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# COVID-19: KNOWLEDGE PROGRESSES AND FALTERS (July-September 2020)

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

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# 1. INTRODUCTION

1.1. Mid-July 2020 concerns

Talking before covid-19 and about science generally, an editorial in the "New Scientist" stated that "there is no such thing as scientific truth, only successive attempts to get nearer to it" (The Leader 2019 p5) (appendix A). This is relevant today with covid-19, and despite knowing more than earlier in 2020, knowledge continues to grow (and recede sometimes) [1].

An editorial in the "New Scientist" in early July 2020 summarised the state of knowledge at the time with these key points (The Leader 2020):

- Covid-19 is more than a respiratory illness.
- Certain groups are affected disproportionately (eg: more deaths among ethnic minorities).
- Warm weather does not suppress it.

## 1.1. MID-JULY 2020 CONCERNS

i) A second wave of covid-19 in the UK in the winter 2020-21 could be worse, particularly if the weather is unusually cold, there is a flu epidemic, and with a backlog of routine care from the first wave of covid-19 (Hamzelou 2020) [2].

ii) The Infection Fatality Rate (IFR) (ie: number of infected individuals who die) may be declining. An IFR of 0.6 to 1% appears to be the general rule globally.

Possible reasons for the apparently declining number of deaths from covid-19 relative to the number of cases includes (Le Page 2020b):

- Better treatment and earlier arrival at hospital.
- Increased testing (and so finding more cases).
- More younger individuals infected (who are less likely to die).

[1] This paragraph was written on 14th August 2020.

[2] But in other countries, the number of infections is peaking as WHO data suggested that the cumulative number of cases worldwide roughly doubled through June and July 2020 (Vaughan 2020a).

## 2. SYMPTOMS AND CONSEQUENCES [3]



There is emerging evidence of multiple symptoms and impacts of SARS-CoV-2 on the body. "It can kill via a two-pronged attack, through provoking our immune systems and disrupting blood clotting" (Editorial 2020).

In other words, it is more than just a respiratory illness.

In terms of the effect on blood clotting, autoposies have found the lungs suffused with small clots more often in covid-19 cases than with "bird flu" (Ackermann et al 2020 quoted in Wilson 2020a). The virus appears to enter blood vessel walls which have ACE2 receptors (a known method of attack in the lungs of SARS-CoV-2) (Teuwen et al 2020 quoted in Wilson 2020a).

There are also reports of diverse, long-term symptoms, like exhaustion, muscle pain, and rashes (Editorial 2020).

Geddes (2020) reported 140 responses within 24 hours from an online covid-19 support group after asking about prolonged or unusual symptoms. Many of the respondents had only experienced mild "traditional" covid-19 symptoms. For example, "Abbi" had lost 19 kg in two months after gastric problems, and over a similar period "Zoe" described "fatigue beyond description". Many of the longer term effects are linked to the immune system's response.

There is a parallel with SARS and MERS, where a small number of infected individuals had varied symptoms many months later. Neuroscientist Ed Bullimore said: "If covid-19 plays out anything like SARS and MERS, there will be quite a bit of longer-term mental illnesses and fatigue" (quoted in Geddes 2020).

Initial observations from the Covid Symptom Tracker App suggest variety. It's founder, Tim Spector, stated: "Hardly anyone's symptoms are the same the whole way through, and we think we are actually seeing six different sub-types of diseases, based on the groupings of symptoms and their timings" (quoted in Geddes 2020).

A SARS-CoV-2 variant (Δ382) which produces milder symptoms has been reported (Young et al 2020). It was first detected in a cluster of cases in January and February 2020 in Singapore (Su et al 2020).

[3] Initially written 6th July 2020.

Young et al (2020) retrospectively identified individuals with this variant from the PROSPECT study that covers seven hospitals in Singapore between January 22nd and March 21st 2020 (n = 432). Twenty-nine individuals were found to have the Δ382 variant, and they were compared to matched patients with covid-19. The clinical outcomes in the variant patients were significantly better (eg: less need for oxygen), but it still produced a "clinically significant illness".

## 2.1. LONG-TERM IMPACT [4]

Neuroscientist Athena Akrami, who has suffered long-term consequences of covid-19, outlined the false belief: "Everybody talks about a binary situation, you either get it mild and recover quickly, or you get really sick and wind up in the ICU [intensive care unit]" (quoted in Couzin-Frankel 2020). Akrami and many others online are reporting "lingering maladies" from covid-19, including fatigue, shortness of breath, aching joints, concentration problems ("brain fog"), and damage to the heart [5], lungs, kidneys, and the brain [6] (Couzin-Frankel 2020).

How many individuals have longer-term symptoms varies with the cohort studied. For example, in Italy, over 80% of acute hospital patients had problems two months after "recovery", while in UK data 10-15% of cases do not recover quickly, including individuals who only had mild covid-19 symptoms (Couzin-Frankel 2020).

The unpredictability and variability of the symptoms and consequences are in seen in this example by German radiologist, Gotz Martin Richter: "a middle-aged man who experienced mild pneumonia from COVID-19, and an elderly woman already suffering from chronic leukaemia and arterial disease, who almost died from the virus and had to be resuscitated. Three months later, the man with the mild case 'falls asleep all day long and cannot work'... The woman has minimal lung damage and feels fine" (quoted in Couzin-Frankel 2020).

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[4] Written on 18th August 2020.

[5] "The virus ravages the heart, for example, in multiple ways. Direct invasion of heart cells can damage or destroy them. Massive inflammation can affect cardiac function. The virus can blunt the function of ACE2 receptors, which normally help protect heart cells and degrade angiotensin II, a hormone that increases blood pressure. Stress on the body from fighting the virus can prompt release of adrenaline and epinephrine, which can also 'have a deleterious effect on the heart'" (Couzin-Frankel 2020 pp615-616) (eg: Mitrani et al 2020).

[6] Eg: Paterson et al (2020).

## 2.2. NEUROLOGICAL SYMPTOMS [7]

Neurological symptoms of covid-19 have appeared in a few patients (eg: dizziness and headache among early Chinese cases) (Varatharaj et al 2020). This tallies with other pandemics of respiratory pathogens, like SARS, and it may reflect the powerful immune response.
"Additionally, occasional neuropsychiatric and psychiatric presentations have been reported in severe coronavirus infections, although such presentations could reflect broader socio-economic implications of the pandemic on mental health. These complications are relatively uncommon, but such patients are often the most severely affected, necessitating protracted intensive care admission and often resulting in poor outcomes" (Varatharaj et al 2020 p2).

Because of the variety of such symptoms, data are lacking. Varatharaj et al (2020) reported an online case report notification portal ("CoroNerve") to overcome this problem. The portal included participation by the Association of British Neurologists, and the Royal College of Psychiatrists, among other UK professional associations. One hundred and fifty-three cases were posted in April 2020 (of which complete clinical data were available for 125 of them).

Almost two-thirds of the cases "presented with the broad clinical syndrome of a cerebrovascular event" (eg: stroke) (Varatharaj et al 2020 p5), and around one-third with "altered mental status" (eg: encephalitis; psychosis). The mean age of the sample was 71 years overall, but the latter group were younger (eg: in their 50s).

Varatharaj et al (2020) summed up: "Although cerebrovascular events and altered mental status were identified across all age groups, our cohort confirms that cerebrovascular events predominate in older patients; however, these early data identify that acute alterations in mental status were disproportionately over-represented in younger patients in our cohort. Our rates of neurological and psychiatric complications of COVID-19 cannot be extrapolated to mildly affected patients or patients with asymptomatic infection, especially those in the community, but give a broad national perspective on complications severe enough to require hospitalisation" (p6).

The study was dependent on the accuracy of information posted on the CoroNerve website by the hard-pressed professionals (ie: the potential for reporting bias). Varatharaj et al (2020) also noted that "as many

[7] Initially written 10th July 2020.

patients with COVID-19 are managed in intensive care units with sedative and paralytic medications, which can both mask and contribute to iatrogenic complications, our cohort might under-represent the rate of neurological or psychiatric symptoms" (pp6-7).

This research was the first major surveillance study of neurological and neuropsychiatric symptoms in the UK. Such a method is crucial when information is lacking, though the sample was opportunist. Causation could not be established, however.

## 2.3. HEARING PROBLEMS

Almufarrij et al (2020) commented: "A significant number of central and peripheral nervous system manifestations have been reported including cerebrovascular disease, impaired consciousness and impaired vision; however, it is unclear if these are a complication of covid-19 or side effects of medication" (p487).

These authors concentrated on hearing loss and problems after "unsubstantiated and anecdotal cases reported in national newspapers" with a "rapid systematic review". Seven studies covering SARS-CoV-2 and hearing issues published in 2020 were found. In terms of methodological quality, four studies were "fair" and three "poor".

Four studies reported hearing loss, four studies tinnitus, two studies rotatory vertigo (ie: dizziness), and four studies other problems.

Overall, the incidence of "reported audio-vestibular symptoms was below 1%, indicating that either these symptoms are uncommon or attention, so far, has concentrated on life-threatening symptoms. The incidence of audio-vestibular symptoms between those infected with other types of coronavirus (ie: MERS and SARS) is unknown. Indeed, no records of audio-vestibular symptoms were identified in the literature with either MERS or SARS. This can be partially explained by the low incidence of these two types of coronaviruses relative to SARSCoV-2" (Almufarrij et al 2020 p490).

The studies often lacked details about the type or severity of hearing loss, about pre-covid-19 hearing problems, and lack of controls. Treatments for covid-19 might have been the cause (eg: side effects of anti-viral medication).

Three studies were case reports of a single individual, while the largest sample size was 1420 confirmed covid-19 cases. The diagnosis of covid-19 also varied between the studies or was not reported in two studies (Almufarrij et al 2020).

Almufarrij et al (2020) ended: "High-quality studies

are required in different age groups to investigate the acute effects of coronavirus, including temporary effects that may be caused by, for example, medication, as well as for understanding long-term risks, on the audio-vestibular system" (p491).

# 3. TRANSMISSION



## 3.1. ROUTES AND RISKS

Morawska and Milton (2020) raised awareness of the potential for "airborne spread" (appendix B) (ie: microscopic respiratory droplets or micro-droplets or aerosol [8]) [9]. This is beyond the transmission via large respiratory droplets (and contact with infected surfaces). The micro-droplets potentially remain aloft in air longer, and may travel further (eg: tens of metres) (Morawska and Milton 2020).

There is evidence from a study of a Chinese restaurant (Li et al 2020), where analysis of surveillance videos found no direct or indirect contact between individuals who became infected with covid-19. The only conclusion for Morawska and Milton (2020) is airborne spread.

But Paul Hunter, for example, was critical, suggesting that "taking measures to prevent aerosol spread could give people a false sense of security, making them less likely to take other steps, such as washing their hands" (quoted in Le Page 2020a p7).

The ability of coronavirus in the micro-droplets to infect individuals is questioned (Le Page 2020a).

The World Health Organisation has accepted an aerosol risk related to intubation (inserting a tube in the airway of a patient to aid breathing), but not aerosols produced by talking, laughing or singing (as of July 2020) (Le Page 2020a).

Another transmission route could be mother to foetus/newborn. But is it via the transplacental or the transcervical route (ie: before birth) or through environmental exposure after birth?

Vivanti et al (2020) reported a case study in France of transplacental transmission. The researchers noted "the viral load is much higher in the placental tissue than in the amniotic fluid or maternal blood: this suggests the presence of the virus in placental cells..."

[8] Droplets less than 5 micrometres in diameter.
[9] This was supported by over 200 scientists (Le Page 2020).

(Vivanti et al 2020 p3). The mother was infected with covid-19 in late pregnancy. The newborn showed neurological problems, probably as a result of the maternal immune system response.

### 3.2. SPREADING

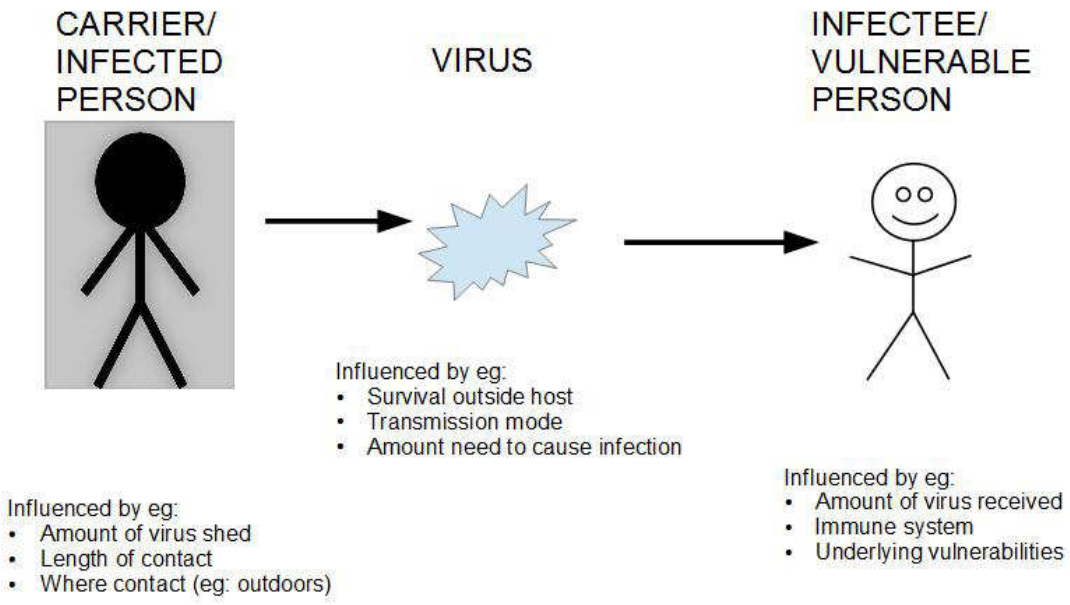
Dawood et al (2020) described the global spread of covid-19 using web-based surveillance by the US Centers for Disease Control and Prevention (CDC). Cases of covid-19 outside of China were collected from various data sources, including official government websites, press releases, and social media feeds. This was only publicly available material, which varied in completeness from country to country. The period of analysis was 31st December 2019 to 10th March 2020 ("pre-pandemic period" or epidemiological weeks 1-11).

By 10th March 2020, ninety-nine countries and locations outside of China had reported cases of covid-19, and where identified (76% of cases), the first infected individual had a history of travel to China, Iran, or Italy, in the main. Subsequently, the main transmission settings the household, non-health-care occupational settings, and community gatherings in that order.

