flu vaccine manufacturing techniques are safe and effective from earlier trials, do not require the updated vaccines to be put through randomised controlled trials (RCT).

The Centres for Disease Control (CDC) states that randomised control trials for the flu vaccine are unethical because they would require denying a potentially life-saving vaccine to a "control" group to compare outcomes with a vaccinated group.⁵⁸ The potential benefits of an RCT, in confirming safety efficacy, are outweighed by the potential costs to human life when we already know a vaccine to be safe.

Instead, each batch is quality tested by regulators before it is filled into glass bottles and distributed. They also use observational studies, witnessing different outcomes for those who choose to get vaccinated and those who do not, and non-randomised studies that test an individual's immune response after a vaccine. This process means humanity can benefit each year from flu vaccines, rather than waiting years each time.

If we are to have any hope in combating Covid-19 variants without repeated lock-downs and limits on global travel, it will be necessary to apply the same regulatory approach to updated Covid-19 vaccines. Now that Covid-19 has spread so widely it has effectively become endemic, meaning it is likely to constantly mutate and require annual immunisation like the flu.⁵⁹

The process should be straightforward: a vaccine-resistant variant is identified by genomic sequencing, the existing mRNA, vector and protein vaccines are updated and immediately produced for small-scale testing to recheck safety and efficacy. They are then mass produced under the usual regulatory supervision and the public is provided with "booster" jabs. They could even be provided as part of enhanced vaccine distribution infrastructure in sync with annual flu shots.

One of the key merits of the mRNA type vaccines (of Pfizer/BioNTech and Moderna) is the speed with which scientists can sequence the genetics of the virus and then produce a sequence for mRNA to produce a custom tailored vaccine. The speed and specificity of this process is arguably a unique selling point, and creates an opportunity to combat the Delta variant more effectively head-on.

⁵⁸ https://www.cdc.gov/flu/vaccines-work/effectivenessqa.htm (Last accessed 10 August, 2021)

⁵⁹ https://theconversation.com/covid-19-will-probably-become-endemic-heres-what-that-means-146435 (Last accessed 10 August, 2021)

Pfizer and BioNTech have publicly announced they are developing a tailor made vaccine to target Delta's spike protein. ⁶⁰ Similarly, while based on a different vaccine platform, AstraZeneca have begun phase 2 and 3 trials for a vaccine tailored against the Beta (or South African) variant of Covid-19 and are understood to be working on a vaccine against Delta.

The entire process of updating a vaccine, according to Britain's vaccine minister Nadhim Zahawi back in February 2021, could take as little as "30 to 40 days." In the US, the Food and Drug Administration (FDA) has released updated guidance stating that existing vaccines updated for new variants will not require randomized control trials. They can instead be tested in small trials to confirm safety and immune system response. The UK's MHRA have previously suggested updated Covid vaccines would not require brand new approval or 'lengthy' clinical studies. Yet Oxford University and AstraZeneca have begun a Phase II/III trial of a vaccine designed to tackle the Beta variant, first identified in South Africa. Pfizer announced a Delta-specific vaccine trial would begin in August, 2021.

In practice, however, all UK government orders for boosters appear to be focused on existing formulations. This is despite the knowledge that the existing vaccines are less effective against the Delta variant. It is essential that the UK Government has extensive orders of vaccine updates from various manufacturers, both to specifically tackle the Delta variant and also to insure against the risk of future variants. These plans should be published transparently to provide confidence about the ongoing ability to tackle Covid-19.

Recommendation 4: Update regulatory process to enable rapid approval of vaccine updates every time there is a new variant of concern, following the annual flu vaccine process.

THERE ARE ALSO A RANGE OF NEXT-GENERATION COVID-19 VACCINES THAT COULD MEAN THE ELIMINATION OF VIRUS

The first generation of Covid-19 vaccines have proven extremely successful. But they may prove to just be the beginning. There are a range of efforts, using innovative technologies, to develop even better vaccines. There has been substantial work on a "universal vaccine" that targets the core of the coronavirus which is less likely to mutate. There is even a nasal spray vaccine, currently being tested in animals,

⁶⁰ https://investors.biontech.de/news-releases/news-release-details/pfizer-and-biontech-provide-update-booster-program-light-delta (Last accessed 10 September 2021)

⁶¹ http://theguardian.com/world/2021/feb/04/about-4000-covid-variants-across-world-uk-minister

⁶² https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-issues-policies-guide-medical-product-developers-addressing-virus (Last accessed 10 August, 2021)

⁶³ http://www.pharmatimes.com/news/modified_covid-19_vaccines_can_avoid_lengthy_clinical_studies, says mhra 1364671 (Last accessed 10 September 2021)

⁶⁴ https://www.nihr.ac.uk/news/first-trial-participants-vaccinated-with-oxford-covid-19-variant-vaccine-in-nihr-supported-study/28022

⁶⁵ https://cdn.pfizer.com/pfizercom/2021-07/Delta_Variant_Study_Press_Statement_Final_7.8.21. pdf?IPpR1xZjlwvaUMQ9sRn2FkePcBiRPGqw (Last accessed 10 September 2021)

⁶⁶ https://www.telegraph.co.uk/news/2021/02/13/exclusive-universal-vaccine-can-conquer-covid-variants-could/ (Last accessed 10 August, 2021)

that takes this approach.⁶⁷ Scientists are also hopeful of developing a "pancoronavirus vaccine" that could work against all coronaviruses in future.⁶⁸ Early experiments involving mice indicate cross-reactive immune responses to vaccines which contain multiple coronaviruses.⁶⁹ The side benefit of this could be to reduce the severity of the common cold, many versions of which are coronaviruses.

Last year, the UK's procurement of promising vaccines before the completion of trails saved many lives and shortened lockdowns. The same approach should be applied to these new generations of vaccines, to ensure advance purchase orders and manufacturing capacity, so that more lives can be saved in future.

Recommendation 5: Purchase a diverse range of new Covid-19 vaccines including updated Delta-variant specific vaccines and oral/nasal and "universal" vaccines.

"MIX-AND-MATCH" VACCINATION ENABLES GREATER SUPPLY FLEXIBILITY AND ENHANCED PROTECTION

There is growing evidence that a "mix-and-match" approach to vaccines is effective, if not more effective than two doses of non-mixed vaccines. The Oxford/AstraZeneca vaccine uses a harmless adenovirus to carry genetic material from Covid-19, while the Pfizer/BioNTech and Moderna vaccines use messenger RNA. They are both extremely effective vaccines, however have their respective advantages. The former are potentially slightly better at producing a strong T-cell response, while the latter are potentially more likely to generate a stronger antibody response. Both have a role to play in preventing infection and protecting against severe disease, suggesting that a combination could provide the best overall resilience. An Oxford study (funded by the Vaccine Task Force and the National Institute for Health Research) found the "the highest T cell response from application of the Oxford/AstraZeneca vaccine followed by a second dose with Pfizer/BioNTech"⁷⁰. Similar results have been found in two German studies. To "mix-and-match" trials have reported severe side effects.

The initial reaction to these studies has been that as non-mixed vaccines are a known quantity and supplies are stable, no change to policy is planned. Indeed, the current policy stance appears to penalise those with "mix-and-match" doses, with travelers having to remain in isolation after arrival at the UK, even if they have comparable or arguably better protection.⁷³ That is, if the individual is lucky

⁶⁷ http://newsweek.com/scientists-hope-save-world-next-pandemic-work-universal-coronavirus-vaccine-1569081 (Last accessed 10 August, 2021)

⁶⁸ https://www.nytimes.com/2021/02/09/health/universal-coronavirus-vaccine.html (Last accessed 10 August, 2021)

⁶⁹ https://www.vbivaccines.com/wire/preclinical-coronavirus-data-candidate-selection/ https://science.sciencemag.org/content/371/6530/735

⁷⁰ https://www.ox.ac.uk/news/2021-06-28-mixed-oxfordpfizer-vaccine-schedules-generate-robust-immune-response-against-covid (Last accessed 10 August, 2021)

⁷¹ https://www.medrxiv.org/content/10.1101/2021.05.19.21257334v2 (Last accessed 10 August, 2021)

⁷² https://www.medrxiv.org/content/10.1101/2021.06.13.21258859v1 (Last accessed 10 August, 2021)

⁷³ https://www.telegraph.co.uk/news/2021/08/15/europeans-mix-match-jabs-face-quarantine-

enough to come from one of few locations that the UK recognises vaccinations (the European Union or the United States).

In embracing a 'war effort' spirit, even marginal gains are worth pursuing. This makes it desirable to introduce "mix-and-match" for wider rollout (with any further testing and validation happening outside of trials).

A "mix-and-match" approach would provide greater logistical and supply chain flexibility, while most importantly potentially enhancing protection, which is of particular relevance for boosters.

Recommendation 6: Embrace "mix-and-match" doses, to enable greater supply flexibility and enhanced protection.

