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COVID-19: KNOWLEDGE DEVELOPS (1st half of 2020)

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

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

CONTENTS

1. INTRODUCTION

1.1. SCIENCE

Beer (1980) argued that "contemporary scholarship is trapped in its present organisation of knowledge in which, while a man 'who can lay claim to knowledge about some categorised bit of the world, however tiny, which is greater than anyone else's knowledge of that bit, is safe for life', and in which, while papers increase exponentially, and knowledge grows by 'infinitesimals', our understanding of the world 'actually recedes'" (Wynter 1984 p21). Though this was written in relation to the development of rational thought, it is applicable to any situation where information is required and questions are asked. But how to provide that information or answer the questions when nobody knows?

In science, individuals set about systematically finding out about the "new thing", and, in time, hopefully, information is collected to answer the asked questions.

Yet as knowledge increases, there is a feeling that the understanding of the world is actually less. The discovery of one answer produces many more questions.

The speed of scientific knowledge about covid-19 is impressive (compared to past pandemics), yet key gaps in understanding exist. But "uncertainty is intrinsic to science. Normally, a gradual accumulation of evidence and scrutiny by the community means that mistakes get weeded out and a consensus emerges. That system works well normally, but science is now under the full glare of the public spotlight and under pressure to provide quick answers. In these circumstances, scientists must make clear the uncertainties in their evidence. They must acknowledge that, when faced with such uncertainties, different scientists may occasionally reach different conclusions about the relative likelihood of various possibilities, which will affect their advice" (Ramakrishnan 2020 p5).

1.2. PRE-PRINT PUBLICATION

The Leader (2020b) stated: "The covid-19 pandemic has upended many of the things that we once took for granted, but perhaps the most insidious is what it is doing to our ability to tell fact from fiction. Science

remains the best tool we have - though by no means a perfect one - for creating reliable knowledge. It is playing a central and mostly heroic role in the fight against the coronavirus. Yet it is also becoming hard at times to sort good science from bad, and worthwhile hypotheses from conjecture, hyperbole and nonsense" (p7).

One cause is the pre-print publication of studies [1], which are picked up and spread by non-experts via social media for reasons from the desire for knowledge to malicious ones [2] [3].

Ioannides (2020) pointed out that at the beginning of March 2020, the most popular pre-print publication suggested an "uncanny similarity" between SARS-CoV-2 and HIV-1 (Pradham et al 2020 quoted in Ioannides 2020). "The paper was rapidly criticised as highly flawed, and the authors withdrew it within days. Regardless, major harm was already done. The preprint fuelled conspiracy theories of scientists manufacturing dangerous viruses and offered ammunition to vaccine deniers. Refutation will probably not stop dispersion of weird inferences" (Ioannides 2020 p1). Other cases of retracted pre-print publications have occurred (Ioannides 2020).

1.3. NUMBERS AND RECOMMENDATIONS

Predictions of the death toll from covid-19 are of limited use because of a number of factors (The Leader 2020a) including [4]:

i) Lack of information about the fatality rate of the virus, and there are environmental factors that influence this rate like the availability of medical equipment.

ii) The number of people who will catch the virus, and then inflect others (which depends on policies restricting movement).

iii) The nature of immunity - temporary or permanent.

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[1] Pre-print publication websites allow others in the field to see preliminary findings and to comment, but now "people who wouldn't normally be interested in biomedical pre-prints, and don't necessarily understand or care about their limitations, have started reading and sharing them. That includes politicians, policy-makers, journalists, bloggers, social media influencers, armchair pandemic warriors, political agitators and conspiracy theorists" (Lawton 2020c p12).

[2] Lawton (2020c) described the emergence of a parallel pandemic of "rumours, unverified claims and malicious falsehoods" (p12).

[3] A good example is the drug hydroxychloroquine (appendix A).

[4] There is a feeling that numbers give truth to a phenomena (appendix B).

iv) The development of vaccines and/or drugs.

Ioannides (2020) warned against exaggerated claims and non-evidence-based recommendations. In the former case, an early speculation that 40-70% of the world's population will be infected, for example, has remained in circulation despite subsequent downward estimates.

In another example, the World Health Organisation (WHO) made an early estimate of case fatality rate (CFR) (ie: the number of infected individuals who die) over 3%, but subsequently more complete data suggested below 1% (Ioannides 2020) [5].

In terms of non-evidence-based recommendations, national lockdown has been adopted by many countries. Evidence from previous respiratory virus epidemics advocate the benefits of physical hygiene (eg: frequent hand-washing; appendix C) and avoidance of sick individuals (Jefferson et al 2011). There is limited research on personal protective equipment (Ioannides 2020).

"Given the uncertainties, one may opt for abundant caution and implement the most severe containment measures. By this perspective, no opportunity should be missed to gain any benefit, even in the absence of evidence or even with mostly negative evidence. This reasoning ignores possible harms. Impulsive actions can indeed cause major harm. One clear example is the panic shopping which depleted supplies of face masks, escalation of prices and a shortage for medical personnel. Masks, gloves and gowns are clearly needed for medical personnel, and their lack poses healthcare workers' lives at risk. Conversely, they are meaningless for the uninfected general population. However, a prominent virologist's comment that people should stock surgical masks and wear them around the clock to avoid touching their nose went viral" (Ioannides 2020 p2).

Phrases like "once-in-a-century" pandemic, and comparisons with the 1918 influenza pandemic (that killed 20-40 million people) are not necessarily helpful (Ioannides 2020).

Ioannides (2020) ended his editorial (written in early March 2020) warning: "If COVID-19 is not as grave as it is depicted, high evidence standards are equally relevant. Exaggeration and over-reaction may seriously damage the reputation of science, public health, media and policymakers. It may foster disbelief that will jeopardise the prospects of an appropriately strong response if and when a more major pandemic strikes in the future" (p4).

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[5] The CFR of other coronaviruses is 8% in elderly care homes (eg: Patrick et al 2006; Canada) (Ioannides 2020).

2. EARLY UNDERSTANDINGS [6]

2.1. VIRAL LOAD AND SYMPTOM SEVERITY

What is the relationship between the number of virus particles in the body and the severity of sickness? Logic would suggest that more particles will produce greater severity. For influenza, for example, higher doses of virus lead to worse symptoms (Geddes 2020a).

Firstly, there is a minimum number of particles needed to establish an infection (known as the infection dose - "the spark that gets the fire going"; Edward Parker in Geddes 2020a). This is probably low (a few hundred or thousand particles) based on the rapidity of spread (Willem van Schaik in Geddes 2020a).

Viral load is "the number of viral particles carried by an individual and shed into the environment" ("how bright the fire is burning"; Edward Parker) (Geddes 2020a p8). Viral load does not necessarily correlate with symptom severity.

For example, a study of 5000 infected people in the Lombardy region of Italy, found no difference in viral load between those with symptoms and those without (Cereda et al 2020) [7].

Similarly in China, throat swabs from ninety-four patients (at Guangzhou Eighth People's Hospital) found no relationship between viral load and symptom level (He et al 2020).

On the other hand, another study from China found a strong association between severity of the covid-19 symptoms and amount of virus present in the nose (Liu et al 2020) [8]. The mean viral load of severe cases was about sixty times greater than of mild cases.

2.2. SUMMER AND THE VIRUS

In winter, viruses cause more cases of illness because of colder, drier conditions with lower levels of ultraviolet light (which suit viruses) (environmental factor - virus), humans in closer contact indoors and

[6] Initially written 6th April 2020.
[7] This was based on nasal swabs of the first 5830 laboratory-confirmed cases in the area.
[8] Based on nasal swabs from both nostrils of seventy-six patients admitted to the First Affiliated Hospital of Nanchang between 21st January and 4th February 2020. The patients were divided into mild (61%) and severe (39%) based on characteristics like severe complications, and breathing problems requiring oxygen.

have a weakened immune system (environmental factors - humans) (Lawton 2020a) [9]. These change in the summer and so there are less cases of illness (table 1). What about the situation with covid-19, will the number of cases decline in the northern hemisphere summer?

Studies on viruses in previous outbreaks have found a relationship between transmission and temperature, including:

- The optimum environmental temperature for transmission of SARS (severe acute respiratory syndrome) was 16-28 °C based on cases from Hong Kong, and Guangzhou, Beijing, and Taiyuan in China (Tan et al 2005).
- Laboratory studies on coronaviruses found them "inactivated more rapidly at 20 °C than at 4 °C" (p4), and less stable and viable at 38 °C, say (Xie and Zhu 2020) (appendix D).

Table 1 - Temperature and previous outbreaks.

Luo, W et al (2020) (table 2) suggested not. A comparison of countries in south-east Asia involving cold and dry (low absolute humidity [10]) areas with humid and tropical (high absolute humidity) ones found no significant difference in transmission rates.

- Daily epidemiological data were collected for 23rd January to 10th February 2020 for each province of China, and, as comparison, for Thailand, Singapore, Japan, South Korea, Hong Kong, and Taiwan, along with weather reports.
- A reproductive number (R) (or measure of potential disease transmissibility) for the virus was estimated (ie: "average number of people a case infects before it recovers or dies") (table 3).
- Dry and cold areas - eg: Jilin and Heilongjiang provinces of China.
- Warm and humid areas - eg: Guangxi province of China; Singapore.

Table 2 - Details of Luo, W et al (2020).

Also Xie and Zhu (2020) reported no relationship between increased temperature and reduced cases of covid-19 using data from 118 cities in China for the period 23rd January to 29th February 2020. But the data covered winter in China and the maximal mean temperature was 27 °C [11].

[9] Influenza viruses, for example, survive longer on surfaces or in droplets in cold and dry air (Luo, W et al 2020).
[10] Absolute humidity is defined as the "water content in ambient air" (Luo, W et al 2020).
[11] This paragraph was initially written on 22nd April 2020.

Bannister-Tyrell et al (2020) reported the opposite. Up to the 29th February 2020, all global confirmed cases (n = 13 479) in forty-seven countries (but mostly in China) fitted the pattern of higher temperatures/lower disease incidence [12].

The R number has four elements (DOTS) (Kucharski 2020):

- Duration (D) - how long an individual is infected.
- Opportunities (O) - the number of interactions (opportunities) to infect others.
- Transmission probability (T) - how likely transmission is during an interaction.
- Susceptibility (S) - of the non-infected person.

Isolation and social distancing can control D, O and T, while wearing a face mask in public places lowers T. A vaccine is a solution for S.

Table 3 - The R number [13].

[12] The researchers controlled potential confounders, like median age of national population and capacity of country to detect cases, in their analysis.
[13] Written 24th June 2020.

3. SEARCH FOR A VACCINE

3.1. VACCINE TESTING

Cohen (2020a) outlined the situation: "As desperately as the world wants a shot that provides protection from the new coronavirus afflicting one country after another, proving that a vaccine works safely can be painfully slow. Clinical trials start with small numbers of people and at first only look for side effects and immune responses, slowly building up to a large study that tests efficacy — a process that will take at least 1 year for the new virus. But as the scale of the pandemic becomes clearer, a provocative, ethically complicated proposal to shave many months off that timeline is gaining traction: Give people an experimental vaccine and then deliberately try to infect them" (p16). These are called "human challenge" trials, and have been used with dengue fever and cholera, for example (Cohen 2020a). Bioethicist, Jonathan Ives summed up the ethical dilemma - individuals put their lives at risk for the good of society (McKie 2020) (appendix E).

But US immunologist Matthew Mermoli pointed out that covid-19 is "so new it is not clear how often it makes people seriously ill or leaves them with long-term complications. 'When you're going to give somebody a virus on purpose, you really want to understand the disease so that you know that what you're doing is a reasonable risk'. He also questions how quickly a proper human challenge of the new pathogen could be done. The challenge virus would first have to be grown under contamination-free, high-quality standards, and researchers would also have to determine the proper dosing of the challenge virus with, say, a monkey model, and confirm the dose in unvaccinated people" (Cohen 2020a p16) [14] [15].

Two safeguards with a "human challenge" trial would

[14] The hope of a vaccine has to be tempered by the reality. For example, it has been estimated that the average experimental vaccine has a 6% chance of "reaching the market" (according to one study). While, in another study, the probability of success of the vaccines that make it to trial is 33.4% (Arnold 2020a). Furthermore, the average vaccine takes 10.7 years to develop from start ot finish, or five years in the case of the fastest-developed one for Ebola (Arnold 2020a).

[15] There is the possibility of the BCG vaccine (for tuberculosis) as a stopgap. A negative correlation between number of BCG vaccinations and covid-19 cases/deaths by country has been reported (Lawton 2020b).

be only enrolling young adults (who seem to have less severe symptoms), and use a weakened version of the coronavirus (Cohen 2020a). Immunologist, Eleanor Riley pointed out that having an effective drug that cleared the infection would also be desirable (McKie 2020).

Another possibility is the use of volunteers already "trained to take risks", like healthcare workers rather than the general population (bioethicist Seema Shah in Cohen 2020a).

Iwasaki and Yang (2020) stressed the importance of using knowledge about anti-bodies in response to SARS-CoV when considering vaccines for SARS-CoV-2 and developing anti-body responses. "The quality and quantity of the anti-body response dictates functional outcomes" (Iwasaki and Yang 2020 p339) (eg: neutralising anti-bodies which block viral entry to the cell [16]).

In rare cases, "pathogen-specific anti-bodies can promote pathology, resulting in a phenomenon known as anti-body-dependent enhancement (ADE)" (Iwasaki and Yang 2020 p339). ADE for SARS-CoV has been studied in mice, for example (Iwasaki and Yang 2020). There are multiple factors that determine whether an anti-body neutralises a virus, or causes ADE and acute inflammation. "These include the specificity, concentration, affinity and isotype of the anti-body" (Iwasaki and Yang 2020 p339).

Iwasaki and Yang (2020) were clear: "We argue that ADE should be given full consideration in the safety evaluation of emerging candidate vaccines for SARS-CoV-2" (p341).

3.2. ALTERNATIVES

Valk et al (2020) found eight studies on blood plasma from recovered covid-19 patients being used to treat current patients (known as "convalescent plasma"). The studies had methodological flaws which made a conclusion about the effectiveness of the treatment not possible. Methodological issues included small samples (total 32 patients), no randomisation usually because no control group, follow-up varying between three and 37 days, and various outcome measures used. Where there was an improvement, it was unclear if this treatment was responsible, another treatment, or it was the natural progression of the disease.

Furthermore, if the treatment is effective, it is difficult to perform on a large scale (Hamzelou et al 2020).

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[16] In one study (Wu et al 2020), 70% of individuals who had recovered from mild covid-19 in China had measurable neutralising anti-bodies (Iwasaki and Yang 2020).

3.3. ANIMAL STUDIES [17]

Development of a vaccine will make use of animal models, like Syrian golden hamsters, for example, which have recently been infection with covid-19. Chan et al (2020) found that eight infected hamsters lost weight, became lethargic, developed ruffled fur, and rapid breathing (Cohen 2020b).

