The COVID-19 Pandemic

The Longevity Science Panel

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Introduction

The Longevity Science Panel is a group of experts brought together to advise L&G on the factors that affect life expectancy in the UK. The Panel uses a multidisciplinary approach to monitor the ever-changing influences on life expectancy, drawing on its members' expertise in social/actuarial science, epidemiology, medicine, and healthcare system development.

Each year, the Panel releases an Annual Report on a topic of interest, aiming to advise key persons across industries in the UK who have a professional interest in life expectancy, such as risk managers, planners, investors and modellers.

The 2021 Annual Report will focus on the COVID-19 pandemic and its implications for life expectancy, with a definite emphasis on the UK situation but without losing sight of the global picture. The aim is to condense a variety of useful, unbiased information into one convenient reference guide that the target audience may use to better understand and navigate their responsibilities in a domain of great uncertainty.

The Report will firstly provide an overview of the current state of the pandemic, with a focus on the UK situation within the global context. We will then summarise the development and deployment of vaccines and treatments for COVID-19, and the behavioural insights we gained from the social change brought on by the pandemic. We will devote one chapter to the economic fallout of the pandemic in the UK and its effect on pre-existing social inequalities. One chapter will focus on how COVID-19 has affected the NHS and the social care system. Lastly, we will summarise the development and adoption of new technologies in healthcare in the wake of the pandemic.

For each area of interest, we will provide a summary of the current knowledge first ("What we know"), drawing on data from a variety of academic, regulatory, governmental and media sources. We will then offer a few evidence-based insights ("What we have learnt") and outline the main challenges that lie ahead ("What are the uncertainties?"), both in the short and the long term.

Past issues of our Annual Report have looked at life expectancy through the lens of socio-economic and gender differences, international comparisons, impact of new treatments, and access to data sources. Our previous findings pointed to a significant slowing down of the long-term increase in life expectancy during the last decade and a widening of health inequalities across British society. Against this background, the COVID-19 pandemic of 2020 has been something of a black swan event whose impact on life expectancy trends is still hard to quantify, as the situation continues to evolve. However, with over 155,000 deaths from COVID-19 registered in the UK since the pandemic began, a further slowing down in life expectancy increase is likely. Moreover, the future evolution of the virus, which many experts predict will become endemic, the emergence of new variants, and the unknown long-term prospect of Long COVID raise more questions than we can confidently answer at present. The only certainty at present is that the pandemic is far from over, and the roadmap back to normality fraught with uncertainties.

On the other hand, the pandemic has also spurred a triumphant effort of scientific and medical research. Technologies that had been in development for years of decades have been rapidly boosted and readied for large-scale implementation. Access to data sources has also seen tremendous improvement over the course of just a few months and has undoubtedly contributed to this achievement. From the very beginning, the NHS has been at the forefront of the fight against COVID-19 and has demonstrated remarkable flexibility in responding to the emergency.

Executive summary

Across the world, the pandemic has brought on the largest disruption to society and the economy since World War II. Its impact has not only affected all sectors of society but also brought to our collective attention the burden of underlying socioeconomic inequalities and their repercussions on public health. At the same time, COVID-19 has been the catalyst for an unprecedented surge of collaboration and advancement in scientific research, and for the quick adoption of new technologies in healthcare. The need for decisive responses has also driven governments and public health authorities to take initiatives of a scale and reach that would have been unconceivable in normal circumstances. This, in turn, may be signalling a tidal change in society's broader attitudes towards work, public health and economics.

The main concern driving the initial emergency response was that the high transmissibility of the virus could quickly overwhelm the capacity of healthcare services. Although this did in fact occur during the first wave of the pandemic, with a fearsome cost in human lives, the NHS has since shown remarkable resilience in adapting and upgrading its systems to face the emergency – see for instance the rapid expansion of critical care facilities and the shift to telehealth technologies in hospitals and primary care. This, of course, has come at a cost. The pressure placed on a system already under pressure has been immense, and it is reasonable to predict that these changes will have an impact on public health and life expectancy in the years to come.

It is however reassuring to note that the concerted effort of policy makers to tackle the pandemic has also laid the foundation for more effective research and collaboration. Pre-existing rapid reporting system for deaths, for instance, have been swiftly redesigned to enable tracking of case numbers (and later vaccinations) across the UK. A host of cross-institutional projects, implemented during the pandemic to enable researchers to communicate more efficiently and facilitate large-scale data analysis and modelling, have undoubtedly contributed to the rapid technological developments we have observed. While the overall trend has been towards repurposing established technologies – as in the case of mobile phone or telehealth applications – even niche, largely proof-of-principle technologies have been brought into play.

The development and roll-out of COVID-19 vaccines tells us a similar story. The first clinical trial was already underway as of March 2020 and, thanks to the efforts of regulators and manufacturers to ensure speedy approval and distribution, several vaccines of various designs are now available. Mass vaccination programmes are underway – and largely proving successful – in many countries. Unfortunately, even with successful vaccination campaigns worldwide, a scenario where COVID-19 is completely eradicated appears unlikely. Several factors point instead to the disease becoming endemic, much like the flu virus, requiring periodic booster shots to maintain a sufficient level of protection within the population. The emergence of new variants is another concern, although we are now in a position of advantage compared to pre-pandemic times, thanks to better epidemiological monitoring systems and vaccine technologies that can be quickly adapted.

Similarly quick advancements have occurred in the development of treatments for COVID-19. Eighteen months into the pandemic, we can now count on an arsenal of five treatments, not developed ex novo but rather repurposed off-label, that have proved to be effective to some degree, with many more still being trialled.

The UK economy shrank by nearly ten percent in 2020 in the wake of the pandemic. This ushered in a dramatic rise in unemployment, which the government's support measures could only in part mitigate. Unsurprisingly, the pandemic has exacerbated historical and persistent inequalities by gender, age, ethnicity and income. Not all workers were affected equally and the worst impact was felt in historically low job-security sectors such as retail and hospitality. Lack of access to remote working, for instance, has undoubtedly been one driver of higher mortality among pink- and blue-collar workers.

Women, children, low earners and certain ethnic groups have borne the largest economic cost of the pandemic. COVID-related health inequalities have also become evident in terms of mental health, employment status, education, and future financial prospects – not to mention the still largely unexplored issue of Long COVID. Men have experienced higher mortality than women, otherwise the same vulnerable groups have also experienced higher mortality rates. While the lockdowns have had the positive short-term effect of reducing the number of accidents and the incidence of infectious diseases such as flu, unhealthy behaviours such as alcohol consumption have increased. In addition, the NHS is now facing a massive backlog of routine care. Until this is cleared, delays in diagnosis and treatment will likely lead to more deaths from major causes of mortality such as cancer or cardiovascular disease. The combined effect of all these factors on the health and life expectancy of UK citizens will only become clear over time. Immediate concerns are the NHS's ability to withstand pressure in the coming Winter season and a worsening of health inequality once the government's support initiatives are eventually phased out.

Aside from financial considerations, the pandemic has also had a profound psychological impact. Lockdowns and social distancing have severely disrupted the usual rituals and patterns of social interaction. Faced with a looming threat, uncertainty and forced isolation, and cut off from the informal support networks of family and friends, many households have become pressure cookers. Mental health problems have spiked during the pandemic, and so has domestic abuse, disproportionately targeting women and children.

Despite this, the British public has largely been supportive of the government's initiatives due to a widespread sentiment that major threat such as COVID-19 would necessarily require a drastic response. Social and psychological sciences have played a major role in advising policy makers during the pandemic, and several different behavioural management strategies have been tested. Three-way communication between policy makers, the public and scientists has been a constant feature during the pandemic and has certainly proved effective, as shown by the success of the vaccination campaign in the UK. However, there are limits to what a democratic government can achieve through behavioural management alone; at the same time, the dangers of misinformation have become painfully evident, as exemplified by the rise of no-vax movements worldwide. At present, it is probably too early to tell what shape the "new normal" will take and whether the new behaviours adopted during the pandemic will become established in the long term or not.

For all its devastating impact the pandemic has also tapped a previously unimagined reservoir or energy, flexibility, and proactive approach to challenges. This has come through many times over and allows for some cautious optimism, in spite of the many challenges that remain.

Current pandemic position

One of the unique features of the COVID-19 pandemic is that it may have been the first one in human history to be truly "global", both in its impact and in the concerted reaction it elicited from political, scientific, and advisory bodies, as well as the media. The pandemic has put to the test the strengths and weaknesses of a globalized, interconnected world, causing enormous socioeconomic disruption. At the same time, it has also focused the efforts of the scientific, medical, and pharmaceutical sectors to an unprecedented degree. Large efforts have been undertaken to facilitate collaboration and information sharing, while technologies pertaining to epidemiology, diagnostics and telehealth have seen a massive development acceleration and rapid uptake by health care providers, including the NHS.

Over one and a half year since the initial outbreak in China, there seems to be a creeping sense among the British public that COVID-19 is no longer breaking news. With immunisation programmes well underway and social restrictions easing, the collective attention is inevitably turning to what the "new normal" will look like as COVID-19 is poised to become a permanent feature of the global landscape. However, we should stress that complacency at this time would be extremely dangerous. Far from being "old news", COVID-19 is still rampant in many parts of the world and even more economically advanced nations such as the UK cannot consider themselves safe. The global character of the pandemic cannot be overstressed: in a highly connected world, no one can be safe until everyone is safe.

This section will start by providing a timeline of the pandemic so far. We will then focus on the emergence of new variants, the current projections on the future behaviour of SARS-CoV-2 in the population, and the implications of long COVID, particularly in terms of its impact on health care provision. The specific challenges that new variants pose to treatment and immunisation will be discussed in the respective sections.

What we know

Timeline of the pandemic

First wave and subsequent waves

Figure 1 shows the number of cases, admissions and deaths on the log scale over the course of the pandemic, up to the beginning of September 2021. Figure 2 shows the cases, admission and deaths by age group from the end of April 2020 to the beginning of September 2021. It can be seen that since February 2021, people of working age have dominated the admissions to hospital, probably because of the lower vaccination rate in this group compared to the elderly.

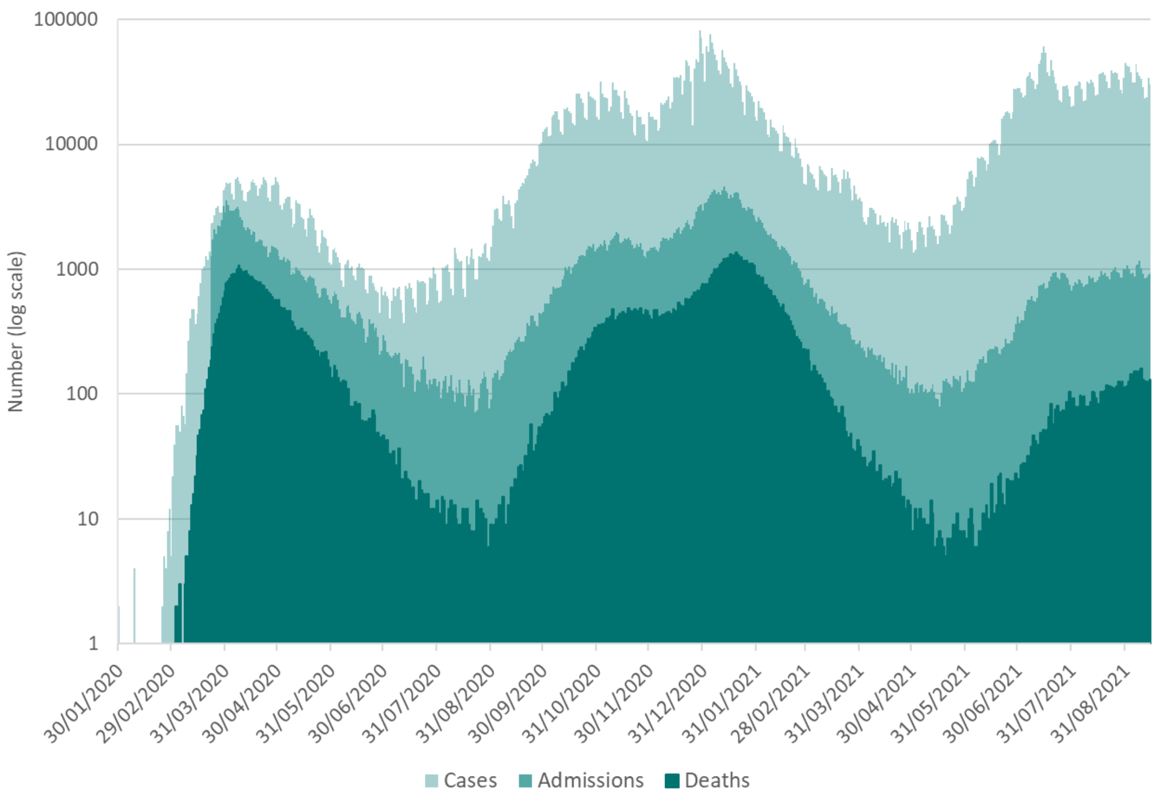

Figure 1. Numbers of COVID cases, admissions, and deaths within 28 days of a positive test in the UK.

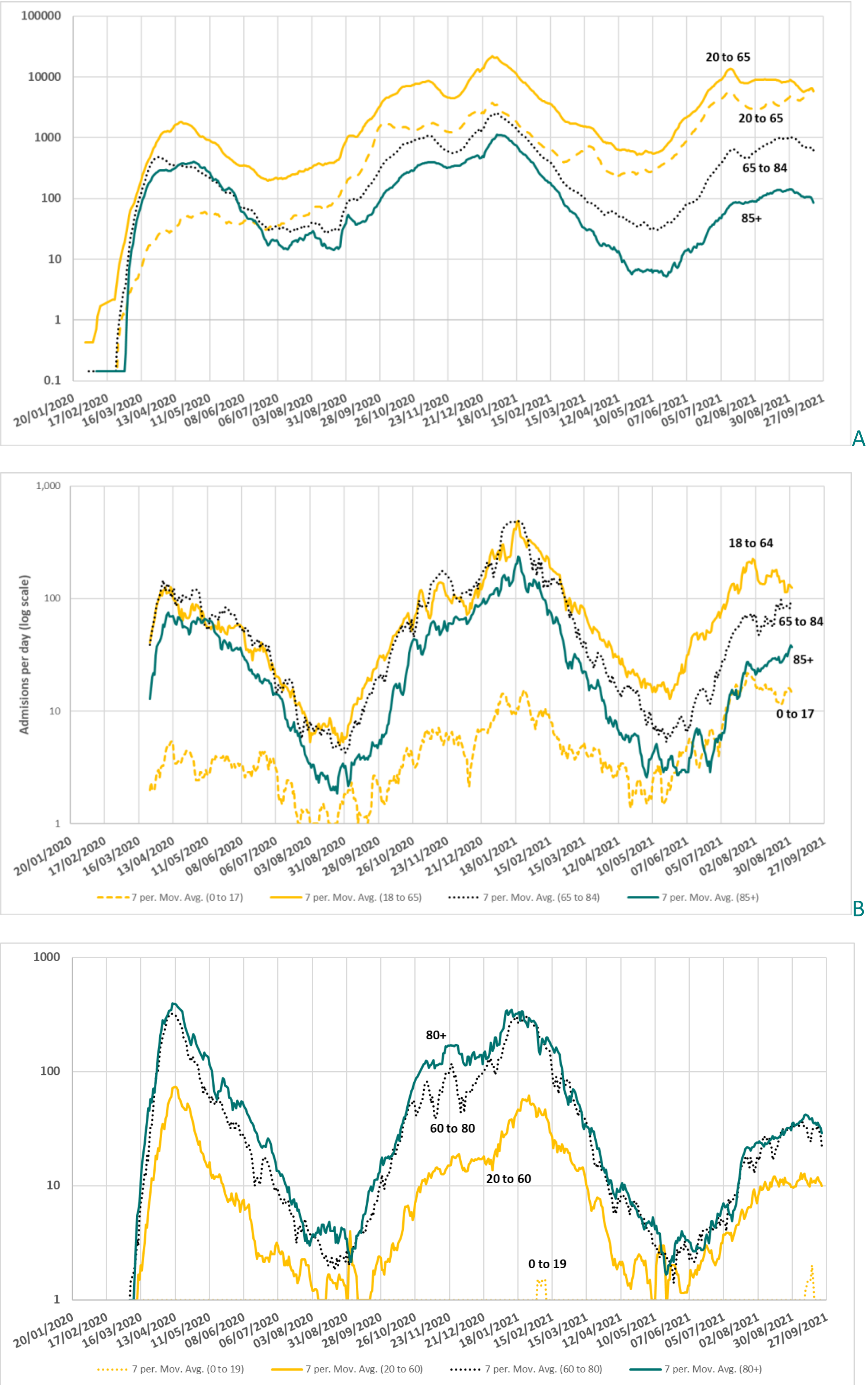

Figure 2. Three graphs showing the numbers of cases (A), admissions (B) and deaths (C) by age group. Note: the age bands for the deaths differ slightly due to the aggregation of the source data.

Figure 3 shows the proportion of admissions accounted for by age group. It can be seen that the first wave was dominated by admissions in the 65 to 84 year-old age group, but that in the Autumn admissions were dominated by admissions in people of working age (18 to 64 years) as the alpha variant emerged. At the peak of Winter, admissions were again dominated by the 65 o 84 year-old age group, but from February 2021 the proportion accounted for by those over 85 fell dramatically. This probably reflects the demographics of the vaccination programme, which called for older people to be vaccinated first. From June 2021 onwards, the proportion of the 65 to 84 year-old patients and those of working age have begun to converge. This probably reflects the continuing progress in vaccination in the working age group.

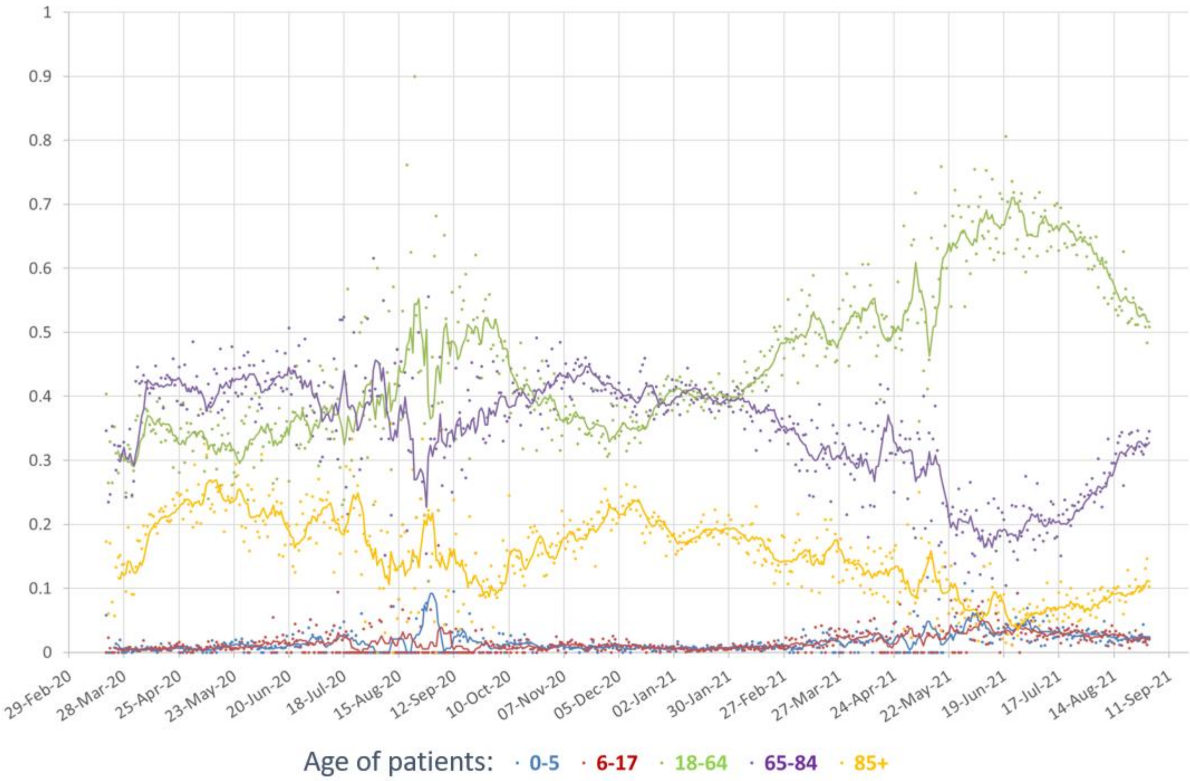

Figure 3. The proportion of COVID-19 admissions accounted for by each age category.

Excess deaths and COVID-19

Not all deaths with COVID-19 on the death certificate could be considered excess deaths, since they may have occurred in debilitated people who would have died in any case. **Figure 4** shows the excess deaths by week along with the number of deaths with COVID-19 on the death certificate (*Excess Mortality in England*, 2021). The correlation between the excess deaths recorded and the number of deaths mentioning COVID-19 on the death certificate is 89%, suggesting that the bulk of the excess deaths are in fact accounted for by COVID-19.

Population based surveys of infections

Several important population-based surveys have provided key evidence and information that have fed into decision-making in the management of the pandemic.

The Coronavirus Infection Survey is run by the Office for National Statistics, Oxford and Manchester Universities, Public Health England, The Wellcome Trust and two commercial organisations, IQVIA and the Lighthouse Laboratory. It samples the population and tests for the coronavirus to give estimates of the true infection rates (ONS, 2021a).

The Real-time Assessment of Community Transmission (REACT) Study was commissioned by the Department of Health and Social Care and is being carried out by Imperial College London in partnership with Ipsos MORI and Imperial College Healthcare NHS Trust. Each month, over 150,000 people in England are randomly selected and sent nose and throat swabs for an antigen test that could detect current infection. In addition, over 100,000 volunteers are sent antibody tests to measure the prevalence of prior infection and immune response.

The ZOE COVID Study is an international study based on a smartphone app that users can use to report symptoms. It has generated a great deal of information and insights into patterns of symptoms and symptom prevalence. Initially established by health science company ZOE, the study is now supported by grants from the Department of Health and Social Care (Zoe Company, 2020).

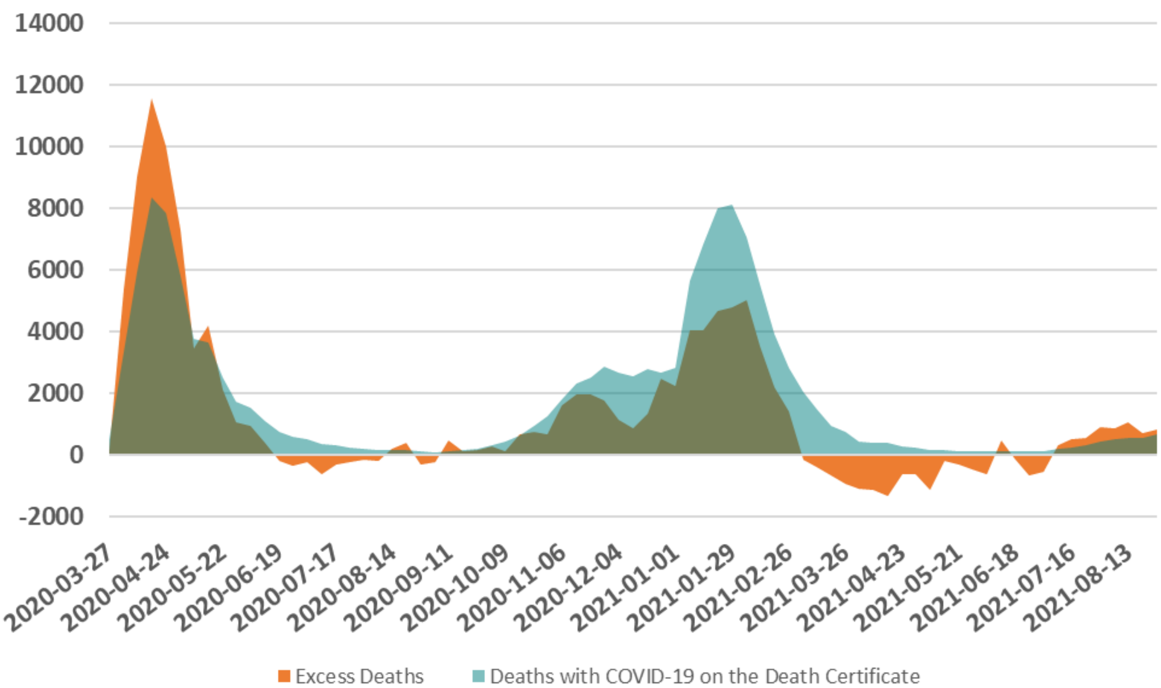

Figure 4. Excess deaths by week during the pandemic with deaths that have COVID-19 on the death certificate. Excess calculated using the previous 5-year average (2015 – 2019) monthly death rate as reference. (Excess Mortality in England, 2021).

Impact on life expectancy

The report "Health Profile for England 2021", released in September 2021, states that life expectancy at birth fell by 1.3 years for men and 0.9 years for women in 2020. However, this needs some interpretation. The life expectancy calculation used was a 'period' life expectancy, which simply projects the mortality rates experienced in 2020 by age forward for the remainder of a person's lifetime. It takes no account of how mortality rates might change in the future, and it would be reasonable to assume that the excess mortality experienced in 2020 will not persist into the future at the same magnitude.

The Office for National Statistics life-tables are averaged over a three-year period, and the September 2021 release covering 2018 to 2020 suggested no change in the life-expectancy at birth in the UK for women and a fall of only 7 weeks for men, despite also being a period life-expectancy (Office for National Statistics, 2021e). This results from averaging over three years, including two non-pandemic ones.

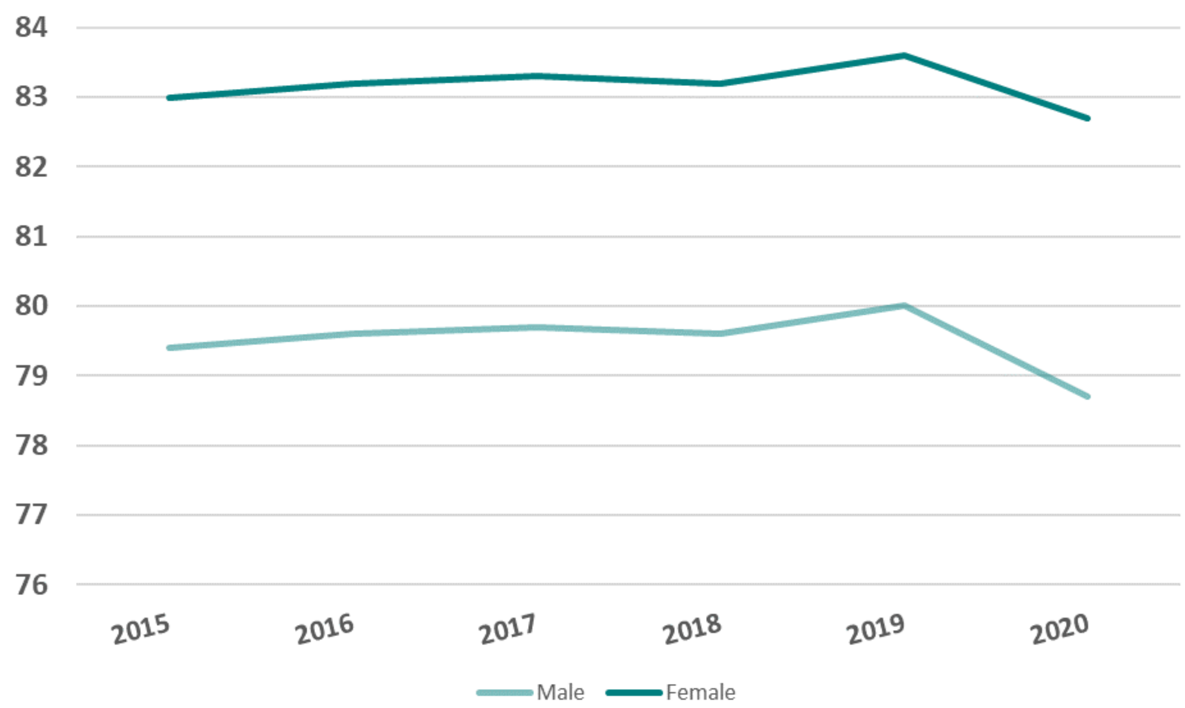

Figure 5. Period life-expectancy at birth for England between 2015 and 2020 (Public Health England, 2021f).

On the other hand, cohort life expectancies incorporate expected changes in mortality rates going forward. Over the past decade, as mortality improvement rates have stagnated, so estimates from the pensions and insurance industry of mortality improvement have declined. **Figure 6** shows the cohort life expectancy aged 65 for men and women in defined benefit schemes in the UK, generated using the Continuous Mortality Investigation (CMI) projections model. Life expectancies fell from 2012 through to 2018 as estimates of short to medium term mortality improvement rates fell (Continuous Mortality Investigation, 2021). However, it can be seen that the life expectancy in 2020 barely changed in relation to the previous two years. This is based on an assumption that the increase in mortality rates experienced in 2020 is a short-term phenomenon and that mortality improvement rates will gradually return to a commonly used assumption of 1.5% per year.

There are still too many unknowns on the impact of the SARS-CoV-2 virus on future mortality rates to be able to estimate life expectancy changes with the level of confidence we had before the pandemic. There may well be long-term consequences of surviving infection with the virus that impact on future mortality rates and that we are unaware of. The Public Health England period life expectancy estimate of a 1.3 year fall in life expectancy at birth for men, and 0.9 years for women, is a reasonable worst-case scenario for the change in estimates.

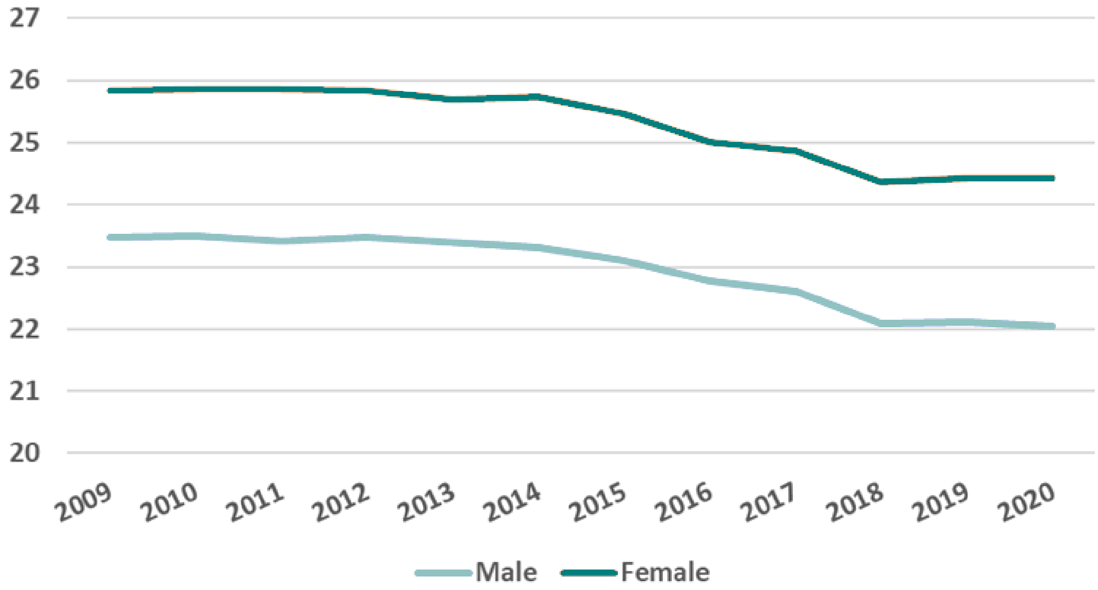

Figure 6. CMI projection model estimates of cohort life-expectancy at age 65 in defined benefit schemes with an assumption of a 1.5% long-term mortality improvement rate. (Continuous Mortality Investigation, 2021).

Risk factors

Severe illness from COVID-19 is defined primarily by dyspnoea (difficulty breathing) leading to progressive respiratory failure and Acute Respiratory Distress Syndrome (ARDS), sometimes accompanied by multi-organ failure as a consequence of unregulated immune response. Efforts started in the early stages of the outbreak to identify and profile the risk factors for severe illness from COVID-19.