CHILDREN SHOULD BE OFFERED THE VACCINE, BUT WITHOUT COERCION AND AS A LOWER PRIORITY THAN BOOSTERS FOR THE VULNERABLE

The vaccination of children has consumed much recent policy and media attention. First, the UK extended its campaign to those over 16 in August, and now JCVI has advised against vaccinating those aged 12 to 15.74

In this respect, the UK is again behind many other developed nations by currently only offering the vaccine to the most vulnerable children. By comparison, the United States recommends *everyone* over 12 should get the jab.⁷⁵ Many European countries have taken a similar approach following the EU's approval of Pfizer/Bi-oNTech for over-12s in May.⁷⁶ Spain, for example, has spent over a month vaccinating teenagers. ⁷⁷

When formulating policy in relation to children, it is essential that the main focus should be on their wellbeing and the benefits they gain versus the risks. This is very much aligned to the Government's and JCVI's stance on paper.⁷⁸

The impact of Covid-19 is much milder for children than adults, with negligible risk of death (with only thirty confirmed deaths over the first year of the pandemic).⁷⁹ So, vaccination for young people is likely to have the broader aim of minimising the role of children in becoming vectors for virus transmission. If the Government allows children to access vaccines on the basis of these broader, non-medical benefits, they must be transparent about such motives and show publicly the evidence

england/ (Last accessed 31 August, 2021)

⁷⁴ https://www.bbc.co.uk/news/health-58438669 (Last Accessed 3 September 2021)

⁷⁵ https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/adolescents.html

⁷⁶ https://english.elpais.com/society/2021-08-05/spains-vaccination-drive-moves-to-teenagers-amid-fears-of-delta-strain.html (Last accessed 30 August, 2021)

⁷⁷ https://www.reuters.com/world/europe/spain-vaccinate-school-kids-two-weeks-before-term-starts-2021-06-04/ (Last accessed 30 August, 2021)

⁷⁸ https://www.gov.uk/government/publications/jcvi-statement-august-2021-covid-19-vaccination-of-children-and-young-people-aged-12-to-17-years/jcvi-statement-on-covid-19-vaccination-of-children-and-young-people-aged-12-to-17-years-4-august-2021 (Last accessed 30 August, 2021)

that is being used to drive vaccination policies focused on children, otherwise they risk undermining trust.

This is especially true since existing vaccines are less effective at stopping the spread of the Delta variant than other variants, reducing the incremental societal benefit of vaccinating children.

However, children can get sick from Covid-19 and suffer from post-Covid-19 syndrome (or "long Covid"), which could provide grounds alone to offer them (and their guardians) a choice. The risks of complications and blood clots are much higher with a Covid-19 infection, than from the vaccine, and with Covid-19 becoming endemic, there is a good case on balance for allowing children to be vaccinated.⁸⁰

An important factor for this age group is that getting vaccinated should make a contribution to reducing the spread of the virus, hospitalisations and deaths. Indeed, a new study to be published in The Lancet project that this extension of the vaccine campaign would reduce hospitalisation and deaths by 21% and 18% respectively. This would not only support wider society, but reduce the risks that politicians would impose further restrictions. Thereby vaccinating children could help avoid further lockdowns and their associated adverse effects on children through school closures, restrictions on socialising, and damage to their mental health.

However, there is a risk that the Government strays towards a coercive stance, implying or actually mandating that those who are not vaccinated would face discrimination, such as exclusion from on-site schooling. Coercion should be avoided as a heavy handed approach is simply not justified — especially since the direct health impact of Covid-19 is so low for the young.

To further ensure the process is grounded in consent, it should be made explicit that vaccines for children are being offered but not mandatory, and that there will be no disadvantages to being unvaccianted domestically. Before the vaccine is given to a child aged 12 to 15, their parents or guardians should sign a formal consent form, mirroring the process used for the HPV injections in schools. There should be clear guidance to schools that they are not to pressure or manipulate children to get the vaccine. Outside any mass school campaign (as with HPV and established UK medical principles around consent), a child should be able to get the vaccine from their doctor without parental consent⁸², so long as the doctor determines they are making a competent informed decision based on an understanding of the benefits and risks.⁸³

⁸⁰ https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3886421 (Last accessed 10 August, 2021)

⁸¹ https://inews.co.uk/news/jabs-children-under-16-deaths-long-covid-cases-reducing-infections-research-finds-1190056 (Last accessed 8 September 2021)

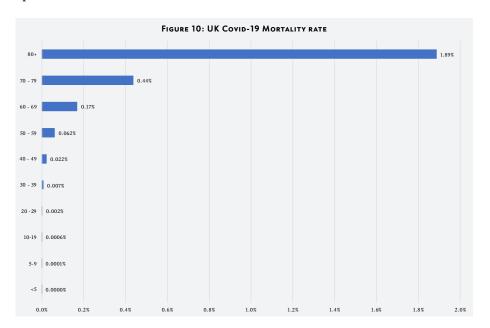
⁸² This is politically contentious and has attracted debate about the capability of a child to make such a decision. It is not in the scope of this paper to revisit precedents set over multiple court cases since 1985, Gillick v West Norfolk and Wisbech Area Health Authority. However, for any mass vaccination campaign (e.g. in schools) parental consent ought to be sought by default to maintain trust. The use of Gillick competence as a justification to vaccinate against a parents wishes could thus in practice be reserved for those who actively seek out a vaccine outside of the mass vaccination setting (and having proven their competence to make an informed decision)

⁸³ https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/994850/PHE Greenbook of immunisation chapter 2 consent 18 June21.pdf

This stance mirrors the current guidance (with additional clarification around political implications), as children over 12 are already able to get the vaccine today if they are at risk or in an immunocompromised household. According to NHS England:

"Prior to vaccination, appropriate consent must be obtained in all cases. For 12-15 year olds, this would be parental consent or the child's own consent where they have been assessed as competent to consent to vaccination (this is known as Gillick competent). Where the child is not considered competent to give their own consent and does not object to vaccination, consent must be provided by those with parental responsibility" 84

Moreover, while the vaccine should be offered to the young (including to children), this should be consistently deprioritised relative to protecting the most vulnerable groups. Age and preexisting conditions are the key drivers of Covid-19 causing fatalities, as clearly shown by fatality ratio data and the UK's mortality rate (see Figure 10). 85 86 Since current vaccines are only partially effective in preventing the spread of the Delta variant, vaccinating the young would have a reduced benefit in respect of reducing deaths and hospitalisation. Though this could change when vaccines are updated and newer, more effective vaccine technologies are developed.



The chart shows the UK's mortality rate by age group from 31 July 2020 to 31 July 2021 expressed as a percentage of the population. Mortality rates are calculated using 2019 ONS population estimates data. Data Source: Public Health England⁸⁷

⁸⁴ https://www.england.nhs.uk/coronavirus/wp-content/uploads/sites/52/2021/08/C1384-Vaccinating-children-and-young-people-frequently-asked-questions.pdf

⁸⁵ https://ourworldindata.org/mortality-risk-covid (Last accessed 30 August, 2021)

⁸⁶ https://idpjournal.biomedcentral.com/articles/10.1186/s40249-020-00785-1 (Last accessed 30 August, 2021)

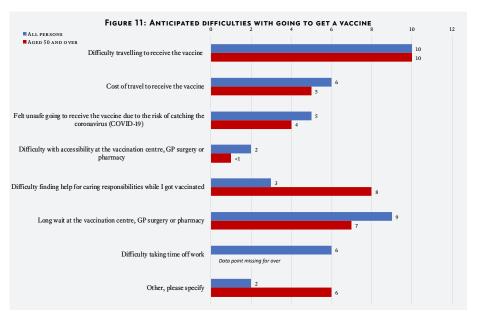
⁸⁷ https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1010508/COVID-19 monthly report July 2021-data tables.xlsx (Last accessed 10 September

Recommendation 7: Offer vaccination to children aged over 12, with parental/guardian consent. This should be undertaken without coercion or implied restrictions, mirroring the rules of other vaccines offered to children and as a lower priority initiative than boosters for the vulnerable.

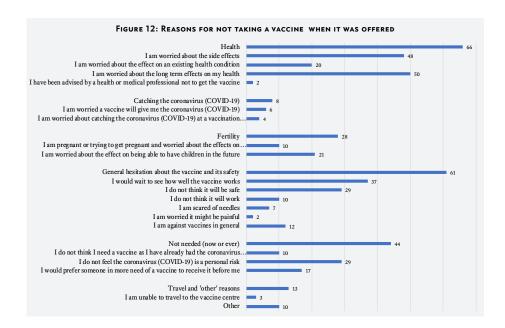
COUNTER MISINFORMATION TO ADDRESS ANTI-VAX CONCERNS AND ENHANCE TARGETED MARKETING AND DISTRIBUTION FOR THOSE WHO ARE READY AND WILLING TO BE VACCINATED BUT HAVE YET TO ARRANGE VACCINATION

Making further progress with the "Phase 1" vulnerable (and wider take-up across the population in general) requires investigation into the underlying causes for their failure to have been vaccinated so far. These range from missing and not reorganising their second appointment, to many scenarios in which they have failed to receive any jabs.