Mice, on the other hand, show no response to infection because of differences to humans in a protein receptor on the cells called angiotension-converting enzyme 2 (ACE2) (Cohen 2020b). One possibility is to genetically engineer mice with the human version of ACE2, but when this was tried with the SARS coronavirus (similar to SARS-COV-2 that is causing covid-19; appendix F), the animals showed only mild symptoms, but later died of a brain disease (Cohen 2020b).

Rats are also less susceptible to covid-19 than humans (Cohen 2020b).

Ferrets, used in influenza research, have been tested with covid-19 (Kim, Y-I et al 2020), but with limited success (eg: increased body temperature and a few other symptoms) (Cohen 2020b). However, the researchers did learn about respiratory transmission: "The animals they infected not only spread SARS-CoV-2 to cage mates, but to two of six ferrets in adjoining cages. Although researchers suspect SARSCoV-2 primarily transmits through relatively large respiratory droplets that quickly fall to surfaces, this finding suggests finer particles, able to drift in the air for longer periods and over longer distances, can also carry infectious virus" (Cohen 2020b p222).

Monkeys have been tried in a Dutch study (Rockx et al 2020). None of the eight infected cynomolgus monkeys developed symptoms, but autopsies found some lung damage from the virus in two of four animals (Cohen 2020b).

In China, two rhesus monkeys that recovered from infection with SARS-COV-2 were resistant to reinfection four weeks later (Cohen 2020b). "The finding provides a hint of good news, as it suggests both natural infections and vaccine-triggered immunity will provide at least some subsequent protection" (Cohen 2020b p222).

Cats have also been studied (eg: Shi et al 2020), and autopsies showed that the virus "led to 'massive' lesions in their nasal passages, trachea, and lungs" (Cohen 2020b p222).

Santini and Edwards (2020) assessed the limited research on anthroponosis of SARS-CoV-2 (ie: humans infecting non-human species) (and the risk of reverse

[17] Initially written 23rd April 2020.

anthroponosis - non-human species re-infecting humans). The animals may or may not suffer symptoms of covid-19, but they would be a reservoir for the virus.

The authors summed up: "Domestic species whose population numbers are sufficient to act as a reservoir include cats and dogs... Farmed wildlife such as mink and pigs could also become reservoir species. In addition to wild bats, rodents could potentially act as a reservoir species because they have sufficient numbers and densities for continuous transmission..." (Santini and Edwards 2020 p1).

3.3.1. Ethics

"The Belmont Report" by the US Department of Health and Human Services in 1979 established the principles of human research ethics across science and health studies, summarised as "respect for persons (generally articulated as respect for autonomy), obligations to beneficence and justice, and special protections for vulnerable individuals and populations" (Ferdowsian et al 2020 p19). It grew out of a concern that researchers had not given sufficient attention to such ideas.

Ferdowsian et al (2020) advocated an equivalent for non-human animal research. Though there are laws related to animal welfare in different countries, "there continue to be significant inconsistencies among animal research regulations, and individuals serving on institutional review committees still have no clear set of ethical principles from which to ground decisions about protocol approval" (Ferdowsian et al 2020 p20).

The authors suggested "reconceptualising and restructuring animal research to be more akin to human clinical research. Such an approach involves 'animal patients', who may be considered 'natural' models for human disease since they spontaneously develop a condition or disease analogous to that found in humans. Rather than being genetically modified or bred for the sole purpose of experimentation, and housed in laboratory conditions, animal patients live in homes with non-institutional human caregivers and guardians. They can be enrolled into a clinical trial in a way that is analogous to the way human patients are enrolled into multi-centre clinical trials. That is, when animal patients present to a veterinarian and are diagnosed with a condition or disease of interest for which experimental subjects are being sought, they could be offered participation in the research. If the animal's guardian consents to their becoming a research participant, they could remain in the guardian's care, and depending on the nature of the research, they could continue to reside in their own home environment while participating in the research" (Ferdowsian et al 2020 p32).

4. PREVALENCE AND RISK

4.1. GENERAL PREVALENCE [18]

Accurate assessment of the risk of covid-19 depends on the reporting of all symptomatic cases, and estimates vary between countries (eg: 3- 95% of the population get infected) (Hamzelou 2020c). "What these statistics don't reflect is the number of symptomless cases, which some evidence suggests can account for between a quarter and half of all coronavirus infections" (Hamzelou 2020c p10).

Because of the variety in data from reported cases, prevalence estimates that sample a population is one method to use, and/or including anti-body tests. However, these methods also produce a huge variation (eg: 0.4 - 59% of the population infected in different countries) (Hamzelou 2020c).

The difference in figures may be real, in the sense of differences between populations, or a product of the methodology (eg: coronavirus tested used). Tests vary in specificity (false positives) and sensitivity (false negatives) (Hamzelou 2020c).

4.2. FATALITIES [19]

Rodriguez-Morales et al (2020) reported an approximate fatality rate of 2-3% (from data up to 8th March 2020). The key risk factors for a poor outcome are older age, a history of smoking (appendix G), and hypertension and heart disease (eg: from the background of the first patient deaths in Italy) (Ogen 2020) [20].

The cause of death is often actually "cytokine storm syndrome"- uncontrolled release of pro-inflammatory cytokines - ie: "a severe reaction of the immune system, leading to a chain of destructive processes in the body

[18] Written on 24th June 2020.
[19] Initially written 22nd April 2020.
[20] Clark et al (2020) calculated that one in five individuals globally has a health condition that increases their risk of severe covid-19 disease. "However, for many of these individuals the underlying condition will be undiagnosed or not severe enough to be captured in health systems, and in some cases the increase in risk may be quite modest. There is an urgent need for robust analyses of the risks associated with different underlying conditions so that countries can identify the highest risk groups and develop targeted shielding policies to mitigate the effects of the COVID-19 pandemic" (Clark et al 2020).

that can end in death" (Ogen 2020 p2) (table 4).

- Elevated levels of cytokines is not accepted by everyone as the cause of death in patients. For example, some autopsies have found blood clots or cardiovascular diseases as the cause of death in confirmed covid-19 sufferers (Wadman et al 2020).

- "Scientists are struggling to understand exactly what causes the cardiovascular damage. The virus may directly attack the lining of the heart and blood vessels, which, like the nose and alveoli, are rich in ACE2 receptors. Or perhaps lack of oxygen, due to the chaos in the lungs, damages blood vessels. Or a cytokine storm could ravage the heart as it does other organs" (Wadman et al 2020).

- Another cause of death is kidney failure, as reported in a quarter of 85 patients in Wuhan (cases up to 3rd March 2020) (Diao et al 2020), and kidney-related problems in around half of 193 covid-19 patients in Wuhan and surrounding areas of China (Anti-2019-nCoV Volunteers et al 2020). Elsewhere a case of gastro-intestinal-related cause of death has been found (a 71 year-old woman; Carvalho et al 2020). Xiao et al (2020) reported SARS-CoV-2 in faecal samples in China, which raises the "unsettling possibility" of transmission via that means (Wadman et al 2020) [21].

- Zhang et al (2020) reviewed the studies on liver damage (2-11% of covid-19 patients) and up to half had elevated levels of enzymes indicating liver damage (Wadman et al 2020).

- The possibility that the virus could penetrate the central nervous system has also been reported (a 24 year-old man in China; Moriguchi et al 2020) [22].

Table 4 - Different causes of death [23].

Ogen (2020) suggested a role also for air pollution (particularly, nitrogen dioxide; NO^2) (appendix H). Data on fatalities in sixty-six administrative regions in Italy, Spain, France and Germany were collected along with NO^2 concentrations for those areas for January-February 2020. NO^2 "hotspots" were observed in five regions (four in northern Italy and one in central Spain), and these areas had the highest number of covid-19 fatalities in their selected countries (up to 19th March 2020). Of 4443 covid-19 fatalities, 83% were in regions of high NO^2 pollution (>100 $\mu mol/m^2$) (compared to 1.5% of fatalities in low pollution areas - <50 $\mu mol/m^2$).

The explanation proposed is that higher air

[21] More generally, Hart and Halden (2020) proposed that testing waste-water could reveal which areas have large numbers of carriers (Barras 2020).

[22] There are more reports of neurological symptoms (Hamzelou 2020b). These may be caused by the virus, or the result of lack of oxygen caused by the virus in the lungs, or the reaction of the immune system to the virus producing brain inflammation, or a facet of testing - ie: SARS-CoV-2 found in the spinal fluid due to contamination from virus-infected blood (Hamzelou 2020b).

[23] Initially written 28th April 2020.

pollution increases respiratory problems and inflammation which makes individuals more vulnerable to respiratory disease and deaths from covid-19. Ogen (2020) ended: "As earlier studies have shown that exposure to NO^2 causes inflammatory in the lungs, it is now necessary to examine whether the presence of an initial inflammatory condition is related to the response of the immune system to the coronavirus. Hence, poisoning our environment means poisoning our own body and when it experiences a chronic respiratory stress, its ability to defend itself from infections is limited" (pp4-5).

4.3. UK DATA [24]

Docherty et al (2020) analysed the characteristics of 16749 individuals with covid-19 between 6th February and 18th April 2020 in 166 hospitals in England, Wales and Scotland. The data were collected via case report forms by NHS staff under the Clinical Characterisation Protocol for Severe Emerging Infection developed by the International Severe Acute Respiratory and emerging Infections Consortium (ISARIC) (ie: "near real-time analysis").

These patients represented 15% of all people who tested positive for covid-19 in the UK (appendix I). The median time from onset of symptoms [25] to presentation at hospital was four days, and the median duration in hospital was seven days. The median age was 72 years old. About half the patients had a physical condition (co-morbidity), like heart disease, diabetes, or asthma.

In terms of the outcome of hospitalisation (where 17% needed intensive care treatment) [26], 49% left alive, 33% had died, and the remainder were still hospitalised. Older patients died (median age 80 years old), and the vast majority had a co-morbidity (88%). As well as age as a key variable with in-hospital mortality (figure 1), co-morbidity was a risk then, and being male. After adjustment for these variables, obesity was also a risk factor [27].

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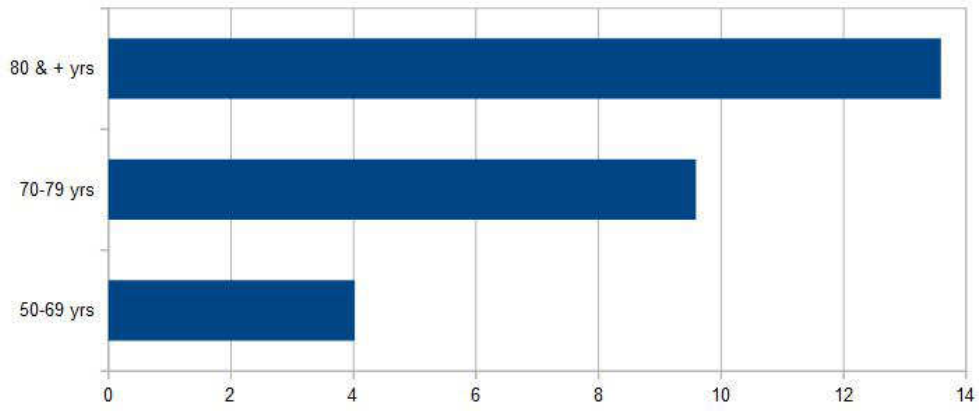
[24] Initially written on 6th May 2020.

[25] The most common first symptoms were cough (70% of cases), fever (69%), and shortness of breath (65%). But 4% of the patients reported no symptoms prior to hospitalisation.

[26] Wilson (2020a) raised the issue of post-intensive care rehabilitation for patients who had been placed on ventilation machines. The individuals "feel extremely weak, partly due to ordinary muscle wasting because they may have lain in bed for several weeks, and also because their muscle tissue has broken down as they were critically ill" (Wilson 2020a p9).

[27] Obesity was not assessed by weight or body mass index, but by observation by clinician at admission.



(Source: Docherty et al 2020)

Figure 1 - Hazard ratio of in-hospital mortality from covid-19 based on age (where 1.00 = <50 years old).

The age distribution of covid-19 in-hospital mortality was described as a "J" shape, as compared to "U" shaped in seasonal influenza [28], and "W" shaped in the 2009 influenza pandemic [29] (figure 2) (Docherty et al 2020).

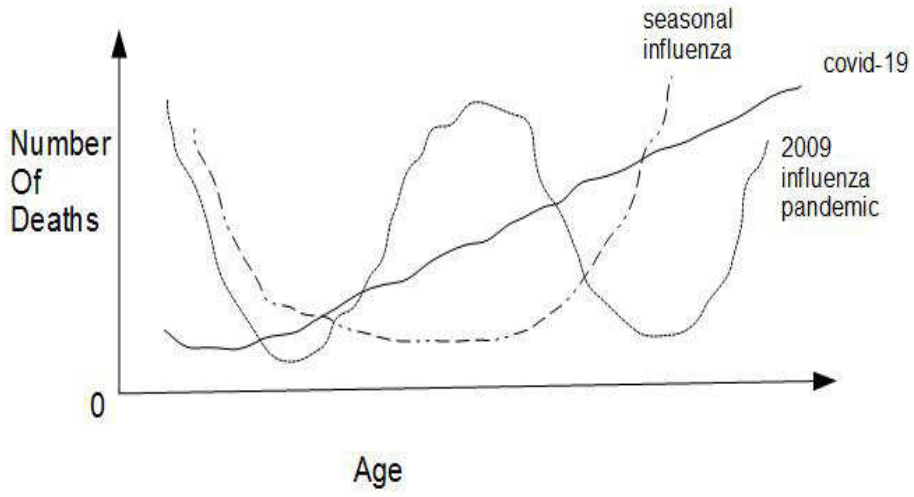


Figure 2 - Representation of death rate patterns in three outbreaks based on age.

In terms of the high risk groups, explanations are

[28] Death rate higher in younger and older patients.
[29] Death rate higher in younger, middle-age and older age groups.

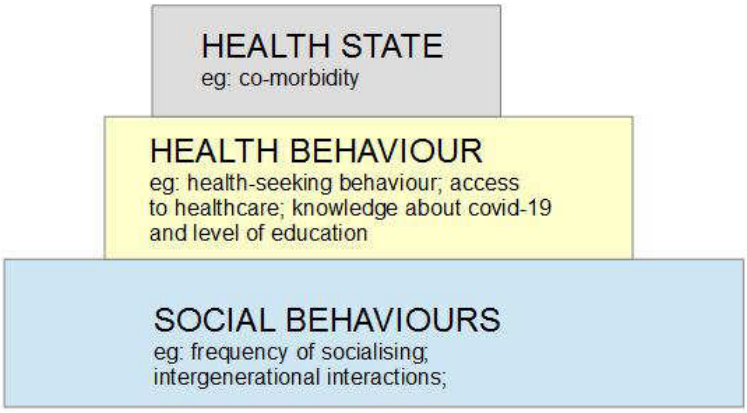
being sought, including (Arnold 2020b):

- Age - The immune system of younger individuals is less aggressive towards the virus, and it is the reaction of the immune system causing serious illness and death.