The data supported a role for physical distancing to slow the progression of the infection.

Writing in July 2020, Dawood et al (2020) ended their article: "Much remains unknown about COVID-19, including how its epidemiology will evolve in the context of more widespread community transmission, the effect of community mitigation measures on spread, risk factors for severe disease, how risk factors and severe outcomes might vary between low-resource and high-resource settings, the effect of COVID-19 on vulnerable populations, and the economic and social effects of the virus. Additional studies with detailed epidemiological and clinical data, and ideally with systematic testing of suspected cases, including among special populations (eg, health-care workers, children, and pregnant women), could further our understanding of COVID-19 and inform preparedness and response measures for the current pandemic" (p8).

It is possible to produce a simple model of transmission and infection risk (figure 1) (addendum).




(Clip art from http://www.veezzle.com)

Figure 1 - A simple model of transmission and infection risk of covid-19.

### 3.2.1. Super-Spreader Events

Between 7th and 16th August 2020, nearly half a million motorcycle enthusiasts travelled to a rally at Sturgis, South Dakota, USA. Such an event with minimal mask-wearing and social distancing "could serve as a covid-19 'superspreader'" (Dave et al 2020a p abstract).

Dave et al (2020a) used anonymised geolocation data from cell phones to map travel, and official data on covid-19 cases for the post-event period. They estimated that the Sturgis (county) area had an increase of 6-7 covid-19 cases per 1000 population due to the influx of the visitors. This is a 35% increase on the average for that county.

Comparing counties from where attendees came with counties without any such attendees, the former were estimated to have a 7-12% increase in covid-19 cases.

Dave et al (2020a) concluded that the event "generated public health costs of approximately $12.2 billion" (p abstract).

Recent mass protests in the USA related to "Black Lives Matter" has been a concern for the spread of covid-19. But analysing 315 protests in large US cities, Dave et al (2020b) found that any spread of covid-19 by protestors was evened out by increased stay-at-home behaviour by local non-protestors ("avoiders"). The avoiders' behaviour was influenced by city curfews, but

also fear of protestors and covid-19, and of violence. Data on covid-19 cases were analysed for five weeks after the onset of the protests.

Dave et al (2020c) found a similar case for Donald Trump's mass campaign rally in Tulsa on 20th June 2020. Despite the movement of non-residents to the event, there were offsetting events, including voluntary closure of local restaurants and bars, and local residents staying at home. Also the attendance at the rally was smaller than expected (Dave et al 2020c).

### 3.2.2. Non-Pharmaceutical Interventions

Social distancing and face-mask wearing (non-pharmaceutical interventions; NPIs) do reduce transmission, as reported by geolocation data, for example. But such data are proxies for actual behaviour (Clipman et al 2020).

Surveys give more details about individual behaviour, as the Pandemic Pulse Study sample in Maryland, USA (Clipman et al 2020). Between 17th June and 28th June 2020, 1030 respondents were recruited online. All questions referred to behaviour in the previous two weeks.

Over 90% of respondents had travelled for essential services (eg: food shopping), two-thirds had visited friends and family, and 18% had used public transport. Self-reported covid-19 was significantly more common in the last group, and among individuals who visited places of worship, but less common among those who practised social distancing.

The sample was self-selected, and required an Internet connection, so it was not representative of the whole state. "The sample also likely misses homeless populations and very low-income groups, two populations where NPI adoption may be especially challenging" (Clipman et al 2020 p14).

The US state of California introduced lockdown (or stay-at-home or "shelter-in-place") on 19th March 2020, which limited travel to essential activities only. Using daily state-level covid-19 data for the following month and statistical modelling, Friedson et al (2020) calculated that the lockdown reduced covid-19 cases by 125 - 219 per 100 000 population. The researchers estimated 1661 fewer covid-19 deaths during the four weeks of lockdown. "Back-of-the-envelope calculations suggest that there were about 400 job losses per life saved during this short-run post-treatment period" (Friedson et al 2020 p abstract).

Candido et al (2020) analysed the spread of covid-19 in Brazil. "Although NPIs initially reduced virus

transmission and spread, the continued increase in the number of cases and deaths in Brazil highlights the urgent need to prevent future virus transmission by implementing rapid and accessible diagnostic screening, contact tracing, quarantining of new cases, and co-ordinated social and physical distancing measures across the country" (Candido et al 2020 p1259). Air travel was key to wider transmission.

### 3.3. TESTING

Service (2020) noted a move in mid-2020 in testing strategy "away from diagnosing people who have symptoms or were exposed and toward screening whole populations using faster, cheaper, sometimes less accurate tests" (p608). Such a move would help in the reopening of societies after lockdown.

The main covid-19 testing method uses the polymerase chain reaction (PCR) technique to amplify the virus' genetic material and aid detection. Though these tests are highly accurate, they are expensive (because of the need for specialised equipment) and take time (up to two weeks) (Service 2020). A public health expert in the USA: said "It's like calling the fire department after your house burns to the ground" (Daniel Paltiel in Service 2020), as the infected individuals spread the virus while waiting for the test result. For example, one study in China followed 1178 individuals in January to April 2020 and their 15 648 contacts (Hu et al 2020). Individuals were most likely to spread the virus 1.8 days before the onset of symptoms. "The finding suggests testing people only when they show symptoms and giving them test results days to weeks later does little to slow viral spread" (Daniel Larremore in Service 2020).

Modelling of more frequent, but less accurate, tests show reduced viral transmission - eg: Larremore et al 2020 - tests every 3 days prevent 88% of transmission compared to no tests (Service 2020). Paltiel et al (2020) modelled a university campus with ten infected students at the start of a semester, and compared a 70% accurate test every two days with every seven days for a more accurate test. The former would lead to 28 infections by the end of the semester compared to 108 (Service 2020).

### 3.4. SEVERITY OF SYMPTOMS [10]

There were increasing numbers of asymptomatic cases in March-June 2020, but "it is not clear whether the

[10] Written 21st September 2020.

apparent increase in people with mild or no symptoms is due to the change in the extent of testing, or some other characteristic of the SARS-CoV-2 virus" (Kifer et al 2020 p4). Kifer et al (2020) wondered whether ambient temperature and humidity contributed to this situation.

They analysed data from 6914 hospitalised covid-19 patients from eight European countries, and one province in China, and used the reports from the Covid Symptom Tracker.

Controlling for age, and hospital admission and treatment policies, Kifer et al (2020) found that ambient temperature "strongly correlated with decrease in covid-19 mortality" (p12) (ie: covid-19 severity declined with increased temperature).

These researchers explained that the low relative humidity of indoor air impairs the mucosal barrier, and this accounts for the increase of the virus during the winter season. Thus the importance of humidification of dry air in indoor heated spaces.

# 4. IMMUNE SYSTEM



## 4.1. IMMUNE MEMORY

The Leader (2020) focused on the concern of the moment in July 2020 - immune memory. Whether having covid-19 produces an immunity response that protects against future re-infection, and for how long. For example, with the common cold virus, individuals are vulnerable to re-infection relatively quickly, while protection against SARS and MERS is believed to last years (Lawton 2020a).

Immune memory can be divided into two parts (Lawton 2020a):

i) When a novel pathogen enters the body, B-cells respond, and the successful ones encourage development of the specific anti-bodies for that pathogen. These are "neutralising anti-bodies" (producing "shielding" or "sterilising immunity").

ii) Some B-cells mature into memory B-cells, and along with T-cells, wait ready to respond to re-infection (giving "functional immunity") [11].

The presence of neutralising anti-bodies can be determined by an anti-body, immunoglobulin G (IgG) in the blood. Studies are finding IgG in recovered covid-19 sufferers.

For example, Wajnberg et al (2020) collected blood samples from 1343 recovered covid-19 cases in the New York City area in March-April 2020. Self-reported date of symptom onset, positive SARS-CoV-2 test (where taken), and last date of symptoms were also recorded.

Only 3% of the cases had required emergency hospital treatment, and the overall median duration of symptoms was nine days (range 1-67 days).

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[11] Mice can be genetically engineered to lack adaptive immunity, and in these animals neurological conditions like Alzheimer's disease, develop more severely and rapidly than in normal mice (Kipnis 2018).

Kipnis (2018) reported work that has shown that "the mice lacking adaptive immunity exhibit not only impaired spatial learning behaviour but also compromised social behaviour, preferring to spend their time with an inanimate object rather than another mouse" (p25).

There is growing acceptance of the interaction between the brain and the immune system as seen in the new field of neuroimmunology (Kipnis 2018).

Of the total sample, 57% had relevant anti-bodies in their blood sample, 5% "weakly positive" (ie: a small number of anti-bodies), and the remainder negative. "Neither age, gender, nor symptom duration was associated with anti-body response" (Wajnberg et al 2020 p6). The median was 15 days between symptom resolution and anti-body test (range 4-77 days).

It was calculated that IgG anti-bodies developed between 7-50 days after symptom onset (median 24 days), and between 5-49 days after symptom resolution (median 15 days). The researchers admitted that they could not say if the IgG conferred any immunity to covid-19.

The study involved volunteers with mild disease. Also Wajnberg et al (2020) explained that "given recruitment via an English language online survey and our use of a single collection site, our sample likely included more recovered participants of younger ages with internet access and the ability to travel to our site for testing. Furthermore, we did not collect rigorous data regarding symptom severity which could potentially be related to the timeline and strength of IgG antibody response to SARS-CoV-2" (p10).

In terms of more serious cases, Staines et al (2020) analysed the blood samples of 177 confirmed covid-19 patients at St. George's Hospital in South London (between 29th March and 22nd May 2020) (of which 166 were hospitalised). Less than 10% of them had no detectable anti-bodies up to 60 days post-infection. These individuals were more likely to be younger (mean age 41 years vs 66 years for anti-body group), and healthier generally (eg: no co-morbid illnesses).

Peng et al (2020) found that fourteen individuals who recovered from severe covid-19 had a significantly higher memory T-cell response that 28 mild cases (and sixteen controls) [12]. But the immune response may dwindle over time (Lawson 2020).

In a study of 37 asymptomatic covid-19 cases in China, Long et al (2020) found a weaker immune response and consequently lower levels of anti-bodies post-infection than symptomatic cases.

The patients were part of a sample in the Wanzhou District hospitalised before 10th April 2020, of which 22 were female, and the overall median age was 41 years (with a range of 8-75 years) [13].

The anti-bodies were declining 2-3 months after infection, and "these data might indicate the risks of using COVID-19 'immunity passports' and support the

[12] The study took place at a hospital in Oxford, England, between March and May 2020.
[13] Total sample = 178 (21% asymptomatic).

prolongation of public health interventions, including social distancing, hygiene, isolation of high-risk groups and widespread testing" (Long et al 2020 p5) [14]. In previous pandemics, anti-bodies against SARS and MERS were found 1-2 years after infection (Long et al 2020).

In a London study (Seow et al 2020), the transient nature of neutralising anti-bodies (nAbs) was confirmed for individuals with mild symptoms in particular, but not exclusively. However, the researchers admitted that it was "not clear whether this decline will continue on a downward trajectory or whether the IgG level will plateau to a steady state" (Seow et al 2020 p9). The study included patients and healthcare workers between March and June 2020, and weekly or fortnightly blood samples were taken.

Anti-bodies are usually resident in the blood, but Cervia et al (2020) found healthcare workers with anti-bodies detected in their nasal fluids and tears, but not in their blood. This meant that memory B and memory T cells were resident in mucosal membranes in the nose and lungs, and could block re-entry of the virus into the body (Lawton 2020a). The "mucosal IgA" anti-body response was found in younger individuals with mild SARS-CoV-2 infection (Cervia et al 2020).

The study by Cervia et al (2020) involved fifty-six mild and severe covid-19 patients and 109 SARS-CoV-2-exposed healthcare workers in Switzerland. Generally, the strength of anti-body response correlated with disease duration in severe cases, but the response was transient and/or delayed in mild cases.

Cervia et al (2020) distinguished four grades of anti-body response based on covid-19 severity:

i) Oligosymptomatic disease (ie: few or minor symptoms) and mucosal anti-body response only.

ii) Mild-to-moderate disease and transient/delayed anti-body response.

iii) Severe disease and high anti-body response.

iv) Very severe disease and very high response.

One study has found an immune response to SARS-CoV-2 in two individuals not infected, which seems to be cross-reactivity due to infection with seasonal "common cold" coronaviruses (Weiskopf et al 2020). This study compared ten patients with moderate to severe covid-19 and ten

[14] Also noteworthy was that the asymptomatic individuals had a significantly longer duration of viral shedding (ie: infectious) than the symptomatic cases.

health controls in the Netherlands. The patients were confirmed to have SARS-CoV-2-specific T cells in their blood within two weeks after onset of symptoms. The cross-reactive immune response was found in two of the healthy controls.

### 4.2. IMMUNOTYPES [15]

Mathew et al (2020) outlined the rationale of their research: "How human immune responses control or exacerbate COVID-19 is currently poorly understood, and defining the nature of immune responses during acute COVID-19 could help identify therapeutics and effective vaccines" (p1209). This highlighted the fact that the immune system can both help and hinder in the reaction to covid-19.

Mathew et al (2020) analysed the blood of 125 patients hospitalised with covid-19, 36 recovered mild sufferers, and 60 healthy controls in Pennsylvania, USA, and found differences in immune response, which could be divided into three immunotypes (related to poor outcomes):

- 1 - severe disease experience; some immune response, but also "hyperactivated or exhausted" T cells.
- 2 - less severe disease; weaker immune response in some ways.
- 3 - severe disease; little immune response (similar to non-infected individuals).

The researchers were able to give details of these immune responses. They stated: "Respiratory viral infections can cause pathology as a result of an immune response that is too weak, resulting in virus-induced pathology, or too strong, leading to immunopathology. Our data suggest that the immune response of hospitalised COVID-19 patients may fall across this spectrum of immune response patterns, presenting as distinct immunotypes linked to clinical features, disease severity, and temporal changes in response and pathogenesis" (Mathew et al 2020 p14).

In another study, Arunachalam et al (2020) found the activation of some aspects of the immune system, but a reduction in others. This was based on 76 covid-19 patients and 69 healthy individuals in Hong Kong and the USA (addendum).

[15] Written 14th September 2020.

## 4.3. RE-INFECTION

The decline of anti-bodies over time, and thus immunity, opens up the possibility of re-infection. To et al (2020) reported the case of a patient in Hong Kong with a second episode of covid-19 4-5 months after the first episode. Is this "true re-infection"?