As shown in Figure 11, the main difficulties anticipated with getting the vaccine for over-50s include fear around travel, long waits and covering caring responsibilities. To help close the gap, the Government should revisit the establishment of Mobile Vaccination Units and ramp up such capability to make it more generally available on a national basis. Moreover, GP and vaccination centres should be incentivised and compensated to arrange home visits for this vulnerable group. While costly at a population-wide level, such an approach can be justified for the benefits of delivering these final maximum-impact four million doses. The productivity of this could also be increased by seeking to combine vaccinations. In Israel, for example, individuals who could not leave home were vaccinated by mobile units in which nearby residents were invited to be vaccinated at the same time.



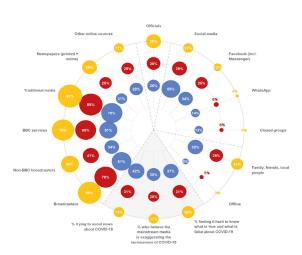
The charts show how respondents who have not yet received a vaccine reacted to: "Would you anticipate any of the following difficulties when going to get a vaccine?". The respondents were able to choose more than one option. Data Source: August ONS survey data extract.⁸⁸



The charts show how respondents "who are fairly or very unlikely to have a coronavirus (Covid-19) vaccine if offered or decided not to take a vaccine when offered" explained their "Reasons for not taking a vaccine for the coronavirus (Covid-19) if/when it was offered". Data Source: August ONS survey data extract. ⁸⁹ The respondents were able to choose more than one option. Individual response options have been grouped into key themes. A respondent is included only once within each theme, regardless of how many options were selected within that theme. Data Source: August ONS survey data extract. ⁹⁰

As for those who are genuinely hesitant about getting the vaccine, the challenge is more intractable. They cite (see Figure 12) diverse reasons, though the biggest themes are concerns around health and safety. The Government should attempt to address these worries while also remembering that the UK has consistently among the highest pro-vaccine sentiment (See Figure 15 below) and that deep concerns about the role of the state, trust in institutions and nature of vaccines will be difficult to counter.

Countering of vaccine hesitancy among the "Phase 1" vulnerable in the media is best addressed in collaboration with national broadcasters, the BBC and traditional media, which provide the majority of their news (see Figure 13). By comparison, for those under the age of thirty four, social media is the third biggest source used to obtain information about Coronavirus with 55% citing it as a source (against just 17% over the age of 55).



The chart shows the percentage of respondents who said they used each Covid-19 news source in the prior week by three age groups. Data Source Ofcom (fieldwork by Tonder 2-4 July 2021)

The battle of ideas around Covid-19 and vaccines is politically polarized and not taking place on neutral ground, with vast amounts of disinformation, much with potential links to state-sponsored by adversaries of the UK. 9192 Even before Covid-19, social media disinformation was effective in reducing vaccination coverage, and was used substantially to increase negative content by 15% in the median country. 93 Much of the content is generated by bots. 94

Russian, Chinese and Iranian sources have propagated stories that Covid-19 originated as a US bio-weapon. The safety of the mRNA Pfizer/BioNTech and Moderna vaccines were questioned by Chinese media and officials as risky or deadly and negative editorials have been spread widely by state sponsored sources such as The Chinese Global Times calling for the Pfizer/BioNTech vaccine's use to be stopped for the elderly. Of the most-retweeted content mentioning Pfizer from Russian state media, 86% mentioned an adverse reaction or were negative about the company (though Oxford/AstraZeneca and Moderna coverage has been less negative to date).

⁹¹ https://pubmed.ncbi.nlm.nih.gov/29370265/ (Last accessed 1 September 2021)

⁹² https://www.nature.com/articles/d41586-018-07034-4 (Last accessed 1 September 2021)

⁹³ https://gh.bmj.com/content/5/10/e004206 (Last accessed 1 September 2021)

⁹⁴ https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6137759 (Last accessed 1 September 2021)

⁹⁵ https://www.axios.com/coronavirus-misinformation-china-russia-iran-bdd7f45a-4212-497c-8c77-c00b4c7c2379.html (Last accessed 1 September 2021)

⁹⁶ https://www.politico.com/newsletters/global-pulse/2021/01/28/what-chinas-vax-trolling-adds-up-to-491548 (Last accessed 1 September 2021)

⁹⁷ https://www.globaltimes.cn/page/202101/1212939.shtml (Last accessed 1 September 2021)

⁹⁸ https://www.globaltimes.cn/page/202101/1212915.shtml (Last accessed 1 September 2021)

⁹⁹ https://securingdemocracy.gmfus.org/russia-china-iran-covid-vaccine-disinformation (Last accessed 1 September 2021)

The Oxford Coronavirus Explanations, Attitudes and Narratives Surveys (OCEANS) has identified a nexus of reasons why people refuse to be vaccinated: they believe that vaccines provide limited benefits and that Covid-19 is not a substantial danger to their health; they also worry that vaccines are ineffective or downright harmful. Dehind this often sits distrust of authority and the aforementioned misinformation. Countering this misinformation, that is subsequently spread among private and community groups, is likely to require a personal approach. This includes enabling conversations with family members, authority figures like doctors and nurses, and others in their community whom they trust. Specifically, it may be necessary to highlight the benefits to the individual, with respect to limiting severe disease and death, provided by the vaccine.

Recommendation 8: Counter misinformation to address vaccine hesitancy and enhance targeted marketing and distribution for those who are ready and willing to be vaccinated but have yet to make bookings.

OFFERING THE FLU VACCINE ACROSS THE WHOLE POPULATION, NOT JUST TO OVER-50S, WOULD STRENGTHEN UK RESILIENCE AGAINST WINTER SPIKES IN RESPIRATORY DISEASES, HOSPITALISATIONS AND DEATHS

The flu vaccine is recommended in other developed countries like the USA, Canada and Australia for all people over the age of six months, and specifically for entire families with young children. ¹⁰² ¹⁰³ By comparison, the NHS only offers the flu vaccine to those over 50. ¹⁰⁴

The flu vaccine is updated annually, as is expected to apply for Covid-19, and has proven an effective platform against cases, hospitalisation and deaths. ¹⁰⁵ ¹⁰⁶ According to the CDC, it reduces the risk of illness by between 40 and 60% during seasons when the circulating viruses are well matched to the vaccine. ¹⁰⁷ As for hospitalisations, a recent study showed that between 2012 and 2015 flu vaccines in adults reduced intensive care unit admissions by 82%. ¹⁰⁸

The UK manages a challenging flu season annually without the threat of restrictions upon liberty or lockdowns. Offering flu vaccines for the wider population is

¹⁰⁰ https://www.cambridge.org/core/journals/psychological-medicine/article/covid19-vaccine-hesitancy-in-the-uk-the-oxford-coronavirus-explanations-attitudes-and-narratives-survey-oceans-ii/C30FDB5C3D87123F28E351FDAAD5351A (Last accessed 10 September 2021)

¹⁰¹ https://theconversation.com/covid-vaccine-hesitancy-spell-out-the-personal-rather-than-collective-benefits-to-persuade-people-new-research-160824 (Last accessed 10 September 2021)

¹⁰² https://www.healthdirect.gov.au/flu-vaccine-faqs (Last accessed 27 August)

¹⁰³ https://www.canada.ca/content/dam/phac-aspc/documents/services/publications/healthy-living/canadian-immunization-guide-statement-seasonal-influenza-vaccine-2019-2020/NACI_Stmt_on_Seasonal_Influenza_Vaccine_2019-2020_v12.3_EN.pdf (Accessed 27 August)

¹⁰⁴ https://www.nhs.uk/conditions/vaccinations/flu-influenza-vaccine (Accessed 27 August)

¹⁰⁵ https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(11)70295-X/fulltext (Accessed 31 August)

¹⁰⁶ https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6491184/ (Accessed 31 August)

¹⁰⁷ https://www.cdc.gov/flu/vaccines-work/vaccineeffect.htm (Accessed 31 August)

¹⁰⁸ https://www.cdc.gov/flu/spotlights/vaccine-reduces-risk-severe-illness.htm (Last accessed 10 September 2021)

prompted would help minimise pressure on the NHS, discourage Covid-19-like restrictions in future if flu hospitalisation and deaths rise in a bad year.

Recommendation 9: Offer the flu vaccine across the entire population — not just to those aged over 50 and vulnerable — to build resilience against winter spikes in respiratory diseases, hospitalisations and deaths.