During the first wave of the pandemic, the NHS used the QCovid® risk prediction model developed by the University of Oxford in an early effort to identify high-risk groups as part of the COVID-19 Population Risk Assessment programme (Clift et al., 2020; NHS Digital, 2021). Some of the main predictors of severe illness, hospitalisation and mortality include:

- Old age
- Immunosuppression (whether due to pre-existing illnesses or as a consequence of medical treatments affecting the immune system, such as chemo- or radiotherapy)
- Diabetes
- Obesity
- Chronic heart disease
- Chronic kidney disease
- Pre-existing, severe respiratory illness, such as asthma or Chronic Obstructive Pulmonary Disease (COPD)

The stratification of risk factors across the population is complex, due in no small part to the interaction between individual factors. Moreover, the impact of certain factors directly correlates with their severity (e.g. Stage-5 chronic kidney disease is associated with a higher risk than Stages 1-4) whereas other factors may affect one gender more than the other.

The QCovid® validation study found that patients in the top 5% for highest predicted risk accounted for approximately 76% of total COVID-19 deaths, while patients in the top 25% accounted for approximately 96% of deaths (Clift et al., 2020). Several studies have examined risk factors for death after infection with COVID-19 and many features associated with an increased risk of death have been identified. By far the most substantial of these is age with the risk of death increasing about 10% for each year of age. Many of the other factors are significantly correlated with age, and so it is important to adjust the estimates of increased risk for these correlations (Williamson et al., 2020). The more important risk factors are indicated in **Figure 7**.

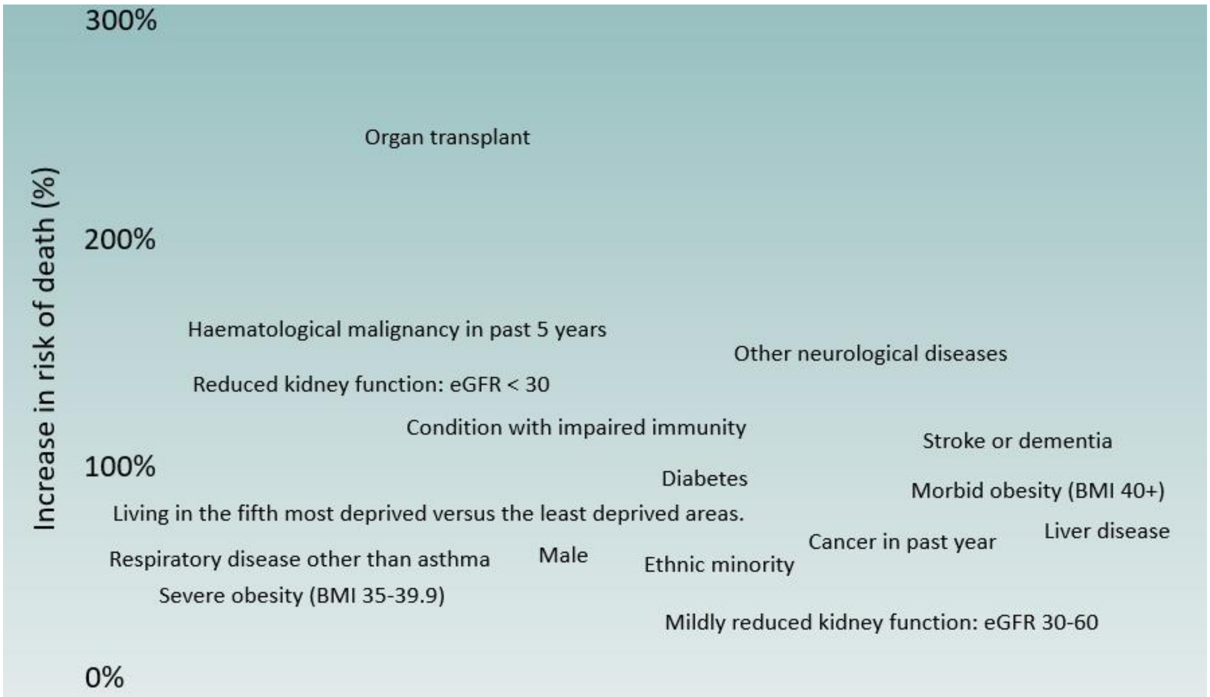

Figure 7. Risk factors for death from COVID-19. The position of the text vertically indicates the approximate increase in risk (Williamson et al., 2020).

Notably, hypertension was associated with a reduced risk after adjusting for correlated risk factors, as was being a current smoker.

It is also worth mentioning that several COVID-19 risk factors – obesity, cardiovascular disease and diabetes above all – are to a large extent preventable and have long been the targets of public health initiatives. There is already a wealth of evidence supporting the notion that these conditions are a reflection of socioeconomic inequalities, as they tend to have higher prevalence, and a heavier burden of disease, among people from disadvantaged backgrounds, with obvious implications for life expectancy. An overview of the evidence is provided in previous issues of the Longevity Science Panel Annual Report that focused on life expectancy by socio-economic group and mortality trends in developed countries (Longevity Science Panel, 2011, 2018).

Basic reproduction number (R0)

This is used to measure the transmission potential of a disease, by giving a measure of the maximum potential rate of spread in a given population. It is measured as the expected number of secondary infections produced by a typical case of an infection, in a population where everyone is susceptible, and assuming that no other individuals are infected or immunised. R0 is affected by biological, socio-behavioural and environmental factors and therefore depends on:

1) the transmissibility (probability of infection when a susceptible individual comes into contact with an infected individual)
2) the average rate of contact between the susceptible and the infected individual
3) the duration of infectiousness

R0 can describe the spread of a disease at the start of an outbreak and help determine whether an outbreak will evolve into an epidemic. If R0 is larger than 1, the number of infected people will increase exponentially, and this will result in an epidemic or a pandemic. If R0 is less than one, the disease should, in theory, disappear. However, in the real world , at least repeated reintroductions from other populations might prevent the disease from disappearing completely. In a viral pandemic such as SARS-COV-2, variants of the original strain are produced as the virus replicates. R0 values can be calculated for each of these variants, in order to make comparisons and adjust public health policies accordingly.

It is worth noting that R0 is not sufficient to fully describe how a virus propagates across a population unless accompanied by a measure of its dispersion, i.e. whether it spreads in an even manner or in bursts. In the case of SARS-CoV-2, in particular, there is a wealth of empirical and experimental evidence indicating that the virus is over-dispersed, in that it tends to spread in a non-linear manner. We will explore this in further detail in the **Transmission routes** section of this chapter.

The original strain of SARS-CoV-2

One of the first estimates of transmissibility of the original strain detected in China was made in January 2020, based on data collected from the World Health Organization Disease Outbreak News reports, bulletins issued by the Chinese National Health Commission and the Wuhan Municipal Health Commission, as well as a recent study published in The Lancet (Majumder & Mandl, 2020). Modelled R0 estimates varied between 2.0 and 3.1 with a mean of 2.5 becoming the commonly used and quoted figure.

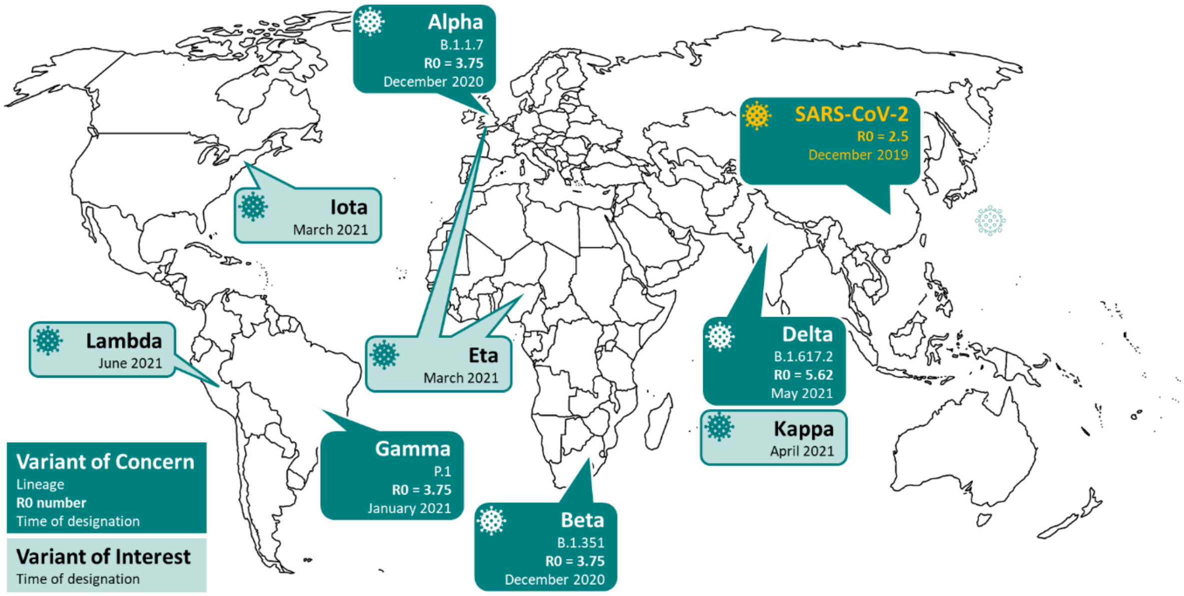

Figure 8. Origin, R0 and time of designation of VOCs and VOIs (as of 30 June 2021).

Kent variant (Alpha)

In November 2020, a novel variant was detected in Kent, with limited spread to other areas of London, Anglia, and Essex (Public Health England, 2020b). Other terminology used since then includes VOC-20DEC-01 and lineage B.1.1.7 but the variant is now known as Alpha according to the new WHO naming system (World Health Organisation, n.d.).

One study carried out during the lockdown in England in November/December 2020 estimated the R value of the Alpha variant to be approximately one and a half times higher than other circulating strains (Vöhringer et al., 2020). This would lead to a **R0 value of approximately 3.6**. This finding is consistent with another report published later in December 2020, which, based on multiple behavioural and epidemiological data sources with statistical and dynamic modelling, estimated the Alpha variant to be between 43% and 82% more transmissible then pre-existing variants (Davies et al., 2021).

This increased transmissibility could be linked to the fact that the Alpha variant has a large number of genetic changes in the spike protein, the most concerning one being mutation N501Y. This mutation affects key contact residues within the receptor-binding domain (RBD) and has been identified as increasing binding affinity to human ACE2, therefore improving transmissibility of the virus (Public Health England (technical briefing 1), 2020).

South African variant (Beta)

Based on findings from one rapid scoping review, the Beta variant has a similar R0 to the Alpha variant. The Rt for this variant was estimated at 1.55, meaning it is 55% more transmissible than the original strain and gives **an R0 of about 3.9** (Curran et al., 2021).

Brazilian variant (Gamma)

An early report found that the Gamma variant could be 1.4 to 2.2 times more transmissible than non-P.1 lineages (Faria et al., 2021). This results in an **R0 of 3.5 to 5.5.** It seems to be commonly accepted that the Gamma variant has a similar R0 to the South African one (3.75).

Indian variant (Delta)

One of the recent technical briefings produced by PHE has shown that the secondary attack rate of the Delta variant is 12.4% compared to 8.2% for the Alpha variant. This is a 51% increase in infectiousness which gives an **R0 of 5.625** (Public Health England, 2020b). As of 11 June 2021, the Delta variant is now the dominant variant in the UK. Early data suggest that it has a higher secondary attack rate and can result in an increased risk of hospitalisation, compared to the Alpha variant (Public Health England, 2021c).

Frequency of new variants

Early estimates based on the analysis of viral sequence data and sampling dates have suggested that SARS-Cov-2 evolves at a rate of about 1.1×10^{-3} substitutions per site per year, which is in the same order of magnitude as other known coronaviruses (Duchene et al., 2020).

Table 1 is a summary of the current variants of concern (VOC) and variants under investigation (VUI) at the time of writing this report. The Lambda variant was given VUI status on 23 June 2021 based on global spread and a novel combination of mutations (Public Health England, 2021d).

Table 1. Summary of VOC and VUI 21 June 2021 adapted from SARS-CoV-2 variants of concern and variants under investigation in England Technical briefing 17

WHO nomenclature	Lineage	Designation	Status	R0 number
Original strain		SARS-CoV-2		2.5 (Majumder & Mandl, 2020)
Alpha	B.1.1.7	VOC-20DEC-01	VOC	3.75 (Vöhringer et al., 2020)
Beta	B.1.351	VOC-20DEC-02	VOC	3.75 (Curran et al., 2021)
Gamma	P.1	VOC-21JAN-02	VOC	3.75 (Faria et al., 2021)
Delta	B.1.617.2, AY.1, AY.2	VOC-21APR-02	VOC	5.625 (Public Health England, 2021b)
Zeta	P.2	VUI-21JAN-01	VUI	
Eta	B.1.525	VUI-21FEB-03	VUI	
	B.1.1.318	VUI-21FEB-04	VUI	
Theta	P.3	VUI-21MAR-02	VUI	
Kappa	B.1.617.1	VUI-21APR-01	VUI	
	B.1.617.3	VUI-21APR-03	VUI	
	AV.1	VUI-21MAY-01	VUI	
	C.36.3	VUI-21MAY-02	VUI	
Lambda	C.37	VUI-21JUN-01	VUI	

What we have learned

Transmission routes

COVID-19 is primarily transmitted via airborne droplets and aerosol (i.e. droplets nuclei smaller than 5 µm), and direct contact with infected individuals. Contact with droplet-contaminated objects (fomites) occurs but is less important than originally thought. There has been an ongoing debate on which route is predominant in human-to-human transmission, and whether there is a correlation between infection route and severity of illness. From early on, public health initiatives have acknowledged the fact that proximity, confined environment and frequency of contact are the main drivers of transmission (K. Sun et al., 2021), and taken a broad, precautionary approach aimed at disrupting the chain of transmission across all routes, through the promotion of adequate ventilation, enhanced cleaning and disinfection, use of personal protection equipment (PPE) and social distancing.

One of the reasons that make it difficult to weigh the relative importance of different transmission routes is that while viral RNA can be consistently detected in air and surface samples, this does not directly relate to the presence of active, infectious virus. In the case of fomite transmission, for instance, viral genetic material can persist on contaminated surfaces for up to seven days. This may have initially led to overestimating the importance of this route of transmission; in fact, there are indications that the virus degrades rapidly on exposed surfaces in real-world conditions, and that fomites probably lose most of their infectious viral load after about two days (Matson et al., 2020). At present, there is a growing consensus that transmission by fomite may be less important than initially thought, and that airborne transmission is in fact the predominant route.

With airborne transmission, the virus is carried by droplets and aerosol expelled by an infected individual through breathing. Because of their larger size and weight, droplets tend to travel a relatively short distance before depositing on the ground or other surfaces and are therefore a driver of close-contact and fomite transmission. Aerosols, on the other hand, due to their small size and weight are more susceptible to airflow and can spread the virus over a wider radius around an infected person, which is especially problematic in confined spaces.

This is borne out by the empirical observation that SARS-CoV-2 transmission is exponential over time and tends to occur in clusters (Adam et al., 2020; Lau et al., 2020). There have been several examples in which a high number of cases and deaths has occurred in a confined geographical area within a short time – one notorious case was the outbreak centred around the northern Italian town of Bergamo during the first wave. Conversely, we have also seen locales with comparable environment and population experiencing different outcomes (Endo et al., 2020), which has often made it difficult to model the evolution of outbreaks based on past experience.

There is now accumulating evidence that a large proportion of COVID-19 transmission may be effected by a relatively small number of infected people, the so-called super-spreaders, leading to localised hotspots of over-dispersion. Unsurprisingly, super-spreading events are facilitated by known environmental risk factors such as crowding, confined spaces and close proximity (Cevik et al., n.d.), all of which amplify the effect of airborne transmission.

These findings have informed the increasing emphasis placed on improving ventilation of indoor spaces by public health guidelines, both nationally and worldwide (Health and Safety Executive, 2020; World Health Organisation, 2020a). The rationale is that enhanced ventilation would reduce the aerosol-borne viral load per unit volume of air and thus the distance at which any one infected individual can spread the virus. This would work synergistically with other behavioural measures targeting airborne transmission such as face coverings and social distancing.

As of August 2021, a breakthrough study published in Nature has established a correlation between route of transmission and severity of illness (Port et al., 2021). Airborne transmission appears to be associated with more severe cases, as the viral load is deposited directly within the host’s respiratory tract; droplet size also appears to have an impact, because inhaled aerosols, which carry a highly concentrated viral load, can penetrate further into the lower respiratory tract, resulting in higher risk of early and/or severe respiratory symptoms. Large droplets, on the other hand, are more likely to deposit in the upper airways, and the resulting illness less likely to feature massive pulmonary involvement. The study also found that the route of infection may indirectly affect further transmission, as severe illness tends to correlate with early viral shedding. It should be noted that the

Nature study was carried out on an animal model and that such a correlation in human has yet to be established. However, the findings are consistent with previous observations on other respiratory viruses and will undoubtedly provide a springboard for further research.

Mutations and virus behaviour

All viruses mutate as they replicate. RNA viruses, such as the SARS-COV-2, are more susceptible to mutations as they use an error-prone enzyme called RNA-dependent RNA polymerase. However, it has been suggested that, given that it contains an enzyme that corrects potentially fatal copying errors, SARS-CoV-2 has a lower mutation rate compared to other RNA viruses such as influenza or HIV (Manzanares-Meza & Medina-Contreras, 2020).

Most of the mutations will have little or no impact on the behaviour of the virus but, occasionally, a mutation will configure a survival advantage e.g., transmissibility, virulence or evading the immune system. Theoretically, viruses tend to develop mutations that increase their transmissibility but decrease their virulence over time. The rate at which these advantageous mutations develop is linked to infection rate, since a high infection will lead to a high mutation rate, which, in turn, increases the risk of variants with advantages occurring. In the real world, however, the evolutionary pressure towards lower virulence (and therefore lower mortality) is weaker than the pressure towards higher infectiousness. With COVID-19, the vast majority of COVID-19 deaths occur after the infectious period is over, therefore any evolutionary pressure from people dying while still infectious would be negligible.

Currently, the evidence broadly suggests that the selective pressures influencing the evolution of SARS-CoV-2 are in favour of increased transmissibility. This is reflected, for instance, by mutations in the genetic domain coding for the spike protein that SARS-CoV-2 uses to bind to ACE2 receptors on the host’s cells (much like a key inserting into a lock) prior to entry and infection. One of the first such mutations thought to arise was the D614G mutation. It is unclear whether this mutation arose independently in many different geographical locations (suggesting an adaptive benefit) or whether strains of SARS-CoV-2 that started the initial outbreak already contained the D614G mutation. Recent modelling studies have shown some evidence suggesting that viruses containing the mutation did have increased transmissibility, but the results are still inconclusive (Volz et al., 2021).

Another mutation, discovered in animals from mink farms in the Netherlands and Denmark, was Y453F, located in the receptor binding domain of the spike glycoprotein. It is thought that this mutation enabled the virus to have an increased binding affinity for mink ACE2. This suggestion that SARS-CoV-2 can infect animals is concerning, since continued evolution of the virus in animals could lead to further transmission from animals to humans and between animals (European Centre for Disease Prevention and Control, 2020).

Stronger evidence to suggest that SARS-CoV-2 is developing increased transmissibility as it evolves is found in the Alpha variant. When this variant was discovered, it had already accumulated 17 mutations, 8 of which were in the spike glycoprotein. One of these spike glycoprotein mutations found in the receptor binding domain is called N501Y and is thought to increase the affinity of the virus for ACE2 in humans. Studies have shown a 56% increase in transmissibility of variants with this mutation (Davies et al., 2021). Unlike the D614G mutation, the N501Y mutation was not present in the original genome sequence; it developed as the pandemic progressed and it may have driven Alpha to become the dominant variant in the UK at the time.

As the immunity against the virus grows in the infected population, so does the evolutionary pressure for the virus to keep evading the immune system. Apart from the N501Y mutation to the spike protein, the Beta variant also has a number of other mutations, including E484K, which is thought to enable the virus to escape detection by the host's immune system. Some studies highlight the reductions in neutralising antibody activity against this variant following either natural infection or vaccination, with clear public health implications of re-infection or less-effective vaccine (WHO, 2021).

The Gamma variant shares mutations which had already been identified, namely E484K and N501Y. Again, the transmissibility of this variant is increased and several cases of re-infection suggest that it is may also go undetected in previously infected individuals.

The latest variant of concern, Delta, presents at least 13 mutations, four of which are substitutions in the spike glycoprotein code and are of particular concern. As mentioned above, it is evident by now that Delta has, by far, the highest transmissibility among the current variants of concern (Public Health England, 2021b). There are indications that Delta is also more virulent than previous variants, with several sources reporting a significantly higher risk of severe disease and hospitalisation compared to the Alpha variant (Public Health England, 2021c; Sheikh et al., 2021); preliminary data from the ZOE COVID Symptom Study also indicate that, unlike previous variants, Delta may present with symptoms more closely resembling a common cold in mild cases, which may result in infected people not recognising it as COVID-19 and ignoring the customary precautions (Zoe Company, 2020). The Delta variant is now confirmed to be the driver of the third wave of the pandemic in the UK and is expected to cause further waves in Europe and Africa (World Health Organization, 2021a). As of July 2021, it is the most widespread variant in the UK and several other European countries and the World Health Organization has warned that it is very likely to become – or may already be – the most common variant worldwide (World Health Organization, 2021b).

The impact of Long COVID

Post-COVID-19 syndrome refers to signs and symptoms that develop during or after an infection consistent with COVID-19, which continue for more than 12 weeks and are not explained by an alternative diagnosis. According to NICE (National Institute for Clinical Excellence), 'long COVID' is commonly used to describe signs and symptoms that continue or develop after acute COVID-19. It includes both ongoing symptomatic COVID-19 and post-COVID-19 as defined previously (National Institute for Health and Care Excellence et al., 2020).

Studies vary in terms of the proportion of patients affected and the time frame that COVID is reported in. For example, one study carried out in Italy showed that 87% patients still had symptoms 60 days after being discharged from hospital (Carfi et al., 2020), whereas a study in China found a similarly high proportion of hospitalised patients (76%) who were experiencing symptoms 6 months after discharge (C. Huang et al., 2021).

A recent community-based study carried out on over half a million adults in England found that over one third (37.7%) of those who were still symptomatic after the acute infection reported at least one symptom while 14.8% experienced three or more symptoms lasting 12 weeks or more (Whitaker et al., 2021).

The COVID Infection Survey report that in the four week period ending on the 1st August, the prevalence of long-COVID was about 1.5% of the population, or 970,000 people (ONS, 2021b).

Ongoing studies on long COVID

The PHOSP-COVID study is a national consortium led by experts at the University Hospital of Leicester, which aims to assess the short- (0-6 months), medium- (6 – 12 months) and long-term (12 months +) effects of long-COVID.

What are the uncertainties?

Will SARS-CoV-2 become endemic?

The majority of scientists working on SARS-CoV-2 believe that the virus will not become extinct but will become endemic, although some consider it possible to eliminate SARS-CoV-2 from some parts of the world (Phillips, 2021). The endemic phase is when the number of infections becomes constant across years with occasional resurgences.

Waning immunity and behaviour of previous endemic coronaviruses

There is a possibility that SARS-CoV-2 will become a disease first caught in early childhood, when it would typically cause either mild infection or no infection at all, similarly to the common cold. These usually cause a mild upper respiratory tract infection in adults, although reinfection does occur. The evolutionary pressure as more adults develop immunity, either via natural infection or vaccination, may push the virus to find alternative susceptible hosts, namely children, who typically have a milder disease. One study supporting this theory developed a model that explored the potential changes in both transmission and disease severity of new human coronaviruses as they become endemic (Lavine et al., 2021). This model predicted that once the endemic stage is reached, primary cases will occur almost entirely in infants and young children. Re-infection in older people will occur but the disease will be less severe because of immunity acquired in childhood.

This scenario is similar to four existing endemic coronaviruses (OC43, 229E, NL63, and HKU1) that cause the common cold. There is evidence that levels of neutralising antibodies start to decline after around six to eight months after infection with SARS-CoV-2. If a new infection arises, memory B cells can manufacture antibodies and T cells that can eliminate virus infected cells. However, it has yet to be established whether this immune memory can block viral reinfection (Dan et al., 2021).

Re-infection/ability of virus to evade host's immune system through developing variants

Preliminary results from laboratory studies suggest that neutralising antibodies in the blood of people who have had COVID-19 are less capable of recognising a viral variant first identified in South Africa (called 501Y.V2) than variants that circulated earlier in the pandemic (Cele et al., 2021).

More than 70% of the researchers surveyed by the journal Nature believed that the ability to adapt and evade immune defences would drive continued circulation of SARS-CoV-2 (Phillips, 2021). SARS-CoV-2 may then become seasonal and may require a new vaccine to be produced each year to keep up with new variants, in a similar way to the influenza A virus. SARS-CoV-2 has already shown that it is capable of producing variants that are less vulnerable to antibodies. At the moment, current vaccines seem able to remain effective against the dominant strain but with populations in some countries being vaccinated rapidly, this may put pressure on the virus to find ways to evade the immune system more quickly (Gray, 2021).

Effective vaccine programmes and public health policies are required to achieve herd immunity

One model has shown that achieving herd immunity is dependent on the efficacy of a vaccine, the proportion of individuals receiving the vaccine and co-existing social distancing policies. A vaccine that is 90% effective would need to reach at least 55% coverage to achieve temporary herd immunity with some social distancing measures, such as face masks and many people working from home. The same vaccine would need 67% coverage to provide herd immunity if all social distancing measures were lifted, and even higher levels of coverage if the vaccine was less than 90% effective at blocking transmission or if transmission increased because of a new variant (Hogan et al., 2020).

Achieving all three aspects may be difficult, especially in some regions of the world where healthcare is less developed. With the increased R0 of more transmissible variants, a larger proportion of the population, including children, will need to be vaccinated to achieve herd immunity. Also, while the more developed regions vaccinate their populations first, they leave themselves open to new variants, which may be able to evade the immune system, developing in the less developed regions, which are unable to afford vaccinations or lack the infrastructure to support a vaccination programme and therefore still have a high transmission rate.

Animal reservoirs

Zoonotic pathogens can naturally transmit between humans and animals (e.g., humans can be infected with avian, swine and other zoonotic influenzae viruses). Identification of animal reservoirs of these pathogens plays an important part in effective disease control.

Although the exact origin of SARS-CoV-2 is not known, it is thought to have come from an animal, with the most likely species being bats. It is also thought that another animal such as a pangolin could be acting as an intermediary host. There is evidence that SARS-CoV-2 can infect domestic animals, for example dogs and cats, but also wild animals in zoos or farms such as lions, tigers and minks. In some cases owners of these animals had tested positive for COVID-19, suggesting human to animal transmission is possible (Abdel-Moneim & Abdelwhab, 2020).

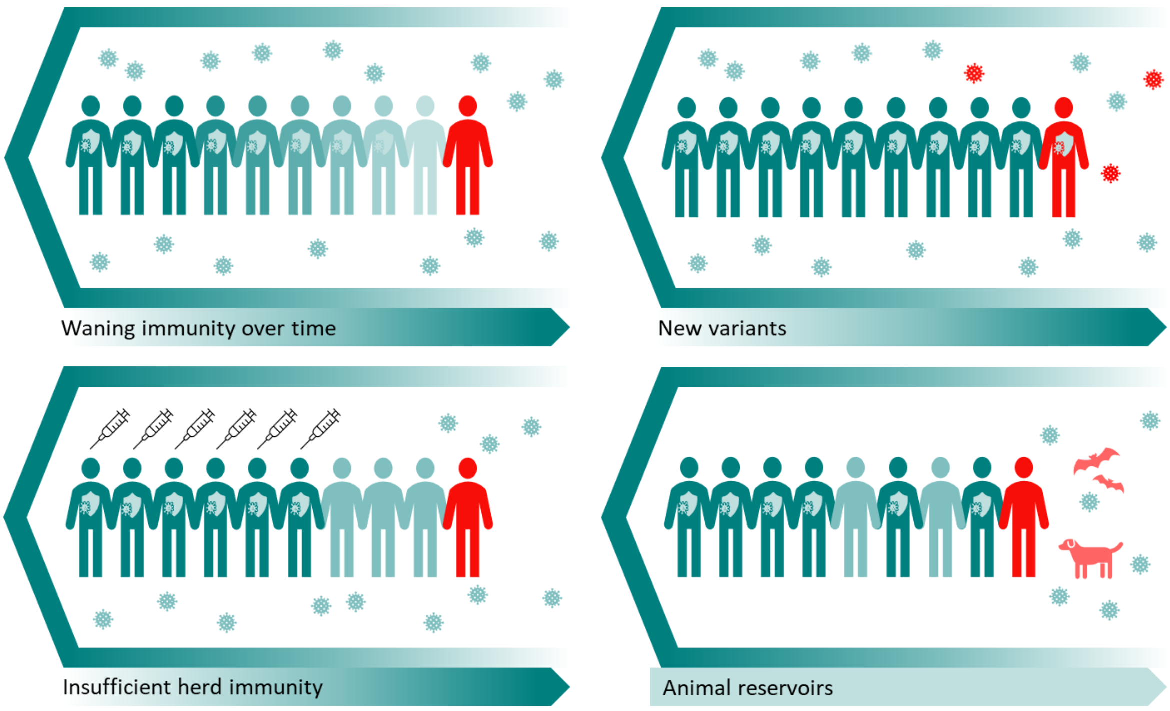

Figure 9. Most likely driving factors of the future endemicity of SARS-CoV-2.

Hospitalisation and mortality after the pandemic

In order to predict what may happen after the pandemic, it is necessary to think about what is happening now (July 2021). Currently, the dominant strain of SARS-CoV-2 in the UK is the highly transmissible Delta variant, which is responsible for the sharp increase in positive COVID-19 test results (increase of 71.8% between 11 June and 24 June 2021). There has also been a small recent increase in deaths (10.7%) and hospitalisations (11.4%); however, as of the end of June 2021, 85% of the adult population have received one dose of a COVID vaccine and 67% have received two doses (Coronavirus Data, 2021). Recent data from Public Health England and University of Cambridge's MRC Biostatistics Unit suggests an estimated 7.2 million infections and 27,000 deaths have been prevented in England due to the vaccination programme (Birrell et al., 2021).

While this reduction in infection rate and mortality is in essence positive news, it is known from previous pandemics that immunity to strains of a virus wanes and new variants occur that enable the virus to evade the immune system.

The current COVID vaccine is effective against the dominant strain of SARS-CoV-2 but emerging variants are being detected by surveillance from the COVID-19 Genomics UK (COG-UK). Data from this consortium supplies a large amount of genomic data to the GISAID initiative, which carries out real time surveillance of the pandemic globally. COG-UK is working with the G2P National Virology Consortium to evaluate how mutations may affect the transmissibility of new variants, the severity of the illness they cause and their response to vaccines and treatments (Mahase, 2021). This will enable the detection of variants that can evade the immune system and the production of updated vaccines.

Data from studies exploring how long immunity to COVID-19 lasts show that antibodies last for several months before beginning to decrease. The SIREN study was a large multi-centre prospective cohort study carried out by Public Health England to better understand whether people who had already had COVID-19 were protected against future SARS-CoV-2 infections. It found that the median protective effect was 5 months after primary infection but, despite immunity, there was still a risk of transmitting the virus to others (Hall et al., 2021).

Another ongoing study by PHE known as the PITCH study is looking at the trajectory of the immune response to SARS-CoV-2 six months after COVID-19 infection (Tomic et al., 2021). So far, data from this study has shown that there is highly variable immune response, and that maintenance or loss of immunity depends on the initial immune response during the primary infection. It also showed that previous infection did not provide ongoing protection against variants of concern months later, and that people who had an asymptomatic infection had a lower immune response.

Although the studies are yet to be published, PHE acknowledge that there is good evidence that two doses of any of the vaccines offered will provide good protection against severe disease for six months. For many people, especially the most vulnerable populations, this protection will start to decrease in the autumn. In line with this, the Joint Committee on Vaccination and Immunisation (JCVI), are recommending a booster vaccination programme starting September 2021 (JCVI, 2021a).