The researchers found that genome analysis of SARS-CoV-2 showed different strains responsible for the two episodes of infection. There was also a gap of 142 days between the two episodes, and this is much longer than any reported continuation of the virus in the body. In one case, a pregnant woman was found to have virus in her body 104 days after a positive test for covid-19 (Molina et al 2020).

To et al (2020) noted the implication of their case report that "it is unlikely that herd immunity can eliminate SARS-CoV-2, although it is possible that subsequent infections may be milder than the first infection as for this patient. Covid-19 will likely continue to circulate in the human population as in the case of other human coronaviruses" (pp10-11). There is also the implication for long-term protection from a vaccine.

To et al (2020) pointed out: "Although our patient is asymptomatic during the second infection, it is possible that re-infection may result in more severe infection" (p12).

## 4.4. ANTI-BODIES AS TREATMENT

nAbs created by individuals who are infected with covid-19 could "represent potential prophylactic and therapeutic options and could help guide vaccine design" (Rogers et al 2020 p1). Such anti-bodies are used in the case of other diseases (eg: respiratory syncytial virus; RSV) (Rogers et al 2020).

"Generally, nAbs with outstanding potency ('super-anti-bodies') can be isolated by deeply mining anti-body responses of a sampling of infected donors" (Rogers et al 2020 p1). Rogers et al (2020) reported a small study with seventeen swab-positive covid-19 sufferers in California. Anti-bodies from eight of them were used with Syrian hamsters in experiments. Those given anti-bodies at one of five different concentrations showed some benefit compared to the control animals when infected with covid-19. The use of nAbs is a possibility with humans and covid-19, the authors concluded, though there were unanswered questions, like the best concentration of anti-bodies.

# 5. KNOCK-ON EFFECTS [16]



## 5.1. OTHER DISEASES

With the reorganisation of hospitals and health services to deal with covid-19, other health issues have taken a backseat. Anecdotally, cardiologists, for example, have reported reduced patients presenting with heart problems. Mafham et al (2020) investigated this formally in the UK.

Official data on NHS admissions with acute coronary syndrome from 1st January 2019 to 24th May 2020 were extracted from the Secondary Uses Service Admitted Patient Care (SUSAPC) database.

A 40% decline in hospital admissions was found for mid-February 2020 to the end of March 2020 (mean: 1813 admissions per week compared to 3017 at 2019 baseline), but a reversal during April and May 2020 (2522 admissions per week). "Measured against this baseline, from January, 2020, until the end of May, 2020, there had been around 8000 fewer admissions for acute coronary syndromes than would be expected, including 5000 fewer admissions for myocardial infarction, and this deficit will continue to grow until weekly admission numbers return to normal" (Mafham et al 2020 p5).

The period of decline was before the first UK death from covid-19 (on 5th March 2020), and the official lockdown (on 23rd March 2020). This suggests that individuals with heart attack symptoms delayed seeking medical help because of fear of acquiring covid-19, while "environmental changes (eg: reduced air pollution), decreased physical activity, or diminished stress because of lockdown are unlikely to be major contributors to the noted trends in acute coronary syndrome admissions in the current pandemic" (Mafham et al 2020 p6).

The increase in hospital admissions later in spring 2020 coincided with a publicity campaign encouraging help-seeking by the British Heart Foundation, for example. The long-term consequences of delaying medical help will become evident in time (eg: avoidable deaths; complications and disability) (Mafham et al 2020).

HIV, tuberculosis (TB), and malaria are major health concerns in low- and middle-income countries (LMICs), and covid-19 has an impact upon them, primarily from disruptions to usual activities and services. "These

[16] Written initially on 17th July 2020.

disruptions include mitigation strategies being undertaken in response to the COVID-19 pandemic, leading to the scaling back of certain activities and care-seeking; reduced capabilities of the health system due to overwhelmingly high demand for the care of patients with COVID-19; and interruptions to the supply of commodities as a result of effects on both domestic and international supply chains" (Hogan et al 2020 pp1-2).

Hogan et al (2020) modelled the impact of covid-19 with four different scenarios:

- "No action" - no government interventions in response to the pandemic.

- "Mitigation" - interventions, like physical distancing rules, for six months, that reduce "R" (the number of new infections caused by a single infected individual) by 45%.

- "Suppression-lift" - major interventions, like full lockdown, for two months, and R is reduced by 75%.

- "Suppression" - as previous but implemented for one year.

Overall, covid-19 could increase the deaths due to HIV by up to 10%, due to TB by up to 20%, and due to malaria by up to 36% over five years compared to no covid-19, it was estimated.

The "indirect impact of the pandemic might be largely avoided through maintenance of core programme elements and recovery campaigns. For HIV, individuals receiving ART should continue to access treatment even in periods of highest health system demand (eg: via multi-month prescriptions or dispensing away from health facilities). For tuberculosis, routes for individuals to seek care and diagnosis must be provided despite interventions that promote social distancing. For malaria, preventative measures must be prioritised, ensuring LLINs [long-lasting insecticide-treated nets] and prophylactic treatments, such as mass drug distribution or seasonal malaria chemoprevention, are conducted at scale as soon as possible" (Hogan et al 2020 p8).

Hogan et al (2020) admitted three groups of uncertainty with their modelling - "uncertainty about the scale of the COVID-19 pandemic; uncertainty about the extent to which other disease programmes will actually be disrupted; and uncertainty about how those disruptions will impact on population health" (p8).

Headey et al (2020) predicted increased childhood malnutrition in LMICs due to "steep declines in household

incomes, changes in the availability and affordability of nutritious foods, and interruptions to health, nutrition, and social protection services" (p519). United Nations estimates, for example, suggest that an extra 140 million people will be pushed into extreme poverty (less than US $1.90 per day) as a result of covid-19 (Headey et al 2020).

Headey et al (2020) calculated over 128 000 extra deaths of under 5s in 118 LMICs in 2020 (over half of these being in Sub-Saharan Africa).

## 5.2. AIR POLLUTION

Data from China for 23rd January to 13th February 2020 (a period of covid-19 lockdown and the Lunar New Year) showed large reductions in air pollution (appendix C) due to the absence of motor vehicle traffic, and the suspension of industrial production (Le et al 2020). Satellite-monitored air pollutants, like nitrogen oxide (NO2), compared to the same period in 2019 showed over 90% reduction in Wuhan, for example. But certain other areas of the country (eg: Beijing) had increased particulate matter (PM) and ozone levels as a result of changes in relative humidity and low wind, for example, and the continued emission from power plants and the petrochemical industry (Le et al 2020).

Le et al (2020) ended: "As the COVID-19 pandemic is still ongoing, the unexpected PM elevation has potentially profound implications for the airborne transmission of virus. An emerging study shows plausible virus transmission through aerosols in populous areas. Meanwhile, exposure to high levels of PM can cause adverse effects on the respiratory and cardiovascular systems and possibly increase the fatality rate of COVID-19" (p705).

# 6. HUMANS FIGHTING BACK



## 6.1. TREATMENTS

The bacillus Calmette-Guerin (BCG) vaccine is commonly used to prevent childhood tuberculosis disease (TB). There is the suggestion that this vaccine may be beneficial with covid-19 (appendix D).

There is historical evidence that the BCG vaccine has health benefits beyond TB. For example, in 1927, children in Sweden who received this vaccine at birth had a threefold lower mortality than unvaccinated children (Naslund 1932 quoted in Escobar et al 2020). "This decrease of mortality could not be explained by TB infection, and thus, early on, it was suggested that the very low mortality among BCG-vaccinated children may be caused by non-specific immunity" (Escobar et al 2020 p1).

While in Guinea-Bissau, more recently, infants with acute viral infections of the lower respiratory tract were less likely to have received BCG vaccination than matched controls (Stensballe et al 2005). Among older adults (above 65 years old), a small study found that BCG vaccination prevented acute upper respiratory infections (Wardhana et al 2011). So, there is a "rational biological basis" for the BCG vaccine benefiting in covid-19 (Escobar et al 2020).

Recently, a number of authors have proposed this benefit (eg: Sharquie 2020). But such articles lacked statistical evidence, which Escobar et al (2020) rectified.

They collected data on covid-19 mortality by country up to 22nd April 2020, and the country's BCG vaccination policy (ie: current, interrupted, never). The percentage of the population over 65 years old, urbanisation, and Human Development Index score were controlled for in the analysis.

Simply, countries with a current BCG vaccination policy had lower covid-19 deaths than countries with interrupted or no policy. This analysis was quite general, and the researchers were aware of the need for randomised controlled trials. For example, health workers in Holland have been given the BCG vaccine or a placebo saline injection (quoted in Escobar et al 2020).

Escobar et al (2020) noted relevant factors for the efficacy of the BCG vaccine with covid-19 might include the age of vaccination (an early "critical window"), BCG strain used, or the administration route.

Promising treatments (as of August 2020) include

(Vaughan 2020b):

- Dexamethasone (steroid) - reduces the immune response to covid-19, which is often the cause of death in severe cases.

- Remdesivir (anti-viral used with Ebola disease) - some evidence.

- Tocilizumab (anti-inflammatory used with arthritis).

- But not hydroxychloroquine (despite earlier claims and "hype").

## 6.2. VACCINE DEVELOPMENT

As of August 2020, more than 160 different vaccines in development, of which around 25 have been tested on humans (table 1) (Vaughan 2020c) (addendum).

| Number of Vaccines | Phase |
|---|---|
| **164** | Total |
| 139 | Animal testing |
| 25 * | Human testing |
| 18 | Phase I - small number of healthy individuals for safety check |
| 11 | Phase II - larger number and more diverse individuals to see if immune response triggered |
| 5 | Phase III - hundreds or thousands of individuals with placebo groups to test for effectiveness |

(* some vaccines in combined phases and that is why numbers greater than 25 in rows below)

Table 1 - Vaccine situation in July 2020 (WHO data in Vaughan 2020c).

The ChAdOX1 nCoV-19 vaccine used a chimpanzee adenovirus to deliver a gene for coronavirus spike protein to human cells and trigger an immune response to the SARS-CoV-2 surface protein ("Trojan horse" method; Le Page 2020d). It had been tested successfully in rhesus macaques (van Doremalen et al 2020).

Phase I and II trials were conducted in five centres in the UK comparing this vaccine to a meningococcal one (in order to blind the participants to their trial

condition [17]) (Folegatti et al 2020). In April and May 2020 over 1050 healthy adult volunteers were tested (after recruitment by local advertisements) (appendix E).

Neutralising anti-bodies for SARS-CoV-2 were produced in response to the vaccine by Day 28, and remained elevated to Day 56, while the side-effects/adverse reactions were "mild or moderate in severity" (eg: fatigue; headache) [18].

This was the "first in-human clinical trial" with this vaccine, but the follow-up was short-term [19], the researchers were not blind to the vaccine type given (though laboratory staff were), the volunteers were aged 18-55 years old (with median age 35 years), and mostly White (91%). "Further studies are required to assess the vaccine in various population groups including older age groups, those with co-morbidities, and in ethnically and geographically diverse populations" (Folegatti et al 2020 p11) (appendix F).

One vaccine ("Ad5"; Le Page 2020c) being developed in China underwent a phase I (single centre, open-label, non-randomised) trial in March 2020 (Zhu et al 2020a), and subsequently a phase II (randomised, double-blind, placebo-controlled) trial (Zhu et al 2020b). It is an "AD5-vectored" vaccine (ie: using an adenovirus, type 5, to carry covid-19 particles and trigger an immune response) [20].

In phase II, 601 healthy volunteers were recruited in Wuhan in early April 2020, of which 508 completed the trial in one of three conditions - placebo, or two dose levels of the vaccine. Anti-body response at Day 28 was the main outcome measure. The majority of the participants in the vaccine groups had an anti-body response, and the side effects were "mild or moderate" (eg: fever; fatigue) and short-term (eg: 48 hours) (Zhu et al 2020b).

The use of the vaccine in relation to covid-19 will be tested in phase III.

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[17] "Use of saline as a placebo would risk unblinding participants as those who had notable reactions would know they were in the ChAdOx1 nCoV-19 vaccine group" (Folegatti et al 2020 p3).

[18] Adverse reactions were defined as "mild (transient or mild discomfort for <48 h, no interference with activity, and no medical intervention or therapy required), moderate (mild to moderate limitation in activity [some assistance might be needed] and no or minimal medical intervention or therapy required), severe (marked limitation in activity [some assistance usually required] and medical intervention or therapy required), and potentially life-threatening (requires assessment in emergency department or hospitalisation)" (Folegatti et al 2020 p4) (appendix G).

[19] Follow-up is intended for Days 184 and 364 (ie: 6 and 12 months).

[20] The vaccine made use of an already existing immune response to the adenovirus.

# 7. RISK FACTORS



## 7.1. OVERALL RISK

Spiegelhalter (2020) began: "As covid-19 turns from a societal threat into a matter of risk management, it is vital that the associated risks are understood and clearly communicated. But these risks vary hugely between people, and so finding appropriate analogues is a challenge" (p1). He wanted to communicate the risk of death from covid-19 in relation to "normal" risks.

Such a risk calculation is based upon the population fatality rate (PFR), which is the proportion of a total population who become infected and die in a specific time period. It is calculated using death certificates which mentioned covid-19 (ie: "those dying both from and with the virus"). Though it is probably an underestimation as individuals who were not tested or did not show "classic symptoms" would not have covid-19 on the death certificate (Spiegelhalter 2020).

Spiegelhalter (2020) used official data for England Wales for the sixteen weeks between 7th March and 26th June 2020. There were 218 354 registered deaths in that period, compared to an average of 159 595 for the same sixteen weeks in the previous five years. This gives an absolute excess of 58 759 deaths in 2020 (an increase of 37%), of which 84% (n = 49 607) of these had covid-19 on the death certificate.

These deaths varied with age; for example, 39 deaths for under 24s compared to 7 319 for 65-74 year-olds (Spiegelhalter 2020).

Overall, 1 in 1192 of the population of England and Wales died and had covid-19 on their death certificate (the covid-19 PFR), which is a 31% increase on the "normal" risk. But comparing age groups, for instance, 1 in 807 dying from or with covid-19 among 65-74 year-olds versus 1 in 2.4 million for 5-14 year-olds (Spiegelhalter 2020).

Spiegelhalter (2020) noted: "All this analysis refers to averages over populations, and although age seems to be the overwhelmingly dominant influence on mortality, clearly other factors affect individual risk. More than 90% of people who have died with covid-19 had pre-existing medical conditions" (p6).