PERMIT PHARMACIES AND PRIVATE DOCTORS TO PURCHASE, DISTRIBUTE AND REGISTER VACCINES

Private pharmacies like Boots support the annual flu vaccination programme, distributing millions of vaccines, with qualified staff on hand. ¹⁰⁹ They were rebuffed at the start of the vaccine campaign despite this and their additional capacity has primarily sat unexploited. Now this policy is being relaxed, with the NHS in London collaborating with 100 high street branches since mid July 2021 to make the vaccine more accessible, perhaps because the inner cities lag the wider UK in adoption. ¹¹⁰

The next logical step is to permit the private purchase and distribution of vaccines (assuming they acquire their supplies from international markets, rather than consuming UK supplies). For now there would be limited demand for such a service, given vaccines can be acquired at no further expense through the NHS. However, for those not registered with the NHS, businesses travellers, and others with special scenarios (e.g. desirous of an early booster), a private jab could well appeal. It could also broaden the range of choice around vaccines, if pharmacies were permitted to use other recognised vaccines that have not yet been purchased or distributed by the UK (e.g. Sputnik and Janssen respectively)

Recommendation 10: Permit pharmacies and private doctors to purchase, distribute and register vaccines from the international market, enabling more flexible boosters, greater vaccine choice and enhanced distribution capacity.

SUPPORT EXPANDING HUMAN CHALLENGE TRAILS TO RAPIDLY TEST UPDATED AND NEW VACCINES

Human challenge trials present an ethical way to accelerate the development of updated and new vaccines. A human challenge trial means exposing individuals (with their consent and compensation) to a virus (the challenge), in a carefully controlled environment, to learn how they respond to a treatment. The first such trials were used by vaccine pioneer Edward Jenner in 1796, who exposed a patient to live cowpox virus. They have since been used to develop vaccines and treatments for typhoid, cholera, and malaria. Challenge trials provide reliable and accurate results while involving few individuals and costing substantially less than a randomised control trial. They can also be undertaken before a virus is circulating in the community.

¹⁰⁹ https://www.chemistanddruggist.co.uk/news/pharmacies-break-201920-flu-vaccinations-record-under-two-months (Last accessed 10 September 2021)

¹¹⁰ https://www.england.nhs.uk/london/2021/07/14/high-street-pharmacies-in-london-now-offering-grab-a-jab-services (Last accessed 10 September 2021)

The UK began the first challenge trial for Covid-19, involving healthy 18-30 year olds, earlier this year.¹¹¹ This came after lobbying by 1Day Sooner, who have registered over 38,500 volunteers in 165 countries.¹¹² The beginning of this study is less miraculous than it took so long. If scientists had begun human challenge trials last February we might have known the safety and effectiveness of the vaccines many months earlier, speeding up regulatory approval, manufacturing, and distribution and potentially saving hundreds of thousands of lives

Recommendation 11: Support expanding human challenge trials to rapidly test updated and new vaccines.

¹¹¹ https://www.gov.uk/government/news/worlds-first-coronavirus-human-challenge-study-receives-ethics-approval-in-the-uk (Last accessed 10 August, 2021)

A WIDER CAMPAIGN IS NEEDED BEYOND VACCINES TO PREVENT THE NORMALISATION OF RESTRICTIONS AND PROTECT LIBERTIES WHILE ALSO ENHANCING RESILIENCE

NOT ALLOWING THE TEMPORARY TO BECOME PERMANENT

In March 2020, and subsequently throughout the last almost 18 months, the Government introduced an array of extraordinary, unprecedented and extremely authoritarian measures. ¹¹³ In a time of emergency, in which the Government appeared to be taken by surprise by the speed of events, perhaps some of this was justifiable. However, now that many many months have passed it is no longer acceptable for the Government to 'rule by decree'. The use of secondary legislation to strip away liberties, including under legislation that was never intended to confer these powers to the Government, is seriously problematic.

The time has come for this matter to be reassessed. To start, the Coronavirus Act has passed its worthwhile utility. The original act, which is 348 pages, was passed in a single day. It is unlikely members of parliament had the opportunity to read it in its entirety before it became law. Additionally, the Public Health (Control of Disease) Act 1984, which has been used to introduce lockdowns, was never envisaged for this particular purpose. The Government should instead focus on developing new legal mechanisms, that include extensive parliamentary scrutiny before taking away fundamental liberties during any manner of future public health emergency.

Recommendation 12. Allow the 'Coronavirus Act' to automatically lapse and introduce new limited emergency mechanisms, including extensive parliamentary oversight, for future public health-related emergencies.

AVOID STATE-SANCTIONED DISCRIMINATION BASED ON VACCINE PASSPORTS, WHILE MAINTAINING VENUE-CUSTOMER AND EMPLOYEE-EMPLOYER FREEDOM OF CONTRACT

State imposed domestic vaccine passport requirements would amount to a serious infringement of fundamental liberties. While often presented as just a minor inconvenience for a limited range of activities, they amount to coercion and fundamentally extend the reach of government into the field of bodily autonomy. They mean denial of services, opportunities and everyday freedoms unless an individual is willing to undertake a medical procedure (even against their wishes or without consent).

Scottish First Minister Nicola Sturgeon has already announced that vaccine passports will be required, pending sign off in the Scottish Parliament (which is expected to be forthcoming). These will initially cover nightclubs, adult entertainment venues, indoor live events with over 500 attendees, outdoor live events of 4,000 attendees and any event which has more than 10,000 attendees. Wider UK policy

¹¹³ For discussion of the legal rights and process issues raised by the Government's approach to Covid restrictions, see Lord Sumption's Cambridge Freshfields Lecture: 'Government by decree - Covid-19 and the Constitution' https://www.youtube.com/watch?v=amDv2gk8aaO (Last accessed 10 September 2021)

is likely to follow, with No 10 suggesting a similar plan will be introduced in England.¹¹⁵ It is also likely that your Covid-19 status will not be demonstrable through testing or recovery from the virus, though this matter appears to be unresolved.

Rather than easing restrictions at a time when the vaccines have made the UK population much more resilient to Covid-19, this amounts to a new and substantial extension of state power, which will be challenging to unwind. Moreover, once the principle has been yielded that this is an acceptable domain for government intervention, the slippery slope to wider restrictions is not a rhetorical fallacy but a highly plausible scenario. If vaccine passports are a requirement for nightclubs, they might later be extended to restaurants, gyms, public transport or schools. If vaccine passports are necessary for Covid-19, then why not for other viruses, medical conditions or personal diagnostics?

The goalposts of policy move with less friction in times of crisis and so substantial evolution is likely. Covid-19 passports are dependent upon the continuation of somewhat arbitrary control over daily activities. For example, it is unclear why 500 attendees were chosen, with what assumptions and models (if any). Perhaps the goalposts will soon move to just 50 attendees, or to segment between different types of events. Vaccine passports open social and economic activity to torturous micromanaging from top down planners. It affirms their legitimacy to do this despite being unelected, untransparent and unaccountable to those they are now governing for a substantial portion of their lives. Once domestic passports are introduced the rules can change at a moment's notice, perhaps ruining long standing plans of deep sentimental value and interfering in what it means to live as a free person, from cultural events to birthdays, religious services, weddings and funerals.

The fear of a ratchet effect with vaccine passports is not paranoia, but reflects the most likely scenario based on other Covid-19 policy domains so far. The first lockdown was introduced as "three weeks to flatten the curve" to spread out the same number of cases and hospitalisations so that the NHS wasn't overwhelmed. This was later extended to attempting to outright reduce the number of cases with the Government's five tests. Lockdowns were then reintroduced with future waves of the virus (see figure 6), with a three-tier restrictions model being introduced in October, followed by a 2nd lockdown, the reintroduction of the three-tier system, the introduction of a fourth tier, and a third full lockdown. With the success of the vaccine campaign the Government set out a roadmap to ease restrictions aligned to the vaccination of Phase 1 group, with a June 21st "freedom day". This milestone was then postponed by a month to make further progress on the Phase 2 group, a clear change in mandate. A similar trend is likely with vaccine passports, which were first discussed in relation to nurses in ICU, care home workers, and others who may come into contact with very vulnerable people. Now vaccines passports are set to be implemented to regulate nightclubs and events.

Treating personal liberty as nothing more than a variable to be adjusted in blackbox models or at the whim of a committee is foolish and we must seek to reassert the historical notion of fundamental human freedom — on which civilisation is based — as something sacred and immensely valuable. Regardless of precise scenarios requiring domestic passports, they shift the remit of the state towards a long term "papers, please" society. One's medical records and treatments become determinants of which freedoms you retain and activities you can partake in — a dangerous precedent to impose on the nation. State imposed vaccine passports are unfair at their core as they undermine an individual's right to make their own medical decisions with informed consent. While this paper makes the case for vaccines, and for their extension, there are always uncertainties and trade offs to make, and those ought to be made by the recipient of the treatment. Informed consent is a fundamental pillar of medicine which should not be discarded.

