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COVID-19: MORE KNOWLEDGE?
(October - End of 2020)

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1. INTRODUCTION

Writing in mid-October 2020, Hamzelou et al (2020) stated: "We have now been living with SARS-CoV-2, the virus that causes covid-19, for the best part of a year. In that time, our knowledge has expended dramatically, but there is still so much we don't know - and even when we think we know things, the science can change fast" (p12).

Writing at the same time, Alwan et al (2020) summarised the "current evidence-based consensus": "SARS-CoV-2 spreads through contact (via larger droplets and aerosols), and longer-range transmission via aerosols, especially in conditions where ventilation is poor. Its high infectivity, combined with the susceptibility of unexposed populations to a new virus, creates conditions for rapid community spread. The infection fatality rate of COVID-19 is several-fold higher than that of seasonal influenza, and infection can lead to persisting illness, including in young, previously healthy people (ie: "long covid"). It is unclear how long protective immunity lasts, and, like other seasonal coronaviruses, SARS-CoV-2 is capable of re-infecting people who have already had the disease, but the frequency of re-infection is unknown. Transmission of the virus can be mitigated through physical distancing, use of face coverings, hand and respiratory hygiene, and by avoiding crowds and poorly ventilated spaces. Rapid testing, contact tracing, and isolation are also critical to controlling transmission" (p1) [1].

Stone et al (2020) responded to claims about the world today: "While many speak of these as unprecedented times, they are not. Humans have experienced many other pandemics, and the questions of how, why, when and where have been the subject of much research from historical, archaeological and biological perspectives. Such questions, however, are not limited to pathogens that have caused pandemics; we know that even 'everyday' pathogens and parasites have had long-term evolutionary consequences on our genome and our history. For example, pathogens such as those causing the flu, measles, diarrhoea, tuberculosis and the plague have had large effects on human populations and our domesticates. In turn, human practices, including subsistence patterns and technology, have impacted our resident microbes, their ecology, with varied health outcomes" (p1) (table 1).

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[1] Houser (2020) used the term "infowhelm" to describe the situation where there is so much (new) scientific information on a certain topic that it can become detrimental. She said: "What I was capturing with that term is a deluge in which knowledge can be changing a lot, and then people in power can be poking holes in it. This creates a very difficult 'information situation' for us to process and understand" (quoted in Vince 2020).

- Stone et al (2020) explained how ancient biomolecules, like DNA (and RNA [2]), provide information "to model the evolution of infectious pathogens and to show how the interaction of the macro-world and the microbial world leaves behind an array of physical legacies that provides novel information for understanding ancestral lifeways and biology" (p1).

- Research on ancient pathogens began in the 1990s, but it has been boosted in the last decade by technological developments "in such areas as DNA extraction, DNA capture, library construction [3], and bioinformatics [4] as well as the adoption of next-generation sequencing and new methods in proteomics [5]" (Stone et al 2020).

- The problem for researchers is that extracting biomolecules from ancient skeletal and mummified remains is difficult because, Stone et al (2020) explained, "the total amount of these biomolecules is small even in a heavily infected individual and environmental contaminants can challenge our ability to identify causative agents of disease" (p1).

- Stone et al (2020) ended: "Whether studying the biology of an individual microbe or a community of organisms, ancient biomolecular research lays the foundation for understanding evolution of pathogens and the shaping of our microbial self. There can be little doubt that our globalised society and socio-political character, provided a framework for the SARS-CoV-2 pandemic. Yet, to understand the nature of this framework and to predict similar threats, microbial research profits from historical and prehistoric contextualisation" (p3).

Table 1 - Ancient biomolecules.

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[2] RNA translates genetic code into protein-assembling instructions (Brody 2020). It was once thought to exist only in cells, but it is now known that extra-cellular RNA (exRNA) travels to tissues throughout the body in tiny lipid sacs (extra-cellular vesicles) in the bloodstream (Brody 2020) . There is interest in tracking exRNA as an early warning sign for disease, and tests are being developed (Dolgin 2020).

[3] Eg: a gene library.

[4] The application of computer technology to biological information.

[5] The study of proteins, particularly related to genes.

2. EPIDEMIOLOGY [6]

2.1. INDIA

Epidemiological studies measure the number of cases (prevalence) of a disease in a population, and the number of new cases (incidence) over a particular period of time. Such studies of covid-19 have been undertaken in China (eg: Zhou et al 2020 [7]), Italy (eg: Grasselli et al 2020 [8]), and the USA (eg: Lewnard et al 2020 [9]). Laxminarayan et al (2020) reported the fist such study in a low- and middle-income country, namely India.

The study concentrated on two southern states, Andhra Pradesh and Tamil Nadu, with over 120 million residents in total. They are "among the states with the largest healthcare workforces and public health expenditures per capita, and are known for their effective primary healthcare delivery models. Both states initiated rigorous disease surveillance and contact tracing early in response to the pandemic. Procedures include syndromic surveillance and SARS-CoV-2 testing for all individuals seeking care for severe acute respiratory illness or influenza-like illness at healthcare facilities; delineation of 5 km 'containment zones' surrounding cases for daily house-to-house surveillance to identify individuals with symptoms and daily follow-up of all contacts of laboratory-confirmed or suspect covid-19 cases, with the aim of testing these individuals 5-14 days after their contact with a primary case, irrespective of symptoms, to identify onward transmission" (Laxminarayan et al 2020 p1).

Laxminarayan et al (2020) analysed this surveillance and contact tracing data up to 1st August 2020. The overall case fatality rate was 2%, but this ranged from 0.05% of children and adolescents to 17% of adults aged 85 years and above. Males had a higher risk of death in all age groups. At least one co-morbidity (eg: diabetes) was found in around two-thirds of the covid-19 fatalities (which compared to one-fifth in the USA in official data in April-May 2020; Laxminarayan et al 2020).

The cases in these two states had a younger age distribution

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[6] Written on 13th October 2020.

[7] The study involved 191 patients in Wuhan province who were discharged or died by 31st January 2020.

[8] This study from the Lombardy region for the period 20th February to 18th March 2020 included 1591 patients.

[9] This study covered 1840 patients before 22nd April 2020 in hospitals in Southern and Northern California, and Washington state.

than in the USA (Laxminarayan et al 2020). The researchers attempted to explain this finding: "Imperfect surveillance systems may have contributed to under-ascertainment of cases among older adults, although this circumstance is unexpected given strong public and clinical awareness of covid-19 and the predisposition of older adults to severe disease. Case-based surveillance may likewise under-estimate attack rates among younger adult age groups in high-income settings. It is plausible that stringent stay-at-home orders for older Indian adults, coupled with delivery of essentials through social welfare programmes and regular community health worker interactions, contributed to lower exposure to infection within this age group in Tamil Nadu and Andhra Pradesh. Our finding may also reflect survivorship bias if older adults in India are at disproportionately low risk for SARS-CoV-2 infection in comparison to the general population, for instance as a result of higher socio-economic status" (Laxminarayan et al 2020 p4).

Other key findings included that secondary infections were less common generally (ie: an infected individual transmits the virus to a healthy person), and that children had a high prevalence of the infection. The former point needs to be seen in the context that only 20% of tracing data were analysed. "Another limitation was the lack of data on timing of exposure and symptoms onset in relation to testing dates; this necessitated assumptions about identification of true index cases. More robust temporal data would reduce the dependence on such assumptions, provide greater insight into the directionality of transmission, and reduce risk for misclassification of infection status among contacts with positive or negative results at the time of testing" (Laxminarayan et al 2020 p4).

2.2. RISK FACTORS

The COVID-19 Host Genetics Initiative (2020) has analysed the human genome, and found that genes on chromosome 3 were significantly associated with severe covid-19. The difference between two variants of the genes is around one and half times more likely to be hospitalised (Zeberg and Paabo 2020) [10] [11]. This study compared 3199 hospitalised patients and their controls.
Zeberg and Paabo (2020) investigated the genes on chromosome 3 further, and found that the genomic segment is inherited from

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[10] The whole-genome sequence of SARS-CoV-2 was shared online as early as 11th January 2020 (Watson 2020).

[11] Sequencing the versions of the virus in a particular country, say, can help in following lines of transmission. Microbiologist, Torsten Seemann explained the benefits: "For example, the sequence data helped to resolve the true source of exposure for one health-care worker [in Australia], proving that they contracted the virus at a social event and not from a patient in hospital. That information prevented the need for an investigation into a possible outbreak at the hospital" (quoted in Watson 2020).

Attempts to sequence all versions is limited as symptomatic individuals will be missed. Also it is a technology available only to high-income countries (Watson 2020).

Neanderthals. This segment occurs in South Asia at a frequency of 30% compared to less than 10% in Europe, East Asia, and the Americas. The role of these Neanderthal genes as a contributing risk factor is seen in that "individuals of Bangladeshi origin in the UK have about two times higher risk to die from covid-19 than the general population" (Zeberg and Paabo 2020 p2).

Zeberg and Paabo (2020) had no explanation for their findings: "It is currently not known what feature in the Neanderthal-derived region confers risk for severe COVID-19 and if the effects of any such feature is specific to SARS-CoV-2, to other coronaviruses or to other pathogens" (p2).

Children are much less likely to experience severe covid-19 than adults [12]. Explanations for this difference include a stronger immune response, or some immunity from recent exposure to similar viruses (Cyranoski 2020).

Varga et al (2020) suggested that the difference was due to children having healthier arteries. SARS-CoV-2 can infect endothelial cells in blood vessels, which causes malfunctioning in adults, and blood clotting and inflammation-related complications. "The endothelium is typically in much better condition in children than in adults" (Cyranoski 2020 p325).

Varga et al's (2020) study was based on three adults, of whom two died (Cyranoski 2020).

2.3. DEATHS

Measurement of the number of deaths from covid-19 varies between countries [13]. Such figures also ignore the indirect effects of the pandemic with individuals who die from non-covid conditions, but because they did not receive treatment that they would have in non-pandemic times. So, a better measure overall is seen as excess deaths (ie: the number of total deaths in a set period compared to the average for that period of time in the past) [14].

Kontis et al (2020) analysed data from 21 industrialised countries for mid-February to the end of May 2020 (15 weeks) (and compared them with the previous five years for the same period). It was estimated that around 206 000 more people died than if there had been no pandemic.

This overall figure hid differences between the countries,

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[12] An exception is PIMS-TS (appendix A).

[13] The number of deaths is also a topic of modelling. Coronavirus simulation and modelling depends on underlying computational code, which should allow replication. An example is the Imperial College London model which predicted in mid-March 2020 that no official response in the UK to covid-19 would lead to half a million deaths (Ferguson et al 2020 quoted in Chawla 2020). Criticisms of the code used have been made, particularly in relation to replication. Though this has been done subsequently (Chawla 2020).

[14] McPherson et al (2020) warned about the "twin killers" of heat and covid-19 because the same individuals are vulnerable to both. "Heatwaves could make covid-19 shelter-in-place policies dangerous, for example, if elderly people or those with low incomes do not have air conditioning" (McPherson et al 2020 p32).

which the researchers distinguished as four groups:

- No detectable rise in all-cause mortality (eg: New Zealand).
- Low effect (eg: Switzerland).
- Medium effect (eg: France).
- Highest increase in all-cause mortality (eg: England and Wales, and Scotland).

Kontis et al (2020) outlined the main findings thus: "Taken across all 21 countries, the number of excess deaths from all causes was 23% (7-38%) higher than the number of deaths assigned to COVID-19 as underlying cause of death. The difference between all-cause excess and COVID-19 deaths was largest in Spain and Italy, where all-cause excess deaths were 69% (47-90%) and 46% (14-77%), respectively, higher than deaths assigned to COVID-19. This difference might be due to a combination of undetected infections, whether or not deaths from 'suspected COVID-19' (based on clinical symptoms) are assigned to COVID-19, and some increase in mortality from other diseases due to reductions in acute and chronic care. In contrast to Italy and Spain, the overall (all-cause) number of excess deaths was smaller than deaths assigned to covid-19 in France, Belgium and Switzerland. This situation might have arisen because some countries have assigned any death in a person with confirmed or suspect SARS-CoV-2 infection to COVID-19; some of these deaths might have been in patients with multiple existing chronic conditions who already had a high risk of dying. Finally, there might have been a reduction in deaths from influenza and other respiratory infections because of reduced contact among people, as well as a decline in traffic injuries, falls and violence as people spent more time at home" (pp4-5).

The researchers later admitted that "we are not yet in a position to provide an overall unified explanation for the observed quantitative differences among countries, if such a task is ever possible. Rather, the reasons are likely to lie in complex interactions of the social, economic, environmental and health system features of each country and specific events and responses that promote or suppress transmission" (Kontis et al 2020 p6).
However, they speculated about three key groups of variables:

i) Baseline characteristics of the population and their communities - eg: general health of the nation; inequalities; environmental factors like housing.

ii) The official response policies to the pandemic - eg: lockdown; routine services closure; timing and length of these events.

iii) Preparedness, resilience and flexibility of health services - eg: test and trace systems; ability to continue

providing non-covid life-saving services; hospitalisation and discharge policies (Kontis et al 2020) .

2.4. INEQUALITIES AND SYNDEMIC

There is a belief that covid-19 "does not discriminate" (as a British politician said in March 2020), but this is a myth argued Bambra et al (2020).
These authors structured their argument in three parts:

i) Inequalities in pandemics generally - Historical studies of the 1918 Spanish influenza pandemic, for example, have found inequalities in prevalence and mortality between high- and low-income countries, between rich and poor within each country, and between urban and rural settings.

ii) Covid-19 is a "syndemic pandemic" - "A syndemic exists when risk factors or co-morbidities are intertwined, interactive and cumulative — adversely exacerbating the disease burden and additively increasing its negative effects: 'A syndemic is a set of closely intertwined and mutual enhancing health problems that significantly affect the overall health status of a population within the context of a perpetuating configuration of noxious social conditions' [Singer 1996]" (Bambra et al 2020 p965) (appendix B).
Put simply, an individual does not become infected with covid-19 in a vacuum, but in a context of their lives, including the political, economic and environmental conditions (eg: housing; food and diet; access to services), and health-related practices and co-morbidities (Bambra et al 2020). These factors are often described as the "social determinants of health" [15].

iii) The consequences of covid-19 - "The impact of covid-19 on health inequalities will not just be in terms of virus-related infection and mortality, but also in terms of the health consequences of the policy responses undertaken in most countries" (Bambra et al 2020 p966). For example, an "emergency lockdown" will be experienced differently again in the context of an individual's life (eg: loss of income and job; overcrowding; key worker roles). There may also be longer term mental health consequence.
"So, the health consequences of the covid-19 economic crisis are likely to be similarly unequally distributed — exacerbating heath inequalities" (Bambra et al 2020 p966).

Along similar lines to Bambra et al (2020), Horton (2020) commented that the response to SARS-CoV-2 has tended to narrowly focus on the virus, and has ignored its interaction with "an array

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[15] Uzoigwe (2020) raised concerns about a single composite R (reproduction) number for covid-19 when there is great diversity in impact based on ethnicity, say.

of non-communicable diseases (NCDs)" (eg: hypertension, obesity, diabetes) [16].

"These conditions are clustering within social groups according to patterns of inequality deeply embedded in our societies. The aggregation of these diseases on a background of social and economic disparity exacerbates the adverse effects of each separate disease. COVID-19 is not a pandemic. It is a syndemic" (Horton 2020 p874) [17].

Horton (2020) continued: "The most important consequence of seeing COVID-19 as a syndemic is to underline its social origins. The vulnerability of older citizens; Black, Asian, and minority ethnic communities; and key workers who are commonly poorly paid with fewer welfare protections points to a truth so far barely acknowledged — namely, that no matter how effective a treatment or protective a vaccine, the pursuit of a purely biomedical solution to covid-19 will fail. Unless governments devise policies and programmes to reverse profound disparities, our societies will never be truly covid-19 secure" (p874) [18].

2.4.1. Specific Studies

OpenSAFELY was a study of over seventeen million adults' health records in England, of which over 10 000 had covid-19-related deaths (between 1st February and 11th May 2020) (Williamson et al 2020). Risk of covid-19-related death was strongly associated with age (over 80 years old, in particular), being male, Black and minority ethnicity (BAME), living in a deprived neighbourhood, obesity, and co-morbidity (eg: asthma, diabetes).

The researchers described the findings as a "preliminary picture" of the demographic characteristics that impact covid-19 outcome, but they cautioned against claims of causality.

Table 2 summarises the key strengths and weaknesses of OpenSAFELY.

ICNARC (2020) reported 1233 patients critically ill with confirmed covid-19 between 1st September and 15th October 2020 in England, Wales and Northern Ireland. These patients were compared with 10 900 confirmed cases up to 31st August 2020 in terms of demographics, including:

i) Age - mean in both cases 58-59 years old.

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[16] Bukhman et al (2020) went further and talked of "NCDI poverty", where "I" stands for injuries that disproportionately impact poorer individuals.

[17] "A syndemic is not merely a co-morbidity. Syndemics are characterised by biological and social interactions between conditions and states, interactions that increase a person's susceptibility to harm or worsen their health outcomes. In the case of COVID-19, attacking NCDs will be a prerequisite for successful containment" (Horton 2020 p874).

[18] Singer et al (2017) observed: "A syndemic approach provides a very different orientation to clinical medicine and public health by showing how an integrated approach to understanding and treating diseases can be far more successful than simply controlling epidemic disease or treating individual patients" (quoted in Horton 2020).

Strengths	Weaknesses
1. Size of the sample. 2. Use of primary care patient records which provide more detail that covid-19 hospital admission records. 3. Controlling for deaths from non-covid-19 causes.	1. "Covid-19-related death" was not always based on a confirmed test. 2. The sample may not have been fully representative of the population of England (Williamson et al 2020). 3. Dependent on the accuracy of patient records.

Table 2 - Key strengths and weaknesses of the OpenSAFELY study.

    ii) Gender - 70% male in both cases.

    iii) Ethnicity - Around two-thirds White in both cases (around 80% of total population), but around one-fifth Asian (covering heritage from south Asia - 13% of the total population of the three countries) (table 3) (which was increasing) (figure 1).

- White: White – British; White – Irish; White – any other.

- Mixed: Mixed – white and black Caribbean; Mixed – white and black African; Mixed – white and Asian; Mixed – any other.

