PSYCHOLOGY MISCELLANY

No.156 - December 2021

Covid-19: Looking Back to Look Forward (1st July 2021 - 30th November 2021)

Kevin Brewer

ISSN: 1754-2200

orsettpsychologicalservices@phonecoop.coop

2. Details of the author are included so that the level of expertise of the writer can be assessed. This compares to documents which are not named and it is not possible to tell if the writer has any knowledge about their subject.

Kevin Brewer BSocSc, MSc

An independent academic psychologist, based in England, who has written extensively on different areas of psychology with an emphasis on the critical stance towards traditional ideas.

A complete listing of his writings at http://psychologywritings.synthasite.com/.

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1. COVID-19 MODELLING IN THE UK IN 2020

1.1. INTRODUCTION

"Infectious disease modelling is the mathematical description of how an infectious disease will spread in a population. Unlike statistical modelling, disease modelling involves building a mechanistic description of the epidemic processes, incorporating knowledge of pathogen biology, disease natural history in a host, routes of transmission between hosts and host behaviour" (Brooks-Pollack et al 2021 p2). The components include "surveillance data" (eg: hospitalisations), demographic data (eg: make-up of households), travel and social contact information.

The Chief Medical Officer for the UK commented: "An 80% right paper before a policy decision is made is worth ten 95% right papers afterwards, provided the methodological limitations imposed by doing it fast are made clear" (Whitty 2015 quoted in Brooks-Pollack et al 2021).

1.2. COLLATED ARTICLES

Early modelling of covid-19 in 2020 was based on data from the initial outbreak in Wuhan, China (Brooks-Pollack et al 2021).

Brooks-Pollack et al (2021) collated twenty articles detailing the evidence used to advise the UK government between January and July 2020. A key issue was the use of pre-prints (appendix A) as publication in a peer-reviewed journal took too long in a "constantly evolving situation". Transparency of data and reproducibility of analysis were also important (Brooks-Pollack et al 2021).

1. Read et al (2021) – Early R estimation

Read et al (2021) provided an early estimate of the reproduction number (R) of the virus using data from Wuhan, China, for the period of 1st to 22nd January 2020. The basic R was calculated as 3.11 (ie: one individual

with covid-19 infects just over three people).

This figure was "significantly greater than 1, the epidemic threshold, suggesting a concerted effort is required to control the outbreak, requiring between 58% and 76% of transmission to be averted to control the epidemic" (Read et al 2021 p3).

The statistical model used by Read et al (2021) made use of parameters of SARS (eg: duration of viral shedding), but no account of infection control measures was made.

Other models have subsequently estimated R at between 1.9 and 6.5 (with the majority between 2.0 and 3.0), depending on the assumptions of the model (Read et al 2021).

Read et al (2021) reflected back on the modelling: "Despite the reliance on aggregated, publicly reported data, and invoking key assumptions about the natural history of the disease (notably the latent period) albeit informed by that of a closely related virus, our approach provided reasonable estimates of both the basic reproduction number and the likely true scale of the epidemic at the pandemic source" (p7).

2. Pellis et al (2021) – Doubling time

Pellis et al (2021) argued that the real-time growth rate ("doubling time") of cases, and the time between infection and case detection [1] are "often more informative" than the R number.

These researchers calculated a doubling time of three days on average for unconstrained conditions (ie: no public health measures) using data from European countries for February and March 2020. This was significantly lower than the 6-7 days estimated from China at that time (Pellis et al 2021).

The doubling time in unconstrained conditions is "essential to plan worst-case scenarios", while "recognising detection delays can help to avoid overconfidence in epidemic control when interventions are relaxed: new infections can build up unnoticed for several days while detected cases appear to be consistently decreasing. Similarly, when interventions are tightened, there will be a delay between the new control policies and seeing their effect in the data" (Pellis et al 2021 p8).

[1] The time between infection and case detection includes the incubation period of the virus, the time between symptom onset and hospitalisation, and the time to receive a positive test result (Pellis et al 2021).

So, for example, a nine-day delay between the implementation of physical distancing and its positive impact on transmission would mean that a virus with a three-day doubling time had grown eightfold (ie: doubling x doubling x doubling = 2^3).

Pellis et al (2021) presented their estimates to the UK government on 23rd March 2020. Pre-print versions of the paper were posted on 31st March 2020 (Pellis et al 2020a), 15th April 2020 (Pellis et al 2020b), and 11th June 2020 (Pellis et al 2020b updated) to reflect reviewers' comments. In times of publication in a scientific journal, Pellis et al (2021) explained that "the review process took a month, and the paper was rejected as the results, albeit valued as scientifically robust, were perceived to be insufficiently novel and not changing the understanding of SARS-CoV-2 spread at the time" (p9).

They continued: "Although we agreed that by April 2020 an expert in the field might not have been surprised by the main results of the paper, we appealed on the basis that (i) the key messages, together with the discussion of the relevant merits of R and the growth rate as indicators of viral spread,were of continued importance for policy makers and general audiences, especially in a context of rapidly changing interventions, and (ii) the publication offered robust multi-country, multi-datastream estimates, and hence filled a gap in the referenceable literature" (Pellis et al 2021 p9).

These authors raised some questions from their experience of publication:

a) "How rigorous should a scientific analysis be under time constraint?".

b) "When should a scientific result be considered 'well known' and hence not worth publishing?".

c) "To whom should scientific publications be targeted?".

d) "How can timely, visible, publication be ensured?" (Pellis et al 2021 p9).

3. Danon et al (2021) – Peak timing of epidemic

Modelling the spread of a disease is important, particularly the likely timing of the peak of the

epidemic" (Danon et al 2021 p1).

Danon et al (2021) adapted an existing model of influenza transmission in Britain based on political districts using 2011 census data about the population, and SARS parameters for incubation period and infectious period. With thee disease assumed to arrive in three cities simultaneously on Day 1, for example, the median peak of the epidemic was calculated as 133 days (without any control measures). Varying the location of the outbreak, and changing other variables (eg: season of outbreak) produced a peak ranging from 78 to 241 days.

The model used was a Susceptible-Exposed-Infectious-Infectious-Recovered (SEIIR) one involving five stages, each with assumptions or estimates:

- Susceptible – eg: percentage of the population vulnerable, or age differences in susceptibility.
- Exposure – eg: amount of contact between infected and non-infected individuals.
- Infectious – eg: length of symptom onset and transmissibility.
- Infectious – eg: period of pronounced symptoms.
- Recovered – eg: level of immunity for future infection.

Other assumptions included the same length of time of infection and equal transmissibility for mild and severe symptoms; no underlying immunity at the start of the infection; no account of morbidity, mortality and the treatment of cases and influence on spread; and no change in behaviour in response to the epidemic.

4. Gog and Hollingsworth (2021) – Simple model and interventions

Gog and Hollingsworth (2021) presented to the UK Government in February 2020 predictions based on a "simple model" (susceptible-infected-removed; SIR). This included calculations on infection spread with or without interventions.

In the SIR model, "susceptible" refers to the proportion of the population who could be infected, "infected" is the proportion of the population actually

infected, and "removed" includes individuals no longer susceptible (eg: through post-illness immunity) or infected.

Gog and Hollingsworth (2021) noted three insights from their analysis:

a) Interventions, like lockdowns, to reduce R to less than 1 must be applied long enough and early enough.

b) As population immunity increases, less stringent interventions are required.

c) If (a) is achieved, "then there is diminishing additional benefit from using an even stronger intervention" (Gog and Hollingsworth 2021 p5).

5. Challen et al (2021); Sherratt et al (2021) – Different ways to measure R

It is important to know if social distancing measures will and do reduce the R of the virus. Challen et al (2021) used a combination of data sources in their retrospective analysis – hospital admissions, cases of covid-19, deaths, and telephone calls to emergency services.

The first lockdown in the UK began on 23rd March 2020, and the R declined subsequently. Estimates for the UK looking back on 4th July 2020 showed slight differences between the four countries. "The pattern in all nations is similar with R rapidly decreasing following lock-down on 23rd March and becoming less than 1 in early April. Northern Ireland and Scotland have maintained a lower R for a longer period of time than England and Wales, with R values in Northern Ireland and Scotland at or below 0.75 for much of May, June and July compared to those in England and Wales, which have been between 0.75 and 1 for the same period" (Challen et al 2021 pp3-4).

There were also some regional differences in England (eg: London and the South West differed to the rest of the country).

Importantly, the different data sources produced similar calculations for R. The use of triage telephone calls to NHS 111 and 999 services offered an alternative to hospital data. They "provide a rapid indication of infection risk and capture a broad representation of age groups, but may be influenced by changes in behaviour and testing policy" (Challen et al 2021 p6).

"Real-time monitoring" of the pandemic depends on "surveillance data", each type having weaknesses (Sherratt et al 2021) (appendix B):

a) Number of positive tests for covid-19 - influenced by test availability [2].

b) Number of hospital admissions - influenced by threshold of severity for hospitalisation.

c) Number of new deaths - depends on the definition of a "covid-19 death" [3].

"Each of these indicators provides a different view on the epidemic and therefore contains potentially useful information. However, any interpretation of their behaviour needs to reflect these biases and lags and is best done in combination with the other indicators" (Sherratt et al 2021 p2).

Sherratt et al (2021) estimated R from the above three sources using data from March to August 2020 in England. The estimate of R varied with the data sources used, and there was "no clear superior choice of data source" (Sherratt et al 2021 p7). So, "no clear superior choice of data source, while R estimates are sensitive to assumptions about the underlying population of each data source. This means that both producers and users of R estimates should understand relevant biases in the data source's population sampling strategy, such as by community case detection or patient severity, before drawing conclusions about transmission in the population as a whole" (Sherratt et al 2021 p7).

The researchers also recommended "presenting concurrent R estimates jointly, rather than pooling estimates of R from different data sources. Pooling estimates would both suffer from unclear weighting and lose useful information about variation in sub-population transmission" (Sherratt et al 2021 p7).

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[2] In subsequent waves of infection, the number of cases have been higher than the first wave, but there is because more testing is taking place. So, many cases were missed in the first wave (Le Page 2020).

[3] When an individual stops breathing and their heart ceases beating, they are dead. That seems obvious, and it was the case until the twentieth century and medical technological developments, like mechanical ventilation. This led to death being defined around loss of brain function (ie: irreversible coma) as well (Koch 2019). But the latter definition is potentially being challenged in the twenty-first century. Vrselja et al (2019) reported the ability to "revive" the brain of a decapitated pig with "synthetic blood". There was evidence of biochemical processes, but no electrical activity (ie: brain waves). The "synthetic blood" suppressed neuronal function, but could the brain have been "rebooted"? Many medical, scientific, legal, ethical, philosophical, and political questions are raised by this study (Koch 2019).

Sherratt et al (2021) have continued with regular R estimates from each of the three data sources, and they observed that since vaccinations began, "R estimates from deaths are now consistently below those from hospitalisations and cases. This is a strong indicator of the positive impact of vaccination..." (p8).

6. Brooks-Pollack, Read et al (2021) – Large gatherings

Large gatherings were banned as part of lockdowns in the countries of the UK in March 2020. Brooks-Pollack, Read et al (2021) attempted to estimate the contribution of mass gatherings to virus transmission. The concept of population attributable fraction (PAF) was used, which is "a measure of the importance of a risk factor to disease burden or death in a population, borrowed from non-communicable disease epidemiology. The PAF of a risk factor is the percentage of disease burden or mortality that can be attributed to the presence of that increased risk..." (Brooks-Pollack, Read et al 2021 p2).

Data on social contacts were taken from surveys in 2009 and 2010 (Social Contact Survey; SCS; eg: Danon et al 2012), which covered over 5000 adults in the UK. Based on a single day, the information on number of contacts and length of contact were collected (table 1.1).

- Contact - face-to-face conversations within 3 metres and/or physically touched skin-on-skin.
- Length of time spent with each contact - less than 10 min, 11-30 min, 31-60 min, or over 60 min.
- Other information – distance from home; frequency of contact.

(Source: Brooks-Pollack, Read et al 2021)

Table 1.1 – Details of SCS.

Using this data, Brooks-Pollack, Read et al (2021) calculated the PAF based on group size. For example, for groups of 20, the PAF was estimated at 5.5%, 25.2% for groups of ten, but only 0.6% for groups larger than 100. "The pattern of decreasing PAF with increasing group size is seen for both groups of individuals who are known to each other and groups of individuals who are unknown to each other" (Brooks-Pollack, Read et al 2021 p3).

The researchers concluded that "large groups of individuals have a relatively small impact on an epidemic, under the assumption that contact patterns remain otherwise constant" (Brooks-Pollack, Read et al 2021 p3).

However, the SCS data were self-reported, and based on a single day. Brooks-Pollack, Read et al (2021) admitted: "The SCS specifically asked about groups of similar contacts. These groups are not necessarily public or mass gatherings and represented groups that both knew each other and those that did not. The group sizes reported in the SCS were not necessarily the same size of an event where contacts may have taken place [4]. Therefore, this analysis should be considered in terms of contacts per person, rather than to guide the acceptable size of organised events" (p3).

The researchers did not include factors about mass gatherings like increased distance travelled in their analysis (Brooks-Pollack, Read et al 2021).

The resurgence of covid-19 cases in 2021 may be due to mass gatherings, and decreased adherence to public health measures, as well as increased transmissibility of new variants of SARS-CoV-2. But also structural and social determinants of health. Talking about the Eastern Mediterranean region, Alsaba (2021) noted factors like political turmoil, the hosting of large numbers of refugees, and "how the livelihoods of Syrian, Lebanese, and Sudanese people, among others, are dependent on daily wages in the informal labour markets, or that many social gatherings in these countries are, in fact, queues for food and medication" (p116).

The surge in covid-19 cases in India in early 2021 may have had a threefold explanation - the relaxing of restrictions on social contact, more transmissible variants [5], and waning immunity acquired in 2020 (Le Page 2021a).

Reflecting on this surge in cases in May 2021, The Leader (2021a) warned against complacency elsewhere as "vaccines alone won't halt a surge in cases" (p5).

[4] For example, if an individual attended an event with 1000 people, but only spoke to ten, then ten was recorded as number of contacts (Brooks-Pollack, Read et al 2021).

[5] The variant B.1.617 (common in India originally) was called a "double mutation", but this is misleading. Technically, there are fifteen mutations, but two mutations of particular concern (ie: related to spike protein and entry into cells). However, these mutations have also been found elsewhere (Le Page and Wilson 2021). The B1.617 variant has three sub-lineages (Vaughan 2021c).

7. Birrell et al (2021); Jombart et al (2021) – "Nowcasting"

Birrell et al (2021) reported their real-time pandemic influenza monitoring work being adapted for covid-19. They provided the UK government with transmission models covering three periods in 2020 – pre-lockdown (before 23rd March), lockdown (until 11th May), and post-lockdown (3rd and 19th June).

Data on England were age-stratified from the seven NHS regions based on laboratory-confirmed covid-19 diagnosis and anti-bodies presence in blood samples. Contact and mobility came from varied sources (eg: Google mobility study). The model was run daily during the study period and subsequently weekly.

This was an example of real-time monitoring ("nowcasting") as much as forecasting. For example, lockdown was estimated to have reduced transmission by 75% (with regional variations) (on 10th May 2020) (ie: R dropped from 2.6 pre-lockdown to 0.61).

Regional variations in the growth of R post-lockdown were also estimated. Birrell et al (2021) pointed out: "We were, controversially, the first to highlight the regional heterogeneity in transmission, leading to local changes... in policy" (p7).

Regular publication of estimates was also a strength of this modelling team. Birrell et al (2021) continued: "We have developed a monitoring tool and progressively adapted it to deal with emerging challenges. Inevitably, the rate at which results had to be provided demanded compromises. We have not been able yet, for instance, to understand and incorporate data on hospitalisations, nor account properly for waning anti-body responses..." (p7).

Monitoring the incidence (ie: new cases) is important to understand the progress of a disease. Jombart et al (2021) developed an algorithm to detect "departures/aberrations from past temporal trends" (p2). In other words, the monitoring of whether new cues are a sign of a flare-up. Data from England in the summer of 2020 were used to train and test the algorithm. The researchers felt that, as an "early warning system", their algorithm "may be best used in conjunction with human judgment rather than as a purely automated algorithm" (Jombart et al 2021 p10).

The algorithm was dependent on the quality of the data provided, and did not account for case reporting delays by health authorities, for example.

8. Brooks-Pollack, Read, McLean et al (2021); Keeling et al (2021) - School re-opening (table 1.2; appendix C).

If lockdown succeeds in reducing the R number, then it will increase again when restrictions are lifted. The re-opening of schools is one such lifting. Brooks-Pollack, Read, McLean et al (2021) calculated R for this situation using SCS (2010) and Google mobility data [6].

If schools opened, but all other social contact restrictions remained, the R would not rise by a large amount. A calculation of R of 0.7 during lockdown would rise to 0.89 with primary schools re-opening and 1.22 with both primary and secondary schools re-opening.

High adherence to social distancing measures would be important, as well as successful contact tracing and isolation (eg: 60% of contacts of symptomatic cases within 48 hours) (Brooks-Pollack, Read, McLean et al 2021). "While tracing 20% of contacts has a positive impact on the R number, it is insufficient to prevent epidemic growth if all schools are fully open" (Brooks-Pollack, Read, McLean et al 2021 p5).

Brooks-Pollack, Read, McLean et al (2021) explained: "The greater risk arises from contact with people outside the home and school contexts. It is likely that the re-opening of schools will also lead to an increase in contacts made outside school, due to caregivers returning to work and interactions between parents" (p5).

There was limited data on young people's contact patterns, and the estimates did not account for essential contacts outside the home with key workers and essential services. Brooks-Pollack, Read, McLean et al (2021) added: "The SCS data that we used are built up around disconnected 'egos', so our approach does not capture household structures, clusters, cliques and higher-level social organisation which influence epidemic spread at a population level. Furthermore, as the epidemic progresses, immunity plays an increasingly important role in dynamics. Our approach uses the basic R number to characterise transmission and therefore does not capture the build-up of immunity in a population as all contacts are assumed to be susceptible to infection. Depending on the age distribution of immunity, social distancing measures are likely to lead to different

[6] The Google mobility data covered 3rd January to 6th February 2020, and provided "a point estimate for the percentage change in a number of visits to, and length of stay at places categorised as grocery and pharmacy, parks, transit stations, retail and recreation, residential, and workplace" (Brooks-Pollack, Read, McLean et al 2021 p2). (See https://www.google.com/covid19/mobility/) .

changes in the R number" (p5).

- Studies appeared in 2020 on school reopening showing that the "key is vigilance on hygiene and physical distancing, a swift public-health response to halt the spread of any infections and, most crucially, low levels of viral spread in the community" (Mallapaty 2020b p503).

- For example, in South Korea between May and July 2020, there was no sudden increase in covid-19 cases among children in the two months following reopening (Yoon et al 2020). While Macartney et al (2020) analysed data in New South Wales, Australia, for January-April 2020, and found that only 25 of 7700 schools or day-care centres reported infections.

- When community transmission is high, then schools can become sites of outbreak (eg: Jerusalem, Israel in May 2020; Stein-Zamir et al 2020).

Table 1.2 - School reopening around the world.

Keeling et al (2021) modelled eight school opening options for England in June 2020:

a) Reception (year 0), year 1 and year 6 primary schools (full class sizes).

b) As (a) but half class sizes.

c) All primary schools.

d) As (a) and years 10 and 12 secondary schools.

e) As (d) but half class sizes.

f) As (c) and years 10 and 12.

g) All secondary schools.

h) All schools.

Compared to keeping schools closed, it was calculated that R would increase with all scenarios due to increased contact between children, and adults (eg: parents taking children to school). "However, the magnitude of increase is predicted to be relatively low, depending on the age-groups that return to school. In general, the more year groups allowed to return to school at one time, the greater the effect on R, with the

return of secondary school children having the greatest impact" (Keeling et al 2021 p6). There would be regional variations depending upon the R in the local community, and the other relaxing of controls at the same time as school re-opening would be relevant.

The analyses were performed in May 2020 and used data available at that time. Reflecting back on their work and with subsequent knowledge, Keeling et al (2021) ended: "Our research would indicate that re-opening schools (especially secondary schools) are associated with an increased risk of transmission both within the school-aged pupils and into the wider community. The scale of this increase will inherently depend on the strength of control measures within the classroom and the compliance with mass testing as well as measures in the local community" (p10).

9. Morgan et al (2021) - Non-Pharmaceutical Interventions (appendix D)

Non-pharmaceutical interventions (NPIs) is the term used for outbreak control strategies ranging from lockdowns to advice to increase hand-washing. "Intervention optimisation" is the use of such measures most effectively based on their timing, duration, and magnitude (Morgan et al 2021).

Morgan et al (2021) developed a mathematical modelling framework in early March 2020 to help policy-makers in intervention duration, strength, and trigger point. Five scenarios for NPIs were modelled (eg: immediate and constant measures; alternating interventions).

All scenarios produced reductions in transmission, but all were sensitive to the uncertainty of a pandemic (eg: whether individuals are immune for life after infection). It was not always best to apply the severest and longest NPIs because of other consequences of such restrictions (eg: the mental health of the public; economic effects). The models assumed adherence to the measures imposed.

Overall, the study highlighted the need for a "highly nuanced" use of NPIs. The best approach was to match the timing of the severest intervention with the peak of infections, which is easier said than done. Morgan et al (2021) observed that "attaining these optima in practice is likely to be difficult. The ongoing covid-19 outbreak has highlighted the limited capacity of policymakers to effectively micro-manage the course of an

outbreak. Factors such as varying public compliance, imperfect disease surveillance, policy miscommunication, confounding parallel interventions and implementation lag between the introduced interventions and observable changes in disease prevalence will contribute to large levels of intervention implementation error" (pp7-8).

10. Hall et al (2021) - Care Homes

Disease outbreaks in institutional (closed) communities, like care homes for older people, people with learning disabilities, looked-after children, people with mental health problems and substance misuse problems, and hospices, is a concern [7]. "Care homes are at risk of disease importation through connections with community (via staff and visitors) and hospital settings (the frailty of resident population means trips to hospital increased and further discharges to care homes were arranged to ensure capacity on hospital wards)" (Hall et al 2021 p2).

Forecasting the disease burden in such settings is important. Hall et al (2021) did so using official data on daily cases of covid-19 for sixteen weeks in March-June 2020 in England. For the next eight weeks, "a reasonable worst-case" prediction of 73% prevalence of outbreaks in care homes without intervention was made. There would be local variations depending on the prevalence of covid-19 and general public health measures in the vicinity of the care homes.

The modelling did not take account of the size of the outbreak in a care home, nor the possibility of multiple importations of the disease into the institution.

The care home staff are key to disease importation, particularly where individual staff work at multiple care homes. "This is not a sign that staff are being unobservant of the current severity of the situation but highlights the challenges they face and the high numbers of cases with mild symptoms" (Hall et al 2021 p5).

Social care settings face a triple risk of infection: (i) a closed population, (ii) that is vulnerable to infection, and (iii) where "transmission is boosted due to close and frequent contact" (Hall et al 2021 p5).

This is not helped by high levels of individuals

[7] The 150 biggest coronavirus outbreaks in the USA have been in closed communities (eg: prisons, nursing homes, and psychiatric hospitals), and/or with close contact (eg: meat-packing plants) (Editorial 2020b).

with no overt symptoms reported in other studies (eg: 90% of 147 infected individuals in a homeless shelter in Boston, Massachusetts; Baggett et al 2020) (Editorial 2020b) [8].

11. Stage et al (2021) - Schools closure and re-opening

Closing schools may help in reducing the spread of covid-19, but re-opening them becomes an issue. "Re-opening presents a myriad of further questions, such as the ages of those returning, the physical circumstances and timing of their return, and the necessary conditions that must be met on a community level before a return can be deemed safe enough" (Stage et al 2021 p1).