- Gender - Women may be protected by oestrogen, and/or better behaviours (eg: less likely to smoke; more likely to wash hands generally).

- Ethnicity - eg: "lack of access to healthcare, medical bias and the immune-eroding stress of poverty, which is more common among ethnic minorities" (Arnold 2020b p31).

Pareek et al (2020) observation that ethnicity is "a complex entity composed of genetic make-up, social constructs, cultural identity, and behavioural patterns" (p1421). These researchers presented a model to explain ethnicity and disease differences (figure 3).



(After Pareek et al 2020 figure p1421)

Figure 3 - A model of the interaction between ethnicity and covid-19.

4.4. US STUDIES [30]

Evidence of ethnic disparities in covid-19 infections have been found in the USA. For example, Rast et al (2020) reported a clustering of cases in Milwaukee County, Wisconsin, in "African American areas" (irrelevant of income) (Rentsch et al 2020).

While in a national sample of 580 hospitalised

[30] Written 26th May 2020 onwards.

patients (Garg et al 2020), Black individuals were over-represented. "However, most studies investigating racial and ethnic disparities have focused on hospitalised patients or have not characterised which individuals were tested or those who tested positive for covid-19. In addition, it is not yet known whether such disparities are driven, at least in part, by differences in underlying health conditions, smoking and alcohol use, geographic location, or urban versus rural residence" (Rentsch et al 2020 p3).

Rentsch et al (2020) made use of the electronic health database of the Department of Veteran Affairs (VA) (n = 5.8 m individuals). Tests results for covid-19 taken between the 8th February and 4th May 2020 were the focus, and positive results and subsequent 30-day mortality.

Around 62 000 individuals had been tested for the virus (62% White, 29% Black, 9% Hispanic individuals), and 9% were positive (49% Black, 40% White, 11% Hispanic individuals). The positive tests were mainly urban residents, and the geographical hotspots mirrored the general population data (north-eastern and mid-western states, Louisiana, and Colorado).

After adjusting for age, the following characteristics were significantly associated with a positive test - Black (three times greater than White) individuals, Hispanic individuals (over twice as likely), generally male greater than female, and overall urban over rural residents. After controlling for multiple co-variates, like underlying health conditions, Black and Hispanic individuals were around twice as likely as White individuals to test positive.

There was no difference based on ethnicity for 30-day mortality after a positive test.

This study was the largest to-date, and it "utilised patients' records from an entire healthcare system, which made it less prone to collider bias (ie: non-random selection of individuals into a study) than other Covid-19 studies limited to individuals testing positive and admitted to hospital" (Rentsch et al 2020 p9). But the cohort was limited to military veterans, "who are older and have a higher prevalence of chronic health conditions and risk behaviours than the general US population" (Rentsch et al 2020 p9). Only 9% of the total sample is female. Information on socio-economic status was lacking (Rentsch et al 2020).

The possible reasons for the ethnic differences in positive tests include underlying health conditions, access to care, socio-economic conditions, population density of neighbourhoods, number of persons in household, ability to implement physical distancing (eg: limited in prison), and continuing to work during the pandemic (Rentsch et al 2020).

Putting these factors together for Black (and Hispanic) (compared to White) Americans:

- More likely to have underlying health conditions like diabetes or obesity.
- Less access to healthcare either lack of facilities in the neighbourhood, or lack of resources to pay for the available services.
- More likely to live in poorer neighbourhoods and in poverty.
- More likely to live in urban areas, and in high density neighbourhoods of these urban areas.
- More likely to live in multi-generational households.
- More likely to be incarcerated.
- More likely to continue working either through need of money and/or in an "essential" industry.

4.5. PREGNANT WOMEN [31]

Are pregnant women more or less vulnerable to covid-19, and what is the effect on the foetus? Evidence from previous coronavirus outbreaks (SARS and MERS) suggested "that pregnant women and their foetuses are particularly susceptible to poor outcomes" (Zaigham and Andersson 2020 p2).

Also, the "physiological changes occurring during pregnancy make the mother more vulnerable to severe infections. Anatomical changes such as an increase in the transverse diameter of the thoracic cage and an elevated level of the diaphragm, decrease maternal tolerance to hypoxia. Lung volume changes and vasodilation can lead to mucosal edema and increased secretions in the upper respiratory tract. In addition, alterations in cell-mediated immunity contribute to the increased susceptibility of pregnant women to be infected by intracellular organisms such as viruses. With regard to the foetus and the newborn, the immaturity of the innate and adaptive immune systems makes them highly susceptible to infections" (Zaigham and Andersson 2020 p2).

Specifically with covid-19, Sutton et al (2020) reported a study of 215 pregnant women about to deliver at a New York hospital between the 22nd March and 4th

[31] Written 25th May 2020 onwards.

April 2020. On admission, nasal swabs were taken, and thirty-three women were positive for SARS-CoV-2. But 29 of them had no symptoms. This is evidence that the prevalence of covid-19 may be under-reported generally.

Zaigham and Andersson (2020) performed a review of studies on pregnant women and covid-19 as of the 4th April 2020. Fourteen case reports covering 108 pregnant women hospitalised with the virus (mostly from China) were found.

Adverse birth events were uncommon (eg: one neonatal death), and pregnant women who suffered badly with covid-19 has co-morbidities (eg: poorly controlled diabetes).

The vertical transmission of covid-19 from mother to foetus was rare, and the testing for covid-19 in the newborns could have been a false-positive. "Vertical transmission of the covid-19 could not be ruled out" (Zaigham and Andersson 2020 p1).

Caesarean sections were performed in most cases, but it was not clear for pre-term births if this was part of a precautious early delivery strategy or that the virus might trigger an early labour (Hamzelou 2020a).

Zaigham and Andersson (2020) lamented that "the primary studies currently available in the literature were not of sufficiently high quality regarding their methodology. Several studies had missing outcome data and selective reporting bias could not be ruled out" (p6).

To sum up, the majority of women were discharged after birth without any major complications (Zaigham and Andersson 2020).

In a study of 427 pregnant women in the UK admitted to hospital with covid-19 (up to the 14th April 2020), "most had good outcomes and transmission of SARS-CoV-2 to infants was uncommon" (Knight et al 2020). In terms of characteristics, these women were more likely to be an ethnic minority, overweight/obese, older, and have co-morbidities, but less likely to smoke (Knight et al 2020).

4.6. DECLINING LETHALITY [32]

SARS-CoV-2 lethality may be decreasing. Flacco et al (2020) analysed data from Ferrara and Pescara provinces in Italy for March and April 2020. The sample consisted on 1946 confirmed cases of covid-19, of which 177 died. The overall case-fatality rate was 10.8% in March and 6% in April [33]. The rate declined even more in the older age groups (eg: 23.4% to 6.1% of 70-79 year-olds).

[32] Written on 17th June 2020.

[33] Case-fatality rates in different studies have varied from less than 1% to 16% (and estimated elsewhere at 14% in Italy) (Flacco et al 2020).

The findings could be due to a less virulent virus strain "with consequent reduced lethality" (Flacco et al 2020). But there may also be alternative explanations, including (Flacco et al 2020):

- Changes in the response of the healthcare system (eg: earlier treatment; less overcrowding of hospitals).

- The more vulnerable individuals died in the earlier phase of the pandemic.

Data from New York may also suggest a decline in lethality of the virus, though many experts disagree (Whipple 2020).

5. PROTECTIVE MEASURES

5.1. EVERYDAY USE OF FACE MASKS [34]

Does wearing a facemask outside of health care facilities protect against respiratory illness (like covid-19)? Brainard et al (2020) answered that the "evidence is not sufficiently strong to support widespread use of facemasks as a protective measure against COVID-19. However, there is enough evidence to support the use of facemasks for short periods of time by particularly vulnerable individuals when in transient higher risk situations" (p2).

This conclusion was based on a rapid systematic review of thirty-one relevant studies (twelve of which were randomised controlled trials; RCTs). Three of the RCTs found a very slightly reduced odds of developing influenza-like illness/respiratory symptoms (6% reduction of risk). Observational studies (cohort and case-control) found a larger effect for casual community contact. Brainard et al (2020) admitted: "We expect RCTs to under-estimate the protective effect and observational studies to exaggerate it" (p2) (eg: poor compliance and controls in RCTs; self-reports of symptoms and recall in observational studies).

In a household, where both infected and non-infected members wore a facemask, further members becoming ill was moderately reduced (19% reduction of risk) as compared to only the well (5% reduction) or infected person (7%) wearing a mask.

"Many barriers exist that can make it difficult for individuals to wear facemasks correctly for hours over a multi-day period, including perceived breathing impairment and other discomforts... Facemasks are perceived to or genuinely do interfere with ordinary physical activities such as heavy exertion, sleep, oral hygiene and eating. Facemasks can be uncomfortable, hot, cause skin rashes or simply feel anti-social" (Brainard et al 2020 p8).

Brainard et al's (2020) review did not distinguish the severity or duration of symptoms, the duration of wearing facemasks, nor the combination of facemasks with other personal protective measures (eg: goggles). No

[34] Initially written 22nd April 2020.

cost-benefit analysis was provided. "The sudden emergence of COVID-19 led to high community demand for face barriers and raised valid concerns that insufficient supplies of facemasks were available for health care workers... The environmental and economic costs of regularly using facemasks are notable, and only partly abated by reuse. Wearing facemasks consistently and correctly for long periods may not be easy for many people" (Brainard et al 2020 p10).

Brainard et al (2020) concluded: "We do not consider that the balance of evidence across all available studies supports routine and widespread use of facemasks in the community. However, using a mask for short periods of time by particularly vulnerable individuals during transient exposure events may be justified" (p10).

Concerning mass gathering and mask-wearing, the studies found related exclusively to the Hajj pilgrimage (by Muslims to Mecca), "which may not be a typical mass gathering event (especially large and prolonged)" (Brainard et al 2020 p8). The authors continued: "Limited effectiveness of primary prevention at Hajj or secondary prevention within households may be because of the multiplicity of transmission pathways within these settings and high level of recurring contact. It may also be due to the late use of facemasks, usually > 24 hours after a household or group member became symptomatic which could be 48 hours after they became infectious" (Brainard et al 2020 p8).

An influential "robust study" by MacIntyre et al (2009) (included in Brainard et al's 2020 review) in Australia in 2009 compared the wearing of respirator masks, standard masks, and no masks by the general public during the influenza epidemic. It showed "benefits of masks over no masks, but no benefit of respirator masks over standard ones, and also showed that masks were worn less than 50% of the time" (Greenhalgh et al 2020 p1).

"Makeshift" or "home-made" cloth masks used by the general public has not been tested, though one study (MacIntyre et al 2015) found them least effective for healthcare staff compared to surgical masks and "stanard practice" (Greenhalgh et al 2020).

In terms of specific RCTs on masks and covid-19, Marasinghe (2020) reported no studies existed. This was an "empty review" [35] (Greenhalgh et al 2020).

The main arguments for not wearing masks in public can be summarised as (Greenhalgh et al 2020):

[35] Version 3 of this pre-print paper posted on 10th April 2020.

a) Little evidence for the benefits.

b) People are unlikely to wear them properly.

c) The tendency to create a false sense of security leading to disregarding of other advice like social distancing and hand-washing.

d) Fear that public demand for face masks will lead to a shortage for healthcare workers.

Despite the limited (and contested) evidence on everyday use of face masks, Greenhalgh et al (2020) advocated their use in public places by the general population under the "precautionary principle". Put simply, it is "better to be safe than sorry". It is not for the benefits of the wearer, but of others, particularly as individuals can be infectious before symptom onset, and the potential transmission of the virus in speech droplets (table 5) (Greenhalgh et al 2020). These authors pointed out that there are times when evidence from RCTs is not available (eg: parachutes; table 6).

- Respiratory viruses can be transmitted via droplets expelled during coughing and sneezing, but also in speech. The ability of such droplets to pass on infection depends on how long they are airborne, and this is influenced by evaporation. So, "in an environment of stagnant air, droplet nuclei generated by speaking will persist as a slowly descending cloud emanating from the speaker's mouth, with the rate of descent determined by the diameter of the dehydrated speech droplet nuclei" (Stadnytskyi et al 2020 p1).

- Stadnytskyi et al (2020) measured droplet transmission by asking volunteers to say "stay healthy" loudly for 25 seconds while a fan varied the humidity and movement of air. Highly sensitive laser light was used to observe the speech droplets. It was found that "normal speech generates airborne droplets that can remain suspended for tens of minutes or longer and are eminently capable of transmitting disease in confined spaces" (Stadnytskyi et al 2020 p3).

Table 5 - Transmission by speech droplets.

- The randomised controlled trial (RCT) is presented as the "gold standard" for evidence-based medicine.

- Smith and Pell (2003) gave an example of where evidence-based medicine may not always be appropriate - namely, the use of a parachute. The researchers, not surprisingly, found no RCTs that compared deliberate parachute use and non-use.

- They concluded: "Only two options exist. The first is that we accept that, under exceptional circumstances, common sense might be applied when considering the potential risks and benefits of interventions. The second is that we continue our quest for the holy grail of exclusively evidence based interventions and preclude parachute use outside the context of a properly conducted trial" (Smith and Pell 2003 p1460).

Table 6 - The use of parachutes.

5.2. IMPROVING KNOWLEDGE [36]

Chu et al (2020) found 172 studies on physical distancing, face masks, and eye protection (published up to 3rd May 2020) related to covid-19, SARS and MERS for their review. Forty-four of these were comparisons (eg: face mask vs no mask) and so provided data to include in a meta-analysis. All studies were observational, and most related to SARS and MERS [37].

The following conclusions were drawn (table 7):

	Risk of 1.00	Lowered risk
Physical distance	< 1 metre	> 1 m (risk 0.18)
Face mask	None	0.15
Eye protection	None	0.22

Table 7 - Adjusted odds ratio of infection from meta-analysis.

a) Closer proximity to an infected person was associated with risk of illness. Thus, physical distancing of at 1 metre reduced infection, but 2 m or more was "more effective" [38] (table 8).

[36] Written 11th June 2020.

[37] Chu et al (2020) explained: "The primary limitation of our study is that all studies were non-randomised, not always fully adjusted, and might suffer from recall and measurement bias (eg: direct contact in some studies might not be measuring near distance)" (p12).

[38] "Many studies did not provide information on precise distances, and direct contact was equated to 0 m distance; none of the eligible studies quantitatively evaluated whether distances of more than 2 m were more effective..." (Chu et al 2020 p12).