Therefore, it could be proposed that, as long as there is continued surveillance of the virus and its variants, there is an effective vaccine programme in place, and the effectiveness of the current vaccine is continually assessed against the dominant variant, there will be a decrease in the hospitalisations and deaths from COVID-19. However, while morbidity and mortality from COVID-19 will hopefully decrease post-pandemic, it is likely that there will be an increase in overall mortality due to delayed care or avoidance of care during the pandemic. This effect has been studied extensively in cancer patients with one UK study predicting that for four common types of cancer (breast, bowel, lung and oesophageal cancers), delays in diagnosis due to the COVID-19 pandemic will result in approximately 3500 avoidable cancer deaths, equating to 60,000 years of life lost, reflecting the younger age profile of many cancer patients (Maringe et al., 2020).

Long COVID, long term

Impact on healthcare services and staff

Primary, secondary and community healthcare services will have to be able to meet the needs of patients with long-COVID with specialist services e.g., designated long-COVID Clinics. This will increase the demand on a system already trying to deal with thousands of missed routine appointments and operations and having to cope with the uncertain impact of new variants.

Although there are numerous studies gathering information (e.g. PHOSP-COVID), it is still unknown how long new clinical consequences will persist. From the evidence gathered so far, it is probable that some of these patients will have highly complex multi-morbid needs.

Impact on patients

It appears that all patients who have COVID-19 are at risk of long-COVID. However, evidence suggests that older patients with pre-existing conditions who have been hospitalised are the most likely to have persistent long-term symptoms. Patients who were not hospitalised and therefore had a milder form of COVID-19 are still at risk of developing clinical consequences, although the risk is not as high as for the former group (Daugherty et al., 2021).

The list of potential clinical sequelae that a patient can develop (defined as new clinical diagnoses at 21 days from the index date) include chronic respiratory failure, cardiac arrhythmia, hypercoagulability, encephalopathy, peripheral neuropathy, amnesia, diabetes, liver test abnormalities, myocarditis, anxiety and fatigue. Some patients may only have one clinical diagnosis as a result of their COVID-19 infection, whereas others may end up with numerous new diagnoses, which could affect their physical health, mental health, overall social wellbeing and ability to return to pre-COVID levels of employment.

There is growing evidence that the proportion of people with an asymptomatic infection or an infection so mild that they do not register it as having COVID-19, is larger than originally thought. Consequently, if asymptomatic people are going on to develop long-COVID, this could pose a much larger public health problem than was perhaps anticipated.

One study, which developed a SEPIAR (Susceptible, Exposed, Pre-symptomatic, Infectious, Asymptomatic, Recovered) model (SEIR plus pre-symptomatic and asymptomatic) and used data from New York City, showed that the probability of an individual exposed to COVID-19 developing symptoms is low and that a large proportion of infections are asymptomatic. These asymptomatic individuals will contribute to transmission within the community as well as contribute to building herd immunity (Subramanian et al., 2021).

Another study performed in California, which focused on non-hospitalised patients, developed a model that aimed to predict which patients would still have persistent symptoms after apparent resolution of the acute COVID-19 infection (Y. Huang et al., 2021). The study found that 27% patients reported symptoms after 60 days, women being more likely to be present in this category. In addition, while all age groups were represented, 72% were 50 - 59 years old (±20 years). Interestingly, 32% of patients reporting symptoms at day 61 were asymptomatic at the time of being tested for SARS-CoV-2.

It has also been hypothesised that people who experience asymptomatic infection can suffer from Long-COVID. One observational study carried out in the U.S. found that of the asymptomatic patients, 18.95% had a post-COVID condition (FAIR Health, 2021) whereas another showed subclinical lung changes on CT consistent with COVID in asymptomatic patients with a positive test (Oran & Topol, 2020). However, the data is not sufficient to draw any conclusions; at present, the consensus places the prevalence of long-term sequelae among COVID-19-positive patients at approximately 20%

(symptoms lasting 5 weeks or longer) and 10% (symptoms lasting 12 weeks or longer) (Office for National Statistics, 2020).

Vaccines

What we know

The speed at which vaccines have been developed and approved for use against the SARS-CoV-2 virus that causes COVID-19 has been remarkable. The first clinical trial for a COVID-19 vaccine was undertaken in the US by the pharmaceutical company Moderna in March 2020 (*Moderna Ships MRNA Vaccine Against Novel Coronavirus (MRNA-1273) for Phase 1 Study*, 2020). The first vaccine to be approved was that developed by a collaboration between Pfizer and BioNTech; emergency use authorization for this vaccine was granted in the UK in December 2020 (Health England, 2021).

Vaccine development for SARS-CoV-2 has been around ten times as fast as traditional vaccines, in the region of 12-16 months rather than 10-15 years (Kashte et al., 2021). This has been in part due to Emergency Use Authorisation (EUA), which has streamlined the process for testing and approval.

Vaccine research has been pursued via five main approaches: 'traditional' live-attenuated vaccine or inactivated virus, viral-vector-based, mRNA-based, and DNA-based (Soleimanpour & Yaghoubi, 2021). As of December 2020, the majority of vaccine development streams were using protein or whole-virus approaches (114 of 214), but gene-based approaches made up almost as many (98 of 214), and the first two vaccines to be granted clinical approval were both mRNA-based (Pfizer's BNT162 and Moderna's mRNA-1273) (Pushparajah et al., 2021). Genetic vaccines offer a significant advantage over traditional vaccines in that they require only genetic sequence information from the pathogen instead of attenuation or deactivation of live samples, or synthesis of viral subunits. This makes them ideal candidates for rapid response against pandemics and fast-mutating strains, as recognised by the US government as early as 2011. On the other hand, their development history has notoriously been plagued by difficulties in scaling up manufacture, inefficient delivery and poor stability

The rapid development we have witnessed during the pandemic has not occurred in a vacuum but has been in fact the crowning point of decades of research – Pfizer and Moderna, for instance, have been developing this technology since the early 2000s. It is largely thanks to the gradual improvement in molecular genetic techniques in the last thirty years that mRNA vaccines could be successfully deployed on a mass scale against the COVID-19 pandemic (Erasmus & Fuller, 2020).

As of late July 2021, a total of 21 vaccines have been approved for use against the SARS-CoV-2 virus. These are presented in table 1. In addition, there are 72 candidate vaccines in clinical trial phases 1, 1-2, and 2, and 19 in phase 3 (RAPS, 2021).

Table 2. Approved COVID-19 vaccines as of 07/06/2021.

Name	Vaccine Type	Primary Developers	Country of Origin	Date of first regulatory approval
Comirnaty (BNT162b2)	mRNA-based vaccine	Pfizer, BioNTech, Fosun Pharma	Multinational	02/12/2020 (MHRA)*
Moderna COVID-19 Vaccine (mRNA-1273)	mRNA-based vaccine	Moderna, BARDA, NIAID	US	18/12/2020 (FDA)*
COVID-19 Vaccine AstraZeneca (AZD1222); also known as Vaxzevria and Covishield	Adenovirus vaccine	BARDA, OWS	UK	30/12/2020 (MHRA)*

Name	Vaccine Type	Primary Developers	Country of Origin	Date of first regulatory approval
Sputnik V	Recombinant adenovirus vaccine (rAd26 and rAd5)	Gamaleya Research Institute, Acellena Contract Drug Research and Development	Russia	11/08/2020 (Russian Ministry of Health)*
COVID-19 Vaccine Janssen (JNJ-78436735; Ad26.COV2.S)	Non-replicating viral vector	Janssen Vaccines (Johnson & Johnson)	The Netherlands, US	11/03/2021 (EMA)
CoronaVac	Inactivated vaccine (formalin with alum adjuvant)	Sinovac	China	01/06/2021 (WHO)*
BBIBP-CorV	Inactivated vaccine	Beijing Institute of Biological Products; China National Pharmaceutical Group (Sinopharm)	China	07/05/2021 [WHO (COVAX)]*
EpiVacCorona	Peptide vaccine	Federal Budgetary Research Institution State Research Center of Virology and Biotechnology	Russia	14/20/2021 (Russian Ministry of Health)*
Convidecia (Ad5-nCoV)	Recombinant vaccine (adenovirus type 5 vector)	CanSino Biologics	China	25/06/2020 (China's Central Military Commission)*
Covaxin (BBV152)	Inactivated vaccine	Bharat Biotech, ICMR; Ocugen	India	02/01/2021 (CDSCO)*
WIBP-CorV	Inactivated vaccine	Wuhan Institute of Biological Products; China National Pharmaceutical Group (Sinopharm)	China	25/02/2021 (National Medical Products Administration)
CoviVac	Inactivated vaccine	Chumakov Federal Scientific Center for Research and Development of Immune and Biological Products	Russia	20/02/2021 (Russian Ministry of Health)*
ZF2001	Recombinant vaccine	Anhui Zhifei Longcom Biopharmaceutical, Institute of Microbiology of the Chinese Academy of Sciences	China, Uzbekistan	01/03/2021 (Uzbekistan govt.)
QazVac (QazCovid-in)	Inactivated vaccine	Research Institute for Biological Safety Problems	Kazakhstan	26/04/2021 (Kazakhstan govt.)*
Sputnik Light	Recombinant adenovirus vaccine (rAd26)	Gamaleya Research Institute, Acellena Contract Drug Research and Development	Russia	06/05/2021 (Russian Ministry of Health)*
Minhai	Inactivated vaccine	Minhai Biotechnology Co.; Kangtai Biological Products Co. Ltd.	China	20/05/2021 (National Medical

Name	Vaccine Type	Primary Developers	Country of Origin	Date of first regulatory approval
				Products Administration) *
COVIran Barekat	Inactivated vaccine	Shifa Pharmed Industrial Group	Iran	13/06/2021 (Iranian Government)
Unnamed vaccine candidate	Inactivated vaccine	Chinese Academy of Medical Sciences, Institute of Medical Biology	China	09/06/21 (National Medical Products Administration) *
Abdala (CIGB 66)	Protein subunit vaccine	Center for Genetic Engineering and Biotechnology	Cuba	12/05/2021 (Cuban Health Ministry)
Soberna 02	Conjugate vaccine	Finlay Institute of Vaccines; Pasteur Institute of Iran	Cuba, Iran	12/05/2021 (Cuban Health Ministry) 29/06/2021 (Iranian govt.)
MVC-COV1901	Protein subunit vaccine	Medigen Vaccine Biologics Corp.; Dynavax	Taiwan	19/07/2021 (Taiwan Ministry of Health and Welfare)

*KEY: *limited or emergency use only.*

In normal circumstances, the drug development and approval process take years and manufacturing further adds to this timescale. Of course, the pandemic has presented us with a unique challenge, which has laudably been met head-on by both pharma companies and regulators in a bid to bring an end to the pandemic.

The aim of any vaccination programme is to protect the population from vaccine-preventable diseases and reduce the associated morbidity and mortality through a combination of individual and herd immunity (PHE, 2019). Achieving herd immunity, i.e. indirect protection through population immunity (either from vaccination or previous infection) is dependent largely on the transmissibility of a disease. A much greater proportion of a population will require vaccination in the face of a more highly transmissible variant.

Early clinical trial evidence from a number of vaccine candidates suggested that around 90% efficacy could be achieved with a COVID-19 vaccine. Real-world evidence has now confirmed this, as well as significant reductions in hospitalisation (Bernal et al., 2021; Drury & O'Connor, 2021; Haas et al., 2021).

Vaccine rollout has been hugely successful in the UK; as of 27 July 2021, 88.2% of people over the age of 18 years in the UK have received a first dose of a COVID-19 vaccine, and 70.8% have received a second dose. For those aged under the age of eighteen, only about 7% had received a first dose and about 2% had received a second dose by the 19th September 2021 (NHS, 2021).

What we have learned

Vaccine effectiveness

The effectiveness of a vaccine relates to its ability to prevent the outcomes of interest in the real world (contrasted with efficacy, which refers more specifically to how the vaccine works in the controlled conditions of a clinical trial). Outcomes of interest, in turn, define the desired effect of the vaccine. Usually, the main outcome of interest would be infection, which an effective vaccine is expected to prevent. For the COVID-19 vaccines currently available in the UK, on the other hand, the main outcomes of interest are severe illness and death. This means that the vaccine may not necessarily prevent a person being infected (although it will reduce the odds) but it is expected to reduce the chances of hospital admission, death or long-term sequelae, in turn relieving the burden on critical care facilities and on the NHS as a whole.

Protection against COVID-19 appears from around 12 days onwards following a first dose. Peak protection is reached approximately one week following the second dose which is administered, per protocol, four to eight weeks after the first dose. In the UK, this interval was reduced from a maximum of 12 weeks in May 2021 for individuals in the first 9 priority groups who had not yet received both doses, in order to ensure those most vulnerable had the strongest possible protection against the virus at an earlier opportunity.

Analysis of serological responses in adults following administration of either the Pfizer or the AstraZeneca COVID-19 vaccines in England found high rates of seroconversion: in previously uninfected adults, in both vaccines, 95% had developed antibodies 35-55 days after the first dose and 100% by seven or more days following the second dose.

An extended interval of between 65-84 days resulted in a six-fold increase in antibody levels for the Pfizer vaccine compared to the AstraZeneca vaccine. Both sets of results were higher still compared to Pfizer with a 19-29 day interval (Amirthalingam et al., 2021).

It should be noted, however, that effectiveness rates vary depending on existing health status (for instance, in immunocompromised people) and the specific virus variant (Public Health England, 2020a). All of the approved COVID-19 vaccines thus far require two doses, apart from the Janssen vaccine which requires only a single dose. However, it is becoming apparent that early booster doses are needed effectively making most regimes three dose vaccines.

Effectiveness of vaccines against variants

Studies undertaken by vaccine manufacturers and public health bodies report varying degrees of efficacy against the emerging variants of concern.

Public Health England report vaccine effectiveness against the Delta variant during the period 5 April to 16 May 2021 (Health England, n.d.). Both the Pfizer/Biontech and AstraZeneca vaccines were 33% effective against symptomatic disease from Delta three weeks after the first dose, compared to around 50% effectiveness against the Alpha variant. Two weeks after the second dose, the Pfizer-BioNTech vaccine was 88% effective against symptomatic disease from the Delta variant compared to 93% effectiveness against the Alpha variant, and for the AstraZeneca vaccine, it was 60% effective against symptomatic disease from the Delta variant, compared to 66% effectiveness against the Alpha variant.

The AstraZeneca vaccine is largely ineffective against the Beta variant (Madhi et al., 2021). However, evidence of neutralizing antibodies may still be sufficient to protect against severe COVID-19 even where low efficacy against variants is reported (Rubin, 2021).

Serious adverse events after COVID-19 vaccination

Serious adverse events following COVID-19 are rare. There are three main types of adverse event.

Anaphylaxis

Anaphylaxis is a severe, life-threatening allergic reaction to an allergen. In the USA the rate of anaphylaxis with COVID vaccination is less than 5 per million people vaccinated (CDC, 2021). To put this in perspective, the prevalence of anaphylaxis with peanut exposure in European adults is about 35 per thousand (Baseggio Conrado et al., 2021).

Thrombosis with thrombocytopenia syndrome

This syndrome presents with thrombosis of any venous or arterial vessels associated with a low platelet count. It has been reported after using the Johnson & Johnson and the AstraZeneca vaccines. In the UK, it appears to occur in about 15 per million doses, but the incidence is age dependent with higher rates in younger people and lower rates in the elderly (Medicines & Healthcare products Regulatory Agency, 2021).

Myocarditis and pericarditis

Myocarditis is an inflammation of the heart muscle and pericarditis is an inflammation of the fibrous wrapping around the heart called the pericardium. They may be severe, and sometimes fatal. In the UK they have been linked with the Pfizer/Biontech and the Moderna vaccines (Medicines & Healthcare products Regulatory Agency, 2021). Myocarditis appears to occur at a rate of about 7 per million doses of the Pfizer/Biontech vaccine and 25 per million doses for the Moderna vaccine. The corresponding rates for pericarditis are 5.5 per million doses with the Pfizer/Biontech vaccine and 16 per million doses for Moderna. For the AstraZeneca vaccine myocarditis is reported about 2 per million doses and for pericarditis about 4 per million doses.

To put this in perspective, the background annual incidence of myocarditis is about 60 per million people and for pericarditis about 100 per million people.

What are the uncertainties?

Variants

One major challenge is that a viral variant will emerge that will be more transmissible, carry a greater mortality risk and have the ability to escape the vaccines. For vaccine manufacturers, the next step is to evaluate the effectiveness of the currently approved vaccines against variants of concern (VOC) and if necessary, ‘tweak’ the existing vaccine to fit the new variants. Vaccinating populations helps to reduce the rate at which new variants emerge, as the reduction in the number of cases proportionally reduces the number of opportunities for a variant to evolve.

The emergence of variants of the SARS-CoV-2 virus represents a challenge to a vaccination programme. The efficacy of a vaccination effort ties in with the concept of herd immunity – as more and more individuals in the population are vaccinated (on top of people who are immune from prior infections), the protection against chains of transmission is strengthened. However, the presence of the vaccine also represents an evolutionary pressure towards the emergence of vaccine-resistant variants. Even if not resistant, new variants may be more infectious, which requires a higher level of herd immunity in the population, or more lethal, resulting in a higher number of serious infections or deaths and increased pressure on health services.

Indeed, without global suppression of the SARS-CoV-2 virus, healthier vaccinated populations may find themselves subject to outbreaks as variants emerge in non-vaccinated populations and cases are imported. Stockpiling of vaccines may result in prolonging the pandemic and increasing the risk of further pandemic waves.

Vaccine technologies and variants

The development of messenger RNA (mRNA) vaccine technology (N. A. C. Jackson et al., 2020) has enabled the rapid development and manufacturing of two of the lead COVID-19 vaccines, Pfizer/BioNTech and Moderna. In part, this is because once the genomic sequence of the virus has been identified, clinical batches can be very quickly mass-produced, and, more importantly, tweaked as necessary to deal with potential variants. It is suggested that a new RNA vaccine could be designed and manufactured for clinical testing within as little as six weeks (Callaway & Ledford, 2021).

Other vaccine technologies, such as the inactivated vaccine technology platform, are likely to take longer to respond to variants, but this does not negate their usefulness now and going forward. In addition, the more traditional vaccine technologies are easier for low- and middle-income countries to develop and roll out, both economically and logistically. One of the key challenges with the Pfizer/BioNTech vaccine, for example, has been the need for cold storage, which makes it particularly inaccessible for countries that cannot afford this specialised distribution chain or the additional costs of medical supplies required.

"Leaky vaccines" and long-term variant selection

There is a broad understanding that a virus circulating unchecked in a host population should be expected to become less virulent in the long term. The rationale is that less virulent strains have an evolutionary advantage: the longer the host survives and remains infectious, the longer the window of opportunity for the virus to spread, whereas more virulent strains may self-sabotage by killing the host before onward transmission can take place. It should be noted, however, that the evolutionary pressure towards decreased virulence would be weak unless the change in mortality was so obvious as to trigger a profound change in the host's behaviour that limits reproduction of the virus. In the case of COVID-19, we know that death almost always occurs after the infectious period is over, so it would take both a shift towards death in the earlier stages of the disease and a substantial increase in mortality for this pressure to become evident.

Most human vaccines are of the sterilising type, i.e. they halt the transmission of the virus by preventing infection and replication from occurring in the first place. However, so-called "leaky vaccines" – such as the ones currently available for COVID-19 – while effective in reducing morbidity and mortality, do not necessarily prevent infection or transmission. This presents a unique challenge because it can remove the natural evolutionary pressure towards lower virulence. In this scenario, virulent variants, instead of being outcompeted by less virulent ones, may continue to circulate if their increased virulence provides an evolutionary advantage, for instance by prolonging the infectious period in an "imperfectly vaccinated" host (Boots, 2015). Increased virulence, of course, also poses a direct threat to any non-vaccinated individuals.

The imperfect vaccination hypothesis has been predicted by theoretical models and observed empirically in animals (Gandon et al., 2002; Read et al., 2015). The best-known example is the herpes virus causing Marek's disease in chickens, which has become increasingly more virulent since routine inoculation of poultry with leaky vaccines began in the 1970s, reaching a mortality rate close to 100% in unvaccinated animals at present (Read et al., 2015).

The imperfect vaccination hypothesis has never been verified in humans, partly because the vaccines used for traditional routine immunisations are sterilising vaccines, and partly because of bioethical concerns due to the experimental design this type of study requires. Moreover, there are significant differences in the implementation and expected outcomes of vaccination in humans compared to farm animals. Nevertheless, as the global COVID-19 vaccination programme is the first instance of using leaky vaccines in humans on such a scale, the point is worth considering, at least on a theoretical basis.

At present, the benefits of COVID-19 vaccines in reducing morbidity and mortality are indisputable by any evidence-based cost-benefit analysis. If the imperfect vaccination hypothesis should be borne out in the long term, close monitoring of and rapid response to new variants, and sustained efforts to maximise vaccination levels worldwide, will be all the more necessary.

Distribution and administration

Vaccine distribution and administration has its own problems. The Pfizer/BioNTech vaccine, for example, requires storage at -70°C to remain stable and viable. Ultracold freezers have generally only been supplied to pharmaceutical companies, hospital labs and universities; hospital systems, logistics and delivery have had to gear up where possible. Cold chain compliance has been central to the vaccination training programme; new policy and procedure guidelines have been developed because the mRNA vaccine is highly unstable and can be rendered ineffective if not stored as required.

In a centralised health system such as the NHS, an efficient appointment and booking system with the establishment of mass vaccination centres has been very successful with a weekly delivery rate of approximately 2,700,000 doses as of 13 June 2021. While the number of doses delivered daily has since tapered off, as of 24 August 2021 over 47 million first doses and 42 million second doses have been delivered (Coronavirus Data, 2021). In contrast, in some countries the onus is largely on the individual to organise their own vaccine appointments. This may have contributed to the relatively slow initial progress in countries such as France, where the vaccination programme has taken much longer to gain traction. (Public Health France, 2021). Additional challenges include those of vaccine hesitancy, misinformation and public trust.

Meeting global demand for a COVID-19 vaccine will require global collaboration and is constrained by several factors. This includes development and production, affordability, allocation, and deployment (Wouters et al., 2021). Failure to rapidly vaccinate the global population in a timely way will result in more cases, more opportunities for variants to emerge, and more deaths globally.

The rapid development of COVID-19 vaccines has resulted in part from a collaborative approach between governments, non-profit organisations, and private companies. One bottleneck is the capacity for manufacturing, which presents a distinct problem for lower income countries. Some manufacturers have developed relationships with contract manufacturers in order to allow for the expansion of manufacturing capacity in local populations.

Vaccine prices are especially important for COVID-19, on account of the volumes demanded. Some manufacturers have committed to selling their vaccine at cost, without profit, though it is not certain when this commitment will end. Furthermore, some manufacturers are planning to sell COVID-19 vaccines at a premium in private markets; this presents a significant risk to those without sufficient funds to access a vaccine, creating widening health inequalities.

As one might expect, demand for a COVID-19 vaccine has exceeded supply. To enable resource-poor countries to deliver an adequate number of vaccinations in a timely way, the World Health Organisation created the COVID-19 Vaccine Global Access (COVAX) Facility. This aims to develop a pooled procurement initiative that secures low prices, and gives all countries access to a diversified vaccine portfolio. Low- and middle-income countries can purchase vaccines at a much-reduced rate. To date, COVAX has shipped more than 80 million COVID-19 vaccines to over 129 countries. The continuing success of the COVAX programme will rely on ongoing funding from governments worldwide.

Deploying the vaccine presents a unique set of challenges, not least the cold storage requirements of the Pfizer/BioNTech vaccine as an example. This underlines the importance of a diverse portfolio of vaccine types. Simplification of the logistical and administrative challenges can be achieved through, for example, single dose schedules, and simple storage requirements, such as room- or simple fridge-temperature. Indeed, whilst the rapid development of mRNA vaccines has been enabled by the specific technology behind them, it is clearly not economically and logistically feasible to simply rely on this method if we move into a scenario where annual COVID vaccines are required, as seems likely.

Future vaccination needs

Monitoring and recording of those vaccinated allows for efficient allocation of resources, and effective prioritisation strategies. In addition, evidence of vaccine status could provide individuals with greater freedoms, such as attending mass sporting events and international travel, although the introduction of vaccine passports is considered controversial. Issues include lack of standardization (possibly leading to forgery), discrimination, particularly against already marginalized groups or those who have medical reasons for not being vaccinated, and the potential for onward transmission even in vaccinated individuals.

There may be a need for repeated vaccinations, such as an annual booster in the style of the current influenza vaccination programme. This may be necessary over time to address flagging immunity or the changing immunogenicity. The novel nature of the SARS-CoV-2 virus, and the resulting response to vaccinations, means that there is not yet sufficient evidence to state with any confidence the length of time that an individual is protected from the virus following vaccination. In order to address this, Pfizer/BioNTech have commenced clinical trials to evaluate the safety and immunogenicity of a third dose of their vaccine given to participants 6 to 12 months after receiving their initial two-dose regimen (Pfizer Inc., 2021). Also, trials are underway to explore the potential advantages of having different first and second doses of vaccine (Callaway Ewen, 2021).

It is possible that the SARS-CoV-2 virus will become a permanent (endemic) feature of the infectious disease landscape of the world, much like the flu virus. As is the case with flu, regulators may not require evidence from large-scale clinical trials to approve new vaccines, but smaller studies may be necessary to ensure that the modified antigen triggers a similar antibody response to the original one. The European Medicines Agency (EMA) suggests that, in the case of a modified vaccine, at least one trial should be conducted in a SARS-CoV-2-naïve population (EMA Committee for Human Medicinal Products, 2021).

Additionally, we must consider seasonality. Will COVID-19 follow a seasonal pattern such that we can be fully prepared for the next season, as we do with flu? The frequency of emerging new variants, vaccine efficacy in the face of variants, and the impact of non-pharmaceutical interventions (NPI) makes it challenging to conclude with any certainty whether COVID-19 will become a chronic seasonal disease (Murray & Piot, 2021).

However, we already know that several other coronaviruses causing the common cold do follow a seasonal pattern of circulation. It has been suggested that SARS-CoV-2 has the potential to become ‘Just Another Seasonal Coronavirus’ (JASC). This could not only improve planning of vaccine development but also mean that the virus tends towards decreased virulence over time, with mild or asymptomatic infections by SARS-CoV-2 becoming more typical (Beams et al., 2021).

As we mentioned in the first section, a recent survey undertaken by the *Nature* journal (Phillips, 2021) asked more than 100 immunologists, infectious-disease researchers and virologists working on the coronavirus whether it could be eradicated. Around 90% thought that the virus will become endemic. A number of different scenarios are thought to be possible; this includes:

- Regional herd immunity
- Endemic with only mild to moderate disease going forward
- Endemic with severe disease still possible
- Spillback from animal reservoirs
- Eradication

Elimination in some regions was thought to be possible according to some respondents, although continuing outbreaks may be expected to occur even in these zero-case regions. Immune escape, waning immunity and uneven vaccine distribution were the top three reasons given for driving SARS-CoV-2 circulation to become endemic (**Figure 10**).

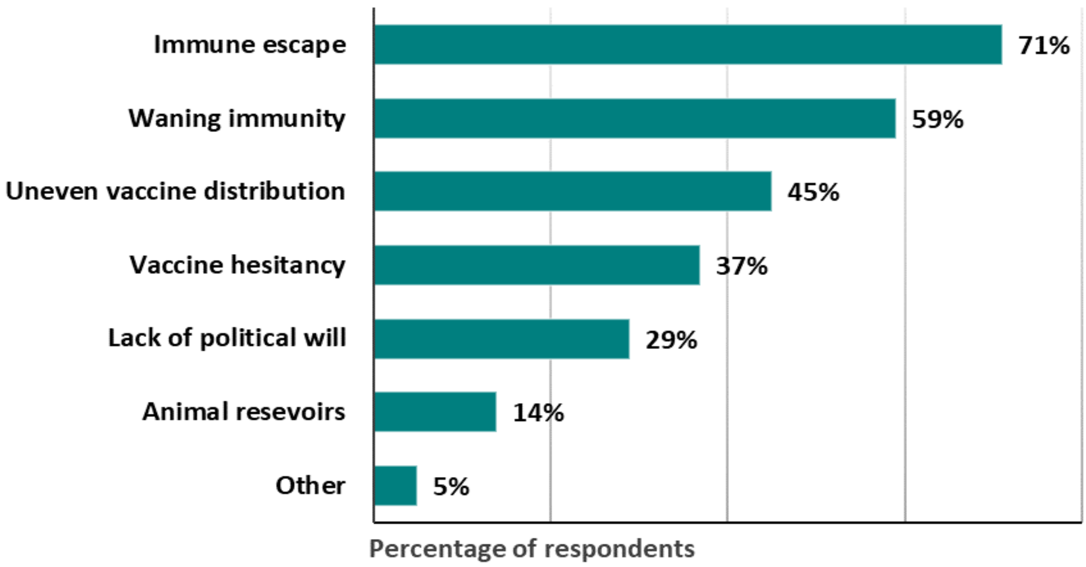

Figure 10. Potential driving factors of continuing SARS-CoV2 circulation (Phillips, 2021)

Vaccines and children

There is ongoing debate on whether children should receive a COVID-19 vaccine. Many countries are already including those aged 12 years and older in their vaccination schedules, with some specifying that the vaccine is only indicated in those aged 12-17 years if they have an underlying health condition that could put them at higher risk of serious illness from COVID-19. In the UK, this has included children aged 12-15 years with severe neurodisabilities, Down’s syndrome, immunosuppression and multiple or severe learning disabilities (JCVI, 2021b). Healthy children aged 16 and 17 have been offered one dose of the Pfizer vaccination, with a second to be administered at a later date. As of 13 September 2021, healthy children aged 12 to 15 years will be offered one dose of the Pfizer vaccine. The JCVI recommended against vaccinating children on health grounds alone as the net benefit was considered very small with too much uncertainty (Department of Health and Social Care, 2021c). The risk of myocarditis after a single dose is estimated to be between 3 and 17 per million doses, but between 12 and 34 per million after a second. This is weighed against a benefit of preventing about two paediatric intensive care admissions, 87 hospitalisations and 15 cases of paediatric inflammatory multisystem syndrome per million first vaccinations. However, after taking into account externalities such as the disruption to schooling and the harm that this does, all four Chief Medical Officers in the UK recommended vaccination with a single dose of the Pfizer vaccination. In addition, it is known that children can, and do, develop long COVID.

The vaccine response to the pandemic has been an extraordinary technological and organizational achievement, and has saved many lives. Going forward, world leaders and local populations need to build on these successes and continue to work towards overcoming the challenges of development, production, affordability, allocation, and deployment. Vaccines are only one part of the exit strategy from the pandemic. Effective testing programmes, leading to rapid response tracing and isolation when local outbreaks occur in the face of an endemic environment, are essential along with effective and timely implementation of non-pharmaceutical interventions.

Treatments

Introduction

The COVID-19 pandemic spread with alarming speed but has been countered by the extraordinarily quick development of vaccines and treatments. The first large drug trial was designed within a month of the virus entering the UK and the result published within the next 3 months. The genome sequence of the virus was shared within a few weeks across the world and subsequently updated with each new mutation. Part of the explanation for this rapid progress in treatment is a result of drug repurposing rather than de-novo drug development.

This involved bench studies and parallel computerised simulation in a bid to find the most suitable molecules that might already be in clinical use for other diseases, avoiding the need for lengthy phase one studies to check the safety of these drugs in human use. Thousands of trials and many cross-border collaborations were launched across the globe. The European Medicines Agency lists 70 candidate drugs in research and development at the time of writing (June 2021) (European Medicines Agency, 2021).

At times, the enthusiasm for implementation did get ahead of the evidence. An example of this was hydroxychloroquine, which had been identified in laboratory studies as an effective antiviral agent for SARS-CoV (Vincent et al., 2005). It was widely adopted in the early part of the COVID-19 pandemic before an accumulation of evidence in humans showed that it was, at best, ineffective, and at worst, harmful (Lewis et al., 2021; B. Singh et al., 2021). This section will discuss the therapies that were proven to be successful in robustly performed studies. At the time of writing, only inhaled budesonide, systemic steroid (dexamethasone), remdesivir, a monoclonal antibody cocktail against viral spike protein, colchicine and tocilizumab have been proved to be of benefit, to varying degrees, in patients with COVID-19. Some of these treatments reduce mortality, while others are effective in reducing the length of hospital stay.