Data to answer these questions usually came from past studies with other infections, or covid-19 data from other countries. Stage et al (2021) considered the issue for the UK with data from Denmark, Norway, Sweden and Germany in spring 2020.

The effect of school closure was estimated using hospitalisation data in Denmark and Norway (low national covid-19 case numbers), and daily confirmed cases in Germany and Sweden (medium-to-high case numbers). For modelling purposes, it was assumed that the four countries were the same in terms of adherence to measures, testing, and national policies.

Stage et al (2021) noted a key problem of decoupling the effect of school closure and re-opening from other interventions.

Overall, school closures led to a reduction in the growth of covid-19 cases around one week after implementation. "Limited school attendance, such as older students sitting exams or the partial return of younger year groups, does not appear to significantly affect community transmission" (Stage et al 2021 p1). But school closure in isolation was not deemed sufficient to prevent the spread of covid-19.

School re-opening had no impact in countries with low community transmission of covid-19 (eg: Denmark), but transmission statistically significantly increased in Germany, where community transmission was relatively high. It was found that "the added return of most

[8] "Nature" reported in May 2020 the disturbing fact in the USA that "officials are reluctant to survey people in communal spaces, because infected individuals will then need to be isolated, and their contacts potentially tested and quarantined, too. This could, in turn, mean providing housing, or paying wages to quarantined essential workers. These are difficult and expensive interventions..." (Editorial 2020b p239).

(primarily older) students in Germany has increased transmission among students, but not staff. It is unclear whether older students transmit more, or if physical distancing is practically unfeasible in classrooms at high capacity" (Stage et al 2021 p9).

Stage et al (2021) advised that "a small, strategically chosen, proportion of students should return in the first instance, with dedicated testing and monitoring of cases among staff and students (over time scales where the effect can be assessed). Any significant return of students to schools, particularly in countries with a high incidence, should not be considered unless an infrastructure is in place that would be able to swiftly identify and isolate most new cases as they appear. Such a strategy may not be feasible if the community incidence is too high" (p10).

Stage et al (2021) presented their findings to the UK Government in mid-June 2020. They commented: "Since the writing of this manuscript, a growing body of work on school interventions has accumulated, highlighting the need for monitoring via age stratified case data, dedicated testing in schools and distinguishing between older and younger students. The findings reflect transmission patterns in early 2020, and so do not account for vaccinations in the population, nor the presence of more transmissible variants. Care should, therefore, be taken when applying the results in a different context" (p10).

12. Fyles et al (2021); Lucas et al (2021) - Contact tracing

A key NPI is the contact tracing policy, which has three main components - (i) isolation of infected individuals (cases); (ii) tracing of recent contacts; and (iii) quarantine of contacts (Fyles et al 2021).

In the UK in August 2020, a contact was defined as "a case's household member or a sexual partner and/or someone with whom they have: had skin-to-skin contact; coughed on; been within 1 m of for more than 1 min; had a face-to-face conversation with within 1 m; been within 2 m of for at least 15 min; or shared a vehicle with (or sat near if a plane or large vehicle)" (Fyles et al 2021 p2).

Fyles et al (2021) modelled the impact of contact tracing . Early models predicted success if contact tracing was immediate, and 70-90% of contacts traced (Fyles et al 2021). But there are problems with contact

tracing, including (Fyles et al 2021):

- Identifying asymptomatic cases.
- Immediate isolation of the case.
- Ability of the case to recall contacts (and/or where technology like smartphone apps is not available).
- Availability of tests for contacts.
- Adherence of contacts to quarantine.
- Time delay in all the stages.

It is good to have "two-step tracing" (ie: contacts of the case's contacts) (as used in Vietnam, for example) (Fyles et al 2021).

Tracing can also be forward or backward. Forward tracing seeks the case's contacts after their infection started, while backward tracing looks for the infector of the case and who else they infected. "For some diseases, backwards tracing can be an important strategy as a backwards step can then be followed by a forwards tracing step again to discover 'sibling' infections who share the same infector" (Fyles et al 2021 pp3-4).

Fyles et al (2021) produced various simulations, and found that "implementing a contact tracing, isolation and quarantine policy could contribute to controlling the SARS-CoV-2 epidemic if lockdown levels of physical distancing are partially relaxed, but not if they are relaxed completely" (p14). A key variable was the probability that an untraced case is identified. It was also found that "household-level tracing was more effective in reducing the growth rate of epidemics than individual-level tracing, though this and other strategies need to be considered in terms of the increased number of individuals who would need to be traced and go into isolation" (Fyles et al 2021 p15).

Another important variable was the ability and/or willingness of individuals to isolate and quarantine. Contact tracing policies need to be hand-in-hand with other NPIs, like lockdowns, and Fyles et al (2021) predicted most success when everyday contacts were 40-70% less than pre-pandemic levels.

Isolation of whole households had some success, according to the simulations, along with early isolation of contacts, and backwards tracing.

"However, for each of the strategies that could theoretically improve the effectiveness of contact tracing, there are implementation challenges that could erode their effectiveness" (Fyles et al 2021 p15). For example, increasing the number of contacts to isolate

versus level of adherence to isolation.

Fyles et al (2021) did not include the "costs" of contact tracing policies (both financial and non-financial), nor immunity (natural or vaccine-acquired).

Fyles et al (2021) presented their findings to the UK Government in early May 2020. The researchers reflected back from 2021: "Throughout the pandemic, it has been clear that support and communication for members of the public to get tested, self-isolate and quarantine is extremely important, as these are the foundations of a successful contact tracing-based public health response" (Fyles et al 2021 p17).

Adherence to self-isolation could be increased by legal enforcement (eg: fines). Lucas et al (2021) modelled such an approach using different scenarios that varied the rate of adherence, the length of isolation, and the effectiveness of SARS-CoV-2 tests.

Encouraging reporting of contacts (ie: self-reporting) was as important as self-isolation by the individual case. So, policies that encourage the former would be better. Strict legal enforcement of self-isolation could reduce self-reporting as individuals do not report close contacts to save them having the inconvenience of self-isolation. Lucas et al (2021) suggested that, for instance, "economic support and employment protection for individuals that self-isolate would be expected to improve self-isolation rates without decreasing self-report rates. Similarly, efforts to communicate the reasons why people should self-report and self-isolate may improve both of these rates simultaneously" (p6).

The main outcome measure of the modelling was a large outbreak, and the costs to the individual were not considered (eg: enforced self-isolation as an infringement of personal liberty).

The modelling occurred in mid-2020, and subsequently on 28th September 2020 the UK Government introduced fines for breaching self-isolation after a positive SARS-CoV-2 test or contact by NHS Test and Trace.

On reflection, Lucas et al (2021) noted that adherence is better understood as "a multi-faceted continuous variable rather than a binary variable" (p8).

13. Danon, Lacasa and Brooks-Pollack (2021) - Household bubbles

Because of the potentially detrimental effects of

complete isolation, the concept of "bubbling" has been used. This is defined as "small, non-overlapping, groups of households that are permitted to come into contact with each other" (Danon, Lacasa and Brooks-Pollack 2021 p1). These social support bubbles, in practice, create one large household from two or more smaller ones.

In the UK in 2020, support bubbles were two households where one household contains a single adult or young children, which allowed one household to provide childcare for the other household. For the period 23rd - 27th December 2020, three-household "Christmas bubbles" were permitted (Danon, Lacasa and Brooks-Pollack 2021).

Danon, Lacasa and Brooks-Pollack (2021) modelled the bubbling strategy using percolation theory, which analyses infectious disease transmission analogous to the flow of liquid through a porous medium. Simulations included two-household and three-household bubbles, two single-persons, and variations (eg: 33% of total households form a bubble, half of which are two-household bubbles and half are three-household bubbles). Household data were taken from the UK 2011 Census (eg: around eight million two-person households and 3.6 m three-person households).

Using no bubbling as the baseline (ie: one in two persons has a social contact outside the household), bubbling increased the risk of transmission, but this varied depending on the circumstances. For example, the joining of two single-person households in a bubble had a "minimal impact". Three-household bubbles increased the risk of transmission, but this could be mitigated by individuals reducing their external contact. Also important was the size of the household bubbling - two or three large households, for example, would produce a substantial increase in transmission. "The ubiquitous generation of bubbles for all households has the potential to make transmission extremely hard to control, therefore household bubbles should not be encouraged in general" (Danon, Lacasa and Brooks-Pollack 2021 p6).

In terms of the R number, if each person in the household had a single link to other households, this was estimated at 0.79, but in a two-household bubble scenario (mean of five persons per bubble) 1.38, and 1.81 for a three-household bubble scenario (mean of seven persons).

The modelling included a limited number of external contacts, and did not vary the time period of bubbling, nor the geographical distance of households who bubble. The UK Government estimated that around 40% of adults were bubbling in 2020, but there was no information on household sizes.

Danon, Lacasa and Brooks-Pollack (2021) ended thus: "We find that, in a UK setting, the formation of bubbles can be detrimental if taken up by a sizeable proportion of the population. Therefore, messaging around bubbling should be framed in a way that communicates the negative implications as well as the benefits. In particular, large gatherings of many households should be discouraged unless absolutely necessary" (p6). Out-of-household social mixing and external contacts generally were key variables.

14. Evans et al (2021) - Within-hospital transmission

SARS-CoV-2 has spread within hospitals (known as nosocomial transmission) involving in-patients and healthcare workers (appendix E), and so control of such outbreaks is crucial.

Evans et al (2021) modelled two scenarios - suspected patients with covid-19 are placed in a ward together while waiting for test results to confirm the infection, or isolated in single rooms/bays. English data covering March-July 2020 were used, and a simulation hospital was created with 1000 beds and 800 staff.

Placing suspected patients in single rooms/bays was estimated to reduce hospital-acquired covid-19 among patients by 35%. Periodic testing of all staff reduced transmission among them by a similar amount, but had little impact of hospital-acquired covid-19 in patients.

The modelling assumed constant parameters (eg: 100% accuracy of tests), and did not include interactions of healthcare workers outside the hospital.

Subsequent real-world studies found that healthcare worker to worker transmission in hospital was an important transmission route (Evans et al 2021).

15. van Bunnik et al (2021) - Segmenting and shielding

Rather than imposing lockdown on the whole population, segmenting and shielding (S&S) could be a strategy. This is the division of the population into groups based on healthcare characteristics (segmenting), and minimising interactions with others for the most vulnerable groups (shielding). "S&S addresses the concern that while the economic, social and psychological costs of lockdown are distributed across the entire population

the public health burden is highly concentrated in identifiable populations of persons 'vulnerable' to covid-19" (van Bunnik et al 2021 p2).

van Bunnik et al (2021) modelled S&S using UK data from April-May 2020, and varied the size of the population shielding, the length of shielding, and the risk of the disease to the vulnerable population.

Overall, shielding for 20% of the population and relaxation of restrictions for the non-vulnerable rest was a positive strategy. But maintaining NPIs, like social distancing and masking wearing, for the majority of the population was still a good policy because the transmission rates between the vulnerable and population segments were key. It was noted that "S&S could be greatly strengthened by infrastructure and technological support for effective biosecurity, both at institutional (eg: care homes, hospitals) and household levels in order to keep transmission rates low between and within shielders and vulnerable populations. For maximum effectiveness, biosecurity requires training, high standards of hygiene, effective personal protective equipment and screening of everyone in contact with the vulnerable population" (van Bunnik et al 2021 p9).

van Bunnik et al (2021) continued: "Intensive screening would, ideally, include daily checks for symptoms, daily tests for virus presence (preferably with results available the same day to prevent pre-symptomatic transmission), regular serological testing and monitoring of frequent contacts (eg: household members) of shielders. If too large a fraction of the population were to be classified as 'shielders', this would quickly overwhelm current testing capacity in the UK" (p9).

The researchers accepted sources of uncertainty that limited any predictions, including the change in behaviour in the general population if lockdown is ended and the transmission rate, and the contact between vulnerable and non-vulnerable individuals.

van Bunnik et al (2021) concluded that S&S has "potential applications for any infectious disease for which there are defined proportions of the population who cannot be treated or who are at risk of severe outcomes" (p1).

16. Crellen et al (2021) - Waning immunity

Most of the models assumed that infected individuals became immune to re-infection (permanent immunity), and that social contacts were the same for everybody

(homogeneous mixing). Crellen et al (2021) included waning immunity, and non-homogeneous mixing in their model.

Four scenarios of immunity were modelled - permanent, and waning after twelve, six, or three months. Average daily contacts were based on age groups (taken from a BBC "citizen science" project; Klepac et al 2020). Data on covid-19 from March 2020 were used.

The possibility of waning immunity impacted a secondary peak of infections, and how many cases there would be. In terms of contacts, transmission was driven disproportionately by individuals of working age, and particularly 20-39 year-olds. "Higher immunity among individuals of working age has the effect of slowing the subsequent epidemic when immunity is permanent. Conversely, when immunity wanes, previously infected individuals of working age rejoin the susceptible pool and so contribute again to transmission, leading to a high growth rate and a larger secondary peak of infected cases" (Crellen et al 2021 p8). Waning immunity means that a stable population immunity threshold ("herd immunity") "can never be reached in the absence of a vaccine with lifelong efficacy" (Crellen et al 2021 p9).

This work was presented to the UK Government in July 2020, and Crellen et al (2021) revised their manuscript in October 2020. They ended: "We now know that re-infection with SARS-CoV-2 is possible, however population level parameters such as the expected duration of immunity following recovery from asymptomatic, mild or severe infections are still unknown" (Crellen et al 2021 p10).

1.3. SCREENING EFFECTIVENESS

Effective screening of asymptomatic (or pauci-symptomatic) cases for isolation depends upon factors like screening frequency, test sensitivity/accuracy, individual's behaviour, and the dynamics of viral transmission.

Modelling these factors, Skittrall (2021) found that screening (and isolation of positive cases) alone reduced infections only by a "modest" amount, and that screening can result in relaxation of precautions by individuals with minor symptoms and so produce an increase in infections compared to no screening. Rapid turnaround of test results was key to success.

Two basic scenarios were modelled - ideal and realistic. In the former situation, daily testing with

rapid turnaround high-sensitivity tests (ie: miss few positive cases - known as false negatives) and immediate isolation reduced onward transmission of the disease by 70%. In the realistic scenario, testing is weekly and test turnaround takes some time, while isolation is not immediate and fully complied with. It was estimated that onward transmission was reduced by 7% here.

Skittrall (2021) varied the behaviour of individuals in relation to positive tests and isolation with three groups - continue with daily lives (ie: no isolation), immediate isolation after test, and isolate only when symptoms appear. This last group meant that infections increased (by an estimated 13%) in the realistic scenario (and transmission obviously increased with the no-isolation group).

Test turnaround is influenced by laboratory capacity. This was varied in the modelling, and Skittrall (2021) found that "reliably keeping laboratory demand slightly below capacity results in a greater reduction in transmissions than when capacity is exceeded" (p2). Varying the turnaround time and the sensitivity of the test was also important.

Engagement with screening was also highlighted as important - ie: the proportion of those offered tests who take them.

Skittrall (2021) stated: "A holistic approach considering the social, economic and political impacts, acknowledging the incidence of false-positive results and balancing their impact, and combined with good communication, is therefore a key part of a successful programme" (p3).

The model assumed that "those being offered screening are representative of the overall population in terms of potential infectiousness and behaviour" (Skittrall 2021 p4).

1.4. MISCELLANEOUS MODELLING

Betti et al (2021) used Ontario, Canada, as a case study to model NPIs and vaccination. Data for the period 8th September to 8th December 2020 were used. The modelling occurred in late December 2020.

Vaccine deployment began in mid-December 2020, and assuming 75% of the population were reached by September 2021, the outbreak was predicted to end around July 2021 (compared to January 2022 with no-vaccine roll-out), but only with NPIs remaining in place. This benefit would be lost if NPIs were immediately removed when vaccinations

began (ie: end of outbreak predicted as September 2021).

Maintaining NPIs until May 2021, Betti et al (2021) predicted that "we are able to reopen without risk of significant increase of new cases" (p5).

Betti et al's (2021) modelling predicted a picture of balance - vaccination and NPIs together for a while, at least.

The model made a number of assumptions including that testing and reporting rates were constant, as were the number of severe to mild cases. The vaccination programme was assumed to continue at a constant pace, and the variability of vaccine production and supply was ignored.

2. LONG COVID AND COMPLICATIONS

2.1. LONG COVID

The existence of "long covid" is a challenge to those who argue for letting younger adults gain natural immunity, and, in time, herd immunity (Hamzelou 2020a).

Studies started to emerge later in 2020 of the normality of prolonged effects among covid-19-hospitalised individuals (eg: studies in England, Italy, and France) (Hamzelou 2020a).

Comparing to other post-viral syndromes – 80% of Ebola survivors had problems one year later, and 40% of SARS sufferers in 2003 had chronic fatigue four years later (Hamzelou 2020a).

Editorial (2020e) emphasised listening to patients: "In deciding how to act on long covid, researchers and policymakers must take heed of what happened in the case of myalgic encephalomyelitis, also called chronic fatigue syndrome (ME/CFS). The condition shares some of the symptoms of long covid, and people with ME/CFS struggled for many years to be recognised as having a serious and debilitating medical condition that needed specialised treatment and research" (p170).

The term itself is important, and patient groups (among others) have argued for "long covid" rather than "post-covid syndrome" or "chronic covid-19" (Editorial 2020e). Perego et al (2020) argued that terms "such as 'post', 'syndrome' and 'chronic' risk delegitimising suffering..., and that will make it harder for people to access care. Such terms also carry assumptions about the condition's underlying physiology that have not yet been properly investigated. Long covid, by contrast, states clearly that people's experience of illness after infection is long, but it doesn't presume to know anything else" (Editorial 2020e p170).

Davis et al (2021) reported an online survey undertaken in September-November 2020 with 3762 respondents from covid-19 support groups and social media. There were 257 questions including disease duration (eg: number of days symptoms lasted), symptoms

(from a list of 203), time-course (length of symptoms and recovery), and symptom onset. The Fatigue Assessment Scale (FAS) (de Vries et al 2004) was included to cover the past week.

The average was fifty-five symptoms experienced covering nine organ systems, and lasting thirty-five weeks. After six months, fatigue, post-exertional malaise, and cognitive dysfunction were most reported.

Davis et al (2021) argued that their findings showed "the importance of all patients having adequate time off to recover, being able to qualify for disability benefits if long-term assistance is needed, and receiving accommodations at work including tele-commuting, flexible hours, and phased returns. Lower wage earners may find it especially challenging to access accommodations and benefits, yet they are in need of protections the most to ensure financial stability" (p14).

Davis et al (2021) described the following limitations: "The retrospective nature of the study exposes the possibility of recall bias, which could impact the reliability of symptom prevalence estimates. Because participants were asked to report any symptoms experienced within the designated time periods, both over-reporting and under-reporting of symptoms are possible. As the survey was distributed in online support groups, there exists a sampling bias toward Long covid patients who joined support groups and were active participants of the groups at the time the survey was published. The effort to complete the survey may have deterred some respondents who experienced cognitive dysfunction, or were no longer ill and did not have incentives to participate. Furthermore, most respondents (91.6%) had not been hospitalised. The severity of illness that the survey captured may not be representative of the average 'Long covid' patient because of these issues" (p15).

Also the majority of the respondents were female (79%), White (85%), and over 40% from the USA (of 56 countries).

A survey in June 2021 by the Office for National Statistics reported a total of 945 000 people with long covid (and 380 000 had had symptoms like fatigue for at least one year) in the UK ("The Times" 6th August 2021 p11).

Possible explanations for long covid include "a hidden reservoir of SARS-CoV-2, a misfiring immune

system, or a metabolic problem triggered by the infection" (Kaiser 2021 p1429).

One idea is that long-term health problems after severe covid-19 may be because the immune system has prematurely aged (ie: "premature immunosenescence"). Three studies reported at the conference of the UK Coronavirus Immunology Consortium and the British Society for Immunology in April 2021 provided evidence for this (Lawton 2021e).

One group of severe covid-19 survivors had a loss of B- and T-cells, other survivors had dysfunctional neutrophils, and the last study showed changes in the gene expression in the immune system. "All three studies are at an early stage and more data is needed to fully explain long covid. The good news is that interventions, such as exercise and diet, have been shown to reverse immunosenescence, so if severe covid-19 does cause premature ageing, the health consequences aren't necessarily irreversible" (Lawton 2021e).

2.2. COMPLICATIONS

Individuals admitted to hospital with covid-19 may develop non-respiratory complications, which increase the risk of death, or add a substantial burden for recovery. Drake et al (2021) investigated the short-term complications beyond the presenting features of covid-19 using the International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC) WHO Clinical Characterisation Protocol UK (CCP-UK), which was developed in 2012-14 for severe emerging infections. It was reactivated in January 2020 for covid-19.

Between 17th January and 4th August 2020, patients with suspected covid-19 admitted to 302 healthcare facilities in the UK were included. Data entered into standardised electronic case reports were used (n = 80 388 adults aged nineteen years and above).

The overall mortality rate was 31.5%, and the overall complication rate was 49.7%. Among survivors, 43.5% had at least one complication, and age was a key variable (ie: sixty years and above). The most common complications were heart-related, followed by pulmonary disease, and kidney disease. Complications were higher in Black than White and Asian ethnic groups, and generally in obese individuals. The number of complications increased with the number of pre-existing illnesses that an individual had (particularly for those forty years years and above). Complications were higher in men than

women.

Altogether, "the presence of any complication, in addition to increasing age and male sex, was associated with death. In younger people, the presence of a complication was associated with a large increase in the risk of mortality, compared with older people, in which the presence of a complication was associated with a much smaller increase in mortality" (Drake et al 2021 p230).

Table 2.1 summarises the main strengths and weaknesses of the CCP-UK study.

There are a number of discussion points of this study compared to others, including:

a) Other studies up to that point were either smaller samples, single centre, patients in critical/intensive care only, one type of complication, or "lack systematic approaches to data collection" (Drake et al 2021 p232).

b) Most studies concentrated on mortality as the outcome measure. "Characterising the burden of complications is important for health-care system preparedness for further waves of infection, determining future population morbidity, understanding the full repercussions of covid-19 for society, and for informing future research and clinical guidelines" (Drake et al 2021 p224).

c) The observed covid-19 hospital fatality rate was higher than other international cohorts. "The reasons for this are multi-factorial, and could relate to differences in testing strategy, thresholds for hospital admission, pre-existing population morbidity, and health-care system preparedness" (Drake et al 2021 p234).

Drake et al (2021) ended: "Policy makers and health-care planners should anticipate that large amounts of health and social care resources will be required to support those who survive covid-19. This includes adequate provision of staffing and equipment; for example, provision of follow-up clinics for those who have sustained in-hospital complications such as acute kidney injury or respiratory tract infection. Beyond the short term, further work is underway to establish the consequences of these complications and whether these are transient or linked to worse long-term outcomes" (pp234-235).

Strengths

1. Comprehensive medical data on hospitalised individuals, both in wards and critical/intensive care.

2. Multi-centre in four countries of the UK.

3. Prospective study.

4. Clear definitions and standardised measures used.

5. "Recruitment to our study continues, enabling us to capture trends and incidence of complications in near real time" (Drake et al 2021 p232).

6. Large sample, which allowed sub-group analysis and detection of rare events.

7. Confirmation of SARS-CoV-2 by PCR test.

8. "All patients who provided biological samples were required to provide informed, written consent. If patients only provided routinely collected clinical data, written consent was not required" (Drake et al 2021 p235).

9. Multiple time points of data collection - admission, 1, 3 and 9 days in hospital, and discharge or at 28 days if not discharged.