Disease	Risk	Number of studies
SARS	0.35	17
MERS	0.23	8
Covid-19	0.15	7

(Source: Chu et al 2020 figure 2)

Table 8 - Adjusted odds ratio for physical distancing of over 1 metre (compared to less than 1 metre) based on disease.

b) The use of a face mask reduced the risk of infection compared to no face mask. Respirators were better than disposable surgical masks or reusable multi-layered cotton ones [39].

c) Eye protection was associated with less infection.

"However, none of these interventions afforded complete protection from infection" (Chu et al 2020 p10). Environmental factors are also relevant, like ventilation of a room (Chu et al 2020).

Duration of exposure to infected individuals was not assessed (Chu et al 2020).

5.3. ISOLATION AND CLOSURE

School closures has been a key strategy in many countries. Such a move can "affect deaths during an outbreak either positively, through reducing transmission and the number of cases, or negatively, through reductions in the health-care workforce available to care for those who are sick" (Viner et al 2020 p397). Contacts between child, and with adults still continue outside school (eg: half as much in school holidays as in term time) (Viner et al 2020).

Evidence for the effectiveness of school closures comes from studies of influenza outbreaks, where children play a key role in transmission (Viner et al 2020).

What are coronavirus outbreaks? Viner et al (2020) found sixteen articles - nine published articles covering the 2003 SARS outbreak, one pre-print publication on coronaviruses generally, and the remainder (pre-prints) on covid-19.

"Data from the SARS outbreak in mainland China,

[39] "Few studies assessed the effect of interventions in non-health-care settings, and they primarily evaluated mask use in households or contacts of cases, although beneficial associations were seen across settings" (Chu et al 2020 p12).

Hong Kong, and Singapore suggest that school transmission played no substantial role in the outbreak, and that school closures and other activities such as school temperature monitoring did not contribute to control of infection transmission" (Viner et al 2020 p401).

Concerning covid-19, the studies from China and Hong Kong in the early days of the outbreak found that school closures "likely contributed" to the control of covid-19, but "as part of a package of very broad measures" (Viner et al 2020 p401).

The pre-print publication on coronavirus generally (Jackson et al 2020) studied a five-day school closure in Seattle, USA, in February 2019 due to extreme weather. It estimated around a 6% reduction in coronavirus infections (and 3-7% in influenza) (Viner et al 2020).

One study (O'Sullivan et al 2009), concentrating on healthcare workers in Canada during the SARS outbreak, found that these workers "experience substantial personal dilemmas in balancing work and family commitments, particularly relating to childcare needs if schools are closed and childcare services are unavailable. The study concluded that there was a need for provision of adequate resources to protect the families of health-care workers during outbreaks to maintain maximal staffing" (Viner et al 2020 p401). It is also important to note that many grandparents provide childcare outside of school time, and older people have the greater risk from covid-19 (Viner et al 2020).

Viner et al (2020) made the following point: "As evidence from coronavirus outbreak control is scarce, we must turn to evidence for the benefits of school closures from influenza epidemics and pandemics. School closures have been widespread in some countries during influenza pandemics, and many studies report important effects on reducing transmission and the size of the pandemic. Yet, there is considerable heterogeneity in the impact of school closures on transmission depending on characteristics of influenza serotype transmission. Systematic reviews of influenza outbreaks suggest that school closures are likely to have the greatest effect if the virus has low transmissibility ($R<2$), particularly if attack rates and transmission are higher in children than in adults" (p402).

In terms of general risk of infection, Luo, L et al (2020) studied 4950 close contacts of 347 confirmed cases in Guangzhou, China, between 13th January and 6th March 2020. Household contact was the highest risk (ie: frequent contact), while transmission on public transport vehicles and in healthcare settings was low.

As severity of illness increased, so did the risk of transmission. Only 1 of 305 close contacts was infected

by asymptomatic cases, and nineteen of 576 contacts by mild cases. The number of close contacts infected by severe cases was double the latter figure.

Virologist Seema Jasim commented on the risk of infection outside the home: "what we can say is that SARS-CoV-2 spread tends to be higher in communal areas where there are higher numbers of people passing through, or in areas where there is more physical engagement with the surroundings, for example door handles, desks and computer keyboards" (quoted in Geddes 2020b).

5.3.1. Controlled Study [40]

The USS Theodore Roosevelt at sea in January-March 2020 provided a controlled environment to study covid-19 among 382 volunteers in the crew, who completed questionnaires and provided blood samples. The symptoms were mild among the sample of "mostly young, healthy adults with close, congregate exposures" (Payne et al 2020 p714). The infection rate was lower among individuals who took preventive measures (table 9).

Preventive Measure	Used	Not Used	Odds Ratio for Use *
Wearing face covering	55.8	80.8	0.3
Avoid common areas of ship	53.8	67.5	0.6
Social distancing	54.7	70.0	0.5

(* where Not Used = 1.00)

Table 9 - Rates of infection (%) for three preventive measures on the USS Theodore Roosevelt.

The risk of infection was nearly twice as high for male than female crew members, "but did not differ significantly by age, race, ethnicity, or history of a pre-existing medical condition" (Payne et al 2020 p715). Loss of taste (ageusia) and smell (anosmia) were the most common symptoms reported, followed by fever and chills, but nearly one-fifth of infected individuals were asymptomatic.

Information on timing, duration, and severity of symptoms was not collected (Payne et al 2020).

[40] Written 17th June 2020.

6. CONSEQUENCES

6.1. NON-COVID DEATHS

It is possible that non-covid deaths will increase during the period of the covid-19 outbreak.

The Office for National Statistics (ONS) reported for the week ending 10th April 2020, there were nearly 8000 more registered deaths in the UK than the equivalent five-year average for that week. Many of these deaths were attributable to covid-19 (over 6000), but not all (Appleby 2020).

Appleby (2020) considered the reasons for this increase:

i) People not seeking hospital treatment for serious conditions through (a) fear of contracting covid-19, or (b) not wanting to burden the health services. Attendances at emergency departments were around one-quarter less than one year ago.

ii) An administration problem in that covid-19 was not given as the cause of death (when it was) for some reason (eg: lack of knowledge). In other words, "that deaths from covid-19 have been undercounted and that increases in other causes have been artificially boosted" (Appleby 2020 p1).

On the other hand, heart-related deaths were lower than the five-year average. "Are these figures random variation around the average, or could they suggest that some of those whose deaths might previously have been classified from these causes have succumbed instead to covid-19?" (Appleby 2020 p1).

"The current intense public scrutiny and interest in data on deaths from covid-19 has exposed — even in statistically sophisticated countries such as the UK — the difficulties of constructing a comprehensive and consistent picture of the situation as it unfurls from week to week" (Appleby 2020 p1).

6.2. MENTAL HEALTH [41]

"Stay at home" orders/self-

[41] Written 24th June 2020.

isolation/quarantine/physical distancing can have an impact on mental health.

Davenport et al (2020) reported an increase in maternal depression and anxiety in an online survey of 520 pregnant women and 380 in their first year after delivery (completed in April-May 2020).

The Edinburgh Post-Natal Depression Scale (EPDS) (Cox et al 1987) was included in the survey. It consists of ten questions about post-natal depression (but can be used during pregnancy). Of the sample, 15% answered the questions about pre-pandemic to suggest that they were above the cut-off point for depression, while 41% were currently classed as "a likely diagnosis of depression".

Anxiety was measured by the 40-item State-Trait Anxiety Inventory (STAI) (Speilberger et al 1983). Moderate to high anxiety was identified pre-pandemic in 29% of the sample compared to 72% currently.

There was a significant negative association between moderate intensity physical activity (ie: 150 minutes per week), and anxiety and depression scores.

Note that the data about pre-pandemic states were obtained through recall, and "were cross-sectional in nature, thereby precluding the ability to make causal inferences. As these data are correlative the underlying reason for the observed relationships cannot be determined and only associations could be identified. Indeed, a number of external factors may influence both likelihood of depression/anxiety and physical activity participation. These include fear of the virus, financial stresses, increased domestic workload, lack of motivation to exercise and social isolation, among many others" (Davenport et al 2020 p4).

The sample was mostly Canadian (as the researchers themselves) (around three-quarters), and recruited via social media platforms (ie: volunteer sample) [42]. "The number of individuals who saw the survey and chose not to participate could not be determined; however, it is plausible that women who had a pre-existing interest in physical activity and/or mental health would be more likely to respond to the survey" (Davenport et al 2020 p4).

On the plus side, validated self-report measures of anxiety and depression were used. Though they do not allow full diagnosis at a distance, cut-off scores are based on established predictions of the likelihood of the mental health problems (Davenport et al 2020).

The UK Covid-19 Social Study involves a panel of over 90 000 adults contacted weekly since 21st March 2020 (when the UK government introduced "lockdown") [43].

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[42] The sample was not very diverse (eg: over 80% White; over 90% living with a partner).

[43] This survey was interesting in many aspects of mental health including subjective stress (appendix J).

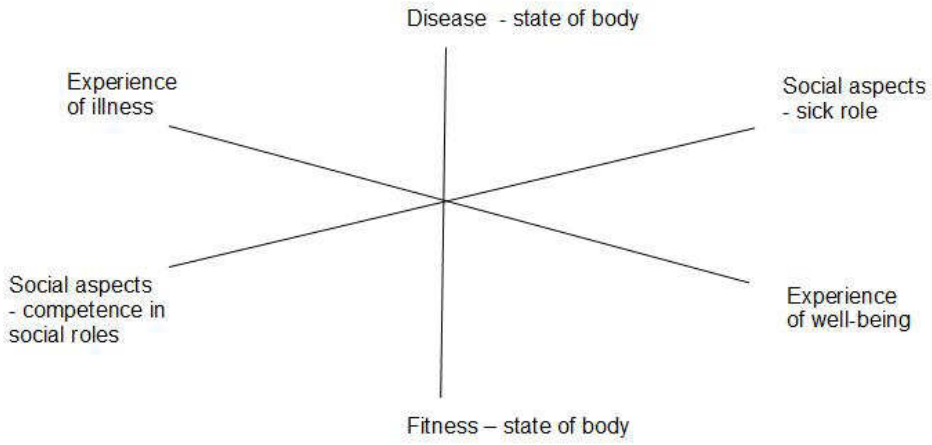
Fancourt et al (2020) summed up the findings of the first twelve weeks (with the easing of lockdown measures):

- Worries about family and friends declined with time.
- Depression and anxiety dropped as time passed, but then plateaued at around 5-6%.
- Thoughts of self-harm, and reports of loneliness have remained relatively unchanged.
- Trust in the central government's handling of the crisis remained low (table 10).

- Calnan et al (2020) defined trust as a multi-layered concept consisting of a "cognitive element (grounded in rational and instrumental judgments) and an affective dimension (grounded in relationships and affective bonds) generated through interaction, empathy and identification with others". "Competence trust" and "intentional trust" can be distinguished. The former is the ability to do the job, while the latter is belief that the government, say, is working in the best interests of the public (Calnan et al 2020).
- Countries in South-East Asia (eg: Singapore, South Korea, and Taiwan) that appear to be doing better in containment of covid-19 have more confidence in their public institutions, and high levels of neighbourhood social capital (Samanta 2020).
- Samanta (2020) commented: "While we remain optimistic about the laudatory appeals to social capital, we should be wary of what the American political scientist Robert Putnam [1995] called its 'dark' side. Simply put, the same set of informal norms and codes that bind communities together can become exclusionary and harmful when a particular in-group attempts to aggressively enforce compliance, creating an oppositional out-group. As Putnam said, 'Social capital is often most easily created in opposition to something or someone else'".

Table 10 - Trust in Authorities

There is always an issue of how to conceptualise health, and figure 4 gives one example.



(After Kat 1995 figure 4.2 p64)

Figure 4 - A conceptualisation of health.

6.3. BIO-DIVERSITY

The impact of covid-19 on biodiversity is both positive and negative (table 11).

POSITIVE	NEGATIVE
* Better air quality from less transport and industrial pollution as populations stayed at home. * Less pressure on vulnerable species in the world with less tourists and less human activity generally (eg: in protected areas less "trampling pressure on popular trails"; Corlett et al 2020 p2).	* The focus on covid-19 means that other issues are pushed into the background (eg: protecting endangered species; wildlife smuggling) (Corlett et al 2020). * Loss of income from reduced ecotourism and legal trophy hunting may have increased poaching both as compensatory income, and as rangers are not being paid and on duty (Marshall 2020).

Table 11 - Key consequences of covid-19 for biodiversity.

6.4. MISCELLANEOUS EFFECTS

A positive consequence of self-isolation, and increased hand washing related to covid-19 is a reduction in seasonal flu cases, as reported in Australia. For example, 229 cases in April 2020 compared to 18 705 in the same month one year before (Klein 2020).

7. COMMUNICATION AND INFORMATION

7.1. HEALTH MESSAGES

Commenting on the health messages from governments like in the UK, Reicher and Drury (2020) argued that individual-focus ones (eg: "change your behaviour so that you will survive") were not the right approach. "At a practical level, those least at risk (young, fit, healthy) may well feel it isn't worthwhile to make the necessary changes and so continue to act in ways that put the most vulnerable (old and infirm) at risk of infection. Additionally, at a moral level, we have the right to disregard dangers to ourselves and some even glory in being risk takers" (Reicher and Drury 2020 p10).

Based on their research on emergencies, Reicher and Drury (2020) recommended emphasising the "we" (ie: the shared social identity). "The emphasis must lie on how we can act to ensure that the most vulnerable amongst us are protected and losses to the community are minimised - after all, from a collective perspective, a loss to one is a loss to all" (Reicher and Drury 2020 p10).

Research has shown that health messages using posters with a "bright, clear design with minimal text and an emphasis on the step-to-step procedure" were recalled best (Lawton 2020d).

Morally charged messages are also effective (Lawton 2020d).

Talking generally, Ley and Llewelyn (1995) offered some "desirable characteristics" for health messages, including:

- Noticeable - eg: use of words like "warning".
- Readability - eg: short, familiar words.
- Understandable - eg: no using technical terms.
- Memorable - eg: high repetition.

7.2. MISINFORMATION AND CONSPIRACY BELIEFS

Popper (1969) used the term "the conspiracy theory of society", Hofstadter (1964) "conspiratorial fantasies", and Douglas et al (2019) "conspiracism" to describe "the tendency to assume that major public events are secretly orchestrated by powerful and malevolent entities acting in concert" (Allington et al 2020 p1).

Holding such views tends to be associated with reluctance to engage in health-protective behaviour (HPB) generally, and specifically with covid-19 (Allington et al 2020).

"YouTube and Facebook have been identified as major vectors for dissemination of conspiracy beliefs and misinformation on medical and other topics" (Allington et al 2020 p1). Allington et al (2020) explored the relationship between social media usage, conspiracy beliefs about covid-19, and HPB with data from three online surveys in the UK.