- Asian: Asian or Asian British – Indian; Asian or Asian British – Pakistani; Asian or Asian British – Bangladeshi; Asian or Asian British – any other.

- Black: Black or black British – Caribbean; Black or black British – African; Black or black British – any other.

- Other: Other ethnic group – Chinese; Any other ethnic group.

(Source: ICNARC 2020)

Table 3 - Ethnicity categories used in 2011 Census.

    iv) Deprivation - Half of cases in both sets of data from the most deprived two quintiles (ie: 40% of total population) using postcodes and Index of Multiple Deprivation (IMD) (figure 2).

    v) Body mass index - Towards half of cases classed as obese (from 30% of total population) (ie: BMI >30) (figure 3) [19] [20].

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[19] BMI is calculated as weight (kg) ÷ height (m)².

[20] Body mass index (BMI) can be a poor measure for individuals with bone structure and muscle mass that produces high weight (eg: weightlifters), and thus high BMI that may appear as obese (BMI >30). On the other hand, some athletes (eg: long-distance runners) can have a very low BMI, and thus appear as underweight (BMI <18.5) (Best
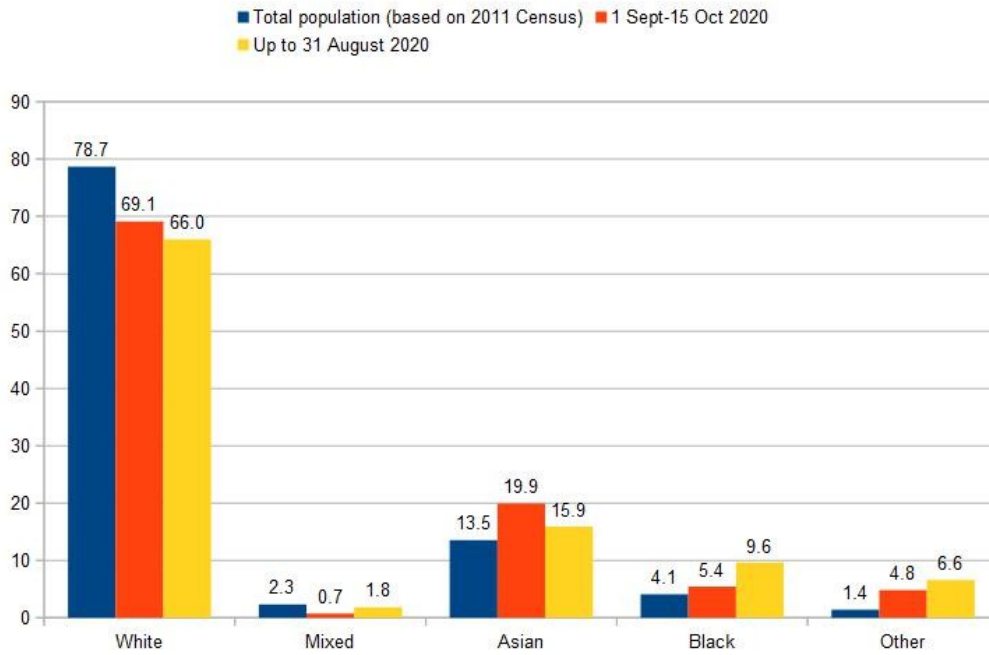
Figure 1 - Confirmed covid-19 hospitalised cases based on self-reported ethnicity in England, Wales, and Northern Ireland (%).
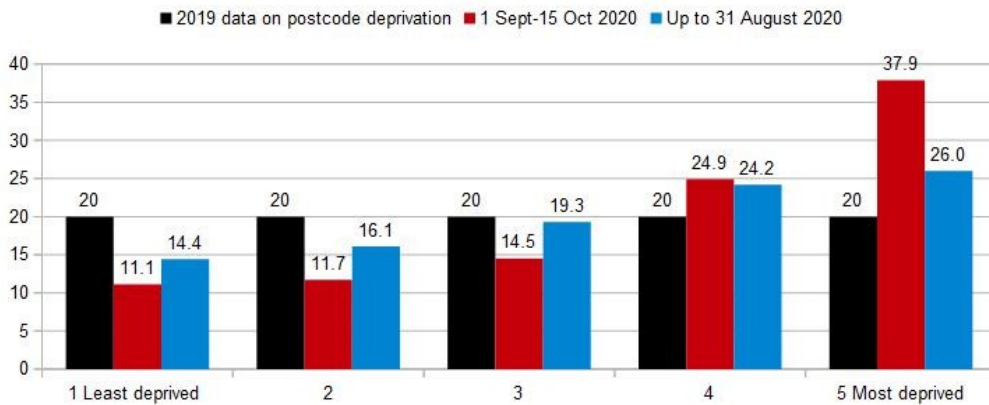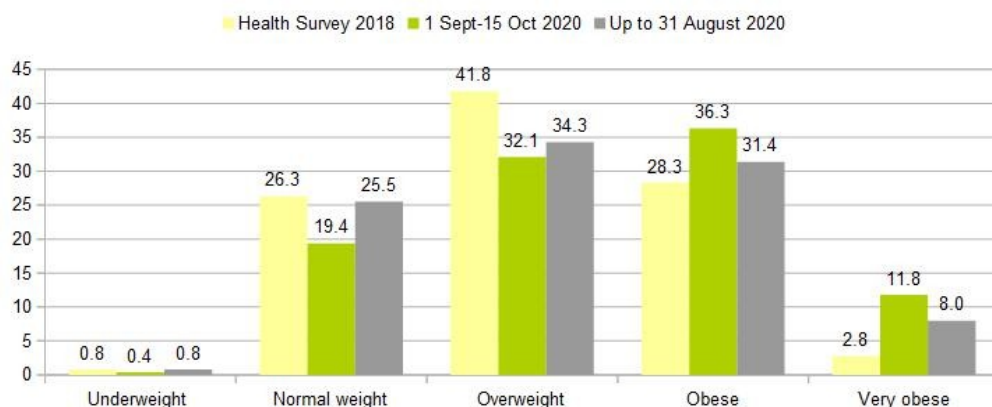
Figure 2 - Confirmed covid-19 hospitalised cases based on postcode deprivation quintiles in England, Wales, and Northern Ireland (%).

2020).

(Underweight = BMI <18.5; normal weight = 18.5 - <25; overweight = 25 - <30; obese = 30 - <40; very obese = ≥40)

Figure 3 - Confirmed covid-19 hospitalised cases based on body mass index (BMI) categories in England, Wales, and Northern Ireland (%).

2.5. OTHER HEALTH PROBLEMS

A very small number of covid-19 cases have "spontaneously developed diabetes after being infected with SARS-CoV-2" (eg: German student, "Finn Gnadt) (Mallapaty 2020c p17).

The following lines of evidence provide support for these observations (Mallapaty 2020c):

a) Severe covid-19 cases arriving in hospital with extremely high levels of blood sugar and ketones, which are signs of not enough insulin to break down the sugar.

b) Organs in the body involved in controlling blood sugar have high levels of ACE2, and it is receptors for this protein that are used by SARS-CoV-2 to enter cells.

c) Various viruses, including SARS-CoV-2, have been linked to autoimmune conditions, of which type 1 diabetes is one.

d) Laboratory-grown pancreas organoids.

Research on the impact of covid-19 on the organs of the body has used organoids (miniature laboratory-grown organs. "Virologists typically study viruses using cell lines or animal cells cultured in a dish[1]. But these don't model SARS-CoV-2 infection well because they don't mimic what happens in the body, say researchers. Organoids better demonstrate what SARS-CoV-2 does

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to human tissue... They can be grown to include multiple cell types, and take the shape of the original organ in weeks... They're also less expensive than animal models, and avoid the ethical concerns they pose" (Mallapaty 2020b p15).

But the limitation is that in the body organs "crosstalk" between each other, and organoids do not have this process (Mallapaty 2020b).

There are a number of questions that arise from these observations including (Mallapaty 2020c):

i) Does SARS-CoV-2 induce type 1 diabetes or a new variant of the disease?

ii) Is this sudden-onset diabetes a permanent change?

iii) Are the cases individuals who were on the way to developing type 2 diabetes and covid-19 speeds up the progress?

iv) What is the exact physiological mechanism by which SARS-CoV-2 triggers diabetes? For example, the virus triggers an extreme inflammatory state, and this damages organs like the pancreas and the liver, and their ability to detect/respond to insulin (Mallapaty 2020c).

Gastro-intestinal complications have been observed in critically ill covid-19 patients, but whether these are "a manifestation of critical illness in general or is specific to covid-19 remains unclear" (El Moheb et al 2020 p1899). El Moheb et al (2020) attempted to clarify this issue with a comparison of critically ill patients with or without covid-19.

The data came from the the Massachusetts General Hospital in the USA - covid-19 cases between 13th March and 7th May 2020, and matched non-covid-19 cases from 2018 and 2019. The matching was based on characteristics like age, gender, smoking, body mass index, and co-morbidities.

Covid-19 patients with acute respiratory distress syndrome (ARDS) were significantly more likely to develop gastro-intestinal complications (74% of 92 individuals) than non-covid-19 ARDS patients (37% of 92).

El Moheb et al (2020) stated: "High expression of angiotensin-converting enzyme 2 receptors along the epithelial lining of the gut that act as host-cell receptors for SARS-CoV-2 could explain involvement of abdominal organs" (p1901). However, there were differences between the two groups in use of drugs (eg: opioids), say, that could explain the findings (El Moheb et al 2020).

3. IMMUNE SYSTEM AND VACCINATION

3.1. IMMUNE SYSTEM OVERVIEW

"The mammalian immune system is a remarkable sensory system for the detection and neutralisation of pathogens" (Pulendran and Davis 2020 p1582). However, much of the knowledge about this system has come from animal models, in particular, rats, mice, and fruit flies (Pulendran and Davis 2020).

Immunologists have come to rely on genetically inbred strains of mice in recent years. "In such mice, the immune system can be studied without the confounding effects of genetic variability, and genes can be deleted or over-expressed in a given tissue or cell type. However, these mice are genetically homogeneous and are usually housed in abnormally hygienic and specific pathogen-free (SPF) environments. Hence, they are far from ideal models for the immune system of humans" (Pulendran and Davis 2020 p1).

The applicability of treatments in such models to humans is always debated. Successes in non-humans, but not when used with humans has been called the "valley of death" (Pulendran and Davis 2020).

There is a move to follow the advice of Sydney Brenner in 2008, who said: "We don't have to look for a model organism anymore. Because we are the model organisms" (quoted in Pulendran and Davis 2020). The advent of "omics" technologies has helped (eg: proteomics (analysis of proteins and genes); transcriptomics (studying of RNA)), and the growing knowledge about genes [21]. For example, the "omics" technologies have "enabled scientists to probe the immune response to vaccination in a comprehensive way, by analysing the cellular and molecular networks driving immune response to vaccination. These omics technologies can measure changes in cellular subsets, transcriptome, metabolome, or epigenome, even at the single-cell level. Coupling these with computational approaches developed to analyse and interpret such data has led to the generation of the new field of 'systems vaccinology'. The aim of systems vaccinology is to comprehensively analyse the immune response to vaccination with a view to defining new mechanisms and correlates of protective immunity" (Pulendran and Davis 2020 p3).

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[21] These technologies are part of changing described as "bioeconomy" (appendix C).

Peter Medawar (1969 quoted in Pulendran and Davis 2020) referred to humans as the "obstinately diverse species". This summed up the great variety in humans through demographic, socio-economic, and environmental differences (eg: from malnutrition to obesity). "These wide disparities no doubt impinge on the physiological states of humans and on variations in their immunological states in particular. This in turn is likely to affect responses to vaccination or susceptibility to inflammatory diseases" (Pulendran and Davis 2020 p6). This point is important when there is a temptation to focus so much on genes.

Pulendran and Davis (2020) ended: "we are firmly convinced that human immunology will form an ever-larger part of the field going forward. This does not mean that the work with mice will disappear. It is too valuable a system built up over 70 years for that; it presents too many excellent opportunities for well-controlled, mechanistic experiments and will remain an absolutely essential part of biology. But exploration of the immune system in humans offers both a much more direct link to medicine (eg: translation) and the very real prospect of discovering new immunological phenomena, with thousands of diseases and the genetic diversity that come with a more true-to-life immune system" (p8).

3.2. INFECTION

Virus transmission has a period between the release from the infected host to the uptake by a new host. The viability (infectiousness) of the virus at this time depends upon key environmental factors like temperature and humidity [22], particularly when "waiting" on a surface.

Morris et al (2020) studied SARS-CoV-2 in laboratory conditions at three relative humidities (RH) [23] (40, 65 and 85%) three room temperatures (10, 22 and 27 °C). Virus decay was measured (including water loss), but this is not the same as the ability to infect an individual.

Virus decay increased with temperature, but showed an inverted U-shape for RH (ie: fastest at 65% RH). So, for example, the virus could survive on a surface for 24 hours at 10 °C and 40% RH [24] compared to 90 minutes at 27 °C and 65% RH.

3.3. REINFECTION

Reinfection is a growing concern. Tillett et al (2020)

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[22] The amount of water vapour in the air.

[23] RH is higher in cool than warm air, and is defined as "the ratio of the partial pressure of water vapour to the equilibrium vapour pressure of water at a given temperature" (Wikipedia; https://en.wikipedia.org/wiki/Relative_humidity#Definition; accessed 9th November 2020, 10.23 GMT).

[24] This could explain the "observed superspreading events in cool indoor environments such as food processing plants" (Morris et al 2020 p2).

reported a case study of a 25 year-old man in Nevada, USA. The researchers explained: "The patient had two positive tests for SARS-CoV-2, the first on April 18, 2020, and the second on June 5, 2020, separated by two negative tests done during follow-up in May, 2020. Genomic analysis of SARS-CoV-2 showed genetically significant differences between each variant associated with each instance of infection. The second infection was symptomatically more severe than the first" (p1).

They continued: "These findings suggest that the patient was infected by SARS-CoV-2 on two separate occasions by a genetically distinct virus. Thus, previous exposure to SARS-CoV-2 might not guarantee total immunity in all cases. All individuals, whether previously diagnosed with COVID-19 or not, should take identical precautions to avoid infection with SARS-CoV-2. The implications of reinfections could be relevant for vaccine development and application" (Tillett et al 2020 p1).

This case has differences to the three reinfections previously reported in English [25] [26]. These involved a primary illness followed by a secondary one from the same virus strain, though genetic analysis was not necessarily performed in all cases (Tillett et al 2020).

Tillett et al (2020) speculated about the worse symptoms in the second infection of their case study with three possible reasons:

i) Higher dose of the virus the second time led to more severe symptoms.

ii) Reinfection occurred from a more virulent version of the virus, and/or for the patient.

iii) The immune system enhanced the virus's impact somehow the second time. "This mechanism has been seen previously with the beta-coronavirus causing severe acute respiratory syndrome" (Tillett et al 2020 p5).

The patient had "no immunological disorders that would imply facilitation of reinfection. They were not taking any immunosuppressive drugs. The individual was negative for HIV by antibody and RNA testing... and had no obvious cell count abnormalities" (Tillett et al 2020 p5).

The researchers considered an alternative hypothesis: "It is possible that we have reported a case of continuous infection entailing deactivation and reactivation. However, for such a hypothesis to be true, a mutational rate of SARS-CoV-2 would be

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[25] Hong Kong (To et al 2020), the Netherlands and Belgium (Van Elslande et al 2020), and Ecuador (Prado-Vivar et al 2020). Tillett et al (2020) performed a search of "PubMed", pre-print servers, and general news sources for the period 30th June to 9th September 2020 using keywords like "reinfection" and "secondary infection".

[26] The Ecuador case reported worse symptoms the second time, whereas the others had similar severity on both occasions (Tillett et al 2020).

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required that has not yet been recorded" (Tillett et al 2020 p5).

Tillett et al (2020) ended with a note of caution: "If our patient is a case of reinfection, it is crucial to note that the frequency of such an occurrence is not defined by one case study: this event could be rare. The absence of comprehensive genomic sequencing of positive cases in the USA and worldwide limits the advances in public health surveillance needed to find these cases" (p7).

3.4. MUTATIONS AND VARIANTS

Hodcroft et al (2020) stated: "Real-time genomic epidemiology allows us to track the spread of a pathogen through the mutations that accumulated in the genome during viral replication. The great majority of these mutations are of little functional relevance and merely serve as neutral markers that we can use to link related variants. Some mutations, however, are adaptive and increase in frequency because they increase the rate a which the virus transmits. Such adaptations are expected after a zoonosis when a pathogen is not yet fully adapted to its new host... or in endemic pathogens that escape pre-existing immunity, as is common for example in seasonal influenza viruses" (p7).

SARS-CoV-2 is changing as it spreads, but slowly compared to HIV, say (Callaway 2020a) [27]. One mutation of interest is known as the "D614G mutation", and it is related to the spike protein which helps the virus to penetrate human cells [28].

At the 614th amino-acid position of the spike protein, gene letter "D" (aspartate) was being replaced by "G" (glycine) (Callaway 2020a). The virus with the D614G mutation is predicted to be a more transmissible form of SARS-CoV-2 (Korber et al 2020a) (ie: it is a product of natural selection) [29] [30].

Korber et al (2020a) was a pre-print article (appendix D) and it caused media headlines about covid-19 becoming more dangerous. The peer-reviewed published article (Korber et al 2020b) made sure that any potentially alarmist language was not present (Callaway 2020a).

Grubaugh et al (2020) on the fact that this mutation/variant "now is the pandemic" (quoted in Callaway 2020a).

But subsequent work is not all in agreement about the

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[27] SARS-CoV-2 accumulates two single letter RNA mutations per month compared to 4 for influenza and 8 for HIV (Callaway 2020a).

[28] Over 12 000 mutations have been recorded by early September 2020 (Callway 2020). "Many mutations will have no consequence for the virus's ability to spread or cause disease, because they do not alter the shape of a protein, whereas those mutations that do change proteins are more likely to harm the virus than improve it" (Callaway 2020a p175).

[29] Two SARS-CoV-2 viruses from anywhere in the world vary by an average of 10 RNA letters (out of 29 903 in total) (Callaway 2020a).