10. The "data were collected from real-world observed clinical practice and patients did not undergo any additional tests to detect the presence of complications. Therefore, the true burden of complications is likely to be higher. However, doing large numbers of invasive tests might not be acceptable for patients, particularly in patients who are unlikely to survive or cannot tolerate investigations, and would be logistically challenging in a study of this size" (Drake et al 2021 p234).

Weaknesses

1. "It was not possible for us to causally link complications and consequent poor outcomes" (Drake et al 2021 p234).

2. Only hospitalised cases.

3. No data on longer term impact (ie: beyond 28 days after hospital admission).

4. No data on non-medical outcomes (eg: quality of life).

5. The "complications that were captured were pre-defined by a pragmatic outbreak preparedness study protocol, and case report forms developed for disease X, long before the emergence of SARS-CoV-2. The outcomes we chose are both clinically important and associated with complications observed in other infectious viral diseases. Local investigators could enter other complications as free text, but this approach might have missed some important outcomes that were otherwise unexpected..." (Drake et al 2021 p234).

6. No non-SARS-CoV-2 comparator group.

7. "[O]wing to logistical constraints, we did not capture data on the timings of each complication. As our study was an urgent response to the emerging pandemic, it would not have been possible to identify exactly when each complication started for such a large number of patients. Data around timings could in the future help to identify sequences of events that lead to further deterioration" (Drake et al 2021 p234).

8. Dependent on the accuracy of medical records.

9. Adults 19 years and above only. Drake et al (2021) defended this decision: "We used this WHO age cut-off as children exhibit other patterns of complications including multi-system inflammatory syndrome" (p224).

Table 2.1 - Main strengths and weaknesses of the CCP-UK study (Drake et al 2021).

2.3. MUCORMYCOSIS

Mucormycosis is a fungal infection (caused by Mucor species, for instance) that has increased in India during the second wave of covid-19 [9]. "Although generally harmless to an immunocompetent host, the infection can be deadly in patients with an impaired immune system, such as in those with haematological malignancies or poorly controlled diabetes, or in individuals receiving steroids or other immunosuppressants" (Stone et al 2021 p1).

Key factors in the increase include the use of steroids as treatment for covid-19 (even mild versions), and poorly controlled diabetes exacerbated by covid-19. "Additional hypotheses that need investigation include factors related to the host, pathogen (heightened prevalence and virulence of Mucorales strains in India), or the antecedent SARS-CoV-2 infection (with an increased risk imposed by variants predominating in India [ie: the Delta variant])" (Stone et al 2021 p1) [10].

Fungal diseases are generally neglected, in terms of research and health resources, compared to bacterial, viral and parasite infections (Stone et al 2021).

2.4. MISCELLANEOUS

Some individuals with covid-19 have been observed

[9] "Dubbed the so-called black fungus in popular media (due to the black and necrotic tissue seen in sufferers, rather than the mould itself)…" (Stone et al 2021 p1).

[10] Official data from Scotland in June 2021 showed the delta variant approximately doubled the risk of hospitalisation for unvaccinated individuals compared to the alpha variant (Lawton 2021i).

with chilblain-like lesions (CLL) [11], and Frumholtz et al (2021) reported a formal study at a French hospital in April 2020. The study compared 13 patients with CLL and 13 with seasonal chilblains (SC) (ie: not related to covid-19) [12], and healthy controls (n = 4).

The patients with CLL and SC had similarities ("a common pathophysiology") linked to changes in aspects of the immune system, put simply.

The impact of covid-19 on the brain is a concern, though it is only a minority of infected individuals affected (Le Page 2021e). For example, Taquet et al (2021) found that one-third of 236 000 infected individuals had a neurological or psychiatric diagnosis in the following six months (for 13% this was the first such diagnosis) (Le Page 2021e).

In another study of 267 hospitalised cases in the UK it was found that around half had bleeding and clots in the brain (Le Page 2021e).

[11] Called "covid toes" in the popular media.

[12] Chilblains are painful inflammations of small blood vessels in the skin (usually on the hands and feet).

3. VACCINES

3.1. INTRODUCTION

Writing, prior to a vaccine was manufactured, in October 2020, Subbarao (2020) emphasised the uncertainty that goes with new vaccines with a series of questions – "whether one vaccine is more effective than another, how vaccines will work in people who are at the greatest risk of severe illness (people who are often excluded or under-represented in trials), whether vaccines will prevent transmission or severe disease, how long immunity will last – and which groups might resist or reject immunisation because of ideology, mistrust or misinformation" (p475).

Correlate of protection (CoP) is a measure of the individual's immune response to a disease or infection. It is based on the number of anti-bodies in the blood in relation to a standard score. Establishing the CoP for SARS-CoV-2 is important (Lawton 2021a).

3.2. TYPES

Writing in October 2020, Krammer (2020) reported 180 vaccine candidates in development, varying in their type:

a) Inactivated vaccine - Traditional approach that involves chemically inactivated SARS-CoV-2 virus. The immune system will learn to recognise the whole virus.

b) Live attenuated vaccine - Use of a genetically weakened version of SARS-CoV-2 that has limited ability

to replicate.

c) Recombinant protein vaccines - Three different types (spike-protein-based, recombinant receptor-binding domain (RBD)-based, and virus-like particle (VLP)-based), which present the immune system with a key protein that the SARS-CoV-2 virus has to recognise later (eg: Yang et al 2020 tested one type with mice, rabbits, and macaques).

d) Replication-incompetent vectors - Use of an adenovirus, say, that is genetically engineered to be disabled, but express the spike protein.

e) Replication-competent vectors - Attenuated versions of other viruses genetically engineered to produce a transgene (a gene not found naturally in the virus) (ie: the spike protein).

f) Inactivated virus vectors - Other viruses that already display the spike protein on their surface, which are inactivated (ie: cannot reproduce).

g) DNA vaccine - Using genes that encode the spike protein.

h) RNA vaccines - The RNA information of the spike protein, say, is delivery into the body, which the immune system will learn for future reference.

As part of pandemic preparedness research, Corbett et al (2020) had been working with MERS-CoV and mRNA vaccine techniques. The technique produced neutralising anti-bodies in mice.

3.2.1. Mixture

Heterologous vaccination is where an individual is given two doses but of different vaccines [13].

In terms of the effectiveness of such an approach, Borobia et al (2021) reported a study in Spain. The first dose of the Oxford/Astra-Zeneca (ChAdOx1-S) vaccine was followed 8-12 weeks later by the BioNTech/Pfizer (BNT162b2) vaccine, and it produced a "robust immune response" (Duarte-Salles and Prieto-Alhambra 2021). But the comparison group received only one dose, the study

[13] Anti-bodies from having covid-19, and the double dose of the Pfizer or Moderna vaccine have been described as conferring a "superhuman immunity" or "hybrid immunity" (Hardy 2021). This "type" of immunity was found to combat six variants of concern of SARS-CoV-2 (Schmidt et al 2021).

had very strict eligible criteria (eg: exclusion of vulnerable individuals), and the follow-up was short (eg: fourteen days) (Duarte-Salles and Prieto-Alhambra 2021).

"Heterologous schedules are of interest for numerous reasons, including logistical considerations and clinical efficacy. The approval of heterologous vaccination will be an opportunity to make vaccination programmes more flexible in response to fluctuations in supply, which is of particular importance for countries with scarce vaccine access and in countries where different vaccines might become available at different times. Heterologous regimens also have the potential to produce a stronger response, therefore leading to higher efficacy. Finally, it is predicted that mixing vaccines will be necessary with the appearance of new SARS-CoV-2 variants" (Duarte-Salles and Prieto-Alhambra 2021 p94).

3.3. EFFICACY

Vaccine efficacy can be established by measuring immune correlates of protection (eg: number of anti-bodies). One way to experimentally test this is the non-human primate (NHP) model (appendix F).

Corbett et al (2021) used rhesus macaques and the Moderna vaccine, and measured anti-bodies in the upper and lower airways. Different doses of the vaccine were administered to healthy animals (ie: it was a covid-19 challenge test).

Anti-body numbers varied with the dose size of the vaccine (ie: dose-dependent), and viral replication of SARS-CoV-2 was reduced. "Lower anti-body levels are needed for reduction of viral replication in the lower airway than in the upper airway" (Corbett et al 2021 p1). The lower airway links to the disease severity for the individual, while the upper airway relates to transmission of the virus. It is possible that vaccine boosters would be better for the latter (Corbett et al 2021).

Much of the data on vaccine efficacy comes from studies of generally healthy volunteers without known chronic diseases. Kearns et al (2021) were concerned about "potentially immune vulnerable patient groups" (eg: individuals with rheumatoid arthritis, kidney disease requiring haemodialysis, or solid cancers). Are covid-19 vaccines equally effective for individuals with profound immune impairments?

The OCTAVE (Observational Cohort trial T-cells Anti-

bodies and Vaccine Efficacy in SARS-CoV-2) is an ongoing trial in the UK of the vaccination programme. in the first half of 2021, over 2500 patients were recruited with chronic health conditions that are likely to impact the immune system.

Kearns et al (2021) reported data in August 2021 on the first 600 participants up to four weeks after their second dose of the vaccine. A significant number (11%) of the participants had a lower immune response (based on anti-bodies in the blood) after the vaccines compared to that seen in healthy volunteers (a sample of healthcare workers). In fact, these individuals had no anti-bodies to SARS-CoV-2 spike protein four weeks after the second dose. This was even higher among certain sub-groups (eg: kidney disease patients). However, T-cell response was similar to healthy individuals.

Kearns et al (2021) made this point: "OCTAVE is an on-going study with participants still accruing and in follow up, and therefore we have not been able to provide an in-depth formal analysis of all aspects including but not limited to the impact of medication on vaccine response. Moreover, we do not yet have clinical infection data, though such data will be available over time as NHS linkage records are interrogated for this cohort. As such we are unable to draw functional protection conclusions from this dataset" (p10).

The study did not have pre-vaccination data for all participants, and the researchers accepted that "within disease categories there is heterogeneity in terms not only of disease duration, disease severity and vaccine received but also therapeutic regimens and intercurrent co-morbidities, which may all potentially impact vaccine response" (Kearns et al 2021 p11).

A number of studies around the world by late 2021 (eg: US Centers for Disease Control and Prevention; Israel's Ministry of Health) suggest that the Pfizer/BioNTech (BNT162b2) vaccine remains highly effective against hospitalisation after six months (appendix G). However, its effectiveness against covid infection generally drops (Gregory 2021).

In relation to the effectiveness against virus variants, there is emerging evidence for the different vaccines (table 3.1) (appendix H).

Vaccine	"Original" virus	B.1.1.7 variant
Pfizer/BioNTech (2 doses) [1 dose]	up to 95%	93% [51%]
AstraZeneca (2 doses) [1 dose]	up to 74%	66% [51%]
Novavax	up to 96%	86%
Johnson & Johnson	72%	64%

(Source of data: Le Page 2021d)

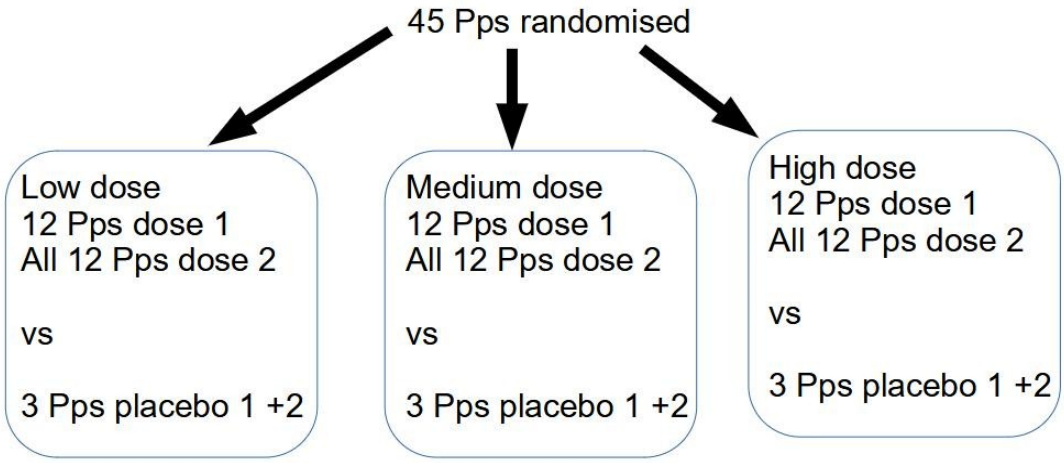
Table 3.1 - Effectiveness in preventing symptomatic infections with the B.1.1.7 variant (at May 2021).

3.3.1. Clinical Trials

Phase I/II trials aim to evaluate short-term safety, check dosage level, and assess the body's response to the vaccine (reactogenicity and immunogenicity). Reactogenicity includes local physiological effects (eg: redness at vaccine injection site), and global symptoms (eg: fever). Immunogenicity is the detectable immune response to the vaccine target (eg: specific anti-bodies). Next Phase III investigates how susceptible individuals are to the disease after vaccination (Gaebler and Nussenzweig 2020).

In October 2020, combined Phase I/II data for the Pfizer/BioNTech (BNT162b1) vaccine were published (Mulligan et al 2020; Sahin et al 2020). Mulligan et al (2020) gave one of three dose levels to 36 healthy adults with nine more participants receiving a placebo (figure 3.1), while Sahin et al (2020) gave one of five dose levels to sixty participants (table 3.2). There was a three-week gap between the two vaccine doses (known as a "primate-to-boost regimen") (Gaebler and Nussenzweig 2020).

Providing an overview at the time, Gaebler and Nussenzweig (2020) described the early clinical data as "promising", but with unanswered questions like the optimal dose, and the length of the immune response.



(Based on Mulligan et al 2020 figure 1 p590)

Figure 3.1 - Mulligan et al (2020) study design.

	Mulligan et al (2020)	Sahin et al (2020)
Details	4th May - 19th June 2020 USA?	23rd April - 22nd May 2020 Germany
Participant numbers	76 recruited; 45 involved	60
Mean age (range)	35 (19-54 yrs)	37 (20-56 yrs)
Gender/White	51% male/82% White	50% male/97% White

Table 3.2 - Comparison of participants in two clinical trials.

3.3.2. State of Knowledge

The covid-19 vaccines have been created in record time, and long-time data are being collected with their widespread use. However, nearly three-quarters of the world's population was unvaccinated as of August 2021 (Wilson et al 2021).

In mid-August 2021, the "New Scientist" summed up "what we know so far" about the different vaccines (Wilson et al 2021).

1. Oxford/AstraZeneca - A genetically altered chimpanzee adenovirus with the coronavirus' spike protein is used to create an immune response to that protein.

Widely approved by health authorities and extensively used around the world. Effectiveness of 75-99% at reducing covid-19 deaths after two doses. Information on length of immunity is not known at this point.

2. Pfizer/BioNTech - Based on messenger RNA (mRNA) that triggers an immune response to a protein from the coronavirus produced by the body. Widely approved (but not as much as the Oxford/AstraZeneca vaccine), and used. Highly effective at preventing intensive care hospitalisation, and still so at six months post-injection, though efficacy slowly declines.

3. Moderna - The same technology as the Pfizer/BioNTech vaccine. Less widely approved and used the previous above, but still important globally. Effective against severe symptoms of covid-19.

4. Johnson & Johnson - Similar to the Oxford/AstraZeneca vaccine in technology, but uses a human adenovirus. Similar approval levels to the Moderna vaccine, but less use. Effective for severe covid-19 prevention.

5. Covaxin - Uses an inactive coronavirus. It is produced and approved in India, but few other countries (including the USA) due to lack of data. Some evidence of effectiveness against severe covid-19.

6. Sputnik V (or Gam-COVID-Vac) - Russian-made, but widely approved in a number of low-income countries, mostly for "emergency use" (Wilson et al 2021).

It uses a combination of adenoviruses as vectors of the SARS-CoV-2 spike protein (ie: a different one in each of the two doses). The carrier viruses have been modified and cannot produce their infection, but they can enter the cells and express spike protein, which thus triggers an immune response to this protein (Jones and Roy 2021).

Phase I/II data were published in September 2020 (Logunov et al 2020), and phase III preliminary data in February 2021 (Logunov et al 2021). The latter included more than 20 000 participants, and vaccine efficacy at twenty-one days after the first dose was calculated at 91.6% (Jones and Roy 2021).

Reviewing the study, Jones and Roy (2021) stated: "The development of the Sputnik V vaccine has been criticised for unseemly haste, corner cutting, and an

absence of transparency. But the outcome reported here is clear and the scientific principle of vaccination is demonstrated, which means another vaccine can now join the fight to reduce the incidence of covid-19" (p643).

7. Others - eg: three key Chinese vaccines (BBIBP-CorV, Coronavac, and Ad5-nCoV) using inactivated SARS-CoV-2. Some use in low-income countries outside China, and "their efficacy varies" (Wilson et al 2021 p15) [14].

A small number of vaccine candidates have been abandoned, and others are needing approval. The technologies include replicating viral vector (RVV) (a non-SARS-CoV-2 virus used to deliver SARS-CoV-2 genes) (Wilson et al 2021). There are 130 coronavirus vaccines still in clinical trials (Wilson et al 2021).

Cuba is unique in Central and South America to be developing its own covid-19 vaccines (eg: "Abdala"; "Soberana 02"), and so, by May 2021, had not ordered any other vaccines (Taylor 2021b).

Though these vaccines do not require specialist refrigeration, three doses may be required. In Phase III trials, over 80% of people had generated anti-bodies after two doses, and over 90% after three (Taylor 2021).

3.3.3. Safety

"Adverse events" in randomised controlled trials are defined by the International Conference on Harmonisation in 1994 as "[A]ny untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment" (quoted in Blais et al 2021). But an "adverse reaction" is "an event that is judged to be caused by the vaccine [drug] under study" (Blais et al 2021 p1121) (appendix I).

Blais et al (2021) lamented the "lack of clarity" in the use of these terms in relation to covid-19 vaccine randomised controlled trials. These researchers, using the published data, compared three different vaccines being purchased by the Government of Hong Kong - "CoronaVac", "Comirnaty", and "Vaxzevria".

CoronaVac had the lower adverse reactions, but "[I]t is not clear to us whether the investigators of CoronaVac

[14] The Russian and Chinese vaccines account for "a significant and growing share of the global vaccination drive" (Lawton 2021c p10).

used different definitions or different processes to ascertain whether an adverse event qualified as an adverse reaction, which could have resulted in a much lower frequency of reported adverse reactions when compared with Comirnaty and Vaxzevria, but this is difficult to ascertain from the published article" (Blais et al 2021 p1121).

3.3.4. Post-Vaccination Infection

Many individuals have received covid-19 vaccinations, and so there is growing evidence that vaccination reduces severe symptoms, hospitalisation, and death from the disease, as well as reducing asymptomatic and symptomatic infections (Antonelli et al 2021).

"Nonetheless, some people will contract covid-19 after vaccination..." (Antonelli et al 2021 p2). Who are these individuals? Antonelli et al (2021) analysed data from the smartphone app-based Covid Symptom Study to answer this question. The app was launched in the UK on 24th March 2020, and by 4th July 2021, nearly 4.5 million participants had used it.

The focus was upon individuals who developed test-verified covid-19 at least 14 days after first vaccination (cases 1) or seven days after the second dose (cases 2). The prevalence rates were 0.5% and 0.2% respectively. Covid-19 was "less severe (both in terms of the number of symptoms in the first week of infection and the need for hospitalisation) in participants after their first or second vaccine doses compared with unvaccinated participants" (Antonelli et al 2021 p8).

The Cases 1 group included older adults with frailty, thus "highlighting the need for ongoing caution in this clinically vulnerable group" (Antonelli et al 2021 p8). Also individuals with health co-morbidities (eg: kidney disease), living in deprived areas, and with obesity had a higher risk of being in this group. The Cases 2 group included frail individuals of any age, but less likely to be those living in lower deprived areas, and non-obese individuals. Overall, the data suggested that "the risk of post-vaccination SARS-CoV-2 infection is reduced in older age groups" (Antonelli et al 2021 p11).

Antonelli et al (2021) ended: "Fully vaccinated individuals with covid-19, especially if they were 60 years or older, were more likely to be completely asymptomatic than were unvaccinated controls. This finding might support caution around relaxing physical

distancing and other personal protective measures in the post-vaccination era, particularly around frail older adults and individuals living in more deprived areas, even if these individuals are vaccinated" (p11).

The study sample was disproportionately more female than male, and included individuals with a smartphone (ie: not the most economically deprived). "Additionally, the data were self-reported; recording of co-morbidities, test results, and vaccination status might not have been completely accurate and there might have been temporal gaps in reporting" (Antonelli et al 2021 p11).

Hacisuleyman et al (2021) reported the case of two otherwise healthy women in New York who had "break-through infections" after full vaccination. "Patient 1" (51 years old) received the mRNA-1273 vaccine on 21st January and 19th February 2021, and nineteen days later tested positive for SARS-CoV-2, while "Patient 2" (65 years old) had the BNT162b2 vaccine on 19th January and 9th February 2021, and thirty-six days later tested positive. Both women were infected with variant viruses. Though this case study involved only two individuals, the findings "underscore the importance of the ongoing race between immunisation and the natural selection of potential viral escape mutants" (Hacisuleyman et al 2021 p2218).

3.4. ALLOCATION

Wester (2021) reported the principles used to decide on vaccine priority in Norway:

i) Values – In line with WHO recommendations, five core values were used: equal respect for all, welfare (ie: benefit and harm reduction), equity (ie: reduce inequity), trust, and legitimacy.

ii) Goals – Five of the vaccine programme were proposed in order of importance: reduce the risk of death, and severe illness; maintain essential services; protect employment; and re-open society.

iii) Recommendations – In a situation of low to moderate infection, prioritise high risk groups (based on age and/or underlying health conditions), and healthcare personnel. But in a situation of high infection, prioritise healthcare personnel, then high risk groups, and critical workers.

How to measure success in the covid-19 vaccines roll-out? Metrics based on speed include total doses administered, doses administered per 100 people, or total population who had received a first dose, for instance (Smith 2021).

But focus on speed misses the fact that some populations take longer to vaccinate (eg: remote geography; marginalised and "hard-to-find" groups) (Smith 2021).

Smith (2021) advocated measures that reflected equity, like reaching populations at greatest risk, and the reduction of disparities.

Fears over the unequal purchasing of vaccines by the wealthy countries were voiced in mid-2020 (ie: the pre-ordering of million of doses). Richard Hatchet (of the Coalition for Epidemic Preparedness Innovations; CEPI) was reminded of the 2009 H1N1 influenza outbreak when a small number of wealthy countries secured the majority of the available vaccines (Callaway 2020).

Writing in October 2020, Nkengasong et al (2020) voiced concerns for Africans because of pre-ordering. They said: "We've seen a scramble for access to therapies before. It happened with HIV and H5N1 influenza, for example. And Africa has ended up at the end of the queue every time. Yet the global economy depends on the continent for its exports of raw materials, food, energy and labour" (Nkengasong et al 2020 pp197-198). While Editorial (2021b) stated: "A continent of 1.2 billion people should not have to import 99% of its vaccines. But that is the tragic reality for Africa" (p487).

The African Centres for Disease Control and Prevention (AfricanCDC) proposed a strategy with three pillars to overcome the problem (Nkengasong et al 2020):

a) African involvement in the development of a vaccine - eg: clinical trials on the continent.

b) Ensure access to a share of the global supply of vaccines - eg: funding to buy them.

c) Remove barriers to vaccine uptake - eg: distribution problems; countering social media untruths about covid-19.

Former UK Prime Minister, Gordon Brown, writing in mid-August 2021, made this observation: "In a shocking symbol of the west's failure to honour its promise of equitable vaccine distribution, millions of covid

vaccines manufactured in Africa have been shipped to Europe in recent weeks" (Brown 2021 p3). While The Leader (2021b) was blunt: "Many people will die because higher-income countries are vaccinating their entire populations rather than sharing doses once they have vaccinated the most vulnerable" (p5) (table 3.3).