What we know

It is important to outline the temporal profile of the disease to understand the role of different therapies in disease cure or symptomatic improvement (Figure 11). The virus usually gains entry through the respiratory tract, followed by viral replication lasting about a week, which may or may not be associated with mild to moderate symptoms. This phase is usually followed by disease remission when the host’s immune response eliminates the virus. However, in a small group of patients, it is followed by persistent and sometimes severe disease driven by an initial high viral load or a dysregulated immune response resulting in damage to tissues throughout the body. Lung damage from the immune response can cause an acute respiratory distress syndrome (ARDS), resulting in the need for oxygen and sometimes ventilation.

Appropriate treatment depends on the stage of illness because of these different mechanisms. Here we will report on proven therapies for mild, non-hospitalised cases, including monoclonal antibodies, inhaled steroids and colchicine; proven therapies for moderate to severe disease requiring hospitalisation, including remdesivir, systemic steroids, monoclonal antibodies, other immunomodulating drugs and supportive treatment; and discredited treatments that have been found to be ineffective or even actively harmful.

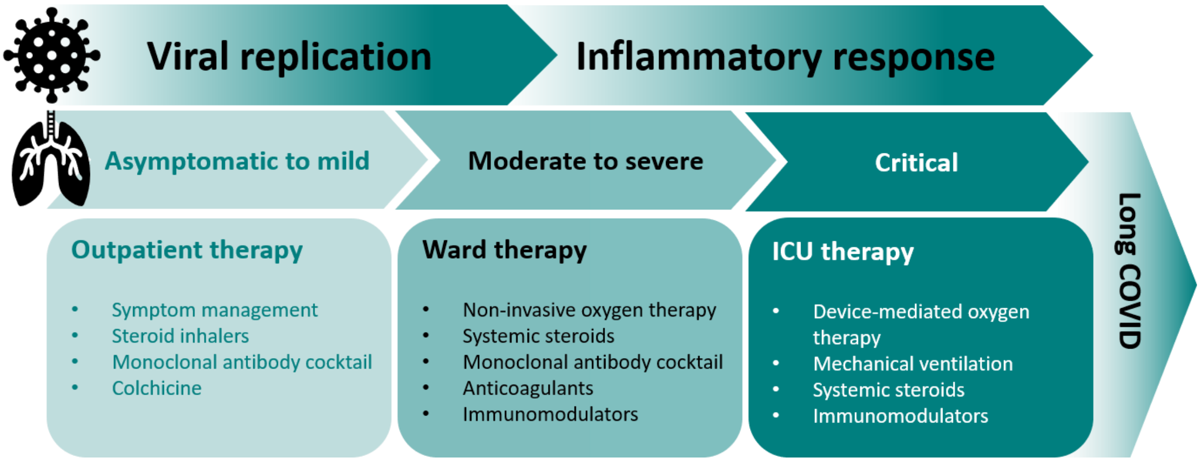

Figure 11. Temporal and therapeutic profile of COVID-19 infection.

Proven therapies for mild disease for patients at home

Monoclonal antibodies targeted against viral protein

Monoclonal antibodies (MAbs) are artificially engineered antibodies targeted at disease-inducing proteins. Sometimes these targets are antigens on cancer cells, receptors on human cells that may influence a disease process, or antigens on an infectious agent, such as the spike protein on SARS-CoV-2. A cocktail of MAbs containing the monoclonal antibodies casirivimab and imdevimab (REGEN-COV) has been shown to reduce admissions and death but only if it is started within a week of symptoms beginning (Weinreich et al., 2021).

Inhaled corticosteroid

Budesonide is a commonly used inhaled drug for asthma that is safe, cheap and widely available, which makes it an attractive treatment option for clinicians in managing patients at home. It reduces the time to recovery in older adults in the community with mild symptoms of COVID-19 (PRINCIPLE Collaboration, 2021; Yu et al., 2021). As well as making patients feel better quicker, this has the potential for reducing the loss in economically productive days, with patients likely to be able to return to work sooner after being ill with COVID-19. It is possible that inhaled budesonide reduces the risk of death in older people in the community, but the studies conducted so far have been of insufficient power to show a difference, given the much lower risk of death in a community sample compared to a hospital sample.

Colchicine

Colchicine is a well-known drug for treating gout, but it has also been found to alleviate inflammatory conditions in the outer lining of the heart (pericarditis) and coronary artery disease (Hemkens et al., 2016). It appears to reduce the risk of hospitalisation and death in high-risk people with PCR positive COVID-19 in the community (Hariyanto et al., 2021; Tardif et al., 2021).

Proven therapies for moderate to severe disease requiring hospitalisation

Remdesivir

Remdesivir was initially developed to treat hepatitis C, was investigated as a potential treatment for Ebola and has been repurposed for COVID-19. In hospitalised patients on minimal oxygen with evidence of lower respiratory tract infection, it reduced the time to recovery from 15 days to 10 days (Beigel et al., 2020).

Systemic steroids

Steroids are known to reduce inflammation and have been widely tested in multiple different conditions. They have long been the mainstay for asthma therapy and the treatment for many autoimmune conditions. Following an infection, the body tries to get rid of the infective organism by mounting an inflammatory response. On occasion, this inflammatory response is inadequately regulated and it results in harm to the patient's own organ systems.

In influenza-related pneumonia, systemic steroids have been shown to be possibly harmful (Lansbury et al., 2019), but in early 2020, a study showed that dexamethasone was useful in improving clinical outcomes in moderate to severe lung damage due to pneumonia (Villar et al., 2020). Dexamethasone yielded an absolute mortality reduction at one month of 2.8% (RECOVERY Collaborative Group, 2020). This meant that around 35 patients hospitalised with COVID-19 needed to be treated with this therapy to save one life (number needed to treat or NNT = 35). Notably, this beneficial effect was only found in patients needing supplemental oxygen.

The greatest benefit was observed in patients needing mechanical ventilation in the intensive care unit (mortality improved from 41% in the usual care group versus 29% in the dexamethasone group, meaning that 8 patients needed to be treated in order to save one life in this severely affected group). When analysing patients by age group, there was no statistically significant benefit in those over the age of 70, but a 6% reduction in mortality (17% versus 11%) in those under 70. However, there is no current recommendation not to use it in patients over 70.

Dexamethasone, as an anti-inflammatory agent, is useful only after 7 days from symptom onset, with a relative risk of death in this patient population of 0.69 (24.1% vs 17.9%). This makes sense as the inflammation starts later in the disease process, as shown in **Figure 11**.

It is not clear whether the benefits seen with dexamethasone can be extended to other steroids, or if there is a general class effect. A meta-analysis of multiple steroid studies (7 trials involving 3 agents: dexamethasone, hydrocortisone and methylprednisolone) in patients needing respiratory support showed a reduction in mortality with the use of steroid, with an overall summary odds ratio of 0.66 (95% C.I. 0.53, 0.82) (Sterne et al., 2020). The reduction in mortality with dexamethasone was about 36%, but the results for the hydrocortisone and methylprednisolone trials did not show a clear mortality benefit.

An umbrella review of 12 meta-analyses on the use of systemic steroids in COVID-19 found that mortality was reduced by 20% in those critically or severely ill with COVID-19, while the risk of needing mechanical ventilation was reduced by 27% (Cheng et al., 2021). However, the time to viral clearance and the duration of hospital stay were increased. This may not be surprising, as steroids are immuno-suppressant and could slow down the process of eliminating the virus. Also, there will be fewer admissions cut short by death causing the average duration of admission to rise..

In conclusion, dexamethasone reduces mortality in patients in hospital needing oxygen, with the greatest gain in mortality benefit in patients on mechanical ventilation. Since June 2020, it has become the mainstay therapy across the world for hospitalised patients with COVID-19 needing oxygen.

Monoclonal antibodies

REGEN-COV (a cocktail of monoclonal antibodies casirivimab and imdevimab, as mentioned above) has recently been found to significantly reduce mortality by about 20% in patients with COVID-19 admitted to hospital and with no circulating neutralising antibodies against the virus (Landray et al., 2021). In this study, 24% of seronegative patients treated with REGEN-COV died versus 30% of those who received usual care only, a difference of 6%. This means that out of every 17 seronegative hospitalised COVID-19 patients receiving this treatment, one will survive who would not have otherwise (NNT = 17).

Other immunomodulators

Multiple molecules are involved at various stages of the inflammation triggered by COVID-19 in a human body. Thanks to therapeutic advances in other medical fields like rheumatology, there are treatments available that can bind to some of these inflammatory molecules and neutralise their effects. All of these were studied during the first year of the pandemic in hospitalised patients with severe inflammation. The only agents that demonstrated evidence of benefit were the interleukin-6 (IL-6) inhibitor tocilizumab (REMAP-CAP Investigators, 2021) and another agent (baricitinib), which showed a reduction in recovery time.

Tocilizumab

Tocilizumab blocks IL-6 and therefore reduces the inflammatory response. It reduces mortality about 11%, with 31% patients dying within 28 days with tocilizumab compared to 35% with usual care, and the recovery time in survivors is quicker (RECOVERY Collaborative Group, 2021). The improvements were seen in all pre-specified sub-groups of age, although the benefit was the smallest in patients over 80 years (REMAP-CAP Investigators, 2021).

It is possible that tocilizumab must be administered with dexamethasone for a mortality benefit to become evident. The main difference between the two trials (RECOVERY and REMAP-CAP) that showed improvement and the earlier trials that did not, was that the latter did not include as many patients on steroids, as this was not the standard of care in the first six months of the pandemic (Rosas et al., 2021; Salama et al., 2021; Stone et al., 2020).

An absolute reduction in mortality of approximately 4% is associated with the use of tocilizumab and about 25 patients have to be treated in order to save one life (NNT=25). Furthermore, there is a potential to reduce hospital stay by 9 days, significantly reducing healthcare expenditure, which can offset some of the costs associated with tocilizumab use. NICE now recommends tocilizumab in select groups of hospitalised patients (National Institute for Health and Care Excellence, 2021).

Baricitinib

Baricitinib is licensed for use in rheumatoid arthritis and eczema and is another example of a drug that might be repurposed for COVID-19. It showed promise in earlier trials and is currently being studied in the RECOVERY trial. At this point, there is no strong evidence that it reduces COVID-19 related mortality but it may result in shorter time to recovery if used in conjunction with remdesivir (Kalil et al., 2021). This was more evident in severe cases needing high-flow oxygen or non-invasive ventilation (10 days versus 18 days).

Baricitinib is not recommended in the current UK NICE guideline, although this may change as new evidence accumulates (National Institute for Health and Care Excellence, 2021).

Supportive treatment

Pronation

Alongside medicinal treatments, other modalities of treatment have gained attention. For example, prone positioning of awake COVID-19 patient was investigated and practised. Prone positioning in mechanically ventilated patients has been used widely in general critical care practice and already has a strong evidence base in patients with acute respiratory distress syndrome (Guérin et al., 2013). In patients with COVID-19, it improves oxygenation and reduces the need for mechanical ventilation (Coppo et al., 2020; Ehrmann et al., 2021).

Anticoagulation

Anticoagulation has also been widely touted as a necessary therapy, on the basis of the proposed pathophysiology of COVID-19. The disease initially causes widespread coagulation or clotting in blood vessels, including in the lungs, as noticed early on in the pandemic (Reines & Ninham, 2020). The obvious answer to this could have been the use of high-dose blood thinners or anticoagulants to prevent blood clots. However, preliminary data from multiple studies examining the effects of therapeutic anticoagulants have shown potential harm in severely affected patients (*ATTACC, ACTIV-4a & REMAP-CAP Multiplatform RCT, Results of Interim Analysis*, 2021) and therefore high-dose anticoagulation is not recommended by the current guidelines.

Discredited treatments

Hydroxychloroquine

During the early stages of the pandemic, hydroxychloroquine, a drug used for the treatment of malaria and several autoimmune diseases, was widely investigated and even used in several countries as an off-label treatment for hospitalised patients with COVID-19. However, further studies have shown that hydroxychloroquine not only has no discernible benefit on patients with severe COVID-19 but may also be associated with increased mortality (Axfors et al., 2021). Its use is currently not recommended by NICE guidelines (National Institute for Health and Care Excellence, 2021).

Azithromycin

The antibiotic azithromycin has also come to attention as a potential treatment for COVID-19 early on in the pandemic, due to its known activity against several viral strains. However, a 2021 meta-analysis of available studies failed to show any benefit in patients with COVID-19 (Kamel et al., 2021) and the use of azithromycin is therefore not recommended by current NICE guidelines (National Institute for Health and Care Excellence, 2021).

Vitamin D

Vitamin D deficiency is a well-known risk factor for severe respiratory infections, which has prompted interest in its potential benefits in the prevention and management of COVID-19 infection. As of 2021, however, the results are not conclusive: while some reviews suggest an association between low vitamin D levels and a higher risk of COVID-19 infection (Liu et al., 2021; Teshome et al., 2021), other evidence is uncertain (Orchard et al., 2021; Shah et al., 2021). At present, the NICE guidance on vitamin D supplementation remains unchanged, with the caveat that it must not be prescribed for the treatment or prevention of COVID-19 outside of a clinical trial (National Institute for Health and Care Excellence, 2020).

Convalescent plasma

Convalescent plasma (i.e. plasma from patients who have successfully recovered from COVID-19) has been proposed as a potential treatment early on in the pandemic and even received emergency use authorisation in the US in 2020. However, the latest review and meta-analysis failed to show any benefits in using convalescent plasma compared to placebo (Janiaud et al., 2021).

What we have learned

Developing new drugs from scratch is an extremely time-consuming and expensive process, with timescales of a decade and costs in the billions of pounds. Existing drugs, on the other hand, can be repurposed very rapidly. Within a year of the beginning of the pandemic, a number of candidate drugs had been evaluated, and some found to be beneficial, such as dexamethasone and remdesivir.

The timing of interventions is important. There may be a physiological rationale as to why antivirals might not be significantly useful in hospitalised patients. As shown in **Figure 11**, by the time a patient comes to hospital, the phase of viral replication is mostly on the wane and the inflammatory state is on the rise: targeting the viruses with antivirals may no longer be useful in patients at this stage. Similarly, steroids reduce mortality in severe hospitalised cases, but are of little or no value in the early phase of active infection and could conceivably reduce general immunity and increase risk from SARS-CoV-2 at a time of active infection, or increase risk from other infections such as mucormycosis, which has been linked to the inappropriate use of steroids (Patel et al., 2021; A. K. Singh et al., 2021).

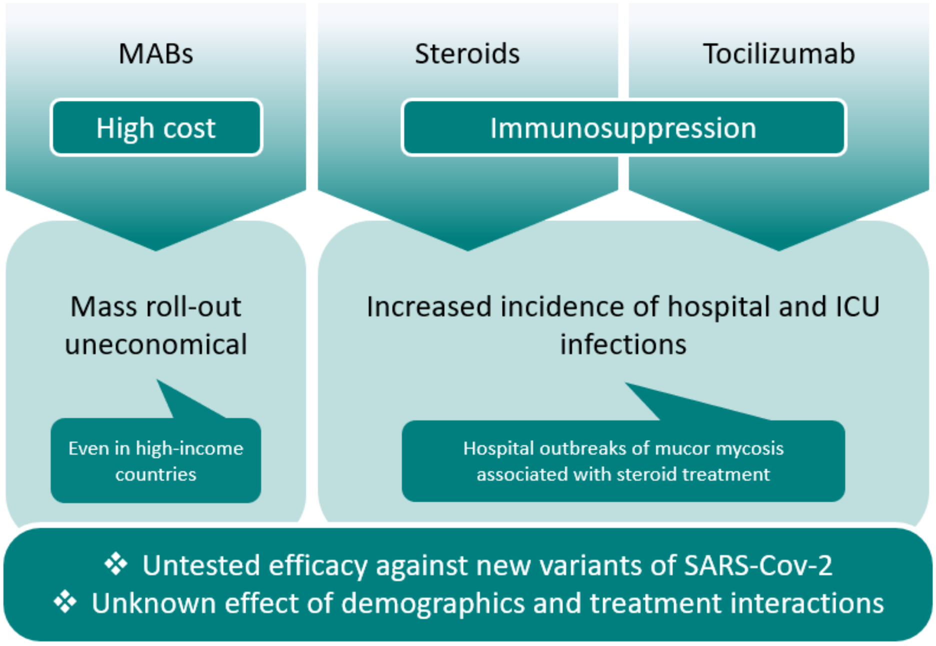

Figure 12. Concerns and open questions around COVID-19 treatments

At a time of crisis, there is a temptation to adopt a treatment based on possible theoretical benefit or experimental lab results before evidence of efficacy from randomised controlled trials has been obtained. This is not always harmless. The widespread adoption and promotion of hydroxychloroquine before there was sufficient evidence of benefit may have resulted in harm to some of those who took it, and a shortfall in the supply to patients with systemic lupus erythematosus, for whom it may have been the only effective treatment (Mendel et al., 2021).

What are the uncertainties?

When a new variant of SARS-CoV-2 emerges, it may be more infectious, it may escape existing immunity from vaccination or prior infection, or it may be more lethal. The probability of this happening is proportional to the number of infections, as there is a risk of mutation giving rise to a variant of concern with each viral replication. As the pandemic is global, wherever in the world a variant arises, it poses a threat to all countries. Whilst remarkable progress has been made in vaccinating some developed countries, others still have very low levels of vaccination at the time of writing. The need for worldwide vaccination has motivated the founding of the COVAX programme, whose mission is to facilitate access to COVID vaccination for poorer countries by co-ordinating the global vaccination effort and by pooling procurement (Gavi: The Vaccine Alliance, 2021). There are vaccination technologies, such as the mRNA vaccines from Pfizer/Biontech and Moderna, that lend themselves to the rapid iteration needed to adapt to the emergence of new variants. Also, there are serious challenges to the rapid distribution of these vaccines globally, due to their cost and the very low storage temperatures required. The speed with which these could be developed, distributed and administered *en masse* may well be insufficient to prevent catastrophic waves of COVID-19.

Whilst a few effective treatments for COVID-19 have been identified, there is a natural evolutionary tendency for infectious diseases to develop resistance if that increases the likelihood of subsequent infection. This would be true of those treatments that are effective in the early phase of viral replication and it explains why, for instance, it is important to combine more than one monoclonal antibody in the treatment of early infection (such as with REGEN-COV), as resistance is far less likely to arise. The FDA has revoked the emergency use authorisation of another MAb (bamlanivimab) for the early treatment of COVID-19 precisely for this reason. This agent was shown to be useful in reducing viral load, hospitalisation, ICU admission and death (Bariola et al., 2021; Gottlieb et al., 2021). If resistance were allowed to develop, however, its benefits would be lost forever and may result in cross-resistance to other beneficial treatments with a similar mechanism of action.

The speed with which resistance to these treatments will develop is unknown and will partly depend on medical and regulatory discipline internationally. Whilst monotherapies have been avoided in the USA, other countries may not necessarily follow suit, and clinical discipline in following those rules may not always prevail. Once a resistant strain developed in one country, it would inevitably spread internationally if the use of the treatment in question was widespread.

The timing of treatment and combinations of different treatments may influence efficacy. For instance, IL-6 inhibitors like tocilizumab, used in the late, immunity-driven phase of the illness, may have their effect enabled or enhanced by the used of dexamethasone.

There are many permutations of treatment combination and timing with the potential to deliver enhanced effects or, on the flipside, neutralisation of effects or harmful effects. It will take time, experience and fastidious collection of data to unravel these complexities.

The search for new treatments continues and there are many candidate drugs. However, there is great uncertainty as to what progress will be made. Two particularly promising candidates at the time of writing are dimethyl fumarate and interferon β.

Dimethyl fumarate

Dimethyl fumarate, a drug used for the treatment of psoriasis and multiple sclerosis, has come to the attention of researchers as a possible new treatment for COVID-19 due to its immunosuppressant properties, analogous to systemic steroids such as dexamethasone. At the time of writing, its efficacy and safety is still being investigated as part of the RECOVERY trial (*RECOVERY Randomised Evaluation of COVID-19 Therapy*, 2021).

Interferon β

Interferons are a family of proteins produced by the human immune system in response to viral infections. A virus-infected cell will typically release interferons as a means of triggering the protective defences of nearby cells. Interferons are thus named because of their ability to interfere with viral replication. In purified form, interferons are currently used not only as antivirals (e.g. in the treatment of hepatitis B and C) but also in the treatment of autoimmune disease (multiple sclerosis) and as adjuvants in chemotherapy for certain forms of cancer. Interferon β, in particular, has already shown promise as an effective agent against the coronaviruses causing Severe Acute Respiratory Syndrome (SARS) and Middle-Eastern Respiratory Syndrome (MERS) and therefore is of obvious interest as a potential treatment for COVID-19. Its safety and efficacy is currently under investigation in the SOLIDARITY trial, although preliminary results have failed to show any benefit of interferon β as of February 2021 (WHO SOLIDARITY Trial Consortium, 2021).

Summary

Table 3. Review of benefits of current approved treatments.

	Prehospital	Hospitalised		
		No O2 needed	**On O2**	**Ventilated**
Younger (under 65)	Colchicine in over 40s (25% reduction in hospitalisation & mortality)	-	Dexamethasone (2.8% absolute mortality risk reduction), remdesivir (reduced time to recovery by 5 days)	Dexamethasone
Older (over 65)	Inhaled budesonide (recovery 3 days quicker), colchicine (25% reduction in hospitalisation & mortality).	-	Dexamethasone (2.8% absolute mortality risk reduction), remdesivir (reduced time to recovery by 5 days)	Dexamethasone
High risk	Casirivimab & imdevimab (~70% reduction in hospitalisation & mortality).	-	Dexamethasone. IL-6 inhibitor (tocilizumab or sarilumab) in patients on dexamethasone with marked inflammation. REGEN-COV in seronegative patients (20% reduction in mortality)	Dexamethasone. IL-6 inhibitor (tocilizumab or sarilumab) in patients on dexamethasone with marked inflammation. REGEN-COV in seronegative patients (20% reduction in mortality)

There have been significant therapeutic additions in the armoury of clinicians against COVID-19. At the forefront are systemic steroids in hospitalised oxygen-dependent patients, followed by tocilizumab for patients needing oxygen and with a high degree of inflammation. In the community, combinations of monoclonal antibodies in high-risk individuals with PCR-positive COVID-19 can reduce hospitalisation and mortality.

We have learnt that it is possible to repurpose existing drugs for the treatment of COVID extremely quickly and relatively cheaply compared to the high cost and decade-long timelines of developing new drugs; that the timing and combination of treatments may be critical; and that the hasty adoption of theoretically promising treatments can lead to more harm than benefit.

Behavioural insights

There have been substantial changes in behaviour during the COVID-19 pandemic, most notably as a result of either enforced or recommended actions aimed at reducing the spread of the disease.

The key question is whether these behaviours and the subsequent effects will persist beyond the perceived end of the pandemic. There are several psychological theories pertaining to this, with the general theme being that changes in behaviour motivated by an external force or situation are limited to the lifespan of that force, whereas changes in behaviour motivated by an internal shift in understanding or beliefs are more likely to be maintained over the long term (Jalloh et al., 2021; Lee et al., 2021; Michie & West, 2021; West et al., 2020).

This section will look at the indirect effect of behavioural measures on other diseases and mortality factors. We will also touch upon the psychological motivators of both positive outcomes (such as support for the lockdown) and negative ones (such as vaccine hesitancy) and highlight some of the key questions as to what shape the "new normal" will take once the emergency is over.

What we know

The new behaviours introduced early on to reduce the spread of COVID-19 ranged from minor changes in everyday practice to dramatic life-style changes, including but not limited to:

- using and discarding tissues when coughing or sneezing
- wearing a face mask
- maintaining physical distance
- limiting gatherings or contact outside of the household
- washing hands with soap or hand sanitiser
- disinfecting surfaces and objects
- avoiding touching the T-zone (eyes, nose and mouth)
- self-isolation when feeling unwell.

These behaviours, explicitly intended to slow or stop the spread of COVID-19, will consequently have had a direct impact on the incidence rates of other infectious diseases. There are also likely to be indirect effects on disease incidence and other-cause mortality resulting from these changes. For example, enforced lockdowns and working-from-home orders reduced the volume of cars on the road, which has been followed by a reduction in the number of road traffic accidents by 14% from the previous year (Department for Transport, 2021), as well as reducing pollution and any associated health problems (Jephcote et al., 2021).

Other examples include changes in alcohol and smoking consumption, mental health problems associated with social isolation, and reduced opportunities to exercise (Clay & Parker, 2020; Kadakia et al., 2020; Pollard et al., 2020; Yang & Ma, 2021)

Changes in influenza rates

The 2020/21 winter season has not long ended, therefore the data are still incomplete and should be interpreted with caution, as corrections and redactions are not uncommon.

Cases

Despite increased testing in some countries, global **influenza rates were lower than expected in the first quarter of 2021** (World Health Organisation, 2021). A likely cause of this drop in cases are the

COVID-19 restrictions in place, but these rates will also have been influenced by lower levels of reporting, whether due to individuals staying at home or to a disruption of surveillance systems.

A Public Health England report, using data from Respiratory DataMart, shows lower levels of positive samples of influenza subtype A and B (**Figure 13**) for 2020/21 compared to previous years (Public Health England, 2021e).

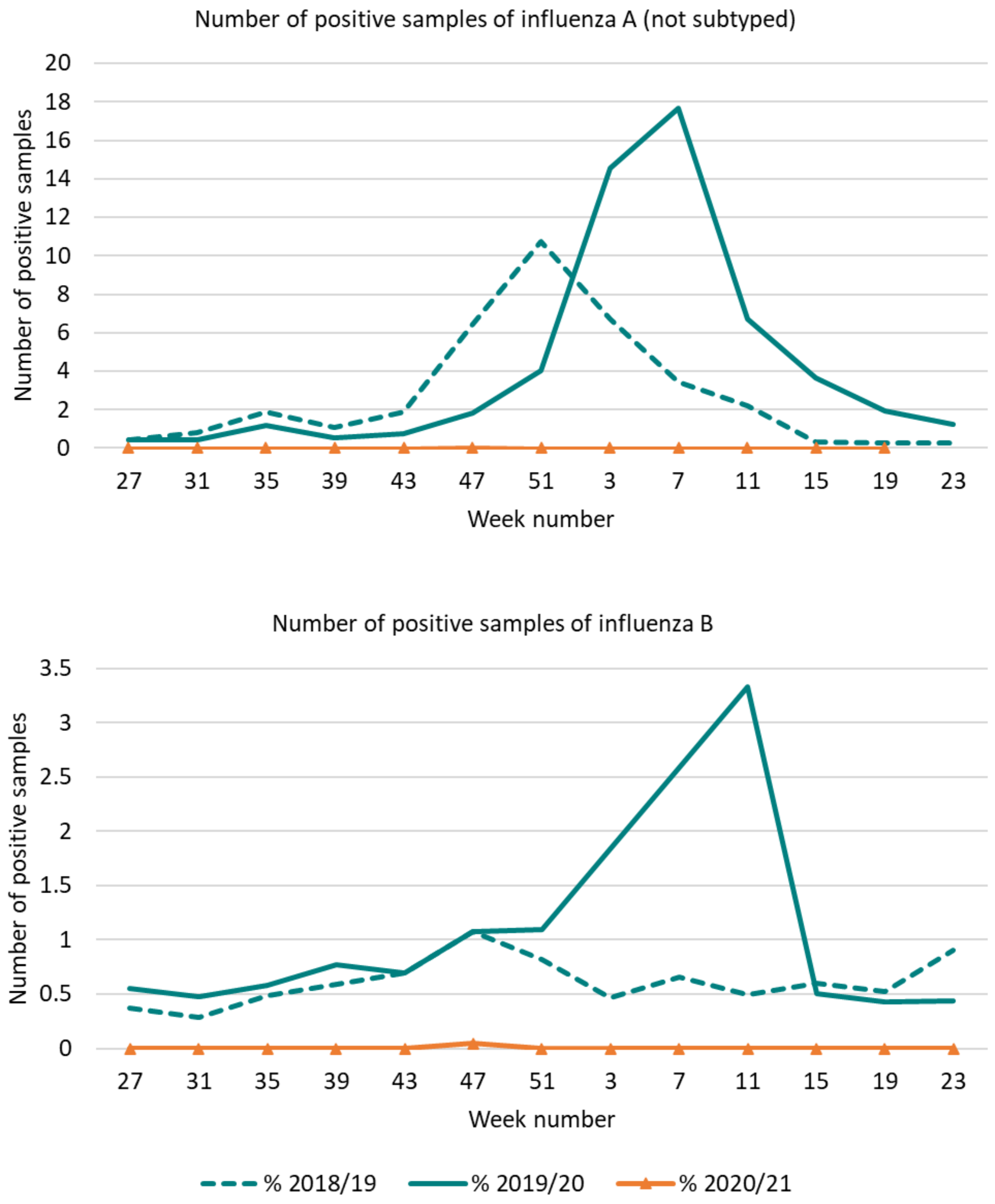

Figure 13. Adapted from Public Health England 2021. "Weekly Influenza and COVID-19 Surveillance graphs" (12)

Hospitalisations

Hospitalisation data for influenza for the 2020/21 period paints a similar picture: a total of 40 hospitalised confirmed influenza cases were reported from sentinel NHS acute trusts across England from week 40 2020 to week 14 2021 (**Figure 14**). Over this period, the hospital admission and ICU/HDU admission consistently remained far below the baseline threshold levels of 0.99 per 100,000 and 0.11 per 100,000, respectively – by comparison, in 2019 the hospitalisation rate for influenza-like-illnesses was 7.3 per 100,000 and the ICU admission rate was 0.45 per 100,000 (Public Health England, 2021e, 2021a).

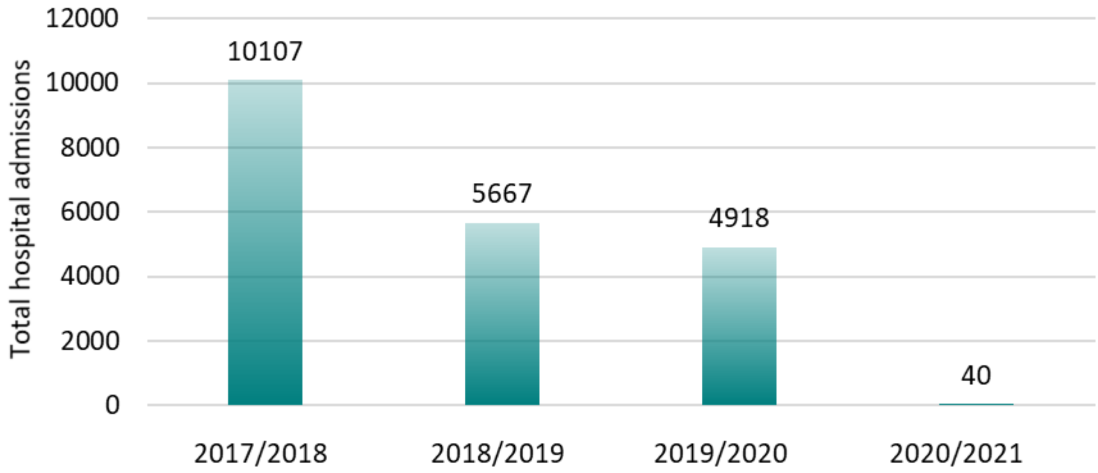

Figure 14. Seasonal influenza admissions 2017 - 2021. SARI watch data sourced from (Public Health England, 2021b).

Deaths

Preliminary ONS released on October 2020 showed that monthly mortality from influenza and pneumonia in England and Wales was significantly lower than the 5-year average during the period between January and August 2020 (**Figure 15**) (Office of National Statistics, 2020).