Simultaneously, venues and customers or employers and employees should retain freedom of contract. This could entail many scenarios where a proof of vaccine is requested but in a setting of voluntary exchange between consenting adults. For example, a care home might introduce a clause into new contracts (or through a consulting process for existing employees) that requires a proof of vaccination. A more reasonable employer ought also to make provision for alternatives, like antibody or PCR tests. Similarly, this means that a restaurant might decide it requires a vaccine proof for admission, or that a customer might reject a venue that does (or does not) have these requirements. However, to impose this top-down as law is a much more significant step and undermines choice. Regardless of any polling suggesting passports could be popular, the actual revealed preferences of the hospitality industry and their customers since restrictions were unlocked are that they generally would not impose such restrictions willingly. The same is true for almost all employers and employees.

It's not clear that mandating vaccine passports would increase vaccination, particularly since the threat of vaccine passports in recent months has not led to a substantial change in the trend of younger people getting vaccinated. There's a risk, particularly among populations more skeptical about vaccination, that this level of pressure could simply encourage more hesitation.

Domestic passports also risk significant demographic-based discrimination, since vaccine hesitancy is correlated with ethnicity, religion, household types and deprivation. The Pakistani, Bangladeshi, Black Caribbean and Black African communities have had relatively low take-up of the vaccine. It's also unclear how they might apply to pregnant women and those with allergies or other medical challenges. Much of vaccine hesitancy has nothing to do with anti-vax misinformation or a lack of reason, but reflects culturally ingrained scepticism of the state. There is also a risk of excluding the technologically disenfranchised, with 19% not having access to a smartphone, particularly those earning under £20,000, the disabled and those with long term health conditions. 116 Even though this paper strongly encourages

vaccination, individuals and their children ought to retain the right to make their own judgements, balancing the benefits and risks. Efforts ought to be focused on community outreach, education and engagement, not on forcing adoption with a two-tier society.

Even if vaccine passports were broadened to account for those who have developed natural immunity, or allow for regular testing to prove one is not infected, this does not negate the fundamental challenges of government overreach, reduced choice and discrimination against the young and minorities.

Recommendation 13: Reject 'vaccine passports', a form of statesanctioned discrimination that would effectively coerce some people into undertaking a medical procedure without informed consent (but maintain venue-customer and employee-employer freedom of contract).

ESTABLISH AN ENHANCED ANTIBODY TESTING CAPABILITY TO BETTER INFORM INDIVIDUALS ABOUT THEIR LEVELS OF PROTECTION AND GOVERNMENT ABOUT OVERALL SOCIETAL RESILIENCE, WHILE REDUCING THE NEED FOR REGULAR PCR TESTS

The Government has launched a UK-wide antibody surveillance programme, with up to 8,000 tests available per day.¹¹⁷ It will be offered on an opt-in basis to those who have tested positive following a PCR test.

The antibody programme could help develop a better understanding of those who catch Covid-19 again, despite already having antibodies. This in turn could guide policy on those who do not develop a robust immune response to the virus or in response to vaccines. It also could develop insights into the level of antibodies typically required to stop somebody from being symptomatically infected again (known as correlates of protection), informing typical booster timings.

This programme could be expanded dramatically to provide more societal resilience. General availability of antibody tests could guide personalised booster shots, particularly for those who are most vulnerable or who have not developed a robust immune response. At an individual patient-doctor level, antibody testing could be used to understand patients' current antibody levels, how these relate to variants currently spreading in the UK, and to develop a more informed view of the likelihood of reinfection or severe symptoms. This also enables more informed judgements on how active or cautious individuals should be, from visiting family to voluntarily self isolating.

Antibody testing would reduce the need or demand for repeat PCR and lateral flow testing of individuals. This could be particularly appealing for families and children who have been doing multiple tests per week for months. The reduction in overall testing required could potentially make the increased antibody testing capability cost neutral, by saving time and costs elsewhere.

¹¹⁷ https://www.gov.uk/government/news/government-launches-uk-wide-antibody-surveillance-programme (Last accessed 2 September 2021)

With pan-UK surveying, antibody testing could also give the government a good understanding of societal resilience levels, providing further confidence in minimising restrictions. Further investment in testing technology, such as the testing serums (assays) for different variants and proteins could enable more nuanced analysis of variants like Delta or those that emerge later.

Recommendation 14: Establish an enhanced antibody testing capability, better informing individuals about their levels of protection and public health officials about overall societal resilience.

SIMPLIFY TRAVEL RESTRICTIONS FURTHER TO ENCOURAGE GLOBAL ECONOMIC ACTIVITY, WITH BETTER COLLABORATION WITH AIRLINES, A FURTHER EASING OF RESTRICTIONS FOR THE VACCINATED, AND A SIMPLIFICATION OF THE "TEST TO RELEASE" SCHEME

Travel restrictions previously were justified to minimise the importation of new variants and new cases. With the Delta variant now widespread and dominant in the UK, travel restrictions have diminished in value, except as an initial line of defence against new variants. Accordingly, the Government should refocus and simplify its travel restrictions to tackle new variants, while encouraging a broader return to normality.

The current range of international travel scenarios is highly complex, imposes significant additional costs on travelers, and is highly uncertain and, in areas, confused. To simplify the system, the focus should be on the red list, which should be regularly updated to manage the emergence of new variants of concern and reinforced with high quality infection control to prevent cases escaping from the system. This delivers the bulk of meaningful protection. The restrictions for red list countries should be tightened so that passengers are only permitted to visit for and return from strictly essential travel.

For all other countries, the restrictions should be simplified and eased both for the vaccinated and unvaccinated to more closely mirror the risks of domestic travel. The typical green list country has no greater risk than the UK, so all requirements should now be removed. For countries of concern where the government is hesitant about putting them on the green list, the restrictions should again be lifted, but only for the vaccinated. For the unvaccinated, they should follow the simplified and more limited restrictions currently associated with the green list. The 2 and 8 day tests, with the optional 5 day test would best be rationalised to a single 2 day test.

FIGURE 14: SIMPLIFICATION OF INTERNATIONAL TRAVEL
RESTRICTIONS TO TIGHTEN ANTI-VARIANT RED LIST
WHILE RELAXING WIDER TRAVEL

FROM	CURRENT POLICY	PROPOSED SIMPLIFICATION
Green	Regardless of vaccination status: Test in the 3 days before you travel Book and pay for day 2 test Complete passenger locator form After arrival, test on or before day 2	Remove all requirements
Amber	If unvaccinated: Test in the 3 days before you travel Test on or before day 2 and on or after day 8 Optional "test to release" scheme on day 5 10 day quarantine at home or place of stay If vaccinated: As per green list	If unvaccinated (as per current green list for vaccinated): • Test in the 3 days before you travel • Book and pay for day 2 test • Complete passenger locator form • After arrival, test on or before day 2 If vaccinated: remove requirement for tests altogether
Red	Regardless of vaccination status: Test in the 3 days before you travel Book a quarantine hotel and 2 test package Complete passenger locator form After arrival, quarantine in a hotel for 10 days	As per current guidance: + Add a restriction that visits are permitted for essential travel only

To further support ready compliance with the travel restrictions, the Government should collaborate more closely with airlines to integrate the latest rules into booking and check-in systems. It should be possible to automatically generate a Gov.UK tailored guidance page to accompany any flight booking, which is automatically updated to reflect any policy or list changes. This should be accompanied by the latest Foreign Office travel advice about visiting the target destination, to support compliance abroad too.

Where possible, the Government should also support airlines to integrate the same data sources into their own booking systems, so travellers are optimally informed before booking. This may prove challenging as it requires a change to existing systems and processes, so should not be mandated. By producing open APIs (Application Programming Interface), 3rd party booking providers (who are likely to be more nimble and less dependent upon legacy systems) like Google, Bing, Expedia, SkyScanner and Kayak could potentially add this functionality quickly. Travel booking could also integrate pre-approved testing providers and quarantine hotels at the destination and in the UK, for lower cost and simpler compliance with the restrictions.

Recommendation 15: Simplify travel restrictions further to encourage global economic activity, with better collaboration with airlines, a further easing of restrictions for the vaccinated, and a simplification of the "test to release" scheme.

ENCOURAGE VENTILATION AS A LOW-COST, HIGH-REWARD MEASURE TO HINDER'S COVID-19'S SPREAD AND INCREASE CONSUMER CHOICE THROUGH AL FRESCO RETAIL, HOSPITALITY, AND LEISURE ACTIVITY, USE OF OUTDOOR HEATERS, A TEMPORARY TAX REBATE ON ENERGY AND HEATING TAXES FOR THESE SECTORS, AND BETTER VENTILATION IN SCHOOLS AS THEY REOPEN.

While early Covid-19 guidance focused on washing hands and cleaning surfaces, it soon became apparent this advice missed a more important vector for transmission, the air. Evidence emerged that it is primarily spread through droplets and aerosols and that people primarily catch the virus through inhalation, with little evidence of fomite (touching) transmission. The Government recognised this evidence in November 2020, with guidance on how to keep homes ventilated, concluding "a room with fresh air can reduce the risk of infection from particles by over 70%". However, the core guidance and slogans did not keep up.