- One argument is that vaccinations "should go to those that are most vulnerable, in most urgent need and where they can make the most difference" (Krishna Udayakumar in Le Page and Liverpool 2021).
- COVAX was set up to distribute vaccines fairly, initially for 3% then 20% of the world to be vaccinated. It depends on sharing of vaccines by richer countries, and finding from them. But most poorer countries requesting vaccines through the scheme had not received them by May 2021 (Le Page and Liverpool 2021).
- Using limited doses efficiently could be achieved by giving only one dose to previously infected individuals. But this would need large-scale anti-body testing (Le Page and Liverpool 2021).
- But many poorer countries have poor infrastructure to allow older and vulnerable individuals to get vaccines, as well as high level of illiteracy and digital illiteracy. "As a result, jabs are being given to whoever can get to mass vaccination centres rather than to those who are supposed to get them" (Le Page and Liverpool 2021 p9).

Table 3.3 - Sharing vaccines globally.

African leaders talked of "vaccine apartheid" when the European Union has administered 496 million vaccine doses to a population of 440 million people, while in Africa 77.3 m doses have been given to 1.3 bn people (Brown 2021).

Brown (2021) argued for two urgent actions:

1. The creation of "a virtuous circle" where the rich countries guarantee funding to increase manufacturing of vaccines in poorer countries.

2. The countries with excess supply of vaccines must release the excess to Africa.

Brown (2021) ended: "We must keep reminding ourselves of the reason for ensuring the mass vaccination of the entire world: no one is safe anywhere until

everyone is safe everywhere" (p3). Some low- and middle-income countries may not be vaccinated until the end of 2023 (Editorial 2021b).

Open letters about sharing have been written by charities like the Wellcome Trust and UNICEF along celebrities like Billie Eilish and David Beckham in 2021 (Wilson 2021).

Wagner et al (2021) modelled a scenario of "vaccine nationalism" with one region having high access to vaccines (HAR) (eg: stockpiling and not sharing) and another region with low access (LAR). The researchers explained: "In general, we find that stockpiling vaccines by countries with high availability leads to large increases in infections in countries with low vaccine availability, the magnitude of which depends on the strength and duration of natural and vaccinal immunity" (Wagner et al 2021 p1488). A movement of people from the LAR to the HAR would increase the risk of infections in the latter. This would cost the HAR in terms of infection surveillance, but dose sharing between regions would reduce this need.

In late August 2021, the UK Government announced a deal with Pfizer for 35 million booster vaccine shots (Boland 2021). "Among the scientific community, news of the order raised some eyebrows" (Boland 2021 p29) [15].

This order was on top of 500 million doses on order from eight vaccine-makers (Boland 2021) [16].

Meanwhile the "tarnished reputation" of AstraZeneca's vaccine has meant less demand and use (eg: 700 000 doses administered in the UK between 21st July and 11th August 2021; Boland 2021). Note that the risk of blood clogs is "similar" for both Pfizer and AstraZeneca vaccines (Boland 2021).

But there is emerging evidence that AstraZeneca's vaccine immunity takes longer to decline compared to Pfizer's vaccine (Boland 2021).

The idea of booster vaccines is growing in popularity in the West, but it depends on three "unknowns" - the length of immunity, the success of the vaccines against coronavirus variants, and whether booster shots work (Lawton 2021d). In terms of the latter, problems include "original antigenic sin". An

[15] "Airfinity" (a science analytics company) reported that the billionth dose of vaccine was produced on 12th April 2021 (Le Page 2021b).

[16] In terms of stockpiling, the USA was reported to have more than 300 million excess doses in July 2021 (Le Page 2021c).

updated vaccine may reactivate an earlier immune memory rather than create a new one. This would make a variant-specific booster relatively useless. Alternatively a booster shot may just boost the immune response to the harmless virus that is the vehicle to carry the active ingredient (Lawton 2021d).

3.4.1. Solidarity

Kienzler and Prainsack (2021) described "solidarity" as "one of the most over-used terms" during the covid-19 pandemic. They stated: "During the covid-19 pandemic, politicians, policymakers, journalists and community organisers have embraced the concept of solidarity to justify different, sometimes opposing goals. The concept has been used to ask nations to share vaccines with people around the globe while, at the same time, it has also been employed by states to justify vaccine nationalism as an expression of solidarity at national levels" (Kienzler and Prainsack 2021 p1).

Kienzler and Prainsack (2021) defined solidarity as "a practice whereby people express their support for other people or groups with whom they see themselves as having something in common" (p1). However, covid-19 vaccines is not an example of this, according to Kienzler and Prainsack (2021). Rich countries signed deals with pharmaceutical companies for themselves, and sharing with the rest of the world was secondary. Giving "left-over" vaccines to poorer countries is not solidarity, and it "goes hand in hand with an unquestioned position of privilege" (Kienzler and Prainsack 2021 p2).

Global health information is another area of potential solidarity (ie: sharing of information and the willingness to learn from others). "More than a year after the covid-19 outbreak, researchers and politicians in the Global North still dismiss expertise and know-how developed in the Global South over decades of lethal epidemics and pandemic experience, including the effective use of community health teams. The often lower covid-19 infection and death rates, and the absence of catastrophic health emergencies in many, though not all, countries of the Global South, are attributed to different forms and quality of data collection, younger populations and climate. These are cited as arguments to dismiss the need to look deeply at what these countries might be doing right" (Kienzler and Prainsack 2021 p3).

Kienzler and Prainsack (2021) made four

recommendations for genuine solidarity and co-operation in relation to pandemics:

i) All participants as equals.

ii) Reduce structural inequalities - "Although vaccines receive a lot of attention at the moment, the most effective way to increase pandemic preparedness and control across the globe is to avoid poverty and discrimination, and to improve public infrastructures and services" (Kienzler and Prainsack 2021 p3).

iii) Solidarity when there is no apparent self-serving benefit.

iv) "Enabling the curation and sharing of high-quality data for pandemic preparedness and control on a global scale" (Kienzler and Prainsack 2021 p4).

Behague and Ortega (2021) described the mutual aid offered in Brazil: "In the face of persistent neglect and denial of the severity of covid-19 by the administration of President Jair Bolsonaro, residents in many of Brazil's favelas have been left to organise their own responses to the pandemic. Community leaders have raised funds and volunteers are going door-to-door to distribute food, masks, and hygiene kits, using megaphones to educate residents about mask use, physical distancing, and handwashing. Local journalists are also using social media to counter fake news, and activists are converting schools into isolation wards, facilitating cash transfers, and fighting for the accurate documentation of covid-19 deaths" (p575). This seems to be closer to "real" solidarity.

3.5. VACCINE HESITANCY

There is emerging evidence of the number of people not wanting a covid-19 vaccine declining throughout 2021 (Vaughan 2021a), but hesitancy is still higher among ethnic minorities in the UK, say (Vaughan 2021a), and among EU countries, like France, particularly after the short-lived suspension of the Oxford/Astra-Zeneca vaccine by several European governments in mid-March 2021 (Liverpool 2021) [17].

[17] An English critic of covid-19 vaccines, Leslie Lawrenson, died of the disease on 2nd July 2021. He had posted videos on Facebook saying covid-19 was "nothing to be afraid of" in the previous ten days ("The Times" 6th August 2021 p11).

Hesitancy and mistrust has been reported among Indigenous peoples, like the Nasa in Colombia, who prefer to rely on traditional medicine. Good communication by governments and involvement of Indigenous leaders can help (eg: Canada) (Rasolt 2021).

In terms of surveys asking about attitudes towards the covid-19 vaccinations, "out of the fear of being considered as 'anti-vaxxers', people with concerns may choose to restrain themselves from expressing their genuine opinions... or not to participate in them at all" (Wu et al 2021 p2). So, analysis of social media posts may present a more "honest" picture of attitudes.

Lyu et al (2020), for example, used Twitter data in the USA, while Wu et al (2021) analysed Reddit posts. These latter researchers found over 172 000 comments from 6466 sub-reddits generated between 1st March and 15th December 2020 related to covid-19 and vaccination. Based on the keywords, the topics were ranked for popularity, and "sceptical/aggression remarks" was most popular, followed by "clinical trials/research/testing", and "life/family/kids".

Then the researchers focused on the three most popular sub-reddits: "r/coronavirus", "r/worldnews", and "r/conspiracy", and compared the users. Overlapping users tended to express more negative emotions in their posts, but these were small numbers of individuals. In the main, "each of the most active subreddits has its own user bases. Hence, reliable news posted in r/Coronavirus would not draw attention from users in r/conspiracy, while the latter may be the group of people who need reliable information sources the most" (Wu et al 2021 p8).

3.5.1. Intention to Accept Future Vaccine

The Worldwide Independent Network of Market Research (WIN) World Survey is an annual measure of thoughts and attitudes on relevant topics collected via the Internet, telephone and in-person interviews. The WIN World Survey collected data from 26 759 individuals across thirty-two countries between 21st October and 15th December 2020 on intention to accept the covid-19 vaccine (de Figueiredo and Larson 2021).

The key question was: "When a vaccine for coronavirus becomes available will you get vaccinated?", with the response options: "definitely will" (4), "unsure but probably" (3), "unsure but probably will not" (2),

and "definitely will not get vaccinated" (1). "Intention to accept a covid-19 vaccine" was operationalised as responses (3) and (4).

This was highest in Vietnam (97%), India (91%), China (91%), and Denmark (87%), but lowest in Serbia (38%), Croatia (42%), France and Lebanon (both 44%). Response (1) was highest in Lebanon, Pakistan, and Paraguay, and response (4) was highest in Vietnam, India, and Brazil.

In terms of demographic variables globally, these included:

- Sex - males were likely to accept than females.
- Age - over 65s more than younger adults.
- Education - higher educated more so.
- Country - high-income more than low- and middle-income.
- Trust in government and intention to be vaccinated.

Overall, there was substantial country-level and individual-level variations in the intention to be vaccinated.

de Figueiredo and Larson (2021) analysed secondary data in the sense that the WIN World Survey was designed for other purposes. Thus the researchers noted relevant variables that were not measured (eg: risk perception; general attitudes to vaccines). They pointed out that "the estimates of uptake provided here are static and could change drastically in response to factors such as vaccine misinformation. Moreover, the online nature of the surveys in the majority of countries may introduce computer literacy or access biases that may impact the overall estimates of vaccination intent. In countries where computer access and literacy are high, we would expect these biases to be small, but this is nonetheless a source of potential bias for which we have not controlled. Social desirability biases may also impact our estimates of intent to accept covid-19 vaccines that may also vary by mode of questionnaire (eg: online versus telephone surveys)" (de Figueiredo and Larson 2021 p9).

It should also be noted that stated intention about future behaviour is not necessarily the same as actual behaviour in the present.

3.6. MISCELLANEOUS

(1) The concern has been raised about breastfeeding mothers being vaccinated. Generally, two case reports have found harm to the infant, but this was with the live yellow fever vaccine (Sarchet 2021).

In terms of the covid-19 vaccine, an early, small study of the mRNA vaccines found no vaccine material in the breastmilk of five Pfizer/BioNTech and one Moderna recipients up to 48 hours after vaccination (Sarchet 2021).

On the other hand, there is merging evidence of vaccine-generated anti-bodies against covid-19 in breastmilk (Sarchet 2021).

(2) Public money and charitable investment has been crucial to fund the vaccine development (Editorial 2021e). For example, 98% of the funding of the vaccine technology for the Oxford-AstraZeneca vaccine was public money (Cross et al 2021).

(3) The town of Serrana in Brazil was the site of a real-world test of CoronaVac, and 98% of adults had been vaccinated. Data reported in May 2021 showed that covid-19 deaths fell by 95% and symptomatic cases by 80% (Lewis 2021).

It was also noticed that symptomatic cases among unvaccinated children had similarly dropped. Along with evidence from countries with high adult vaccination rates, this appears to be an example of "herd immunity" (Lewis 2021).

Critics, however, argue that unvaccinated children are still important spreaders of covid-19, and they may be "reservoirs" for infection or new variants. So, the question is whether to vaccinate children, which is being debated around the world (Lewis 2021).

(4) Writing in October 2020, Kate Bingham, chair of the Covid-19 UK Vaccine Taskforce, said that what kept her up at night was worry about the practicalities of vaccine supply (not the science) - "the boring stuff" (eg: manufacturing scale-up; legal approval). She pointed out that changes to speed up vaccine supply "must be set up to last beyond covid-19" because of the risk of future pandemics (Bingham 2020 p171).

Global vaccination depends on the supply chain not

breaking down. Generally, vaccination production can involve more than 200 companies in different countries in the manufacture of glass vials, filters, resin, tubing, and disposal bags, for instance. Specific to the mRNA vaccines are biological compounds like enzymes and lipids (Irwin 2021).

Intellectual property (IP) rights (eg: the lipid nanoparticle that holds the RNA in mRNA vaccines) may also be a bottleneck, and in March 2021 the World Trade Organisation (WTO) debated waiving them. Not surprisingly, IP rights-holders opposed the proposal. Alternative strategies include "technology transfer" (eg: licensing of IP rights to third parties) or "co-ordinated technology transfer" (via the WHO) (Irwin 2021).

(5) In late October 2020, “Nature” presented an assessment of scientific progress and knowledge in relation to covid-19. The key issues were natural immunity (anti-bodies), and the production of a vaccine (artificial immunity) (Editorial 2020f).

(6) Up to 17th May 2021, there were nearly 4000 reports of altered periods after covid-19 vaccination made to the MHRA (Medicines and Healthcare products Regulatory Authority) in the UK (Giles 2021).

(7) A scandal emerged in February 2021 in Peru that 470 politicians, researchers, and family members not enrolled in a phase III covid-19 vaccine trial (by Chinese state-owned pharmaceutical company, Sinopharm) had received the vaccine (Taylor 2021a).

"The events in Peru aren't the only instances in which members of the elite have jumped vaccine queues during the pandemic. In Argentina, for example, a similar list [of those secretly receiving the vaccine] has emerged, resulting in the health minister's resignation and a national investigation" (Taylor 2021a p175).

4. CRUISE SHIPS

4.1. LEGAL ISSUES

The growing industry of international cruise tourism was hit in the early days of covid-19 when seven hundred people were infected on the "Diamond Princess" in February-March 2020. Over forty cruise ships had confirmed cases of covid-19 by mid-2020 (Zhang and Wang 2021). "During this period, many countries closed their borders and blocked international cruise ships from docking in order to prevent and control the pandemic. The United States Centres for Disease Control and Prevention (CDC), for instance, issued a No Sail Order effective on 13 March 2020 that suspended all cruise ship passenger operations. As a consequence, thousands of passengers were quarantined on board for weeks before coming ashore, while seafarers were trapped at sea for an even longer time before being repatriated, resulting in 'a humanitarian, safety and economic crisis' as described by the International Maritime Organisation (IMO)" (Zhang and Wang 2021 p1).

Cruise ships are a high risk for respiratory infections generally because of the high population density, shared food supplies, and semi-enclosed environments. "Both the prevention and the control of infectious diseases on cruise ships are relatively more complicated and problematic, especially for those international ships with passengers of different nationalities and docking ports located in different countries. Apart from the limited healthcare and medical conditions onboard, there are also difficulties with respect to the rule-based international co-operation and co-ordination of treatment measures" (Zhang and Wang 2021 p2). For example, the "MS Westerdam", which departed Hong Kong on 1st February 2020, spent two weeks drifting at sea after ports at five countries denied entry because of suspected covid-19 cases. Eventually, it was accepted in Cambodia (Zhang and Wang 2021).

Zhang and Wang (2021) considered the legal issues of such a situation, including:

- The right to deny entry.

- The measures to deal with docked and disembarked passengers.

- The co-operation of the flag state, the coastal state (ie: waters where ship is), and the ship operator/owner's state.

The researchers collected data on covid-19 outbreaks on international cruise ships in 2020 from a variety of sources (eg: IMO). It was found that "the inadequacy and even failure of co-operation by involved parties were incredibly salient. The WHO [World Health Organisation] has indicated that health on international cruise ships is a shared responsibility of all relevant stakeholders, involving equitable access to essential care and collective defence against transnational threats" (Zhang and Wang 2021 p4).

One problem was a large number and variety of laws and regulations. The United Nations Convention on the Law of the Sea (UNCLOS) is meant to be foremost, but Zhang and Wang (2021) "discovered that there are certain ambiguity and even inconsistency with regard to the relevant international norms and the domestic regulations of individual states. Such a lack of regulatory harmony directly led to problems of conflicted jurisdictions, unbalanced liabilities, and an uncertainty of rescue obligations during the covid-19 pandemic" (p4).

Furthermore, some rules were not mandatory, nor enforceable, like IMO resolutions on places of refuge for ships in distress. The WHO (International Health Regulations; IHR) has limited enforcement power also (Zhang and Wang 2021).

In terms of the general principles, there is the right of free pratique of the IHR (ie: ships shall not be prevented from entry for public health reasons). "A limitation to the free pratique principle is that, when infection or contamination sources are found on board, a country may require disinfection, decontamination, disinsection or deratting [18], or other necessary measures that should be taken to prevent the spread of the infection or contamination" (Zhang and Wang 2021 p5).

There is also the "rescue obligation" of the UNCLOS upon the coastal state, and the port state (ie: port already entered; scheduled to enter; or home port). "The rescue obligations of coastal and port states have limitations. Under the UNCLOS, the rescue obligation

[18] Measures to control insects or rodents that may transmit infections.

primarily concerns dangerous situations such as typhoons and collisions at sea, under which circumstances the nearby ships are obliged to render assistance when a cruise ship calls for rescue in international waters. The covid-19 pandemic, whereas, is somewhat different from those circumstances. When a pandemic occurs, not only does the cruise ship require special treatment, but the rescuers, including the port states, also need to consider whether they have the necessary capability to prevent and control infectious disease" (Zhang and Wang 2021 p6). The "MS Westerdam" was denied entry because of port states' lack of capacity of control of infection (Zhang and Wang 2021).

Coastal states can refuse entry to its waters if there is a serious threat, like environmental pollution from an oil tanker. This is the denial of the UNCLOS "innocent passage" principle. The right of all ships to move freely through waters is based on the premise that there is no threat to the coastal state. Some states deemed covid-19 a serious threat (Zhang and Wang 2021).

Other states will be involved including the flag state (ie: the country under whose laws the ship is registered), the cruise ship company's state, and the state of the passengers. In the first case, there is no uniform standard of rules for flag states, and especially in the case of "flag of convenience". "Under covid-19, even though they are legally bound, flag states have neither pressure nor motivation to undertake epidemic prevention and control responsibilities" (Zhang and Wang 2021 p7). Similar issues arose with the cruise ship company's state, while a number of states of passengers, like China and the USA, arranged evacuation and quarantine in the home country (Zhang and Wang 2021).

Finally, Zhang and Wang (2021) noted similar problems with the legal situation of quarantine at sea, and prohibition of disembarking at port of entry. For example, the IHR states that ships "shall not be prevented from embarking or disembarking" for public health reasons, but port states have contradictory control rights under other regulations to protect the spread of infection or contamination (Zhang and Wang 2021).

Zhang and Wang (2021) ended by recommending greater co-operation between the different parties. "First, it must be recognised that in the era of globalisation and in the face of a global pandemic, no single state can manage everything, nor can any single international organisation solve the problems independently" (Zhang and

Wang 2021 p9). Other issues include the design of ships, which encourage infection spread (eg: air-conditioning systems) or limit quarantine facilities, information sharing between different parties, and clarification of jurisdictions. Zhang and Wang (2021) recommended the precedence of the flag state on international waters to rescue the ship, and the port state of the territorial sea of a coastal state. Always supported by the co-operation of other parties (Zhang and Wang 2021).

4.2. LEARNING ABOUT COVID-19

Cruise ships, like the "Diamond Princess", provided a closed population to study. This ship was quarantined in Japan in February 2020 with 3711 passengers. Regular testing was possible, and over 700 passengers were infected (of which 18% of these showed no symptoms) (Mallapaty 2020a).

Azimi et al (2021) retrospectively analysed transmission data from the "Diamond Princess" to show that airborne transmission of smaller aerosols was a risk (compared to the primary transmission through larger respiratory droplets). The study involved modelling over 21 000 scenarios to try and explain the actual spread of infection. The index case was a passenger who boarded on 20th January in Yokohama and disembarked in Hong Kong on 25th January. Ten cases of covid-19 were confirmed on the ship on 4th February 2020.

Airborne transmission was "most likely the dominant mode" of transmission (ie: >50% of overall transmission).

As with any mathematical modelling study, there were assumptions made (eg: "every passenger was assumed to have the same probabilities of close-range contact with others and every infected individual was assumed to have the same emission rates of droplets in aerosols"; Azimi et al 2021 p7).

5. DRUGS, TREATMENTS, TESTS AND RESTRICTIONS

5.1. DRUGS AND TREATMENTS

5.1.1. Drug Utilisation

Distinguishing facts from fiction (and disinformation) has always been an issue with covid-19, especially in relation to drugs to treat (or cure) it. Islam et al (2020), for example, found that around one-fifth of over 2300 rumours and conspiracy theories in the media covered this.

A number of drugs have been tried (with varying success) [19] [20]. Enners et al (2021) surveyed drug utilisation using the database of the German Institute for Drug Use Evaluation (DAPI). The analysis was divided into three time periods: (A) January to early March 2020 (pre-pandemic), (B) mid-March to mid-April 2020 (first wave of the disease and lockdown), and (C) late April to June 2020 (relaxation of lockdown restrictions). Drug utilisation was defined as number of packages dispensed per week. Data from 2019 were used as the baseline.

Drug utilisation increased during period A (by 43% at the peak compared to 2019), and subsequently declined to 18% below 2019 figures by period C. Hydroxychloroquine saw a massive increase (by 110%) in period A, particularly related to claims of its success with covid-19. Anti-biotics and paracetamol were among general drugs to see changes in utilisation.

In summary, Enners et al (2021) stated that "drug prescribing, utilisation, and purchasing behaviour was

[19] Drug production involves three basic stages - (i) synthesis of the active ingredient; (ii) modification of the drug to make it stable; and (iii) packaging it into tablets, say (Ledford 2020b).

[20] "Drug-discovery efforts generally require a target, such as a protein that has an important role in disease. Promising drug compounds bind to the protein, affect its function and act safely in the body" (von Delft et al 2021 p330).

By late January 2020, Chinese scientists had made publicly available 3D structures of SARS-CoV-2 proteins (von Delft et al 2021).

significantly altered, particularly during the first weeks of the covid-19 pandemic in early 2020, possibly influenced by misinformation and speculations on potential treatment efficacy as well as hypothetical concerns on harmfulness of commonly used drugs" (pp1497-1498). The increased utilisation at the end of period A indicated stockpiling "most likely caused by the anticipated intensification of nationwide restrictions for public life and social interactions and, hence, concerns with regard to continuous drug supply" (Enners et al 2021 p1498).

The researchers ended that their analysis "can inform post-pandemic policy to prevent unfounded over- and under-prescribing and off-label use as well as drug shortages during a public health crisis" (Enners et al 2021 p1493).

There was no information on patient use of individual drugs (eg: prescribed for one purpose but used by patients for covid-19), and any consequences of use.

5.1.2. Statins

Statins (lipid-lowering HMG-CoA reductase inhibitors) protect against covid-19 mortality according to a Swedish study (Bergqvist et al 2021).

Data were available for the whole population of the country from detailed official records, but the researchers focused on all 45 year-olds and older in Stockholm county (excluding individuals with liver disease and thus unable to take statins) (n = 963 876). The variables were prescriptions of statins between March 2019 and March 2020, and death from covid-19 before 11th November 2020.