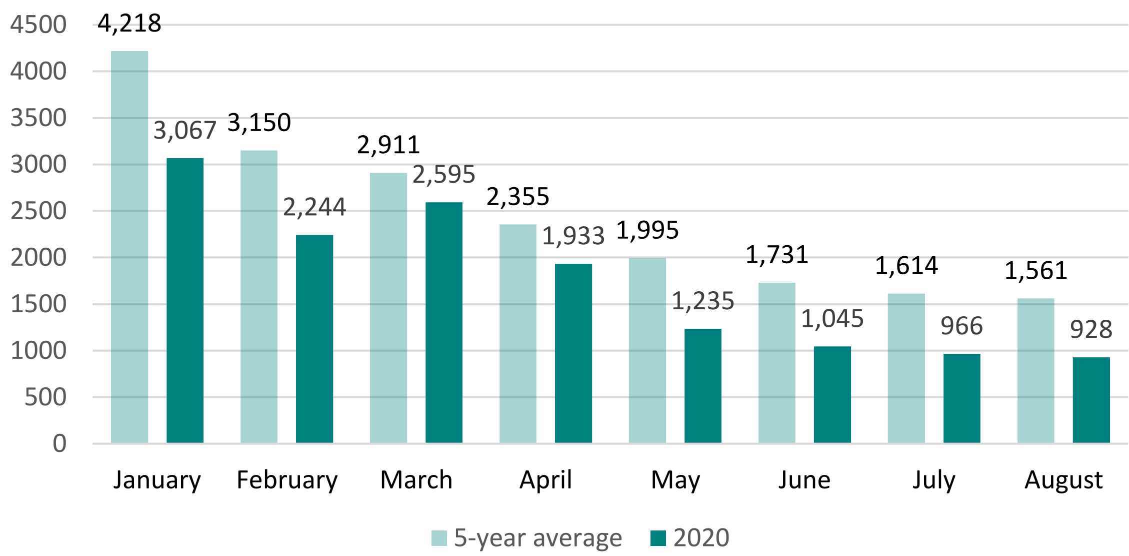

Figure 15. Monthly deaths from influenza and pneumonia in England and Wales, January to August 2020.

A historical look at yearly mortality over the last eight years also shows that deaths from influenza and pneumonia were remarkably lower than usual during 2020, with a 22% decrease on 2019 (**Figure 16**) (Office for National Statistics, n.d.)

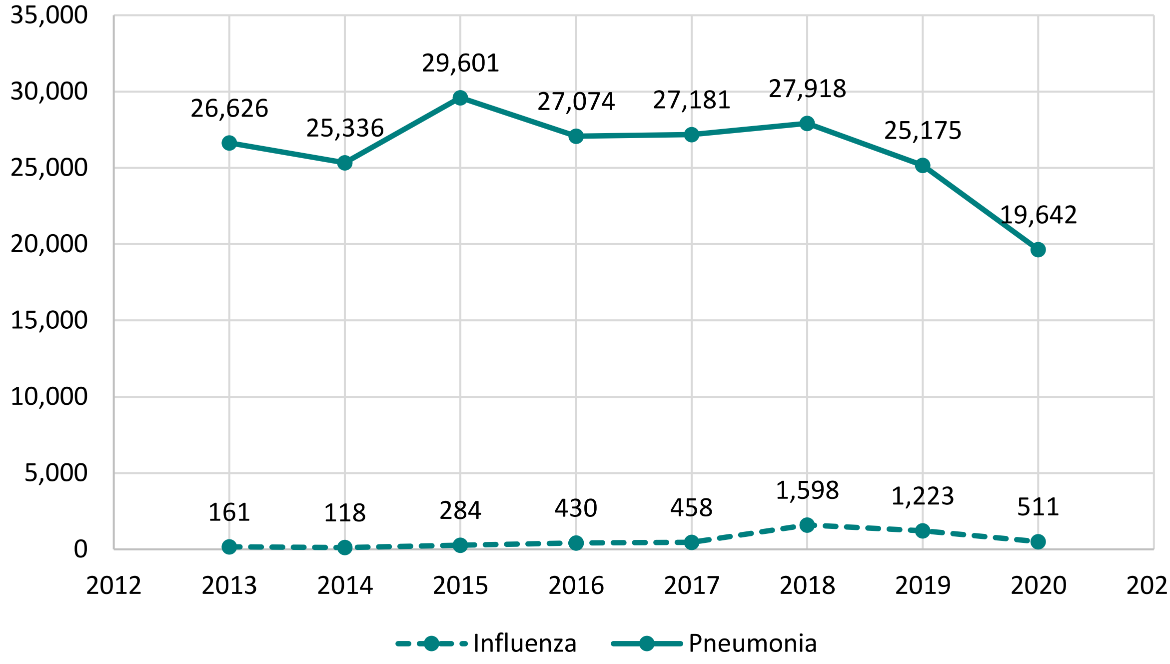

Figure 16. UK mortality by influenza and pneumonia, 2013-2020 (ONS, 2021).

Other infectious diseases

In addition to influenza, many other infectious diseases are likely to have been suppressed by the COVID-19 restrictions. **Figure 17** shows a substantial drop in incidence rates of many statutory notifiable infectious diseases in 2020 compared to 2018 and 2019. It is likely these diseases were suppressed by the change in behaviours in 2020 although lower reporting rates may have also had an impact. This is best evidenced by the fact that reported rates of food poisoning were also substantially lower in 2020 (Public Health England, 2021g). While it is possible that temporary restaurant closures have meant lower numbers of food poisoning outbreaks, many cases of food poisoning may have gone unreported as people were isolated at home.

There has been a significant impact on help-seeking behaviour, making it more likely that people with mild symptoms do not present to healthcare services (Public Health England, 2021h). This could be due to application of social distancing measures or the result of entreaties for people not to add to the burden of general practice and A&E with what might appear to be less severe illness.

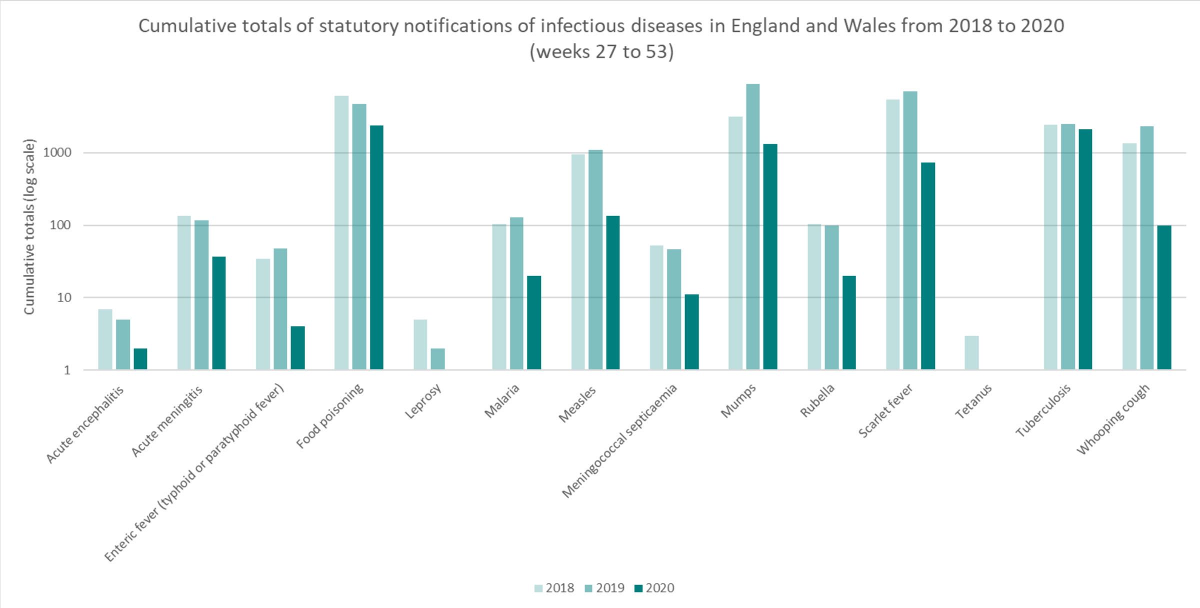

Figure 17. Cumulative totals of statutory notifications of infectious diseases in England and Wales from 2018 to 2020 (weeks 27 to 53). Adapted from [PHE. 2021. "Notifiable diseases: weekly reports for 2020"] (13)

Indirect impacts on mortality

In addition to behaviours explicitly directed at reducing disease transmission, other behaviours exhibited during the COVID-19 pandemic may have subsequent health effects and impacts on mortality.

Working-from-home

YouGov conducted online focus groups in June 2020, and although there were mixed messages from the respondents, for some it was clear that they would continue working-from-home if given the opportunity (YouGov, 2020). COVID-19 lockdowns forced many companies to adopt practices suited to remote working and, with these now in place, it is likely many people will continue to work from home. In some cases, remote working may become a necessity as businesses scale back on what is now unnecessary office space and overhead costs.

There are various potential impacts of this with subsequent effects on mortality. Firstly, less commuter traffic on roads may lead to less pollution and lower respiratory diseases, and less road-traffic accidents (Brown et al., 2021). The caveat here is that many commuters who would have used public transport changed to driving in order to social distance thus the volume of cars on the road may not change as much as expected.

Also, fewer commuters on public transport means less exercise walking to and from transport hubs. Reduced social contact with co-workers and increased overlap between home- and work- life may result in higher rates of depression, anxiety, and stress.

Personal health practices

Changes in **smoking behaviour** were seen early on in China as consumption levels significantly decreased following the initial nationwide outbreak (Yang & Ma, 2021). These changes were likely driven by internal motivations and therefore are likely to be maintained after the pandemic, thus reducing associated mortality and negative health effects. In England, the first lockdown has been found to be associated with an increase of smoking prevalence among young adults, although there was also an increase in attempts to quit smoking within the same demographic (S. E. Jackson et al., 2021).

During COVID-19 there were increased efforts to promote **healthy lifestyles** and behaviours in order to improve overall health and resistance to illnesses. Given the state or worry caused by the pandemic it is likely that many people were receptive to these initiatives. In addition, healthcare, healthy eating and exercise became more accessible through remote-video platforms and specialised delivery services, however the benefits of these changes are still competing with the disadvantages of local services closures and lock-downs (Kadakia et al., 2020; Sport England, 2021).

One health behaviour that appeared to increase during the pandemic was **alcohol consumption** (Pollard et al., 2020)**.** Various media outlets reported concerns over increased alcohol consumption, particularly during lockdowns. Concerns over alcohol misuse during the pandemic stem from the associated health problems and increased mortality, and continued monitoring of the situation was recommended (Clay & Parker, 2020; Pollard et al., 2020). Evidence from a 2021 study indicates that there are sex- and deprivation-related disparities in drinking behaviour during the pandemic, with women and people from deprived backgrounds more likely to engage in high-risk drinking. Conversely, there has been an increase in the frequency of attempts at reducing alcohol consumption during lockdown have only increased among people from more affluent backgrounds (S. E. Jackson et al., 2021).

What we have learned

The implementation of large-scale public health initiatives during the pandemic has been the catalyst for rapid social change and accelerated trends that may have otherwise taken years to become mainstream, such as remote working and reliance on home delivery for goods and services. The pandemic has also provided an unprecedented opportunity to field-test different behavioural management approaches, all of which can be called upon when it becomes necessary to adjust public health policies to rapidly changing circumstances.

Another emerging theme is the role of inequalities in shaping the epidemiological profile of the pandemic and the public's response to public health initiatives. This will be discussed further in the section on inequalities. One example is the higher prevalence of vaccine hesitancy among some ethnic minority groups, which are a heavily impacted demographic group. In this section we will take the UK perspective and provide an overview of the targeted interventions put in place by the government.

Changing behaviours: the "new normal" or "just a phase"

The previous sections focused on behaviours that have changed during the COVID-19 pandemic and the long-terms effects these may have on mortality, however a key question is whether these behaviours will be maintained after the pandemic is perceived to be over. A key factor in whether behaviours will continue beyond the pandemic is the motivation behind them.

Behavioural theories of motivation suggest that bottom-up approaches (internally motivated and voluntary) are more likely to be sustainable than top-down approaches forced by an external party (**Figure 18**).

	TOP-DOWN APPROACHES	INTERMEDIARY APPROACHES	BOTTOM-UP APPROACHES
	Forced behaviour adoption	Reinforced behaviour adoption	Voluntary behaviour adoption
Measures	• Government enforced lock-down • Fines and penalties for breaking COVID-19 restrictions	• Institutional rules i.e. shops requiring mask wearing and social distancing	• Better health practices
Advantages	• Quick implementation • Potential for high uptake in the short-term	• Low cost • Potential for high uptake in the short- and long-term	• Low cost • Potential for high uptake in the short- and long-term • Trust building
Disadvantages	• High cost • Sustainability difficulties • Dependence on political will and socioeconomic feasibility	• Reliance on institutional will and capacity to implement	• Lengthy implementation • Requires high quality engagement • Difficult to measure direct impact

Figure 18. Adapted from [Jalloh et al., 2021] (8)

National lockdowns and legally enforced mask-wearing and social distancing made a drastic change to everyday behaviour. However, this type of motivation is short-term and temporary, meaning that as soon as the "enforcement" ends, many people will abandon the new behaviour as well. In other cases, peoples understanding of infectious diseases has increased and, for some, the behavioural changes have been motivated by an internal shift toward better health practices. These behavioural changes are likely to be more permanent. In a way, the pandemic confronted many with the harsh realities of their negative health behaviours, for example smoking, poor diet, lack of exercise, and as a result may have prompted people to make decisions to improve their general health. Again, being internally driven, these behavioural changes are likely to be more sustainable than those driven by government guidelines.

In a 2020 national poll 29% of respondents said that they would be "less likely" to continue to follow COVID-19 related guidance on behaviours once they had been vaccinated, and 11% reported that they "would not" continue to follow the guidance. In contrast, in a poll of 1,662 British adults in May 2021, more than half of respondents said that after all restrictions on behaviour are lifted in the UK they would "definitely" or "probably" continue to wear a face mask in some public spaces, social distance in public spaces, and use hand sanitizer frequently (64%, 66% and 78% respectively). The proportion of people reporting that they would "definitely" continue these behaviours was 28%, 20%, and 38% respectively. The results were slightly higher in respondents aged over 65 years (YouGov, 2021b).

Several authoritative bodies including the UK government, the British Psychological Society, the Lancet COVID-19 commission taskforce, and the World Health Organisation have recognised the importance of sustained behaviour change beyond the pandemic and offer recommendations to achieve long-lasting behaviour change. There is a consensus that embedding behaviours into society requires changes to both physical and social environments, such as fostering safe workplaces and norms on hygiene behaviours. In order to achieve this, these environments need to be underpinned by a collaboration between community action, organisation regulation and national legislation (Lee et al., 2021; SPI-B, 2020; World Health Organisation, 2020b).

Popular support for lockdown

The introduction of a nationwide lockdown in the UK on 23 March 2020 has been the largest curtailment of individual freedoms since the end of World War II. This was done in response to fear and uncertainty in the early days of the pandemic, amplified by the worrying reports from other European countries that were ahead of the contagion curve at the time. The popular support for such a draconian measure has surpassed all expectations.

As early as April 2020, analysis of a survey by researchers at the London School of Economics indicated compliance with lockdown rules among respondents was not only overwhelming (**Figure 19**) but also largely voluntary rather than driven by compulsion (J. Jackson et al., 2020)

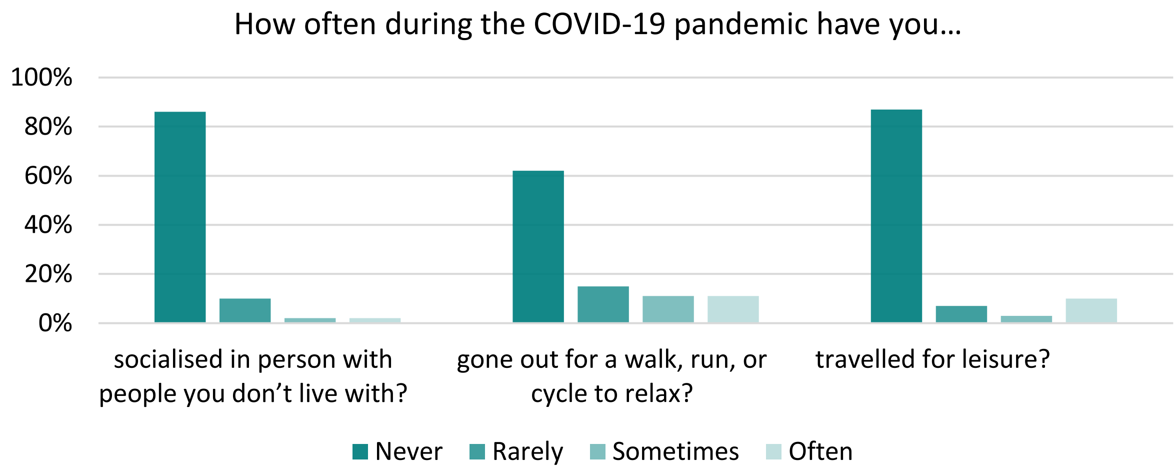

Figure 19. Responses to April 2020 multi-wave survey (J. Jackson et al., 2020).

A possible rationale for this is that, for most respondents, compliance was not driven by fear of consequences when breaking the rules (deterrence) nor by an abstract sense of respect for the law (legitimacy) but by two different behavioural levers: the fact that they are sensible measures to take in a pandemic and the pressure of social norms.

According to the LSE analysts, "The law, through its expression, influences beliefs and guides behaviour": in other words, once social distancing was made a legal requirement, a clear signal was sent to the public that the rule had to be taken seriously, and a clear boundary between licit and illicit behaviour was set. This was borne out by the survey response: 35% of respondents *somewhat* agreed making unwarranted travel out of bounds 'helped to clarify what we should and should not be doing' and 53% *completely* agreed.

Social norm – the sentiment people in a community share about what constitutes correct behaviour and what does not – also concurs to shape individuals' behaviours through fear of social disapproval. During the pandemic, this social pressure tied in with the notion of sharing a burden for the greater good, summarised by the slogan "we are all in it together" and symbolised by support for key workers in the NHS and other essential sectors.

Another survey conducted around the same time by Ipsos MORI and analysed by King's College London (Duffy & Allington, 2020) also indicated overwhelming popular support for the lockdown, with only 9% of respondents in overt opposition. However, the analysis also highlighted some clear differences in the psychological motivators and responses of the respondents, which are summarised in **Figure 20**.

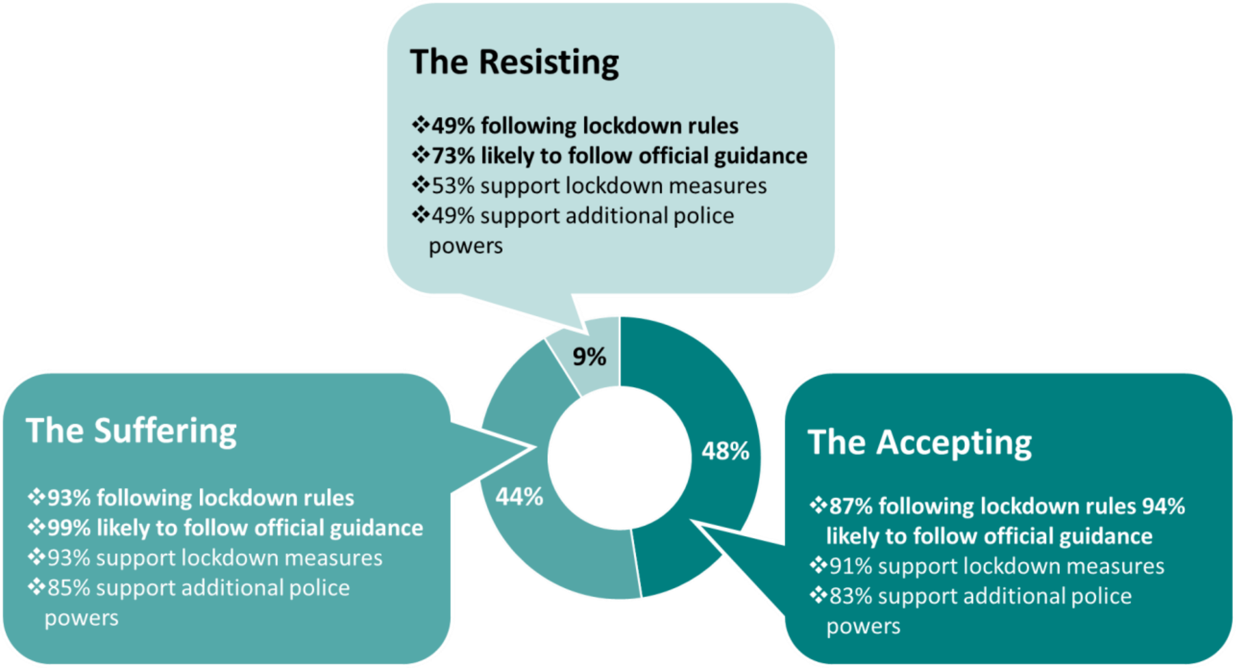

Figure 20. The different profiles of psychological response to lockdown (Duffy & Allington, 2020)

The "Resisting" respondents were also far more likely to express concern about facing financial hardship as a consequence of lockdown compared to the "Accepting" (65% and 28%, respectively).

The first lockdown eventually came to an end in June 2020, but the threat of rising COVID-19 cases forced the government forced to reintroduce restrictions – albeit more limited in range and area – throughout the autumn and early winter. It is noteworthy that popular support for these measures did not flag significantly even after their severe financial and social costs had become evident. A YouGov poll revealed that 79% of the public supported the idea of the UK entering another lockdown as of January 2021, with an 8% increase on the previous month. However, the number of those opposing a tightening of restrictions had increased to 16% of respondents (YouGov, 2021a)

The postponement of "Freedom Day"

The much-anticipated lifting of most social restrictions across the UK, initially set for June 2021, was postponed on short notice by about four weeks due to ongoing concerns about case numbers weighed against the progress of the vaccination campaign. A YouGov snap poll released on 14 June 2021, however, indicated that the English public was largely supportive of the delay, with 71% of respondents in favour. Support was more or less unanimous across the political spectrum, although there was a clear stratification based on age group, with those in the 18-24 years group showing much weaker support (54%) and stronger opposition (34%) compared to those over 65 (81% and 17%, respectively) (Walden, 2021). This may reflect the fact that restrictions are likely to impact young people's social lives to a greater extent, and that risk perception is understandably much higher among older people.

Overall, the headline polls portray a country standing by the government's decisions, no matter how harsh. While this is certainly true to some extent – as shown, if nothing else, by the relatively low traction of anti-lockdown protests in the UK compared to other European countries – we should bear in mind that polls and surveys inevitably oversimplify reality. The importance of using these tools correctly, and the implications of poor framing in policy-making, will be discussed in more detail in the last section of this chapter.

Vaccine hesitancy – something old and something new

Reluctance and hostility to vaccination are nothing new. Even as far back as the early 18th Century, the earliest attempts at inoculation against smallpox in Europe were met with fierce opposition. Religious beliefs, poor education, and the objective risks associated with the early techniques of vaccine production, all contributed to spreading anti-vaccination sentiments across Europe. This sometimes resulted in political and legal quarrels that dragged for decades, such as the ones seen in the UK after the introduction of compulsory smallpox vaccination in the first half of the 19th century.

The utility and efficacy of vaccination are now universally recognised. However, while exceptionally rare, incidents due to human errors in development or production, such as the 1955 Cutter incident and the 1976 "swine flu fiasco" (Center for Disease Control, 2019), have done little to pacify vaccination opponents.

Nowadays the anti-vax front is by no means a unified one. Anti-vaxers variously cite a number of rationales for refusing vaccination: safety concerns around the side or long-term effects of the vaccine, or the toxicity of vaccine ingredients; purported associations between vaccines and unrelated pathologies (as in the MMR-autism *cause celebre*); generic mistrust of government or health authorities; and more outlandish conspiracy theories. These concerns have been repeatedly debunked, yet vaccine hesitancy in Western countries has persisted through the last few decades. The rise of the Internet and social media has presented new challenges, by affording the public unprecedented access to complex (and easily misinterpreted) information, while at the same time providing countless platforms from which misinformation can be spread and amplified.

Vaccine hesitancy in France

Vaccine scepticism has been historically entrenched in France, largely due to two major health scares that plagued the country in the last two decades of the 20th Century. In the 1980s, contaminated blood products were knowingly allowed to enter the distribution chain in France and several other countries, infecting thousands of patients with HIV and hepatitis C. In the following decade, rumours of a link between the hepatitis B vaccine routinely administered at the time and new occurrences or relapses of multiple sclerosis spread across France, eventually bringing the government to suspend the school-based vaccine programme in 1998. This was erroneously interpreted at the time as a blanket ban on hepatitis B immunisation and had a long-lasting impact on vaccine confidence among large swathes of the French population. It is therefore unsurprising that anti-vax sentiment – along with a historical, general mistrust of government and health authorities – has resurfaced in full force during the pandemic.

As of early July 2021, the vaccination rate in France lagged slightly behind the EU average, and well behind countries such as the US and the UK. First, inoculation rate per day had fallen to approximately 200,000 from a maximum of 400,000 at the end of May, raising concerns as to France's ability to achieve the proposed target of herd immunity by autumn 2021 (Caulcutt & Collins, 2021). Vaccine hesitancy among health care workers, with only 60% of care home workers and 80% of private medics having received the first vaccine dose (Sante Publique France, 2021), was especially concerning in the face of rising case numbers and the increasing prevalence of the Delta variant, which, according to some projections, may account for as many as 90% of new cases by the end of August 2021.

On 12 July 2021, President Emmanuel Macron announced the introduction of a public health programme that would require a clear health pass, certifying either full vaccination or a recent negative COVID test, to access most public spaces. The programme came into force on 21 July 2021 and has since been extended to restaurant, cafes, hospitals and long-distance trains. Free COVID tests are to be made unavailable from September, in a bid to increase pressure on French citizens to get vaccinated as soon as possible, and vaccination is to become mandatory for health workers, care home workers and anyone working with vulnerable people, with sanctions (including suspension and termination) coming into force in September.

While similar measures have been implemented across the European Union with the introduction of the "green pass" system, the French government's openly top-down approach has been somewhat unique in its bluntness. In Macron's own words:

"Vaccination is not immediately obligatory for everyone, but we're going to extend the health pass to the maximum, in order to push a maximum [of citizens] to go and get vaccinated".

In the short term, the move has certainly been effective: online vaccination booking systems logged almost one million new appointments, mostly by people under 35, in the 24 hours following Macron's announcement, breaking all previous records since the start of the vaccination campaign (The Guardian, 2021a). As of early August 2021, although still slightly behind the EU average in terms of proportion of the population vaccinated, France appears back on its way to achieve its target of fully vaccinating 50% of the population by the end of August.

It remains to be seen whether Macron's initiative will maintain its momentum into the autumn and winter months. As mentioned earlier, one of the main downsides of top-down approaches to behavioural management is that, while often hugely successful in the short run, they rely heavily on political will and public compliance to remain so in the long term. So far, support for the government's initiative has been almost unanimous across the political spectrum. However, several mass protests have taken place across France since Macron's announcement, bringing together staunch anti-vaxers and citizens who may not object to the vaccine per se but view the health pass as a threat to civil liberties. If public opposition should increase in the coming months, other parties may choose to capitalise on popular discontent in sight of the upcoming general election. In a country where anti-vax and anti-government sentiments are often hard to separate, this could prove disastrous for the long-term prospects of the vaccination programme, especially if SARS-CoV-2 does become endemic.

Vaccine hesitancy in the UK

In contrast to France, the COVID-19 vaccination campaign in the UK has been well received overall. According to a March 2021 survey by Ipsos MORI on vaccination intent, 83% of respondents were willing to take the vaccine if available (Ipsos MORI, 2021).

A practice guideline published in the British Medical Journal in late May 2021, based on responses to the UK Household Longitudinal Survey gathered in November 2020, places vaccine hesitancy among the British public at approximately 18% overall - a result very much in line with the Ipsos survey mentioned above. However, there is a very definite divide in vaccine acceptance between ethnic groups, with hesitancy much more prominent among people of Black ethnicity (72%), followed by

South Asians (42%) and mixed ethnicities (32%). In this sense, it appears that socioeconomic status and ethnic identity do correlate with level of confidence in vaccination in general – and therefore willingness to accept a COVID-19 vaccine in particular (Razai et al., 2021).

The drivers of low confidence in COVID-19 vaccines are manifold, but they all point to a substrate of systemic inequalities – socioeconomic, racial and educational – that make respondents more vulnerable to misinformation and misconceptions about vaccines or less trusting of government, and less willing, or able, to access the vaccination programmes implemented by the government (**Figure 21**).

Among the concerns mentioned by respondents, the potential long-term effects of COVID-19 vaccines are the most prominent, as well as the potential effects on fertility, pregnancy and breastfeedingYounger people are more likely to consider themselves at lower risk. Notably, people from Black ethnicities are much more likely to report a general lack of trust in vaccines compared to White people (29% and 6%, respectively). This may tie in with the widespread perception of systemic racism, and with past instances of unethical medical practices targeting ethnic minorities (Center for Disease Control, 2013).

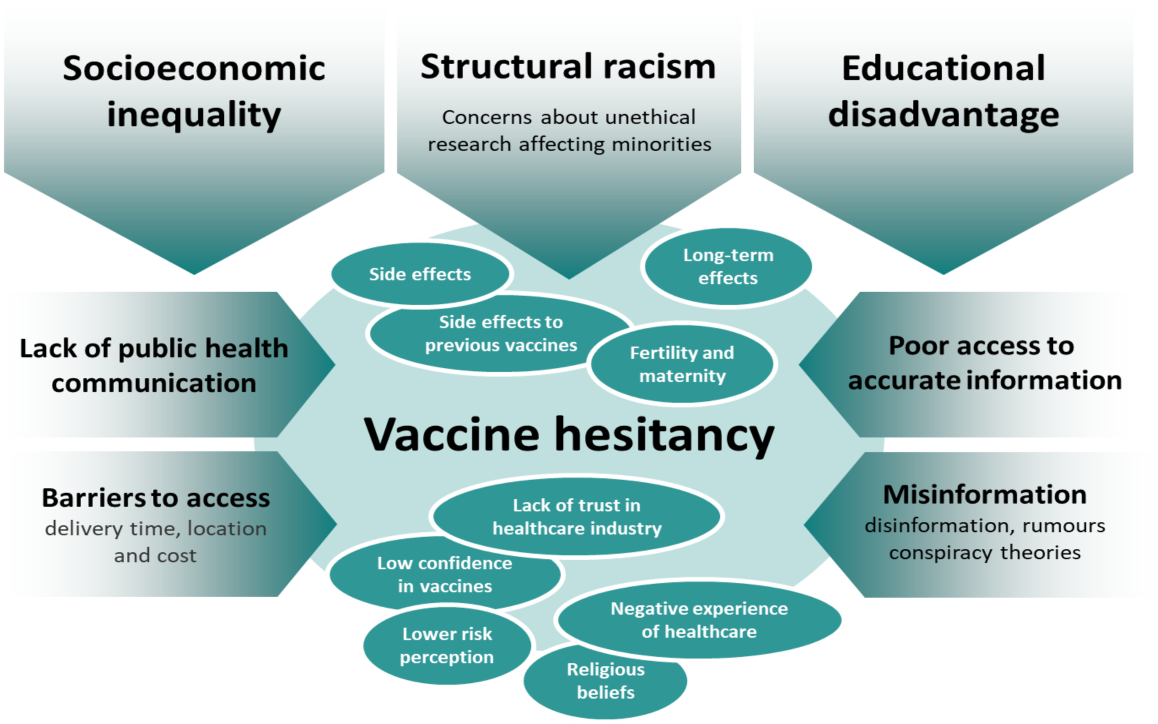

Figure 21. Causes and features of hesitancy towards COVID-19 vaccines.

The data presented above refer back to the end of 2020. Starting in February 2021, however, the UK government launched a public health campaign to tackle vaccine hesitancy across the country. The approach of the campaign is multipronged and aims at improving collaboration between the NHS and local / national authorities; removing barriers to access; disseminating information and combating misinformation; and lastly, promoting public engagement with the public through traditional and social media (**Figure 22**).