He continued: "Importantly, all the risks quoted are

the average (mean) risks for people of the relevant age but are not the risks of the average person. This is because, both for covid-19 and in normal circumstances, much of the risk is held by people who are already chronically ill. So for the large majority of healthy people, their risks of either dying from covid-19, or dying of something else, are much lower than those quoted here. Of course, while death is the most serious and easily recorded outcome, information is growing on the number of people experiencing prolonged symptoms of covid-19" (Spiegelhalter 2020 p6).

## 7.2. BLOOD TYPE

In terms of risk factors for covid-19, Zhao et al (2020), in Wuhan, China, reported a "possible association" between blood type A and a higher risk of infection and mortality, but the opposite for blood group O (table 2).

Support from this finding came from a genome-wide association study of respiratory failure, which is the cause of mortality in covid-19 patients most commonly. The Severe Covid-19 GWAS Group (2020) used data from 1980 patients with respiratory failure in Spain and Italy as the cases in this case-control method (with 2381 controls from the same countries). Two loci (gene locations) were found to be significantly associated with the cases. A locus related to blood group A was associated with increased risk, and one will blood group O as a protective factor.

- "Blood type" is two main groupings in humans (Lawton 2020b):
- i) ABO - Three variants (alleles), A, B, and O. O is recessive and so needs two Os (one from each parent) to give the O blood group overall. A and B are dominant, and require only one version. So, individuals will be O, A (AA or AO), B (BB or BO), or AB.
- ii) Rhesus positive (Rh+) (dominant allele) and negative (Rh-) (recessive). The options are Rh+ (Rh+/Rh+ or Rh+/Rh-) or Rh- (Rh-/Rh-).
- "The groupings are independent of each other so somebody who is A can be either rhesus positive or rhesus negative, for example" (Lawton 2020b p11).

Table 2 - Blood types.

However, Latz et al (2020) did not find this. They made use of US data from five major hospitals in Massachusetts from 6th March to 16th April 2020 (n = 1289 patients). In summary, "there was no association noted between ABO blood type and covid-19 disease severity

defined as intubation or death" (Latz et al 2020 p5). But a "novel finding" was an association between rhesus positive and covid-19, which "warrants further investigation".

The researchers pointed out that their study was observational, and "while attempts were made to control for confounding, where such controls were possible, there is always the possibility that unmeasured confounding is driving the results" (Latz et al 2020 p5).

### 7.3. PREGNANCY

Concern for pregnant women and increased risk of serious covid-19 symptoms has emerged from US data. Pregnant women were 50% more likely to end up in intensive care units than non-pregnant peers (CDC data June 2020 in Wadman 2020a). But pregnancy status was not known for many women officially recorded with covid-19 by the CDC (Wadman 2020a).

Elsewhere, data from Sweden for a small number of women found a sixfold greater risk of intensive care treatment for pregnant or immediately post-partum women with covid-19 in March and April 2020 than non-pregnant women (Wadman 2020a).

The explanation is that pregnancy causes a change in the woman's immune system, and stress on the lungs and cardiovascular system, which the SARS-CoV-2 virus is able to take advantage of (Wadman 2020a).

For the foetus, SARS-CoV-2 appears not to pass into the placenta from the mother as it is not a blood-borne infection, but the health of the mother (eg: increased blood clotting risk) could affect growth (Wadman 2020b). Births towards the end of 2020 will show more evidence as these babies would have conceived during the pandemic, and the mothers may have been infected early in embryonic development (Wadman 2020b).

### 7.4. WEIGHT

Obesity has been reported as key to the severity of covid-19 symptoms at all ages. There is a variety of emerging evidence. (Wadman 2020c).

For instance, a meta-analysis by Popkin et al (2020) covered 75 studies up to 15th July 2020 that had been carried out in the first half of 2020. There were five case-control studies (table 3; appendix H), 33 cohort studies (retrospective or prospective), and 37 observational cross-sectional studies.

Eighteen of the twenty studies that assessed the association between obesity and covid-19 found a significant positive relationship. The two exceptions had

- Advantages

1. Relatively cheap compared to experiments.

2. Useful for the study of rarer conditions.

3. Quick results.

4. Matching cases and controls overcomes confounding variables.

- Disadvantages

1. Selection bias.

2. Risk of confounding variables explaining the difference between cases and controls (Bowling 2014).

3. Retrospective, and so a risk of recall bias.

4. Problems of matching cases and controls (eg: hospital patient cases matched with other hospital patients). A risk of "over-matching", where the controls are to similar to the cases (Bowling 2014).

Table 3 - Advantages and disadvantages of the case-control study.

methodological issues (eg: body weight at hospital discharge used - ie: after covid-19 hospitalisation) (Popkin et al 2020). Overall, the pooled data showed that the odds of individuals with obesity being diagnosed with covid-19 was one and a half times greater than for non-obese persons.

Among individuals with covid-19, obesity increased the risk of being hospitalised by about twofold, and admittance to ICU or invasive mechanical ventilation by one and a half times (based on 19 studies).

Data from 35 studies showed that "patients with obesity were more likely to have unfavourable outcomes with a 48% increase in deaths" (Popkin et al 2020 p5).

Alterations in metabolism, for example, associated with obesity seem to explain the increased risk of severe covid-19, while the immune system can be less effective in certain ways. "Importantly, being an individual with obesity has also been shown to impair the development of immunological memory. Influenza vaccination in adults with and without obesity results in equivalent influenza-specific anti-body titres at 30 days post vaccination, but anti-body titres wane significantly more in adults with obesity compared with adults who are lean at 1 year post vaccination" (Popkin et al 2020 p9).

Popkin et al (2020) also considered the social impact of covid-19 upon obesity. One possibility is increased food insecurity and malnutrition (ie: reduced obesity), especially for low-income families. On the other hand, Popkin et al (2020) explained: "We will see

diet shifts in not only how we eat and drink but also how we move if inactivity grows greatly. If the diets shifts to increased consumption of refined carbohydrates, fried food and other unhealthy aspects of the traditional diet or to increased highly or ultra-processed food we may experience increases in the prevalence of individuals with obesity" (p9). Such foods store well and are relatively cheaper.

Hamer et al (2020) used data from the UK Biobank (appendix I), that covered over half a million 40-69 year-olds, and linked it to covid-19 hospitalisation information. The final sample was 330 000, of which 640 of them (0.2%) were hospitalised for covid-19 between 16th March and 26th April 2020. After adjustment for demographic characteristics, there was an association between obesity and severe covid-19. The risk was 2-3 times greater for severely obese individuals (BMI $\geq$35 kg/m$^2$), and around one and a half times greater for obese cases compared to normal weight.

### 7.4.1. Losing Weight and Health

Losing weight is beneficial in relation to the severity of covid-19 experienced (eg: Tan et al 2020; table 4). But this can be easier said than done, for a number of reasons including (Wilson 2020b):

a) Doing enough exercise to burn off significant amounts of fat, though exercise is good for health generally.

b) Increased exercise leads to increased hunger and eating.

c) Losing the weight and then maintaining the weight loss (eg: regaining weight common within one year).

d) Which method to use - eg: a particular diet (eg: low-carb) or surgery - and the issues related to each.

e) Modern Western environment in particular, with more food available, often highly processed, and less exercise.

Though children and adolescents have less risk from covid-19 infection, the imposed lockdown and physical inactivity may have negative health consequences for them. There is also a risk of increased eating with sedentary behaviour, and the mental health impact of lockdown (Margaritis et al 2020).

- Two UK studies together showed the relative risk of serious covid-19 illness as one and a half times greater for overweight individuals and twice as great for those individuals with obesity compared to normal weight individuals. These studies and others have confirmed the increased risk of death from covid-19 for overweight and obese individuals (Tan et al 2020).

- Tan et al (2020) outlined the possible physiological explanations: "Angiotensin converting enzyme-2 (ACE-2), the trans-membrane enzyme that SARS-CoV-2 uses for cell entry, exists in larger quantities in people with obesity. Whether this is the result of higher ACE-2 expression in the adipocytes of people with obesity or having more adipose tissue in general (and thus a greater number of ACE-2 expressing cells) is not yet clear. The adipose tissue of people with obesity may therefore be a potential target and viral reservoir for SARS-CoV-2 before it spreads to other organs, as has proved to be the case for other viruses" (p1). Or altered immune responses due to obesity, or diminished lung function "through greater resistance in the airways and more difficulty in expanding the lungs" (Tan et al 2020 p1).

- Tan et al (2020) aimed their criticisms at an environmental factor: "It is now clear that the food industry shares the blame not only for the obesity pandemic but also for the severity of covid-19 disease and its devastating consequences. During the covid-19 pandemic an increase in food poverty, disruptions to supply chains, and panic buying may have limited access to fresh foods, thus tilting the balance towards a greater consumption of highly processed foods and those with long shelf lives that are usually high in salt, sugar, and saturated fat. Moreover, since the start of the covid-19 pandemic the food industry has launched campaigns and corporate social responsibility initiatives, often with thinly veiled tactics using the outbreak as a marketing opportunity (for example, by offering half a million 'smiles' in the form of doughnuts to NHS staff)" (p1).

Table 4 - Weight and covid-19.

Members of the weight-loss organisation, "Slimming World", in the UK are surveyed regularly about their weight and behaviour as part of membership. Bennett et al (2020) analysed data from 222 members in April-May 2020 (the period of lockdown) (and this was compared to 637 non-members).

Covid-19 and lockdown created challenges in relation to managing weight. Respondents reported limited choices of "good food" in the shops, when individuals could go shopping, and increased snacking through boredom, being at home, stress and anxiety, as well as reduced physical activity. However, there were a number of individuals who reported positive consequences in the form of more time to "plan and cook", and to be more active. Members, who had social support and weight management targets, were more likely than the general population to report positive impacts. For example, 25% of members reported increased physical activity compared to 17% of non-members.

## 7.5. MISCELLANEOUS

Women tend to live longer than men, and are less susceptible to certain diseases, including covid-19. Wilson and Moalem (2020) placed the reason in the presence of two X chromosomes that women possess (or put another way, men only have one X chromosome). In the case of covid-19, women have two populations of certain immune cells which can recognise the coronavirus (ie: toll-like receptor 7 (TLR7)) (Wilson and Moalem 2020).

Clinicians also assess risk in terms of death among those hospitalised (ie: a prognostic score). Knight et al (2020) developed the "4C Mortality Score" [21] using data from 260 hospitals in Great Britain (covering 6th February to 20th May, and 21st May to 29th June 2020) (n = 35 463 patients).

Three groups of predictor variables were collated:

- Patient and clinical variables that influence outcome in pneumonia and flu-like illnesses (eg: co-morbidities).

- Clinical biomarkers identified in studies as potential predictors of covid-19 outcome (eg: age).

- Clinical values shared by at least two-thirds of the sample in this study (eg: respiratory rate - breaths per minute).

An algorithm (appendix J) was trained with retrospective data to score patients for risk of death, and four categories were distinguished - low (0-3 points), intermediate (4-8), high (9-14), and very high (15-21).

The final 4C Mortality Score was based on eight variables (eg: age; sex at birth; number of co-morbid health conditions with covid-19; respiratory rate) [22].

The purpose of developing such a model to predict outcome was to aid in hospital decision-making, particularly when under pressure. For example, only 1-2% of individuals given a low score had died compared to two-thirds of "very high" scorers. Knight et al (2020) explained: "Patients with a 4C Mortality Score falling within the low risk groups (mortality rate 1%) might be suitable for management in the community, while those within the intermediate risk group were at lower risk of mortality (mortality rate 10%; 22% of the cohort) and might be suitable for ward level monitoring... Meanwhile

[21] C = category.
[22] Eg: 50-59 years old = +2 points; 80 years old and above = +7; being male = +1.

patients with a score of 9 or higher were at high risk of death (around 40%), which could prompt aggressive treatment, including the initiation of steroids and early escalation to critical care if appropriate" (p9; 10).

# 8. MENTAL HEALTH



## 8.1. SELF-HARM

Iob et al (2020) reported on abuse, self-harm, and suicidal ideation in the UK using data from the University College London's (UCL) Covid-19 Social Study (began on 21st March 2020). Over 44 000 individuals had been surveyed by 20th April 2020.

Of these, 9% reported physical abuse (ie: harmed or hurt by someone else) or psychological abuse ("bullied, controlled, intimidated, or psychologically hurt by someone else"), 18% thoughts of suicide or self-harm ("thought that you would be better off dead or of harming yourself in some way"), and 5% harmed themselves since the start of the lockdown in the UK.

Self-harm thoughts and actions, and abuse "mirrored usual demographic characteristics" - ie: higher among younger adults, women, ethnic minority individuals, and those experiencing socio-economic disadvantage, physical or mental illnesses. "The elevated prevalence of abuse and self-harm thoughts/behaviours in people who had been diagnosed with COVID-19 could indicate a heightened psychological risk during infection, or increased risk of exposure due to either behavioural or occupational factors among individuals already self-harming" (Iob et al 2020 p3).

Only a small number of individuals experiencing these things had spoken to someone about it, formally (eg: less than 10% a mental health professional), or informally (eg: around one-third to a friend).

The frequency and intensity of the behaviours were not measured, nor other types of abuse, like sexual or financial.

## 8.2. CHINA

Increased anxiety and stress among younger children in China during covid-19 has been reported, for example. This was manifest as clinginess, and fear that family members may become infected. Older children showed attention problems (Margaritis et al 2020).

Shi et al (2020) reported a study on mental health in China conducted online in late February/early March 2020. Over 56 000 adults completed the questionnaire on

the Chinese website "Joybuy" (an online health products and services provider).

Four mental health conditions were surveyed:

- Depression - 28% of the participants reported symptoms that categorised them as depressed.
- Anxiety - overall 32%.
- Insomnia - 29% of all participants.
- Acute stress - 24%.

These four conditions were more prevalent among covid-19 patients, friends and family members of patients, and those in close contact with patients (eg: healthcare workers) and their families. Shi et al (2020) noted: "However, in the present study, frontline work was not significantly associated with depression or anxiety. A previous study [Chan et al 2005 [23]] suggested that people at moderate infection risk (eg: individuals who might come in contact with patients with suspected cases) had more adverse mental health outcomes than those at high risk (eg: individuals who worked in infectious wards). The high infection risk group may be more aware of the risk, have better coping skills, have less uncertainty, and have more access to personal protective equipment and social support" (p11).