Overall, 17.6% of the sample were prescribed statins in the year prior to the covid-19 pandemic, and 2545 individuals died in total. Of these, 765 were statin users (ie: 0.5% of all users), and 1780 non-users (0.2% of all non-users). But, when confounders, like age, residential area, household crowding, and long-term health conditions, were controlled in the analysis, "statin treatment was associated with a moderately lower risk of covid-19 mortality" (Bergqvist et al 2021 pp6-7).

In terms of other studies, hospitalised covid-19 patients who took statins were less likely to die than non-users (eg: Daniels et al 2020). While meta-analyses (eg: Kow and Hasan 2020) calculated a reduction in risk of unfavourable covid-19 outcomes for users. But the

meta-analyses demonstrated "substantial heterogeneity between studies" (Bergqvist et al 2021 p8), while a Danish study found no association between statin use and covid-19 mortality (Butt et al 2020).

Bergqvist et al (2021) criticised the other studies for being "limited in their appreciation of the complexity of causal inference when using observational data and may thus be prone to the critical pitfalls of observational studies of clinical interventions...[]... These include failure to differentiate between new and prevalent users (leading to survival bias), using post-baseline information to establish exposure (leading to immortal time bias), introducing collider bias by sampling only hospitalized patients and/or conditioning on positive PCR test results or adjusting for potential mediators (such as disease severity)" (p8).

Table 5.1 summarises the main strengths and weaknesses of Bergqvist et al (2021).

STRENGTHS	WEAKNESSES
1. Rigorous methodological to avoid above-mentioned biases. 2. Controlling for confounders, and "avoid confounding that may arise from altered behaviour during the covid-19 pandemic" (Bergqvist et al 2021 p9). 3. Large sample size. 4. General population rather than hospital-based. 5. Lower limit of 45 years old excluded pregnant women, and that there had been few covid-19 deaths among younger adults.	1. Potentially uncontrolled confounders (eg: smoking; body mass index). 2. It was assumed that a prescription for statins meant adherence. 3. No differentiation of statin dosage, type or brand. 4. Data from one area in one high-income northern European country. 5. Official data sources used misses statin prescriptions outside of those records (eg: in another country; privately).

Table 5.1 - Main strengths and weaknesses of Bergqvist et al (2021).

5.1.3. Others

There was interest in convalescent plasma early in the pandemic. This is infusing patients with (anti-body-laden) blood of recovered covid-19 patients (Maxmen

2020).

In some situations it is not possible to perform a randomised controlled trial for such a treatment, at least initially in 2020. Though there were data on patients in the USA who had received plasma, there was no control group (Ledford 2020c).

But Joyner et al (2020) used an opportunist or quasi-experimental design. They compared 3500 plasma recipients based on the level of covid-19 anti-bodies in the blood given. Individuals receiving plasma with high levels of anti-bodies were less likely to die than with lower anti-body levels. There was no randomisation of participants, however, and so individuals receiving the high level-plasma may have also received better treatment generally. In other words, "We're just seeing an association... We're not seeing cause and effect" (Anthony Gordon in Ledford 2020c).

Kemp et al (2021) analysed the blood of a man in his 70s with a weakened immune system with severe covid-19, who was given remdesivir, and convalescent plasma. The individual died 102 days after a nasal swab confirmed infection. It was possible to compare the genome of the virus at the first swab and from subsequent swabs (23 time-points in total). The researchers also studied the SARS-CoV-2 samples in the laboratory.

The convalescent plasma created strong selection pressures for the evolution of the virus, "which is associated with the emergence of viral variants that show evidence of reduced susceptibility to neutralising anti-bodies in immunosuppressed individuals" (Kemp et al 2021 p277).

This was a single case study, but it suggested caution about the use of convalescent plasma in individuals with weakened immune systems (eg: due to chemotherapy).

Rodriguez Mega (2020) reported the extensive use of ivermectin for covid-19 in Latin America without evidence. It is a drug used to treat individuals infected with parasitic worms, but it became very popular as a protection against covid-19.

Some early studies in cells (eg: Caly et al 2020), and humans hinted at anti-viral properties. Some of these studies were withdrawn soon afterwards (Rodriguez Mega 2020).

A Cochrane review up to the end of May 2021 (Popp et al 2021) found a lack of reliable evidence to support the use of ivermectin. Cochrane reviews are detailed literature searches for the evidence on a particular topic. In particular, randomised controlled trials are reviewed, and the quality of the studies are rated.

Popp et al (2021) found fourteen studies with 1678 participants that compared ivermectin to no treatment, placebo, or standard care, but no studies comparing ivermectin to a proven treatment for covid-19. Nine of the studies involved in-patients and moderate covid-19, four studies out-patients and mild symptoms, and one study investigated ivermectin for prevention of SARS-CoV-2 infection. Only six studies were double-blind and placebo-controlled.

The authors concluded: "Based on the current very low- to low-certainty evidence, we are uncertain about the efficacy and safety of ivermectin used to treat or prevent covid-19. The completed studies are small and few are considered high quality" (Popp et al 2021 p2). Thirty-one ongoing studies were found, however.

5.2. TESTING

In an analysis of thirty-five providers of PCR tests in the UK by "The Times", it was found that they were not providing the cheaper versions for travellers in early August 2021. The UK Government website listed 415 approved providers, but only 6% had been accredited by the agency that assesses covid-19 tests (Courea 2021).

SARS-CoV-2 antigen rapid lateral flow tests (LFT) are quicker than reverse transcriptase polymerase chain reaction (PCR) tests in providing a result. The latter detects genetic material of the virus in symptomatic individuals, whereas LFTs "are primarily being used to identify likely infectious individuals by detecting SARS-CoV-2 antigen from people who are shedding virus but who may not have classical covid-19 symptoms, or at least do not use symptomatic testing centres" (Petersen et al 2021 p936).

The validation of LFT for asymptomatic testing is crucial (ie: the accuracy). This is usually studied by giving individuals PCR and LFT together, and comparing their conclusions. A variety of figures for the accuracy of LFT have been found in studies (eg: 36-64%; Petersen et al 2021). "These diverging figures have provoked debate about the sensitivity of the LFTs and concerns

have been raised about their utility in the context of testing asymptomatic individuals" (Petersen et al 2021 p936).

Petersen et al (2021) saw the problem as the difference between PCR and LFT, and the dynamics of the epidemic. Bearing these in mind, these authors produced a mathematical formula to assess the accuracy of LFT. Their conclusion was around 80% (ie: true-positive - correctly identifying an infected individual; table 5.2).

Petersen et al (2021), however, accepted: "Further studies are needed to ascertain the absolute sensitivity of LFT as a test of infectiousness in covid-19 responses. These studies should include longitudinal series of LFT and PCR, ideally in cohorts sampled from both contacts of cases and the general population" (p935).

	Individual infected	Individual not infected
Test says infected	True positive	False positive
Test says not infected	False negative	True negative

Table 5.3 - Accuracy of tests compared to reality.

5.3. RESTRICTIONS

5.3.1. Impacts

Lockdown has affected smoking and drinking in two directions. "Some people may have used tobacco or alcohol as a means of coping with increased stress or boredom. Others may have taken the opportunity to quit smoking or drink less while daily routines are disrupted and social activity is reduced" (Jackson et al 2021b p2).

Jackson et al (2021b) analysed data from the "Smoking and Alcohol Toolkit Studies" during the first lockdown in England in March-July 2020. Data were also available for pre-lockdown (2018-19). The Smoking and Alcohol Toolkit Studies are monthly, and involve a new random sample of about 1700 adults each time. Jackson et al (2021b) developed an analysis of the first month of lockdown (Jackson et al 2021a).

Smoking prevalence was found to be fairly stable from before covid-19 and during lockdown, except for an increase among 18-34 year-olds. Cessation of smoking and quit success also increased.

Among all adults, lockdown was associated with an increase in the prevalence of "high-risk drinking", but

“particularly pronounced rises were seen in women and people from less advantaged social grades (C2, D, E)” (Jackson et al 2021b p8).

Note that data collection was face-to-face before covid-19, but via telephone during lockdown. The researchers argued that the data collected by these different modes are comparable.

Though young children (ie: under five years old) "have largely been spared from the severe health and mortality complications associated with SARS-CoV-2 infection, they have not been immune to the impact of the stay-at-home, masking, and social distancing policies. These policies, meant to limit spread of the SARS-CoV-2 virus, have closed daycares, schools, parks, and playgrounds, and have disrupted children’s educational opportunities, limited explorative play and interaction with other children, and reduced physical activity levels" (Deoni et al 2021 p3).

What are the actual impacts of these changes? Longitudinal data may be able to answer such a question, and Deoni et al (2021) referred to the RESONANCE study (now part of the NIH Environmental Influences on Child Health Outcomes (ECHO) programme). The RESONANCE study began in 2009 in Rhode Island, USA, and has recruited around 1600 caregivers and 0-5 year-olds.

Data for children up to March 2020 (pre-pandemic group) were compared to the following year (pandemic group). Verbal, non-verbal, and overall cognitive test scores for three-month to three year-olds were significantly reduced in the latter group, and males were "more heavily affected. Deoni et al (2021) explained: "we find that children born before the pandemic and followed through the initial stages do not show a reduction in skills or performance, but rather that young infants born since the beginning of the pandemic show significantly lower performance than infants born before January 2019. Thus, our results seem to suggest that early development is impaired by the environmental conditions brought on by the pandemic" (p11).

The researchers did not find an increase in general (pre- and post-natal) maternal stress during the pandemic, which others had suggested as a mechanism to impact child development (eg: Provenzi et al 2021). Deoni et al (2021) accepted that this variation may be due to differences in the measurement tool for stress used, or "the potential selection bias in the families included in our study; or strong family and social support networks available to the pregnant individuals" (p11). Deoni et al

(2021) used the perceived stress scale (PSS) (Cohen et al 1983), which is a ten-item measure of perceived and experienced stress to general life events, whereas Provenzi et al (2021) (MOM-COPE study) collected data on worries specific to covid-19, pregnancy, and the child's health.

During the pandemic, mothers and children were studied in clinics, so these participating were happy to travel there, which may mean, Deoni et al (2021) pointed out, "parents less concerned about the pandemic, and those with strong social support networks, may have been more likely to participate than those with greater concerns. Thus, our observation that maternal stress (PSS) did not significantly increase may simply reflect the reality that we only tested less stressed and anxious mothers. These parents may also have greater financial security or other socio-economic characteristics" (p12).

No data were collected on parent- or caregiver-child interactions, nor the impact of adult mask-wearing. This latter point could have been relevant during the testing of the children. "The inability of infants to see full facial expressions may have eliminated non-verbal cues, muffled instructions, or otherwise altered the understanding of the test questions and instructions" (Deoni et al 2021 p13).

Deoni et al (2021) ended: "What is unclear from our data, however, is if observed declines or impairments are temporary and will normalise as employment and school closures are lifted and children return to pre-pandemic levels of play and interaction, and family financial insecurity and mental health challenges subside" (p13).

During the first UK lockdown (March-May 2020) air pollution fell by 50%, but only by 28% during the January-March 2021-lockdown. Any benefits from reduced traffic in the latter case were lessened by increased air pollution from gas boilers in the winter weather (and from working from home) (Vaughan 2021b).

The 2020 lockdowns in different parts of the world were a "natural laboratory" to study bird song, for instance. Anecdotal reports appeared in the media of the bird song sounding louder.

Derryberry et al (2020) quantified the change in the San Francisco Bay Area with the white-crowned sparrow (a common songbird in the area). Pre-pandemic data had been collected in June 2015 and 2016, which were compared to recordings made in April and May 2020 (during a

California State shelter-at-home mandate).

Previous work had established that in noisy urban areas, birds sing higher-amplitude songs (known as the "Lombard effect" [21]) (Derryberry et al 2020).

Derryberry et al (2020) found evidence of changing songs during the covid-19 shutdown - ie: lower amplitudes - and the sounds travel longer distances. The data indicated "the impact of noise pollution on communication during normal conditions. This doubling in communication distance could elevate fitness by reducing territorial conflicts and increasing mating potential" (Derryberry et al 2020 p577). Derryberry et al (2020) continued: "Birds also exhibited greater vocal performance in response to being released from masking by high-energy, low-frequency noise" (p577).

Note that the same individual birds were not sampled in 2015-16 and 2020, so, Derryberry et al (2020) explained, "we cannot determine whether the observed shift in vocal performance was due to immediate flexibility or if it was because males with higher performance (but typically more masked) songs outcompeted males with lower performance (but less masked) songs for breeding territories during the covid-19 shutdown" (p578).

5.3.2. Miscellaneous

(1) Categories of risk for countries for travellers is problematic. For example, at the beginning of June 2021 Portugal was on England's "low risk" ("green list"), then on 8th June it was moved to the "amber list" (10 days quarantine after returning to England), but, all the time, the US Centers for Disease Control and Prevention (CDC) rated Portugal as "avoid all travel" (Lawton 2021h).

(2) Scientists facing anger over lockdown measures is like blaming firefighters when your home is on fire (Devi Sridhar in Vaughan 2021d).

(3) Oliu-Barton et al (2021) reported that for the period February 2020-21, countries that had stricter pandemic suppression strategies also fared better on health, wealth, and civil liberty measures. Of thirty-seven

[21] This is "an involuntary vocal response by speakers to the presence of background noise" (Zollinger and Brumm 2011 pR614), discovered in 1911.

wealthy nations compared, five had "elimination strategies" (Australia, Iceland, Japan, New Zealand, and South Korea), and the others mitigation policies (Lawton 2021j). Elimination strategies include mass testing, supporting infected individuals to isolate, tracing their contacts, swift lockdowns as required, and border controls.

(4) The NHS Covid-19 app was introduced in England and Wales in late September 2020, and it was downloaded to twenty-one million separate devices in the rest of that year. Using Bluetooth-based technology, the app stores the codes of phones that had been in close physical contact over the previous fourteen days. If the individual tests positive for covid-19, then a message can be sent via a central server to all phones in physical contact with that individual (Wong 2021).

Wymant et al (2021) modelled data for this app, and estimated that for every 1% increase in app users, the number of covid-19 cases could be reduced by 0.8-2.3%.

It was assumed that individuals who receive a message via the app will test for covid-19 and/or self-isolate as appropriate. In a UK survey (Smith et al 2021), only 20% reported actually isolating fully for seven days, while 70% said they would if the situation arose (Wong 2021).

An indirect effect of the app could be that "users maintain a greater distant from others than they otherwise would have done, being aware that the app monitors distance and could later advise quarantine" (Wymant et al 2021 p411).

6. ORIGINS OF SARS-CoV-2

6.1. OFFICIAL RESPONSE

Responding to criticisms, members of the World Health Organisation's (WHO) team sent to China in January 2021 to understand the origins of SARS-CoV-2 outlined their mission. There were eight items that their mandate covered (Koopmans et al 2021):

1. Respiratory illness in Wuhan and Hubei in the second half of 2019.

2. Review of 76 000 patient files of suspected cases of covid-19 in Wuhan in the second half of 2019.

3. An analysis of death certificates during the same period and place.

4. A reconstruction of the investigation of the early outbreak.

5. Mapping of the supply chain of products sold at the Huanan seafood market in Wuhan.

6. Testing of a range of livestock, wildlife, pets, and zoo animals for SARS-Cov-2.

7. Analysis of genomic data of the virus.

8. A review of relevant literature related to the above items.

Koopmans et al (2021) emphasised: "The possibility of a laboratory origin for the virus's introduction into the local human population — what has come to be called the lab-leak hypothesis — was not part of the WHO's original terms of reference for the team" (p483) (table 6.1). Though this was considered by the WHO team.

The twenty-eight-day mission to China was supported by general WHO staff, and over 1000 healthcare professionals in China who collected much of the data beforehand. But there was some reluctance "to share raw

- This suggests that "gain in function" experiments were being performed at the Wuhan Institute of Virology. This type of research is where pathogens are modified to be more harmful in order to understand them. There is no documented evidence of such work here (Lawton 2021g).

- But supporters of the lab-leak idea posit secretive experiments. Evolutionary virologist, David Robertson refuted this proposal: "It loses all meaning at that point because it's not about facts any more. Unless you have evidence that they [Wuhan Institute] are working on viruses very closely related to the one that 'escaped', then that's where it becomes conspiracy theory" (quoted in Lawton 2021g).

Table 6.1 - The "lab-leak" hypothesis.

data (for instance, on the 174 cases identified in December 2019), citing concerns over patient confidentiality" (Koopmans et al 2021 p483) by the China team.

The joint report of the WHO and China teams (WHO 2021), Koopmans et al (2021) explained, "concluded unanimously that there was clear evidence of widespread SARS-CoV-2 circulation in Wuhan during December 2019. We reported evidence for earlier emergence but reached no resolution on when, where and how that occurred. We concluded that the Huanan seafood market had a significant role in the early part of the pandemic, and that there were credible links to wild-animal markets to follow up [22]. We agreed that the earliest cases of covid-19 had probably been missed, as is common for outbreaks of new diseases" (pp483-484).

A zoonotic origin of SARS-CoV-2 via an intermediate host (ie: spillover from wild animals) was noted as "most plausible", but "there was no definitive proof for or against any of the four proposed pathways" (Koopmans et al 2021 p484). The other possibilities were zoonotic introduction via consumption of contaminated food, handling infected farmed animals, and escape from a laboratory working with infected animals.

Koopmans et al (2021) responded to some of the many criticisms of their report, including:

a) Failure to investigate many aspects - The report was phase 1, and recommendations were made for phase 2 (including another visit to China).

[22] Chinese researchers took sample swabs in early 2020 from the Huanan market (including animals, doors, rubbish bins, and stalls). The positive samples came from stalls that sold seafood, livestock, and poultry, but the samples from 188 animals of eighteen species were negative (Maxmen 2021).

b) China did not share data - Despite some reluctance mentioned above, "much new information was shared by the Chinese team as a result of the agreed studies, and that even more was shared as part of the iterative process between the international and Chinese teams" (Koopmans et al 2021 p484).

c) Ignoring the lab-leak hypothesis - This was not part of the team's mandate as mentioned, but it was considered.

d) Criticisms based on information that came to light after the WHO report - This needs to be considered in phase 2.

Koopmans et al (2021) continued: "Some of the public discourse around the report probably originates from miscommunication and misunderstanding about the nature of the work. Although the published report correctly calls it a joint study to reflect what was laid out in the World Health Assembly resolution and terms of reference, it was publicly called an investigation by journalists, by representatives from some member states and, on occasion, by representatives of the WHO. This might have led to expectations that the report would provide watertight evidence based on formal audits of the institutes involved in the studies" (pp484-485).

Phase 2 is "in the pipeline", and Koopmans et al (2021) urged the WHO to expedite it. There are six priorities for these authors:

i) Further trace-back studies before Wuhan in December 2019.

ii) Anti-body surveys (inside and outside China) to find where SARS-Cov-2 may have been circulating without notice in 2019.

iii) Trace-back of the wildlife supply chain.

iv) Investigate possible reservoir and intermediate hosts.

v) Analyse "pockets of earlier cases".

vi) Follow-up "any credible new leads" (Koopmans et al 2021 p485).

6.2. GENOMICS

In the search for the origins of SARS-CoV-2, genetic sequences of the virus are important. However, early data are limited (eg: samples from patients in Wuhan, China, in late December 2019). "This paucity of sequences could be due in part to an order that unauthorised Chinese labs destroy all coronavirus samples from early in the outbreak, reportedly for 'laboratory biological safety' reasons" (Bloom 2021 p1).

Bloom (2021) addressed the problem that the earliest sequences from Wuhan (and in particular, the Huanan Seafood Market) were quite different from the virus's bat coronavirus ancestors, and were "notably more different from these bat coronaviruses than other sequences collected at later dates outside Wuhan" (Bloom 2021 p1).

Bloom (2021) considered the explanations for the Huanan Seafood Market sequences of the virus being more evolutionarily/phylogenetically distant from bat coronaviruses than later sequences:

i) The Huanan samples just "happen" to be sequenced before more ancestral sequences.

ii) Confusion over the categorisation of sequences (ie: technical error).

iii) The faking of the genetic sequences. This has been popular on social media, but is "less plausible" (Bloom 2021).

iv) Multiple zoonoses at the same time.

Bloom (2021) was able to find online apparently "lost" early genetic sequences of SARS-CoV-2 [23], and to reconstruct thirteen early partial sequences. From this work, Bloom (2021) concluded that the Huanan sequences were not representative of all SARS-CoV-2 in Wuhan in early 2020. In other words, other "versions" of the virus, of which there is little genetic data, were circulating in Wuhan at the time, and these were closer to bat coronavirus ancestors (eg: by three mutations).

Bloom (2021) accepted that he was working with partial reconstructions of the virus's genome. "Therefore, it is impossible to unambiguously place them phylogenetically, or determine exactly when they were collected" (Bloom 2021 p8).

[23] Genomic sequences were deposited early in the pandemic in 2020 on a US database ("Sequence Read Archive"), but later removed for reasons unclear (News in brief 2021).

6.3. BATS

SARS-Cov-2-related viruses have been reported in the bat genus Rhinolophus in the last decade (eg: Cambodia in 2010; Japan in 2013; Thailand in 2020) (Temmam et al 2021).

Temmam et al (2021) reported evidence of bat-borne SARS-CoV-2-like viruses in caves in Northern Laos. The closeness of these viruses to SARS-CoV-2 suggested that an intermediary species, like the pangolin, is not needed to spread to humans.

Temmam et al (2021) collected over 200 blood samples from various bat species, which allowed complete genome sequences of sarbecoviruses (respiratory viruses) to be generated.

Overall, twenty-five different coronaviruses were identified in ten bat species. Viruses closest to SARS-CoV-2 were found in three different bat species. Temmam et al (2021) concluded that the findings supported "the hypothesis that SARS-CoV-2 could originally result from a recombination of sequences pre-existing in Rhinolophus bats living in the extensive limestone cave systems of South-East Asia and South China, which provides ideal conditions for interspecies interactions among Rhinolophus bats. They are restricted to limestone caves for their roosting sites and forage in the vicinity of these caves, and many species have been found foraging in the same cave areas, including R. malayanus and R. pusillus. In addition, the distribution of R. marshalli, R. malayanus, and R. pusillus overlaps in the Indo-Chinese sub-region, which means they may share caves as roost sites and foraging habitats" (p9).

6.4. LAB-LEAK HYPOTHESIS

The Chinese government has responded negatively to the lab-leak hypothesis, and the fact that information has been suppressed in the past, has "fuelled suspicions" (Maxmen and Mallapaty 2021 p313).

Maxmen and Mallapaty (2021) outlined the key arguments:

a) There is "not yet any substantial evidence for a lab leak" (p313), but neither is there evidence to rule it out or to establish a natural origin for SARS-CoV-2. Origins investigations take time (eg: fourteen years for SARS) (Maxmen and Mallapaty 2021). Probability and consensus favours a natural origin.

b) The lab-leak proponents focus on unusual features of the SARS-CoV-2 which could suggest the engineering of the virus. Other researchers feel it is "improbable", for example, some of these features are found in other coronaviruses.

c) The presence of the Wuhan Institute of Virology (WIV), working on coronaviruses, in the area where SARS-CoV-2 was first noticed by the world. But laboratories work on diseases in their locality. So it is an association rather than a causation. Also the variables for a natural origin are present in Wuhan, like wildlife transported from the countryside.

Much of the debate revolves around surmises and speculations, and whether the WIV and/or Chinese government are hiding information.

7. THE MENTAL SIDE

7.1. MENTAL HEALTH

Hu and Qian (2021) investigated face-to-face and virtual contact during the covid-19 pandemic among older adults in the USA and the UK. The US data came from the 2020 Health and Retirement Study (HRS), while the Understanding Society (USOC) covid-19 survey was used in the UK. Each of these representative longitudinal studies included data about mental well-being prior to covid-19.