[30] "Many researchers suspect that if a mutation did help the virus to spread faster, it probably happened earlier, when the virus first jumped into humans or acquired the ability to move efficiently from one person to another. At a time when nearly everyone on the planet is susceptible, there is likely to be little evolutionary pressure on the virus to spread better, so even potentially beneficial mutations might not flourish" (Callaway 2020a p175).

increased transmissibility of the D614G variant. In fact, "many scientists say there remains no solid proof that D614G has a significant effect on the spread of the virus, or that a process of natural selection explains its rise. 'The jury's out', says Timothy Sheahan, a coronavirologist at the University of North Carolina at Chapel Hill. 'This mutation might mean something, or it might not'" (Callaway 2020a p175).

Because of biosafety concerns with laboratory experiments that test the SARS-CoV-2 mutations, "pseudo-viruses" are used, like a genetically modified HIV that involves spike proteins to infect cells. The D614G mutation makes infection more efficient here. But this research has been criticised. For example, Nathan Grubaugh (viral epidemiologist) stated: "What's irritating are people taking their results in very controlled settings, and saying this means something for the pandemic. That, we are so far away from knowing" (quoted in Callaway 2020a).

Callaway (2020a) took up the point: "The pseudo-viruses carry only the coronavirus spike protein, in most cases, and so the experiments measure only the ability of these particles to enter cells, not aspects of their effects inside cells, let alone on an organism. They also lack the other three mutations that almost all D614G viruses carry. 'The bottom line is, they're not the virus', says [virologist Jeremy] Luban" (p176).

Other than gaining the knowledge about SARS-CoV-2 generally, mutations like D614G have implications if they become more or less affected by the immune system. Weisblum et al (2020), for example, has reported a mutation that "could help the virus to avoid some anti-bodies" (Callaway 2020a p177).

Hodcroft et al (2020) reported a variant of SARS-CoV-2 (20A-EU1) that was first observed in Spain in June 2020. The researchers were not sure if this variant was "increasing in frequency because it has an intrinsic advantage, or because of epidemiological factors" (Hodcroft et al 2020 p7). One key factor was holiday travel across Europe in the summer.

3.5. IMMUNE SYSTEM AND VACCINES

Comparing 659 patients with life-threatening covid-19 pneumonia with 534 asymptomatic or mild cases [31], Zhang et al (2020) found minor genetic differences related to the immune system between the two groups [32]. All participants had their whole genome sequenced.

Bastard et al (2020) found similar differences in a larger study involving 987 patients with life-threatening covid-19, 663 asymptomatic or mild cases, and 1127 healthy controls.

These two studies offer the possibility of screening covid-19 patients to identify the presence of the genetic mutations. And

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[31] The samples came from a number of global cohorts.

[32] Technically, the severely ill patients had mutations in interferon-related genes.

these "patients recovering from life-threatening covid-19 should also be excluded from donating convalescent plasma for ongoing clinical trial, or at least tested before their plasma donations are accepted" (Bastard et al 2020 p4).

Tortorici et al (2020) reported two ultra-potent neutralising anti-bodies, from among almost 800 taken from twelve individuals who had recovered from covid-19, that proved highly effective in protection against covid-19 experimentally in hamsters.

Different types of vaccines are being produced (Callaway 2020b) [33]:

i) Virus vaccines - Use the virus itself, either (a) in weakened form, or (b) inactivated chemically.

ii) Viral-vector vaccines - A genetically engineered non-coronavirus to produce coronavirus proteins, which can either (a) replicate, or (b) not.

iii) Protein-based vaccines - Use fragments of coronavirus proteins.

iv) Nucleic-acid vaccines - Genetic instructions to the body's cells to produce coronavirus proteins.

In each case, the aim is to get the immune system to recognise the coronavirus and/or its proteins, and to produce anti-bodies in response to a weakened attack, which will defend against the full attack of the virus.

The search for individuals to study when researching covid-19 has led to ongoing population-based cohort studies involving their participants. The search for anti-bodies has included the Rhineland Study in Germany, the Norwegian Mother and Child Cohort, and the UK Biobank (Abbott 2020).

Ward et al (2020) reported data from over 300 000 SARS-CoV-2 anti-body tests in England in June to September 2020 on the prevalence and persistence of anti-bodies. This was the REACT-2 Study, which used a randomly selected sample of adults from General Practitioners' records.
There was a decline in the proportion of the sample with detectable anti-bodies over the three rounds of testing. Ward et

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[33] Generally, developing a pharmaceutical from scratch is time-consuming (eg: ten years) and expensive (eg: 2-3 billion $US) (Corcoran and Schultz 2020). Corcoran and Schultz (2020) commented that "for every 5000 compounds made and tested, only one will become an approved drug. Indeed, a high-school basketball player is twice as likely to end up playing in the US professional league as any single compound tested in a drug-discovery programme is to become a marketed drug" (p592).

One solution is "late-stage functionalisation", where "previously prepared test compounds are decorated with new atoms in the hope of favourably adjusting their pharmacological properties" (Corcoran and Schultz 2020 p592).

al (2020) ended: "These data suggest the possibility of decreasing population immunity and increasing risk of reinfection as detectable anti-bodies decline in the population" (p12).

3.5.1. Self-Experimentation [34]

The testing of vaccines is time-consuming in terms of regulatory demands, and some groups (eg: "citizen scientists") have proposed self-experimentation ("DIY (do-it-yourself) vaccines") as a way to sidestep regulatory bodies, like the Federal Drug Administration (FDA) in the USA [35]. But Guerrini et al (2020) pointed out that this "belief is legally and factually incorrect, and the misunderstanding has potentially important public health implications. Any failure by the FDA to regulate DIY vaccines would permit vaccines of dubious safety and effectiveness to endanger public health and would signal a lowering of standards that — in an age blighted by vaccine scepticism and during a highly politicised pandemic — could undermine public trust in all vaccines, however developed. Further, some self-experimentation can qualify as human subjects research that is required to undergo ethics review, by law or institutional policy" (p1570).

One example is the "Rapid Deployment Vaccine Collaborative" (RaDVaC), and "its stated mission is a humanitarian one, animated by a belief that open, crowd-sourced vaccine efforts will hasten the widespread availability of a potentially life-saving vaccine through development activities that it believes are not subject to FDA regulation" (Guerrini et al 2020 p1570). This organisation has published online instructions on how to make and administer their "DIY vaccine" (Guerrini et al 2020) [36].

The potential harms related to "DIY vaccines" include (Guerrini et al 2020):

- Users having a false belief of immunity after vaccination and subsequently infecting others with covid-19 by not social distancing or isolating as appropriate.

- Users might be unwilling or ineligible for subsequent formal trials and vaccines.

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[34] Written 5th October 2020.

[35] Clinical trials of different drugs to treat covid-19, like anti-depressants, HIV and dementia medications, have struggled to recruit participants. Part of the problem is the rush to try and test drugs that get media attention, like hydroxychloroquine in April 2020 (Ledford 2020a). Clinical trials performed quickly, as in the case of much early covid-19 research, relied on "proprietary data gathered from medical centres... [and]... the raw data were not made available to other researchers" (Ledford 2020b p19).

[36] "1 Day Sooner", a "grass-roots effort" to develop a vaccine, was reported to have nearly 4000 potential volunteers for a human challenge trial (ie: infecting healthy individuals with covid-19 and then testing the vaccine) in April 2020 (News In Brief 2020).

- Risks of injury from the "DIY vaccine" as "a result of improper preparation, incorrect administration, or heightened allergic or other reactions. These risks raise questions about whether such users are able to give meaningful consent to a DIY vaccine" (Guerrini et al 2020 p1572).

Guerrini et al (2020) concluded: "During a pandemic, it is tempting to believe that an intervention that shows early promise has been 'proven enough' to justify widespread use. Those who are intellectually invested in an intervention may be especially so tempted, perhaps even deeming RCTs [randomised controlled trials], which randomise some participants to placebo, unethical. All scientists must resist the temptation to view the rigorous study of COVID-19 vaccine safety and effectiveness as a bureaucratic step that can be skipped. Research that enables us to confidently conclude that a vaccine is safe and effective will take time, whether or not it is overseen by the FDA. But that research, simply, is critical" (p1572).

3.5.2. Vitamin D

Vitamin D has drawn interest in relation to covid-19. Joliffe et al (2020) suggested that the "anti-viral and anti-inflammatory actions of vitamin D makes it an interesting candidate for prevention of viral respiratory infections" (quoted in Kmietowicz 2020). They advocated clinical trials with covid-19 as needed (appendix E).

Specific to covid-19, the National Institute for Health and Care Excellence (NICE) in the UK in a rapid review in June 2020 reported no evidence for vitamin D supplementation to reduce the risk or severity of the disease (Kmietowicz 2020).

3.6. VACCINE ALLOCATION

Emanuel et al (2020) outlined a reality that will soon arrive: "Once effective coronavirus disease 2019 (covid-19) vaccines are developed, they will be scarce. This presents the question of how to distribute them fairly across countries. Vaccine allocation among countries raises complex and controversial issues involving public opinion, diplomacy, economics, public health, and other considerations" (p1309) (table 4).

Ethics have to play a part in the distribution of the scarce resource. Emanuel et al (2020) proposed the "Fair Priority Model".

Fair allocation is important because of the concern over "vaccine nationalism" (Bollyky and Brown 2020) - ie: countries retaining vaccine developed within their borders, and/or competing to obtain as much of the vaccine developed elsewhere. The ethical basis used here is "national partiality: a country's right and

- Manufacture of sufficient vaccine is a "big worry" - ie: "supply constraints both physical and political" (Khamsi 2020 p579).

- The physical constraints relate to scaling up manufacturing infrastructure to produce the required vaccine in the numbers needed. A related "bottleneck" could be the ingredients (Khamsi 2020).

- Political constraints include payment of the manufacturers (eg: before production begins to help in scaling it up), as in "advanced market commitments" (an agreement to buy a certain amount of drugs at a certain price in the future). But such moves favour those countries who can afford it (Khamsi 2020).

Table 4 - Manufacture of the vaccines [37].

duty to prioritise its own citizens" (Emanuel et al 2020 p1309).

Unlimited national partiality, however, is not seen as ethical. Miller (2005) argued that "[A]ssociative ties only justify a government's giving some priority to its own citizens, not absolute priority" (Emanuel et al 2020 p1309). Reasonable national priority "does not permit retaining more vaccine than the amount needed to keep the rate of transmission (Rt) below 1, when that vaccine could instead mitigate substantial COVID-19-related harms in other countries that have been unable to keep Rt below 1 through ongoing public-health efforts" (Emanuel et al 2020 p1310).

The World Health Organisation (WHO) proposes a dose distribution proportional to a certain percentage of the population initially (eg: 3%). Once every country has down this, the next 3%, say, will be vaccinated, and so on. This is a population-based distribution (Emanuel et al 2020).

But this proposal does not take account of the differing disease burden in each country. Emanuel et al (2020) argued that "it would be unethical to allocate anti-retrovirals for HIV on the basis of population, rather than on HIV burden. Likewise, a fair distribution of COVID-19 vaccines should respond to the pandemic's differential severity in different countries" (p1312).

An alternative proposal by the WHO is to distribute vaccine based on the number of front-line health care workers, over 65s, and vulnerable individuals in a country. Emanuel et al (2020) were critical: "Preferentially immunising health care workers may not substantially reduce harm in higher-income countries where personal protective equipment effectively protects health workers. Instead, vaccinating those whose housing or occupation or age puts them at greatest risk of spreading infection, or people at highest risk of becoming infected, might best prevent harm" (p1312).

Emanuel et al (2020) outlined three fundamental values to consider in vaccine allocation:

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[37] SinoPharm in China reported adding capacity to make one billion doses of its coronavirus vaccine in 2021 ("Daily Telegraph" 22nd October 2020).

a) Benefiting people and limiting harm.

b) Prioritising the disadvantaged.

c) Equal moral concern - this means "treating similar individuals "similarly and not discriminating on the basis of morally irrelevant differences, such as sex, race, and religion" (Emanuel et al 2020 p1310).

The "Fair Priority Model", based upon these values, takes account of three dimensions of harm - irreversibility, devastation, and the potential for compensation - and thus three phases of vaccine distribution.

Phase I - Reduce irreversible harms (eg: premature deaths);

Phase II - Address health harms from indirect consequences (eg: economic deprivation);

Phase III - Reduce community transmission and so allow for the return to pre-pandemic life.

The allocation of number of vaccine doses to a country should be based on these phases. For example, Phase I could make use of a metric like the "Standard Expected Years of Life Lost" (SEYLL) (ie: the life years lost compared to standardised life expectancy calculations). So, "minimising SEYLL might mean immunising those at high risk of death, those most likely to transmit infection, or those most at risk of initial infection. The vaccination strategy that best averts SEYLL depends on each country's demography, prevalent co-morbidities, and health system capacity, as well as open scientific questions: Will vaccines reduce severity but not transmission, be less effective in the elderly, or require periodic boosters?" (Emanuel et al 2020 p1311).
Then Phase II might begin when a vaccine reduces worldwide SEYLL due to covid-19 to an "acceptable level" (eg: similar to annual influenza). While, "the transition to phase 3 might begin once additional vaccines either successfully narrow the poverty gap to pre-pandemic levels or encounter substantially diminishing returns in that effort" (Emanuel et al 2020 p1311).

Emanuel et al (2020) considered three potential objections to the "Fair Priority Model":

i) Vaccine should only be allowed to countries that have the infrastructure to distribute it appropriate, otherwise it is a waste of doses, or who distribute it inappropriately (eg: to the ruling elite).
Emanuel et al (2020) countered that making vaccine conditional on fair distribution is problematic. "As long as

individuals benefit, fair global distribution among countries should neither require that intra-national distribution of a vaccine be perfectly just nor seek to punish unrelated injustices" (Emanuel et al 2020 p1312).

ii) Some critics "might suggest that the Fair Priority Model unfairly disadvantages countries that have effectively suppressed viral transmission without a vaccine and rewards those who have responded ineffectively" (Emanuel et al 2020 p1312).

But, argued Emanuel et al (2020), the "fair distribution of vaccine among countries must mitigate future health, economic, and other harms spawned by COVID-19. It should not be backward looking, punishing or rewarding countries for their COVID-19 response or aiming to redress past injustices. The individuals whose lives and livelihoods are at risk often had little say in their governments' response to COVID-19. Further, medicine espouses treating people regardless of responsibility for their illness. Smokers who develop lung cancer and malaria patients who did not use bed nets are not denied care" (p1312).

iii) Metrics like SEYLL are difficult to calculate objectively.

Emanuel et al (2020) responded: "In a novel, rapidly evolving pandemic, any approach sufficiently sophisticated to meaningfully operationalise ethical values will require approximations as well as judgments about the relative weight to assign different metrics, such as SEYLL and the poverty gap. Simple metrics like population size avoid approximations and trade-offs but fail to measure what morally matters" (p1312).

Talking about another issue, the chief economist of the United Nation's Food and Agriculture Organisation, Maximo Torero emphasised the challenge to food from covid-19: "The coronavirus pandemic has laid many things bare, none more so than how interconnected our world is. The impact of globalisation is most obvious in the stuttering supply chains that threaten food security worldwide. Maintaining or reweaving these webs is going to take technology, innovation and political determination" (Torero 2020 p588).

Worryingly, he observed: "The pandemic has emboldened divisive arguments - such as that open borders have enabled the virus to spread, that refuges and immigrants must be kept out, and that out-sourcing should end. But such policy positions ignore how much nations depend on each other for staple ingredients, pesticides, fertilisers, animal feed, personnel and expertise" (Torero 2020 p589).

His solution is collaboration: "It is precisely because the coronavirus doesn't respect borders that global co-operation is the only shot at defeating it. The people who are working on vaccine trials, health care, drug discovery and economic recovery must all still eat. We can either stand together or many millions

will starve separately" (Torero 2020 p589).

In reference to scarce medical resources, like hospital and protective equipment, and tests, to leave to "market forces" (ie: the highest bidder), Cramton et al (2020) described as unethical - "hospitals cannot and should not pay exorbitant prices for life-saving equipment" (p334). Private manufacturers should be paid an amount that governments or health authorities can afford, but guarantee orders into the future as compensation to the companies (Cramton et al 2020).

If a third party co-ordinates the distribution of resources, then an individual hospital would not be forced to grab as much as it could get at the expense of other hospitals. This is a "central clearing house" model (Cramton et al 2020).

4. NON-PHARMACEUTICAL INTERVENTIONS

4.1. TEST AND TRACE

Moon et al (2020) outlined the situation: "'Test and Trace' systems are key components of national responses to the ongoing covid-19 pandemic. Each country has its own set of measures for testing covid-19 cases, finding contacts, and isolating and supporting those affected by the SARS-CoV-2 virus" (p2). These researchers then compared six countries - Germany, Ireland, Spain, South Africa, South Korea, and the United Kingdom for their "Find, Test, Trace, Isolate and Support" (FTTIS) frameworks (appendix F).
The five elements in detail are:

- Find the virus (ie: those with symptoms and without them).

- Test those who may have the virus quickly and easily.

- Trace all those with a positive diagnostic test and their contacts to avoid them infecting others.

- Isolate those who are infectious.

- Support those in isolation [38] (appendix G).

Moon et al (2020) (ten authors) included researchers from each of the six countries being studied who collected details for their country.

a) Find - Two strategies emerged: passive (encourage individuals with symptoms to come forward for testing), and active (seek out asymptomatic individuals).
Key to the passive strategies was public information about who can/should be tested, where and how (in the appropriate language). For example, Germany published such information in nineteen languages. Mobile apps were successful where available.
Among the active strategies, in South Africa, for example,

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[38] Coyle (2020), writings in early June 2020, observed: "There is still a tendency to suggest a facile trade-off between lives and livelihoods. To be clear: whatever lockdown policies governments impose, or not, the pandemic will have a devastating economic impact. Every nation is groping for an approach that will save lives, mitigate the economic harm and prove feasible" (p9).

community health workers undertook door-to-door symptom screening in hotspots and high risk areas.

Testing at points of entry into a country was popular (appendix H).

b) Test - The reliability of diagnostic tests was important here, as well as practical issues like laboratory facilities to analyse the samples. "Rapid scale-up of testing, fast turnaround, and prompt reporting are essential for ensuring chains of infection are broken. In all study countries, tests are free to the patient at point of access, which is appropriate as tests for those less likely to become seriously unwell nevertheless serve as a public good, where this testing aids prevention of onward transmission" (Moon et al 2020 p6).