Following wide pressure, the Government overhauled their public health messaging in July 2021 to focus on ventilation and the "Hands, Face, Space" tagline was ditched. The official Gov.UK Covid-19 guidance now (as of publication) starts with "Meet outside, or open windows and doors for indoor visitors" Unfortunately, significant inertia has been established, with continued efforts to encourage handwashing and hand sanitizer at both public and private venues while little effort has been put into encouraging ventilation. This indicates that many are adhering to the old guidance over the new guidance.

The most significant concern in this respect is proper ventilation in hospitals. A study estimated that as many as 11.3% of patients with Covid-19 in hospitals were infected after admission. There is also speculation that mutations which make the virus more transmissible, such as those found in the Alpha variant, evolve within immunocompromised patients in hospitals. This highlights the need to focus on avoiding Covid-19 spreading through hospitals.

The hesitancy to support outdoor ventilated activity is further demonstrated by state entities such as Westminster Council looking to unwind their prior al fresco initiative by 30 September 2021.¹²⁴ Similarly, councils in Newcastle, Manchester, Durham, Northumberland, North Tyneside and Oxfordshire and Gateshead have

¹¹⁸ https://www.medrxiv.org/content/10.1101/2020.02.28.20029272v2 (Last Accessed 2 September 2021)

¹¹⁹ https://www.gov.uk/government/news/new-film-shows-importance-of-ventilation-to-reduce-spread-of-covid-19 (Last Accessed 2 September 2021)

¹²⁰ https://inews.co.uk/news/nhs-government-reveals-new-covid-guidance-ventilation-hands-face-space-ditched-1117893 (Last Accessed 2 September 2021)

¹²¹ https://www.gov.uk/coronavirus (Last Accessed 2 September 2021)

¹²² https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)01786-4/fulltext (Last accessed 10 September 2021)

¹²³ https://www.medrxiv.org/content/10.1101/2020.12.05.20241927v2 (Last accessed 10 September 2021)

¹²⁴ https://www.thecaterer.com/news/soho-al-fresco-hospitality-council-ban-parasol-heater (Last accessed 10 September 2021)

implemented or are looking to implement smoking bans outside hospitality venues. While in France, plans to ban heated terraces were announced mid-pandemic. 125

To genuinely embrace the updated guidance, ventilation should be prioritised as a low-cost but high-reward measure to hinder Covid-19's spread. The Business and Planning Act 2020 (Pavement Licences) made "made temporary provision for a fast-track process to allow businesses selling food or drink to obtain authorisation from the local authority for the placement of furniture such as tables and chairs on highway adjacent to their premises". While this was due to expire in September 2021, and has now been extended to 2022, it should to become a more permanent fixture so businesses feel empowered to invest in more costly, permanent and robust fixtures such as outdoor heaters. The emphasis on ventilation ought also to be extended across industries to other crowd-forming areas, like gyms, leisure centres, and schools where there is limited support.

Recommendation 16: Encourage, using guidance, ventilation through continued al fresco retail, hospitality, and leisure activity, use of outdoor heaters and better ventilation in schools as they reopen

Vaccines, ventilation, and continued social distancing efforts are effective ways to protect yourself against the risk presented by Covid-19. Masks also contribute, at the very least on the margins, to reducing the spread of the virus. This follows from the basic logic of a respiratory virus: the droplets, both big and small, that carry the virus are intruded by some manner of a barrier. They are unlikely to be one hundred percent effective.

Authorities initially advised against mask wearing to prevent the risk of medical professionals running out — what became known as a 'noble lie'. 128 But this likely backfired by creating a false impression about whether masks worked. Later into 2020, authorities began encouraging and then mandating the wearing of masks. This began just with cloth masks, again, to prevent health systems from being unable to access more effective surgical and respirator masks. 129 However, this is less of an issue now that global factories have been repurposed into producing masks of all standards. There is no longer a shortage of more effective masks and prices have fallen.

¹²⁵ https://www.bbc.co.uk/news/world-europe-53552526 (Last accessed 10 September 2021)

¹²⁶ https://www.legislation.gov.uk/uksi/2021/866/made (Last accessed 10 September 2021)

¹²⁷ https://www.pnas.org/content/118/4/e2014564118

¹²⁸ https://www.nytimes.com/2020/03/17/opinion/coronavirus-face-masks.html

¹²⁹ https://bmjopen.bmj.com/content/10/9/e039424.full

Since January 2021, Germany has mandated the use of surgical masks or respirator masks on public transport and stores.¹³⁰ Austria mandated respirator masks.¹³¹ Meanwhile, France recommends surgical masks.¹³²

The UK's advice, however, still only recommends 'face coverings' which, the guidance states, does not include surgial or respirator masks. ¹³³ This advice perhaps made sense in July 2020, when it was first written, and the NHS did not have stable supplies of masks. However, it no longer seems sensible to not encourage people to people, who wish to take such precautions, to wear higher quality masks. In particular, more vulnerable groups who could face a serious risk were they to become infected by the virus, should be encouraged to wear the most effective possible mask.

Recommendation 17: Encourage, using guidance, for vulnerable people to use masks with respirators, such as N95, KN95, FFP3, and FFP2, rather than less protective cloth or surgical masks.

THERE ARE VARIOUS NEW TREATMENTS THAT COULD ALSO HELP TACKLE COVID-19

There are a range of new and forthcoming treatments that could prove effective at saving lives among those who do come into contact with Covid-19.

Vaccination is the lowest cost, most effective and safest tool to tackle the pandemic. However, vaccinations are not, and nor were they ever expected to be, 100% effective. Even a 95% effective vaccine against death means that one-in-twenty will still die. There remains some whose immune systems are too weak to respond effectively and others for whom the protection does not prove effective. There are also some who are incapable, or refuse, to get vaccinated for various medical, spiritual and cultural reasons. While the utmost should be done to encourage vaccination, we should accept that some people will still need treatment.

Thankfully, there are a number of existing and emerging treatment options. The NHS' groundbreaking RECOVERY trial found that the likes of Dexamethasone and Tocilizumab do reduce deaths among severe patients, albeit to a limited extent.134 Some studies have found Remdesivir from Gilead Sciences to be effective, though potentially less so in hospitalised patients and more so earlier in the treatment process.¹³⁵

 $[\]textbf{130} \ \ https://www.bundesregierung.de/breg-en/news/decision-of-federal-and-state-governments-1841104$

¹³¹ https://www.ots.at/presseaussendung/OTS_20210124_OTS0029/anschober-ab-mitternacht-sind-ffp2-masken-und-2-meter-mindestabstand-als-praezise-antwort-auf-die-ausbreitung-der-mutationen-verpflichtend

¹³² https://www.reuters.com/article/us-health-coronavirus-france-veran-idUSKBN29Q2R7

¹³³ https://www.gov.uk/government/publications/face-coverings-when-to-wear-one-and-how-to-make-your-own/face-coverings-when-to-wear-one-and-how-to-make-your-own

 $[\]textbf{134} \quad \text{https://www.thelancet.com/journals/lancet/article/PIISO140-6736(21)00676-0/fulltext \ \text{https://www.nejm.org/doi/full/10.1056/NEJMoa2021436}$

¹³⁵ https://www.nejm.org/doi/full/10.1056/nejmoa2007764 https://www.who.int/news-room/feature-stories/detail/who-recommends-against-the-use-of-remdesivir-in-covid-19-patients https://www.newindianexpress.com/cities/bengaluru/2021/sep/06/remdesivir-reduces-mortality-when-taken-within-seven-days-of-symptoms-covid-19-study-2355028.html

There are also several monoclonal antibody therapy treatments, such as Ronapreve and Sotrovimab, that have been shown to protect against acute Covid-19 infection. The UK has only procured Ronapreve, however does not appear to have any orders of Sotrovimab, despite the maker, GSK, being a London-headquartered firm. ¹³⁶ By contrast, the European Union has ordered 220,000 doses of Sotrovimab. ¹³⁷ Most recently, AstraZeneca reported that their antibody therapy, AZD7442, reduced the risk of people developing Covid-19 symptoms by 77%. ¹³⁸ Three-quarters of the subjects had chronic conditions including ones that lower immune response to vaccines.

There are also a number of emerging antiviral drugs that are showing promise in early trials to tackle Covid-19 transmission and severity among non-hospitalised individuals. Pfizer is trialing PF-07321332/Ritonavir in a Phase II/III trial. ¹³⁹ Merck and Ridgeback Biotherapeutics's Molnupiravir recently began a Phase III trial following earlier studies demonstrating effectiveness at limiting virus transmission. ¹⁴⁰

Furthermore, a recent trial of fluvoxamine (a SSRI previously approved for treatment against obsessive-compulsive disorder and depression) was found to reduce the need for hospitalization among outpatients with an early Covid-19 diagnosis. ¹⁴¹ There are dozens of other treatments being trialled that could also prove promising. ¹⁴²

The Government should be forward-looking in procurement to ensure they are not left behind. This is a similar situation to vaccine procurement last year. Considering the high societal costs presented by the pandemic it is worthwhile to invest early to secure access to treatments.

