SARS-COV-2: Learning the Lessons from our Experiences, A Critical and Personal Review

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ABSTRACT---- ***The aims and objectives of this paper is to question established scientific thinking and medical protocols surrounding SARS-COV-2, stimulate debate, and consider alternative and more effective ways of screening and treating the severely affected patients which improve therapeutic outcomes and thereby reduce the complexity and cost of treating infected SARS-COV-2 patients.***

The paper argues that national quarantine or lockdown strategies among countries (as a preventive approach) exhibit many shortcomings and are based on a set of erroneous assumptions which enables the independently minded to consider alternative diagnostic and/or therapeutic strategies e.g. to quarantine only the 'at-risk' groups; which could be significant in the future.

It raises for discussion a number of pertinent points e.g. (i) that the virus affects different patient groups in different ways; (ii) that the most severely affected who are at risk of death is currently the vast minority of the population, in particular those who are diabetic, obese and immunosuppressed; (iii) that chasing the virus using 'test and trace' methods should be augmented by advanced, remote screening methods to determine those in the most 'at-risk' groups who should be quarantined; and (iv) reviews the fundamental limitations of seeking only drug-based solutions instead of considering and focussing upon scientifically sustainable solutions based upon an understanding of the fundamental chemistry of biology.

1. BACKGROUND

The science being used to justify lockdowns in countries throughout the world exhibits many shortcomings. How someone becomes infected or how the SARS-COV-2 virus transmits between patients remains very poorly understood [1]. This article reviews the various factors which make some people less vulnerable to infection than others e.g. children rarely transmit the virus [2], the effect which SARS-COV-2 has on the body, why some therapies work and others do not, and ultimately how patients can best be treated.

It is clear that locking-down a population by minimising the transmission of the virus to a country from another country, or between infected people within a country, will slow the transmission of the virus and reduce the numbers of people who are infected but it has now been recognised that only 0.075-0.08% [3] of the UK population die (after being infected, developing complications). Other countries appear to have significantly lower rates of infection and death [4] allegedly because they activated their plans to combat such events much earlier than the UK authorities. Some countries have comparable rates of infections and deaths but did not implement a severe lockdown and some countries which did not implement a lockdown appear to have had much worse outcomes.

In the case of a severe outbreak of influenza, there have been up to 20-30,000 deaths in the UK yet a severe lockdown was not considered to be necessary so why on this occasion did the authorities adopt a different model and lock down almost the whole population? Their decision-making was heavily influenced by experts in disease modelling who forecast 250-500,000 deaths in the UK [5], perhaps more, yet their models were clearly based upon a set of assumptions in which they erroneously assumed the homogeneity of the population, and failed to take into account age, the significance of pre-existing morbidities, etc.

The prevailing model for a severe influenza outbreak is not to test everyone but instead to test and/or treat those who had the most severe symptoms however with SARS-COV-2 it was decided to effectively reverse the prevailing model and test as many people as possible. 'Test, test, test' became the mantra – the same philosophy used to manage the Ebola outbreak in Central Africa – yet identifying someone who was infected often had little effect on the overall course of the outbreak because the infection was not seriously inconveniencing the vast majority of the population.

Any testing regime should (a) look to identify those who have been infected, (b) those who are currently infected, and (c) those who could be infected in future. This latter aspect of the testing regime – testing to determine who are most 'at-risk' - is almost completely missing from consideration at present yet it conceivably presents the best way of containing the virus and, in particular, preventing the spread of the virus through 'at-risk' groups who would ultimately require to be admitted to hospital for further treatment. The problem for the authorities is that scientific opinion initially assumed that everyone who was infected would be at risk of hospitalisation and/or death yet it is now recognised that, at least in the UK, only ca 0.075-0.08% of the (ca 50,000 of the UK's 65M) population has died [3]. There is also a further issue: (d) how many have died from the medical interventions and not the consequences of the infection? Perhaps this will never be known. Nevertheless the recent findings that dexamethasone reduces the number of deaths in those who have been placed on a ventilator illustrates that some died as a result of being placed on by ventilators.

Recent studies show that SARS-COV-2 has been circulating earlier than previously thought; perhaps in Wuhan since mid-late Q3 2019 [6]; and hence that the numbers of people who have been infected may be much greater, perhaps up to 40 times greater [7], than was previously thought. This appears to indicate that ca 5-15% of the population, perhaps more, of the population have been infected with this virus.

It is not yet known whether some people e.g. the younger element of the population [2], develop antibodies. There is a vibrant debate around this issue. Do some people become infected and yet do not develop antibodies? An estimated 45% of those infected are believed to be asymptomatic [8]. If so, can anything be done to prevent the virus spreading? Moreover, does it really matter whether it spreads widely in the population? If we can protect the 'at-risk' groups then surely it does not really matter if the virus circulates? Do some people become infected yet are asymptomatic? Do some people become 'superspreaders'? Does the disease only become significant in those who have a specific level of vulnerability? If so, has it already reached the level commonly known as 'herd immunity' **in the at-risk group** [9]?