In each country, the "proven test capacity" (ie: highest number of tests recorded per week per million capita) was less than "stated test capacity" (ie: claimed maximum test capacity per week per million capita). The gap was lowest in South Africa and South Korea.

c) Trace - Three systems were used: decentralised/local, centralised, and digital contact tracing. Only South Korea had successfully implemented all three systems, in the main, because of previous experience in 2015 with MERS.

Digital systems have privacy issues (eg: mobile apps that automatically record where an individual has been; use of CCTV in establishing contacts). "Centralised contact tracing may be slower and less efficient than decentralised, but allows for the rapid collation and sharing of data for evaluation and learning. Decentralised systems are embedded in their localities and can address complex tracing cases, but the lack of centralisation makes it difficult to share data across contexts and to learn. Moreover, local resources may become rapidly overwhelmed, while centralised resources could be used to provide additional capacity to regional hot spots" (Moon et al 2020 p8).

d) Isolate - The World Health Organisation in May and June 2020 recommended ten days of isolation after a positive diagnostic test for asymptomatic cases, thirteen days after symptom onset for symptomatic cases, and a minimum of fourteen days for contacts with an infected individual.

Only Germany formally required all these conditions (and particularly only the state of Baden-Wurttemberg). Fines and risk of imprisonment were threatened for breaking quarantine.

But enforcement and monitoring was often low generally, particularly because health officials became overwhelmed (eg: South Africa). So, self-monitoring was the norm.

e) Support - This included financial support and/or provision of essentials (eg: food). The levels of support varied. Financial support varied in amount, and some individuals did not qualify,

for instance. South Korea and South Africa were very good in providing food and drink. For example, in South Africa, "those making use of isolation or quarantine facilities set up by the government are provided with free meals three times a day for the duration of their stay" (Moon et al 2020 p12).

Moon et al (2020) drew out some lessons to be learned, particularly that "no single country has implemented a comprehensive and fully functioning FTTIS system that could not be improved, possibly using measures demonstrated in other study countries" (p12). The key lessons for each country were as follows:

- UK - More support, and monitoring of compliance to isolation, as well as better use of local testing and tracing.

- Ireland - Improvements to "Find" (eg: testing high risk populations).

- Germany - Shortage of skilled personnel in local trace teams.

- Spain - Increase testing capacity, and tracing staff.

- South Africa - Increase testing capacity in high transmission areas.

- South Korea - Deal with privacy concerns about the digital systems of "Trace".

To end, Moon et al (2020) summarised the best practice:

Find - Active and passive strategies.

Test - Reliable tests that can be processed swiftly.

Trace - All three systems together (local, centralised and digital).

Isolate - Monitoring for adherence and for the individual's well-being.

Support - Practical, financial and material support.

In conclusion, Moon et al (2020) wanted to say that they were not criticising the countries in the study, but trying to encourage best practice in a difficult situation.

4.2. APPS

An editorial in "Nature" on 30th April 2020 highlighted concerns about smartphone apps that log contacts automatically. Leaving privacy issues, "there is scant published evidence on how

effective these apps will be at either identifying infected people who have not been tested or, if widely used, stopping the spread of the disease. Governments are excitedly pointing out the benefits, but are saying less about the risks" (Editorial 2020a p563) [39] [40].

Only some people in a population will have the app on their phone, and so the system will miss individuals without the app and without a smartphone [41].

Underlying the effectiveness of the apps will be the accuracy of covid-19 tests. Contacting individuals, by smartphone app or not, to isolate incorrectly (ie: false positive test) or not to isolate when they should (ie: false negative test) both have consequences.

In June 2020, Morley et al (2020) set out sixteen questions "to assess whether – and to what extent – a contact tracing app is ethically justifiable" (p29) (table 5).

These questions cover four ethical principles derived from human rights conventions (Morley et al 2020):

i) Necessary – It will save lives and is an effective solution to "track and trace" problems.

ii) Proportional – The pandemic situation demands extreme responses, even the compromise of privacy.

iii) Scientifically valid – The apps work effectively.

iv) Time-based – The extreme response is only temporary during the pandemic, and there should be an "exit strategy" for when the apps are no longer required/appropriate/effective.

4.3. TESTING

Africa lacks diagnostic covid-19 testing and this is the "Achilles heel" (Nkengasong 2020). For example, Ethiopia has run 10 tests per 100 000 people compared to 280 in South Africa, 2000 in Australia, and 1560 in the USA (in April 2020) (Nkengasong 2020).

Part of the problem is "a race is on by the powerful to acquire whatever covid-19 tests are available" (Nkengasong 2020 p565). Nkengasong (2020) explained that many countries have imposed export restrictions on medical material. But, he argued,

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[39] Even if covid-19 apps are temporary, rapidly rolling out tracing technologies runs the risk of creating permanent, vulnerable records of people's health, movements and social interactions, over which they have little control" (Morley et al 2020 p29).

[40] Bluetooth signals, which are commonly used by the apps, show that two individuals' phones were in proximity, not that there may have been a wall between them (Morley et al 2020).

[41] Morley et al (2020) commented that apps should be "available and accessible to anyone, irrespective of the technology needed or their level of digital literacy" (p30).

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covid-19 will be defeated by the world working together.
       The drive for covid-19 anti-body tests in mid-2020 saw many

Question	Positive Answer	Negative Answer
1. Necessary?	To save lives	Better alternatives
2. Proportionate?	Grave situation	Impact beyond benefits
3. Accurate etc?	Good evidence	Not work well
4. Temporary?	Only during pandemic	No end date
5. Voluntary?	Optional install	Compulsory
6. Consent over data use?	Can customise data shared	Default settings share everything all the time
7. Privacy/anonymity of data?	Data held on user's phone only	Data stored centrally, and/or (re)identifiable
8. User erase data?	Yes, and/or data deleted automatically at certain point	No provisions
9. Purpose of data collection defined?	Alert about infected people nearby	Not explicit
10. Purpose limited?	Only covid-19 track and trace	Can be used for more general surveillance
11. Used only for prevention?	Allow individuals to voluntarily limit covid-19 spread	Used as "passport" for services
12. Used to gain compliance?	Not to enforce behaviour	Fines and imprisonment based on non-compliance with rules
13. Open-source code?	Publicly available	Code owned by organisation
14. Apps available to all?	Any phone type and/or any person can download app	Limited to certain types and/or restricted access to app
15. Apps accessible to all?	User-friendly	Requires certain level of technical knowledge
16. Decommissioning process?	Clear strategy	No end policy

(Based on Morley et al 2020 p30)

Table 5 - Sixteen questions about the ethical justification of contact-tracing apps.

new kits being produced, but not all were reliable (Mallapaty 2020a). Accurate identification of anti-bodies (ie: true positive), the test's sensitivity, and those who had no anti-

bodies (ie: true negative) (test specificity) have been reported as low as 40% (Mallapaty 2020a). The timing of the test is crucial - ie: not too soon after infection, and whether the test detects anti-bodies from other coronaviruses as well (Mallapaty 2020a).

Tests fall into two categories - those needing laboratory facilities to process them, and "point-of-care" tests that give rapid, on-the-spot results. The problems are more likely with the latter (Mallapaty 2020a).

4.4. A SWEDISH EXPERIMENT?

The response of Sweden to covid-19 in early 2020 was quite different to many other countries. "The government never ordered a 'shutdown' and kept day care centres and primary schools open. While cities worldwide turned into ghost towns, Swedes could be seen chatting in cafés and working out at the gym" (Vogel 2020 p159).

There was a ban on large gatherings introduced in late March, and many Swedes did voluntarily stay at home "at rates similar to their European neighbours, surveys and mobile phone data suggest" (Vogel 2020 p160).

However, in some cases, the official response was opposite to other countries. For example, "Swedish authorities actively discouraged people from wearing face masks, which they said would spread panic, are often worn the wrong way, and can provide a false sense of safety. Some doctors who insisted on wearing a mask at work have been reprimanded or even fired" (Vogel 2020 p160). People were also expected to notify their own contacts if they became ill, and testing lagged behind many countries (Vogel 2020) [42].

Influential Swedish epidemiologist Johan Giesecke (2020) praised the Swedish approach in a letter to the "Lancet" in May 2020. "He said the virus was 'an invisible pandemic' in which 98% to 99% of infected people don't realise they have been infected. 'Our most important task is not to stop spread, which is all but futile, but to concentrate on giving the unfortunate victims optimal care', he wrote" (Vogel 2020 pp162-163).

Whether this approach was best has been hotly debated, particularly among scientists within the country [43]. A group called "The 22" argued for tougher measures from the beginning, for example. This group believes that "the price for Sweden's laissez-faire approach has been too high. The country's cumulative death

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[42] Interviewed in April 2020, Anders Tegnell of Sweden's Public Health Agency talked of individual responsibility as better than "counter-productive" lockdowns, and of less pessimistic conclusions from modelling of the pandemic than other researchers (Paterlini 2020).

[43] "Differences of opinion, critique and robust debate are at the heart of how research advances" (Editorial 2020b p314). But sometimes the debates "cross the line". The "Nature" group publishers surveyed authors and editors in their journals in early March 2020, and up to around one-fifth reported negative experiences and/or inappropriate language in the peer review process and reaction to their research (Editorial 2020b).

rate since the beginning of the pandemic rivals that of the United States, with its shambolic response. And the virus took a shocking toll on the most vulnerable. It had free rein in nursing homes, where nearly 1000 people died in a matter of weeks. Stockholm's nursing homes ended up losing 7% of their 14,000 residents to the virus" (Vogel 2020 p160).

There have been some changes in policy over the summer (of 2020), but time will tell whether Sweden's approach, which has, in fact, been a "control group" in a global experiment, was better or worse than that of other countries.

4.5. LESSONS LEARNED

Writing in November 2020, Gostin (2020) offered seven lessons learned so far from dealing with covid-19:

i) Build resilient health systems - eg: develop "surge capacity" to cope with sudden increases in patients in a health emergency.

ii) Leadership and public trust - The statements and behaviours by politicians, and the public trust in these individuals.

iii) Defend the integrity of science - "Despite remarkable, albeit incomplete, scientific discovery, populist political leaders have sown doubt about the value of science and have undermined public health agencies. In Brazil and the US, for example, political leaders have publicly recommended covid-19 treatments that their own agencies have not approved..." (Gostin 2020 p1816).

iv) Invest in biomedical research.

v) Reduce inequality.

vi) Evidence-based laws - "Emergency health powers should be based on evidence and used only when there are no less restrictive alternatives. Usurpation of power under the pretext of a health crisis threatens to erode democratic freedoms, which can endure even after the crisis ends" (Gostin 2020 p1817).

vii) Support global responses - A pandemic is defeated by global co-operation, not individual countries working alone.

4.6. HERD IMMUNITY

As many countries were facing a "second wave" of covid-19, Alwan et al (2020) were aware of "widespread demoralisation and

diminishing trust", particularly as full lockdown had not solved the problem and restrictions were continuing or being reimposed. But the authors wanted to counter the "dangerous fallacy" of "so-called herd immunity" that was having renewed interest. This means "allowing a large uncontrolled outbreak in the low-risk population while protecting the vulnerable. Proponents suggest this would lead to the development of infection-acquired population immunity in the low-risk population, which will eventually protect the vulnerable" (Alwan et al 2020 p1).

This approach risks "significant morbidity and mortality across the whole population" as well as the impact on the "everyday" work of health care systems (and the economy). "Furthermore, there is no evidence for lasting protective immunity to SARS-CoV-2 following natural infection, and the endemic transmission that would be the consequence of waning immunity would present a risk to vulnerable populations for the indefinite future" (Alwan et al 2020 p1).

Alwan et al (2020) offered their solution: "Effective measures that suppress and control transmission need to be implemented widely, and they must be supported by financial and social programmes that encourage community responses and address the inequities that have been amplified by the pandemic" (p1).

4.7. SENSIBLE MEDICINE

Seymour et al (2020) advocated for "sensible medicine" (SM) for covid-19 patients rather than "unreasoned treatment using unproven interventions in the moment" (p1827). They explained that the "natural response at the bedside of a patient with covid-19 is to act and to act decisively. Imbued with determination, clinicians seek to make a difference for patients who are seriously ill" (Seymour et al 2020 p1827). Along similar lines, Taleb (2012) described an "illusion of control that leads to a default to action rather than inaction" (quoted in Seymour et al 2020).

SM involves the balance between action and inaction, between embracing new (often unproven) treatments and sticking with the old ways. "In the middle is a sensible approach, which acknowledges that some interventions are effective but, perhaps, confidence should be tempered. With sensible medicine, the translation of knowledge to the bedside is appropriately calibrated to the rigor and reasoning of the available" (Seymour et al 2020 p1827).

Seymour et al (2020) outlined five principles to follow:

i) "Medicine without magic" - Accept that no single treatment ("magic bullet") is available for severe covid-19, and so different approaches may be needed in different situations.

ii) "Practice doing (almost) nothing" - Sometimes no or almost no treatment is better than experimental (untested) therapies.

iii) Improve basic and usual care.

iv) Focus on treatments with high-quality evidence - ie: randomised controlled trials.

v) "Think Bayesian" - Assume that a new treatment has the probability of success of any treatment rather than the belief that it must be better. Friedman (2009) observed that "new treatments are a bit like the proverbial new kid on the block: they have an allure that is hard to resist" (quoted in Seymour et al 2020).

Seymour et al (2020) ended: "To be clear, sensible medicine does not mean clinicians should not intervene. Rather, it proposes a gentler, moderate, and humble view of available treatment options and their effectiveness in patients with covid-19. The approach encourages clinicians to elevate usual care, reduce unnecessary interventionism, and focus and rely on scientific rigour. Rather than choose between action and inaction, sensible medicine encourages supportive restraint and heightened therapeutic humility" (p1828).

5. NEGATIVE RESPONSES

    5.1. Pseudo-science and conspiracies
    5.2. Disinformation
    5.3. Challenging science

5.1. PSEUDO-SCIENCE AND CONSPIRACIES

Caulfield (2020) argued for the aggressive counteracting of pseudo-science and misinformation about covid-19 (table 6). While Scales et al (2020) advocated "pre-emptively disseminating factual evidence so that people become more resistant to false information" (p32) (appendix I). Furthermore, the problem is not just a lack of knowledge, but that "[M]any view covid-19 as a political rather than a scientific issue" (Scales et al 2020 p32).

- Popular myths around covid-19 including eating sea lettuce or injecting disinfectant as protection, and holding your breath for ten seconds as a test (Fleming 2020).

- The main reasons for misinformation include "simply misguided"; profit from selling products or revenue from clicks on "Google Ads", for instance; political (Fleming 2020).

- Health sociologist, Samantha Vanderslott (quoted in Fleming 2020) gave some tips for spotting misinformation, including vague and untraceable sources to stories; content that produces strong emotions (eg: anger); and claims of "miracle cures".

Table 6 - Misinformation about covid-19.

Plutzer et al (2020) reported that the proportion of US secondary-school biology teachers presenting creationism as a scientific alternative to evolution had dropped from 32% in 2007 to 18% in 2019. Evolution is important for schoolchildren to learn, argued Reid (2020), because it teaches that "all living things have the same common ancestors, and that they and their fellow humans are much more similar than they are different" (p315). Also today as the "pandemic sweeps the globe, evolution is gain crucial to understanding a pathogen. It helps us to learn how the virus circulates, and to identify its vulnerabilities. It helps to counter conspiracy theories" (Reid 2020 p315).

CST (2020) highlighted the spread of anti-semitic conspiracy theories (ASCTs) (appendix J) about covid-19 on social media. The "direct" version of these ideas blames Jews for the pandemic, while an "indirect" version takes another conspiracy theory and adds an anti-semitic "twist". For example, "when the idea spread that 5G towers and networks were causing or spreading the new

coronavirus, conspiracy theorists were quick to suggest that Jews either owned the telecommunication industry or were deliberately building towers in 'non-Jewish' areas" (CST 2020 p3).

CST (2020) distinguished five categories of ASCTs from social media posts and comments:

i) "The virus is fake - it's a Jewish conspiracy" - A "Jewish plot" to mislead the public.

ii) "The virus is real - but it's still a Jewish conspiracy" - Variations of this idea include a "Zionist agenda" to depopulate the world by killing many people with the deliberately created virus, a plot involving combinations of Israel, China, and the USA, or "Jewish businessmen" who can make money from the deliberate spread (eg: through selling a vaccine).

iii) "Jews are the primary spreaders of the virus - 'the Jew flu'" - This category of ASCTs shows how a factual story can become the basis of a conspiracy. "Genuine media stories about the relatively high prevalence of coronavirus in some Jewish communities, and early reports that British Jews have been disproportionately represented amongst those who have died from COVID-19, have encouraged anti-semites to assume that Jews are the primary spreaders of the virus, either deliberately – to try to kill white people – or inadvertently. Having initially nicknamed coronavirus the 'Wu Flu' (referring to Wuhan as the geographical origin of the virus), some of these online haters have now dubbed it the 'Jew Flu', implying either that Jews are behind it, or that it is most closely associated with Jewish victims and spreaders" (CST 2020 p7).

iv) "Celebrating Jewish deaths" - Comments on social media that celebrate the disproportionate number of Jewish people dying from covid-19.

v) "Let's spread it to the Jews - the 'Holocough'" - "The final station on this hateful journey is to try to use coronavirus to kill Jews. This is the logical conclusion of this anti-semitism, with far right activists talking online about getting infected, either deliberately or accidentally, and then going to synagogues and other Jewish buildings to try to infect as many Jewish people as possible. They have even given it a depraved new name – the 'Holocough'" (CST 2020 p9).

5.2. DISINFORMATION

Bernard et al (2020) described state-sponsored online disinformation campaigns [44], as in the case of anti-vaccination, as

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[44] Bernard et al (2020) distinguished between misinformation ("'accidental falsehood', or wrong of misleading information shared without malice") and disinformation ("'deliberate falsehood', or wrong or misleading information

the "fifth phase of biowarfare with a 'cyber-bio' framing" (p1) [45] [46]. These researchers stated: "Biowarfare in the fifth era aims to undermine socio-political systems through social, political, and economic
means by 'weaponising' or 'virtually escalating' natural outbreaks, rather than directly inducing mortality and morbidity in populations through the deployment of harmful biological agents" (Bernard et al 2020 p1).