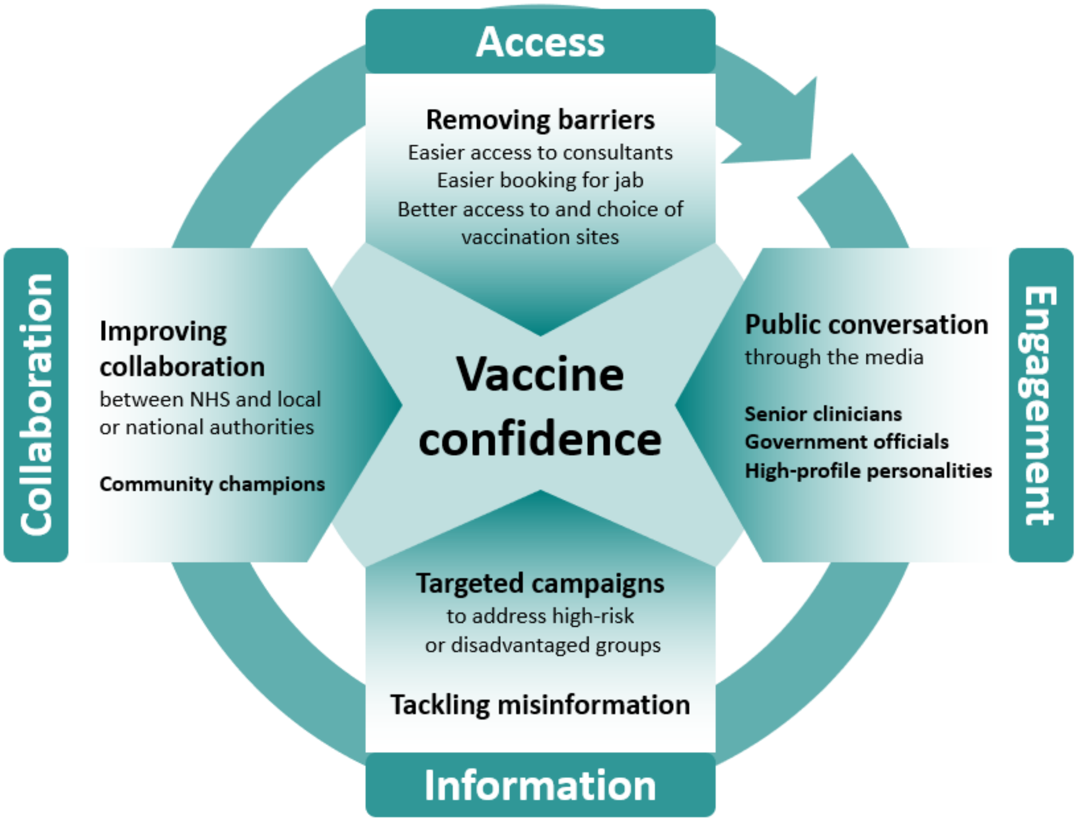

Figure 22. Overview of the UK Government's vaccine uptake strategy

The initial results certainly appeared encouraging. Data collected by ORB International and the Vaccine Confidence Project in April 2021 indicated that the number of adults under 45 who would definitely get vaccinated had increased by over 20% (17% of men and 27% of women), with 63% of respondents saying they would definitely get the vaccine and 21% likely to accept.

Most importantly, the survey recorded a significant improvement in vaccine confidence among people from ethnic and religious minorities. Between February and April 2021, vaccine uptake increased by over three times in Black and Asian communities, and the trend was projected to continue in younger age groups. There was a 21% increase in vaccine confidence among Muslims and an 18% increase among Christians (London School of Hygiene and Tropical medicine, n.d.).

Data from April-May 2021 released by the Office for National Statistics also painted a much rosier picture compared to late 2020, with over 9 in 10 adults reporting positive sentiment towards a COVID-19 vaccine (Office for National Statistics, 2021b). Vaccine hesitancy was only reported by 6% of respondents. The survey also looked into the motivations for vaccine hesitancy, essentially confirming the previous findings. Among women, for instance, 31% reported feeling hesitant due to concerns about fertility or maternity. People in extremely vulnerable conditions and people with disability also felt more concerned about possible undesired effects of the vaccine on their health (44% and 27%, respectively) compared to the general adult population (11%).

One interesting finding is that people living in affluent areas were over three times more likely to feel that coronavirus was not a personal risk to them than people from the most deprived areas (27% versus 8%), which probably reflects their personal circumstances whereby they were indeed at much lower risk. People from affluent districts, for instance, may be more likely to be able to work from home, and therefore less exposed to infection and less affected by social restrictions; or they may be more confident about their opportunities to access high quality healthcare, whether through private insurance or because of better-funded NHS facilities in their local area. They are also less likely to live in multiple occupation or multi-generation homes, are more likely to have cars which reduce the need to use public transport. They are more likely to have access to computers and online banking making remote shopping more accessible and many other features of privileged life that increase control over the environment and increase the ability to avoid exposure.

What are the uncertainties?

If there is one lesson to be drawn from the pandemic, it is that no intervention can be fully effective unless as a part of a broader, multi-pronged strategy, and that re-assessment and re-calibration are needed at every step, as the strategies put in place to tackle the pandemic can also have, far-reaching repercussions on other areas of public health, and on society at large. Even tools of proven efficacy, such as mobile app-based track-and-trace programmes, can backfire unexpectedly due to sudden shifts in sentiment or inappropriate media coverage: one such instance occurred with the so-called "pingdemic" of July 2021, which will be covered briefly in this section.

Some of the measures put in place, moreover, while certainly effective in the short to medium term, may not be sustainable as long-term management tools – either because of their huge direct costs (as in the case of nationwide lockdowns and employment support programmes) or because of wavering public compliance. The success of the first immunisation campaign will undoubtedly be the cornerstone of any future strategies, but the exact shape these will take will depend in large part on hard-to-predict quantities, such as the future evolution of SARS-CoV-2 and the ever-shifting sentiment among public and policy-makers.

One last concern is the possibility of a rebound of influenza and other seasonal respiratory diseases in 2021-2022. Although difficult to predict with any certainty at present, the risk of a "double whammy" on the NHS during the colder season has been deemed substantial enough for the government to start planning preventative measures.

The long road to vaccine confidence

In the previous sections we have given an overview of vaccine hesitancy as an emergent problem and looked at France and the UK as contrasting examples of how this can be tackled during an emergency. In spite of the best efforts of governments, however, it is not unreasonable to assume that a goal of 100% vaccine uptake will remain unrealistic for some time to come.

In most countries, anti-vaxxers have historically been a vocal but small minority, usually confined to the fringes of public debate, yet the phenomenon has always been a concern for health authorities, as even a relatively small fraction of the population refusing vaccination can delay or even derail the achievement of herd immunity, by establishing a reservoir within which the virus can continue to circulate. The unprecedented crisis brought on by the pandemic, however, invested the issue with a whole new urgency.

The importance of mass and social media, in particular, has not been lost on authorities. Anti-vax positions now have much greater potential to spread virally, which could effectively sabotage a national vaccination campaign and lead to catastrophic human and economic loss. Moreover, anti-vax sentiment can become enmeshed within a broader political dispute, as shown by the prevalence of vaccine hostility among Trump supporters in the USA (Hornsey et al., 2020), or by the emerging association between anti-vax movements and populist parties across western Europe (Kennedy, 2019). This can polarise the political debate, in turn destabilising governments and hampering national and international efforts.

It is therefore not surprising that government have put information sharing at the centre of their vaccine uptake strategies, maximising citizens' access to correct information and actively discouraging misinformation. This has gone hand in hand with behavioural management strategies aiming to reward vaccine uptake while at the same time penalising hesitancy. The various ratios of positive-to-negative reinforcement adopted by different governments will provide a unique opportunity to field-test and calibrate future approaches. This will be crucial in the likely scenario of SARS-CoV-2 becoming endemic. Moreover, any lessons learnt from managing vaccine confidence during the pandemic will also help inform more effective immunisation campaigns against other diseases, including those – such as measles, influenza or rubella – that have been resurfacing due to flagging vaccine uptake in recent years.

An influenza rebound?

Generally speaking, if social distancing, working from home, and better personal hygiene practices were to continue, future influenza rates would be expected to mirror those reported in the winter season of 2020/21. If these behaviours cease or become less common, rates may be expected to rise back to those seen in 2018/19 and 2019/20.

However, one troubling implication of the drop in influenza cases during the COVID-19 pandemic is the possibility of a sharp rebound in the 2021/2022 season. As discussed, although a significant number of flu cases may have simply gone unreported due to patients' reluctance to visit GP practices and hospitals during the pandemic, the data indicate that lockdowns, social distancing and enhanced personal hygiene practices have also hindered the circulation of the flu virus. This, however, may have had the undesired effect of reducing immunity levels in the population, and possibly placed evolutionary pressure on the circulating flu strains to become more transmissible. Both factors could pave the way for a particularly virulent outbreak of influenza once restrictions are fully lifted. Other seasonal viruses may also see a resurgence, for similar reasons – reported cases of the common cold, for instance, while still several times lower than historical averages for the period, were already on the rise again as early as August 2020 (Iacobucci, 2020)

Moreover, the scarcity of influenza case records for the past year might make it harder to predict which strain will be more likely to circulate next winter and plan the next flu jab campaign accordingly.

As the current situation is unprecedented, the usual predictive models are not in agreement, and whether the next flu outbreak will be worse or better than usual remains, to some extent, an open question. Nevertheless, a recent rapid review recommended that the NHS prepare for the worst on a precautionary basis (The Academy of Medical Sciences, 2021). Depending on the forecast model used, influenza mortality could range between 15000 and 60000 deaths in 2021/22, compared to the 10,000 to 30,000 observed over the last few years. In the worst-case scenario, a virulent influenza outbreak, with higher-than-usual number of patients requiring hospital care, could coincide with a new wave of COVID-19 cases, not only taxing the capacity of the NHS but also pushing back the backlog of routine care from 2020-21. Several experts have therefore recommended a repeat of 2020's expanded flu vaccination drive, and plans are already in place to offer the vaccine to over 35 million people this year, including, for the first time, all secondary school students up to year 11. The 2021 expanded plan is expected to be rolled out alongside any COVID-19 booster programmes through the autumn and winter, and will almost double on 2020's expanded programme, which reached approximately 19 million people overall and achieved a target of 80.9% vaccination among people over 65 (Department of Health and Social Care, 2021a).

The 2021 "pingdemic"

UK media coverage of the pandemic in July 2021 has been largely dominated by two highlights: the lifting of social restrictions, finally coming into effect on 19 July 2021, and the "pingdemic", a sharp increase in the number of instructions to self-isolate sent via the NHS COVID-19 mobile app, so named after the app's sound alert. This has come in the wake of an uptick in new COVID-19 cases across the UK between June and July 2021, peaking at over 60,000 new cases reported on 15 July 2021 – the highest since January (Coronavirus Data, 2020). As of 29 July 2021, out of approximately 23 million users of the NHS COVID-19 app nationwide, over 690,000 had received instructions to stay at home and isolate, with an average of 3.2 pings per reported case sent over the last month (BBC News, 2021).

The sudden increase in the number of people self-isolating had a snowball effect across all sectors of the economy, particularly where the physical presence of workers is required. Retail and hospitality were among the worst affected, with up to 30% of staff in some businesses having to self-isolate. In retail, the effect was compounded by staff shortages in the logistics sector, resulting in stock shortages in supermarkets across the country, temporary store closures and reduced opening hours. Staff shortages forced public transport services across the UK to cancel services and close lines, while several councils have been forced to roll back non-essential services (The Guardian, 2021b). On 20 July 2021, the government responded by issuing self-isolation exemptions for workers in critical services, including food and drug production, energy, railway transport, the military, and police and border forces (Department of Health and Social Care, 2021e).

Healthcare was not, initially, among the exempted sectors, raising concerns on the impact of the "pingdemic" on healthcare services as the NHS endeavoured to deal with the backlog of routine care from 2020 and the wave of new COVID-19 cases at the same time (The Guardian, 2021b). This led to a rule change from the 19th of July allowing doubly vaccinated frontline NHS and social care workers to continue working with regular testing 'under exceptional circumstances' provided they have a negative PCR test and at least 10 consecutive days of negative lateral flow tests that have been reported to 'Test and Trace' (Department of Health and Social Care, 2021b; England, 2021).However, the evolution of the situation over the coming months will depend in large part on the progress made towards achieving herd immunity, and on the effective containment of viral strains circulating in the unvaccinated population – as long as there is potential for a sudden increase in case numbers, a new "pingdemic", and the attendant disruption, will always be a possibility.

The psychological fallout of the "pingdemic" is another factor that should not be overlooked. Through the late spring and early summer of 2021, the steady decrease in new cases in the wake of the vaccination programme, and the eventual lifting of social restrictions, had undeniably fostered a feeling among the public that a return to normality was underway. In the light of this, it is perhaps unsurprising that the media have largely focused on the "pingdemic" as something of a freak event, rather than on its underlying causes, leading one Sage committee member to label the term "a distraction" and a case of "solutions being treated as problems" (Reicher, 2021). The new rise in cases, however, was a stark reminder that the pandemic is far from over.

Moreover, in a break away from previous trends, the response to the new spate of self-isolation notices has been mixed, particularly among workers in historically low-paying, low-security sectors such as retail and hospitality. There have been several news reports of workers in affected industries either choosing to ignore the app alert, or being instructed to do so by employers trying to avoid closures and loss of revenue. A recent YouGov survey suggested that one in 10 people who had previously installed the app have now deleted it, and *#deletetheapp* has been a trending topic on social media over the last few weeks (BBC News, 2021). Aside from the obvious implications for the safety of workers and customers, if such sentiments became entrenched, they could have worrying repercussions on the future success of policies relying on the public's compliance.

Threat perception and public support

As we discussed, early surveys indicated that one of the main psychological drivers of support for social restrictions was the so-called "expressive function of the law", translating into a feeling that compliance was necessary because the government would not impose such draconian measures unless the threat was, indeed, a serious one. An independent review of data gathered in 2020 (Foad et al., 2021) confirms this, by pointing out that support for restrictions ties in with a perception of COVID-19 as an nation-level threat, and is therefore largely independent of individuals' perceived level of personal threat. One immediate implication is that emotion-leveraged public appeals to comply in order to protect oneself and one's loved ones, frequently used by government and health authorities during the first months of the pandemic, may not be as effective as thought.

However, the study also highlights a few, more general concerns. For one, if threat perception is a direct consequence of the magnitude of the government's response, an untimely lifting of restrictions may usher in a false sense of security and cause people to downplay the danger of COVID-19. Similarly, if the massive support for the first lockdown was a direct consequence of a sudden shift from normality to emergency, there is a concrete possibility of a tolerance effect setting in over the long term, with the public becoming less and less willing to take restrictions seriously once they become established as a routine response to emergency. Lastly, public support for restrictions is probably much more nuanced than the headline polls suggest. When participants were asked to take into account the downsides of restrictions – such as negative effects on mental health, neglect of routine healthcare or economic hardship – the prevailing response was that the costs of lockdown may well outweigh its benefits. This cannot be underestimated, as we now know that social restrictions can and do exacerbate existing inequalities. Therefore, the study warns against over-reliance on polls and surveys when shaping policy:

"[…] if the public uses the magnitude of a policy response (e.g. unprecedented lockdown) to guide their judgement for the suitability of such policies, and the government use public opinion to inform their views regarding the acceptable level of restrictions to implement, then there is a strong potential to maintain symbiosis between government policy and public opinion."

The dangers of such a scenario are obvious. On one hand, policy-makers may be tempted to value public support over objective, evidence-based evaluations. On the other, the public may form a skewed perception of the actual threat, leading to complacency or irrational anxiety – either of which could in turn feed back into the loop.

The relationship between public sentiment and public policy is a complex one, and more research into the psychosocial drivers of mass compliance is necessary. However, it seems clear that successful management of the pandemic (and of other major crises, such as climate change) in the long term will require a more balanced approach to the use of polls and surveys, one that looks past headline results and political point-scoring by offering a realistic picture of the costs and benefits of social restrictions.

The pandemic and inequality in the UK

What we know

Inequalities in society are not only inherently unjust, they also have a negative impact on the economy as a whole. According to some estimates, as the Gini index[1] of a country increases over 27%, there are increasingly negative impacts on the economy (Grigoli & Robles, 2017). The Gini index for the United Kingdom has risen for four consecutive years, reaching 36% in 2019/2020 (Clark, 2021). Also, income inequality appears to be independently related to life expectancy at birth (De Vogli et al., 2005). Reducing inequality is therefore important both from an ethical and an economical standpoint. In this section we will look at how the pandemic has affected inequalities internationally and in the United Kingdom in particular.

The Longevity Science Panel has previously focused on the impact of health inequalities on life expectancy in its 2018 report.

Economics

The COVID-19 pandemic has had the largest effect on the economy recorded in modern times. By 2 June 2021, the virus had infected over 4.5 million people within the UK and claimed over 150,000 lives (Coronavirus Data, 2021). The number of cases and the transmissibility of the virus meant that drastic measures had to be taken to stop the spread of the virus and preserve life and protect the NHS.

On the 23 March 2020, the PM announced the first national lockdown in the UK (Boris Johnson 2020). This was the first in a series of mandated prevention and control measures, including stay-at-home orders, limits on social gatherings and the quarantining of arrivals from abroad. This had an unprecedented effect on the economy. Overall, during 2020 GDP fell by 9.8%, which is the steepest decline since consistent records began in 1948 (OECD Economic Outlook, Volume 2020 Issue 1 2020).

The differential impact of the lockdown on different sectors of the economy has been a major driver of worsening inequality within the population. There are clear age, gender, socioeconomic and ethnic differences in the workforce, meaning that women, ethnic minorities and people in lower-pay jobs have been over-represented in the industries that have borne the worst impact of the pandemic (Marmot et al., 2020).

Gender inequality

Women were more likely to lose their job during lockdown in the UK and internationally, and their incomes fell more than men's (Hai-Anh H. Dang & Cuong Viet Nguyen, 2020; Madgavkar et al., 2020). This is partly explained by the roles that women have played in the workforce (women were about one third more likely than men to work in a sector that was shut down by the pandemic) but is also a reflection of the roles that women play in society at large. For example, women seeking work or in employment were disproportionately affected by school and nursery closures during the pandemic (Blundell et al., 2021; Fawcett Society, 2021).

Age inequality

It was noted early on that the pandemic had a disproportionate effect on the employment and unemployment of young people aged 16-24 years. Between Q1 2020 and Q1 2021 there was a fall of 310,000 (8%) in employment levels for young people, compared to a fall of 117,000 (0.4%) across all

[1] The Gini index is a metric for wealth inequality within a country or any other group of people, usually expressed as a percentage value with 0% signifying perfect equality and 100% maximum inequality.

working ages. Employment levels for older workers aged over 65 years have also fallen considerably by 102,000, a 7% decrease (Office for National Statistics, 2021f).

Adults between 25 and 44 are the group most likely to have dependent children. The disproportionate increase in unemployment in this group would therefore have a corresponding impact on children. It is expected that there will be a substantial increase in the number of children living in poverty (Parkes & Mcneil, 2020).

Young people have also had their prospects disproportionately harmed as a result of the impact of the pandemic on education, with long-term effects on their educational progression and labour market performance (Blundell et al., 2021).

Race inequality

Minority ethnic groups were also disproportionately affected by the pandemic. Between Q1 2020 and Q1 2021, the unemployment rate increased from 6.3% to 8.9% in minority groups, compared to 3.6% to 4.1% in white ethnic groups (Office for National Statistics, 2021a).

Inequality by industry sector

The pandemic did not affect all sectors of the economy to the same degree. The lockdowns and social restrictions, in particular, impacted some industries far more than others. Notably, the output of the hospitality and food sector fell by 91% between February and April 2020. Similarly, output in the arts and entertainment sector was 49% lower in May 2020 than in February. Wholesale and retail, and the transportation sectors, also saw large downturns (Harari & Keep, 2021).

The hospitality sector has seen the largest economic decline of all the sectors since the pandemic. The industry has suffered both in terms of economic output and unemployment rates. Prior to the pandemic, the sector makes up 4% of all businesses, contributed approximately 3% to total economic output and 7% of total employment. (Hutton & Foley, 2021; Office for National Statistics, 2021d).

In July, when dining establishments reopened, output was down 44% compared to February. The sector was stimulated in August by the Eat Out to Help Out Scheme, which fuelled a 71% growth on July, but was still down 14% from February. Output declined again from September due to further restrictions, and was 67% below pre-pandemic levels as of January 2021 (Hutton and Foley 2021).

The ONS reported in early March 2020 that 43% of hospitality businesses were trading, compared to 74% across all industries ("Business Impact of COVID-19 Survey (BICS) Results" 2020). As a result, employment in the sector has been significantly affected. From January-March 2020 to July-September 2020, the number of workers in the sector fell by 6% (147,000) (Hutton & Foley, 2021). There were fears of a further increase in unemployment when the Coronavirus Job Retention Scheme (CJRS) comes to an end, though the hospitality sector seems to be experiencing a labour shortage and is having difficulty in recruitment (Race, 2021).

Mortality

The United Kingdom had a relatively high mortality from COVID-19 in 2020 (Marmot et al., 2020). Predictably, the burden of severe illness and mortality has weighed disproportionately on older people, as indicated by the age distribution of COVID-19 deaths during 2020 (

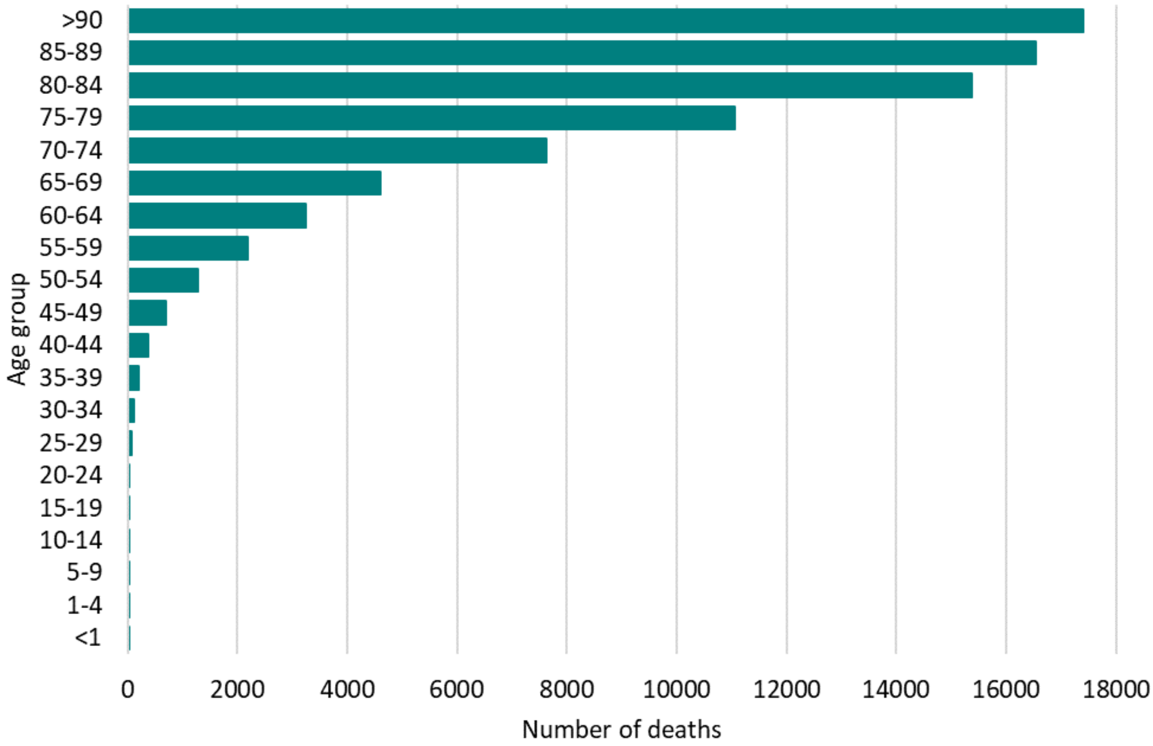

Figure 23).

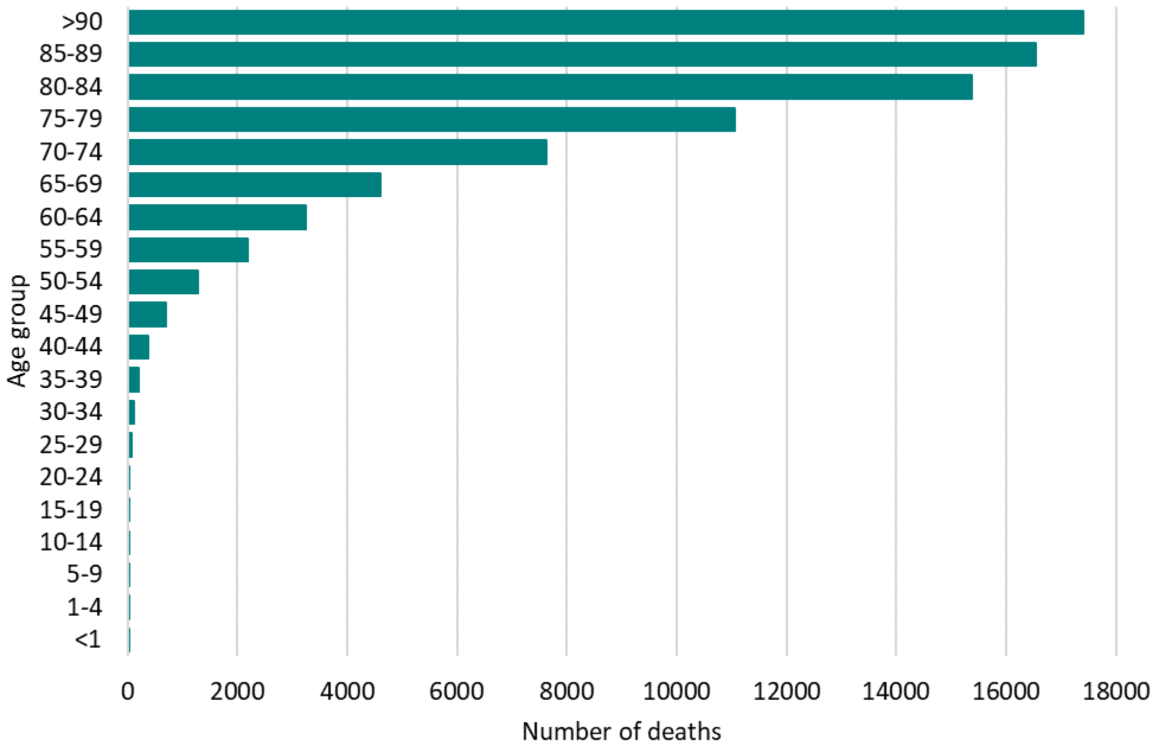

Figure 23. Distribution of COVID-19 deaths by age group in England and Wales, Week 1 to Week 53 2020. Source:

It became evident early into the pandemic that old age, frailty and comorbidities are major predictors on mortality in COVID-19 patients (Chinnadurai et al., 2020; Hewitt et al., 2020). Therefore, it is not surprising that the situation was particularly severe in care homes. However, the impact was exacerbated by a variety of factors including the discharge of hospital patients untested to care homes, a lack of personal protective equipment and care home staff being drawn from groups at higher risk of infection. During the first two waves of the pandemic (from 20 March 2020 to 2 April 2021) out of a care home population of approximately 443,000 in England and Wales, a total 173,974 deaths were registered, representing a 19.5% increase on the 5-years average (Office for National Statistics, 2021c). Of these, 42,341 deaths (24.3%) were COVID-19-related, which would indicate a crude death rate from COVID-19 among care home residents of approximately 9,500 deaths per 100,000. COVID-19 was identified as the leading cause of death among male care home residents during the first and second waves, and the second leading cause of death (after Alzheimer disease and dementia) in female patients. Alzheimer disease and dementia were also the most common pre-existing conditions associated with COVID-19 mortality in both sexes (Office for National Statistics, 2021c).

However, with a very successful vaccination campaign, the rate of excess deaths in the general population per 100,000 population (EDPHK) now ranks 18th in a list of 40 European countries. The United Kingdom's EDPHK, at a value of 36, is one third of that of France, the worst affected country with an EDPHK of 119 (The Economist, 2021). By comparison, the lowest EDPHK belongs to Bulgaria, with a value of only two.

Mortality rates from COVID-19 within the UK tend to be higher in deprived areas and vary by region, with the highest rates observed in the northwest and northeast. Black and Asian minority groups have had significantly higher standardized death rates from COVID-19 than White people, even taking into account deprivation (Marmot et al., 2020). In particular, areas with higher rates of deprivation have generally experienced higher rates of mortality, partly because of overcrowded living conditions an poor-quality housing (Marmot et al., 2020).

People working in social care and men working in healthcare had a high age-sex standardised mortality, but the occupational group at highest risk are those operating machines or doing manual work in processing plants, such as cleaning metal goods, operating printing machines, wrapping, filling, labelling and sealing containers (Windsor-Shellard & Kaur, 2021).

There is a distinct social gradient to the inequality. The age-standardised mortality rate per 100,000 during the first wave of the pandemic was 12 for men and 5 for women in professional occupations, compared to 40 for men and 15 for women in elementary occupations (Marmot et al., 2020). This trend is in keeping with the proportion of workers across different occupation groups who were unable to work remotely in the first wave of the pandemic (**Figure 24**). Workers in lower socioeconomic groups, on lower pay and in more deprived areas tend to have less control over their working conditions, which reduces their ability to protect themselves and other people from the pandemic.

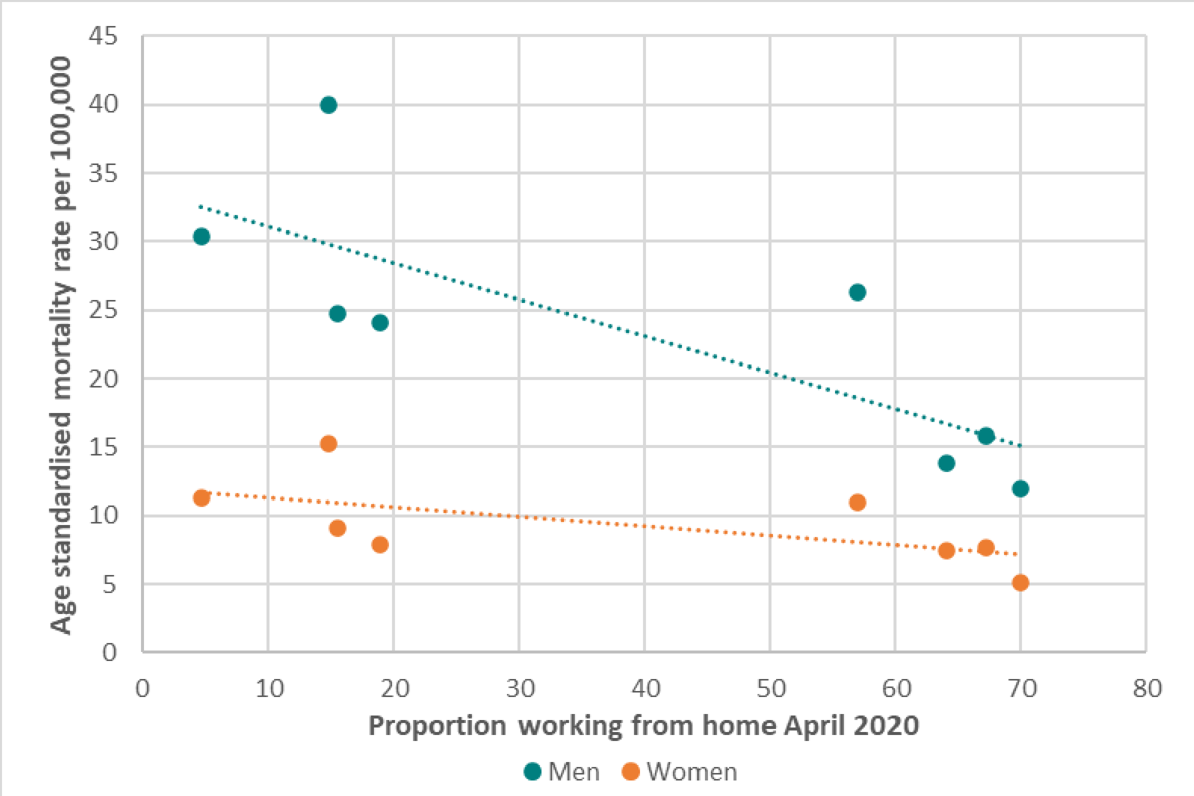

Figure 24. Negative correlation between the age-standardised mortality rate involving COVID-19 and the ability to work from home during the first wave of the pandemic in England.