Recommendation 18: Proactively invest in new and emerging treatments to tackle Covid-19, such as monoclonal antibody therapy drugs (i.e. Ronapreve, Sotrovimab, AstraZeneca's AZD7442), antiviral treatments (i.e. Pfizer's PF-07321332/Ritonavir), and other emerging drugs (i.e. fluvoxamine).

¹³⁶ https://www.gov.uk/government/news/first-monoclonal-antibody-treatment-for-covid-19-approved-for-use-in-the-uk; https://www.nejm.org/doi/full/10.1056/NEJMoa2035002;

¹³⁷ https://www.gsk.com/en-gb/media/press-releases/gsk-and-vir-biotechnology-announce-joint-procurement-agreement-with-european-commission-for-covid-19-treatment-sotrovimab/

¹³⁸ https://www.reuters.com/business/healthcare-pharmaceuticals/astrazenecas-covid-19-antibody-therapy-meets-main-goal-late-study-2021-08-20/

¹³⁹ https://cdn.pfizer.com/pfizercom/2021-09/First Participant Dosed in Phase 2 3.pdf

¹⁴⁰ https://www.clinicaltrialsarena.com/news/merck-ridgeback-molnupiravir-trial/ https://www.nature.com/articles/s41564-020-00835-2 https://www.merck.com/news/merck-and-ridgeback-biotherapeutics-provide-update-on-progress-of-clinical-development-program-for-molnupiravir-an-investigational-oral-therapeutic-for-the-treatment-of-mild-to-moderate-covid-19/

¹⁴¹ https://ad996812-f908-4f9a-ae29-44e0df5347d5.filesusr.com/ugd/4e5c71_cc113a0bc7e54713a4d5443140234dd5.pdf

¹⁴² https://pharmaceutical-journal.com/article/feature/everything-you-need-to-know-about-the-covid-19-therapy-trials#h-trv027

DEVELOPING THE CAPABILITY TO MORE RAPIDLY ASSESS, APPROVE, SUPPLY AND DISTRIBUTE NEW VACCINES IS NEEDED TO ESTABLISH LONG TERM DEFENCES AGAINST COVID-19 AND OTHER POTENTIAL PANDEMIC THREATS

Humanity had a vaccine that countered Covid-19 in January 2020 before its spread had reached pandemic levels. 143 On January 11 researchers published the genetic sequence of Covid-19 and two days later, Moderna had finalized the targeted sequence they would use in the vaccine. By February 24 Moderna had shipped its first vaccine batches. What was lacking was a regulatory system to facilitate rapid assessment of its safety and efficacy or the capacity to manufacture and inoculate at scale. To build robust long term defences requires a new way of thinking about vaccine development.

Last year there were many who warned of the "risks" of accelerating vaccine development. 144 145 146 147 148 149 The Trump Administration's Operation Warp Speed was criticised for the "potential to cause harm" 150 by loosening safeguards and inciting an anti-vaxx backlash. If these "go slow" advocates had been successful we would still be waiting for vaccines.

"It's just like people breaking the five-minute mile or the four-minute mile and things like that," Harvard epidemiologist, immunologist, and physician Michael Mina explained:

"People think, Oh, you'll never do faster than that. It's like, well, actually you can break it by leaps and bounds more. You just have to think differently. So many times we hear people say things like the vaccine trials could never have been sped up any faster. Well, yes, it could. Where there's a will, there's a way"¹⁵¹

The Covid-19 vaccine development experience shows it is possible to produce safe and effective vaccines much faster than previously thought. 11 months need not

¹⁴³ https://www.modernatx.com/modernas-work-potential-vaccine-against-covid-19 (Last accessed 10 August, 2021)

¹⁴⁴ https://www.statnews.com/2020/03/11/researchers-rush-to-start-moderna-coronavirus-vaccine-trial-without-usual-animal-testing/ (Last accessed 10 August, 2021)

¹⁴⁵ https://www.healthline.com/health-news/why-rushing-a-covid-19-vaccine-by-november-could-bedangerous (Last accessed 10 August, 2021)

¹⁴⁶ https://science.sciencemag.org/content/369/6506/885 (Last accessed 10 August, 2021)

¹⁴⁷ https://www.aamc.org/news-insights/here-s-why-we-can-t-rush-covid-19-vaccine (Last accessed 10 August, 2021)

 $[\]textbf{148} \quad \text{https://edition.cnn.com/} \\ 2020/09/01/\text{health/eua-coronavirus-vaccine-history/index.html (Last accessed 10 August, 2021)}$

¹⁴⁹ https://www.chemistryworld.com/news/what-are-the-risks-of-fast-tracking-a-covid-19-vaccine/4012130.article (Last accessed 10 August, 2021)

¹⁵⁰ https://jamanetwork.com/journals/jama/fullarticle/2766651 (Last accessed 10 August, 2021)

¹⁵¹ https://nymag.com/intelligencer/2021/02/harvards-michael-mina-on-covid-seasonality-vaccines. html (Last accessed 10 August, 2021)

be the best society can muster. The challenge now is to figure out how the entire process can go even faster while maintaining, or even improving, safety.

TRADITIONALLY, VACCINE DEVELOPMENT TAKES 10 TO 15 YEARS¹⁵².

The traditional process involved the slow grind of writing and rewriting grant applications, researching and developing the vaccine, preclinical animal testing, waiting for trial approvals, recruiting volunteers, three stages of clinical trials, negotiating with pharmaceutical companies, and then waiting for regulators to get around to looking at the findings for approval before manufacturing could even begin — let alone moving to undertake distribution and inoculation. These steps are normally undertaken sequentially with long delays between each stage. This is an expensive and unappealing process, especially considering the low profitability of success for vaccines (they make up just a few percent¹⁵³ of the trillion dollar global pharmaceutical industry).

Historically, vaccines generally have not been developed and made available until after the bulk of the damage from an infectious disease has been caused. ¹⁵⁴ Covid-19 has changed this model. Just over a year after the emergence of the virus pharmaceutical companies produced a range of safe and effective vaccines, including: mRNA vaccines from Pfizer/BioNTech and Moderna, viral vector vaccines from Oxford/AstraZeneca and Johnson & Johnson, and a protein vaccine from Novavax.

THE CURRENT COVID-19 VACCINES WERE RAPIDLY DEVELOPED BECAUSE OF PREVIOUS RESEARCH, NEW TECHNOLOGIES, AND A WHOLE-OF-SOCIETY FOCUS ON COMBATING THE PANDEMIC.

Scientists knew, from earlier coronaviruses research, that the spike protein on the surface of the virus that causes Covid-19 would be an ideal target for a vaccine. They had also been working on "vaccine platforms": pre-existing vaccine technology that can be rapidly adapted to a new viral threat. So when the Covid-19 genetic code was released in January 2020 they could immediately plug the spike protein into their platforms to create new vaccines.

The Oxford/AstraZeneca vaccine developed by the Jenner Institute, is an exemplar "vaccine platform." It uses a harmless chimpanzee adenovirus (the vector) that contains the genetic information for our cells to make the spike protein from the Covid-19 virus — our immune system responds by building antibodies to defend against the virus. Oxford/AstraZeneca's platform had previously been adapted and tested in humans and mice for influenza, Zika, and prostate cancer.

¹⁵² https://www.historyofvaccines.org/content/articles/vaccine-development-testing-and-regulation (Last accessed 10 August, 2021)

¹⁵³ http://www.boostoregon.org/arent-vaccines-just-moneymakers-for-pharmaceutical-companies (Last accessed 10 August, 2021)

¹⁵⁴ https://www.jstor.org/stable/2172162 (Last accessed 10 August, 2021)

¹⁵⁵ https://www.pnas.org/content/114/35/E7348 (Last accessed 10 August, 2021)

Oxford's vaccine was shown in 2017 to produce neutralising antibodies against Middle East respiratory syndrome (MERS) coronavirus in mice, and <u>later</u> in humans, using the MERS spike protein. ¹⁵⁶ So when Covid-19 emerged it was a relatively straightforward task to update Oxford's work to reflect the latest threat. Johnson & Johnson's and Russia's Sputnik V are also viral vector vaccines that use an inactivated adenovirus to deliver the spike protein.

Moderna and Pfizer/BioNTech developed synthetic messenger RNA (mRNA) vaccine platforms. mRNA vaccines contain a tiny genetic code that teaches human cells how to make a protein — the spike protein in the case of Covid-19 — to trigger an immune response. Moderna's Covid-19 vaccine was developed within just 48 hours of the sequencing of the virus in January 2020 and the first doses were manufactured within a month for a Phase I trial.