This "fifth era of biowarfare" has certain conditions (Bernard et al 2020):

i) The "weaponisation" of online fake news campaigns that are wide-reaching.

ii) The potential for such campaigns to have a significant impact.

iii) The exacerbating effect of social media.

iv) The delegitimisation of science and mistrust of officials.

The consequences of fake news campaigns which show them to be a form of biowarfare is "(1) a negative influence on public health linked by fear, economic and political disruption, and civil unrest, and (2) the incapacitation of a target population, who are now more vulnerable to infectious diseases such as measles" (Bernard et al 2020 p5).
Bernard et al (2020) developed this idea with the following identifiable consequences:

- The continued transmission of the disease.

- Mistrust in authorities which discourages people from seeking treatment.

- Direct misinformation to discourage treatment-seeking.

- Violence against healthcare facilities and personnel.

- Exacerbation of political unrest and anti-government feelings.

Muirhead and Rosenblum (2019) identified three "cognitive biases" that create vulnerability to disinformation (Bernard et al 2020):

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shared in full knowledge of its falsehood, often with malicious intent"; p2).

[45] The four phases of biological warfare (or biowarfare) are pre-germ theory, applied microbiology, industrial microbiology, and molecular biology and biotechnology (Bernard et al 2020).

[46] The first nerve agents were the consequences of insecticide production in Germany in the 1930s (Sydnes 2020).

a) Intentionality - The attribution of a source of events rather than a product of random consequences. This can be seen in the desire to find a definite source of blame for the origin of SARS-CoV-2, and/or to see a "group" behind it. Together this is seen in the "Bill and Melinda Gates Foundation" being accused of engineering the virus to increase vaccine sales (Bernard et al 2020).

b) Proportionality - An event with significant consequences is perceived as having a significant cause. Covid-19 is having a massive impact, so therefore the cause must be something momentous rather than the reality of the mundane.

c) Confirmation bias - The tendency to pay attention to evidence that supports a viewpoint. So, an individual with an anti-vaccination position will notice all the negative cases (eg: sever side effects), and bad practices by vaccination-makers, but miss the vast amount of evidence against their view, say.

5.3. CHALLENGING SCIENCE

The claims of treatments for covid-19 revolve around the idea of "proof" and "works", and what Berlivet and Lowy (2020) described as the "conflicting claims of authority in contemporary medicine — statistical objectivity vs charismatic subjectivities, or activism vs official experts" (p3).

These authors focused on chloroquine (an old anti-malaria drug) and hydroxychloroquine (Hy) (used to treat auto-immune disease) which were claimed as treatment for covid-19 by President Trump among others, despite official warnings about the health risks (let alone the lack of efficacy). "Chinese experts" were promoting chloroquine in February 2020, and later, French microbiologist, Didier Raoult played an important role with a non-randomised clinical trial (Berlivet and Lowy 2020).

Raoult, who quickly developed a following via YouTube, rejected criticisms of Hy treatment - "he denounced the nefarious role of what he called 'methodology maniacs', in the bureaucratisation of clinical research and the consecutive forgetfulness of the physician's first duty: to save lives" (Berlivet and Lowy 2020 pp4-5). Pharmaceutical companies were also blamed (appendix K). But, as Berlivet and Lowy (2020) pointed out, "the introduction of randomised trials in medicine was not the result of an alliance between statisticians and methodologists working for the pharmaceutical industry, but rather started as a medical reform movement led by clinicians appalled by the negative consequences for patients, especially the more vulnerable ones, of ego battles among senior physicians, and clashes between therapeutic schools of thought" (p5).

Criticisms of medical authorities are not new, and "AIDS activists" in the 1990s, for example, created the slogan, "Red Tape Kills" to highlight what they saw as the over-regulation and control of clinical trials for new therapies in the USA. The response was "important changes in the rules that previously governed such trials, with the development of fast-track clinical trials; the legalisation of patients' compassionate access to off-label drugs; the abandonment of the principle that patients who had already received any drug ought to be excluded from trials; the elimination of trials against placebo; and, above all, the routine inclusion of patients' representatives in the planning of clinical trials" (Berlivet and Lowy 2020 p8). This could be called the "democratisation of the clinical trial" [47].

The involvement of patients and lay parties in the process of establishing the effectiveness of treatments can cut both ways. On the positive side, "experts by experience" can share their knowledge and help clinicians, while, on the negative side, the seed of distrust of experts can grow. "We know as much as them with their vested interests", the individual might say.

Berlivet and Lowy (2020) summarised their reflections: "The argument that all concerned citizens, and not only a handful of experts, should be allowed to participate in debates on scientific topics, especially on issues that involve them directly, from air pollution and the use of nuclear energy to access to promising new therapies, is a seductive one. The problem, in our view, lies in the all-too pervasive notion of lay participants, whose abstractness conceals the plurality of motives that effectively prompt individuals and collectives to engage in a scientific discussion, as well as the precise nature of their contribution to scientific debate" (p12).

Social media plays such a key role today in "communicable cartographies" (Briggs 2011) - ie: "cultural models for the production, circulation, and reception of health knowledge" (Briggs and Hallin 2016 quoted in Berlivet and Lowy 2020).

Berlivet and Lowy (2020) ended: "Since the beginning of the covid-19 pandemic, signing an on-line petition, looking at a video posted on YouTube, liking a Facebook site, or re-tweeting a message on health-related issues posted on a celebrity's account have been equated by some commentators with new forms of patient/citizen activism. At the same time, politicians who publicised the use of hydroxychloroquine, such as Bolsonaro and Trump, depicted themselves as courageous defenders of the interests of 'the people' against the stifling views of experts — a strategy they had already adopted previously to justify their rejection of the scientific consensus on climate change... However, far from being the expression of a movement for the democratic re-appropriation of science by lay

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[47] I use this term as mine, but I am not sure if it comes from somewhere else. A basic Internet search found no reference (on 27th November 2020).

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people, enthusiasm for untested and potentially toxic therapies promoted by conservative social media and populist politicians have had just the opposite effect: silencing debates over the social and political underpinnings of science" (p12).

Figure 4 is my representation of the ambivalent attitude towards science from both "pro" and "anti" science sides.
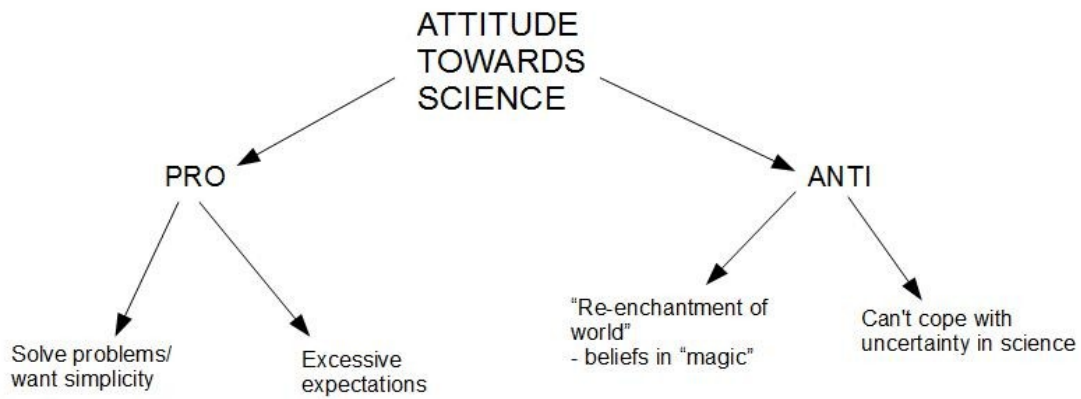

Figure 4 - Ambivalent attitudes towards science.

6. PSYCHOLOGICAL HEALTH

6.1. Psychiatric conditions and covid-19
6.2. Conflict
6.3. Nurse mental health
6.4. Post-traumatic growth
6.5. Other

6.1. PSYCHIATRIC CONDITIONS AND COVID-19

In late 2020, using US data, Taquet et al (2020) reported that for "patients with no previous psychiatric history, a diagnosis of covid-19 was associated with increased incidence of a first psychiatric diagnosis in the following 14 to 90 days compared with six other health events..." (p1).

The researchers used anonymised data from the "TriNetX Analytics Network", which covers electronic health records in 54 health care organisations in the USA and seventy million patients.

Diagnoses of covid-19 between 20th January and 1st August 2020 were collated (n = 62 354), along with 22 variables covering risk factors, like age, obesity, and diabetes, and a psychiatric diagnosis between 14 to 90 days after diagnosis of covid-19. These data were used to assess if covid-19 was associated with a psychiatric diagnosis.

But the researchers were also interested to test whether a psychiatric diagnosis increased the risk of covid-19 diagnosis. Two cohorts were compared here - individuals with a psychiatric diagnosis in 2019 and matched controls (n = 1.7 million in each group).

The first conclusion was an increased risk of a psychiatric diagnosis after covid-19, which was about 1.5 to two times greater than six control health conditions (eg: skin infection; fracture of a large bone) [48]. The most common diagnoses were anxiety and mood disorders. Severity of covid-19 was not a variable, nor socio-economic factors, for instance.

The second conclusion was that "a diagnosis of psychiatric disorder in the year before the COVID-19 outbreak was associated with a 65% increased risk of COVID-19... compared with a cohort matched for established physical risk factors for COVID-19 but without a psychiatric diagnosis" (Taquet et al 2020 p9). Another US study found a higher risk here (Wang et al 2020), while a smaller South Korean study (Lee et al 2020) found no association (Taquet et al 2020). Taquet et al (2020) offered some explanations including "behavioural factors (eg: less adherence to social distancing recommendations) and residual socio-economic and lifestyle factors (eg: smoking) that are not sufficiently

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[48] This could be an underestimate because some individuals have not yet presented for diagnosis (Taquet et al 2020).

captured by the available data in any of the studies. It could also be that vulnerability to COVID-19 is increased by the pro-inflammatory state postulated to occur in some forms of psychiatric disorder or be related to psychotropic medication" (p10).

Taquet et al (2020) accepted some methodological limitations including:

i) Uncontrolled confounders.

ii) Dependence on health records and the information contained therein.

iii) Undiagnosed cases would be missed along with individuals who were treated at hospitals not in the "TriNetX Analytics Network".

iv) The findings cannot be generalised to other populations or health care settings.

Studies after SARS and MERS (eg: Rogers et al 2020) suggested a link with anxiety, depression, and insomnia, for example (Taquet et al 2020).

6.2. CONFLICT

Emergencies with prolonged risk and uncertainty can produce conflict within communities. "It has been suggested that 'therapeutic communities', which are characterised by high levels of cohesion and mutual aid, are more likely to follow natural disasters, while 'corrosive communities' [eg: Cope et al 2020] , which are divided and see conflict, are more likely after human-made disasters" (Smith et al 2020 p1).
"Corrosive communities" emerge through three inter-related factors - "the mental and physical well-being of individuals within the community; perceptions of the failure of Government and other institutions to properly uphold and execute their roles and responsibilities; and continued litigation" (Smith et al 2020 p1).
Smith et al (2020) explored these ideas in relation to covid-19, and anger in the UK. In mid-July 2020, 2237 participants from a market research company's online research panel were surveyed. The key questions covered:

- Anger - eg: arguments with friends and family members about how to behave during the pandemic.

- Confrontation - eg: reporting someone to the authorities for failure to weak a mask in public.

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- Beliefs about covid-19 - eg: perceived personal risk from covid-19.

- Trust in UK government's response - eg: relaxing the lockdown too quickly, too slowly, or just right.

- Psychology - eg: current anxiety level compared to pre-covid-19.

Just over half of respondents (56%) had an argument, felt angry, or had fallen out with someone about covid-19. These individuals were more likely to be younger, experienced or feared significant financial consequences due to the pandemic, experienced anger or confrontation themselves, more anxious or depressed than before the pandemic, feel that the government was relaxing measures too quickly, and perceived covid-19 as a risk to themselves, for example.

"Anger was associated with lower levels of trust in the UK Government to control the spread of Covid-19, thinking that measures were being relaxed too quickly, and greater worry about restrictions being lifted. Those who are worried about the speed with which restrictions are being lifted may perceive a greater risk from Covid-19" (Smith et al 2020 p7).

Smith et al (2020) ended: "Findings from this study reflect those from previous emergencies in which corrosive communities have emerged and suggest that we may be moving from therapeutic communities towards ones characterised more by corrosion" (pp12-13).

This study has the following key methodological limitations:

i) The sample was demographically representative of the UK general population, based on quota sampling, but, Smith et al (2020) admitted, "we cannot be sure that the views and experiences of survey respondents are representative of those of the population. However we assume, following the principles set out by Kohler [2019] that the associations between variables within our sample follow the same pattern as those within the general population" (p12).

ii) This study was cross-sectional, so the direction of causality cannot be established. Furthermore, there was no pre-pandemic baseline, and there is "little research investigating normative rates of anger in the general population" (Smith et al 2020 p7).

iii) There was no breakdown of data for each country of the UK, which had differing rules for face coverings, say.

6.3. NURSE MENTAL HEALTH

A survey of 3500 nurses in the UK in mid-April 2020 (Ford 2020) found that one-third described their mental health as "bad or "very bad", and the vast majority were more stressed than prior to the pandemic (figure 5).
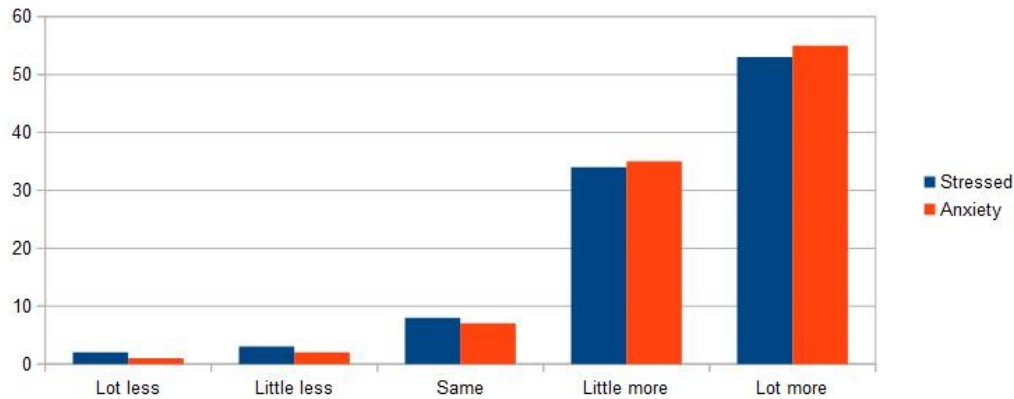
(Source: Based on graphics in Ford 2020)

Figure 5 - Percentage of nurses rating their level of stress and anxiety during the pandemic compared to before it.

6.4. POST-TRAUMATIC GROWTH

Post-traumatic stress after negative experiences has received a lot of attention generally, and has been applied specifically to health care professionals during the covid-19 pandemic.

But what about "post-traumatic growth", which is defined as "'positive psychological change experienced as a result of a struggle with highly challenging life circumstances, [Tedeschi and Calhoun 2004] and through establishing perspectives for a 'new normal', when the old normal is no longer an option" (Olson et al 2020 p1829). Five domains have been distinguished (Olson et al 2020):

a) The development of deeper relationships.

b) An openness to new possibilities.

c) The greater perception of personal strength.

d) A deeper sense of spirituality.

e) A greater appreciation of one's life.

Olson et al (2020) explained: "Ultimately, it is not the

trauma that causes growth, but rather how individuals and organisations interpret and respond to it. Growth may occur by responding to the trauma in a manner that focuses on learning how the trauma might serve as a positive catalyst for the future of medicine to be greater than the previous status quo. When the acute phase of the pandemic subsides, after crisis management and initial psychological support, there is often an opportunity to choose a coping strategy to facilitate growth" (p1830).

6.5. OTHER

Keeping a balance between the past, present, and future is important, particularly in a time of uncertainty as during covid-19. Table 7 summarises the advantages and disadvantages of each period of an individual's life.

Period	Advantages	Disadvantages
Past	Learn from experiences and mistakes	Nostalgia
Present	Focus on moment	No planning or learning from past
Future	Plan and preparation	Miss the "now"

Table 7 - Advantages and disadvantages of "living in" the past, present and future.

7. MISCELLANEOUS AND OTHER RELEVANT RESEARCH

7.1. BATS

Bats are seen as the reservoir of a number of viruses that have jumped to humans (zoonoses), including covid-19. "This seeming preponderance of zoonoses has propelled bats from biomedical obscurity to the forefront of global health. Immunological traits have been proposed to allow bats to control viruses differently from other animals. However, incomplete baselines for broader comparisons across vertebrates and extensive immunological variation among bat species casts uncertainty on their distinctiveness as viral reservoirs. Moreover, common perceptions that bats asymptomatically harbour viruses more often than other animals and that their viruses are more diverse or pose systematically heightened zoonotic risk remain unresolved" (Streicker and Gilbert 2020 p172).

It is argued that the physical challenge of flight in bat evolution led to a strengthened immune system that could harbour viruses without any illness. "Whether bats are exceptional in this respect is unclear because knowledge of vertebrate immune systems largely derives from inbred mice or immortalised cells, which diverge substantially from wild relatives" (Streicker and Gilbert 2020 p172).

Streicker and Gilbert (2020) continued with their questioning of bats as having a "super immune system" by pointing out that there are viruses lethal to both humans and bats (eg: lyssaviruses). The problem once more is lack of research on bats, argued these authors, as with the question: "Once introduced into the human population, are bat viruses exceptionally dangerous?" (Streicker and Gilbert 2020 p172).

Whatever the risk of zoonoses from bats, Streicker and Gilbert (2020) wanted to highlight "the real-world complexity underlying viral zoonotic emergence" (p173), including the wildlife trade, and human land use. Put simply, human behaviour that increases the opportunities for any viruses that bats harbour to move to humans.

Coronaviruses closely related to SARS-CoV-2 have been found in laboratory stocks of bat physiological material in Cambodia and Japan. In the former case, it was two Shamel's horseshoe bats captured in 2010, and the discovered virus may be an ancestor of SARS-CoV-2 (Mallapaty 2020d).