Higher mortality rates have been observed among men and older people, but people with certain co-morbidities have also been significantly affected. The comorbidities with the greatest relative risk are kidney disease, cerebrovascular diseases (such as stroke), other cardiovascular diseases, respiratory disease and hypertension (Biswas et al., 2021). The varying prevalence of these conditions by gender, age, deprivation and ethnic group may, in part, explain the differences in risk observed across population groups.

There are correlations between these different socioeconomic risk factor for higher mortality, but the increased risk across them appears to be accumulative – for instance, the increased risk for those belonging to an ethnic minority is not entirely accounted for by deprivation or by type of occupation, each of which present an independent, additional risk factor instead (Marmot et al., 2020).

Health inequalities

According to August 2021 data from the National Records of Scotland, there is a clear economic divide in health outcomes. For instance, both the overall mortality rate and the COVID mortality rate among people from deprived areas are significantly higher – by 1.9 and 2.4 times, respectively – compared to people from more affluent districts. There may be a causal link between this and the higher prevalence of COVID-19 risk factors such as diabetes, obesity and lung disease in deprived areas. The disparity in COVID-19 mortality rate, moreover, has risen since the early stages of the pandemic, which may point to a worsening of health inequalities as government support initiatives are gradually phased out. People from deprived areas also score significantly worse on mental health outcomes such as addiction, alcohol abuse and suicide, all of which are likely to have been affected by the pandemic (National Records of Scotland, 2021).

The pandemic's effect on health inequality has unfortunately also extended beyond mortality rates. For instance, during the first lockdown there was an apparent increase in domestic abuse, which primarily affects women and children. This has been complicated by diminished access to support services and refuge spaces, and has had an impact on the mental health of victims (Davidge, 2020).

Whilst there has been a large decline in mental well-being through the pandemic in general, the decline among women has been twice as large as for men (Etheridge & Spantig, 2020). Other than domestic abuse, women's mental health may have been disproportionately affected as a result of increased domestic responsibilities, lower incomes, and a higher proportion of single parenthood in comparison to men. It appears that those with larger social networks suffered a greater decline in mental health than others, and women, in general, did tend to have larger social networks prior to the pandemic (Etheridge & Spantig, 2020).

Children are particularly vulnerable to anything that may threaten the determinants of health, which include parental employment and income, education and access to health services (Hefferon et al., 2020; Lawson et al., 2020). The lockdown has severely disrupted the work of the agencies concerned with the safeguarding of children, including health and education. With schools closed, the opportunity for detecting child abuse has diminished. Moreover, there will have been an increase in the number of children witnessing domestic abuse within their home (Hefferon et al., 2020).

The arrival of the pandemic caused a sharp uptick in the use of telephone and digital communication technologies for accessing healthcare (HFMA, 2021). Direct services may be accessed by patients via telephone or video call, or the service itself may be delivered via computer technology – for example, web, computer and smartphone apps have been developed to deliver cognitive behavioural therapy, assess risk, provide health information or participate in community support forums (Kebede & Pischke, 2019; Martinez et al., 2017; "Predicting Risk of Type 2 Diabetes in England and Wales: Prospective Derivation and Validation of QDScore," 2009; Sasseville et al., 2021). The shift to telehealth services has the potential to both reduce and exacerbate difficulties in accessing care (Gov.uk, 2021; Spanakis et al., 2021). For instance, people who have previously struggled with travelling to and from centres of care may find access improved if health services extend their available telehealth options. On the other hand, there may be an increase in difficulty accessing care for those with some barrier to using telecommunications technologies such as telephones, computers or smartphones. There may be several factors behind this: poor internet access in remote areas (with unreliable mobile phone signals or broadband services), lack of access to equipment, computer illiteracy or aversion to technology, or difficulty in using these technologies due to disabilities such as deafness, blindness, special educational needs or difficulties with motor function.

What we have learned

As we recover from the pandemic, it is necessary to ensure that the recovery in provision of services – including clearing the backlogs in routine care – is done inclusively (NHS England, 2020a). The inequalities across different communities are, in part, driven by variation in vulnerability as a result of differences in age distribution, comorbidities, lifestyle factors, obesity or deprivation. One key way to reduce inequalities will be to ensure that services prioritise the groups most at risk (NHS England, 2020a).

Protecting the health of the population from COVID-19 and protecting the economy are not mutually exclusive choices (Marmot et al., 2020). The non-pharmaceutical interventions applied in response to the pandemic have typically reduced the gross domestic product by about 10%, but the countries that were quickest in implementing such interventions have also experienced lower mortality and better economic outcomes (Kunt et al., 2021; Marmot et al., 2020).

Failure to respond quickly and appropriately to surges in the number of cases and hospitalisations from COVID-19 bears an economic cost as well as a cost in lives, both of which fall disproportionately on those with fewer resources, older people, children, ethnic minorities and other vulnerable groups, exacerbating health and economic inequalities (Marmot et al., 2020). We also know that, internationally, high rates of inequality are associated with poorer economic development, a relationship that is likely to be both causal and consequential (Grigoli & Robles, 2017).

The measures taken to address these economic inequalities will need to include some societal change. Sex-based differences in patterns of work and the unequal burden of childcare, for instance, have been seen to influence vulnerability. Whilst the government may implement interventions to tackle these inequalities, such as greater investment in early years care and the removal of the 26-weeks service threshold for employees to request flexible working arrangements (House of Commons Womens and Equalities Committee, 2021; Marmot et al., 2020), attitudes in society as a whole need to catch up with the new economic and workplace realities. This would mean, for instance, ensuring a more even spread in the childcare burden between men and women, and greater access to home-working and flexible hours in the workplace where that is practical. Throughout the pandemic, low-paid key workers were less able to socially distance at work and thus more vulnerable to catching and dying of COVID-19. As a society, we need to learn to value these roles more, financially and otherwise.

Poor housing was found to be associated with higher mortality rates from COVID-19 (Marmot et al., 2020). The poorest housing conditions of all are experienced by the homeless who sleep rough or are temporarily housed in hostels. The 'Everyone In' initiative appears to have been successful, with the number of rough sleepers recorded on one night in the autumn of 2020 being 37% lower than in 2019 (MHCLG, 2020). This has demonstrated that political will and mobilisation of resources can have a significant impact on rough sleeping; once again, a society-wide shift in attitudes with regards to homelessness (and housing inequalities) will be necessary to ensure that these results are sustained in the long term.

What are the uncertainties?

There are a number of possible policy options for a government seeking to address the inequalities arising from surging unemployment, disrupted schooling or unequal vulnerability to future pandemics, but all these options would require either higher public expenditure or lower taxation, the latter of which would then have to be funded by more borrowing, the raising of other taxes, or cuts to public expenditure elsewhere (Blundell et al., 2021). This may represent a political challenge for those in power.

Poor housing and overcrowding has contributed to the inequality in mortality during the pandemic (Marmot et al., 2020). Greater investment will have to be made to improve the housing stock in order to reduce inequalities going forward. Reducing homelessness and rough sleeping will likewise require important investments. This must primarily entail an adequate supply of good-quality housing stock. However, it has been demonstrated that rough sleeping can also be significantly reduced by removing barriers to accessing housing and other legal barriers to qualifying for help based on local connections or immigration status. One prime example of this has been the removal of the 'Right to Rent' scheme checks (Crisis, 2020).

More radical social and workplace reforms may also have to be considered. Some of these include removing conditionalities in welfare and benefits payments, making the £1,000-per-year increase in the standard allowance for Universal Credit permanent, providing a universal basic income, or instituting a four-day week (Blundell et al., 2021; Marmot et al., 2020). Although some of these initiatives have already been trialled, with varying degrees of success, in other countries, implementing any of them in the UK will undoubtedly be challenging.

Lastly, computer literacy and access to smartphones, telephones and laptops have been important factors in maintaining access to health services and education throughout the pandemic; on the other hand, we have seen that lack of access to the technologies and technological illiteracy can present a significant risk, both to one's health in the short term and to one's quality of life prospects in the long term. Financial hardship arising from increased unemployment, reduced wages and the local and global financial consequences of the pandemic may exacerbate this problem unless there are specific measures taken to address it. As discussed in the Science and Technology section, there are indications that the sharp uptake of telehealth technologies during the pandemic signals a shift in the way health services will be provided in the future. Conversely, it will be crucial to ensure that as many citizens as possible are able to access these services in increasingly digitalised health and education.

NHS and Social Care

COVID-19 has undoubtedly been one of the largest challenges in Health and Social Care history. The need to support these sectors during a time of crisis was immediately evident to the UK government, which promptly allocated the necessary funding, and financial constraints have not been a limiting factor in the response to the pandemic. At the same time, services required prompt structural changes and reorganization to rightly prioritize the pandemic, leading to a system backlog. This section will highlight key issues and learning points.

What we know

On 30 January 2020, NHS Improvement and NHS England declared COVID-19 a serious, Level 4 National Incident and actions were put in place to prepare for a surge in cases in the UK. In March 2020, the NHS wrote a letter to trusts highlighting key information on how to support staff and increase critical care capacity (Stevens & Pritchard, 2020). Measures included the postponement of non-urgent surgeries, block-buying space in independent hospitals and methods to ensure patient segregation. Staff were instructed to discharge all medically fit patients to prepare for an increase in demand for respiratory support. This led to trusts urgently reshaping and reprioritizing their services and provisions.

Concerns were raised about the discharge of suspected or confirmed positive cases into care homes to complete their isolation period. Figures provided by the National Audit Office (NAO) report that in the period between 17 March and 15 April 2020, around 25,000 people had been discharged from hospitals into care homes with a lack of knowledge around how many had COVID-19 (National Audit Office, 2020). It was only on 15 April 2020 that the policy of testing all residents prior to care home admission was instituted by the government (Department of Health and Social Care, 2020b). Although a large amount of funding was provided to support enhanced discharge and ensure the safety of staff and residents, it may have been overdue. In an analysis conducted by the Office for National Statistics, by April 2020 those working in social care had significantly higher rates of death compared to the general population, whereas healthcare workers did not.

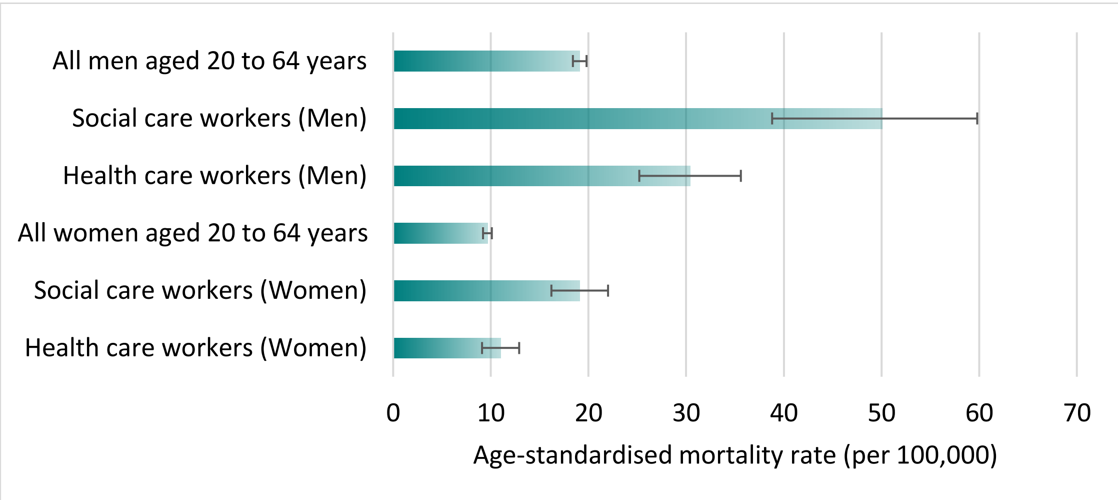

Figure 25. Age-standardised mortality rates involving COVID-19 in England and Wales for deaths registered between 9 March and 25 May 2020 (National Audit Office, 2020)

The impact of COVID-19 on service waiting times should not go unnoticed. Data from NHS England found that A&E attendances had significantly decreased, with April 2020 figures being the lowest number since records began, and a rapid decline in emergency admissions from A&E, which were consistently increasing prior to COVID-19 (J. Davies, 2020). The number of diagnostic tests being conducted fell dramatically in April 2020 compared to April 2019, with 68% less tests being conducted and 56% of patients having waited over 6 weeks for a diagnostic test, the worst performance since records began. Waiting times for consultant-led referrals to treatment have also seen dramatic increases since the beginning of the pandemic (**Figure 26**). These statistics highlight the backlog of care that is likely to arise after COVID-19, as services work to provide care for those whose treatment has been delayed due to the pandemic.

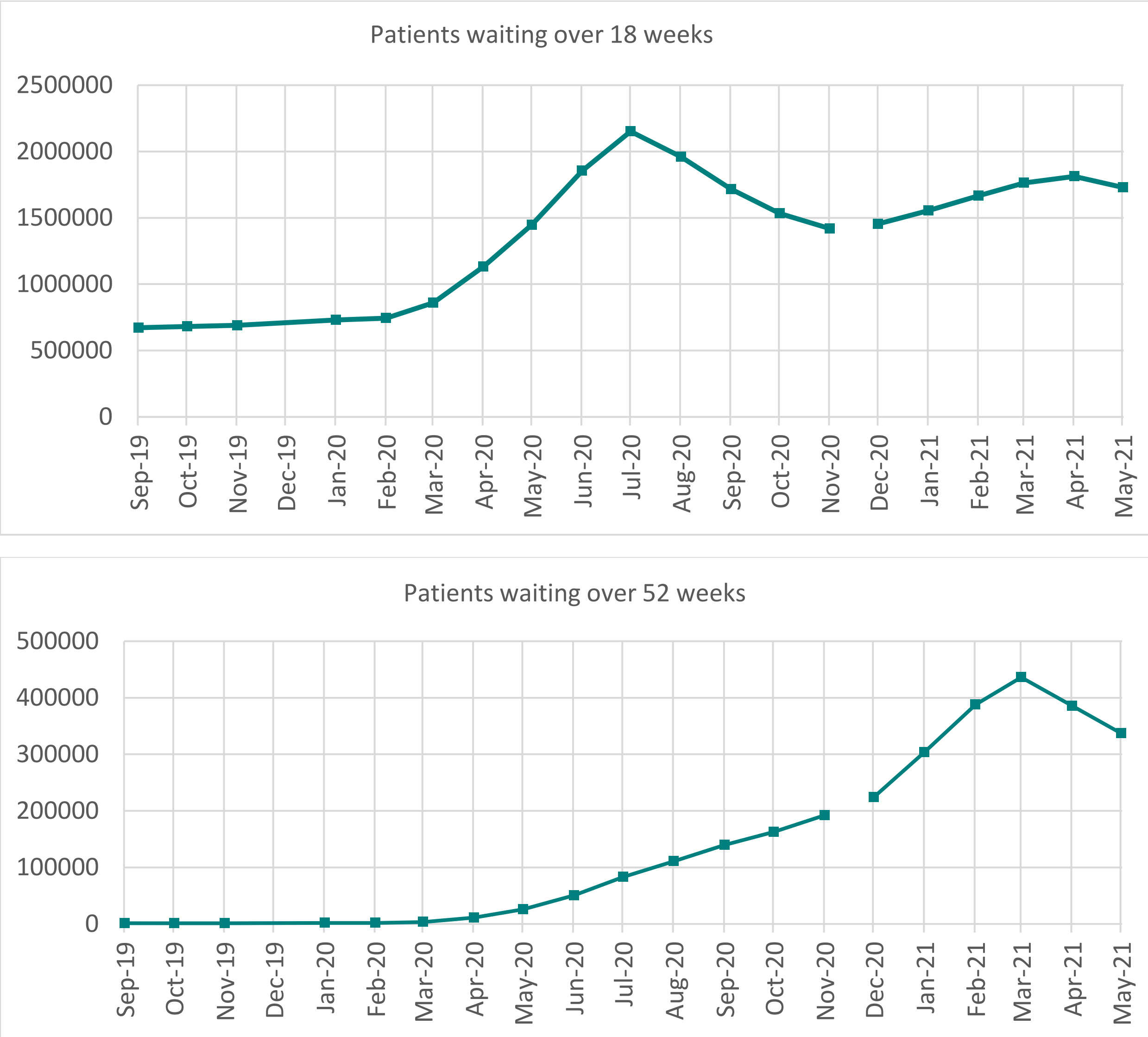

Figure 26. Consultant-led referral to treatment waiting list – patients waiting over 18 weeks (Top) and over 52 weeks (Bottom) (Source: NHS Digital)

The potential decline in staffing levels was recognized from early on, not only due to the outbreak of patient illness and additional measures in place to reduce virus transmission but also because of the increase in staff shortages due to sickness or caring responsibilities (May & et al., 2020). Zero-hour contracts and minimal pay were big issues, mainly within the social care sector. There were already growing concerns around the impact of Brexit and the new points-based immigration system on future workforce capacity (Dixon et al., 2019), due to the significant proportion of international employees working within the health and social care sectors.

The reduced staffing levels during the COVID-19 pandemic due to illness, isolation and burn-out put additional strain on a system already heavily impacted by funding cuts and lost capacity. Results of the NHS Survey Coordination Centre found that 10% of staff had to shield during the pandemic and that 44% of staff had felt unwell as a result of work-related stress.

Staff were also asked to implement social distancing measures for everyone in the care home and shielding for extremely vulnerable groups (Public Accounts Committee, 2020). This is however difficult to maintain when caring for the sick, frail and/or those with learning disabilities. Research conducted by the University of East Anglia found that the rapid spread of the virus in care homes, once it had been introduced, was most strongly linked to PPE shortage, suggesting an inadequate supply of PPE had been a significant problem (Barnard et al., 2021). As a preparation for a no-deal Brexit, the government had stockpiled PPE to distribute to NHS trusts in case of emergency. However, this was designed to accommodate an outbreak of influenza rather than a pandemic, and the limited supply was distributed according to priority. From February 2020, NHS trusts had received at least 654 million items of PPE. An emergency supply of 7 million items of PPE were provided to the social care sector with an additional 34 million items being authorized on 6 April 2020 (Department of Health and Social Care, 2020a). The government utilized the armed forces to help distribute further PPE to NHS trusts. The difference in operation between the NHS and social care sectors was also acknowledged and arrangements were made with external suppliers to ensure PPE was accessible to CQC registered homes. However, even after this initial and prompt distribution, many still reported a lack of sufficient PPE and concerns around staff safety. It is worth noting that to prevent spread and protect patients/staff, the free provision of PPE to care homes has now been extended to March 2022 (Department of Health and Social Care, 2021a).

What we have learned

Pre-pandemic, the NHS and social care sectors had problems recruiting and retaining staff, with an estimated turnover rate of 27% (Skills for Care, 2019). COVID-19 only highlighted the critical concerns and consequences of the workforce crisis, and the need for measures to be implemented to recruit and retain staff. Throughout the pandemic, several strategies were introduced to enhance the capacity of the workforce. In July 2020, the government announced the introduction of a new Health and Care visa for registered staff to come from overseas to work in the NHS and/or care sector. This option provided benefits such as prompt enrolment and reduced fees, as well as exemption from paying the Immigration Health Surcharge. Additionally, recruitment campaigns were rolled out to encourage people to apply for vacancies in social care (Department of Health and Social Care, 2021b) and to provide free access to *Skills For Care*, a charity focused on workforce development that provides training resources and guidance to support individuals and organizations working in the social care sector. This ensured that new employees had the skills required to provide high quality care. Stretching the current workforce by modifying work schedules and hours and allowing leave to be carried forward was also a frequent practice.

Several profession councils, such as the General Medical Council (GMC) and the Nursing and Midwifery Council (NMC), put measures in place to increase workforce capacity. These measures included automatic re-registration for recently retired staff, temporary registration for qualified health professionals and deploying medical and nursing students into clinical practice (NHS Providers, 2020).

Maximising staff capacity through workforce planning and transformation has proven crucial throughout the pandemic and continuing these measures should be a priority for service recovery and backlog reduction.

Additionally, the virus took a disproportionate toll on those with poorer health outcomes and illness, and mortality risk was increased in ethnic minority groups (Charles & Ewbank, 2021). This is particularly relevant in authorities and workplaces where BME staff represent a large proportion of employees. Measures to protect these groups should be implemented as a priority.

Private sector engagement

There is a long-standing history of collaboration between the NHS and the private sector to tackle peaks in activity, such as the ones associated with the increase in respiratory symptoms during the winter months. This has usually been done on an *ad hoc*, transactional basis. The sheer size of the routine care backlog that the pandemic created, however, will make it necessary to rethink this framework. The private sector has already been contracted to help clearing the backlog of waiting lists and it is expected that collaboration between public and private healthcare will become more systematic over the next few years, until the current crisis is resolved.

Digitalisation

As a result of COVID, there has been substantial modernization within the system with the use of digital tools and telecommunication. While the UK healthcare sector has historically been slow in adopting technology to aid service provision, it has however become strongly reliant on it throughout COVID, particularly in primary care (Hutchings, 2020).

Waiting lists

As part of the response to COVID-19 to limit spread and protect patients, GP's used measures such as telephone-only triage telephone systems and remote-only appointments. In addition, CCG's were advised by NHS England to set up ''hot-hubs'', where non-hospitalised patients could be seen locally to access advice, diagnosis and required treatment (The Health Foundation, 2020). Scheduling treatment for suspected or known COVID-19 patients at a specific time of day and utilising separate entrances and facilities for those with and without COVID-19 were other approaches used to minimise cross-infection by grouping and segregation (National Institute for Health and Care Excellence (NICE), 2020).

What are the uncertainties?

An immense amount of effort was put into tackling the COVID-19 pandemic by government officials, the NHS and Social Care sectors, and the additional strain placed on a system already under severe pressure will have had a significant, detrimental impact. Prior to the pandemic, the NHS and social care sectors were already under significant financial pressure and the workforce was strained with increasing referrals, staff shortages and underfunding (Bottery, 2019).

Projections

In projections conducted by The Health Foundation, it is estimated that without action and reform, elective care waiting times and backlog will continue to increase beyond the end of the pandemic through to 2023/2024 (Kraindler et al., 2020). The delay in testing and treatment initiation is likely to have caused a deterioration in many patients' health and wellbeing, potentially requiring additional or longer treatments (Charles & Ewbank, 2021). The latter review also highlighted the effect of COVID-19 on mental health, with a significant rise in anxiety and reduction in overall wellbeing. The knock-on effect of COVID-19 due to the loss of loved ones, lack of employment, and isolation, is likely to further impact the need for mental health support, particularly in children and young people (NHS England, 2020). It is anticipated that there will be a surge in referrals to mental health services, which will undoubtedly put intense pressure on an already underfunded sector.

In May 2021, a new £160m NHS initiative was launched with the aim of reducing waiting lists. The money will fund evening and weekend clinics, home-based ''virtual wards'', one-stop testing facilities and mobile CT and MRI trucks (NHS England, 2020c)). Additionally, the funding will be used to expand COVID-friendly cancer treatments. This includes treatment changes to anti-cancer drug therapies that offer benefits such as fewer side-effects or home-based self-treatment requiring fewer hospital visits, instead of undergoing hospital based treatment that can leave patients more susceptible to coronavirus (NHS England, 2020b)). The stepping up of cancer hubs to consolidate cancer surgeries in COVID-free sites is also an initiative put in place by the NHS (Palmer & Johnson, 2020). This approach aims to optimise outcomes by ensuring patients get the necessary treatment, whilst protecting the vulnerable from infection risk.

Projection models have predicted a significant increase in demand for care at home and residential requirements by 2038 (**Figure 27**), mainly due to the increase in the ageing population (Hu et al., 2020; National Audit Office, 2021). In addition, the demand from adults with learning disabilities is expected to increase significantly. With these factors in mind, it is essential that strategies are implemented to encourage workforce growth, which is both the key enabler and the main constraint to enhanced services (NHS England, 2020).

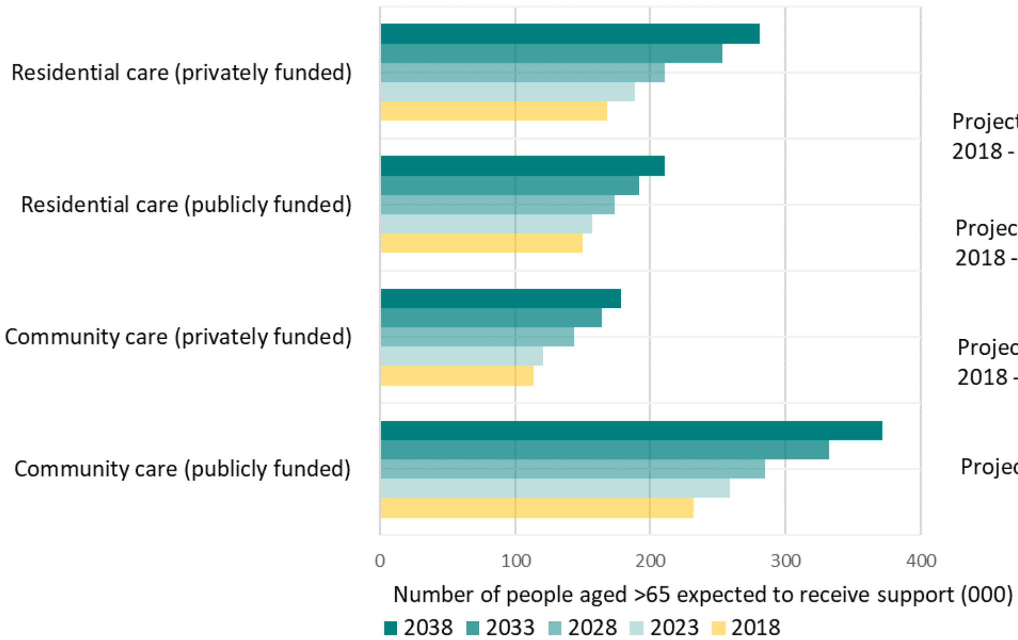

Figure 27. Projected increases in demand for care for adults aged >65, 2018-2038 (Hu, 2020)

Reform

The means-tested system used in social care is very different to the NHS-funded system. The limitation of publicly funded support alongside the high costs associated with social care and care home costs may leave some without the care they need. Also, cultural and structural differences between the health and care sectors may be reasons for the lack of system integration (Bottery, 2019). Patient health outcomes and experience may be improved by narrowing eligibility gaps and reforming the system so that integration is optimised.

In 2018, a new five-year funding settlement for the NHS was announced by the Prime Minister on the basis that NHS bodies provided a long-term plan for the service. Following on from this announcement, in 2019 the NHS published their Long Term Plan, which focused on improving integration between sectors, personalised care and optimising care quality and workforce productivity (NHS England, 2019). A key priority in this document was the introduction of Integrated Care Systems (ICSs) across the whole of the country. The hope was that ICSs would facilitate collaboration between health and care systems in order to better meet the needs of the community.

In November 2020, a further document that built on the Long Term Plan was published, which elaborated on the future direction of ICSs and set out proposals to the government suggesting how ICSs could be embedded in legislation or guidance (NHS England, 2021). This document also acknowledged the need for collaboration between the NHS, care services and voluntary organizations during the COVID-19 pandemic. Following on from these proposals by the NHS, The Department of Health and Social Care published its White Paper in February 2021, setting out legislative proposals for a Health and Care Bill to remove current legislative barriers to fully integrated care and foster collaboration between health and social care and government organizations (Department of Health and Social Care, 2021b). The White Paper discussed the two main components of a statutory ICS: the ICS NHS Body and the ICS Health and Care Partnership. The former will oversee the day-to-day running of the NHS locally and will be responsible for strategic planning and managing local funding. The Partnership will be composed of a wider group of organizations that together form a plan to address the health and care needs of their system. The White Paper also covers other measures such as additional requirements of the CQC to assess how providers are meeting social care needs. The government also suggested a ‘reserve power’ that would impose spending limits on trusts that were not working to prioritize spending.

The use of technology has many benefits, such as better collaboration and clinical productivity, and increased access to care. However, there are disadvantages, such as the lack of physical examination and the potential impact on health inequalities. Technology has great potential and is a key aim specified in chapter five of the NHS Long Term Plan, but a steady and sustainable approach is needed to limit risks (Hutchings, 2020).

As of April 2021, all parts of England were covered by one of 42 ICSs. The proposals are expected to be implemented in April 2022, with the expectation that they will play a key role in the UK’s recovery from COVID-19. This newly reformed system reform has the potential to reduce the gap between health and social care, however there is concern around the fact that such a significant reform and change in legislation will occur whilst services are still struggling to recover from COVID-19 (Mckenna, 2021).

Science and technology

This section discusses the developments in science and technology during the COVID-19 pandemic that could have benefits to medical science, healthcare, epidemiology, and longevity going forward. Some of these developments are direct, such as those associated with viral disease diagnosis and vaccine technology. Others, such as telehealth technologies and remote patient monitoring, are largely systems associated with pandemic management and social distancing conditions and therefore may not continue to develop beyond the short term.

For all these technologies, the ongoing challenge is deploying them in a way that maximises their material impact on the progress of the pandemic. Experience has shown that technologies do not work in a vacuum: in many cases, their efficacy may be limited by the unwillingness of the public to adopt them or change behaviours when necessary (for instance, after being diagnosed with COVID). In this sense, innovations in technology can only be fully effective if accompanied by innovations in social policy – one prime example being the schemes adopted by various national governments to provide financial support for people to isolate.

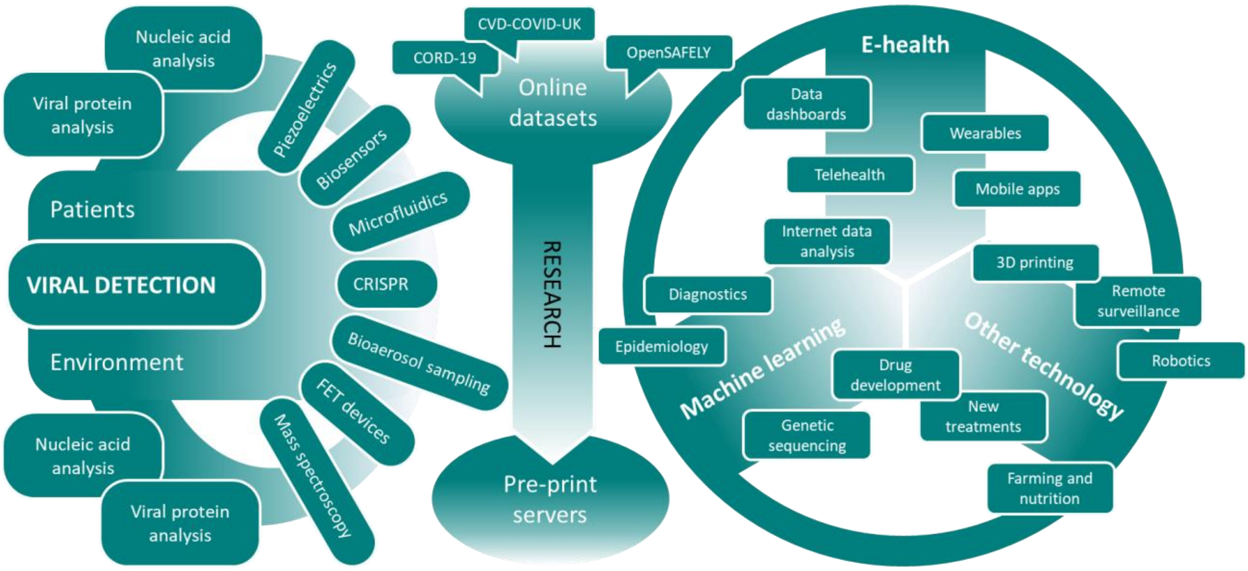

Figure 28. Conceptual map of areas of technological development in the wake of the COVID-19 pandemic

What we know

Vaccines

A great deal of advancement has been seen in vaccine technology, as discussed in more detail in the Vaccines section. It is worth noting here that while more vaccine candidates are still undergoing clinical trials, there is also ongoing research on the delivery methods of approved vaccines. For instance, both the Pfizer and Moderna mRNA vaccines use lipid nanoparticles in their delivery system (Milane & Amiji, 2021). Clinical trials are underway assessing the safety and efficacy of intravenous or inhaled extracellular vesicles as a delivery method for SARS-CoV-2 proteins for the purpose of vaccination (Machhi et al., 2021).