Quarantine was also associated with poor mental health. Shi et al (2020) explained: "People may experience fear of infection, frustration, and boredom during quarantine. Insufficient basic supplies and disruptions of information flow can increase both fear and anxiety. In the present study, both centralised quarantine and home quarantine enhanced the odds of adverse mental health outcomes. Moreover, centralised quarantine can have a more pernicious outcome because of fear of infection, being in an enclosed space, and being in an unfamiliar and crowded environment. The environment plays a vital role in maintaining healthy emotions and sleep. An unfamiliar and crowded environment may be a catalyst for the unique association between centralised quarantine and poor mental health status" (p12).

Another important finding related to work, as the researchers outlined: "A high probability of symptoms of depression and anxiety was found among people who had not yet returned to work. Among people who had returned to work, those who worked at home had a higher risk of mental health symptoms compared with those who did not work at home. Being occupied with work activities can

[23] This related to SARS in Hong Kong.

serve as a distraction from epidemic-related information. Interpersonal interactions that occur with conventional styles of work, in contrast to working at home, can ameliorate depression and lower the risk of mental disorders. Our results imply that accelerating people's return to normal work may have a positive influence on mental health" (Shi et al 2020 p12).

Finally, other risk factors included unmarried status, lower income, being male, and being younger generally.

Overall, the study covered a wide range of individuals throughout China, but it was an online convenience sample, and participants self-reported their symptoms.

## 8.3. HEALTHCARE PROFESSIONALS

The experience of healthcare professionals (HCPs) has been studied by surveys like Sharma et al (2020). These researchers designed a 41-question online survey for use in the USA with a wide range of HCPs who cared for covid-19 patients in an ICU between 23rd April and 7th June 2020. The sample was recruited via professional societies, personal contacts, and specialist social media groups.

There were 1651 respondents from the fifty US states. The main worries reported were transmission of covid-19 to family/community (66% of respondents), emotional distress/burnout (58%) [24], and insufficient personal protective equipment (PPE) (40%). Emotional distress/burnout was significantly associated with insufficient PPE access, stigma from the community [25], and poor communication with supervisors. "Insufficient PPE access was the strongest predictor of feeling that the hospital is unable to keep providers safe and worries about transmitting infection to families/communities" (Sharma et al 2020 p3) [26].

The sample was self-selecting, and included more respondents from large urban hospitals, and in the north-east of the country.

## 8.4. GRIEF AND COPING

There are concerns that the restrictions of covid-19

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[24] Pre-covid-19 surveys of burnout among critical care HCPs (eg: Embriaco et al 2007) found lower figures (eg: 50%) (Sharma et al 2020).

[25] "Although HCPs may be perceived as 'healthcare heroes', they can simultaneously experience distancing from their community due to fears that they are at high risk of having COVID-19" (Sharma et al 2020 p14).

[26] Individuals in difficult situations face the risk of "moral injury" (appendix K).

in relation to losing loved ones may lead to a rise in prolonged grief disorder. This is grief that does not decrease with time, and lasts for more than six months. Risk factors include sudden and unexpected death, restrictions on rituals related to death (eg: kissing the loved one), and other life stressors (Klein 2020).

On the other hand, individuals who watch horror films tend to cope better with all aspects of the pandemic (Marshall 2020). Scrivner et al (2020) reported a study showing that "exposure to frightening fictions allow audiences to practice effective coping strategies that can be beneficial in real-world situations" (p2). The researchers were referring to horror films primarily, but also those related to apocalyptic disasters.

Scrivner et al (2020) were inspired by the media report that the film "Contagion" (about a pandemic) [27] was the most streamed movie in the USA in the early weeks of the covid-19 pandemic. Also individuals with the personality trait of morbid curiosity (ie: a motivation to learn about the dangerous aspects of life) will seek out pandemic-themed films (Scrivner 2020).

Scrivner et al (2020) hypothesised that seeking out horror and pandemic-related films would be associated with greater psychological resilience towards the covid-19 pandemic. It has been theorised (eg: Scalise-Sugiyama 2001) that "exploring dangerous situations in imagined worlds is a far safer alternative to exploring these situations in the real world. Though imagined, these simulated worlds allow an individual to learn and prepare for analogous situations in the real world" (Scrivner et al 2020 p3). This is a "preparation" function similar to rough-and-tumble play in young animals as a way to practice for fighting in later life (Scrivner et al 2020).

Scrivner et al (2020) recruited 310 US participants online for a study on "personality, media and current affairs". A number of different sets of questions were used:

- Rating of ten types of movies.
- Interest in pandemic movies currently.
- Psychological resilience, including a specially created Pandemic Psychological Resilience Scale (PPRS) (table 5).
- Preparedness for the pandemic (eg: "I used what I've

[27] Details at https://en.wikipedia.org/wiki/Contagion_(2011_film).

seen in movies or read in novels to help me know how to deal with the coronavirus (covid-19) pandemic").

- Morbid Curiosity Scale (Scrivner 2020) (table 6) [28].

- General personality measure.

| |
|---|
| • I have been able to find things to enjoy during the pandemic. |
| • I am more irritable than usual. |
| • I haven't been sleeping well since the pandemic started. |
| • Life has felt meaningful during the pandemic. |

Table 5 - Example of items from PPRS.

| |
|---|
| • I would be curious to see how an autopsy is performed |
| • I would be interested in watching a documentary on motives behind real murders. |
| • I am interested in seeing how limb amputation works |
| • If I saw a street fight break out, and knew I could not intervene, I would try to watch it. |
| • I would be interested in attending or watching a video of an exorcism |

Table 6 - Example of items from Morbid Curiosity Scale.

Psychiatrist Farhana Mann distinguished between isolation and loneliness: "Loneliness is a subjective sense that your social needs are not being met, while isolation is about being physically separated from others... A person can be physically isolated and not feel lonely, while another can be surrounded by family but may feel lonely because of a lack of meaningful connection" (quoted in Sarner 2020). While another psychiatry, Neil Greenberg, pointed out that the restrictions of quarantine, lockdown and social distancing can be psychological unpleasant, but that "distress and frustration are not mental health problems" (quoted in Sarner 2020).

[28] 24 items covering 4 factors - 1) Motives of Dangerous People, 2) Supernatural Danger, 3) Interpersonal Violence, and 4) Body Violation.

Existing mental health inequalities could be widened, and this will disadvantage individuals from lower socio-economic groups, and ethnic minorities, as in the consequences of Hurricane Katrina in the USA in August 2005, say. Epidemiologist Stephani Hatch said: "We know that unemployment, job loss and financial strain are very detrimental to mental health in the immediate, medium and long term, particularly as there is stress proliferation, which is when an acute stressor becomes a chronic strain over time because of the knock-on effects on relationships and finances" (quoted in Sarner 2020).

# 9. MISCELLANEOUS



## 9.1. INCLUSION AND INEQUALITY

Marmot (2020) argued that health inequalities prior to covid-19 can explain the differences in death rates from covid-19 among ethnic minorities in the UK, and the all-causes excess mortality, and that "austerity" is behind the inequalities. Marmot (2020) stated: "We limped into the pandemic, then, in a parlous state - an unhealthy population marked by growing inequalities and a worsening of the conditions in which people are born, grow, live, work and age; in short, in the social determinants of health" (p2).

Adults with learning disabilities can be an overlooked minority during the time of covid-19. They have a higher prevalence of co-morbid health problems and personal habits which increase infection risk, and face barriers (eg: due to communication problems), as well as depend on others for personal care (Santos 2020). "The stay-home restrictions may create new risks for these persons' autonomy, health and participation/decision making. Those who are living in institutions may be even more vulnerable due to fast and easy spread of the disease" (Santos 2020 p1).

There may be a tension between keeping the individual safe and their autonomy. Santos (2020) argued for inclusion of adults with learning disabilities in decision-making where possible.

## 9.2. AFRICA

Writing in early August 2020, Mbow et al (2020) noted that "more than 4 months after the first cases in Africa were detected, prevalence and mortality are still low. It remains unclear if Africa is really spared from substantial cases and deaths. However, differences between Africa and the most affected countries in reliable reporting and death registration, lockdown stringency, demography, socio-cultural aspects, environmental exposures, genetics, and the immune system could help to explain the experience of COVID-19 in Africa" (p624).

In more detail, three relevant factors include the following. Many African countries introduced travel restrictions and school closures, for instance, before a covid-19 cases was detected. This may have reduced the

intra-country transmission, but how much the restrictions were respected, with large informal work sectors, is unclear (Mbow et al 2020).

The population median age in Africa is 20 years old (compared to nearly double that in the USA), and covid-19-associated deaths are more common with older adults (Mbow et al 2020).

The number of pathogens faced generally by the African population may have produced a "stronger" immune system, which can defend against covid-19 (Mbow et al 2020).

Any advantages that the continent of Africa may have in relation to covid-19 has to be seen in the context of the "everyday problems" (eg: food insecurity; lack of clean water and sanitation services; violence; unemployment) (Graves et al 2019).

# 10. APPENDICES



## APPENDIX A - SCIENCE CHANGES

Cowan et al (2020) began: "In the hypothetico-deductive method, long considered by many philosophers and scientists to be a key to scientific progress..., a hypothesis or expectation is tested and, if the outcomes of experiments do not support it, the hypothesis is abandoned and other hypotheses are devised for future testing" (p1011).

But this process can produce theoretically progressive or degenerative theory-testing paths (Lakatos 1969). "In the progressive path, the data lead to modified versions of theories that remain useful in accounting for a body of evidence, including the new evidence. In the degenerative path, the data lead to modified versions that are increasingly awkward and improbable, with new auxiliary assumptions added only to protect core assumptions of the theory from falsification" (Cowan et al 2020 p1013). The progressive path is obviously better, but theorists may think they are taking this path when actually defending the theory. "Designing one's experiment in a manner that makes it too favourable to one's own theory can be unintentional and can occur because humans, including scientists, are affected by considerable confirmation bias in which they seek to verify rather than disprove their own ideas" (Cowan et al 2020 p1013).

Cowan et al (2020) proposed a solution -

"adversarial collaboration" (AC) as a way for knowledge to progress. This is where "proponents of competing views work together in a sometimes tense but productive joint effort... whether or not each participant adheres to the hypothetico-deductive method. In this effort, different participating groups work together to collect data jointly but openly expect (and often hope for) different results" (Cowan et al 2020 p1011).

An example of AC, of which Cowan et al (2020) were involved, is the three different theoretical positions on the limitations of working memory:

i) Multi-component theory - Working memory has different temporary stores for speech sounds, and visual/spatial information.

ii) Time-based resource-sharing theory - Elapsed time since the encoding of the information is key, and if rehearsal, say, does not occur the memory will decay.

iii) Embedded-process theory - Capacity is limited to a small number of items based on attention.

Experiments were developed using the "storage-then-processing task", where working memory capacity is tested by presenting three letters (to remember) followed by simple arithmetical sums, and then recall of the three letters. Recall was varied as spoken aloud or typed, for example (Cowan et al 2020).

The conclusion of the AC was that no current model of working memory limitations was "judged adequate". Cowan et al (2020) hoped for "a new theory that includes the most successful aspects of each theory. Although we do not believe that we have reached that point and do not know if that goal is realistic, it seems worth striving for" (p1019).

## APPENDIX B - AEROSOLISED FOMITES

It has been shown experimentally that influenza virus is transmissible in the air via microscopic particles called "aerosolised fomites" ("virus-contaminated dust particles") (Asadi et al 2020). This recent research used guinea pigs and the virus was on the body.

The important point was that the airborne particles were non-respiratory, but rather dust aerosolised by animal movements. The animals were kept in cages with special filters that sampled the air.

Asadi et al (2020) also produced aerosolised fomites by crumpling, folding and rubbing dried virus-contaminated paper tissues.

Asadi et al (2020) summed up: "These results show that dried influenza virus remains viable in the environment, on materials like paper tissues and on the bodies of living animals, long enough to be aerosolised on non-respiratory dust particles that can transmit infection through the air to new mammalian hosts" (pp4-5). Whether such particles would infect a human with influenza "remains to be demonstrated experimentally or empirically" (Asadi et al 2020 p5). However, "airborne transmission efficiency depends variably on multiple factors: the infectiousness of the virus donor, the susceptibility of the virus recipient, and the stability of the virus in the environment between them. The transmission chain has many links, any of which could be a weak link that precludes efficient transmission, whether by aerosolised fomites or any other route" (Asadi et al 2020 p6).

In the case of covid-19, air samples in locations in two Wuhan hospitals (Liu et al 2020) found "the highest airborne genome counts of SARS-CoV-2 in rooms where health care workers doffed their personal protective equipment (PPE), hinting that virus was possibly being aerosolised from contaminated clothing as it was removed" (Asadi et al 2020 p6).

## APPENDIX C - AIR POLLUTION

Schraufnagel et al (2019) stated: "Air pollution is a grave risk to human health that affects nearly everyone in the world and nearly every organ in the body. Fortunately, it is largely a preventable risk. Reducing pollution at its source can have a rapid and substantial impact on health. Within a few weeks, respiratory and irritation symptoms, such as shortness of breath, cough, phlegm, and sore throat, disappear; school absenteeism, clinic visits, hospitalisations, premature births, cardiovascular illness and death, and all-cause mortality decrease significantly" (p1478).

These researchers reviewed the benefits of air pollution reduction at three levels of intervention:

i) National/supra-national level - eg: policies to lower pollutant emissions, like the Clean Air Act (initially of 1970) in the USA. The US Environment Protection Agency calculated the benefits for the period 1990 to 2010 from the reductions in major air pollutants to include over 7000 avoided deaths per year, 66 000 fewer hospital admissions per year, and over two million fewer asthma attacks per year (Schraufnagel et al 2019).

ii) Local level - eg: factory closures; traffic restrictions; cleaner fuel for school buses; household

air pollution. In the latter case, for example, "clean" cookstoves and ventilation in rural homes reduce respiratory problems and non-respiratory symptoms (like eye discomfort and headaches) (Schraufnagel et al 2019).

iii) Personal level - eg: high-efficiency particulate air (HEPA) purifiers in the house and reductions in asthma-associated illnesses in the USA (Schraufnagel et al 2019).

From the studies reviewed, Schraufnagel et al (2019) produced a timeline to show the quantified benefits from interventions to reduce air pollution. For example, within one week, an indoor smoking ban has a positive effect, while steel mill closures take months to show benefits, and general air pollution legislation can be seen in terms of years. Many studies found benefits before the end of their follow-up (Schraufnagel et al 2019).