The HRS was administered via postal questionnaires, but online in the UK. The datasets "may have under-represented 1) homeless and institutionalised populations in both countries, 2) those with limited internet access in the UK, and 3) those with disabilities or who were severely ill with covid-19" (Hu and Qian 2021 p4). The final samples of over 60 year olds were 5148 in the UK and 1391 in the USA.

General mental well-being, and perceived loneliness were the two outcome variables. The former was measured by the eight-item Center for Epidemiologic Studies Depression (CES-D) scale in the USA, and the twelve-item General Health Questionnaire (GHQ-12) in the UK. "Despite slight differences, the GHQ-12 is broadly comparable with the CES-D. Most of the CES-D items, such as depression, sleeplessness, enjoyment of daily activities, general happiness, and ability to face problems, are also included in the GHQ-12" (Hu and Qian 2021 p4).

Perceived loneliness was self-reported in both countries as "never/hardly ever", "sometimes", or "often". Both variables were rated for change between before the pandemic and during (no, positive, or negative change).

The explanatory variables related to inter-household contact were:

- Face-to-face contact - eg: frequency (from "never" to "daily").

- Virtual contact - textual (text messaging/email) and audio/visual frequency.

Control variables included age, gender, ethnicity, education level, living alone or with others, working, suffered with covid-19, and self-rated health.

Over half of the US respondents were scored as the best category of mental well-being, but just under half in the UK. Less US respondents reported a decline since pre-pandemic (25% vs 38% from UK), and more reported an improvement in mental well-being (26% vs 20%). "Together, these results suggest that the pandemic and its associated public health and policy responses undermined older adults' general mental well-being in the UK but not in the US" (Hu and Qian 2021 p7).

But the opposite was true for loneliness. More US respondents reported feeling "sometimes" or "often" lonely during the pandemic (43% vs 30% from the UK), and becoming lonelier since pre-pandemic (29% vs 11% in the UK). "Therefore, the negative impact of the pandemic and its associated mitigation measures on older adults' loneliness appears to have been greater in the US than in the UK" (Hu and Qian 2021 p7).

The UK respondents had infrequent face-to-face contacts, but frequent virtual contact compared to the USA. Hu and Qian (2021) offered two possible reasons for this difference: "First, the US respondents were surveyed using paper questionnaires, whereas the UK respondents were surveyed online, suggesting that the latter may have had greater digital access, capacity, and/or know-how and have been less restricted in their digital communication than the former. Second, as lockdown and household-centred pandemic responses were more stringently implemented in the UK than in the US, inter-household face-to-face contact may have been curtailed to a greater degree in the UK than in the US, whereas older adults in the UK may have been more dependent on virtual contact than their US counterparts" (p8).

Putting all this information together, Hu and Qian (2021) summed up thus: "In both countries, more frequent inter-household face-to-face contact during the pandemic was associated with better general mental well-being, but inter-household virtual contact, via means such as telephone and digital media, was not associated with general mental well-being in either the US or the UK. In the US, older adults who engaged more frequently in virtual contact were more likely to feel lonely during the pandemic, particularly if their face-to-face contact was limited. In both countries, the increase in

loneliness following the outbreak of the pandemic was greater for older adults who reported more virtual contact" (p1). So, virtual contact was "not a qualitatively equivalent alternative" to face-to-face contact for the older adults in the two samples.

In terms of the control variables, those living alone, women, those with poorer self-rated health, and "less financial satisfaction" reported poorer mental well-being and more loneliness in both countries.

Because of the limited range of the measurement categories (eg: three for loneliness), there were potential "floor effects" or "ceiling effects". For example, "it was not possible to capture a decline in mental well-being among those already reporting the poorest mental well-being before the pandemic. Similarly, there was little room for improvement among those with the best mental well-being before the pandemic" (Hu and Qian 2021 p11).

The variables were measured at one point in the pandemic in June 2020. Also the relationships were correlational not causality. For example, the relationship between loneliness and more virtual contact could go in either direction - loneliness drives more virtual contact or more virtual contact causes feelings of loneliness. "To fully disentangle possible reverse causality, scholars would need to conduct in-depth and in-situ qualitative research to understand more fully the complex mechanisms underpinning the relationship between inter-household contact and older adults' mental well-being" (Hu and Qian 2021 p12).

It was not possible to analyse the type of virtual contact and loneliness, nor who the contact was with (family or friends).

The two datasets were not fully comparable, and "the findings need to be carefully interpreted in the context of survey mode differences between HRS and USOC" (Hu and Qian 2021 p12).

7.1.1. Anxiety and Depression

US studies have found increased anxiety and depression symptoms reported during the covid-19 pandemic. For example, Vahratian et al (2021), using data from the US Census Bureau Household Pulse Survey (HPS), found significant increases between August 2020 and February 2021, particularly among 18-29 year-olds, and individuals with lower educational qualifications.

"Across the entire study period, the frequency of anxiety and depression symptoms was positively correlated with the average number of daily covid-19 cases" (Jia et al 2021 p1427).

Anxiety was measured by two items - (i) "feeling nervous, anxious or on edge", and (ii) "not being able to stop or control worrying" in the last week, while depression was measured by these two items - (i) "having little interest in pleasure or doing things", and (ii) "feeling down, depressed, or hopeless". The response choices were "not at all" (0), "several days" (1), "more than one half of the days" (2), and "nearly every day" (3). The anxiety scores were combined (out of six) as were the depression scores (Jia et al 2021).

The HPS is biweekly online survey begun in April 2020 to assess the economic and social impacts of covid-19, and the samples are nationally representative (Jia et al 2021).

Jia et al (2021) outlined some of the limitations of HPS, including:

- Only two questions each to measure anxiety and depression.
- The HPS response rate was less than 10%.
- Self-reported data.
- Online mode of administration.

7.1.2. Wider Perspective

Lees-Manning et al (2021) reviewed the effects on mental health and well-being of different types of crises using eight case studies:

i) Disasters (eg: World Trade Centre attack September 11th 2001) - Individuals "closely exposed" (geographically or personally) and key responders had elevated rates of PTSD (post-traumatic stress disorder), and depression afterwards, but "no particularly adverse mental health consequences for the general population" (Lees-Manning et al 2021 p4).

ii) Wars (eg: Syrian civil war) - "a global impact on mental health, with almost the entire population affected directly by pervasive and extreme trauma" (Lees-Manning et al 2021 p4), and "secondary" socio-economic

hardships, especially felt by women and individuals with disabilities.

iii) Recessions (eg: economic collapse in the USSR) - Impact on mental health via loss of income, and social economic deprivation, with increased anxiety, but "below clinical significance for the majority" (Lees-Manning et al 2021 p4).

iv) Other pandemics (eg: Ebola virus) [24].

How can this information, and the emerging research, inform us about mental health and covid-19?

There is more research on mental health and the covid-19 pandemic (in the thousands) compared to 327 with H1N1 flu, and 127 for Ebola virus (Lees-Manning et al 2021). Lees-Manning et al (2021) explained: "This is not surprising, both because of the upward trend in academic exploration of mental health, and because numerous aspects of the pandemic have been expected to have had an effect on mental life. These include the isolation caused by the lockdown and social distancing measures, fears about catching or spreading the virus, grief for lost loved ones, burnout among healthcare workers, the effects of disruption to education, the stress of having to care for young children while schools are closed, or the effect on mental life of domestic violence, which saw an increase during the first lockdown" (p44).

But the impacts of covid-19 on mental health are not evenly distributed across society. For example, depression was rated higher at the beginning of the pandemic by female respondents to surveys, individuals with financial concerns, and those with disabilities (Lees-Manning et al 2021). While anxiety has been reported as higher among key workers, the young, women, those living with children, and individuals with pre-existing mental health conditions (Lees-Manning et al 2021).

Mental distress, based on data from mental health charities, has declined after peaking at the start of the pandemic (Lees-Manning et al 2021). The "negative outcome affecting the general population are relatively short-lived and possibly offset by positive factors and/or innate resilience" (Lees-Manning et al 2021 p46).

"There is mixed evidence as to whether the pandemic

[24] The links between pandemics and mental well-being were observed in the flu pandemics of the late nineteenth century (eg: 1890-91 Russian flu pandemic) and the 1918 Spanish flu pandemic. For example, "The Times" in 1919 wrote that "one of the features of the present influenza wave is the marked depression it leaves behind it" (quoted in Ellis et al 2020).

has been positive or negative for child mental health. But, there is consistent evidence that there have been negative effects for children with special needs, those in low income areas or family, and those in unstable home environments" (Lees-Manning et al 2021 p48).

Poor mental health during covid-19 has been linked to pre-existing health conditions. "However, there is some evidence that those with severe conditions have reported no change in mental health during the pandemic. Coping strategies and protective factors for this group include prior experience of adversity, feeling less accountable to others, hobbies, staying connected, and perceiving social support" (Lees-Manning et al 2021 p48).

In terms of generalisations, individuals experiencing deprivation, and healthcare workers correlate with worse mental health outcomes (Lees-Manning et al 2021).

In conclusion, Lees-Manning et al (2021) stated that the "'Tsunami' narrative of the mental health impact of covid-19 is not only inaccurate, being based on the initial spike without accounting for the subsequent drop-off, but it also becomes a self-fulfilling prophecy if it is overplayed... Moreover, the implication that a wave of mental health will hit the whole population indiscriminately is, whether intentional or not, dismissive of the underlying socio-economic risk factors for poor mental health outcomes both during and predating this crisis..." (p52).

Burnett (2021) took a slightly different position with reference to grief: "Grief during lockdown is even more complex. I say this as someone who like millions of other people, has endured months of it, cut off from friends and family, I fear this is causing genuine problems that are going unrecognised or unacknowledged" (p21). He continued: "Will this make me, and everyone else in the same situation, mentally unwell? I would argue not. But it is something that could harm the mental health of millions of people, long after the initial cause has occurred" (Burnett 2021 p21).

7.1.3. Mortality

Analysis of English data found that individuals with mental disorders had a greater risk of death than the general population (Das-Munshi et al 2021). The data came from the South London and Maudsley NHS Foundation Trust,

and covered 167 122 individuals with a diagnosis of an ICD-10 psychiatric disorder. The study period was 1st January 2019 to 31st December 2020, and the all-cause mortality was 4%. The comparison data covered averages for England and Wales.

Firstly, it was found that the risk of death was over twice as high among individuals with a psychiatric disorder prior to covid-19. This greater risk increased during the period of covid-19 and peak deaths in the general population in the second quarter of 2020. In the remainder of 2020, the risk of death declined for the study group, but it was still double that of the general population.

Das-Munshi et al (2021) summed up: "Our study provides evidence in support of the concern that the covid-19 pandemic has exacerbated pre-existing health inequalities in people living with mental disorders and intellectual disabilities, suggesting that additional excess mortality has been driven by a heightened risk of death from covid-19, added to elevated risks of death from all other causes, which have continued to operate throughout the pandemic" (p7).

7.1.4. Miscellaneous

(1) Anti-depressant prescriptions in England for under 18s have been increasing between April 2015 and 2020, but this trend has accelerated since the covid-19 lockdowns began. For example, in March 2020 an increase in unique patients on March 2019, and 21% on March 2016. Further peaks were observed in December 2020 and January 2021, during further covid-19 lockdowns (Robinson 2021).

(2) A survey by "Anxiety UK" (https://www.anxietyuk.org.uk/blog/post-lockdown-anxiety-survey-reveals-mixed-picture/) of 900 people about the end of lockdown restrictions found that pressure to socialise was the biggest concern, well ahead of return to workplaces and use of public transport (Thomson 2021).

(3) Former UK chief scientific advisor, Ian Boyd, writing in early April 2020, emphasised the need for resilience, and in getting the public to respond to the interventions positively (Boyd 2020).

7.2. MAKING SENSE OF EPIDEMICS

Rosenberg (1989) outlined three stages of the "narrative path" of epidemics (Wailoo 2020):

I - "Progressive Revelation" - "the gradual and grudging acceptance of the epidemic as reality" (Rosenberg 1989 quoted in Wailoo 2020).

II - "Managing Randomness" - Explaining differences among social groups, and searching for who to blame.

III - "Negotiating Public Response" - Not only how to respond, but how to deal with the object of blame. Rosenberg (1989) stated that "the poor and socially marginal, for example, have historically been labelled as the disproportionately likely victims of epidemic illness, and they have been traditionally objects of public-health policy" (quoted in Wailoo 2020).

Rosenberg (1989) discussed social class, whereas Wailoo (2020) added race and ethnicity to the stages, and proposed four "acts" (with the emphasis on the USA and African Americans):

1. "Racial Revelation" - "This is the occasion when health experts and authorities take note of Black people's experiences, illnesses, or mortality as a specific object of curiosity and social commentary" (Wailoo 2020 p605). For example, the Governor of New Jersey first publicly commented on the "racial toll" of covid-19 on 8th April 2020 (Wailoo 2020).

2. "Staging Bodies and Places" - The "racial spaces" "in which infections flourish or where presumed racial immunity resides, the negro quarters (whether of the ghetto or the plantation), the Black neighbourhood, or the Wuhan, China 'wet market' - believed to be the source of covid-19 — with its exoticised food practices and 'wild animal section where live and slaughtered species were for sale: snakes, beavers, porcupine, and baby crocodiles, among other animals' [Maron 2020 quoted in Wailoo 2020]" (Wailoo 2020 p609).

Wailoo (2020) noted the swift appearance of genetic and biological explanations for ethnic differences and covid-19, which "were baseless distractions from the obvious factors at work - systemic inequality and oppression" (p609).

Historically, this "racial susceptibility" can be

seen in different ways in the high level of typhoid fever among Anglo-Saxons in India. A doctor in 1909 asked: "Is it because the latter [Indians], inhabiting a country where hygienic laws are so little recognised, have developed, a considerable degree of immunity?" (quoted in Wailoo 2020).

3. "Making the Racial Spectacle" - The speculations of the previous act become established. "In the racial spectacle of epidemics, questions of social order come into view" (Wailoo 2020 p615).

4. "Fixing Racial Boundaries" - "'Epidemics have always provided occasion for retrospective moral judgment', Rosenberg [1989] observed. Epidemics (or any waves of disease) reveal ruptures and provoke imperatives to remake boundaries that contagion has weakened or exposed" (Wailoo 2020 p617).

Packard (1989), for example, described how the TB epidemic in South Africa in the later twentieth century, which impacted working-class Black Africans most heavily, was used as a justification of the segregation of apartheid of the time (Wailoo 2020).

Wailoo (2020) ended that the "acts are not always performed predictably or sequentially. They are not inevitable. But their recurrence suggests something about the racial repertoire that pre-exists, that anticipates the epidemic [...] Such narratives would not endure unless they fell on fertile soil each time" (p624). One element of the "fertile soil" is the psychological benefits of blaming another group as sick (or disadvantaged) because of their own faults. "Reflecting on the plight of the poor and telling stories about their conditions functions as self-affirmation for many Americans, who take comfort in being fortunate, having different bodies, living better than the poor, and not suffering 'their' fate. But epidemics break down the ritual, psychological social bracketing of self and 'other'..." (Wailoo 2020 pp624-625). Thus, the need to reinforce the "boundaries".

8. LOOKING BACK AND FORWARD

8.1. LOOKING BACK

8.1.1. April and May 2020

(1) Writing at the beginning of April 2020, Editorial (2020a) praised the collaboration of researchers: "As infections and deaths continue to rise, it is only a matter of time before world leaders will have to step up. They have no choice, because there's little point in extinguishing the virus in one country when it's exploding elsewhere. A genuinely global response is needed - and world leaders must follow the fine example being set by researchers" (p7).

On 10th January 2020, researchers in China and Australia (Wu et al 2020) shared the genome sequence of SARS-CoV-2 (Editorial 2020c).

The genome of SARS-CoV-2 has 29 811 RNA bases, and each instructing 25-29 proteins. Collaborations between scientists produced an understanding of the proteins in 2-3 months after publication of the genome. This understanding became the basis of treatments and vaccines (Scudellari 2020).

The phrase "standing on the shoulders of crowds" could be used to describe collaborations between scientists (a variation on the metaphor of science generally as "standing on the shoulders of giants") (Editorial 2021d).

But collaborations between academia and industry, as in some of the covid-19 vaccines, has to deal with tensions over data ownership and intellectual property (Editorial 2021e).

(2) The number of confirmed cases of covid-19 worldwide rose from 41 on 11th January 2020 to 167 515 on 16th March 2020 and over 4.2 million on 14th May 2020 (Scudellari 2020).

(3) Ledford (2020a) commented on the shelving of clinical trials on other illnesses when covid-19 arrived (eg:

Addex Therapeutics delayed the start of a trial related to Parkinson's Disease in March 2020).

It is possible that any gains in reducing covid-19 deaths with lockdowns will be lost in the long-term by increased cancer deaths, for instance, as less people sought help (Hamzelou 2020b).

Covid-19 may have left children vulnerable to other infections because of their reduced interactions during lockdowns (Lu 2021). For example, respiratory syncytial virus (RSV) in Australia was low in winter 2020, but subsequently increased dramatically (Foley et al 2021). Modelling in the USA (Baker et al 2020) predicted a substantial increase in the winter 2021-22 (Lu 2021).

(4) Researchers with animals in laboratories were faced with difficult decisions when lockdowns occurred. "Some scientists are able to care for animals in their usual facilities, with animal-care workers taking extra precautions for social distancing. Others..., have take animals home or re-released wild-caught specimens. And many creatures have been, or will be, killed, particularly small animals such as mice" (Nowogrodzki 2020 p19).

8.1.2. Other Times

(1) Initially, the focus of covid-19 symptoms was respiratory ones, but it became clear in mid-2020 that there are a wide range of symptoms (eg: six clusters), and the effect of the virus varies greatly between individuals. There are also differences between adults and children, and between children of different ages (eg: infants and teenagers) in symptom manifestation (Hamzelou 2020c).

Variables related to the difference between individuals include the amount of virus the individual is exposed to initially, and the mode of infection (nose, eyes or mouth) (Hamzelou 2020c).

(2) Concerns about mass reinfection in 2020 have proved groundless. So, "while reinfection is possible, it is rare and usually produces mild disease at worst" (Lawton 2020j p14).

(3) Uruguay appeared to be a country controlling the spread of covid-19 in 2020 (Moreno et al 2020) (180 deaths and 19 100 cases in the whole year), but then "lost control" in 2021 (5300 deaths and 341 000 cases in the first half of the year) (Taylor 2021c).

The initial success was due to swift lockdown measures in March 2020 when the first case was confirmed. But in 2021 the government was slower to reintroduce such measures. Virologist Gonzalo Moratorio also noted: "National authorities claimed victory too early... Fear of the virus was lost because of all the good things we had done" (quoted in Taylor 2021c).

(4) The B.1.1.7 variant of SARS-CoV-2 (first detected in the UK in September 2020) quickly became the dominant variant worldwide in the subsequent months. It has twenty-three mutations compared to the "original" virus (Thorne et al 2021).

"Although much effort has focused on Spike adaptation for viral entry and adaptive immune escape, B.1.1.7 mutations outside Spike likely contribute to enhance transmission" (Thorne et al 2021 p2). Thorne et al (2021) found evidence of wider adaptations that allowed the B.1.1.7 variant to evade the immune system better via specific protein changes, and to have a transmission advantage.

By mid-2021, the delta variant (B1.617.2; originally seen in India) seemed to be coming to dominate [25]. The risk is in unvaccinated parts of the world, and "high levels of delta leading to new mutations of the variant" (Vaughan 2021e p9).

A nationwide sampling study in the USA (Bolze et al 2021) by genomics company "Helix" found that the alpha variant fell from 70% of cases in April 2021 to around 40% in June 2021. This study looked at nearly 20 000 samples of SARS-CoV-2, and found that the spread of the delta variant was greatest in US counties with low vaccination rates (Callaway 2021).

Mads Albertsen, a bioinformatician in Denmark, said in mid-2021: "What most people are concerned about are the next variants - if we start to see variants that can really challenge the vaccines" (quoted in Callaway 2021).

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[25] "Delta spreads more readily than other variants. In Sydney, one person became infected after just walking past another. With older variants, local health officials said, it was thought infection could happen only with sustained contact for around 15 minutes" (Le Page 2021f p9).

Despite having to show evidence of a negative test or full vaccination, 165 of around 600 people at a nightclub in the Netherlands on 26th June 2021 were infected. "It isn't clear how many were infected at the night club or who may have been infected on arrival" (Le Page 2021f p9).

8.2. FUTURE AND CHANGE

(1) Tooze (2020) made this observation: "In May 2018, President Donald Trump restructured and downsized the pandemic preparedness unit. Of course, it seems ill-judged in retrospect. But he was not the first president to do so. The National Security Council's (NSC) global health security unit was set up under Bill Clinton in 1998. Years later, first George W. Bush and then Barack Obama would shut it down, only to re-establish it shortly afterward. The fact is that bureaucracies have never known how to treat low-probability, high-stakes biomedical risks like pandemics. They sit awkwardly within the conventional silos of modern government and models of risk assessment".

Similarly, von Delft et al (2021) commented that "had drug discovery persevered during the SARS epidemic in 2003, anti-viral drugs would have been available when this pandemic hit" (p332).

In January 2020, the French government was rolling back its pandemic preparedness work undertaken for the 2003 SARS outbreak, for example. The government had been criticised for an "over-reaction" to the 2010 H1N1 flu epidemic, which led to a reduction in funding and depletion of public emergency supply stocks (Beaudevin et al 2021). "The French government was carrying on with the destruction of (admittedly out of date) FFP2 masks just at as Chinese authorities began to warn the world about a possible new epidemic" (Beaudevin et al 2021 pp2-3).
This was seen as important in the shortage of covid-19 PCR diagnostic tests in France in 2020. But this was far from the whole reason, and Beaudevin et al (2021) described three key factors:

i) Shortages of assays (PCR reagents), machines and workforce. For example, in March 2020, a major hospital laboratory had one PCR machine with a maximum capacity of 100 tests per day. Meanwhile, global demand for the relevant materials boomed.

ii) The "institutional peculiarities" of the French health system - eg: long-term lack of investment.

iii) A "pronounced hospital tropism fuelled by the almost knee-jerk preference of French 'medical mandarins' and policymakers alike for 'curative medicine'" (Beaudevin et al 2021 p4).

(2) The Independent Panel for Pandemic Preparedness and Response recommended the creation of a body endorsed by the United Nations to deal with future pandemics (Lehtimaki et al 2021).

In early April 2021, twenty-seven world leaders and the head of the WHO called for a legally binding pandemic treaty for future events because they viewed the response to covid-19 as the "opposite of co-operative" (Editorial 2021a p165).

Editorial (2021a) proposed four conditions for such a treaty:

i) All countries must sign up, especially the most powerful ones.

ii) The involvement of non-governmental organisations (NGOs).

iii) Clarify what a treaty adds that is not working in already existing agreements.

iv) Who is to administer the treaty? If it is the WHO, then appropriate powers must be given to that organisation.

(3) Two letters to "Nature" on 21st May 2020 summed up the desire for major change. One advocated a change to the economic system that "relies on complex webs of growing debt, and that ultimately endorses the ever-increasing use of finite physical resources" (Marinov 2020 p262). While the other one offered a recommendation for citizens participation as in Lombardy, Italy in "creating practical solutions to the crisis and its aftermath" (Simone 2020 p262).

(4) In May 2020, mayors from thirty-eight of the largest cities in the world created the "Global Mayors Covid-19 Recovery Task Force" to redesign their cities to be more sustainable and equitable (Bai et al 2020).