Study 1 - A panel of UK adults who volunteered to answer questions about covid-19 in early April 2020 (n =943).

Respondents were asked to identify which of six statements about covid-19 were true, including "The symptoms of covid-19 seem to be connected to 5G mobile network radiation", and "The virus that causes covid-19 was probably created in a laboratory". There were questions about social media usage, preferred sources of information, and three HPBs (eg: "spending as little time as possible outside your home").

Holding a conspiracy belief was associated with a preference for social media as a source of information (compared to sources like television), and with reluctance to perform HPBs.

Study 2 - A stratified random sample in early April 2020 (n = 2250).

Only one conspiracy belief was tested ("coronavirus was probably made in a laboratory"), but five HPBs related to covid-19, as well as preference for information source. Agreement with the conspiracy belief and preference for social media information were associated again, and reluctance to perform each or all HPBs.

Study 3 - A stratified random sample in mid-May 2020 (n = 2254).

This survey included five conspiracy beliefs, four HPBs, and more questions about social media preference. Social media usage generally was associated with conspiracy beliefs, and individually with YouTube having the strongest relationship. "There was a strong negative relationship between holding one or more conspiracy beliefs and engagement in all health-protective behaviours" (Allington et al 2020 p5).

The three surveys confirmed two significant associations:

i) Holding covid-19 conspiracy belief(s) and preference for social media as a source of information.

ii) A "negative association between COVID-19 conspiracy beliefs and COVID-19-specific health-protective behaviours, with the strongest negative effects being associated with beliefs that imply that the coronavirus may not exist, that its lethality has been exaggerated, or that its symptoms may have a non-viral cause" (Allington et al 2020 p6).

Allington et al (2020) ended: "In the UK, broadcast media are subject to official regulation, and many print media platforms are subject to voluntary regulation, but social media are largely unregulated. One wonders how long this state of affairs can be allowed to persist while social media platforms continue to provide a worldwide distribution mechanism for medical misinformation" (p6).

7.2.1. YouTube

YouTube is a popular social media source for health information. It is "a powerful educational tool that healthcare professionals can mobilise to disseminate information and influence public behaviour, if used inappropriately, it can simultaneously be a source of misleading information that can work significantly against these efforts" (Li et al 2020 p2). For example, around a quarter of videos have been found to be misleading about diseases, like H1N1 influenza (Pandey et al 2010), Ebola virus (Pathak et al 2015), and Zika virus (Bora et al 2018).

Li et al (2020) confirmed this problem with covid-19. On 21st March 2020, a key word search for "coronavirus" and "covid-19" was done on YouTube, and 69 videos were identified for inclusion in the study (eg: in English, with audio and/or visual information, less than one hour in length, and not livestreams). A five-point scoring system (Covid-19 Specific Score; CSS) was created for factual information about transmission, typical symptoms, prevention strategies, potential treatments, and epidemiology as known at the time of the video's creation.

Eight categories for source of the videos were distinguished - government, education, newspaper, professional, internet news, consumer, entertainment news, and network news. Nineteen videos contained non-factual information (ie: at least one non-factual statement). "Professional" and "government" sourced videos, not surprisingly, had higher CSS than "consumer" videos, for example.

APPENDIX A - HYDROXYCHLOROQUINE [44]

1. Overview
2. Gautret et al (2020)
3. Mehra et al (2020)

1. OVERVIEW

Hydroxychloroquine (HCQ) is a derivative of chloroquine used with malaria [45], but there are claims that it could be given to covid-19 sufferers. For example, Gautret et al (2020) reported a small clinical trial showing benefits with covid-19 as a pre-print publication, and this was picked up on social media [46]. But this trial was criticised by Kim, A.H.J et al (2020), and by Dahly et al (2020).

However, a study in Wuhan, China, with sixty-two patients reported a positive outcome with HCQ in a pre-print publication (Chen, Z et al 2020; table 12). Again methodological problems have been noted, which would be spotted in the peer review process normally (Lawton 2020c).

- Sixty-two patients at a Wuhan hospital admitted between 4th and 28th February 2020 who were willing to be randomised to the treatment or control group. Treatment involved 400 mg of HCQ sulfate per day for five days.
- Fever was significantly shortened (ie: return to normal body temperature) in the HCQ group, as well as cough remission time. There were greater improvements in pneumonia symptoms in the treatment than control group.
- Compared to Gautret et al (2020), this study randomised the participants, took place at a single site, was double blinded (neither the researchers nor participants knew their group during the study), and reported no difference in age and gender distribution between the treatment and control groups. There was no drop-out of participants. However, severe and critically ill patients were excluded.

Table 12 - Details of Chen, Z et al (2020).

Elsewhere, Geleris et al (2020) found no benefits in an observational study in New York (table 13). There are also other studies appearing (table 14).

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[44] Mostly written mid-May 2020.
[45] HCQ is also used with rheumatoid arthritis, for example (Kim, A.H.J et al 2020).
[46] The journal of publication has since issued an "expression of concern" notice about the study (Madhusoodanan 2020).

- Site of study - 1376 patients at New York hospital between 7th March and 8th April (and follow-up to 25th April 2020).
- Design - Observational (ie: data taken from medical records retrospectively).
- Protocol - 400 mg HCQ twice on Day 1, and 400 mg daily for the next four days (and AZM as required).
- Analysis - Controlled for confounders like age, gender, ethnicity, BMI, smoking status, and other medications.
- Findings - The risk of breathing problems requiring intubation (ie: a tube into the airway to facilitate mechanical ventilation) or death was "not significantly higher or lower among patients who received hydroxychloroquine than among those who did not" (p7). The authors continued: "Given the observational design and the relatively wide confidence interval, the study should not be taken to rule out either benefit or harm of hydroxychloroquine treatment. However, our findings do not support the use of hydroxychloroquine at present, outside randomised clinical trials testing its efficacy" (Geleris et al 2020 p7).

Table 13 - Details of Geleris et al (2020).

- Borba et al (2020) - Compared 600 mg twice per day for ten days with 450 mg of HCQ daily for four days. Halted after higher mortality and side effects in the high-dose group (Geleris et al 2020).
- Chen, J et al (2020) - Thirty patients in Shanghai given 400 mg daily for five days. By Day 7, 80% of the treatment group and 93% of the control group had no virus on throat swabs. All patients also received an anti-microbial treatment (Geleris et al 2020).

Table 14 - Example of studies on HCQ and covid-19.

2. GAUTRET ET AL (2020)

Gautret et al (2020) outlined the background to their study - success with HCQ in vitro (ie: cells in the petri-dish) (Wang et al 2020), and with early Chinese patients (Gao et al 2020). However, Dahly et al (2020) questioned this prior evidence - Gao et al (2020) provided no data, but described potential studies that would take place, "though many of these have now been suspended or closed".

Gautret et al's (2020) study took place in a hospital in Marseille, France, primarily, in early March 2020, using 200 mg of oral HCQ sulfate three times per day for ten days. Twenty-six adults with confirmed covid-19 received the drug, and sixteen patients were controls. Six of the former also received azithromycin (AZM) to

combat "bacterial super-infection" [47].

Six patients in the treatment group did not complete the trial, and their data were removed from analysis. One of these had died, and three were transferred to intensive care treatment. Exclusion from analysis of these individuals was a fault. "These patients had treatment failure and should have been analysed as such" (Kim, A.H.J et al 2020 p1).

At Day 6 [48], 70% of the treatment group (compared to 12.5% of the control group) were classed as "virus cured" [49]. This was a significant difference at p = 0.001.

Kim, A.H.J et al (2020) began: "**T**he coronavirus disease 2019 (COVID-19) pandemic has placed the scientific and research communities under extraordinary pressure, to which they have responded with exceptional vigour and speed. This desire to quickly find safe and effective treatments may also lead to relaxed standards of data generation and interpretation, which may have undesirable downstream effects" (p1) [50]. These authors accepted that studies will have limitations because of the "urgency of the situation" (eg: small sample size), but methodological flaws cannot be overlooked.

Gautret et al's (2020) control group were individuals who declined treatment at the study hospital [51], and others were from different hospital in the South of France not offering the treatment [52]. Thus, no randomisation of participants to treatment or control group, which is a key element of clinical (experimental) trials. Dahly et al (2020) argued that the lack of randomisation meant that Gautret et al's (2020) study should be classed as observational (rather than as a randomised clinical trial), and analysis adjusted consequently.

Kim, A.H.J et al (2020) pointed out that the viral load of SARS-CoV-2 at baseline was lower for HCQ and AZM patients, and for nine of the HCQ group, which suggested that they were in a later phase of the infection. Most of these individuals had no viral load at Day 6. So, the

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[47] Combining HCQ, and HCQ and AZM patients to compare to controls was a flaw (Dahly et al 2020).

[48] Dahly et al (2020) questioned the focus on Day 6, "especially in light of the observation that two patients who were positive on day-6 but negative by day-9, and another that was negative on day-6 but positive on day-8".

[49] This outcome measure was dichotomous (virus or not), and a continuous measure (amount of virus) would be better (Dahly et al 2020).

[50] For example, shortages of HCQ were reported by pharmacies after the increased demand resulting from dissemination of Gautret et al's (2020) findings via social media etc (Kim, A.H.J et al 2020).

[51] There are ethical concerns about using such individuals in a study (Dahly et al 2020).

[52] "This introduces the potential for baseline confounding and different treatment regimens at different institutions" (Kim, A.H.J et al 2020 p1). For example, daily viral load tests were not performed in the other hospitals daily as required (Kim, A.H.J et al 2020). Limited information was provided about the characteristics of the control group (Dahly et al 2020).

findings of Gautret et al (2020) can be explained as "baseline viral load, not therapy with HCQ and AZM affects viral load at day 6" (p1).

3. MEHRA ET AL (2020)

Using data from 671 hospitals in six continents [53] [54], Mehra et al (2020) compared 14 888 individuals receiving HCQ (with or without AZM) for covid-19 and 81 144 as the control group (up to 14th April 2020). No differences were found between the groups in terms of in-hospital mortality.

There was an increased risk of heart problems with HCQ use. Mehra et al (2020) explained the medical technicalities: "Chloroquine and hydroxychloroquine are associated with concerns of cardiovascular toxicity, particularly because of their known relationship with electrical instability, characterised by QT interval prolongation (the time taken for ventricular depolarisation and repolarisation). This mechanism relates to blockade of the hERG potassium channel, which lengthens ventricular repolarisation and the duration of ventricular action potentials. Under specific conditions, early after-depolarisations can trigger ventricular arrhythmias. Such propensity for arrhythmia provocation is more often seen in individuals with structural cardiovascular disease, and cardiac injury has been reported to occur with high frequency during COVID-19 illness. Furthermore, individuals with cardiovascular disease represent a vulnerable population that experience worse outcomes with COVID-19" (p8).

This study was a registry analysis, which means the analysis of hospital data retrospectively (ie: an observation study). This type of study is dependent on the accuracy of the data inputs, and there is an issue with missing data. Mehra et al (2020) admitted that "if the patient's electronic health record did not include information on a clinical characteristic, it was assumed that the characteristic was not present" (p4).

There is always the possibility of unmeasured confounders, and a cause-and-effect relationship cannot be established. The data did not include out-of-hospital settings.

Mehra et al (2020) confirmed certain characteristics as increasing the risk for covid-19 in-hospital mortality - namely, older, overweight/obese, Black or Hispanic

[53] This is the "Surgical Outcomes Collaborative", which "consists of de-identified data obtained by automated data extraction from in-patient and out-patient electronic health records, supply chain databases, and financial records" (Mehra et al 2020 p2).

[54] Two-thirds of the patients were based in North America.

ethnicity, prior heart- and/or lung-related health problems, and being a current smoker. There was a reduced risk for women, individuals of Asian ethnicity, and those using certain drugs beforehand (eg: statins; ACE inhibitors but not angiotensin receptor blockers).

APPENDIX B - ESTABLISHING TRUTH

1. Iraqi child mortality
2. Civilian casualties
3. What we know: aliens
4. Reality

Dilnot and Blastland (2010) began: "Numbers saturate the news, politics, life. For good or ill, they are today's pre-eminent public language – and those who speak it rule. Quick and cool, numbers often seem to have conquered fact" (p1).

They continued: "There are lies and damned lies in statistics, for sure, but scorning numbers is no answer" (Dilnot and Blastland 2010 p1).

1. IRAQI CHILD MORTALITY

The imposition of economic sanctions on a country is a strategy used to change certain behaviour of that country. For example, the United Nations (UN) imposed strict economic sanctions on Iraq (led by Saddam Hussein) in 1991 after the invasion of Kuwait. Iraq imported three-quarters of its food supplies (Dyson and Cetorelli 2017).

A "fiction" quickly appeared that child mortality (ie: under fives) doubled as a consequence of the sanctions. The purpose of the deception was "to shake international opinion so that the UN economic sanctions would be lifted. Following its creation and dissemination the deception received considerable attention and was widely believed to be true. Moreover, it continues to be influential" (Dyson and Cetorelli 2017 p1).

The data about the under-fives mortality rate (U5MR) came from different sources, including (Dyson and Cetorelli 2017):

a) International Study Team (IST) (Ascherio et al 1992) - A nationally representative household survey in late 1991, which calculated the U5MR for the five years prior to sanctions as 43 child deaths per 1000 live births, but 128 for 1991 (post-sanctions). The figure of 46 900 excess child deaths was quoted [55].

b) UN's Food and Agriculture Organisation (FAO) (Zaidi and Fawzi 1995) - A small survey in Baghdad in 1995. The U5MR was estimated to have risen from 33 per

[55] Note that in 1991, Iraq also experienced war, aerial bombing, internal rebellions, and mass migrations (Dyson and Cetorelli 2017).

1000 births (pre-sanctions) to 245 (with excess child deaths of 56 700).

This study was carried out in "co-operation" with the Iraqi government, and a follow-up (Spagat 2010) in 1996-7 (ie: re-interviews) did not support the original figures. "Moreover, it emerged that some miscarriages and stillbirths had been wrongly classified as child deaths in 1995" (Dyson and Cetorelli 2017 p2).

c) In 1999 UNICEF conducted the Iraq Child and Maternal Mortality Survey (ICMMS) (Ali and Shah 2000) involving 14 000 households in Kurdish north Iraq and 24 000 in the rest of the country. The U5MR was estimated to have risen from 56 (pre-sanctions) to 131 deaths per 1000 (post-sanctions) overall. The data for Iraq (ie: excluding the Kurdish north) were collected in "co-operation" with the government, and "were a deception" (Dyson and Cetorelli 2017). There is subsequent evidence that the data were "evidently rigged to show a huge and sustained - and largely non-existent - rise in child mortality. The falsification might have occurred during the data entry stage at the behest of the Iraqi government" (Dyson and Cetorelli 2017 p4).