The mRNA vaccines represent a gigantic scientific leap. Before Covid-19, no mRNA vaccine or drug had been approved by regulators and many scientists were sceptical.¹⁵⁷ Now the technology potentially can be used to tackle cancer, HIV, and rare diseases. Already, mRNA technology has been used to develop the first vaccine to fully immunise against malaria.¹⁵⁸ Malaria is one of the most deadly diseases in human history: it was responsible for up to five hundred million deaths in the twentieth century and is continuing to kill around half a million people per year.¹⁵⁹¹⁶⁰

Importantly, mRNA vaccines can be more rapidly developed and produced at scale than other vaccines because they use a synthetic, computer-based process. ¹⁶¹ Scientists can effectively print the necessary genetic code, rather than relying on a biological process involving cell cultures or fermentation like traditional vaccines. This also makes it much safer and more precise than previous vaccine techniques.

In addition to previous research and emerging technologies, the Covid-19 vaccines were supported by plentiful investment, both public and private. This included substantial advanced purchase orders and manufacturing investment. This allowed the companies to construct factories and manufacture vaccines before the completion of Phase III trials without the risk of losing billions.

Moderna received \$2.48 billion from Operation Warp Speed for development and production of 100 million doses. ¹⁶² Pfizer invested \$2 billion into the project. They refused to take Operation Warp Speed cash for vaccine development to "liberate"

¹⁵⁶ https://pubmed.ncbi.nlm.nih.gov/28579232/ (Last accessed 10 August, 2021)

 $[\]textbf{157} \quad \text{https://www.statnews.com/2020/11/10/the-story-of-mrna-how-a-once-dismissed-idea-became-a-leading-technology-in-the-covid-vaccine-race/}$

¹⁵⁸ https://academictimes.com/first-vaccine-to-fully-immunize-against-malaria-builds-on-pandemic-driven-rna-tech/

¹⁵⁹ https://www.sciencedaily.com/releases/2008/01/080131122956.htm (Last accessed 10 August, 2021)

¹⁶⁰ https://www.who.int/news-room/fact-sheets/detail/malaria#:~:text=The%20estimated%20 number%20of%20malaria,of%20the%20global%20malaria%20burden (Last accessed 10 August, 2021)

¹⁶¹ https://www.nature.com/articles/nrd.2017.243

¹⁶² https://www.cnbc.com/2020/08/11/trump-says-us-has-reached-deal-with-moderna-for-100-million-doses-of-coronavirus-vaccine.html (Last accessed 10 August, 2021)

their scientists from any bureaucracy. ¹⁶³ They did, however, accept a \$1.95 billion US government contract for 100 million doses, and advanced orders from other governments.

Previously slow regulators also took a timely approach: rapidly approving trials and allowing trial phases to be undertaken simultaneously. Moderna began with humans rather than animals. Oxford combined Phase I and Phase II while Pfizer/BioNTech combined Phase II and Phase III. Additionally, rather than just taking a look at the end of testing, regulators undertook "rolling reviews" of safety, manufacturing and effectiveness. This meant that when Phase III trial results began to be released in November 2020 regulators already had substantial knowledge of the vaccines and millions of doses were being manufactured. Consequently, immensely effective vaccines could be rapidly developed, produced, and approved without sacrificing safety.

PROACTIVE REVIEW OF PANDEMIC THREATS, VACCINE PLATFORMS, HUMAN CHALLENGER TRIALS AND REFORMED REGULATORY PROCESSES WOULD ENABLE FASTER APPROVALS

There remains a significant risk of future pandemics from animals¹⁶⁶ (which host thousands of viruses that could jump to humans), lab leaks or bioterrorism¹⁶⁷. Frighteningly, the next pandemic could spread faster or be even more deadly than Covid-19. The development of "plug and play" vaccine platforms raises the opportunity to prevent future pandemics and resolves important ethical questions for regulators.

To enhance long term vaccine capabilities the UK and its allies should take the following steps:

- 1. Research viral threats, identifying families of viruses most likely to produce pandemics;
- 2. Develop vaccines in response to those viruses;
- 3. Test vaccines in animals and Phase I (safety) and Phase II (efficacy) human trials:
- 4. Invest in manufacturing capacity for two billion doses per year;
- 5. Develop logistics for distribution and rapid mass vaccination programmes;
- 6. Prepare challenge trials for new pathogens, in which volunteers are given a vaccine and exposed to the virus to test safety and efficacy; and
- 7. Reform regulatory processes to enable faster approval.

¹⁶³ https://www.cbsnews.com/news/transcript-pfizer-ceo-dr-albert-bourla-on-face-the-nation-september-13-2020/ (Last accessed 10 August, 2021)

¹⁶⁴ https://www.statnews.com/2020/03/11/researchers-rush-to-start-moderna-coronavirus-vaccine-trial-without-usual-animal-testing/ (Last accessed 10 August, 2021)

¹⁶⁵ https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31604-4/fulltext (Last accessed 10 August, 2021)

¹⁶⁶ https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3712877/ (Last accessed 10 August, 2021)

¹⁶⁷ https://theconversation.com/coronavirus-is-not-a-bioweapon-but-bioterrorism-is-a-real-future-threat-135984 (Last accessed 10 August, 2021)

One approach, proposed by Florian Krammer of the Icahn School of Medicine at Mount Sinai, is for the investment in the development of vaccines for 50-100 viruses deemed to have the highest likelihood of causing pandemics¹⁶⁸. These would be subjected to Phase I (safety) and Phase II (efficacy) testing. These individuals tested would be monitored for decades, allowing for the assessment of the protective longevity and increasing confidence in safety. Krammer claims this preparation would cost around US\$1-3 billion in total — practically nothing compared to the trillions the Covid-19 pandemic has cost the global economy. Krammer envisages that when a new virus emerges the closest existing vaccine is chosen to develop a new vaccine. This would then immediately be put into a Phase III, randomised controlled trial involving thousands of people.

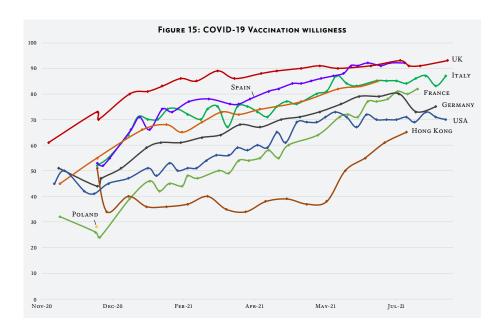
In addition to development and trials, there will also need to be substantial manufacturing capacity that is either idle or capable of being repurposed. This will need to be matched by a global logistics effort and vaccination centres to get jabs into people's arms. We will also need a system of constant global vigilance to identify new viral threats, and systems for effective testing and tracing (unlike in this pandemic) prior to a vaccine.

Finally, regulators will need to update their approach to reflect the latest technology. The relatively fast-moving UK Medicines and Healthcare products Regulatory Agency (MHRA) meant that the British were the first in the world to access the Pfizer/BioNTech and Oxford/AstraZeneca vaccines.

It is unlikely to be necessary to undertake randomised controlled trials on each new use of an existing vaccine platform — in the same way that trials which deny access to a vaccine for influenza or new Covid-19 strains are unethical. A randomised control trial should only be used when "there is genuine uncertainty about whether an untested treatment has benefits or risks that exceed those of conventional care." The justification breaks down when a treatment is known to be safe and effective while conventional care is known to have a substantial risk of death. If previous research and initial smaller trials show a vaccine to be safe and effective in the face of a pandemic which could kill millions, waiting many months for a randomised control trial could be unethical. An alternative approach is the aforementioned human challenge trials.

The final challenge will be persuading the public to take a vaccine. There will no doubt be substantial and genuine hesitancy about a rapidly developed vaccine, as was experienced in response to the Covid-19 vaccines. There are risks associated with speeding up vaccine development. These must be taken seriously and addressed by maintaining the highest of standards and carefully communicating with the public about the potential risks and benefits. Fortunately people in the UK are among the most willing globally to take a vaccine (see Figure 15), and this only rose further as the vaccines were formally announced and rolled-out.

¹⁶⁸ https://www.cell.com/med/fulltext/S2666-6340(20)30027-1 (Last accessed 10 August, 2021)



The chart shows the percentage of people who say they will take the vaccine or have already done so. Data Source: 31 August extract of data collated by YouGov¹⁷⁰

CONCLUSION

Vaccines are protecting the vulnerable and accelerating the end of the pandemic. A final boost is essential to build further resilience against Covid-19 and progress into the winter months with confidence. Resilience is attainable with a renewed focus on the "Phase 1" vulnerable, boosters, and a host of other enhancements to make the vaccine campaign more effective. With that resilience, we can and must learn to live with the virus. This means restoring all liberties that were lost as we responded to the crisis and avoiding a ratchet effect. We must not win the war but lose the peace through the enduring erosion of our freedoms.