Bai et al (2020) surveyed the lessons learned from cities and covid-19 for future pandemics and climate change, including:

i) The need for strong leadership and governance to allow rapid responses. For example, Hanoi (Vietnam) introduced rapid testing, tracing, and quarantine, and avoided a major outbreak of covid-19 in early 2020.

ii) Accurate and science-based information - "Technology is a mixed blessing. Yes, social media spreads information, but it can also amplify misinformation" (Bai et al 2020 p519).

iii) Awareness of the disproportionate impact on the urban poor and certain minority ethnic groups.

iv) The area outside the urban is also important - eg: contracting diseases in forests.

v) Build resilience - eg: collaborations; preparation.

"Cities have survived countless disasters throughout history, from wars to famines. Covid-19 now shows that cities must also learn, adapt and evolve - together" (Bai et al 2020 p520).

(5) Garcia (2020) argued for government spending on the "real threats" of pandemics and climate change, rather than on weapons. "Big armies haven't helped countries to fight covid-19 - precisely the opposite. The five countries with the largest defence budgets were unprepared and were hit hard. The United States, China, India, Russia and Saudi Arabia..." (Garcia 2020 p522).

Garcia (2020) made four recommendations:

i) Stop the "new arms race" (eg: AI uses in war).

ii) Abide by international conventions, like the Arms Trade Treaty 2014.

iii) Implement the 2015 Paris climate agreement.

iv) Invest in the United Nations' Sustainable Development Goals agreed in 2015.

(6) Dibley et al (2021) addressed the challenge of climate change on countries' ability to repay the large national debts created with government spending related to covid-19 [26].

Governments issue sovereign bonds to raise money from domestic and international investors, and they pay interest on these "IOUs". if a country is seen as a high

[26] "Basic, localised climate-risk information should be invested in as a public good, like education, law enforcement and vaccination" (Hill 2021 p9).

risk, then the financial markets will set a higher rate of interest (eg: El Salvador paid around 10% on its 30-year bond in 2020 compared to around 1% for Spain; Dibley et al 2021).

The risk assessment includes whether a country can repay its debt (ie: whether the economy will grow in the future), and climate change has "the potential to severely affect a country's economy" (Dibley et al 2021 p185).

Dibley et al (2021) calculated that around three-quarters of thirty-year sovereign-bond prospectuses issued in 2020 (to mature in 2050) did not take account of such climate change risks. It has been recommended that governments should be transparent about the physical risks of climate change (eg: flooding), and the "transition risks" (ie: the ability of a country to adapt to climate change - eg: reduce emissions from coal). Only three of 26 countries analysed acknowledged the former, two the latter, and one country both types of risk.

Dibley et al (2021) made three recommendations:

i) Governments and financial institutions should include more information about climate change risk and debt repayment in their prospectuses and documentation.

ii) Money borrowed for covid-19-related policies should include climate change strategies.

iii) Wealthier lender countries should support vulnerable borrower countries.

(7) Automation and roboticisation in society is not new, but covid-19 has the potential to accelerate the trend. For example, between February and April 2020, IBM reported a 40% increase in demand for their "Watson Assistant" software which can handle online calls (Ong 2020).

On the other hand, workers' jobs may be safe from replacement by machines for practical reasons. "Automation doesn't come cheap: firms need to have the funds to install new machinery and software, as well as time to reconfigure workplaces and retrain workers to use them" (Ong 2020 pp47-48).

(8) The popularity of AI as applied to healthcare saw many publications in early 2020 claiming that machine learning algorithms could diagnose covid-19 from chest scans and predict the severity of outcome (Roberts 2021).

Roberts et al (2021) reviewed the papers published between 1st January and 3rd October 2020 on this subject. Many papers were published in the early stages of software development, and there were many methodological problems, including in the learning datasets (Roberts 2021).

9. MISCELLANEOUS

(1) Obesity (or high body mass index (BMI)) has emerged as key to covid-19 severity, and it could be an issue with vaccines because "[O]besity correlates with a dulled immune response to covid-19" (Ledford 2020d p488).

Individuals with high BMIs have more adipose tissue, which expresses high levels of ACE2 (angiotension-converting enzyme 2) receptor (used by SARS-CoV-2 to enter cells). This may explain the greater severity of covid-19. Obesity also causes low-grade inflammation, which contributes to increased risk of heart disease, say (Ledford 2020d).

"Obesity is also linked to less-diverse populations of microbes in the gut, nose and lung, with altered compositions and metabolic functions compared to those in lean individuals" (Ledford 2020d p489). Gut microbes, for instance, can influence immune responses as reported in a study on a flu vaccine (Hagan et al 2019). Anti-bodies altered the gut microbiome, which, in turn, altered the response to the vaccine (Ledford 2020d).

(2) Pets catching covid-19 may be occurring (eg: 15-20% of cats taken to a New York veterinary hospital in 2020-21; King 2021), but domestic animals are infected by their own coronaviruses.

Coronaviruses have the largest genome of RNA viruses, and a complex spike protein (around 1300 animo acids) (King 2021). The evolution of coronaviruses can be seen in a common feline version, which produces a relatively harmless stomach illness usually. But one mutation in the spike protein produced the mostly fatal, feline infectious peritonitis (King 2021).

Another example in pig coronaviruses, where a change in the spike protein changed the virus from a gut infection to a mild lung infection (King 2021).

This ability of coronaviruses generally to evolve caused virologist Benjamin Neuman to say in relation to the future of SARS-CoV-2: "Don't make assumptions about coronaviruses" (quoted in King 2021).

(3) Reverse zoonosis (or spillback), where humans infect non-humans with SARS-CoV-2, is potentially a problem. "Persistent infections in a novel host could lead to viral adaptation, strain evolution, and the emergence of strains with altered transmissibility, pathogenicity, and vaccine escape. Cross-species transmission to other

wildlife species and concomitant risks are also a concern" (Chandler et al 2021 p1).

Chandler et al (2021) reported spillback in white-tailed deer in the USA. Blood samples were collected by the US Department of Agriculture/Animal and Plant Health Inspection Services/Wildlife Services National Wildlife Disease Programme in four northern states. The researchers analysed 385 samples collected in early 2021 for SARS-CoV-2. There were 182 control samples collected from 2018 to 2020. Anti-bodies to SARS-CoV-2 were found in 40% of the samples.

In terms of route of transmission, Chandler et al (2021) explained: "Multiple activities bring deer into direct contact with people, including captive cervid operations, field research, conservation work, wildlife tourism, wildlife rehabilitation, supplemental feeding, and hunting. Wildlife contact with contaminated water sources has also been suggested as a potential transmission route, although transmissibility of SARS-CoV-2 from wastewater has yet to be conclusively demonstrated. Transmission from fomites or other infected animal species cannot be discounted" (p2). The ACE2 receptors are similar in certain deer to humans, which allows the transmission of SARS-CoV-2 (Kuchipudi et al 2021).

Kuchipudi et al (2021) noted that "even though experimental evidence suggests that SARS-CoV-2 infected deer remain largely asymptomatic, the clinical outcomes and health implications of SARS-CoV-2 infection in free-living deer are unknown, and warrant further investigation" (p11).

In another study, Kuchipudi et al (2021) found SARS-CoV-2 in one-third of lymph node samples collected in 2020 from 151 free-living and 132 captive white-tailed deer in Iowa state.

While Palmer et al (2021) found that experimentally infected deer can transmit the infection to other deer. "However, evidence of deer-to-deer transmission of the virus in free-living deer has not yet been documented" (Kuchipudi et al 2021 p8).

(4) Krutikov et al (2021) reported on reinfection among residents of long-term care facilities (LTCFs) in England. "Older adults might have less robust immune responses to infection due to age-related immune-senescence and underlying co-morbidities, and although emerging data suggest that most LTCF residents have a detectable immune response following natural infection

with SARS-CoV-2, the extent to which this protects against a second infection is unclear" (Krutikov et al 2021 pe362).

The VIVALDI study is a prospective cohort study of staff and residents in LTCFs in England began in May 2020. Krutikov et al (2021) concentrated on 100 LTCFs (covering 682 residents and 1429 staff members) who gave three blood samples (for anti-body detection) over ten months.

Previous PCR-confirmed covid-19 infection reduced the risk of reinfection by 85% for residents and 60% for staff.

The follow-up period was only ten months.

(5) Basic physiological knowledge about SARS-CoV-2 in the human body has come from autopsies (eg: 20 male and 12 female donors; Delorey et al 2021). This produced a "tissue atlas" to show how individual organs and parts of the body responded to the invasion of the virus. Melsm et al (2021) produced a "lung atlas of lethal covid-19" from nineteen deceased individuals (twelve male and seven female).

(6) Understanding the exact nature of the transmission of SARS-Cov-2 via exhaled breath in the air has been important from teh start of the pandemic, though knowledge was limited initially. "The exhaled flow contains pathogen-carrying droplets of varying sizes, and their trajectory is governed by their initial size, the influence of gravity, the local and ambient temperatures and relative humidity, and the gas velocities. The small droplets can stay suspended in the air for a long time and can carry the pathogens over significantly long distances, whereas the larger droplets follow a ballistic trajectory and tend to settle down quickly under the influence of gravity" (Trivedi et al 2021 p1).

The size of ballistic and small droplets is not completely defined (ie: which droplets suspend in the air and which fall to the ground) (Trivedi et al 201). Two metres from an infectious individual seems a good distance, but the presence of wind is important as distance can be tripled by "typical outdoor wind speeds", while masks "can cut the droplet transmission distance significantly by suppressing the exhaled flow as well as altering the size distribution of the exhaled droplets" (Trivedi et al 2021 p2).

Trivedi et al (2021) experimentally modelled droplet dispersion by a cough, varying the relative humidity of the environment. "The droplet distribution suggests that, in the absence of face coverings, an unprotected cough is not safe at 2 m away from the emitter even outdoors" (Trivedi et al 2021 p1).

10. APPENDICES

APPENDIX A - PRE-PRINTS

Over 125 000 covid-19-related scientific articles have appeared within ten months of the first confirmed case of infection, of which about one-quarter were posted on pre-print servers (Fraser et al 2021).

Fraser et al (2021) reflected on the growing use of such servers. They explained: "New scholarly research has traditionally been communicated via published journal articles or conference presentations. The traditional journal publishing process involves the submission of manuscripts by authors to an individual journal, which then organises peer review, the process in which other scientists ('peers') are invited to scrutinise the manuscript and determine its suitability for publication. Authors often conduct additional experiments or analyses to address the reviewers' concerns in one or more revisions. Even after this lengthy process is concluded, almost half of submissions are rejected and require re-submission to a different journal. The entire publishing timeline from submission to acceptance is estimated to take approximately 6 months in the life sciences; the median time between the date a pre-print is posted and the date on which the first DOI [digital object identifier] of a journal article is registered is 166 days in the life sciences" (Fraser et al 2021).

The research was focused on "bioRxiv" and "medRxiv" pre-print servers for 2020 (1st January - 31st October). Overall, changes in publishing behaviour were observed in that "covid-19 pre-prints are shorter and reviewed faster". Fraser et al (2021) saw the positive in the wider general dissemination of information and greater transparency of publicly available pre-prints, notwithstanding the concerns about "poor quality science" and the limitations of pre-prints as pre-peer review.

The Leader (2020) described the ideal: "One of the special things about science is its inbuilt system of self-correction. There is no such thing as scientific truth, just a set of provisional truths that are subject to revision or rejection when new information comes in. That process isn't always quick or peaceful, but it usually gets to an answer in the end" (p5). The author then lamented the "perverse incentives" that encourage "flashy original discoveries and astounding claims", and so make science "worryingly unreliable" (The Leader 2020).

Though there is a risk of fraud, bias, and unforced errors, Ritchie (2020) highlighted hype as a worry. This is "where scientists are pushed towards writing up their results as if they are much more exciting than they are" (Ritchie 2020 p37). The "perverse incentives" mean pressure to publish to gain funding, and the journals wanting research that finds exciting results. Very simply, scientists should be "more boring", argued Ritchie (2020): "Science is not an endless march of exciting, flashy findings. There are transformative discoveries, and we should try and encourage those. But in general, science is incremental and small scale..." (p39).

An example of a cautionary tale with pre-prints is Zhang et al (2020). This proposed that genes from SARS-CoV-2 could become integrated into the human chromosome. This pre-print appeared in December 2020, though it was subsequently rejected by a journal (Cohen 2021). The proposal "could explain the rare finding that people can recover from covid-19 but then test positive for SARS-CoV-2 again months later" (Cohen 2021 p674).

Not surprisingly, the idea is controversial. Many critics "worried it played into the hands of vaccine sceptics spreading false claims about the newly authorised mRNA vaccines. 'If there ever was a pre-print that should be deleted, it is this one! It was irresponsible to even put it up as a pre-print, considering the complete lack of relevant evidence. This is now being used by some to spread doubts about the new vaccines', Marie-Louise Hammarskjöld, a microbiologist at the University of Virginia, posted in a comment on bioRxiv at the time" (Cohen 2021 p675).

In follow-up work, based on cell cultures, Zhang et al (2021) have argued that "on rare occasions an enzyme in human cells may copy the viral sequences [of SARS-CoV-2] into [human] DNA, allowing them to slip into our chromosomes" (Cohen 2021 pp674-675).

APPENDIX B - RELIABILITY OF DATA AND AROUND THE WORLD

The reliability of data on covid-19 depends on the capacity, resources, and political will to collect such information. Poorer countries struggle to provide extensive and/or accurate official data. This has led to other means to discover the number of deaths from covid-19, say.

For example, the WHO believes that only one in seven

covid cases in Africa detected, and this could mean that nearly 60 million people are/have been infected (reported in "The Times" 15th October 2021).

Gill (2021) used morgue data from a hospital in Lusaka, Zambia. For the period June to September 2020, one in five deceased individuals were found to test positive for SARS-CoV-2, which translated into a prevalence ten times higher than official reports.

Gill's (2021) team sampled every third to fifth death, and, with consent from next of kin, tested the individual for SARS-CoV-2.

Responses to covid-19 in countries in Africa, say, have to be seen in a historical and social context. For example, a series of epidemics (eg: HIV/AIDS; Ebola virus), and Western medicine's sometimes "unethical and racist practices" in Africa (eg: toxic treatments forced on sleeping sickness sufferers) (Aikins 2021).

On 28th September 2020 the milestone of the official global death toll from covid-19 passed one million ("Nature" 8th October 2020).

Officially three million people globally were reported dead from covid-19 by early April 2021 (Editorial 2021c), though "the true figure is probably far higher" (Le Page 2021b p7). US epidemiologist Andrew Noymer suggested between double that and under forty million (Le Page 2021b).

In reference to India, John Burn-Murdoch of the "Financial Times", using local news reports, estimated the number of deaths in April 2021 as ten times higher than official figures (Le Page and Wilson 2021).

Belarus reported its first confirmed case of covid-19 on 28th February 2020, and the total laboratory-confirmed cases were around 300 000 on 13th March 2021 (out of a total population of 9.5 million people) (Nemira et al 2021). But there has been limited testing because of low capacity (Nemira et al 2021).

Belarus has not implemented large-scale lockdowns, though mask wearing and border closures had been used (Nemira et al 2021).

Nemira et al (2021) tried to get a better picture of the situation using genomic data given to the WHO (ie: 41 full genomes between March 2020 and February 2021). A comparison of 116 sequences from Ukraine was used.

The forty-one sequences were estimated to be 0.02% of officially reported cases of covid-19, and they belonged to eleven genomic lineages. Form the data, cumulative incidence was modelled. For example, on 16th

May 2020, the reported number of cases was 28 681, but the modelling predicted 118 521 cases (ie: around four times higher). The underestimation could be even higher (Nemira et al 2021).

Hammoudeh et al (2020) referred to the "double epidemic" in the West Bank and Gaza Strip - covid-19, and the "broader context of settler colonialism and the logic of colonisation" (p1). The Palestinian Authority has limited control over borders, and resources (Hammoudeh et al 2020).

APPENDIX C - EDUCATIONAL INSTITUTIONS

The response of universities in the USA to covid-19 for the academic year 2020-21 varied as there was no national strategy. It has been described as "a gigantic, unorganised public health experiment" (Marris 2020 p511). For example, of 1000 institutions, in August 2020, 42 were operating "fully in person", 421 "primarily in person", and the remainder combinations of in-person and online classes (Marris 2020).

Modelling of the spread of covid-19 on a fully in-person campus (eg: Paltiel et al 2020) suggested that testing students every two days was crucial. "Researchers who are advising universities say that models are imperfect, but they remain one of the few scientific tools available to guide reopening decisions" (Marris 2020 p512).

Schools, colleges and universities may remain open, but employ a strategy of isolation of suspected and/or confirmed cases and of close contacts of cases. Daily contact tracing (DCT) with rapid turnaround SARS-CoV-2 tests allows these institutions to remain open, and pupils, students and staff to continue attending.

Young et al (2021) investigated DCT in an open-label, cluster-randomised trial in 201 English secondary schools and colleges. Schools were randomly assigned to DCT over seven days after contact with a case (intervention condition), or isolation of contacts for ten days (control condition). The study took place between April-July 2021.

Full data were collected on 76 (of 99) control and 86 (of 102) intervention schools. There was no difference between the two conditions in covid-19 transmission. The researchers concluded: "Daily contact testing is a safe alternative to home isolation following school-based

exposures and should be considered an alternative to routine isolation of close contacts following school-based exposures" (Young et al 2021 p12).

Establishing the superiority of DCT over isolation was not possible because of methodological issues like the high drop-out/incomplete data, and the isolation of pupils due to non-school contact with cases. The success of DCT also depends on the effectiveness of the rapid turnaround tests used.

Young et al (2021) stated: "The trial was conducted during periods of low to moderate covid-19 incidence. We therefore did not estimate the impact of DCT in high incidence settings. In the last two weeks of the study, the community rate of infections rose making the DCT protocol unwieldy for some schools, given the space and staff required to perform testing" (p12).

APPENDIX D - NON-PHARMACEUTICAL INTERVENTIONS

D1. Lockdowns and Masks

Personalised public health interventions could be a strategy rather than universal lockdowns, say. So, the advice given to a younger, healthy adult could be different to an older obese one, for example (Vaughan 2020).

Melbourne, for example, underwent a second universal lockdown of 111 days (up to the end of October 2020) (Lu 2020a). While on 5th August 2021, Melbourne (and the state of Victoria) introduced its sixth lockdown (Lagan 2021), which lasted until mid-October 2021 ("The Times" 15th October 2021).

Quarantine for arrivals in Western Australia, for instance, involved fourteen days in a hotel room at the individual’s expense. Some states allowed regular breaks outside, but not in Western Australia in late 2020 (Lu 2020b).

In May 2021, in the UK the social restrictions were released while many people had been vaccinated. The main concern was "whether vaccination has 'decoupled' infection from severe illness..., which would mean that a rise in infection doesn't lead to a surge of hospitalisations, deaths and long covid" (Lawton 2021f p7).

With US President Trump's disparaging of the use of face masks in mid-2020, the concern was to establish that

scientific evidence supporting their wearing. Variables like the type of mask, and wearing the mask "properly" muddy the waters (Peeples 2020).

Data were mostly observational or from controlled laboratory studies rather than controlled trials in real-life situations, so confounding variables become important. For example, mandatory mask-wearing reduces transmission, but it is part of other NPIs (Peeples 2020).

In terms of behaviour, mask-wearing can both reduce adherence to other NPIs like social distancing (ie: over-confidence), and encourage the wearer to better behaviour: "The masks remind them of shared responsibility, perhaps" (Peeples 2020 p188).

Public opinion polls in the USA have found declining trust for the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA) in late 2020, in particular that political decisions are driving the organisations rather than scientific ones (Whyte 2020).

The science journal "Nature" defended its coverage of politics leading up to the US Presidential Election in November 2020 because covid-19 has "propelled the science-politics relationship into the public arena as never before" (Editorial 2020d p169). The authors continued: "Covid-related research is being produced at a rate unprecedented for an infectious disease, and there is, rightly, intense worldwide interest in how political leaders are using science to guide their decisions - and how some are misunderstanding, misusing or suppressing it" (Editorial 2020d p169).

D2. Ventilation

Morawska et al (2021) began: “There is great disparity in the way we think about and address different sources of environmental infection. Governments have for decades promulgated a large amount of legislation and invested heavily in food safety, sanitation, and drinking water for public health purposes. By contrast, airborne pathogens and respiratory infections, whether seasonal influenza or covid-19, are addressed fairly weakly, if at all, in terms of regulations, standards, and building design and operation, pertaining to the air we breathe” (p689).

Covid-19 has made the world aware of the need to address indoor airborne transmission of pathogens.

Morawska et al (2021) advocated an engineering solution – ie: designing and building ventilation systems. They made some general recommendations around demand control and flexibility in public buildings:

- Infection-focused ventilation should be risk-based – ie; aware of how transmission occurs based on the building use (eg: speaking, singing, heavy breathing during exercise).

- Higher airflow rates that distribute clean air as required (eg: higher ventilation rates in gyms that theatres).

- Practicalities like air filtration incorporated into building heating systems.

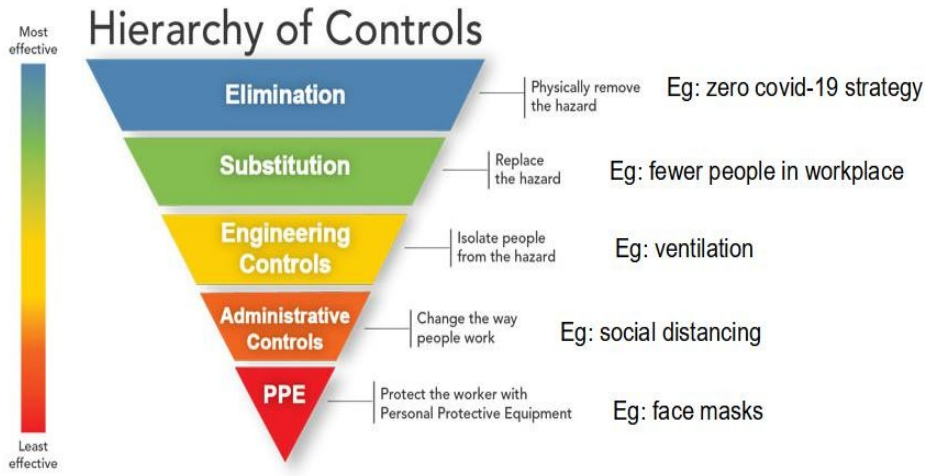
Recommendations like these are expensive, and Morawska et al (2021) responded: "There needs to be a shift in the perception that we cannot afford the cost of control, because economic costs of infections can be massive and may exceed initial infrastructure costs to contain them" (p691).

The World Health Organisation could help by producing detailed guidelines on airborne pathogens, and/or including them in recommendations on air pollution generally (Morawska et al 2021).

Morawska et al (2021) ended: "In the 21st century, we need to establish the foundations to ensure that the air in our buildings is clean with a substantially reduced pathogen count, contributing to the building occupants' health, just as we expect for the water coming out of our taps" (p691).

D3. Hierarchy of Controls

Ventilation is one of the possible risk management measures advocated by the "Hierarchy of Controls" (National Institute for Occupational Safety and Health; NIOSH; https://www.cdc.gov/niosh/topics/hierarchy/) (figure D1).



(Source: https://www.cdc.gov/niosh/topics/hierarchy/ and Marshall 2021 p9)

Figure D1 - Hierarchy of controls applied to covid-19.