Since the US/UK invasion of Iraq in March 2003, information has become available that shows the errors in these previous studies (eg: Iraqi government census in 1997), and subsequent surveys have been undertaken, including (Dyson and Cetorelli 2017):

i) 2004 Iraq Living Conditions Survey (ILCS) (supported by the UN) (Iraq Ministry of Planning and Development Co-operation 2005) - This collected full birth histories from women in 21 000 households.

ii) 2006 Multiple Indicator Cluster Survey (MICS) (Iraq Central Organisation for Statistics and Information Technology and Kurdistan Regional Statistics Office 2007) (supported by UNICEF) - 18000 households.

iii) 2011 MICS (Iraq Central Statistics Organisation, Kurdistan Regional Statistics Office, Ministry of Health, United Nations Children's Fund 2012) - 36000 households.

These data together showed "no sign of a huge rise in child mortality after 1990" (Dyson and Cetorelli 2017 p4). The U5MR was around 40 per 1000 in the 1990s (Dyson and Cetorelli 2017) [56].

[56] Note that "Saddam Hussein's government became increasingly proficient at evading the sanctions and Iraq's basic food rationing system probably also helped the situation" (Dyson and Cetorelli 2017 p4).

What did emerge from "good quality data" was the poor U5MR for Iraq generally. Dyson and Cetorelli (2017) explained: "In the 1970s, there was considerable variation in child mortality, the trend in Iraq broadly paralleling the trends in Syria and Jordan. From the early 1980s onwards, however, progress in Iraq seems to have been much slower. Indeed, by 2010–2015 the U5MR in Iraq was roughly twice that of the other countries. The period of miserable progress in reducing child mortality broadly corresponds to the period of Saddam Hussein. He brought a host of troubles and disasters to his country of which, however evaluated, the economic sanctions constituted a very small part" (p4).

2. CIVILIAN CASUALTIES

Kruger et al (2013) highlighted measurement problems related to the incompleteness and uncertainty in databases of civilian casualties of armed conflicts.

One key problem is "reporting bias". Case data (eg: press accounts; individual testimonies; cases presenting at hospital) can vary "the likelihood that a given event is reported varies with characteristics of the event itself, or with characteristics of the agency collecting the reports" (Kruger et al 2013 p249).

Such data are based on convenience samples, which "capture an unknown proportion of the underlying universe of victims or violations" (Kruger et al 2013 p250).

The reporting of the event can depend on the characteristics of the event (eg: urban killing; large number of victims), individual characteristics of the victim/witness, and the resources of the organisation gathering the data (Kruger et al 2013).

These issues relate mostly to omissions, but databases may also produce conflicting statistics. One reason is that the databases have used different convenience samples.

For example, three data sources were available to measure the number of murders in the Casanare area of Columbia, and each produced different numbers - the coroners' identification of homicide victims, the homicide records of the National Police, and a government database (Kruger et al 2013). They all depended on the cases they saw and defined as such. That is the convenience sampling here.

3. WHAT WE KNOW: ALIENS

Many people are fascinated by the question of whether there is other life in the universe beyond the Earth. A logical approach is that "the sheer size of the universe makes it unlikely that life formed only once"

(Rugheimer 2019 p42). But when people talk of life, they usually mean sophisticated, advanced or intelligent that would meet us (which we will call "aliens").

Frank Drake in 1961 (eg: Drake and Sobel 1992) produced a formula ("Drake Equation") (figure 5) to estimate how many advanced civilisations were likely to be out there. Though the formula is of little use because there is no way of knowing the different variables. Estimates vary from 1 (Earth) to 4 billion (Rugheimer 2019).

N = R* x Fp x ne x Fl x Fi x Fc x L

- N = Number of advanced civilisations than could communicate their existence to use
- R* = Rate of star formation
- Fp = Fraction of stars with planets
- ne = Number of habitable planets per star
- Fl = Fraction of those planets that develop life
- Fi = Fraction of those planets with intelligent life
- Fc = Fraction of civilisations that produce detectable signals
- L = Lifetime of those civilisations

(Source: Rugheimer 2019)

Figure 5 - Drake's equation [57].

Here are some possibilities about contact with aliens:

1. We will never meet or not yet met.

a) Advanced civilisations have a short lifespan and so never meet. One reason is self-destruction by such civilisations (called the "Great Filter"; Rugheimer 2019).

b) The universe is so big that civilisations never come into contact because of the distance.

c) Advanced civilisations on a planet are rare, but other forms of life are more common for longer (eg: single cell organisms dominated the Earth for three billion years; Rugheimer 2019).

d) Aliens have developed in such a way that they are not detectable by use or we by them (eg: different form of matter; different wavelength).

[57] The notation for the equation is slightly different (see https://en.wikipedia.org/wiki/Drake_equation).

2. Aliens have detected us, but are deliberately not making contact.

a) They are afraid of us.

b) They do not want to infer or spoil our planet.

c) They are not interested in contact.

d) They don't think we are worth contacting (eg: so advanced that it is like us trying to teach a ladybird to use the telephone; Rugheimer 2019).

3. They are already here.

a) Keeping it secret from us.

b) Somebody on this planet knows and there is a conspiracy to hide it from the general population.

4. We are alone in the universe (literally or in terms of intelligent life).

Arthur.C.Clarke, the science fiction writer, reportedly said: "Two possibilities exist: either we are alone in the universe or we are not. Both are equally terrifying" (quoted in Rugheimer 2019).

4. REALITY

Attempting to understand the relationship between "objective reality" (the world outside our heads) and "subjective experience" (the world inside our heads), the assumption is made that there is a match between an object out there and my experience/perception of it. Hoffman (2019) questioned this assumption.

It would make sense in terms of evolution that individuals who perceive objective reality accurately will be more likely to survive and pass on their genes. But it is also possible that there is a "pay-off strategy" (Hoffman 2019) - ie: perception of "enough" of the outside world to aid survival etc. So, perceiving a red object as food matters more, say, than perceiving that red object in an objective way.

Based on mathematical simulations, Hoffman (2019) reported that his work (eg: Mark et al 2010) finds that "[A]n organism that sees objective reality is always less fit than an organism of equal complexity that sees fitness pay-off" (p36).

The upshot is that "[P]hysical objects, and indeed the space and time they exist in, are evolution's way of

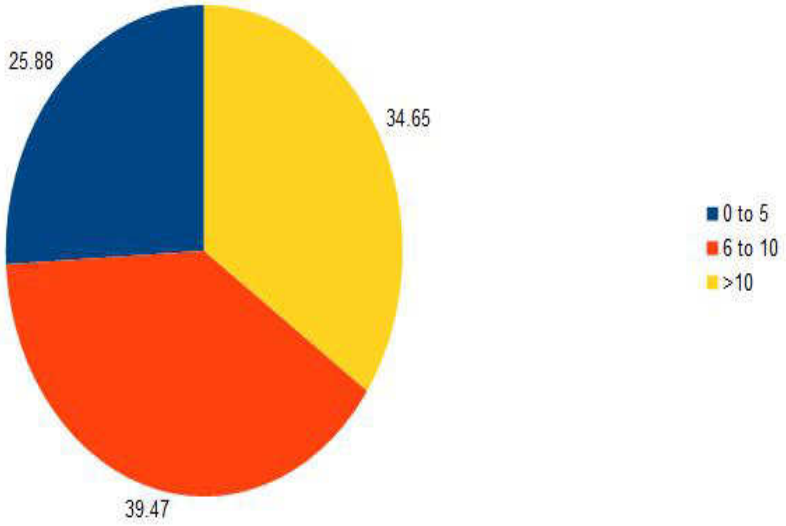
presenting fitness pay-offs in compact and usable form" ["an interface"] (Hoffman 2019 p36).

If this is so, there are implications for science, and the attempts to create theories of reality as in physics (Hoffman 2019).

APPENDIX C - HAND-WASHING

In terms of non-coronavirus studies of hand-washing, the "balance of evidence suggests small but significant reductions in rates of influenza and influenza-like-illness" (Beale et al 2020 p3).

Concentrating on coronavirus infections generally, Beale et al (2020) analysed data from "Flu Watch" (a cohort study in England covering 2006 to 2011). It included 1633 individuals [58] who were telephoned or contacted online weekly during the winters to assess their health in relation to acute respiratory illness [59] [60]. An estimation of daily hand-washing was self-reported based on the previous 24 hours (figure 6) [61].



(Data from Beale et al 2020 table 1)

Figure 6 - Percentage of respondents for each category of daily hand-washing.

Moderate-frequency hand-washing (6-10 times per day) was the best predictor of low risk of contracting a coronavirus (figure 7).

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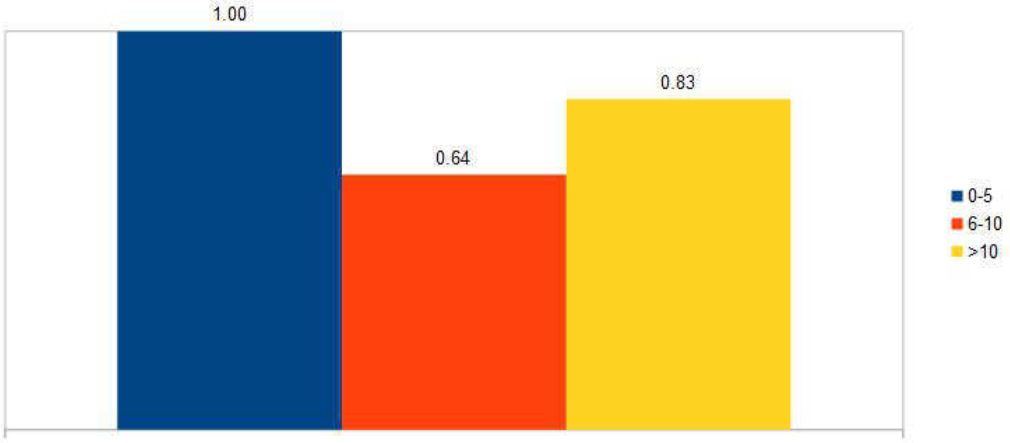
[58] Randomly selected from patient lists of GPs, and the whole household had to agree to participate. "Exclusion criteria were living in a >6-person household, terminal or severe illness or incapacity, and substantial involvement in other ongoing research" (Beale et al 2020 p3).

[59] If individuals reported such an illness, they provided a posterior nasal swab to confirm the virus type.

[60] Asymptomatic cases and those outside the winter season would be missed.

[61] This period "may not reflect usual behaviour for all participants, or behaviour at time of exposure" (Beale et al 2020 p4). There is also the possibility of recall bias, and social desirability of answers.



(Data from Beale et al 2020 table 2)

Figure 7 - Adjusted incidence relative risk of a coronavirus based on daily hand-washing.

The researchers considered why high-frequency hand-washing was not best, noting "numbers in the highest-frequency hand-washing group were lower, limiting [statistical] power. It is also possible that there is residual confounding. For example, while we adjusted for healthcare worker status, those working in other public-facing professions may be more likely to be high-frequency hand-washers and may have increased exposure to coronavirus, which would have mitigated against seeing a protective effect of high-frequency hand-washing. The context of hand-washing and compliance with recommended hand-washing procedures are likely also important. Both longer duration of hand-washing and the context of hand-washing (eg: after shaking hands or before eating) have been associated with lower overall risk of influenza or influenza-like-illness" (Beale et al 2020 p4).

APPENDIX D - LABORATORY STUDIES [62]

In terms of the stability of the SARS-CoV-2 virus on different surfaces (at room temperature of 22 °C and 65% humidity), Chin et al (2020) found the following times:

- Printing and tissue paper - no infectious virus after 3 hours.
- Treated wood and cloth - no virus on Day 2.
- Glass and banknotes - no virus on Day 4.
- Stainless steel and plastic - no virus on Day 7.
- Surgical mask - "a detectable level of infectious virus could still be present at the outer layer of a surgical mask on day 7" (Chin et al 2020 pe10).

The authors noted that the "recovery of virus does not necessarily reflect the potential to pick up the virus from causal contact" (Chin et al 2020 pe10).

Though the virus was stable on some surfaces, disinfectants removed it, and the virus was inactive within five minutes at 70 °C (Chin et al 2020).

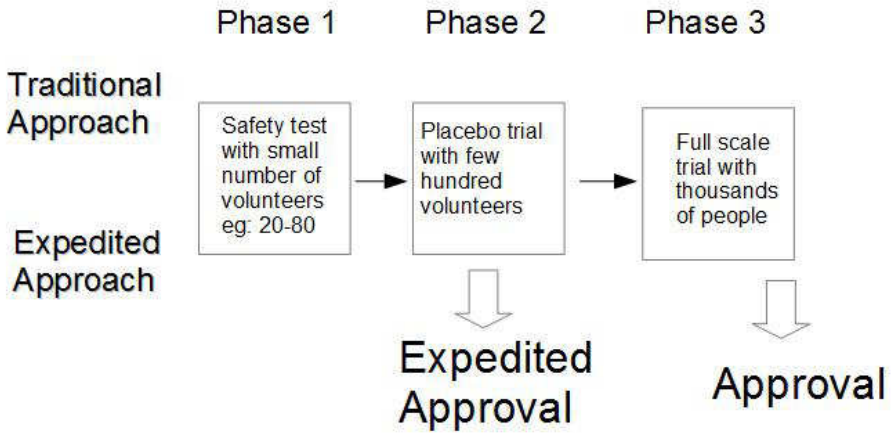
[62] Written on 23rd May 2020 and after.

APPENDIX E - DRUG AUTHORISATION

1. Trial discontinuation
2. Evaluating tests

The development of a new drug from molecule discovery to patient taking it (marketing) is a lengthy process. Much of that time involves clinical trials and providing evidence of effectiveness and side effects for licensing authorities, like the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

But, in some cases like cancer drugs, there has been a call for a swifter decision by licensing authorities (figure 8). For example, in 2008 the FDA introduced an accelerated route to official approval (expedited approval), but critics worried that these pathways are "the norm rather than the exception" (Caleb Alexander in Hamzelou 2019). "When drugs are approved on the basis of slim evidence, it is sometimes on the understanding that testing will be carried out after they [pharmaceutical companies] get the green light... Yet these trials can take years to complete and are often poor quality. In some cases, they just don't happen. Nearly half of post-marketing studies requested by the FDA haven't been completed five years later" (Hamzelou 2019 p36).



(Based on figure p36 Hamzelou 2019)

Figure 8 - Stages of drug testing on humans [63].