## APPENDIX D - OFF-TARGET EFFECTS

It is possible that vaccines using live viruses or bacteria can defend against other infections ("off-target" effects) (eg: Aaby et al 2012). Put simply, the immune response to the particular vaccine stimulates a general improvement in the immune system.

The basic evidence is that children given a specific live vaccine are less likely to be hospitalised or die from other infections. However, not everybody agrees, the vaccinated children might be healthier for other reasons (Moyer 2019).

Immunisation primes the body to make anti-bodies to the specific infection (using "adaptive immunity"), but it may stimulate the general response of "innate immunity" (Moyer 2019). For example, the BCG improves the immune response to yellow fever virus (Arts et al 2018).

## APPENDIX E - WOMEN AND CLINICAL TRIALS

There are concerns that generally women are under-represented in clinical trials. Smeaton et al (2020) considered this issue with reference to HIV clinical trials in the USA. The researchers explained: "US federal law requires research funded through the National Institutes of Health to include women as participants in clinical research as appropriate to the scientific goals, and to ensure that confirmatory trials of interventions report a valid analysis of whether treatment effects differ by sex" (Smeaton et al 2020 p1300).

Smeaton et al (2020) found that less than one-fifth of participants were female.

"Individuals interested in trial participation must complete a formal, in-person screening process to assess whether they meet trial eligibility criteria and to provide informed consent. These persons may fail to enrol (often called screen-out or screen failure), due to not meeting entry criteria, choosing not to participate after learning about trial requirements or other reasons" (Smeaton et al 2020 p1300). There is always concern that treatments are potentially dangerous to pregnant women, and the fear that participants may be or become pregnant without intending, which "may create a higher barrier to recruitment, and impose burdens during trial participation due to contraceptive cost, side effects, or inconvenience" (Smeaton et al 2020 p1300).

Smeaton et al (2020) reviewed 31 clinical trials related to HIV medication in the USA between 2003 and 2013. There was no difference between men and women screened out (ie: not eligible for participation) nor opting out. So, it seems that less women come forward to participate, which may be a product of the means of recruitment. The researchers recommended recruitment procedures that approached more women.

## APPENDIX F - PERSONALISED AND PRECISION MEDICINE

"Personalised medicine" (PeM) refers to the "personalisation" of drug treatments, say - ie: "the matching of drug choice and dosage to genetic markers of individuals that were related to drug metabolism" (Prainsack 2020 p1). However, in practice, it focused on groups. "Assuming that people who shared more of their common ancestry also shared more of their DNA variants, racial and ethnic labels were often used for patient stratification when it was too costly or too onerous to test individual patients for the presence of absence of relevant markers" (Prainsack 2020 p1).

In response to the criticism of over-emphasis on genetic information alone, the term "Precision Medicine" (PrM) has been used. "This term conveys the current trend towards a more granular stratification of patients in prevention, diagnosis, and treatment without being vulnerable to the critique that it promises to truly 'personalise' medicine..., and without the baggage of race-based stratification (which does not mean, of course, that racial and ethnic biases are absent from Precision Medicine)" (Prainsack 2020 p1).

PrM requires large amounts of data about the individual, including genetic, electronic health records, social media information, and personally collected information (eg: wearing portable devices).

Prainsack (2020) questioned "openness" [29] with PeM and PrM. "The increasing availability of online tools and platforms – and, as a whole, 'the Internet – has been imbued with the hope of democratising social and political life by giving wider ranges of people access to these tools and practices that used to be reserved for a small professional or political elite... An often-cited example for this is the way in which patients can access medical information about their or their family members' health problems that used to be restricted to libraries or academic conferences that were inaccessible to them. Much of this information is still practically unavailable to many patients because the information is locked behind paywalls or because patients lack the social, educational, digital, or other means to access the information" (Prainsack 2020 p2).

She summarised the conception of openness and PeM and PrM as "wide and shallow": "It is wide because almost everything involved in Personalised and Precision Medicine – from data to processes to tools – should be open to access to 'the public'. It is shallow because it does not invite asking the hard questions, such as who is excluded from this imagined public that data, tools, and infrastructures should be open to, and who benefits from such openness. It also tends to reduce questions about privacy—namely people's right to control what others know about them and an ingredient of personal autonomy – to compliance with data protection rules and fails to see it as a political value that is of key importance for people and for society as a whole" (Prainsack 2020 p3).

Prainsack (2020) outlined three types of openness in PeM and PrM:

i) Ontological and epistemological - This relates to the understanding of the "person". "At a technical level, the person is considered 'open' in the sense that the data-rich characterisations of individuals do not mean much unless they are compared with others (Prainsack 2015). For example, the assessment of what is 'normal' or 'healthy' at the level of individual biomarkers is contingent on the prior establishment of a norm that is determined on the basis of information from other people" (Prainsack 2020 p3). But who makes up the others ("reference population") to which the individual is compared? The social aspects of the individual (which Prainsack 2017 called "social biomarkers") are often ignored in the mass of data about health, yet social factors are crucial to health.

At a wider level of society, Prainsack (2020) noted

[29] Prainsack and Leonelli (2018) stated: "To be open is typically associated with being transparent, responsible, accountable, inclusive" (quoted in Prainsack 2020).

that "while certain expensive interventions such as whole-body scans or expensive cancer drugs may have marginal, but positive benefits in terms of health outcomes, the systemic harm for a society that channels resources into developing tools that few will be able to afford is something that should be measured against these benefits. If we are serious about the openness of values in connection with Personalised and Precision Medicine, we need to find new understandings and metrics for value in healthcare that include more strongly, and more systematically, factors that patients consider valuable" (p4).

ii) Pluralistic - This is openness related to the individual's and society's perspectives. "These perspectives and values should not merely be seen as the fluffy stuff around the 'hard' data, but they need to be included in a systematic way in designing healthcare provision and also in healthcare decision-making. As part of this endeavour, it is necessary to go to patients, family members, healthcare professionals, and other people working at the coalface of healthcare and ask them what data and information might matter. In other words, we must harness the information that emerges from what Chang and Lee [2018] call 'interpersonal medicine'" (Prainsack 2020 p4).

iii) Emancipatory - With the digitalisation of healthcare has come "the rise to power of new corporate actors... While it could be argued that the influx of new actors into the healthcare domain brings a much-needed fresh thinking into this field, this process also creates an intricate net of new dependencies and constraints. As Linsey McGoey [2015] argued for the domain of global health, the advocacy and investment of philanthropic organisations led by business entrepreneurs and other individuals has problematic effects in that they concentrate power in places where power is already condensed, and it also moves decision-making power and responsibility away from public actors who are democratically legitimised and publicly accountable to organisations that are accountable only to their shareholders" (Prainsack 2020 p5). One upshot of this is the question of whether corporations that gain financial value from data should pay individuals for its use.

Openness in PeM and PrM is as much about what is hidden, for Prainsack (2020) - the assumptions of the individual and "healthiness", the importance of "non-medical" factors in health, and the power of corporations. She ended: "A truly-open Personalised and Precision Medicine needs to protect people who cannot, or do not want to, comply, who refuse prevention or interventions, or who do other things that may not seem

responsible. We also need to be open to people creating their own practices and institutions around health and wellbeing" (Prainsack 2020 p6).

## APPENDIX G - ADVERSE EFFECTS

Live attentuated vaccines (LAVs) use weakened versions of the disease, and so they are not advised for immuno-compromised (IC) individuals "because of a low risk, based on clinical evidence or theoretical considerations, that the partially attenuated vaccine strain could revert to the wild-type form and cause disease. At the same time, individuals with IC conditions need vaccines because they are at an increased risk of severe infections. In cases where alternatives to live vaccines are not available for individuals with IC conditions, the risk of potential adverse events from the vaccine must be weighed against the risk of disease from the wild-type pathogen" (Varghese et al 2017 p46).

Establishing the size of the IC population is not easy. Kemper et al (2002) made a "back of the envelope" calculation of ten million in the USA in 2001 (3.6% of the total population) when considering the case for a smallpox vaccine in that country. This calculation was "based solely on the sum of the numbers of organ transplants, individuals with diagnosed and undiagnosed human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) and patients with cancer" (Varghese et al 2017 p46).

Varghese et al (2017) tried to produce a better estimate using eleven IC conditions, and published studies on the prevalence of these conditions. Sufficient data were found only for the USA and the UK. For 2012, it was estimated that 7.6 m adults in the USA (3.2% of population), and 1.7 m in the UK (3.5%) had one of the IC conditions. Not all individuals with these conditions would be IC, depending, for example, on the use, dosage and duration of immune-suppressive drugs.

The estimate of 2-3% of a population being IC is, Varghese et al (2017) pointed out, "meant as a starting point for understanding the magnitude of the need for alternatives to LAVs. Although the numbers and percentages appear to be reasonable for the UK and the USA, and therefore perhaps also for upper-income countries in general, they may not be accurate for individual countries, especially lower-income countries" (p48).

## APPENDIX H - CASE-CONTROL AND OTHER DESIGNS

### H1. Doll and Hill (1950)

Doll and Hill (1950) produced one of the first reports on tobacco smoking and carcinoma of the lung using the case-control method (appendix H1). Seven hundred and nine cases, recruited from London hospitals, were interviewed, and 709 controls with diseases other than cancer (comparable by age and gender) also. Details of smoking habits were collected for both groups.

The cases were more likely to be cigarette smokers (compared to non-smokers) than the controls, and to show "a slight tendency to start smoking earlier in life, to continue longer, and to be less inclined to stop..." (Doll and Hill 1950 p743).

The authors stated that "there seems to be no doubt that there is a direct association between smoking and carcinoma of the lung..." (Doll and Hill 1950 p744). But, even so, Doll and Hill (1950) considered and dismissed alternative explanations.

i) Unrepresentative sample of cases - Between April 1948 and October 1949, 2370 cancer cases were treated by twenty London hospitals. Individuals over 75 years old were removed, along with cancers other than the lung, and other miscellaneous reasons (eg: unable to speak English; too ill), which left 709 cases. Doll and Hill (1950) stated that "there is no reason to suppose that they were anything other than a representative sample of the lung-carcinoma patients attending the selected London hospitals" (p744).

ii) The controls not comparable - The controls were comparable in age (equal numbers of cases and controls in each five-year age band), and gender (same number of male cases and controls - 649 - and females 60), and "sufficiently comparable" in social class (using the Registrar General's classification), but "not wholly comparable" for place of residence (eg: more cases than controls from rural districts and smaller towns outside London). "Clearly this feature cannot have accounted for the observation that the lung-carcinoma patients smoked more" (Doll and Hill 1950 p744).

Nor that the smoking habits of non-cancer patients was different to that of the cases, or that the interviewers disproportionately selected light smokers as controls. The selection of controls occurred before details were known about their smoking habits.

iii) Cases exaggerated their smoking habits because they believed it was the cause of their disease - No evidence for this, partly because a number of cases only knew they had a respiratory illness at the time of

interviews.

iv) Bias by the interviewers - The four female interviewers (who were not the two named male researchers) did know who was a case or a control before the interview. One test of bias was cases who were later (after the interview) found to have been misdiagnosed. If so, "the smoking habits of the patients thought incorrectly to have carcinoma of the lung would have been recorded as being like those of the true lung-carcinoma subjects and not the same as those without carcinoma of the lung" (Doll and Hill 1950 p745). There was no evidence of "appreciable bias" here.

**H2. Yusuf et al (2005)**

Yusuf et al (2005) performed a large-scale case-control study on obesity and the risk of heart attack (myocardial infarction; Myo). The cases were 15 152 individuals selected within 24 hours of presenting with their first Myo (without a history of heart or major health problems), while the 14 820 controls were age-matched (within five years of age) and gender-matched [30]. "The first control per case was an attendant or relative of a patient from a non-cardiac ward or an unrelated (not first-degree relative) attendant of another cardiac patient. A second control per case was selected from those at the same centre with illnesses not obviously related to coronary heart disease or its risk factors" (Yusuf et al 2005 p1640).

The final sample was 12 461 cases and 14 637 controls recruited from 262 hospitals in fifty-two countries.

Each participant completed a structured questionnaire (covering demographic factors, lifestyle and risk factors, like smoking, diet, and family history of Myo), and underwent a physical examination (including body mass index (BMI), and waist and hip circumference measurement).

Obesity was linked to Myo. Increased waist-to-hip ratio (WHR) best predicted increased risk of Myo, more so than BMI, waist or hip circumference. For every one standard deviation increase in WHR, the risk of Myo increased 1.37 times (compared to 1.10 for BMI and 1.19 for waist circumference).

[30] Known as the INTERHEART study.

## H3. Barreto et al (1997)

Around the world, death rates from motor-vehicle injury are particularly high for young males, and the usual risk factors are speed, intoxication, and low level of safety (eg: not wearing a seat belt) (Barreto et al 1997). But Barreto et al (1996) found exceptionally high deaths and injuries from motor vehicles among a cohort of Brazilian steelworkers in Minas Gerais state.

Barreto et al (1997) performed a nested case-control study (ie: sub-samples within a cohort study) to understand the reasons for the twofold excess risk of deaths compared to drivers in the general population. The original cohort (n = 21 816) comprised all male workers at one steel plant employed between 1st January 1977 and 31st August 1990 (with follow-up to 30th November 1992).

The cases (n = 145) were all workers who died of motor-vehicle injury (in cars, lorries, and motorcycles) (as drivers, passengers, or pedestrians) while employed at the plant in the study period. Four controls from the cohort were chosen for each case based on year of birth (ie: age-matched) (n = 553). Information was collected about the participants via personnel and medical records.

The significant risk factors for motor vehicle-injury death were (a) being unmarried/single, and (b) hearing impairment/exposure to high levels of noise at work. The former can be explained by riskier behaviours by single men (and fits with previous research).

But (b) was the risk factor not previously reported in research. Barreto et al (1997) offered the explanation that "individuals who are constantly exposed to noise might not be attentive to hazardous sounds when driving or crossing roads, and there are reports of psychological reactions to noise such as nervousness and insomnia. Those working in noisy areas might also be less attentive to velocity, since perception of speed seems more related to sound than vision" (Barreto et al 1997 p820).

The use of personnel and medical records was both a strength and a weakness.

(+) Records taken at the time and so no issue with recall of information and potential bias.

(-) Records depended on the accuracy of those making them, and in keeping them up-to-date (eg: marital status). But this would be true for both cases and controls (Baretto et al 1997).