In Japan, a virus that shares over 80% of the genome with

SARS-CoV-2 was found in a little Japanese horseshoe bat captured in 2013 (Mallapaty 2020d). This virus (Rc-o319) is unable to bind to the ACE2 receptors as SARS-CoV-2 does to enter human cells (Mallapaty 2020d).

These discoveries, along with a related virus found in Yunnan province, China, in 2013 show that SARS-CoV-2 existed in the bat reservoir before infecting humans (Mallapaty 2020d).

7.2. COMMUNICATION WITH PATIENTS

Communicating medical information clearly to patients is crucial. Failure to understand advice can lead to health problems (Fletcher 2020).

The NIACE (2009) developed a "Simple Measure of Gobbledygook" (SMOG) to show the readability of material. It involves counting the number of words of three or more syllables in ten sentences of text. This is multiplied by three, then the square root is taken, and eight added. "The Daily Telegraph" newspaper, for example, has a score above 17 compared to less than fourteen for "The Sun" newspaper (Fletcher 2020).

7.3. ANIMAL MODELS

The use of rodents to model human health has a number of problems. Esposito et al (2020) outlined one in relation to stroke therapy: "Circadian rhythms affect the mechanisms of disease and response in therapies. Almost all experimental testing of neuroprotectants for stroke are performed during the day, when rodents are normally inactive. By contrast, clinical trials mostly recruit patients in whom strokes occur during the day (when they are active) because of the need to establish time-of-onset" (p395).

Using mice and rats, these researchers tested three neuroprotective approaches to reduce the damage to the brain caused by a stroke. All three treatments reduced the damage in day-time strokes (ie: when the rodents inactive), but not night-time ones (ie: when active). This has serious implications for the application to humans. Esposito et al (2020) stated: "Our findings point to a fundamental difference between currently used rodent models of neuroprotection and human patients with stroke" (p397).

However, the researchers noted other factors that are also relevant to the effectiveness of neuroprotection, including age, stress, hypertension and metabolic disease (Esposito et al 2020).

7.4. PRE-HABILITATION

Many surgical patients, particularly older ones, experience post-operative delirium, including impaired cognitive function and

attention problems. One approach to reducing the problem is pre-habilitation (ie: ie- pre-operative preparation, like physical exercise and nutrition) (Humeidan et al 2020).

Increasing cognitive reserve via playing computer games or reading, for instance, is a form of pre-habilitation that can help. Tow et al (2016), for example, reported lower post-operative delirium in older orthopedic patients who did such activities. But this was an observational study (Humeidan et al 2020).

The Neurobics trial investigated pre-operative cognitive exercise by comparing an intervention and a control group (Humeidan et al 2020). At a US hospital between March 2015 and May 2019, 251 patients over 60 years old, undergoing major, non-cardiac, non-neurological surgery under general anaesthesia were randomised to pre-operative cognitive exercises (covering memory, attention, and problem-solving) or not, for ten hours over the days prior to the surgery. The main outcome measure was post-operative delirium scored on two psychometric measures by researchers or nurses in the seven days after surgery.

The delirium rate for the control group was 23% of patients compared to 14% for the cognitive exercise group. This was evidence of the benefits from the cognitive pre-habilitation, but compliance was low (with less than 10% completing ten hours of cognitive exercises, and the mean was 4.5 hours). The use of the tablet device for the exercises may have not helped compliance, and non-technology-based brain exercises, like crossword puzzles, may have been better. "The ideal activities, timing,and effective dosage for cognitive
exercise-based interventions to decrease post-operative delirium risk and burden need further study", Humeiden et al (2020 pE7) stated.

The researchers admitted that "other unquantifiable influences may have affected the study over its duration of more than 4 years, including study personnel changes, growing awareness about post-operative delirium, and implementation of surgical recovery quality improvement programmes at our institution" (Humeidan et al 2020 pE7).

7.5. A/B TESTING

An experiment or controlled trial basically compares a control group ("A"; "usually the current approach") and an alternative group ("B"; "a proposed improvement to a product, service or offer") (Bojinov et al 2020 p49).

Talking about this "A/B testing" in relation to companies testing the market, but relevant to its use generally, Bojinov et al (2020) outlined three pitfalls:

i) The findings will compare the average of A and B groups on the outcome measure(s), but the average of a group includes a wide range. In other words, the individual is ignored.

ii) The assumption is that individuals in groups A and B do not make contact, but online communications, in particular, challenge this. In other words, individuals share information, and participants can learn their experimental condition when the researchers want them to be blind to it.

iii) A/B testing tends to be short-term and so focus on short-term outcomes. But what about long-term changes and effects?

8. APPENDICES

APPENDIX A - PIMS-TS

Among the unusual cases being reported as a consequence of SARS-CoV-2 is a condition named "Paediatric inflammatory multi-system syndrome temporally association with SARS-CoV-2" (PIMS-TS) after seventy children were admitted to a London specialist children's hospital (White et al 2020).

White et al (2020) outlined the cases: "The majority of patients were between 9 years and 16 years of age with the youngest presenting at only 3 months. A higher proportion of patients was male, from black, Asian and minority ethnic groups, and had a parent classed as a key worker. All of the patients presented with a history of fever and most presented with gastro-intestinal symptoms including abdominal pain, diarrhoea or vomiting. A number of patients were transferred following surgery for symptoms and signs classical of acute appendicitis but intra-operatively found to have a normal appendix. Other presenting features included conjunctivitis, rashes and lethargy" (p1). Anti-bodies for SARS-CoV-2 were found in the blood of most of the patients, so PIMS-TS may be triggered by a severe immune response.

At this early stage, information is limited, and so White et al (2020) ended: "We eagerly await the publication of evidence which may support, or disprove an association with SARS-CoV-2. Certainly, the clinical histories taken from this cohort offer fascinating glimpses into the possibilities of an association" (p2).

APPENDIX B - SYNDEMIC

Singer and Clair (2003) observed: "One of the most important functions of any healing system is the imposition of order on the chaos of sickness. Order is imposed in the health arena, in part, through nosology, a classificatory scheme for grouping and separating sickness events and labelling them accordingly on the basis of shared and un-shared features" (p423). Hahn (1995) emphasised the importance of nosology: "A nosology is to forms of sickness what the classificatory schemes of Linnaeus are to the kingdoms of plants and animals, and what the nomenclature of contemporary nuclear physics is to the elementary particles of the universe - electrons, muons, quarks, Z°s, and so on" (quoted in Singer and Clair 2003).

But sickness categories and nosological systems change with time and between cultures. "As these systems change, the ways people - both healers and sufferers, as well as the larger community - think about health and illness change, and, as a result, the ways they respond to sickness change as well. From an applied standpoint, a nosology's value lies in its capacity to provide guidance for mobilising effective responses in prevention

and treatment" (Singer and Clair 2003 p424).

The biomedical approach uses the "International Classification of Diseases" (ICD) produced by the World Health Organisation, or the "Diagnostic and Statistical Manual of Mental Disorders" (DSM) from the American Psychiatric Association. "Normal practice in biomedicine, whether in its diagnostic, research, or treatment capacities, is guided by the conceptualisation of diseases as distinct, discrete, and disjunctive entities that exist (in theory) separate from other diseases and from the social groups and social contexts in which they are found" (Singer and Clair 2003 p424).

This can lead to a disembedded view of disease, whereas the critical biocultural approach and the concept of syndemic, proposed by Merrill Singer, "attempts to identify and understand the determinant interconnections among pressing health problems, sufferer and community understandings of the illness(es)/disease(s) in question, the relevant social, political, and economic forces in play, and (in no small measure as a result of these three influences) the environmental conditions that may have contributed to the development of ill health" (Singer and Clair 2003 p424). Lock (2001) stated: "Recognition that all medical knowledge and practice is historically and culturally constructed and embedded in political economies, and further, subject to continual transformation both locally and globally is essential" (quoted in Mendenhall 2016).

Mendenhall (2016) codified three rules implicit to "syndemic theory":

i) Two or more disease co-exist;
ii) Context con-constructs the disease experience;
iii) An adverse disease interaction is the upshot.

An example would be asthma which often goes with other diseases (co-infection) as well as socio-economic status differences, and environment. For instance, Wright and Steinbach (2001) found that "children exposed to violence in their neighbourhood (eg: hearing gunshots or witnessing physical violence) were twice as likely to experience wheezing and to use bronchodilator asthma medication for wheezing, and almost three times as likely to be diagnosed with asthma compared with children not exposed to violence" (Singer and Clair 2003 p426).

Co-infection refers not just to the individual experiencing two or more diseases together (as in co-morbidity), but that "actual biological interaction occurs" between the diseases. "The nature of this interaction may vary and need not require direct physical interaction to produce new or amplified health consequences (eg: changes in biochemistry or damage to organ systems caused by one pathogenic agent may facilitate the spread or impact of another agent)" (Singer and Clair 2003 p427). The biochemical changes in the body produced by one disease that encourage the development of the second disease can be seen in the

co-infection of hepatitis B and HIV (Singer and Clair 2003).

The term syndemic, for Singer and Clair (2003), also meant the social conditions in which individuals live, and the most obvious observation that living in poverty exacerbates all diseases. Malnutrition and poor diet are "one of the direct routes through which social conditions and inequality impact health and contribute thereby to syndemical enhancement of disease" (Singer and Clair 2003 p429).

As a case study of syndemic, Singer and Clair (2003) quoted their research (eg: Singer et al 2000) with injection drug users (n = 988) in New England, of which 244 were infected with HIV. Among this latter group, 90% had at least one other major disease (con-infection), and most lived in poverty with many homeless (social conditions). Together these factors predict death from AIDS at a higher rate than individuals infected with HIV and having none of the other factors. Singer (1996) referred to "SAVA syndemic" - substance abuse (SA), violence (V) and AIDS (A).

In a similar vein, Mendenhall (2016) coined the term "VIDDA syndemic" to violence, immigration, depression, diabetes and abuse among first- and second-generation Mexican immigrant women in Chicago (figure 6). "VIDDA describes how political-economic and social processes shape and interact with the clustering of depression and Type 2 diabetes... [It] underscores the notion that diabetes is not an endpoint, nor is its overlap with depression the sole focus of the relationship as it is with co-morbidity. Rather, depression and diabetes comprise a biosocial feedback loop wherein they are contributors to and consequences of a stressful life" (Mendenhall 2016 p465).
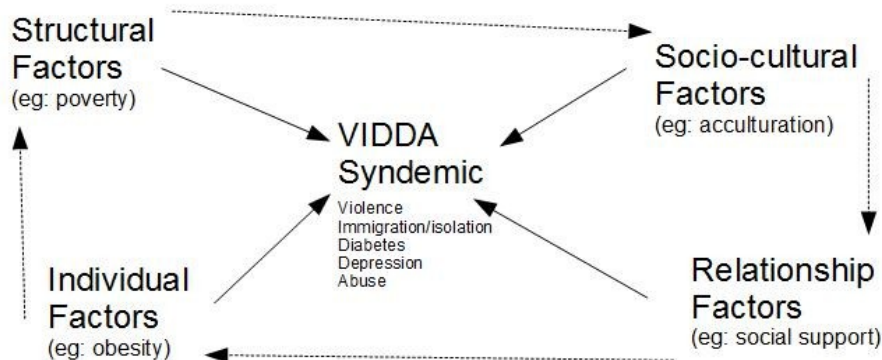
(Based on figure 1 p467 Mendenhall 2016)

Figure 6 - The VIDDA Syndemic.

Mendenhall (2016) considered whether the VIDDA syndemic was applicable to other groups with depression and diabetes, specifically in India and South Africa. The answer was only to a degree. She stated that "syndemic suffering must be realised within a specific context and, although there may be some resemblances to VIDDA, there will be important differences as diabetes emerges among low-income groups in emerging economies and intersects with depression, poverty, structural violence, social problems, and other co-occurring conditions. One notable difference is that because diabetes is relatively new to some lower income communities in emerging economies, which will be discussed below, it may be less recognisable and understood at the community level. This has real consequences for how people identify, understand, care about and seek treatment for their health" (Mendenhall 2016 pp468-469).

Mendenhall (2016) ended with a caution that "there is a risk of using syndemics as a heuristic, much like co-morbidity, without critical review of the social, cultural, and economic factors that may shape the convergence of two diseases" (p473).

APPENDIX C - BIOECONOMY

Rose (2006) referred to "the devolution of many responsibilities for the management of human health and reproduction that, across the twentieth century, had been the responsibility of the formal apparatus of government: devolving these to quasi-autonomous regulatory bodies — bioethics commissions, for example; to private corporations — like private fertility clinics and biotechnology companies selling products such as genetic tests directly to consumers; and to professional groups — such as medical associations — regulated 'at a distance' by the powerful mechanisms of audits, standards, benchmarks, and budgets. These modifications in rationalities and technologies of government have also involved an increasing emphasis on the responsibility of individuals to manage their own affairs, to secure their own security with a prudential eye on the future. Nowhere have these been more telling than in the field of health, where patients are increasingly urged to become active and responsible consumers of medical services and products ranging from pharmaceuticals to reproductive technologies and genetic tests" (p16) [49].

He talked of "an emergent form of life" and the politics of this form of life ("vital politics") to describe changes in the 21st century.

Rose (2006) noted five pathways related to "the space of contemporary biopolitics":

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[49] The definitions of health and disease are changing with pre-state of diseases, like pre-diabetes, which could develop into the full disease. So, to be cynical, it is not possible to say that "I am healthy", rather "I am in a temporary state of undisease".

i) Molecularisation - Life is envisaged at the molecular level, "as a set of intelligible vital mechanisms among molecular entities that can be identified, isolated, manipulated, mobilised, recombined, in new practices of intervention, which are no longer constrained by the apparent normativity of a natural vital order" (Rose 2006 p18).

ii) Optimisation - A desire to find the optimal state for future humans (with no constraints from illness) [50].

iii) Subjectification - The appearance of "biological citizenship" and changes that "recode the duties, rights, and expectations of human beings in relation to their sickness, and also to their life itself, reorganise the relations between individuals and their biomedical
authorities, and reshape the ways in which human beings relate to themselves as 'somatic individuals'" (Rose 2006 p18).

iv) "Somatic experience" - The rise of "multiple sub-professions" to help manage somatic experience (eg: specialists in reproductive medicine).

v) "Economies of vitality" - The growth of private companies making money from the body ("the bioeconomy").

Governmentality

In the late twentieth century, at "a time when the state was seeking to withdraw from so many spheres, and when notions of choice, the customer and the ideal of the entrepreneurial self were gaining such ascendancy", "many socially legitimated authorities seek to interfere in the lives of individuals in sites as diverse as the school, the home, the workplace, the courtroom and the dole queue" (Rose and Miller 2008 p1).
Rose and Miller (2008) reflected on what it meant to govern (or to "conduct conduct"): "If the conduct of individuals or collectivities appeared to require conducting, this was because something in it appeared problematic to someone. Thus, it makes sense to start by
asking how this rendering of things problematic occurred. The term 'problematising' was a useful way of designating this as a process, for it removed the self-evidence of the term 'problems'.

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[50] "Yet the very borders between life and death, borders that are still so final, have become so open to negotiation and dispute. As, indeed, is the liveliness of all those entities such as tissues and ova, hovering between life and death, oscillating between vitality in a test tube or vat and information in a database or biobank. And in so many of our everyday and our medical practices, human bodily and mental capacities are not taken as given, biology is no longer destiny, judgments are no longer organized in terms of a clear binary of normality and pathology, and the familiar distinction between illness and health is blurring. It is becoming increasingly difficult to pretend that there is a line of differentiation between interventions targeting susceptibility to illness or frailty on the one hand, and interventions aimed at the enhancement of capacities on the other" (Rose 2006 p256).

It suggested that 'problems' are not pre-given, lying there waiting to be revealed. They have to be constructed and made visible, and this construction of a field of problems is a complex and often slow process. Issues and concerns have to be made to appear problematic, often in different ways, in different sites, and by different agents. The latter may take the form of accredited experts or professionals, pressure groups, politicians, corporate leaders, the media and others" (p14).

Once there is agreement that there is a problem, then it needs to be rectified. "Many problems came, at some point, to be articulated in terms of a more or less formalised knowledge. Sometimes the formalisation by experts came at an early stage, sometimes it was this formalisation that enabled the problem to become stabilised – for example, as unemployment or maladjustment or dependency – and sometimes the formalisation came after the fact, the problem space being seen as a fertile territory for exploration" (Rose and Miller 2008 p15).

An agreed problem which experts have been instrumental in constructing is now amenable to an intervention, but this could suggest a separateness between the "problem" and the "solution". Rather, "if a particular diagnosis or tool appears to fit a particular 'problem', this is because they have been made so that they fit each other" (Rose and Miller 2008 p15).

In this process of "govermentality" (a term of Foucault's), "technologies" (or "rationalities") become important [51]. These are "assemblages of persons, techniques, institutions, instruments for the conducting of conduct" (Rose and Miller 2008 p16).

Foucault's (1973) description of the development of clinical medicine showed how knowledge and power were inter-related, and "how novel ways of thinking, doing and relating to oneself emerged at a particular historical moment, linked up in all sorts of constitutive ways with the emergence of a new politics and valorisation of health, which was in turn linked with new forms of production in factories, new ways of life in towns and new ways of managing populations and epidemics" (Rose and Miller 2008 p4).

Looking at the history of "psy sciences" and their part in "making up" people, Rose and Miller (2008) argued that "these sciences formed as disciplines around certain 'surfaces of emergence': the line of development did not work from the pure to the applied, the academy to the application, the normal to the abnormal, but the other way round. It was around problems of abnormality, difference and divergence that the psy disciplines took shape. It was because of their perceived or claimed technical capacities to administer persons rationally, in light of a knowledge of what made them tick, that they gained their social credibility" (p9).

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[51] "Technologies of subjectivity" (coined by Foucault), "the aims, methods, targets, techniques and criteria in play when individuals judged and evaluated themselves and their lives, sought to master, steer, control, save or improve themselves" (Rose and Miller 2008 p7).