[63] "Phase 1 studies are uncontrolled studies in humans, generally involving 20 to 80 healthy volunteers, and are intended to gather information about pharmacokinetics and pharmacodynamics, to initially assess a drug's safety at varying doses, and in some cases (such as chemotherapy) to obtain preliminary evidence of efficacy. Phase 2 trials evaluate adverse effects and efficacy in up to a few hundred participants with the condition under study. Despite their formal definition, phase 2 trials

Median FDA review times were 2.8 years in the 1980s, 1.5 years in the 1990s, and by 2018, 10.1 months for standard applications, and 7.6 months for priority applications (Darrow et al 2020).

The FDA has a number of different programmes for expedited approval, including (Kesselheim et al 2015):

- "Orphan drugs" - Drugs for potentially rare diseases that make large clinical trials difficult (ie: lack of eligible participants). One way is a clinical trial with no placebo or comparator drugs, and/or non-randomised, unblinded trials.

- "Fast-track" - For life-threatening diseases (approval after phase II trials).

- "Accelerated approval" - For life-threatening diseases (approval based on "surrogate endpoints likely to predict patient benefits" (Kesselheim et al 2015 p2) rather than actual data).

- Generic drug - This can be "approved if pharmacokinetic testing showed that the generic drug achieved blood levels comparable to those of its reference product (bioequivalence), without the need to independently demonstrate its own clinical outcomes. In addition to meeting technical bioequivalence standards, generic drugs had to be identical in active ingredient, strength, dosage form, and route of administration but could differ in certain respects, such as inactive ingredients and appearance" (Darrow et al 2020 p170). More than 700 generic drugs approved by the FDA in recent years (ie: since 1983) (Darrow et al 2020).

Between 1987 and 2014, the FDA approved 774 drugs,

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generally have no comparison group, are often not blinded or randomized like phase 3 trials, and often use laboratory tests or imaging studies (surrogate measures) to assess results. Phase 3 trials usually include several hundred to several thousand patients. Ideally, these studies use concurrent controls, randomisation, and clinical endpoints, but they might omit any or all of these study components. They are intended to provide sufficient evidence of the benefit-risk relationship of the drug to obtain FDA approval. In some cases, phase 2 trials can serve as such 'pivotal trials', an informal term describing studies used by the FDA to make an approval decision" (Darrow et al 2020 pp166-167).

and Kesselheim et al (2015) found an "increasing number of expedited development" (p4).

Other factors which lower the standard of scrutiny of drugs include (Hamzelou 2019):

i) "Off-label prescribing" where doctors prescribe a drug for a condition other than the one that the drug was licensed to treat.

ii) The relationship between licensing authorities and pharmaceutical companies - eg: in the USA, pharmaceutical companies pay fees to fund FDA staff in order to speed up the licensing process. In 2017 the FDA spent $1.55 bn to regulate drugs for humans, and received 80% of that money from pharmaceutical companies in required user fees (Darrow et al 2020).

Darrow et al (2020) reviewed the US laws and FDA regulations for drug approval since 1983, and stated the following conclusion: "Over the last 4 decades, the approval and regulation processes for pharmaceutical agents have evolved and increased in complexity as special programs have been added and as the use of surrogate measures has been encouraged. The FDA funding needed to implement and manage these programs has been addressed by expanding industry-paid user fees. The FDA has increasingly accepted less data and more surrogate measures, and has shortened its review times" (p174).

1. TRIAL DISCONTINUATION

Steele and Flohr (2020) commented on the premature discontinuation of clinical trials: "Although termination of trials is essential when participants are exposed to harm, many trials terminate for potentially avoidable reasons. Such avoidable trial termination presents many issues. These include ethical issues, from the wasted time and effort of voluntary participants; financial issues, from the use of finite resources; and scientific issues, arising from publication bias" (p1497).

Concentrating on trials related to eczema, Steele and Flohr (2020) analysed ClinicalTrials.gov, which is the largest publicly available register of clinical trials [64]. Three categories were distinguished for the ninety discontinued trials found (out of 653 in total) [65]:

i) "Terminated" - Recruitment of participants had

[64] It is operated by the National Library of Medicine at the National Institutes of Health in the USA since its inception in February 2000 (Williams et al 2015).

[65] This was 14%, which is less than other medical areas (eg: Williams et al 2015; table 15).

- Analysed the "Why Study Stopped?" section of the ClinicalTrials.gov website in February 2013 [66]. Of the 7646 clinical trials posted at that time, 12% (n = 905) were listed as terminated after enrolling at least one participant.

- The researchers used three major categories of reasons for trial termination:

  i) Based on scientific data collected (21% of terminated trials) (eg: side effects assumed as too great compared to benefits).

  ii) Based on reasons other than scientific data collected (68%). Among the sub-categories here, "insufficient accrual rate" (ie: recruit of participants) was most common (table 16).

  iii) No information provided (11%).

- The data on ClinicalTrials.gov came from the self-reports of the trial sponsor/organiser, and "there may have been heterogeneity in how sponsors applied the ClinicalTrials.gov data element definition resulting in (1) the inclusion of trials that achieved their target enrolment but were considered by the sponsor to have ended prematurely (eg: data collection ended early) and (2) the exclusion of trials that had lower than expected enrolment but were identified by the sponsor as 'Completed'" (Williams et al 2015 p8). Kasenda et al (2014) used such self-reports, but from multiple sources, while ethics committee approvals, and funders' administration databases have been used in other studies (Williams et al 2015).

- The researchers admitted that categorisation was their judgment when multiple reasons were given for termination.

Table 15 - Details of Williams et al (2015).

begun, but the trial was later discontinued (35 trials).

ii) "Withdrawn" - Discontinued before participants recruited (27 trials).

iii) "Unknown" - Active trials but no updated information for two years or more (28 trials).

The most common reasons given for (i) and (ii) were recruitment issues (for both industry and non-industry funded trials) (though 2251 patients, over half children, had been recruited by the 35 "terminated" trials), and sponsor decision (for industry-funded trials). Funding issues was a problem specific to non-industry funded trials. But approximately half the discontinued trials gave no reason for their decision (though it is good practice to do so) (Steele and Flohr 2020).

Steele and Flohr (2020) ended: "Terminating trials prematurely, without a valid or stated reason, is

[66] This is an optional free-text field on the website with a 160 character limit. There was also a "Detailed Description" field for more information.

Termination Category	Number of Trials	Percentage (%) of Total Trials*
Total Terminated	**905**	**100%**
1. Scientific data from the trial	**193**	**21.3%**
2. Other than scientific data from the trial	**619**	**68.4%**
a. Insufficient accrual rate	350	56.5%
b. Unspecified business decision/strategic reason	77	12.4%
c. Trial administration or conduct (issues with protocol, investigators, site, etc.)	58	9.4%
d. External information (results from other trials, competing trials, or changes in standard of care)	51	8.2%
e. Funding	34	5.5%
f. Product withdrawal	18	2.9%
g. Lack of drug supply (other than drug withdrawal)	17	2.7%
h. Other (e.g., uninformative or non-specific text)	14	2.3%
3. Termination Reason Not Provided	**93**	**10.3%**

*Sub-category percentages calculated as a percentage of all trials in Termination Category 2 (n = 619)

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(Source: Williams et al 2015 table 1)

Table 16 - Reason for termination of trials.

ethically unfair to patients who willingly take part and who may be exposed to risk through participation. Recruitment, as the major cause of trial discontinuation, should be carefully considered prior to study commencement to reduce the observed rates of trial discontinuation. When a trial is discontinued, the reason for this and any results obtained should be disclosed in order to maximise the study's societal value and reduce publication bias" (p1498).

2. EVALUATING TESTS

Two pharmaceutical companies (Roche and Abbott) had anti-body test validated by Public Health England (PHE) in May 2020, but analysis of Roche's test by PHE had not been published at the time of the decision (Mahase 2020).

The test was reported to have a specificity (accuracy) of 99.73 - 100% by PHE (Mahase 2020).

The test from Abbott had similar specificity in a published study in the USA by Bryan et al (2020), but one of these authors "reported personal fees from Abbott outside of the evaluation" (Mahase 2020 p1).

A separate issue is that anti-body tests tell us who has mounted an immune response to the encountered virus, but "it does not show if these anti-bodies will stop the person getting sick from covid-19 in the future and how long any protection generated might last" (Mahase 2020 p2).

APPENDIX F - CORONAVIRUSES

1. Origins
2. Natural selection
3. Symptoms

Coronaviruses generally are common with four types responsible for about 20-30% of common colds (King 2020) [67].

Coronaviruses are know primarily for causing diseases in livestock, and two "benign" human versions were discovered in the 1960s - HCov-229E (originated in bats and moved to humans in the 18th century approximately) and HCov-OC43 (originated in pigs and cattle and jumped to humans in roughly the late 19th century) (King 2020).

The SARS outbreak (SARS-CoV-1) in 2002 in twenty-six countries, killing over 8000 people, showed that coronaviruses were more dangerous. One in ten infected individuals died. Bats were believed to be the carriers, and then civet cats became infected by a mutated version before another genetic mutation led to human infection (King 2020).

The subsequent search for coronaviruses has found HCoV-NL63 (associated with respiratory tract infection in babies) and HCoV-HKU1 (discovered in Hong Kong in 2005) (King 2020).

Genetic analysis of human and bat HCoV-NL63 viruses have suggested a shared common ancestor between 500 and 800 years ago, and that the leap from bats to humans began in the 13-15th centuries. This leap would have produced a pandemic (probably lost among the high death rate of the times and lack of medical knowledge) (King 2020).

HCoV-NL63 and HCoV-229E are classed as the alpha sub-family of the four sub-families of coronaviruses (along with feline and canine versions), while HCoV-OC43 and HCoV-HKU1 belong to the beta sub-family (plus the viruses behind SARS, MERS (Middle East respiratory syndrome) [68], and covid-19) (King 2020).

1. ORIGINS

The first whole genome sequence of SARS-Cov-2 [69] [70]

[67] Other causes of the common cold include rhinoviruses (around 100 different types causing half of all colds), respiratory syncytial virus and human metapneumovirus, and human parainfluenza (four viruses usually associated with summer colds) (King 2020).

[68] MERS-CoV has passed from dromedary camels (King 2020).

[69] Technically, a betacoronavirus (van Dorp et al 2020), and a "spiky 85-nanometre parcel of protein"

was published on 5th January 2020 (van Dorp et al 2020) [71]. van Dorp et al (2020) analysed it for the virus for genetic diversity using the 7666 genomes publicly available by 19th April 2020. A common ancestor with bat versions was estimated as existing in late 2019 (between October and early December), and so it was then that the virus jumped into a human host (zoonotic transfer - "natural spillover event"), they proposed.

Andersen et al's (2020) analysis of the SARS-CoV-2 genome led them to state that the virus is "not a laboratory construct or a purposefully manipulated virus" (p450).

These researchers offered two main routes from animals to humans:

i) Natural selection in an animal host produced a "version" suited to living in humans and then it jumped to humans - Certain bat species are probably the animal host (eg: RaTG13 bat virus is 96% genetically similar to SARS-CoV-2), or possibly Malayan pangolins.

ii) Zoonotic transfer and then natural selection in humans until SARS-CoV-2 could "live" in the human host - This would mean undetected human-to-human transmission while the natural selection occurred.

Two genetic mutations in SARS-CoV-2 have been distinguished to allow the survival in the human host - binding to ACE2 receptors (evolved by route (i) above), and another change related to entry into the human cell [72] (evolved by route (ii) above) (Andersen et al 2020).

A third possibility is that the natural selection happened in laboratories studying coronaviruses - that is in the cell culture and/or animal model being used (Andersen et al 2020).

Many suggestions have circulated on social media about a "lab accident", particularly from Chinese researchers working bats and coronaviruses. "Could an unknowingly infected researcher showing no symptoms unwittingly have infected family, friends, and anyone else he or she was in contact with? Or was there perhaps an unnoticed leak of a coronavirus from the lab, from

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(Arnold 2020b).

[70] SARS-CoV and SARS-CoV-2 have 79.6 genetic similarity, and "use the same entry receptor (ACE2) and cause similar acute respiratory syndromes" (Iwasaki and Yang 2020 p339).

[71] van Dorp et al (2020) observed: "Pandemics have been affecting humanity for millennia... One positive aspect of the current situation, relative to previous pandemics, is the unprecedented availability of scientific and technological means to face covid-19" (p9).

[72] Technically, change at polybasic furin cleavage site (Andersen et al 2020).

improperly incinerated waste material or animal carcasses that found their way to rubbish bins that rats or cats could have accessed? Another theory is that an infection occurred during fieldwork, when researchers were collecting viruses from bats deep inside mountain caves" (Lentzos 2020). This has been dismissed (eg: Peter Daszak in Lentzos 2020).

Lentzos (2020), not arguing for a laboratory accident, considered the possibility. Firstly, collecting samples from bats in the wild is risky, including bites from captured animals, and contact with bat urine and faeces.

Secondly, the laboratories, not only study the coronaviruses, but engineer chimeric (or hybrid) viruses (ie: a genetic combination of viruses) to test in the petri-dish or in animals, like rats. There are ethical concerns in some countries about such "gain-of-function" studies. Such studies alter pathogens to understand them and their interaction with humans. Simply, making a pathogen more dangerous to humans is obviously worrying, and there have been/are moratoria.

Thirdly, there are accidents at laboratories.

Lentzos (2020) ended: "Countries that establish high containment facilities, or that fund high risk research like chimeric coronavirus studies, have an added responsibility to the international community. They need to demonstrate that they operate these facilities safely and securely, that appropriate risk assessments are conducted, and that there is some accountability in place if they do not".

2. NATURAL SELECTION [73]

Each viral species is a group of closely related strains that are changing in tiny ways as they replicate. These are "quasi-strains" or "swarms". Tiny changes (or copying errors) are rife because replication is so rapid, and because the genes of viruses are encoding RNA (rather than DNA), mutations are even more common (Goodman 2020).

The quasi-strain is central to evolution. Each virus is competing to survive in a host against the immune system, and against other strains. So, some strains will survive in the host, and the species as a whole will continue.

Based on confirmed cases worldwide by early May 2020, there were 3.2 million of them and 230 000 deaths, giving a mortality rate of approximately 7% (Goodman

[73] Written 28th May 2020.

2020). But this ignores unreported cases, and varying definitions of a "confirmed case".

A more complete dataset is the "Diamond Princess" cruise ship (quarantined in Japan in early February 2020), where all passengers and crew were tested, and 1.2% of those infected died (Goodman 2020).

Iceland has attempted to test their whole population, and the mortality rate was about 0.6% in early May 2020 (Goodman 2020).

The different figures may reflect differences in the samples (eg: older sample on the ship), or "it could indicate that the virus is evolving to become less deadly as it spreads" (Goodman 2020 p42).

A virus has an evolutionary trade-off between how lethal it is to a host and its ability to spread. In crowded situations, lethal viruses reproduce best and thrive. But, in time, there will be less hosts and/or less crowded situations, and so natural selection will favour less deadly strains to spread better (Goodman 2020).