## H4. Prospective Studies

Longitudinal cohort studies allow researchers to follow a group of individuals forward through time to see

who develops it and how a disease progresses.

In the UK there are five main long-term cohort studies (Johnson et al 2015):

i) 1946 Medical Research Council National Survey of Health and Development (NSHD) - 5362 singleton births in one week in March 1946 in England, Scotland and Wales (Wadsworth et al 2006).

ii) National Child Development Study (NCDS) - 17 638 individuals born in one week in March 1958 in England, Scotland and Wales (Power and Elliott 2006).

iii) British Cohort Study (BCS70) - 17 287 individuals born in one week in April 1970 (Elliott and Shepherd 2006).

iv) Avon Longitudinal Study of Parents and Children (ALSPAC) - 15 444 births to women living in a former county (Avon) in south-west England (Boyd et al 2013; Fraser et al 2013).

v) Millennium Cohort Study (MCS) - 18 818 individuals born in 2000-02 in England, Scotland, Wales and Northern Ireland (Hansen 2012).

Johnson et al (2015) used data from all five cohort studies combined to understand overweight and obesity patterns in the last 50-60 years. In total, data were available on 56 632 participants.

The average adult was becoming overweight at a younger age with the more recent the data, and "cohorts born after the 1980s already had probabilities of overweight and obesity in childhood that were two to three times greater than those for cohorts born before the 1980s" (Johnson et al 2015 p11). The body mass index (BMI) (ie: weight (kg) divided by height squared ($m^2$)) was the measure of overweight and obesity used (BMI 25.0-29.9 $kg/m^2$ = overweight; 30 and above ($kg/m^2$) = obese).

Another well-known cohort study in the UK is that of male civil servants (aged 40-54 years old) begun in 1967 (known as the Whitehall study). A second cohort was added in the 1980s which included women (Whitehall II study).

These cohorts showed health inequalities not related directly to poverty, but to employment grade. A ten-year follow-up in the Whitehall study found differences in mortality between the highest and lowest grades (eg: Marmot et al 1984). All workers had stable employment, and none were in "absolute poverty as usually understood" (Marmot et al 1991 p1387).

The Whitehall II study included all men and women

aged 35-55 working in the London offices of twenty civil-service departments between 1985 and 1988 (n = 10 314). A detailed questionnaire was completed that included information about health, work characteristics, and socio-demographics, and there was a health screening (eg: blood pressure) (Marmot et al 1991).

The lower the job status (categorised as six grades), the higher the prevalence of heart disease, and greater self-perceived illness, for example (Marmot et al 1991).

## Appendix H1 - Smoking and Mortality

Based on Doll and Hill's (1950) work in the UK, and a small number of others around the same time (eg: Levin et al 1950 in USA), longitudinal prospective studies were started. One such involved British doctors and began in 1951. Findings were reported soon afterwards (Doll and Hill 1954), then intermittently (eg: Doll and Peto 1976; 20 years). Doll et al (2004) outlined fifty years of data (based on the final questionnaire in 2001).

"The decision that this study would be conducted among doctors was taken partly because it was thought that doctors might take the trouble to describe their own smoking habits accurately, but principally because their subsequent mortality would be relatively easy to follow, as they had to keep their names on the medical register if they were to continue to practise. Moreover, as most doctors would themselves have access to good medical care, the medical causes of any deaths among them should be reasonably accurately certified" (Doll et al 2004 p1).

The study began with 34 439 male doctors, and data were available on 31496 in 2001. Overall, lifelong daily smokers died on average ten years younger than lifelong non-smokers. Smoking cessation was beneficial in terms of life expectancy - doctors who stopped at age 50, for instance, gained around six years (compared to continuing smokers), and stoppers at 40 years old gained around nine years.

The men born between 1900 and 1930, when exposure to cigarettes at a young age was high (eg: low cost cigarettes to army conscripts in the UK), who smoked throughout their lives were twice as likely to die in middle age than lifelong non-smokers.

## APPENDIX I - UK BIOBANK

### I1. Chronotype

Norbury (2020) began with a succinct overview: "Circadian rhythms are near-24-hour oscillations that have been observed throughout the brain and body. Set by

the master pacemaker in the suprachiasmatic nucleus (SCN) the circadian timing system synchronises peripheral clocks throughout the body to adapt and optimise physiological processes in response to changes in the environment" (p1).

Add to this, "diurnal preference" (or chronotype), known as morningness ("lark") or eveningness ("owl"). Research has linked these chronotypes to health outcomes (eg: type 2 diabetes and eveningness), personality traits (eg: conscientiousness and morningness), and cognitive processes (eg: attention, memory) (Norbury 2020).

Neuroimaging technology has been used to investigate the brains of the chronotypes (eg: grey matter volume differences in different parts of the brain in younger adults) (Norbury 2020).

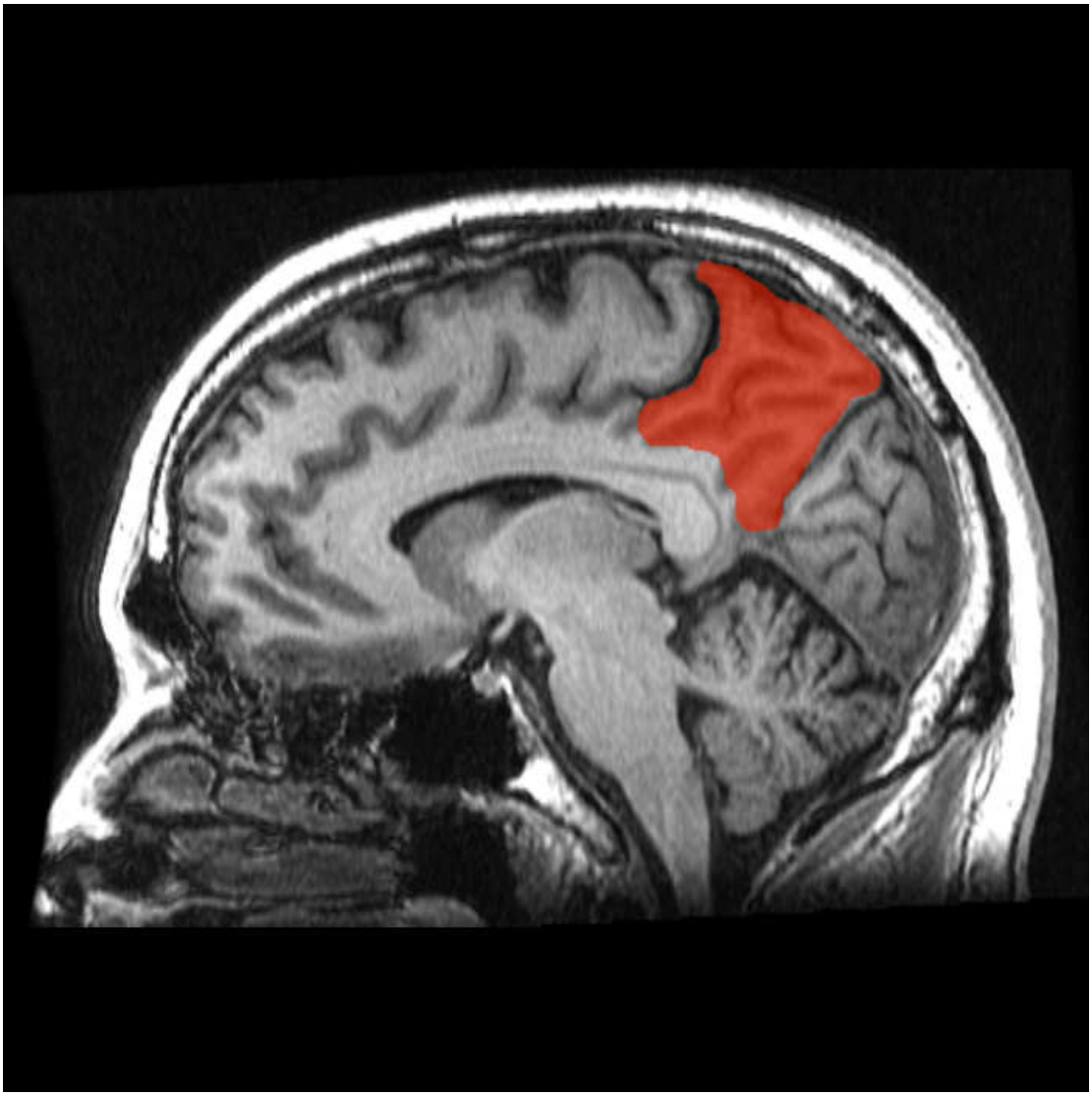
Norbury (2020) concentrated on older adults (average age in mid-50s) with data from the UK Biobank. Diurnal preference was established by one question, "Do you consider yourself to be definitely a morning person/more a morning than an evening person/more an evening person than a morning person/definitely an evening person?". Those chose "definitely" a morning person (n = 2780) or an evening person (n = 950) were the focus. Grey matter volume from 900 of each group were compared.

As hypothesised (based on previous research), "definite eveningness was associated with greater grey matter volume in precuneus (figure 2). Exploratory results (hypothesis-generating) revealed that eveningness was also associated with greater grey matter volume in bilateral thalamus and striatum and orbito-frontal cortex. There were no regions of greater grey matter volume in morning-types as compared to evening types" (Norbury 2020 p4).

These findings are observations, which means causation (and the direction of causation) are not definitely established [31]. However, reduced grey matter volume in the precuneus has been associated with pro-social traits in other research, and morningness has been correlated with co-operativeness, for example (Norbury 2020). Norbury (2020) commented: "Together, the current work and previous imaging studies indicate the precuneus as an important anatomical substrate for diurnal preference in young and older adults and may underlie the proclivity for morning-types to engage in more pro-social behaviours" (p4).

Norbury (2020) continued: "Increasing evidence also suggests that eveningness is associated with indices of risk and reward and here eveningness was associated with

[31] Norbury (2020) admitted: "It is possible that other factors not measured here (eg: diet, social jetlag) impacted on the current findings. Nevertheless, well powered longitudinal studies are required to determine causality and the potential temporal effects of eveningness on brain structure" (p5).



(Source: Geoff.B.Hall; dedicated by owner to public domain)

Figure 2 - Position of precuneus (coloured red) using MRI scan.

increased grey matter volume in a network of regions strongly implicated in risk and reward function [eg: striatum]" (p4).

**I2. Sex Differences**

The mechanisms within the body that regulate circadian rhythms (eg: suprachiasmatic nucleus) differ between males and females (Anderson and Fitzgerald 2020).

Studies with hamsters, for example, (eg: Davis et al 1983) placed into constant darkness found "shorter free-running periods among females, indicating that their core molecular clock machinery oscillates faster than that of males. Females also showed significantly earlier onset of

activity and responded differently to stimuli that shift the intrinsic timing of the circadian clock" (Anderson and Fitzgerald 2020 p1164).

Real-life data from the UK Biobank (eg: Lyall et al 2018) has confirmed differences in humans.

Oestrogen is believed to play a role in the differences (Anderson and Fitzgerald 2020).

**I3. Alcohol Consumption**

Alcohol consumption between two individuals in a long-term romantic relationship is similar. Howe et al (2019) offered four possible explanations for this observation:

i) "Assortative mating" - Individuals who are similar find each other and stay together.

ii) "Social homogeny" - Another factor explains the similarity in behaviour (eg: Socio-economic status).

iii) "Partner interaction effects" - After pairing, the behaviour of the partners come to mirror each other.

iv) "Relationship dissolution" - Only individuals similar in behaviour remain together.

Howe et al (2019) explored another possibility based on the observation that spouse-pairs are "on average more genetically similar across the genome than non-spouse-pairs. Genotypes implicated in the aetiology of height, education, blood pressure and several chronic diseases have been shown to be correlated within spouse-pairs" (p2). Could alcohol behaviour, which has a heritable component, be similarly explained? These researchers analysed UK Biobank data on over 47 000 spouse-pairs.

Self-reported alcohol use was collected, as well as relevant genetic data.

It was found that an individual's alcohol consumption and the presence of a particular gene (ADH1B) linked to alcohol consumption were associated with the partner's. The researchers argued that the presence of this particular gene in the genome of the partners accounted for "a substantial proportion" of the similarity in alcohol consumption. This suggested that gene variation is behind "assortative mating", but other explanations "cannot be completely ruled out" (Howe et al 2019).

Note that the spouse-pairs were identified in the data indirectly (eg: reporting same information about household) as the UK Biobank does not hold explicit spouse information (Howe et al 2019).

## I4. Prostate Cancer

Perez-Cornago et al (2017) investigated the risk of prostate cancer with data from 219 333 men in the UK Biobank cohort. Baseline measures were taken for the 40-69 year-olds in 2006-10, and follow-up continued until 2014. All men were cancer-free at baseline [32].

There were 4575 cases of prostate cancer during follow-up. A number of significant associations were found with the cases. An increased risk existed for individuals with a family history of prostate cancer, having an enlarged prostate, and ever having had a prostate-specific antigen (PSA) test. Ethnicity was also important with being Black associated with an increased risk, but being Asian a lower one. The risk was also lower with higher body mass index, currently smoking, having diabetes, and never having had sexual intercourse. Physical activity, and alcohol consumption, for example, had no association with prostate cancer risk.

A number of the lowering risk factors were surprising, like weight and smoking, and may have been due to "detection bias" (ie: these individuals are less likely to have a PSA test). The researchers admitted further: "Despite the breadth of the exposure information collected at recruitment, we cannot exclude the possibility of residual confounding by unknown or unmeasured factors. In addition, because of the number of tests performed, some of the associations observed might be due to chance. For some of the rare exposures (eg: red hair colour or never having had sexual intercourse), there are small numbers of exposed cases for robust analysis" (Perez-Cornago et al 2017 p1569).

Using the same sample, Monroy-Iglesias et al (2020) found no link between metabolic syndrome and prostate cancer. Metabolic syndrome includes a combination of obesity, diabetes, and high blood pressure.

But an inverse association was found between risk of prostate cancer and high blood sugar level. The researchers noted that unidentified factors or pathways explained this finding.

# APPENDIX J - ALGORITHMS

"Data mining" is "the area of applied mathematics that tries to extract information from large datasets, often stored in huge computer databases" (Tovar et al 2012 p593). Machine learning can be used in different ways with large datasets, including (Tovar et al 2012):

[32] The sample is around 95% White (Monroy-Iglesias et al 2020).

- Clustering (or unsupervised learning) - to find associations between data points.