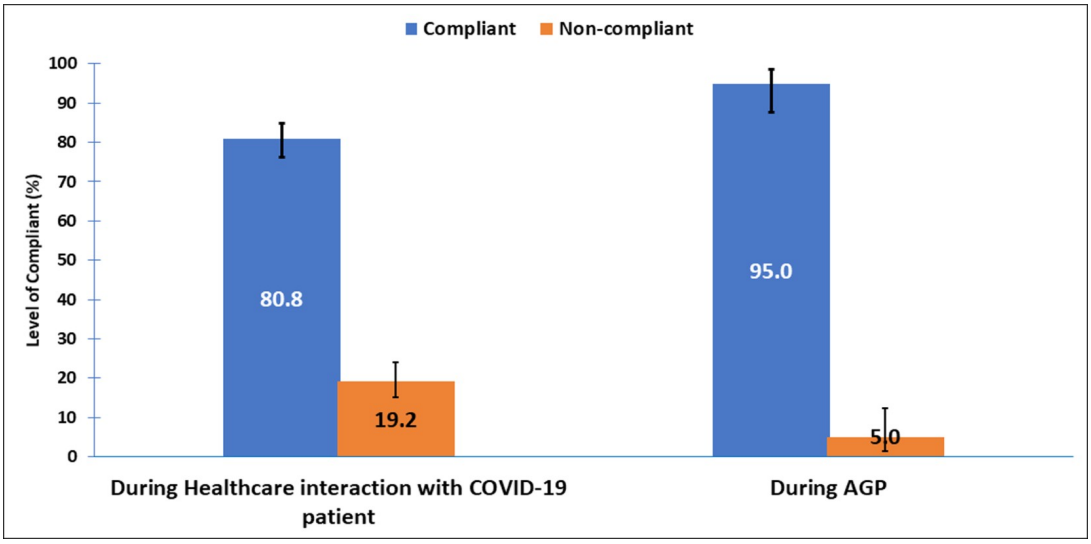
APPENDIX E - HEALTHCARE WORKERS

Adherence (or compliance) to infection prevention and control (IPC) policies, like physical distancing, hand washing, and use of personal protection equipment (PPE), by healthcare workers is crucial. "Clear IPC guidelines, effective communication, support from managers, training, access and trust in PPEs are critical in promoting healthcare compliance with IPC protocols" (Ashinyo et al 2021 p10).

Ashinyo et al (2021) reported a study in Ghana of such adherence. The research was conducted in May to August 2020 at four covid-19 treatment centres via a questionnaire to over four hundred staff. Ten IPC measures were included, and the response options were "always, as recommended", "most of the time", "occasionally", and "rarely".

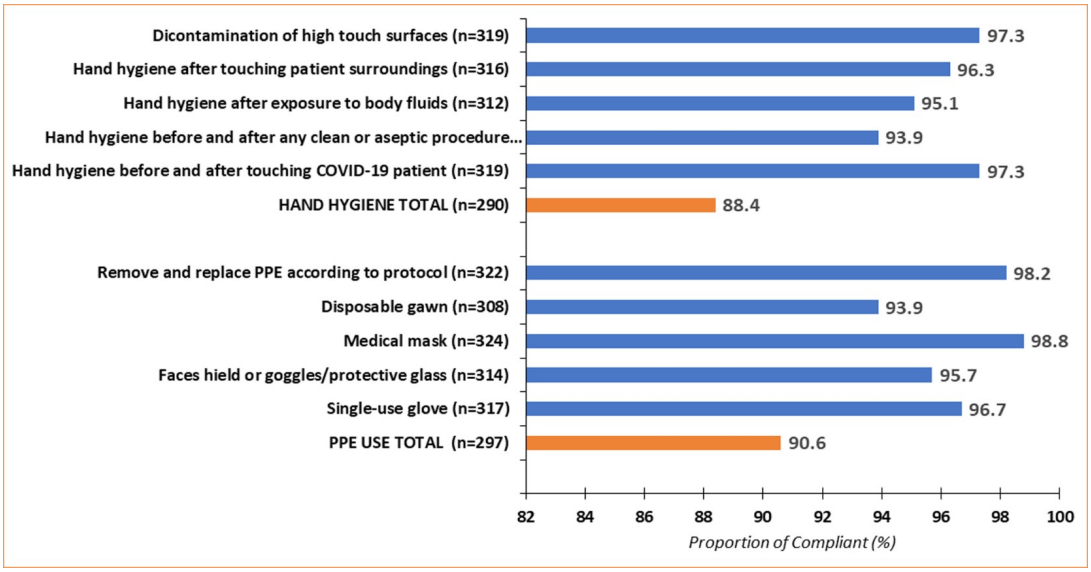
The first two responses were classed as adherence/compliance. Overall, this was reported at around 80% and above during interactions with covid-19 patients, and higher when performing aerosol-generating procedures (AGPs) on covid-19 patients (figures E1, E2 and E3).

Adherence was significantly lower by non-clinical staff (eg: cleaners; pharmacists), and by less qualified healthcare workers.



(Source: Ashinyo et al 2021 figure 3)

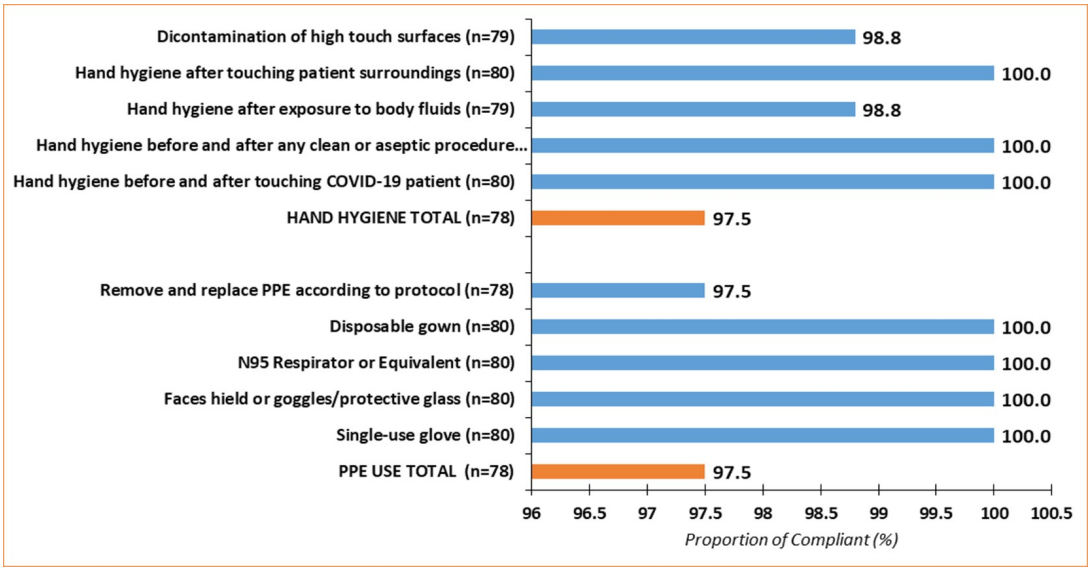
Figure E1 - Total compliance to IPC measures.



(Source: Ashinyo et al 2021 figure 1)

Figure E2 - Compliance for each IPC measure when interacting with covid-19 patients.

This was a self-reported questionnaire study, while an observational study in Tanzania (Powell-Jackson et al 2020) found much lower adherence.



(Source: Ashinyo et al 2021 figure 2)

Figure E3 - Compliance with each IPC measure when performing AGPs with covid-19 patients.

E1. Powell-Jackson et al (2020)

Between 7th February and 5th April 2018 researchers visited 228 health facilities in Tanzania, and observed interactions in outpatient consultation rooms, laboratories, and dressing rooms for six hours in each facility. Powell-Jackson et al (2020) noted that a "long-standing concern with clinical observations is the Hawthorne effect, in which study subjects' awareness of being observed causes them to alter their behaviour. To minimise such bias, fieldworkers were coached to observe discreetly from the corner of the room, limit interaction with either provider or patient, and not disclose that observations were focused on infection prevention and control" (pe782).

A total of 5425 provider-patient interactions were observed and twenty IPC actions were scored. Powell-Jackson et al (2020) reanalysed the data with reference to IPC and covid-19.

IPC "varied substantially". For example, health workers rarely followed hand hygiene practices (7% of observed situations), while glove use was high (75%). In terms of characteristics of the health workers, "older health workers were less likely to use gloves correctly, female health workers were better at hand hygiene, and nurses and midwives performed substantially better than more qualified providers in most of the infection

prevention and control domains" (Powell-Jackson et al 2020 pe787).

Powell-Jackson et al (2020) summed up: "Using secondary data from a 2018 study, we found that, under typical circumstances in Tanzanian outpatient facilities, infection prevention and control compliance was inadequate. Of primary concern was inadequate hand hygiene, which WHO has cited as crucial for covid-19 containment..." (pe787).

The data were collected from faith-based and private-for-profit facilities, but no publicly owned ones. Other studies have reported poorer IPC in public facilities (Powell-Jackson et al 2020).

Powell-Jackson et al (2020) warned that "because the data were originally collected for a different purpose before the pandemic, we did not measure certain supplies or behaviours crucial for the control of covid-19, such as the wearing of personal protective equipment required to manage suspected covid-19 patients" (pe787).

The facilities sampled were opportunistic as were the interactions observed. "However, the lack of variation in compliance by facility level, ownership, and location gives us reason to expect a similar pattern of results elsewhere in the country" (Powell-Jackson et al 2020 pe787).

APPENDIX F - ANIMAL MODELS

In February 2020 the WHO assembled an international panel of experts (WHO-COM (covid-19 modelling))to help develop animal models for covid-19, which could be used for testing vaccines and treatments (Munoz-Fontela et al 2020).

Munoz-Fontela et al (2020) reviewed the state of knowledge half a year later.

i) Mouse - Some possibilities, but "[A]t present, no mouse model recapitulates all aspects of covid-19 in humans, especially the unusual features such as pulmonary vascular disease and hyper-inflammatory syndromes observed in adults and children, respectively" (Munoz-Fontela et al 2020 p511).

As well as using "natural" mice, genetically modified mice to express the human ACE2 have been developed.

An alternative approach is to genetically engineer the SARS-CoV-2 virus to infect mice (SARS-CoV-2 MA), and

then to test treatments and vaccines (Dinnon et al 2020).

ii) Syrian hamster - eg: evidence of transmission between cage-mates.

This is a scarce species compared to mice, say (Munoz-Fontela et al 2020).

iii) Ferret - Good for studying upper-respiratory tract infection.

iv) Non-human primates - eg: macaques.

For example, the ChAdOx1nCoV-19 vaccine (created by Oxford/Astra Zeneca) significantly reduced viral load in the lower respiratory tract of rhesus macaques compared to controls, but not the nasal shedding of the virus (van Doremalen et al 2020). Mercado et al (2020) found similar results with fifty-two rhesus macaques given a single shot of the Ad26 vaccine (produced by Janssen).

Vogel et al (2021) tested two candidates for the Pfizer/BioNTech vaccine on mice over 28 days by measuring the level of anti-bodies in the blood, and in six 2-4 year-old male rhesus macaques. The latter received the vaccine and later SARS-CoV-2 (ie: a challenge study). There were fifteen controls, of which nine received a saline injection (ie: placebo vaccine) before the challenge test, and the others had a mock challenge. BNT162b2 was viewed as better than BNT162b1.

v) Others - including mink, cats, dogs, pigs, and chickens.

Non-animal alternatives include cell cultures, and micro-engineered organs-on-chips (Munoz-Fontela et al 2020).

The use of animals in research is well debated, but the urgent need for covid-19 treatments and vaccines when humans do not have pre-existing immunity is assumed to trump any arguments against their use.

APPENDIX G - LONGER TERM EFFECTIVENESS

Knowledge about vaccines takes time to acquire, in the literal sense of time elapsed since the dose. The effectiveness of BNT162b2 has been established in the short-term, but what about the longer term (eg: six months)?

Tartof et al (2021) reported effectiveness against hospital admission up to six months in a retrospective

analysis of US data (electronic health records (EHRs) from the Kaiser Permanente Southern California (KPSC) healthcare system). This covered individuals aged twelve years old and above (nearly five million people). The EHRs included the dates of vaccinations, and subsequently testing positive for covid-19 (and hospital admission) (between mid-December 2020 and early August 2021).

During the study period, 5.4% of KPSC patients were infected with SARS-CoV-2, and, of these, 6.6% were hospitalised. Individuals in both these groups were much less likely to have been vaccinated.

In summary, it was found that "individuals who were fully vaccinated with BNT162b2 had 73%... overall effectiveness against SARS-CoV-2 infections and 90%... effectiveness against covid-19-related hospital admissions after a mean time since being fully vaccinated of 3-4 months. Effectiveness against SARS-CoV-2 infections waned during the 6 months of this study. Effectiveness against hospital admissions in all age groups did not wane over the duration of the study" (Tartof et al 2021 p1412). In simple terms, the vaccines reduced the risk of severe symptoms of SARS-CoV-2 that require hospitalisation.

However, a study by the Israeli Ministry of Education Epidemiology Division in August 2021 (quoted in Tartof et al 2021) suggested that this benefit may wane for older adults (65 years and above) after six months.

The BNT162b2 vaccine was also effective (in terms of hospital admissions) against variants of SARS-CoV-2 (Tartof et al 2021).

The Tartof et al (2021) study used real-world data, but it could not establish causal relationships as it was an observation study. Controlling for confounders was limited because it was a retrospective study using secondary data.

APPENDIX H - VIRUS VARIANTS

Two variants of a virus that meet in a host cell and join together are "recombinations", and these have been found in analysis of SARS-CoV-2 genomes. How common this process is, and the consequences of these mutations is unclear at present (Lawton 2021b).

"Recombination has been observed in many RNA viruses and is noted to occur at a higher frequency in positive-sense RNA viruses, a category that includes SARS-CoV-2 and other medically important coronaviruses. From an evolutionary biology perspective, it remains unclear why

recombination occurs in RNA viruses" (Pollett et al 2021 p1).

Recombination in RNA viruses (like other coronaviruses - eg: seasonal OC43-hCov, and MERS-CoV) have led to changes in the range of hosts available, host response, and virulence/transmissibility (Pollett et al 2021).

Pollett et al (2021) pointed out that "recombinants may cause rapid escape from naturally acquired immunity, as has been observed in the norovirus genus, which has caused pandemics due to the rapid emergence of new genotypes generated by recombination of structural genes" (p2).

Pollett et al (2021) investigated the frequency and genomic location of recombination events in all medically important coronaviruses (and including SARS-CoV-2). Genomes from publicly available pathogen databases wereanalysed.

There was evidence found of eight recombination events in 100 000 SARS-CoV-2 genomes (up to October 2020). Seasonal coronaviruses showed frequent recombinations as did MERS-CoV, but not SARS-CoV-1.

The conclusion was that recombination is a possible evolutionary pathway for SARS-CoV-2. This paper was posted as a pre-print in March 2021 before a number of variants of concern had been widely reported in detail [27].

VanInsberghe et al (2021) estimated that 5% of SARS-CoV-2 viruses in the USA and UK were recombinant. This was based on the analysis of over half a million genomes.

APPENDIX I - DRUG SAFETY

The voluntary withdrawal of drugs by the manufacturers post-marketing (ie: when available to the general public) is not uncommon (eg: 25 drugs between 1997 and 2011 in Canada; Barry et al 2014). "Identification and reporting of suspected adverse drug reactions through pharmacovigilance [28] is an important patient safety activity that is the responsibility of all clinicians, especially pharmacists. It is particularly important for newer drugs, as rare adverse effects are not always identified in clinical trials and the

[27] E484Q and E484K mutations may help the virus evade anti-bodies (Vaughan 2021c).

[28] The WHO defines pharmacovigilance as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems" (quoted in Barry et al 2014).

prescribing of medications in the 'real world' often yields new drug-related safety concerns" (Barry et al 2014 p233).

In terms of famous examples, "Vioxx" (rofecoxib) is well known. Introduced in 1999 as a novel anti-inflammatory, a "combination of real-world effectiveness and aggressive marketing led rofecoxib to become one of the bestselling prescription drugs of all time" (Barry et al 2014 p233) (eg: over 84 million prescriptions globally by 2004). It was withdrawn at the end of September 2004 due to increased risk of cardiovascular events (according to the Adenomatous Polyp Prevention on Vioxx (APPROVe) study; Bresalier et al 2005). There had been earlier evidence of this risk (eg: Vioxx Gastro-Intestinal Outcome Research (VIGOR) study; Bombardier et al 2000), but this had been attributed to other factors (Barry et al 2014) [29].

One of the problems with drug approval is that relatively short-term and small trials are the basis of approval, but these are "often not powered adequately to detect adverse events especially less common or unknown adverse effects" (Barry et al 2014 p234). Furthermore, long-term effects will not be discovered. "Mandating that all trials be designed with adequate power to detect adverse events would provide more ideal safety data but would require enrolment of thousands of patients over many years and may be cost prohibitive for the development of new drugs" (Barry et al 2014 p234).

The reporting of suspected adverse reactions by healthcare professionals is crucial, particularly for newer medications (ie: less than five years on the market). But "it is important to consider a drug-related cause, too often drugs are blamed for minor or non-specific adverse events. In doing so, some patients may be deprived of first-line therapy in favour of alternatives with less evidence. Furthermore, when patients are taking multiple drugs, it can be difficult to elucidate which is the culprit, if any" (Barry et al 2014 p235). Standardised measures have been developed to help here.

For example, the Naranjo algorithm (Naranjo et al 1981), which contains ten items answered as "yes", "no" or "do not know or not done". A cumulative score is amassed, and a conclusion of "definite", "possible",

[29] "Eric Topol MD, then of the Cleveland Clinic, reported that the manufacturer of rofecoxib had failed to communicate to the FDA cardiovascular safety concerns identified in a phase III clinical trial in
2001. Dr. Topol reported that the FDA was aware of these safety concerns in 2001, but did not respond until the drug was voluntarily withdrawn in 2004" (Bennett et al 2021 p10).

"probable" or "doubtful" can be made for the drug as causing the adverse event (Barry et al 2014) (table I1). Another commonly used tool is the WHO-Upsalla Monitoring Centre Causality Assessment [30].

- Are there previous conclusive reports on this reaction?
- Did the adverse event appear after the suspected drug was administered?
- Did the adverse reaction improve when the drug was discontinued, or a specific antagonist was administered?
- Did the adverse reaction reappear when the drug was readministered?

(Source: Naranjo et al 1981)

Table I1 - Example of items from Naranjo ADR (adverse drug reaction) scale.

Barry et al (2014) raised some points about pharmacovigilance, in relation to Canada, which are relevant generally, including:

a) Whether the reporting of suspected drug-related adverse events should be mandatory for certain healthcare professionals, like pharmacists. "Although this would likely increase the number of reported adverse events, another important consideration is enforcement. Would the cost of ensuring compliance exceed the potential gains? Furthermore, increased reporting of adverse events does not necessarily translate into better patient safety. The sheer volume of reported events may paradoxically make it more difficult to identify rare adverse effects due to the increased workload" (Barry et al 2014 p236).

b) How much data should pharmaceutical companies provide before a drug is approved? Some countries have introduced "accelerated approval programmes" or "progressive licensing".

c) The under-representation of certain groups in clinical trials, particularly if the individuals could have adverse reactions.

Clinical trials of drugs tend to avoid pregnant individuals. The exclusion of pregnant women was a reaction to the drug thalidomide, which caused birth

[30] Details at www.who-umc.org/Graphics/26649.pdf.

defects when taken by pregnant mothers in the late 1950s and early 1960s. Thus, pharmaceutical companies are risk-adverse, and changing trial guidelines requires their support, particularly in relation to legal claims (Newsome 2021).

There is a specific issue with covid-19, where one-quarter of hospitalised cases (between March and August 2020) were pregnant women. In other words, covid-19 vaccine trials did not include pregnant women, and so there are no data on that group until the vaccines were rolled out to the public (Newsome 2021).

d) Physicians prescribing "off-label". Drugs may be approved for certain health conditions, but doctors in many cases have the leeway to use in other situations.

I1. Impact of Serious Adverse Drug Reactions

Adverse drug/device reactions (ADRs) can "result in patient harm, affect the careers of clinicians who report these toxicities, result in substantial costs and harms to patients, and lead to large revenue losses by manufacturers" (Bennett et al 2021 p2). But it is crucial that individuals feel that such events can be reported.

For example, Bennett et al (2019) found that over 80% of fourteen clinicians who had identified serious haematology and oncology ADRs reported negative feedback from manufacturers, half negative feedback from colleagues, and one-third such feedback from regulatory officials (Bennett et al 2021).

Bennett et al (2021) performed a review of the impacts of very serious ADRs (eg: serious toxicity) between 1997 and 2019 in the USA (n = fifteen drugs and one device).

Eleven of 18 clinicians who had initially reported the ADRs had personal or professional repercussions, including five receiving personal threats from manufacturers and three facing lawsuits or threats of lawsuits.

In terms of the patients, around three-quarters of a million individuals received compensation for injuries or death from nine very serious ADRs. Manufacturers experienced massive drops in sales (eg: from $29.1 billion to $4.9 billion for eleven of the drugs), and paid compensation (eg: $39.7 billion publicly declared).

Bennett et al (2021) summed up: "Very serious ADRs have significant economic, financial, and personal impacts on patients, personal and professional

repercussions to physician reporters, and sales and regulatory impacts on manufacturers. In this study, the totality of the ADR impacts represented large human costs in terms of publicly reported payments for safety concerns by manufacturers, public reports of large numbers of injured persons or persons who died from ADRs, large publicly reported clinician costs in terms of loss of job or being involved in litigation with the pharmaceutical manufacturer and large decreases in product sales" (p9). These researchers drew out some lessons from their review, including:

i) The importance of formal monitoring bodies (eg: Data Safety Monitoring Boards), and of independent members. Krumholz et al (2007) noted that the identification of serious ADRs might be delayed when there are not independent members.

ii) The financial costs to manufacturers were small relative to the income from sales of the drugs.

iii) The sharing of knowledge. ADRs were often class-related (ie: different drugs with similar pharmacological actions). For example, "Fenfluramine and phentermine are two drugs that were sold to [US] manufacturers by the French pharmaceutical company that manufactured
benfluorex, a similar weight loss drug associated with tens of thousands of injured persons" (Bennett et al 2021 p9).

iv) Stricter protocols on drug safety for clinical trials - eg: high-likelihood very serious ADRs based on similar types of drugs.

v) Speed of response when ADRs identified.

vi) Education of physicians to "expect the unexpected toxicity" (Bennett et al 2021 p10).

vii) It is important "when causal relationships are identified, clinicians who report these findings should be shielded from personal and professional retribution" (Bennett et al 2021 p10).

This study did not include "ADRs identified by non-clinicians or by clinicians who did not treat persons with the identified very serious ADR or who had not treated persons with implicated drugs or devices (eg:

toxicity secondary to pelvic mesh implants) as the study focused on what happens to the clinicians who identify very serious ADRs, not what happened when very serious ADRs are identified in general" (Bennett et al 2021 p9).

Bennett et al (2021) asked two key questions: "Were these very serious ADRs overlooked by the FDA during the initial drug review period?" and "did manufacturers hide the toxicity data from the FDA and its advisors". They answered: "Our analysis suggests that both questions could be answered with a yes for ten of 15 drugs and one device in the study" (Bennett et al 2021 p10).

I2. Aducanumab

"Aducanumab" was approved to treat Alzheimer's disease in the USA in early June 2021. The drug (which is an intravenously infused anti-body) reduces the level of plaques in the brain, and these clumps of amyloid-beta proteins are believed to be the basis to Alzheimer's (according to the amyloid hypothesis) (Mullard 2021).

However, the Food and Drug Administration's (FDA) decision has been criticised particularly by its own independent panel of experts. The clinical trial data showed successes for some individuals but not for others, and depended on the statistical analysis performed. Claiming success here was akin to "firing a shotgun at a barn and then painting a target around the bullet holes" (Scott Emerson of the independent panel quoted in Mullard 2021).

This drug is part of the "accelerated approval programme", which includes data collection after the drug is on the market. Another panel member, Aaron Kesselheim said: "This opens the door to drug companies seeking to use the accelerated approval programme as a way of getting drugs on the market based on extremely low-quality evidence or post-hoc data fishing" (quoted in Mullard 2021).

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