But a milder version of the virus is not inevitable. While "SARS-CoV-2 is spreading successfully, so short-term evolutionary changes aren't necessary" (Emma Hodcroft in Goodman 2020). Two key unknowns to predicting the evolution of the virus are its transmission (possibly when individuals are asymptomatic), and the huge variability in reaction in the human body (from minor to severe infection) (Goodman 2020).

3. SYMPTOMS

Establishing the complete list of symptoms of covid-19 depends on information from hospitalised patients primarily (ie: case reports). But anecdotes also circulate in the media of other symptoms, like anosmia (loss of smell).

Menni et al (2020) reported the development of an app-based symptom tracker launched in the UK on the 24th March 2020. Volunteers record their daily state of health and any symptoms of disease. Data for the app until 21st April 2020 covered 2.4 m UK and 168 000 US individuals reporting potential symptoms of covid-19 ("Covid Symptom Study app"; Menna, Sudre et al 2020).

In the UK sample, 6452 individuals reported a positive RT-PCR SARS-CoV-2 test [74] and 9186 a negative one. Using the test result as the outcome measure, it is possible to analyse the self-reported symptoms as predictors of covid-19. Of the positive tests, 65% reported a loss of smell and taste compared to 22% of the

[74] Reverse-transcriptase polymerase chain reaction (RT-PCR). This tests for the virus based on its DNA.

negative test individuals (table 17).

The following established symptoms were confirmed as predictors of a positive test in the UK sample - fever, persistent cough, fatigue, shortness of breath, diarrhea, delirium, skipped meals, abdominal pain, chest pain, and hoarse voice.

Altogether, loss of smell and taste along with fatigue, persistent cough and loss of appetite was the group of symptoms best predicting a positive test.

- Anosmia was reported by 16% of individuals with covid-19 who did not show the more established symptoms of fever or cough (Menni, Sudre et al 2020).
- In fact, Menni, Sudre et al (2020) argued that "the predictive ability of loss of smell and taste to be higher than fever or persistent cough" (p1). Furthermore, anosmia lasted longer than fever (median 5 vs 2 days) (Menni, Sudre et al 2020).
- Menni, Sudre et al (2020) advocated that "[D]irect self-testing for new onset loss of smell and taste could improve symptoms capture and should open doors to confirmatory testing. However, loss of smell and taste could be a less discriminating symptom in older people and by those who are less able to report symptoms, such as people in care homes" (p1).

Table 17 - Anosmia as key symptom of covid-19.

Despite the benefits of this app-based collection of data (eg: large-scale; in real-time), all information is self-reported. Specifically, for loss of taste and smell, physiological assessment of olfactory and gustatory function would be ideal. The authors admitted: "Both false negative and false positive reports could be included in the dataset, and because of the way the questions are asked, gustatory and olfactory losses are conflated" (Menni et al 2020).

Self-reports may be influenced by media coverage. Media reports of anosmia as a symptom of covid-19 appeared in late March 2020 in the UK. Menni et al (2020) analysed their data in separate time periods and found "that awareness of loss of smell and taste as symptoms of COVID-19 in the UK has increased following media reports. However, this association was not found in the US cohorts...".

They continued, that "at present, we do not know whether anosmia was acquired before or after other COVID-19 symptoms, or during the illness or afterwards. This information could become available as currently healthy users track symptom development over time" (Menni et al 2020).

Menni et al (2020) also commented on their sample in that they are "not representative of the general population because performing tests for SARS-CoV-2 is not

random. Testing is more likely to be done if an individual develops severe symptoms requiring hospitalisation, if an individual has been known to have had contact with people who have tested positive for SARS-CoV-2 infection, in health workers, and if an individual has travelled in an area of high risk of exposure. Therefore, our results may overestimate the number of expected positive cases of SARS-CoV-2 infection. Additionally, volunteers using the app are a self-selecting group who might not be fully representative of the general population".

APPENDIX G - SMOKING

1. Public smoking ban

The rates of smoking among covid-19 patients has been reported as varying from 1.4% to 12.5% in Chinese samples. These figures are much lower than the general population (eg: 52% of Chinese men) (Miyara et al 2020).

Among 343 in-patients with covid-19 at a large French university hospital in February and March 2020, 4.4% were daily tobacco smokers compared to 25% in the French general population in 2018 (Miyara et al 2020).

Miyara et al (2020) concluded that smoking may be a protective factor for covid-19, and it may be mediated by nicotine (and its influence on the ACE2 receptor) [75]. However, this study was cross-sectional, and causality cannot be confirmed. The data on smoking were self-reports.

Self-reports of smoking has been questioned, particularly where there was a shortage of intensive care beds and non-smokers were perceived as getting priority (Wilson 2020b).

Also hospitalised cases are more likely to be older, and the smoking rate is lower in this group compared to the general population (Wilson 2020b).

Controlling for age and sex, smokers have a 25% higher risk of developing covid-19 symptoms than non-smokers, according to larger scale studies (Wilson 2020b).

While, in a "live rapid evidence review", Simons et al (2020) found that smoking was more common among the sickest covid-19 patients.

1. PUBLIC SMOKING BAN

Public smoking bans have been advocated and implemented in many countries as part of health promotion campaigns to reduce tobacco use.

An early study of the short-term effects in Germany found little reduction in smoking generally as a consequence. "However, individuals who reported going to bars and restaurants regularly – and hence were more exposed to the constraints of public smoking bans in everyday life – did adjust their smoking habits. People who go out more often to bars and restaurants (ie: individuals with a propensity to go out above the median)

[75] Changeux et al (2020) focused their explanation on the nicotinic acetylcholine receptor, while Gonzalez-Rubio et al (2020) suggested that nicotine may reduce an over-reaction of the immune system to covid-19 that causes a cytokine storm.

exhibited a two percentage point lower propensity to smoke following the introduction of a smoking ban. Their likelihood to smoke regularly (ten or more cigarettes per day) also fell, as did their average daily cigarette consumption. The effects were even more pronounced for individuals in the top quartile of those regularly going to bars and restaurants, leading to a four percentage point reduction in these individuals' smoking probability after implementation of the smoking ban" (Anger et al 2011 pp591-592).

This study was based on data from the Socio-Economic Panel Study, which annually interviews around 20 000 adults. The years 2002, 2004, 2006, and 2008 were analysed, while the public smoking ban was introduced in 2007-8 (varying by federal state).

APPENDIX H - POLLUTION

1. Air pollution
2. Occupational health risk

1. AIR POLLUTION

Particulate matter (PM) of different sizes (2.5 - 10 μm [76]) and content (solid and liquid) make up air pollutants, which can pass through the lungs into the bloodstream. It is associated with chronic health affects like respiratory problems and cardiovascular diseases (Wei et al 2019).

Wei et al (2019) showed a relationship between short-term exposure to air pollution and hospital admissions with US data. The claims relating to 214 disease groups of over 95 million inpatients (aged 65 years and older) to Medicare for 2000 to 2012 were used, along with US Environmental Protection Agency data on $PM_{2.5}$ levels for the zip code of residence.

The positive association between hospital admission for respiratory and cardiovascular diseases, and air pollution was confirmed. But the large dataset produced new findings: "Short term exposure to $PM_{2.5}$ was positively associated with risks of several prevalent but rarely studied causes of hospital admissions, such as septicemia, fluid and electrolyte disorders, acute and unspecified renal failure, and intestinal obstruction without hernia" (Wei et al 2019 p1). These associations existed even when $PM_{2.5}$ was within the World Health Organisation's recommendations for exposure.

The study did not control for confounders like smoking, alcohol consumption, and physical activity that "could trigger hospital admission and could vary also with air pollution levels" (Wei et al 2019 p12).

2. OCCUPATIONAL HEALTH RISK

Exposure to silica, and its inhalation, can lead to silicosis, and ultimately respiratory failure. It is estimated to be responsible for more than 10 000 deaths per year worldwide (Leon-Jimenez et al 2020).

Workers in industries like mining and quarrying are particularly vulnerable. High-income countries have implemented occupational health measures which have reduced the risk. "However, in recent years, an increase in the incidence of silicosis has been detected in relation to new occupational exposures" (Leon-Jimenez et

[76] Micrometres (μ = mu symbol) = one millionth of a metre.

al 2020 p2).

Leon-Jimenez et al (2020) were referring to a new construction material used in kitchen and bathroom countertops and in flooring called artificial quartz agglomerate or conglomerate or artificial stone (AS) (composed of finely crushed rock mixed with synthetic resin, and having a high silica content).

AS silicosis cases have been reported in Israel, Spain, Italy, USA, Australia, and Belgium, for example (Leon-Jimenez et al 2020). "Some of these cases have progressed rapidly, suggesting that AS silicosis is more aggressive than classic silicosis" (Leon-Jimenez et al 2020 p2).

Leon-Jimenez et al (2020) reported their longitudinal study of 106 male workers diagnosed with silicosis in southern Spain between 2009 and 2018. "All of the patients worked cutting and polishing slabs of AS in small factories and were also involved during in-home installation performing dry operations (on many occasions without effective personal protective equipment)" (Leon-Jimenez et al 2020 p3).

The key finding was that despite the cessation of exposure (ie: stopping working in the factories), there was a rapid decline in lung function. This was much faster than in silicosis caused by natural stone (eg: gold mine workers; granite quarry exposure) (Leon-Jimenez et al 2020).

APPENDIX I - TESTING FOR COVID-19

1. Accuracy of tests

Who to test in a population for the presence of the virus [77] (Le Page 2020)?

a) Random individuals - Helps in finding the asymptomatic or those with mild symptoms, and individuals not aware that they are infected can be isolated.

b) Suspected infections - Could be effective if hand-in-hand with "contact tracing".

c) Key and health workers - Allows the individuals to continue working. It is agreed that such groups should be tested regularly irrespective of symptoms.

d) Universal, regular testing - Expensive to test everybody, say, weekly, as well as the feasibility of doing it.

Peto et al (2020) argued for weekly testing of the whole population in a demonstration site (a town or city) in the UK with strict quarantine for positive tests. After such a feasibility study, weekly testing could be rolled out to the whole country. The authors stated: "If the epidemic is controlled, hundreds of thousands of lives could be saved, intensive care units will no longer be overloaded, and the adverse effects of lockdown on mental ill health and unemployment will end" (p1420).

Complementary strategies could include contact tracing, and penalties for breaking quarantine, while supporting such individuals with income and food as required. Testing could be voluntary to deal with issues of coercion (Peto et al 2020).

1. ACCURACY OF TESTS [78]

Testing for the virus can be done using nasal swabs, throat swabs, sputum/saliva collection, and broncho-alveolar lavage fluid (BALF) methods. Yang et al's (2020) comparison of these methods found that SARS-CoV-2 was detected in sputum/saliva samples, nasal swabs, and throat swabs in that order of best accuracy for simple and safe means of collection (in the first 14 days of infection). However, BALF was best overall, but it requires a suction device and a skilled operator to take

[77] Antigen testing as opposed to testing after the illness for anti-bodies.
[78] Written 23rd May 2020 onwards.

a sample from the lower respiratory tract (Yang et al 2020).

Yang et al's (2020) data came from 213 patients in one hospital in China in January 2020. Throat swabs were felt to produce the most "false negatives" (incorrectly finding no virus) [79], particularly for mild cases of covid-19.

Wyllie et al (2020) confirmed saliva collection as more accurate than throat and nasal swabs. Their sample was 44 in-patients at a US hospital in March 2020, of which 29 had multiple and different tests. Multiple saliva collections in twelve patients never produced a negative result followed by a positive one, whereas multiple swabs for five patients showed this pattern. A negative result followed by a positive one in patients known to be infected is a sign of "false negative".

Wyllie et al (2020) admitted: "As SARS-CoV-2 viral loads differ between mild and severe cases, a limitation of our study is the primary focus on covid-19 in-patients, many with severe disease".

Zou et al (2020) reported the data from eighteen patients in a Chinese hospital in January 2020, who were given a total of 72 nasal swabs and 72 throat swabs. The researchers stated: "Higher viral loads... were detected soon after symptom onset, with higher viral loads detected in the nose than in the throat. Our analysis suggests that the viral nucleic acid shedding pattern of patients infected with SARS-CoV-2 resembles that of patients with influenza and appears different from that seen in patients infected with SARS-CoV. The viral load that was detected in the asymptomatic patient was similar to that in the symptomatic patients, which suggests the transmission potential of asymptomatic or minimally symptomatic patients. These findings are in concordance with reports that transmission may occur early in the course of infection and suggest that case detection and isolation may require strategies different from those required for the control of SARS-CoV" (Zou et al 2020 p1179).

Tu et al (2020) compared testing methods by health care workers and patients themselves. The self-tests were 90% accurate if health care worker-tests were 100% so. This showed that self-testing was a reasonably good alternative to health care workers needing to use personal protective equipment to test the patient. "When patients collect their own samples, health care workers can focus on other patients or other parts of the clinical encounter, increasing practice efficiency

[79] "False negatives" in infected but symptomless individuals could lead to behaviour that spreads the virus (Brooks 2020).

through optimising staff utilisation" (Tu et al 2020).

The patient sample in this study of around 500 individuals came from five clinics in the Puget Sound region, Pacific north-east USA between the 16th to 21st March 2020.

APPENDIX J - SUBJECTIVE STRESS

1. Stress and illness

The physiological stress reaction is summed up in the hypothalamic-pituitary-adrenal (HPA) axis which covers a series of responses linked to the hypothalamus, pituitary and adrenal glands (eg: glucocorticoid release). But this is not the same as subjective feelings of stress (eg: feeling "stressed out"), which are linked to the hippocampus (Goldfarb et al 2020).

"Cognitively, the hippocampal system may contribute to the subjective feeling of stress by supporting memory retrieval, which can either augment or diminish acute stress responses. Impairments in hippocampal function could change stress reactions through generalising from prior stressful contexts and increasing reliance on habitual coping strategies" (Goldfarb et al 2020 p2).

Goldfarb et al (2020) recruited sixty healthy volunteers at Yale university, USA, to undergo a functional magnetic resonance imaging (fMRI) scan while viewing highly aversive images (stressor condition) or neutral one (control condition). The purpose was to evoke a subjective rating of stress and to view the brain activity in that state. A network of brain areas including the hypothalamus linked to the hippocampus was associated with a conscious feeling of stress, while a network linked to the dorsolateral prefrontal cortex was associated with subjective relaxation/non-stress.

1. STRESS AND ILLNESS

Stress and illness have been conceptualised in different ways, but the main approaches include (Cox 1995):

i) A threshold - Stressors build up until it is too much, like weight on a bridge. Thus, it is sometimes called the "engineering model".

ii) Interaction/transaction - There is a mismatch between the person and the environment. The focus is often on the psychology of the individual, and changing their cognitions so they can "fit" into the stressful situation. Coping is also important here and the development of "resources" (eg: coping skills).

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