Biocultural Creatures

"Subject formation" is "the processes through which a human organism comes to be recognised as and to see him- or herself as a specific person within a historically and geographically particular community" (Frost 2018 p897). This idea is linked to Foucault (eg: 1982). Add to this insights from Butler (eg: 1992) that "the subject does not pre-exist the linguistic and cultural forms through which it represents and symbolises itself... When social and political theorists make such a claim, they mean that an individual does not become a person and then, subsequently, use language or enjoy culture. Rather, individuals become persons only through using some form of language and being acculturated and acknowledged in some form of community with symbolic means of self-representation. This... tells us, then, that symbolic and representational forms, as manifest through language, cultural practices, institutional imperatives, economic, social, and political activities, and forms of self-understanding, together shape behaviour, identity, and desire, making us who we are" (Frost 2018 p898).

Yet, at the same time, there are those who challenge "human exceptionalism" (eg: Agamben 2003). "This refusal takes aim at the notion that humans are possessed of some quality — rational, wilful, linguistic, moral, cultural — that exempts them from the forms of conditioning, dependency, and vulnerability that attend living life as a creature" (Frost 2018 p899).

This leaves humans as the same as all animals while constituted by differences. A moving together of biological and political theorists, say, "seeing social norms, political imperatives, institutional organisation, and symbolic forms of self-understanding infuse the embodied subject to an extent that theorists talk of the embodiment of norms, the materialisation of power, or the corporealisation of culture" (Frost 2018 p899). The upshot is an intricate intertwining of biology and culture/society.

Frost (2018) emphasised this point, "through tracing the particulars of how felt psychosocial experiences evoke various biochemical shifts that affect gene transcription and reverse transcription — and thereby the making of the proteins and such that enable our bodies to function — scientists are beginning to assay the ways that experiences of social interaction, and the anticipation and imagination of social interaction, have a constituting effect upon the biological body" (p901). Landecker (2016) talked of "the responsive body".

Frost (2018) proposed ten theses to help in understanding these ideas and in interdisciplinary research:

i) "All living organisms, including humans, are porous" - "The porosity, here, is meant in both the metaphorical sense in which human subjects are constituted in and

through linguistic and cultural forms, and in the literal sense that living organisms, including human subjects, are constituted and compose themselves with and through their engagement with their habitats" (Frost 2018 p904).

The analogy of the cell is used. "There is a continuous movement of substances across the porous boundaries of cells, across the porous boundaries of bodies — and it is this movement and traffic that underpins the process of living and of subject formation" (Frost 2018 pp904-905).

ii) Though the boundaries are porous, it is not the same as no boundary - The difference between the inside and outside of the body is of process rather than substance. This allows for the distinctiveness of an organism while being "embedded among many others and all manner of constituent forces and elements" (Frost 2018 p905).

iii) The movement across the boundary between the inside and outside means that "the biological body is not pure or fixed but rather is constantly building and rebuilding itself. The constant cross-membrane traffic and related cellular activity mean that the form that living human creatures live and experience as ourselves in any given moment is one instantiation of the processes of composing, decomposing, and recomposing that are continuously under way" (Frost 2018 p906).

iv) "All organisms, including humans, are biocultural" - The term "biocultural" is used "to reference the insight that there is no aspect of a living organism that is not cultured" (Frost 2018 p906). Frost (2018) explained: "Such bio-culturing means that bones, cells, DNA, genes—or whatever putatively 'really on the inside' bio-things we can imagine — exist and persist only through the processes of composing and decomposing made possible by the traffic of stuff into and out of cells, across the permeable boundaries of the body. In other words, the 'bio-' of human organisms exists and persists only because stuff on the outside, in the environment, traverses to the inside — and back" (p907).

Four "general groups of phenomena" are involved in the composing and decomposing - biological matter, energy (eg: light), social perceptions, interactions, and experiences, and memory and imagination ("inner-worldly" engagements) (Frost 2018).

v) The habitats that culture living organisms, including humans, are biocultural" - All of the four phenomena mentioned above are involved together.

vi) There is a time lag in the response of creatures to their habitats - Frost (2018) wanted to avoid a simple stimulus-response idea as seen in Behaviourism, say, to explain individuals, by suggesting that responses could be anticipatory (ie: future-looking) as well as to the past.

vii) The living creature is "not reducible to its current habitat" (Frost 2018 p910). This thesis emphasised the previous one and refined the second thesis. So, "the fleshy 'itness' of living bodies — what we experience as the physical form and substance of the embodied self — is a product of that anticipatory carrying forward of past responses" (Frost 2018 p910).

viii) The composing and decomposing of the creature occurs at many different levels, from molecular to global.

ix) "To study subject formation or the development of persons, then, we need to account for all the biocultural constituents formative of living human subjects and to trace the characteristics of those biocultural formations" (Frost 2018 p913).
For example, Wilson (2011) argued that the study of [52]depression "might include not only biochemical imbalances, pharmaceutical prescriptions, dietary patterns, and personal trauma but also social and familial bonds, the experience of health, employment opportunities, institutional inequalities, displacement, cultural norms, political and economic shifts, and cultural or collective trauma" (Frost 2018 p913).

x) The biocultural creature should be understood within the groups that the individual lives.

APPENDIX D - PRE-PRINT ARTICLES

The pre-print server "medRxiv" began in June 2019 as "a means to disseminate research reports before they undergo peer review" (Krumholz et al 2020 p1903) .
Flanagin et al (2020) explained: "A pre-print is a complete manuscript posted to a pre-print server by authors before peer review and publication in a journal. The goals of preprints are to enable authors to obtain timely feedback and comments on research before submission to a peer-reviewed journal, to claim provenance of an idea, and to facilitate and expedite dissemination of and access to research. Pre-prints can be amended or updated, commented on by others, and remain on the preprint server even if subsequently published in a journal. They can be cited and indexed and increasingly are given attention in the news and social media" (p1840).

Krumholz et al (2020) compared the use of "medRxiv" before and after covid-19 in the first year of its existence. The number of submissions increased greatly with the arrival of covid-19, from a median of six per day (during the second half of 2019) to 51 (in the first half of 2020). Most of this increase was due to

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[52] Other pre-print servers have a long history - eg: "arXiv" (1991) for physics research, and "bioRxiv" (2013) for the biological and health sciences (Flanagin et al 2020).

covid-19-related submissions. Overall, 14% of the pre-prints had been published in peer-reviewed journals.

Krumholz et al (2020) ended: "Future studies should evaluate medRxiv after COVID-19, including the extent to which pre-prints that are published change in response to feedback from the scientific community and peer review, and the potential influence that preprints posted to the server have had on clinical research" (p1904).

Malicki et al (2020) analysed 57 open pre-print servers that posted health sciences material, and compared the policies. The majority had "some form of, albeit minimal, screening" (Flanagin et al 2020 p1840) of submissions, but "they provided little explicit guidance on issues that are important for transparency in reporting and research integrity" (Malicki et al 2020 p1903).

Flanagin et al (2020) asked whether the availability of non-peer-reviewed material as in pre-prints benefits patients without causing harm. They could not give a certain answer.

Surveys of researchers report benefits in the free availability of the material to read, but raise concerns about media and public interest before peer review (Flanagin et al 2020). Fraser et al (2020) (a pre-print itself) found that covid-19 pre-prints received more news and social media attention than non-covid-19 pre-prints in the first quarter of 2020. Such coverage did not necessarily relate to "good quality" work (Flanagin et al 2020).

For example, Saltz and Schwitzer (2020) "described concerns regarding the rapid public reporting on the efficacy of hydroxychloroquine and remdesivir for treatment of patients with COVID-19 as examples of how misinformation can damage public trust in science and medicine" (Flanagin et al 2020 p1842).

APPENDIX E – VITAMIN D AND OLDER ADULTS

Maintaining good health into older age is desirable both for the individuals and for the burden of caring on society. A number of interventions have been proposed to help in this. Bischoff-Ferrari et al (2020) reported on three of them – vitamin D supplementation, omega-3 fatty acid supplementation, and strength-training exercise – in the DO-HEALTH trial.

This trial involved over 2100 healthy adults aged at least seventy years old at seven centres in Switzerland, France, Germany, Portugal, and Austria, who were randomised to one of eight groups for three years:

1. Vitamin D supplementation (2000 IU/d) [53].
2. Omega-3 fatty acid supplementation (1 g/d).

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[53] 2000 International Units (IU) per dose (d) is equivalent to 50 micrograms (mcg).

3. Exercise programme (30 minutes three times per week).
4. Vitamin D and omega-3.
5. Vitamin D and exercise.
6. Omega-3 and exercise.
7. All three interventions.
8. Placebo pills and control exercise (joint flexibility).

The outcome measures included blood pressure change, number of infections, physical strength, and cognitive health. These were taken at baseline, and at 12, 24 and 36 months.

None of the groups showed any statistically significant difference from baseline. So, there was no support for the three interventions alone or together. This confirmed other research that "showed no benefit of these interventions in relatively healthy older adults" [eg: Scragg 2019] (Bischoff-Ferrari et al 2020 p1856).

A meta-analysis of omega-3 supplementation (AbuMweis et al 2018) found benefits for reducing blood pressure, but at a higher dose (eg: 3 g/d). Bischoff-Ferrari et al's (2020) finding "may in part be explained by the relatively small dosage of omega-3" (p1866).

In relation to exercise, other research has reported benefits in fall prevention (eg: Uusi-Rasi et al 2015), which was not measured by Bischoff-Ferrari et al (2020).

Here are some methodological issues to consider with Bischoff-Ferrari et al's (2020) study:

i) (+) High adherence to interventions based on telephone monitoring every three months and self-reports, and physiological measures for the pills. It was calculated that 85% of participants took at least 80% of total pills given, and around 60% self-reported adherence to the exercise programme.

ii) (+) Relatively low drop-out and loss to follow-up - 1900 individuals of 2157 completed the study (88%), and 25 deaths were reported "with similar numbers in all treatment groups" (Bischoff-Ferrari et al 2020 p1855).

iii) (-) A large number within the sample were engaging in moderate to high physical activity at baseline, and so "there may have been little potential for further benefit from additional exercise" (Bischoff-Ferrari et al 2020 p1866). The high healthy population was also seen in less fractures than expected, and near maximum scores on outcome measures at baseline.

iv) (+) Standardised procedures in all countries, and "staff dispensing study pills and collecting outcomes, and data analysts were masked to group assignment" (Bischoff-Ferrari et al 2020 p1856).

APPENDIX F - COMPARING HEALTH SYSTEMS

Emanuel (2020) compared eleven health-care systems generally using 22 dimensions (eg: pharmacy prices; finance; workforce), and four countries emerged as better - Germany, the Netherlands, Norway, and Taiwan, while the USA and China were lowest ranked (and France, Switzerland, the UK, Australia, and Canada in the middle). The top systems have choice for patients, universal or near-universal coverage for the citizens, and affordability, for example (Topol 2020). "It is noteworthy that the same four have so far been among the most successful in managing covid-19" (Topol 2020 p332).

Topol (2020) noted that Emanuel's (2020) dimensions did not include adaptation and implementation of new technology, for instance.

Talking about the political leadership in China generally, Pei (2020) made this point in relation to covid-19: "Considering the enormous investments in disease control and prevention that China has made since the SARS outbreak in 2002-3 and the implementation of laws on emergency management in 2007, it has been staggering to see how thoroughly the Chinese government initially mishandled the new coronavirus epidemic. Local authorities in Wuhan - the epicentre of the outbreak - concealed critical information from the public even after medical professionals sounded the alarm... Although they received reports from Wuhan about the spread of the virus in early January, most members of the senior leadership did not take any serious action for two weeks" (p94).

There was also the reaction to Li Wenliang, a doctor, who warned the authorities about covid-19 in December 2019, was forced to "recant" by local police, and died of the disease on 7th February 2020 (Pei 2020).

Pei (2020) argued that the failings "revealed the fragility of [President] Li's [Jinping] strongman rule" (p94).

APPENDIX G - TRANSMISSION-BASED PRECAUTIONS

Outbreaks of a disease will depend upon the movement of the hosts. Jia et al (2020) used mobile phone geolocation data to track the population movement from Wuhan in January 2020. This period included the Lunar New Year (24-25th January), which is a time of great population in China [54].

Jia et al (2020) explained: "The geographical flow of people anticipated the subsequent location, intensity and timing of outbreaks in the rest of mainland China up to 17 February 2020" (p393). This was a better predictor of outbreak than the population size of a prefecture, its wealth or distance from the

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[54] Hubbard (2020) described a potential consequence of covid-19 being "doughnut cities" - "empty centres but vibrant suburbs".

outbreak (ie: Wuhan).

Jia et al (2020) ended: "When people move, they take contagious diseases with them. Their movements are thus a harbinger of the future status of an epidemic, and this offers the prospect of using data-analytic techniques to control an epidemic before it strikes too hard" (p393).

Transmission-based precautions reduce the risk of diseases being transmitted, and are based on contact, droplet and airborne modes (Denton and Hallam 2020).

Contact spread occurs via direct contact (eg: blood of the infected person entering the body of another person), or indirect transmission via a contaminated object or person (eg: a nurse not washing hands between touching an infected and a non-infected patient) (Denton and Hallam 2020).

Droplets spread from the respiratory system of an infected person and make contact with a non-infected individual's respiratory tract, eyes or mouth, while airborne spread (smaller particles) remain in the air after breathing, talking, coughing or sneezing, and are breathed in by another person (Denton and Hallam 2020).

Isolation of infected patients can have negative effects for them (eg: depression and anxiety), and so Denton and Hallam (2020) advised medical staff that "it is the micro-organism(s) that require isolating and not the person. Care should be taken to ensure the precautions taken are appropriate and patients' needs are taken into account" (p30) [55].

APPENDIX H - INTERNATIONAL TRAVELLERS

Quarantine everybody on arrival from abroad, or test everybody and quarantine only the positive tests is a key policy issue.

The UK has a system of covid-19 quarantine for 14 days for all international arrivals, except for countries on an exemption list (known as "travel corridors"). Travellers are not tested [56].

This policy is based on the assumption that testing would detect only 7% of virus cases (Public Health England 2020). Oxera/Edge Health (2020) questioned this conclusion. Using different assumptions in their modelling, these researchers estimated that testing of international arrivals would detect 63% of virus cases [57].

Oxera/Edge Health (2020) made the following criticisms of the theoretical model used by the Public Health England (2020):

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[55] Based on interviews with 18-26 year-olds in Edinburgh and London, McPherson (2020) noted "the disproportionate impact of the pandemic on young people, who are the most likely to have been furloughed, lost their jobs and to have experienced food insecurity".

[56] Writing on 2nd November 2020.

[57] Note that this study was commissioned by the airline and related industries.

i) No consideration of infection rates in the country of origin of the flight, including regional variations within the country.

ii) The individuals likely to fly (eg: richer individuals) are not those in the population most likely to be infected (eg: from deprived communities).

iii) Assumptions are made about the length of infection.

iv) The assumption that self-monitored quarantine compliance is 100%, which overestimates its benefits, whereas real-world data suggests 20% non-compliance (Oxera/Edge Health 2020).

v) Risk from travellers is not assessed in the context of the risk of infection in the UK generally.

Oxera/Edge Health (2020) discussed two other modelling studies:

a) Clifford et al (2020) - This article compared testing on arrival with 6-, 8- and 14-day quarantines. The conclusion was that testing on arrival would reduce the number of infectious travellers released into the community by 45%, while the 14-day quarantine would reduce the number by 99%. This study did not control for passenger demographics, or non-compliance of quarantine (Oxera/Edge Health 2020).

b) Taylor et al (2020) - This paper considered three groups of travellers:

- Non-UK travellers infected prior to travel to the UK;
- Returning UK travellers infected in the UK prior to travel abroad;
- Returning UK travellers infected while abroad.

A number of different policies were compared. It was estimated that testing on arrival would reduce release of infected individuals by 40% compared to 78% for 14-day quarantine. There was no controlling for passenger demographics, and the study ignored the spread of infection by returning UK travellers infected in the UK who had stayed at home (Oxera/Edge Health 2020).

Quarantine

The transmission of SARS-CoV-2 is best observed in controlled situations, of which there are a limited number available. One is a fourteen-day supervised quarantine by US Marine recruits in South Carolina (Letizia et al 2020).

Between mid-May and mid-July 2020, a total of 1848 recruits participated, and "wore double-layered cloth masks at all times indoors and outdoors, except when sleeping or eating; practiced social distancing of at least 6 feet; were not allowed to leave campus; did not have access to personal electronics and other items that might contribute to surface transmission; and routinely washed their hands. They slept in double-occupancy rooms with sinks, ate in shared dining facilities, and used shared bathrooms. All recruits cleaned their rooms daily, sanitised bathrooms after each use with bleach wipes, and ate pre-plated meals in a dining hall that was cleaned with bleach after each platoon had eaten. Most instruction and exercises were conducted outdoors. All movement of recruits was supervised, and unidirectional flow was implemented, with designated building entry and exit points to minimise contact among persons" (Letizia et al 2020 p2). Covid-19 testing was done regularly.

Around 2% of the sample, who were covid-19 negative at arrival, "became positive during the supervised quarantine" (Letizia et al 2020 p4). The majority of the these individuals were asymptomatic. The researchers were able to map the transmission path (ie: the index patient).

What this study shows is the difficulty in stopping transmission completely in large groups, even with highly controlled quarantine measures.

APPENDIX I - INOCULATION AGAINST MISINFORMATION

Maertens et al (2020) discussed an alternative to debunking misinformation, "pre-bunking" or "inoculation". Using the vaccination analogy, it involves "pre-emptively exposing people to weakened doses of persuasive arguments" (Maertens et al 2020). There are two components - forewarning, and refutational pre-emption. A sense of threat is created (forewarning about attempts to change attitudes), and individuals build up skills to refute the misinformation.

The "Bad News Game" (Roozenbeek and van der Linden 2019) was designed on the principles of inoculation theory. "In this free browser game, players enter a simulated social media environment and take on the role of a fake news producer. They design Twitter posts, news article headlines, and memes to gain popularity as a news publisher. Players must gain followers while maintaining a sufficiently high level of credibility. If the credibility meter drops too low, the player loses, and the game ends. This way, the player is forced to think actively about how one can be deceived" (Maertens et al 2020 p3).

The game features six misinformation techniques ("DEPICT") (Maertens et al 2020):

- D - Discrediting opponents (eg: creating doubt around them).

- E - Appealing to Emotions (eg: use of highly emotive language).

- P - Polarising audiences (eg: using "hot-button" issues to divide groups).