Viral detection

Many laboratory methods exist for detecting viral DNA, RNA, and protein molecules in patient samples and in the environment. During the COVID-19 pandemic, the need for this to be done quickly, with high sensitivity, and on a large scale, has driven innovation in detection technology.

Patient testing

While the standard viral nucleic acid detection technology Reverse-Transcription Polymerase Chain Reaction (RT-PCR) has high specificity and is considered the gold-standard for bio-sample detection, it requires long processing times, multiple steps, thermocycler equipment, and RNA extraction processes. Other detection methods for SARS-CoV-2, which are superior in one or more of these respects, are being developed, based on existing molecular biology methods.

These technologies include alternate methods for nucleic acid sequence detection (RT-PCR, RT-LAMP[2], SHERLOCK[3]), immunoassays (serology tests, antigen tests), and other methods, such as electrochemical biosensor for ROS[4], LSPR[5] for nucleic acid, and graphene-based field-effect transistor (FET) based biosensing (Habibzadeh et al., 2021; Taleghani & Taghipour, 2021). Development has focused on reducing dependency on multi-step processes, trained technicians, and specific laboratory equipment such as PCR thermocyclers. This will in turn decrease dependence on central testing facilities and allow faster results (Andryukov et al., 2021).

Future perspectives for these kinds of rapid point-of-care or home-testing devices include lateral flow assays, paper-based assays, microfluidic devices, and piezoelectric devices. (Gowri et al., 2021; Taleghani & Taghipour, 2021). For example, several SARS-CoV-2 detection assays based on recent CRISPR-Cas13[6] technology have been developed (Das Mukhopadhyay et al., 2021; Nouri et al., 2021), one of which uses lateral flow strips in a similar way to a pregnancy test, showing rapid detection (<2 hours), >95% sensitivity, >99% specificity, and costs less than 5 US cents per test (Shihong Gao et al., 2021).

Environmental testing

Several methods have been developed to allow the detection of SARS-CoV-2 molecules in the environment in order to monitor epidemic spread. Wastewater monitoring, first trialled in Japan, Viet Nam, and Indonesia as an approach to assess changing prevalence of SARS-CoV-2 over time (Takeda et al., 2021), is now also in place in most UK districts.

Environmental detection methods include many of the same lab-based methods in use for diagnosis (nucleic-acid-based analysis, protein-based analyses such as enzyme-linked immunosorbent assays (ELISA) and lateral flow immunoassay (LFA), and novel CRISPR-based methods). These also include mass spectroscopy and whole-virion-based analysis, including graphene-based field-effect transistor (FET) technology. Techniques for bioaerosol sampling and microfluidics have also been integrated into environmental detection methods (Yao et al., 2021).

[2] Reverse Transcription Loop-mediated isothermal AMPlification.
[3] Specific High Sensitivity Enzymatic Reporter UnLOCKing.
[4] Reactive Oxygen Species.
[5] Localised Surface Plasmon Resonance.
[6] Clustered Regularly Interspaced Short Palindromic Repeats - CRISPR-associated Genes

e-health

Telehealth

While vaccines against SARS-CoV-2 were in development, social distancing, mask-wearing and other personal protective equipment were the primary measures used by the UK government to reduce viral spread. This was particularly important for workers in the healthcare industry, where positive patients were being treated in the same environment as the elderly and other vulnerable populations. Healthcare workers themselves were also at high risk.

From March 2020 onwards there was a large shift towards the use of telehealth for primary care in the UK (**Figure 29**). Remote appointments in primary care saw a particularly large increase, mostly through telephone consultations, which increased from 3.3 million in February to 9.8 million in June (Hutchings, 2020). Video/online consultations did not see an equivalent rise..

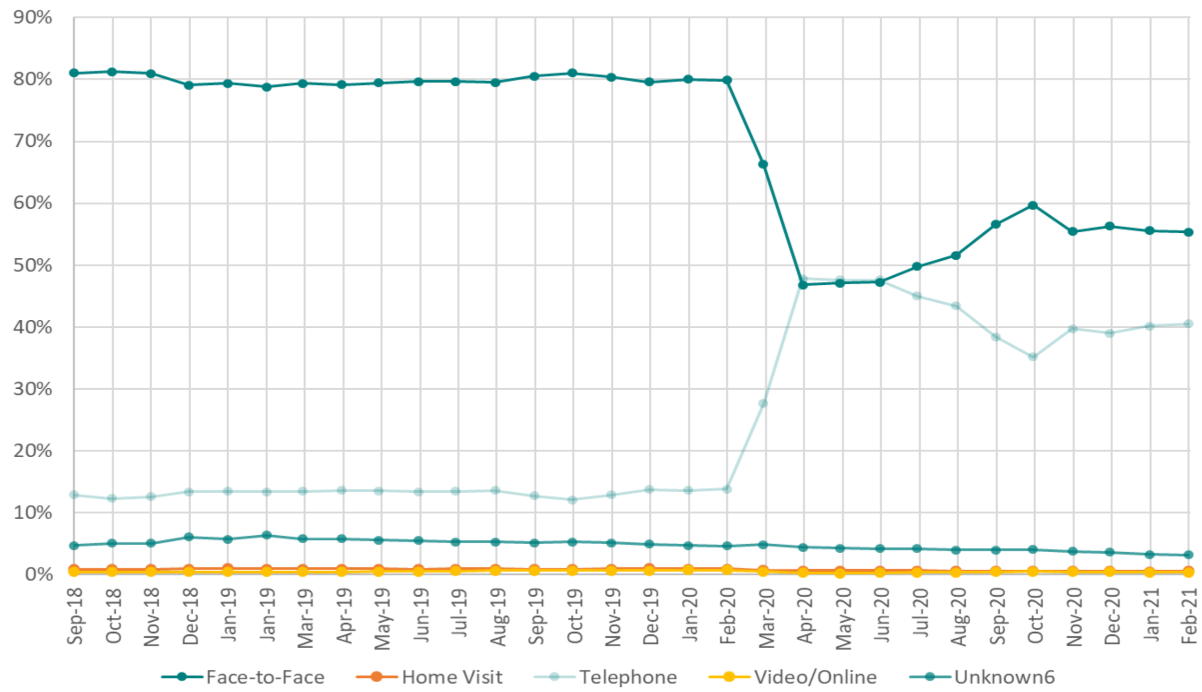

Figure 29. Appointments in general practice by mode of delivery over the pandemic period to date.

2020 also saw a large increase in patient uptake of the NHS app, with a 111% increase in registrations in March as social distancing measures were introduced. Use of the NHS e-prescription service also saw a large increase, with 1.25 million pharmacy nominations registered (Hutchings, 2020).

A global systematic literature review found a range of institutions conducting studies on the implementation of telehealth and e-health interventions due to COVID-19, particularly in the USA and China (Alonso et al., 2021). For example, the USA healthcare provider Providence Health & Services is using AI approaches to develop chatbots to recommend testing or schedule a virtual consultation (Vanian, 2020). A review of COVID-19 digital health solutions for public health found that telehealth approaches dominated publications (40.1%) (Gunasekeran et al., 2021).

Mobile applications

Once the global nature of the pandemic was recognised, the development of mobile phone applications (apps) was rapid. Particularly in developed countries, such as the UK, the proportion of citizens that carry smart phones is extremely high, making mobile phones a key platform for gathering information about incidence, prevalence and symptoms, as well as monitoring and modifying citizen behaviour.

In the UK, from March to April 2020, a smartphone symptom-tracker app (C-19 by ZOE) was voluntarily used by 2,450,569 members of the UK population. In advance of widespread testing, this allowed the identification of symptoms that were predictive of PCR-confirmed SARS-CoV-2 infection (Menni et al., 2020). Between March and September, data provided by app users on symptoms and test results facilitated estimates of prevalence and incidence by geographic area over time (Fry et al., 2021; Varsavsky et al., 2021).

An NHS COVID-19 app uses Bluetooth technology to log the amount of time spent near other users of the app, cross-connects with other UK contact-tracing apps (Protect Scotland, StopCovid NI, Jersey COVID alert, Beat COVID Gibraltar), and uses logged positive test results to alert users to potential proximity to an infected individual. As of November 2020, this app had been downloaded by over 19 million adults in England and Wales (Appleton, 2020).

Some apps in other countries employ a similar approach, often combined with GPS tracking (Grantz et al., 2020). Free mobile health apps available in the UK, Saudi Arabia, Italy, Singapore, the USA, and India focused mainly on contact-tracing via GPS and Bluetooth (Alanzi, 2021).

Singapore, in particular, is a city-state with a very high population density. To improve contract-tracing, it has developed a cloud-based visitor registration system (SafeEntry) and mobile app (TraceTogether) for contact tracing of citizens. In addition, authorities have examined patients' digital footprint, such as public transport movement, credit card payment locations, and ride-sharing app usage (Lai et al., 2020). A similar approach is not viable in the UK at present: while NHS Test and Trace does use a variety of personal and special category information (Department of Health and Social Care, 2021f), digital footprint data collected by third parties would not be available due privacy concerns under GDPR regulations.

Wearable health technology

Traditional wearable health technology allows remote monitoring of patients with chronic or intermittent disease states such as blood glucose in diabetes or cardiac events in atrial fibrillation. These are often specialised devices and may record time series of data for future analysis, but they are not generally designed for live monitoring.

On the heels of smartphone technology, however, a rapidly growing industry of consumer wearables has risen, most recognisably in the form of 'smart' watches. These devices, while far less specialised than the traditional wearables, do allow live monitoring on a huge number of people across a society in a geographically precise way via mobile apps. As such, they hold potential for both citizen health tracking and epidemiological monitoring. Small NHS trials have been conducted in remote monitoring of patients with apps and wearable technology (Horton et al., 2021). The open-source mobile health platform Remote Assessment of Disease and Relapse (RADAR) trial monitored 1062 participants across the UK, Spain, Italy, Denmark and the Netherlands. Changes in behaviours were monitored to assess the effect of public health interventions. This used data from smartphones and wearable devices to measure time spent at home, distance travelled, physical distancing (via Bluetooth), step count, average heart rate, sleep duration, bedtime, phone unlock duration, and social app use duration (S. Sun et al., 2020).

Studies have demonstrated the use of commercial wearables to predict COVID-19 disease onset in users. In the USA, Apple Watch® products with a custom mobile app were used to monitor heart rate variability and predict COVID-19 diagnosis (Hirten et al., 2021), while another study used Fitbit® smart watch products to monitor resting heart rate, reporting an increase in surrounding symptom onset (Marinsek et al., 2020). In a USA and Canada study, a neural network approach was used to predict sickness based on respiration rate, heart rate, and heart rate variability tracked by Fitbit® consumer devices (Natarajan et al., 2020). A Huami device was used for monitoring resting heart rate, activity, and sleep length, using detected anomalies to predict COVID-19 epidemic trends in regions of China, as well as in Italy and Spain (Zhu et al., 2020). The TemPredict study (US and Europe, including UK), started in March 2020, is using temperature data collected from a commercial wearable ring device to evaluate the feasibility of remote fever detection and monitoring (Smarr et al., 2020).

Other e-health

Many other e-health technologies that have been developed during the COVID-19 pandemic can also improve information presentation to citizens. For example, online dashboard data displays have been widely deployed as a method of presenting epidemiological information to the public (Ivanković et al., 2021).

Machine learning

Machine learning, deep learning, and artificial intelligence (AI) technologies are becoming more powerful as available computing power increases, training datasets get larger, and new techniques are developed. Within the context of the COVID-19 pandemic, these technologies have been applied in multiple contexts, mostly in smaller exploratory ways reflecting the novelty and uncertainty that still surrounds them.

In the realm of diagnostics, machine learning and deep learning tools have been quickly developed to identify COVID-19 cases and distinguish these from other viral pneumonias based on radiography, blood tests biomarkers and respiratory patterns. A literature review found 37 publications between November 2019 and July 2020 that demonstrated the use of deep learning for the classification of X-ray or CT images as COVID-19 positive or negative (Ghaderzadeh & Asadi, 2021).

These approaches have also been tested for predicting disease progression, severity and outcomes in patients (Swapnarekha et al., 2020). Exploratory approaches have used blood test biomarkers, and even audio analysis of breathing and coughing symptoms, to aid diagnosis (Alafif et al., 2021).

A review of 130 machine-learning publications during the pandemic identified epidemiological approaches in outbreak forecasting, predicting viral protein structures, identifying candidate antiviral drugs, modelling response policies and social impact (Syeda et al., 2021). For example, one research project used virtual screening of already FDA-approved drugs by predicted binding to a SARS-CoV-2 protein that is highly conserved in the coronavirus family (Feng et al., 2021).

Internet and social media monitoring

As well as smartphone apps and e-health wearables, there have been other technological approaches to monitoring citizens' behaviour using the internet. The rise of social movements opposing social distancing, business closure, mask wearing, and vaccine uptake has demonstrated the importance of monitoring online information and misinformation and the tides of public opinion.

A machine learning neural topic analysis of COVID-19 disinformation demonstrated the main sources of social media disinformation, and trends over time (Song et al., 2021). A machine-learning approach and tweets from 8.97 million Twitter users were used to estimate beliefs relating to SARS-CoV-2 epidemiology and compare the effects of scientific publications and non-scientific events on beliefs (Wang et al., 2021). Linear discriminant analysis (LDA) topic modelling of English-language news and social media text content was used to identify topics of particular social interest and to identify areas of particular misinformation (Chipidza et al., 2021). Topic mining of Twitter data in the USA was used to identify themes related to wearing respiratory masks (Al-Ramahi et al., 2021).Topic modelling and sentiment analysis of Twitter data allowed public health experts to produce useful information with regards to monitoring the population's response to public health interventions in North America (Jang et al., 2021).

A very simple technological approach to tracking epidemics is to query publicly available Google search data, the logic being that people tend to search for their symptoms online before entering the medical system. This approach has been used for over a decade to track influenza trends, with mixed results. Google search queries for COVID-19 symptom have been used to improve short-term forecasting (Lampos et al., 2021).

Research and publication

It is also likely that there has been an acceleration in the development of technologies used to share results and datasets within the scientific community itself.

COVID-19 Open Research Dataset (CORD-19) was set up by a coalition of research groups as a dataset of COVID-19 related publications, which is updated daily with new and past research relating to "COVID-19 and the coronavirus family of viruses for use by the global research community." It is a partnership of multiple institutions, including the Allen Institute for Artificial Intelligence, the Chan Zuckerberg Initiative, Georgetown University's Center for Security and Emerging Technology, Microsoft Research, the National Library of Medicine of the National Institutes of Health, and Unpaywall (Colavizza et al., 2021). Other publicly available COVID-19 publication databases are maintained by the World Health Organization (WHO), the Centre for Disease Control and Prevention (CDC), and the European Bioinformatics Institute (EMBL-EBI) (Tanwar et al., 2021).

In addition to databases of research publications, the use of pre-print servers for faster publishing of study results can lead to a faster dissemination of important epidemiological findings to the media and to the public, provided that the increased uncertainty associated with these non-peer-reviewed results is appropriately considered by news outlets that report them (Fleerackers et al., 2021).

Enabled both by improvements in genomic sequencing and digital storage and transfer capacity, large biological datasets are increasingly easier to share between researchers. For example, a large database of single-cell expression profiles is used to identify tissues and organs with the highest expression level of SARS-CoV-2 entry associated genes (Kumar et al., 2021).

The CVD-COVID-UK initiative collated a linked cohort database of over 96% of the population of England (54.4 million people) using data from primary care, hospital episodes, and death registry (Health Data Research UK, n.d.). Although this dataset was created for the specific case of investigating the relationships between cardiovascular health and COVID-19, datasets of this kind, which combine person-level data across national healthcare settings, allow powerful statistical studies to be performed for a vast range of epidemiological questions.

Another example is OpenSAFELY, a secure, open-source analytics platform created jointly by UK universities and electronic health record software companies working on behalf of NHS England and NHSX, which allows researchers to access a large database of pseudonymised primary care records (OpenSAFELY, n.d.) . The platform is designed to guarantee protection of sensitive patient information (researchers can only access aggregated data) and has already been extensively used to analyse the risk factors of COVID-19 mortality in UK hospitals. This project was implemented on a very fast schedule, with the first analyses delivered within about five weeks of its inception.

The University of Oxford branch of OpenSAFELY is jointly headed by Dr Ben Goldacre, a long-time campaigner for open-access science. In February 2021, following on the success of OpenSAFELY, the UK government also tasked Dr Goldacre with the development of a rapid review aiming to "find safe, secure, collaborative and efficient ways to turn […] raw data into insights and action, to improve patient care for all" (Department of Health and Social Care, 2021d; *Goldacre Review*, 2021).

Access to health data sources in the UK has been historically hampered by inconsistencies and confusion due to the difficulty of balancing the right of access to information against the right to individual privacy. The Longevity Science Panel addressed the topic in its 2015 report, which explored the challenges and potential benefits of using population data to predict and model the life expectancy of an ageing population. The report also identified the importance of anonymised information, according to the principle that granularity of the data, rather than identifiability, is a key requirement for successful planning (Dunnell et al., 2015).

In this context, the rapid adoption of national, open-access, anonymised data platforms has been something of a revolution which will have lasting effects on public-private cooperation and data use policy in Britain. As is the case with other technologies, we can argue that the pandemic has had the beneficial side effect of speeding up a process of streamlining and adoption that may have otherwise taken years to come to fruition.

Personal Protection Equipment

The use of Personal Protection Equipment (PPE), medical devices and face coverings in general has been vital in controlling the spread of SARS-CoV-2. While not all devices provide the same degree of protection, and despite initial uncertainties about the utility of non-certified face coverings, the rationale is that when every effort must be made to disrupt the chain of transmission, even the limited protection afforded by a simple cloth mask is preferable to no protection at all.

The design of PPE has not seen the same amount of innovation as other healthcare technologies during the pandemic, likely because the devices that are currently available are tried-and-tested products with limited scope for improvement. As of June 2021, however, at least one study is investigating the integration of CRISPR-based biosensors into face masks (and other wearables) to allow rapid detection of pathogen molecules such as viral RNA in the environment (Nguyen et al., 2021).

On the other hand, there has been a remarkable investment in scaling up manufacturing and distribution of PPE to meet the increased demand from healthcare providers and the public, with many manufacturers worldwide have swiftly diversifying and/or repurposing their production lines. This has involved companies of all sizes from corporations to small local businesses. Although it is difficult to quantify the economic import of this shift at present, it could be argued that it has not only helped to keep businesses viable which would have otherwise had to close or downsize but also provided a litmus test of the flexibility of the global industry during an emergency (Department of Health & Social Care, 2020; Institute for Manufacturing, 2020).

Ventilation systems

As discussed in previous sections, adequate ventilation of enclosed spaces is essential in order to reduce the potential for airborne transmission. Similarly to what we have seen with PPE, the focus here would not be so much on improving the technology *per se* but on rethinking current guidelines and allocate investments to implement them. This could include assessing the best ventilation practices on a case to case basis by routine monitoring of airflow in buildings, installing new ventilation systems where necessary or upgrading existing ones with high-efficiency particulate air-filters (HEPA) or UV irradiation devices (Center for Disease Control and Prevention, 2021; Health and Safety Executive, 2020, 2021)

Other technologies

In addition to the main areas above, the pandemic has prompted development and testing of a range of technologies that may have narrow or broad healthcare application in the future. In many cases these are not novel technologies but existing ones that have experienced a rapid spurt of development and adoption in the wake of the pandemic. Trial use of drone and robotic technologies for disinfection and delivery applications has been demonstrated, particularly in China (Khan et al., 2021). Infra-red cameras have been deployed to detect people with abnormal body temperature (Shu & Li, 2020). Public camera images and machine learning approaches have been used to monitor social distancing in low-light outdoor environments (Rahim et al., 2021). 3D printing technology has proved useful for rapid prototyping and production of medical accessories such as face shields, medical mask 'ear savers', and adaptors for ventilation support equipment (Perez-Mañanes et al., 2021). An approach to detect respiratory rates based on Wi-Fi signals has also been demonstrated (F. Li et al., 2021).

In the realm of disease treatment, trials with small numbers of patients have begun to assess the safety and efficacy of cell-based treatments (usually mesenchymal stem cells) for the treatment of severe COVID 19 cases (Golchin, 2021). Success in this area would support further development of stem-cell therapeutics, which are still largely in their infancy. Understudied potential drug reservoirs such as cyanobacteria may also receive additional research interest (Jafari Porzani et al., 2021).

What we have learned

As well as developments made in the science and technology areas discussed above, there have been broader lessons relating to the deployment and public messaging relating to these technologies.

Vaccines

The success of mRNA vaccines in the prevention of SARS-CoV-2 infection will increase confidence in applying genetic vaccines in other disease areas, including chronic infections and cancerous cells that are known to display particular surface markers (Fuller et al., 2021). The need to keep abreast of emerging SARS-CoV-2 strains, such as the UK and South African variants, will require continual development and testing of new vaccines (Kashte et al., 2021). The vaccine technologies developed for SARS-CoV-2 will be available for other coronaviruses, and viral illness in general.

Viral detection

Track and trace schemes are highly dependent on the availability and accuracy of testing, and on the speed with which results can be returned.

For governments, including that of the UK, much of the pandemic response has been to balance curbs on population freedoms with the liberty of its citizenry and the operation of its economy. Therefore, there is a huge incentive to prevent outbreaks from happening through improved testing and monitoring.

Track-and-trace approaches to transmission control have had varied success around the world and hinged on the ability of a society to perform both fast detection and the ability and willingness of its citizens to be tested and to then isolate. The development of rapid COVID-19 diagnostic tests, such as a simple breath assay would be transformative for pandemic control and, once developed, this technology would also be available for the control of future respiratory disease outbreaks (Giovannini et al., 2021). The need for a range of advanced diagnostic approaches will also continue to support research into optical technologies for the detection of viral particles, particularly portable, self-contained devices (Lukose et al., 2021). Disease-specific biosensors could result in a continued shift towards home testing generally (Antiochia, 2021).

e-health

Mobile applications

We have learned that technological methods to support tracking and tracing of cases needs to be combined with enabling and incentivising compliance.

Mobile phone apps were rapidly developed and shown to be of use immediately in recruiting volunteers for epidemiological monitoring and for gathering case histories of symptoms and outcomes. This was achieved in a timescale that would not have been possible before the advent of smart phones and filled the gap while traditional health services were organising more systematic measures.

Contact-tracing apps were deployed in the UK, but too late to prevent outbreaks nationwide. Although successful from a technological perspective, those ‘pinged’ by the apps were meant to self-isolate, creating a perverse incentive to not use the apps at all. This revealed the importance of considering both the technological and psychological elements of epidemic control and provide appropriate incentives.

Internet and social media monitoring

The pandemic has brough into focus the need to manage disinformation. If technology such as home testing kits, contact-tracing apps, and vaccination programs are to be effective while remaining optional then the population must be informed and incentivised to use them. COVID-19 misinformation spread around the world even before the virus did. Research into belief and the spread of information on social media has given insight into how disinformation spreads and the importance of public messaging and political narrative.

What are the uncertainties?

There have been significant scientific and technological developments made so far during the pandemic, particularly relating to vaccines. These have shown great utility for preventing and mitigating transmission, disease and death from COVID-19, as well as improving preparedness for future novel viral pandemics. However, future developments are hard to predict, and are dependent on the actions and priorities of governments and individuals within societies.

Vaccines

To achieve herd immunity to a pathogen through vaccination schemes, it is necessary for a key threshold percentage of the population to accept the vaccine. Despite the extraordinary success of vaccine technology, vaccine rejection could threaten to undermine the effectiveness of COVID-19 vaccination efforts, as well as those for other diseases, for example measles. It is unclear whether the rate of vaccine rejection will rise or fall in the future, or how governments can best prevent misinformation and conspiracy theories proliferating online.

Viral detection

Patient testing

Faster, more accurate, and more convenient testing technologies could make a huge difference to the spread of COVID-19 and future novel pathogens, possibly preventing pandemics from occurring in the first place. However, the utility of this technology again relies on the level of population engagement.

Environmental testing

Environmental monitoring also has great promise for early detection of local outbreaks and relies less on active participation by citizens. However, its development will only be cost-effective if coupled to appropriate response measures.

e-health

Telehealth

The response of healthcare professionals and patients to increased use of telehealth has been mixed, and concerns have been raised about its effects on quality of care and potential discrimination towards patients who are less able to engage with phone- or internet-based healthcare. A seven-month UK-wide study was conducted in the second half of 2020 by the University of Oxford to inform and support the continued implementation of video consultations (The Health Foundation, 2020b). A study by the University of Aberdeen is currently running to explore asynchronous consultations at NHS Grampian where patient-consultant communication does not occur in real time (The Health Foundation, 2020a).

Mobile applications

Mobile phone applications have huge potential for contact-tracing, and citizen monitoring. Despite the potential for overreaching government tracking of its citizens, a study of user reviews found that concerns over privacy were generally very low, around 2% across all studied apps (Elkhodr et al., 2021).

Wearable health technology

Increasing uptake in wearable technology featuring biomonitoring presents an opportunity for remote monitoring of chronic and acute disease (Fuller et al., 2021). However, it is unclear if general uptake of this technology will be high enough for its utility to rival that of apps.

Machine learning

Machine learning technologies are still largely in the proof-of-principle phase. When used to aid decision-making in treatment, machine learning techniques are often opaque as to the features and weightings that are used, raising concerns that medically relevant but socially controversial features, such as sex or racial group, might lead to discrimination.

Research and publication

While large-scale data-sharing projects are still in development, and prone to occasional mishaps, this level of data linkage would probably not have been achievable in such a short timeframe without the collective effort spurred by the pandemic. It will remain to be seen how these platforms will evolve in the long term and integrate into the normal functioning of national health services after the pandemic.

Other technologies

More broadly, the impact of the pandemic could increase public interest and investment in related public health areas, such as nutrition and animal farming practices (Rzymski et al., 2021). This has the potential to decrease the rate of emergence of zoonotic diseases and to improve dietary health as well, in line with the World Health Organisation's "One Health" strategy (World Health Organization, 2017).

As we have seen, the general pattern has been one of combining or deploying existing technologies in new ways, or the acceleration of pre-existing technologies and trends. Even the novel mRNA-based COVID-19 vaccines developed by Pfizer and Moderna are the culmination of a development that has spanned several decades.

The NHS transition to increased use of telehealth for consultations, e-health mobile apps and devices for home monitoring was already part of the long-term plan (NHS England, 2019), therefore the rapid changes seen during the COVID-19 pandemic, again, represent an acceleration of existing trends. Use of video technology for consultations will likely rise in concert with the social penetration of the technology, and may show faster uptake in fields such as dermatology and ophthalmology, where disease signs and diagnostics tend to be more visible (J. P. O. Li et al., 2021).

The overall effect of the pandemic on science and technology developments that are relevant for UK healthcare and longevity is likely to depend on the extent to which pandemic preparedness, and epidemiology generally, become a higher public and political priority going forward. Increased awareness that health is not just a personal problem but a social one, and the advantage of preparatory investment over reactive measures, may increase public support for higher spending on healthcare research and public health initiatives generally.

Given the massive costs of the pandemic, governments should be highly motivated to support research into detection and control. Internet trends monitoring and wearables monitoring could be the most cost-effective investment, as identifying emerging epidemics earlier can lead to quicker response and vastly lower costs.

Discussion

The major theme that has emerged from this work is that the coronavirus pandemic has highlighted existing health and economic equalities. Women, young people, those with fewer resources and ethnic minorities have been disproportionately affected economically. Men, the elderly, the sick, people on low incomes and in areas of deprivation, and ethnic minorities have experienced higher mortality. There are several mechanisms linking deprivation and worse outcomes in the pandemic (Figure 30). People in lower incomes in particular live in more crowded conditions where transmission is higher; they are less able to isolate which increases the risk of exposure; they are more likely to be malnourished and sick increasing their risk of contracting COVID-19 if exposed; and they are less able to access effective treatment and are more frail increasing their risk of severe illness and death.

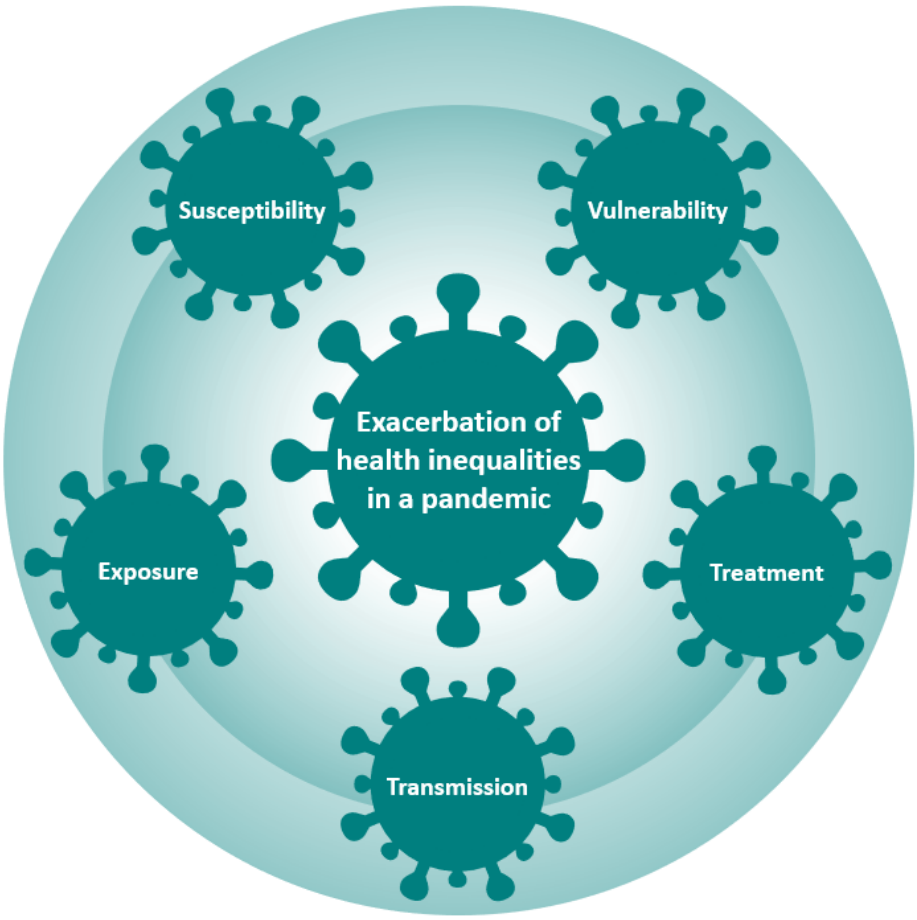

Figure 30. Showing the various dimensions of inequality affecting outcomes from the pandemic.

The mobilisation of global resources has been extraordinary with rapid development of effective vaccines, rapid identification of effective treatments, development of innovative technologies to identify cases and trace contacts, and concerted and coordinated travel and social restrictions that have been effective in reducing the impact of the pandemic. However, inequalities at an international level may yet be the Achilles heel in the global response to the pandemic. Unequal distribution of vaccination leaves some countries with much higher rates of infection than there otherwise would be creating a breeding ground for new variants that can unravel all the good work across the World, even in the wealthier and most highly vaccinated countries.

This pandemic is far from over. Cases in the UK at the time of writing are still close to 30 thousand a day and deaths within 28 days of a positive test are over 100 a day. There is a great deal of uncertainty on how the pandemic unfolds from here, possibly even greater uncertainty than at the start of the pandemic when it's progression in the absence of mitigation measures could be reasonably modelled. We are now left with uncertainty about the emergence of new variants that escape immunity, increase infectiveness or increase mortality. We are still learning about the long-term impacts of the virus and there may still be long term morbidities associated with infection that we are still unaware of, and we do not know what the legacy of the pandemic is in the population and how this might affect long-term mortality rates and life expectancy.

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