- Supervised learning - algorithms are given "a set of data points (data samples) with known properties (features) and the classes they belong (labels)" (Tovar et al 2012 p595). After learning the algorithm is applied to the whole dataset.

Tam Cho and Cain (2020) offered this warning: "As technology advances, computers are able to digest progressively larger quantities of data per time unit. Yet more computation is not equivalent to more fairness. More computation fuels an increased capacity for identifying patterns within data. But more computation has no relationship with the moral and ethical standards of an evolving and developing society. Neither computation nor even an equitable process guarantees a fair outcome" (p1179).

Coronary artery disease risk could be associated with certain facial features (eg: earlobe crease, facial wrinkle, grey hair), and Lin et al (2020) developed an algorithm for prediction purposes. Facial photographs of nearly 6000 patients in China were used for training and testing of the algorithm. The accuracy was around 80%.

Gilligan-Lee (2020) described a situation where an algorithm trained on hospital admissions data in the 1990s predicted that patients with pneumonia were more likely to survive if they also had asthma (which was the opposite to medical knowledge). "It turned out that the algorithm had missed a crucial piece of the puzzle. Doctors treating pneumonia patients with asthma were passing them straight to the intensive care unit, where the aggressive treatment significantly reduced their risk of dying from pneumonia. It was a case of cause and effect being hopelessly entangled" (Gilligan-Lee 2020 p32).

## APPENDIX K - MORAL INJURY

"Individuals who are exposed to traumatic events that violate their moral values may experience severe distress and functional impairments known as 'moral injuries'" (Griffin et al 2019 p350).

Litz et al (2009) described moral injury as caused by events that involve "perpetrating, failing to prevent, bearing witness to, or learning about acts that transgress deeply held moral beliefs and expectations" (quoted in Griffin et al 2019 p350). These events are called "potentially morally injurious events" (PMIEs), and the concept has primarily been applied in military-

related situations like killing enemy combatants, failing to prevent suffering to innocent parties, or betrayal by an individual in a position of power. Though the concept is applicable outside the military situation (Griffin et al 2019).

Griffin et al (2019) reviewed 116 articles on moral injury. "In sum, individuals exposed to PMIEs appear to be at greater risk of developing psychiatric symptoms than those not exposed" (Griffin et al 2019 p351).

Social, cultural and interpersonal consequences have also been reported, like perceived and actual rejection by loved ones, and loss of trust in others. Other studies suggested religious/spiritual consequences, like doubting one's beliefs and questioning one's purpose, and a few studies noted stress-related physical effects (Griffin et al 2019). Table 7 gives some examples of studies included in the review.

- Wisco et al (2017) - 564 US military veterans of Iraq and Afghanistan wars. Individuals classed as experiencing PMIEs were more likely to report psychiatric symptoms than those not exposed to PMIEs.
- Maguen et al (2010) - US military veterans of the Iraq war who killed enemy combatants and non-combatants were more likely to experience subsequent relationship problems than non-killers.
- Korinek et al (2017) - "North Vietnamese" military and civilian survivors of the Vietnam war exposed to killing had psychological symptoms eg: post-traumatic stress disorder) and physical problems (eg: arthritis) in late adulthood (appendix K1).

Table 7 - Examples of studies of moral injury and PMIEs.

The studies in the review had methodological limitations including "the absence of a consensus definition of moral injury, disagreement about what does and does not constitute a potentially morally injurious event, lack of a theoretically comprehensive and psychometrically sound measure of morally injurious outcomes, minimal study of moral injury outside of military-related contexts, and clinical investigations weakened by small sample sizes and unclear mechanisms of therapeutic effect" (Griffin et al 2019 p355).

In summary, Griffin et al (2019) offered two continua by which to understand moral injury - "(a) the extent to which individuals appraise themselves as having committed moral violations, leading to perpetration-based symptoms and (b) the extent to which individuals appraise themselves as victims of another's transgressive behaviour, leading to betrayal-based problems" (p355).

## Appendix K1 - Korinek et al (2017)

"Moral conflict-coloured injury" was the term coined by Litz et al (2009) to describe moral injury afflicted on "civilians in war zones, and women among them, if, for instance, they survived mass violence when others perished, or if they were unable to save children's lives in the face of wartime violence and deprivation" (Korinek et al 2017 p1092). These are "scars" then - "harm received to one's moral centre as a result of things experienced, seen, and done" (Drescher and Foy 2008 quoted in Korinek et al 2017).

Korinek et al (2017) studied the North Vietnamese or Vietnam People's Army side from the Vietnam war using data from the 2010 Vietnam Health and Ageing Pilot Study (VHAPS). This involved 405 respondents in the Red River Delta area, who were at least 55 years old in 2010.

The contributing variables in the study were war exposure, and family-related stressors. The former included having experienced combat, having killed or seriously injured another human being, or having witnesses mass violence/atrocities. Family-related stressors included prolonged separation from spouse, and/or less of a child.

Overall, 43% of the sample experienced disabling arthritis, and 38% at least one symptom currently of post-traumatic stress disorder (PTSD). Both these conditions were higher in individuals with war exposure than not, and who had experienced family-related stressors. Loss of a child had a greater impact on women, and having killed another person had a greater effect on men. This latter points fits with "recent conceptualisations of moral injury as a distinctive, particularly detrimental, element of the combat experience that weighs upon soldiers in their post-conflict lives" (Korinek et al 2017 p1099).

Korinek et al (2017) accepted two key limitations to their research: "First, a more complete enumeration of distress events in a larger sample, such as one incorporating details of combat exposure, would yield more robust and generalisable results and provide greater insight into stress exposure-health physiological pathways. Second, we are ill-equipped to determine the timing of arthritis onset and whether respondents are reporting upon rheumatoid arthritis (which has been examined in association with PTSD in veterans), osteoarthritis, or some combination of conditions" (p1100).

# 11. ADDENDUM



## 11.1. TIMING OF COVID-19 TRANSMISSION

Ferretti et al (2020) emphasised the importance of having a "temporal profile of infectiousness in relation to the onset of symptoms" (pp1-2). This includes the fraction of transmissions when the infected individual is non-symptomatic (ie: before symptoms appear - pre-symptomatic; or when symptoms do not develop - asymptomatic). Symptomatic individuals are easier to identify both by the self and by others, and isolation is an effective strategy. The non-symptomatic individuals are harder to control for.

What fraction of covid-19 transmissions are by asymptomatic individuals? Early indirect evidence from China and Europe suggested less than half of infections (Ferretti et al 2020). But this fraction is "difficult to measure in an unbiased manner; in addition, it is likely dependent on the age of infected individuals and therefore time- and population-specific" (Ferretti et al 2020 p2).

A temporal profile of infectiousness is crucial in relation to the effectiveness of contact tracing strategies. Epidemiologists distinguish four time intervals in infection (figure 3) (Ferretti et al 2020):

a) Incubation period - From infection to symptom onset. Ferretti et al (2020) calculated a mean of 5.7 days from various datasets [33].

b) Serial interval - From symptom onset in person 1 (infector; index case) to symptom onset in person 2 (infectee; secondary case). A mean of 4.1 days (Ferretti et al 2020).

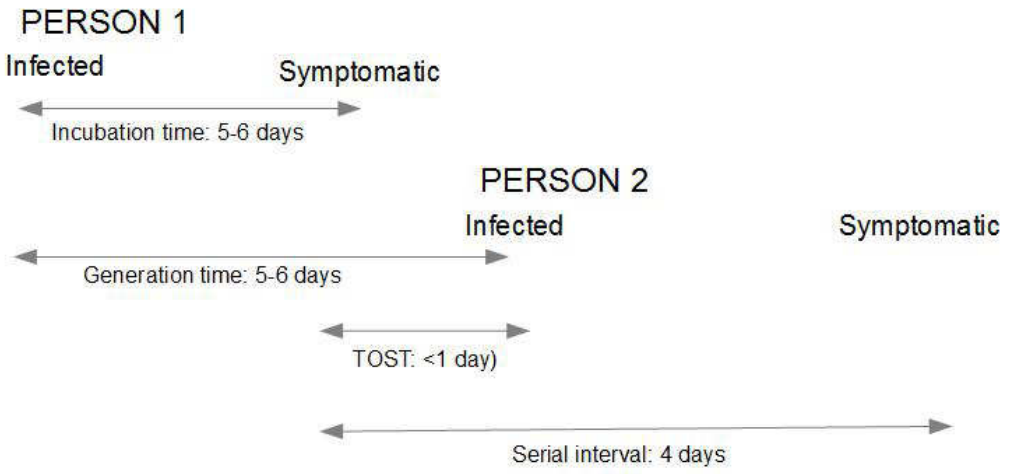
c) Generation time - From infection of person 1 to infection of person 2. A mean of 5.5 days was calculated by Ferretti et al (2020).

d) Time of onset of symptoms to transmission (TOST) - From onset of symptoms to transmission of the disease. This was less than 1 day for covid-19 (Ferretti et al

[33] Ferretti et al (2020) used data from other studies, in China mostly, which included 191 pairs of individuals where transmission of covid-19 had occurred and 2740 control pairs (with no transmission).

2020).

"These four time intervals are delimited by four key time points: the time at which an individual gets infected, the time at which they infect another individual, the times at which the source develops symptoms and at which the recipient does" (Ferretti et al 2020 p3).




(Based on figure 1A Ferretti et al 2020)

Figure 3 - Time intervals in infectiousness and covid-19 means calculated by Ferretti et al (2020).

Ferretti et al (2020) considered three alternative hypotheses for the timing of infectiousness:

i) Infectiousness depends on the time since infection (irrelevant of symptoms developing).

ii) Infectiousness depends on the onset of symptoms (irrelevant of time since infection).

iii) Infectiousness depends on the onset of symptoms, but increases with time since infection.

From analysis of the data, the findings, Ferretti et al (2020) explained, "confirm the observation that for individuals that eventually develop symptoms, the period of SARS-CoV-2 infectiousness is directly related to onset of symptoms rather than being independent of it [ie: not (i) above]. For symptomatic individuals, most transmission events occurred in a range of a few days before and after onset of symptoms. More than 5 days before symptom onset, infectiousness appeared to decrease below a tenth of its peak value, and we observed only a

few percent of transmissions beyond 5 days after symptom onset" (p6).

Further analysis found that 41% of transmissions to be pre-symptomatic, and 35% of transmissions were 0-1 days after symptom onset (ie: the same day and day after). Ferretti et al (2020) stated: "According to our results, perfect isolation of cases from onset of symptoms would stop twice as many transmissions compared to isolation from the second day after onset of symptoms, relative to a baseline with no intervention at all (excluding transmissions from fully asymptomatic individuals). Self-isolation of symptomatic individuals is therefore especially important for the first two days" (p10).

They continued: "Instant, universal, and perfect self-isolation, including from family members, is challenging, given the low specificity of early COVID-19 symptoms and the high prevalence of respiratory viruses with similar symptoms between autumn and spring... Nevertheless, if low-cost good practices that are widely advisable irrespective of symptoms - wearing a face mask, increasing spatial distance, practicing enhanced hygiene (especially hand hygiene), and limiting social contacts (including staying away as much as possible from offices, schools, public transport, and closed public spaces) - were followed strictly at the first onset of symptoms, even if mild, this could have a substantial impact on the epidemic. Such a policy would greatly depend on compliance and collaboration from the public. Symptom tracker apps... could play a role in enhancing public awareness of mild COVID-19 symptoms and compliance. As a further advantage, this policy could also reduce the burden of other respiratory viruses" (Ferretti et al 2020 p10).

These researchers also recommended increasing backward-contact tracing further (ie: 4-5 days before symptom onset) (Ferretti et al 2020).

## 11.2. FIRST-GENERATION VACCINE [34]

Peiris and Leung (2020) noted the "popular assumption" that the first-generation covid-19 vaccine will reduce transmission of SARS-CoV-2, and "lead to a resumption of pre-covid-19 'normalcy'" (p1). These authors suggested that this idea may be "based on illusory assumptions".

For example, the vaccine may only reduce pathology, symptoms, and/or viral load, which could leave the

[34] Written 28th September 2020.

possibility of re-infection. And/or the length of protection might be time-limited. The vaccine may not stop virus transmission even if the individual has no illness (Peiris and Leung 2020).

There is also the question of who should be preferentially allocated vaccine - namely, people at high risk of severe morbidity and mortality. The National Academies of Sciences, Engineering and Medicine (2020), in the USA, identified other criteria for allocation, including mitigation of health inequities, fairness, and transparency (Peiris and Leung 2020). Also "risks of acquiring infection and of negative societal impact. Front-line health-care and essential workers, such as school teachers, belong in both these latter groups" (Peiris and Leung 2020 p1).

Furthermore, "if international travel were to fully recommence, vaccine allocation to different countries with varying means of access will require careful deliberation, based on moral grounds and because no country will be truly protected from COVID-19 until virtually the entire world is" (Peiris and Leung 2020 p2).

Vaccine hesitant individuals could influence the overall success of a vaccine. Models suggest that 25-50% of the population need to be immune to the virus to suppress community transmission, and successful vaccines, according to the World Health Organisation, are recommended to reduce the disease risk by at least 50% (Peiris and Leung 2020).

Peiris and Leung (2020) concluded that vaccines are needed if the impact on transmission is limited. This is because "first-generation vaccines are only one tool in the overall public health response to COVID-19 and unlikely to be the ultimate solution that many expect" (Peiris and Leung 2020 p2).

## 11.3. IMMUNE PROFILING [35]

SARS-CoV-2 enters the cell via human angiotension-converting 2 (ACE2). The immune system has various mechanisms by which to detect pathogens and respond. But if these responses are not controlled in duration and amplitude, "emergency haematopoiesis" leads to organ dysfunction (also via the "cytokine storm") (Mann et al 2020).

However, this abnormal immune response only occurs in some covid-19 patients. Mann et al (2020) investigated this response with data from four hospitals in Greater Manchester, England (Coronavirus Immune Response and

[35] Written 28th September 2020.

Clinical Outcomes (CIRCO) study). Seventy-three adult patients hospitalised between 29th March and 7th May 2020 were recruited and blood samples were taken and analysed. Specific changes in the immune system could be measured, and used to predict disease severity.

Mann et al (2020) noted changes in the innate immune system that were linked to an "over-reaction" to covid-19. Other studies have suggested that "defects in adaptive immunity" were the cause (Mann et al 2020).

Importantly for treatment, the "features of an exaggerated immune response are present early after hospital admission suggesting immune-modulating therapies would be most beneficial at early timepoints" (Mann et al 2020 p1).

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