- I - Impersonation of famous people (eg: using the identity of celebrities online).

- C - Conspiracy theories (eg: providing alternative narratives to the mainstream based on a sinister group behind events).

- T - Trolling (eg: provoking individuals online).

Roozenbeek and van der Linden (2019) found that 15 000 participants rated fake fictitious Twitter posts as less reliable after playing the "Bad News Game" compared to before. This was an immediate effect, but Maertens et al (2020) found a longer term benefit in three longitudinal experiments.

Experiment 1

The participants (n = 151) were recruited via an online platform and paid a small fee for involvement. Initially, real and fake news headlines were rated for reliability on a seven-point scale (Time 1 - T1), then the participants played the "Bad News Game" (intervention condition) or "Tetris" (control condition) for fifteen minutes. The previously seen headlines were rated again (T2), and then one week (T3), five weeks (T4), and 13 weeks later (T5).
The intervention group rated the fake news items as significantly less reliable at T2 than T1, and this difference remained at T3, T4, and T5.

Experiment 2

This experiment was a re-run with an immediate post-intervention testing of the fake news items (T2) and then nine weeks later (T3). Maertens et al (2020) explained the purpose: "To investigate the inoculation effect retention while eliminating the possibility of learning or boosting effects" (p8). In other words, repeated measurement could be a confounder. The participants were recruited in the same way as Experiment 1 (n = 194).
The inoculation effect was found at T2 (ie: lower reliability ratings for fake news items), but not at T3 for the intervention group. The repeated measurement of Experiment 1 was found to be a confounder. But there was still a similar issue - "the fact that the same items were used at each follow-up, which might have led

to item-response memorisation effects" (Maertens et al 2020 p9). Experiment 3 controlled for this.

Experiment 3

Here there was only an intervention group who were presented with the same news items at pre-intervention (T1) and post-intervention (T2), but different items one week later (T3). The sample was 87 adults.

The mean ratings of reliability was 3.48 (out of 7) at T1, and this was significantly lower at T2 (2.83) and with the different items at T3 (2.79).

These experiments showed an inoculation effect to fake news generally for a period of time after playing the "Bad News Game".

APPENDIX J - CONSPIRACIES GENERALLY

In recent years on the Internet (appendix J1), "QAnon" has grown in popularity. There are differing versions, but the mainstay is a threat to democracy in the USA from within (from "The Cabal" or "Deep State") which President Donald Trump is fighting. Other versions include "paedophilia, blood sacrifice, Satanism and other atention-getting transgressions" (Zuckerman and McQuade 2019).

"Q" (or "Q Clearance Patriot") is supposedly an anonymous insider (close to Trump) who leaves cryptic messages around the Internet for followers to interpret ("Q drops") [58].

Zuckerman and McQuade (2019) "A movement like QAnon is an inevitable outgrowth of the Unreal, an approach to politics that forsakes interpretation of a common set of facts in favour of creating closed universes of mutually reinforcing facts and interpretations" [59]. It is a meta-narrative - "an explanation for otherwise disturbing and confusing events that assures believers that they understand the big picture in ways non-believers do not. This master narrative gives believers a sense of control over uncontrollable events" (Zuckerman and McQuade 2019) [60].

Conspiracy theories are "self-sealing", in that "any objection or disproof can be turned into support for the theory, usually by explaining that information is being withheld to

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[58] Over 3000 brief messages (Zuckerman and McQuade 2019).

[59] Pomerantsev (2019) used the earthy phrase, "the great fuck-off to facts". He stated that "facts are not always the most pleasant things: they can be reminders of our place and our limitations, our failures and, ultimately, our mortality. There is a sort of adolescent joy in throwing off their weight, of giving a great 'up yours!' to glum reality" (Pomerantsev 2019).

[60] The democratising of knowledge (ie: the rejection of experts or official versions of events as the only "truth") can lead to claims of "secret knowledge". This is the idea that it is possible to know the "truth" behind it all in the sense of the "Matrix" films. Put simply, what seemed like everyday concrete reality was a computer simulation pumped into the brain.

prevent the panic of an unprepared and potentially hysterical public" (Zuckerman and McQuade 2019). Sunstein and Vermeule (2009) described conspiracies as "crippled epistemologies" (appendix J2).

The process of deciphering and interpreting the cryptic messages of "Q" is part of the "fun" (in the style of the "Da Vinci Code"). Author Walter Kirn noted: "The audience for internet narratives doesn't want to read, it wants to write. It doesn't want answers provided, it wants to search for them" (quoted in Zuckerman and McQuade 2019).

Zuckerman and McQuade (2019) wanted to emphasise the participatory nature of "QAnon", like "fan fiction", or "an improvisational game" where players compete for interpretations of messages that "go viral". Social media has a civic participation where information is retweeted, shared, and remixed.

Zuckerman and McQuade (2019) used the term "the Unreal" to describe the clash of worldviews, such that there cannot be a consensus. An upshot of this is doubt, which means that common action is limited, because there is no agreement. "Those who benefit from the stasis caused by imposed doubt are those who are already in positions of power. Those who suffer the most are those who have been excluded from power. In that sense, unreality and the doubt it generates is an inherently conservative force" (Zuckerman and McQuade 2019).

"As a worldview conspiracy thinking grants those who subscribe to it certain pleasures: if all the world is a conspiracy, then your own failures are no longer all your fault. The fact that you achieved less than you hoped for, that your life is a mess is all the fault of the conspiracy. The system is rigged. More importantly, conspiracy is a way to maintain control. In a world where even the most authoritarian regimes struggle to impose censorship, it is more efficient to persuade audiences that behind every seemingly benign motivation is a nefarious hidden hand" (Pomerantsev 2019). The ultimate consequence is the ordinary person cannot change anything, and so needs the "strong hand" of their "great leaders" to do so (Pomerantsev 2019).

Nostalgia also plays a part here. Svetlana Boym (quoted in Pomerantsev 2019) distinguished two types of nostalgia - "reflective" (using the past and present to guide the future), and "restorative" (the desire to "rebuild lost homelands") (Pomerantsev 2019). The Internet encourages nostalgia. "This is part of the paradox of the new media. It was meant to take us further into the future; instead, it has brought us back to the past. The very structure of social media scrambles time, place, and proportion. Terror attacks sit next to cat videos, the latest jokes surface next to old family photos. The result is a sort of flattening, as if past and present are losing their relative perspective" (Pomerantsev 2019).

Boyd (2019) used the term "apophenia", which "refers to the idea of making connections between previously unconnected ideas. Unlike the concept of learning, apophenia suggests a cognitive disorder because the connections made are not real. They are imaginary. People see patterns that don't exist and devise elaborate internally coherent explanations for non-sensical notions". Boyd (2019) continued: "From the outside, it looks completely unreal, but on the inside, it feels quite real. This is not because any single piece of information is real, but because the process of doubt and discovery is invigorating. It feels like gambling based on lucky numbers or going all-in on a grand theory of life, the universe, and everything".

Miscellaneous

I would use the term "accepting cynicism" or "gullible cynicism" to describe a situation of believing some things or people without evidence or critical reflection, while never believing others, despite supportive evidence, and/or assuming the worst of them (eg: "all politicians are crooks") (figure 7). Those in the ingroup would be the former and the outgroup the latter [61].
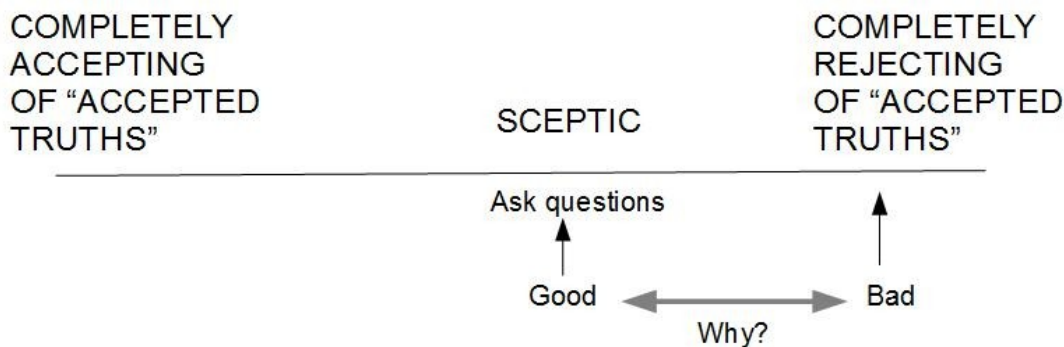

Figure 7 - A representation of accepting and rejecting truth.

Reflecting on general disinformation in the Western Balkans between 2008 and 2020, Greene et al (2020) noted different patterns of disinformation, including:

a) In countries dominated by a single party, disinformation serves their interests and undermines opponents.

b) In competitive political environments, all sides make use

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[61] A survey of 2 244 UK residents aged 16-75 years old in late November 2020, found a negative view of "anti-vaxxers" from the majority (Duffy et al 2020).

of disinformation for short-term gains.

c) Where there are sectarian divides, disinformation exacerbates these.

Covid-19 has provided "fertile ground for disinformation" in these countries. "Governments throughout the Western Balkans have sought to falsify their record on handling the pandemic, while others have injected many of the same false claims found elsewhere. In addition, China and, to a lesser extent Russia, have used the pandemic as an opportunity to build leverage in public opinion, at the expense of the EU [European Union]..." (Greene et al 2020 p6).

Appendix J1 - Moral Contagion

Brady et al (2020) explored the spread of "moralised content" through online social networks - a phenomenon they called "moral contagion", and the Motivation, Attention, and Design (MAD) model to explain it. "The MAD model posits that people have group-identity-based *motivations* to share moral-emotional content, that such content is especially likely to capture our *attention,* and that the *design* of social-media platforms amplifies our natural motivational and cognitive tendencies to spread such content" (Brady et al 2020 p978) (figure 8).
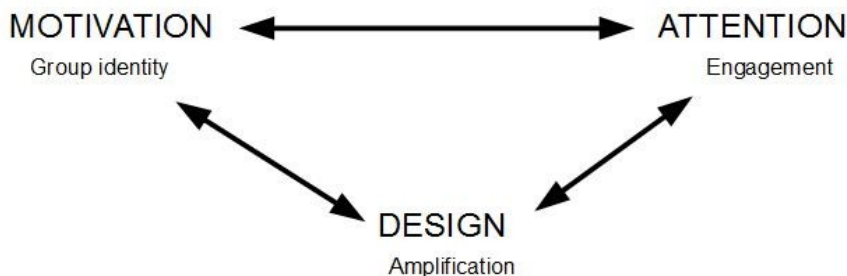
(Based on Figure 3 p984 Brady et al 2020)

Figure 8 - The MAD model.

Moralised or moral-emotional content refers to any material that can be understood in terms like "good" or "bad". "For example, a social-media message communicating thoughts about gun control in America is often construed as moralised content because the topic of gun control is situated in a cultural discussion of whether stricter gun laws are good or bad for American society. On the other hand, a social-media message about cute kittens does not reference a topic that is typically construed in terms of it being

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good or bad for society" (Brady et al 2020 pp978-979).

The spread of content as in "going viral" depends upon it being emotionally arousing. For example, Berger and Milkman (2012) found that, among 7000 news items, those more likely to be shared by email induced awe, anger, and anxiety (Brady et al 2020). "Moralised content", which can describe conspiracy material, is, thus, more likely to be shared in "moral contagion".

Brady et al (2020) emphasised the importance of group identity in the MAD model in that "people are strongly motivated to maintain not only a positive in-group image relative to the out-group (inter-group-identity motivation) but also a positive reputation of themselves in their group (intra-group-identity motivation). Expressions of group-based moral emotions readily serve these motivations by derogating the out-group (eg: outrage, contempt), bolstering the in-group (eg: elevation, awe), and repairing the ingroup's image (eg: guilt, shame)" (Brady et al 2020 p989).

The design of social media amplifies such processes. For example, individuals form networks based on shared identity more than in face-to-face interactions (ie: this hypersensitises the identity), and online interactions deindividuate the out-group (ie: to devalue them) [62]. Also feedback to postings is immediate and the positive social feedback of "likes" is rewarding.

The group identity also influences the attention as does the design of social media (eg: "content algorithms"). "For instance, users embedded in social networks that are composed of anti-vaccine proponents (who consider vaccinations morally wrong because of their supposed harm) are especially drawn to content that is related to the effects of vaccines and specifically content that supported their moral views about vaccines" (Brady et al 2020 pp994-995).

Appendix J2 - Sunstein and Vermeule (2009)

Sunstein and Vermeule (2009) used the definition "that a conspiracy theory can generally be counted as such if it is an effort to explain some event or practice by reference to the machinations of powerful people, who attempt to conceal their role (at least until their aims are accomplished)" (p205).

They continued: "The appeal of some conspiracy theories, then, lies in the attribution of otherwise inexplicable events to intentional action, and to an unwillingness to accept the possibility that significant adverse consequences may be a product of invisible hand mechanisms (such as market forces or evolutionary pressures) or of simple chance, rather than of

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[62] There is less personal cost to expressing negative views about the out-group than might be in face-to-face interactions. "With group identities more salient and reduced personal costs, people on social media are much more likely to use information exchange to derogate out-groups via the expression of moral emotions such as outrage" (Brady et al 2020 p1000).

anyone's plans" (Sunstein and Vermeule 2009 p208).

Sunstein and Vermeule (2009) wanted to emphasise that "those who hold conspiracy theories… typically do so not as a result of a mental illness of any kind, or of simple irrationality, but as a result of a 'crippled epistemology'" (p204).

These authors noted that some conspiracy theories "seem to bubble up spontaneously, appearing roughly simultaneously in many different social networks; others are initiated and spread, quite intentionally, by conspiracy entrepreneurs who profit directly or indirectly from propagating their theories" (Sunstein and Vermeule 2009 p212).

After a "bad event", there are rumours and speculations about the cause. "To some people, those speculations will seem plausible, perhaps because they provide a suitable outlet for outrage and blame, perhaps because the speculation fits well with other deeply rooted beliefs that they hold. Terrible events produce outrage, and when people are outraged, they are all the more likely to seek causes that justify their emotional states, and also to attribute those events to intentional action. Conspiracy theories, like rumours, may simultaneously relieve 'a primary emotional urge' and offer an explanation, to those who accept the theory, of why they feel as they do; the theory 'rationalises while it relieves' [Allport and Postman 1947]" (Sunstein and Vermeule 2009 p213).

Sunstein and Vermeule (2009) outlined the key factors in "conspiracy cascades" (ie: how conspiracy theories spread within a group):

a) The spread of information as part of social interactions.

b) Conforming with others in order to maintain reputation.

c) The cognitive "availability" of an event (ie: it is highly salient to individuals).

d) A strong emotional reaction to the event.

e) Group polarisation - "members of a deliberating group typically end up in a more extreme position in line with their tendencies before deliberation began" (Brown 1986 quoted in Sunstein and Vermeule 2009).

f) Membership of a group – As group polarisation occurs, more extreme members join and the group's views are polarised further.

APPENDIX K - MISDEMEANOURS OF SCIENCE

Pharmaceutical Companies

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Spinney (2020) began: "In the race to find treatments and a vaccine for covid-19, it is more essential than ever that society can trust drug companies seeking regulatory approval" (p26). Jureidini and McHenry's (2020) recent book offered a negative picture. "They warn that when clinical science is hitched to the pharmaceutical industry's dash for profits, the scientific method is undermined by marketing spin and cherry-picking of data" (Spinney 2020 p26).

This work along with other books like Angell (2004), Goldacre (2012), and Gotzsche (2013) showed the continuing "organised crime" (as Gotzsche called it) with pressure on journals to only publish certain articles, and regulators to approve drugs (Spinney 2020).

Concern about the "extent to which the pharmaceutical industry controls the content of journal articles with marketing 'spin' has led some to charge that 'journals have devolved into information laundering operations for the pharmaceutical industry' [Horton 2004]" (Jureidini et al 2016 p34).

Jureidini et al (2016) showed this process in the case of citalopram, an anti-depressant, and its use with children and adolescents, after industry documents became available in a US trial. The clinical trial was published as Wagner et al (2004), and technically was "Forest Laboratories" study CIT-MD-18.

Jureidini et al (2016) explained the situation: "Published reports from pharmaceutical industry-sponsored clinical trials seldom receive critical scrutiny when selective data reporting, statistical manipulation, ghostwriting and academic misconduct are alleged. The fact that the data remain the company's intellectual property protected by trade secrets law, frustrates the efforts of researchers to conduct independent analyses. When injured plaintiffs file suit against the drug manufacturers for fraud or damages, the confidential industry documents often remain sealed by the court unless settlement agreements dictate otherwise. In the United States case of the 'Celexa and Lexapro Marketing and Sales Practices Litigation', part of which settled in 2014, plaintiffs, attorneys challenged the confidentiality designation of Forest's citalopram CIT-MD-18 study documents and of the expert witness declarations submitted as plaintiffs' evidence. As a result, a sub-set of the confidential documents was de-designated as confidential and posted on the Drug Industry Document Archive" (p34).

Analysis of the court documents "revealed that protocol-specified outcome measures showed no statistically significant difference between citalopram and placebo. However, the published article concluded that citalopram was safe and significantly more efficacious than placebo for children and adolescents, with possible adverse effects on patient safety" (Jureidini et al 2016 p33).

Jureidini et al (2016) summed up: "We have concluded that citalopram's apparent superiority arises from Forest management

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and the ghostwriters: (1) presenting favourable post hoc results as though they were protocol designated secondary outcomes; (2) not presenting unfavourable outcomes; (3) failing to publish an unblinding error sufficient to compromise the statistical significance of primary outcomes; (4) obscuring age-by-treatment interaction by presenting misleading effect size results; (5) inaccurately reporting safety results; and, (6) appending the names of academic "authors" to a ghostwritten article, likely to lend it scientific authenticity" (p41).

Nursing Sanctions

Professional bodies for nurses, for example, have codes of conduct with "fitness to practice" criteria. Four different types of sanctions can be applied in cases of "misconduct" (NT 2020):

i) Caution - No restriction on the ability to practice/work.

ii) "Conditions of practice" - The individual is prevented from carrying out certain types of work and/or must attend retraining.

iii) Suspension - Suspended from practice for a set period.

iv) "Striking off" - No longer able to work in that profession in that country. The individual can subsequent apply to practice again at a later date.

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