It is now recognised that most normally healthy people are unaffected by the virus so it really does not matter whether they are in contact with others who have been infected with the virus. For them exposure to the virus leads to an infection which is at worst comparable to infection by the influenza virus. In general most children experience a mild set of symptoms, conceivably because children have far greater levels of T cells, which conceivably intervenes more effectively at the point of infection, and hence have a more robust immune response than adults [10,11]. This raises the intriguing possibility that much greater % of people in the 'at-risk' category have been vulnerable to the virus than those in the wider population.

Those that are worst affected are those who have pre-existing medical conditions, in particular impaired breathing due to an inflammatory response in the lungs which influences the prevailing capacity of the lungs to deliver O_2, the diabetic and obese [12], those with kidney and/or liver insufficiency, those who are immune suppressed, the frail/elderly, and those who are severely stressed [13]. It affects people who live a sedentary lifestyle, who are physically inactive, perhaps who spend a lot of time working on computers, are immunosuppressed e.g. who have had cancer or are being treated for cancer, etc. In general, the 'fit elderly' are not predisposed to this virus.

Although the most vulnerable group is those >65 years a significant number, less than 50%, are in the workforce. In some hospitals 50% of the workforce were infected at some point of the outbreak [14]. Ca 100-200 nurses and doctors in the UK have died in the course of their duties although working in the health and social care frontline makes them 6 times more likely to be infected [15] which illustrates that SARS-COV-2 is primarily a problem for those working in, and/or in regular contact with 'healthcare' and less so for the wider population. These numbers can reasonably be expected to vary between countries – some countries have greater levels of obesity, more people over the age of 65 years, and other risk factors - and hence would expect to have greater levels of SARS-COV-2 hospitalisations and deaths however not all of those who are predisposed to this virus are in the >65 years age group. In Germany the average of age of those infected, and/or dying, is much lower than in other countries because the German authorities have been well prepared for the pandemic, started testing earlier than other countries, implemented lockdown at a much earlier stage, and prevented transmission to care homes.

The transmissibility of the virus appears to be within several days. It occurs earlier than it can be detected using diagnostic tests. This presents a dilemma for those who seek to track the transmission of the virus. Can it ever be tracked down and choked at or before the point of transmission? It appears not because the virus moves faster than the tracers. If not why is the incidence of infection reducing – in the late spring/early summer months?

Accordingly if only 5-15% of the population have had the infection the transmission of the virus will slow down but can be expected to persist in the population unless there are other factors at play which have not been taken into account e.g. if SARS-COV-2 behaves in the same way as all previous coronaviruses it can reasonably be expected to die and/or decline in the wider population during the spring and summer months, at least in those who lead an outdoor lifestyle. Under strong sunlight SARS-COV-2 has a half-life of just 2 minutes [16,17] so as the countries in the northern hemisphere enter the spring period i.e. after 21st March, the length of exposure to the summer sunlight will increase, the intensity of the sunlight

will increase, and the effect of UV light (UVC) can reasonably be expected to have a virucidal effect upon this virus. Sheltering from exposure to sunlight e.g. in air-conditioned environments; or indoors away from heavy rain will reduce the virucidal effect from UVC. If this is the case the usefulness of quarantining everyone indoors must now be questioned. If the most vulnerable groups are kept isolated and free from sunlight they will not develop the vitamin D levels which help them to optimise their immune response and fight against bacterial and viral infections with the result that the virus will circulate for longer in the community. It highlights the fundamentally unsafe practice of containing the vulnerable groups including the most frail elderly patients in care homes (or sheltering from sunlight) where they are often kept isolated and out of natural sunlight i.e. in an environment which is conceivably a breeding ground for the transmission of such viruses.

The utility of testing has been questioned. It is certainly useful to know how many in a population are infected, or have been infected, but the usefulness of quarantine/lock-down is uncertain for the reasons outlined. It may also be useful to know the health profiles of the 0.075-0.08% of the most 'at-risk' groups in the population and quarantine those who are in this 'at-risk' category in order to prevent their infection. This could be done by checking their health profiles (assuming that their health records were sufficiently detailed) however the actual profile of the most vulnerable groups has not yet been clearly established although there is now general acceptance of the medical profiles of the most at-risk groups. Accordingly it is likely that the regular range of tests currently used to screen the health of such patients may be inadequate for this purpose e.g. because it requires access to scanning equipment which are available in hospitals. A more advanced screening, remote, non-invasive test may be required to screen these patients during the latter stages of this pandemic and/or in preparedness for future pandemics.

By early July 2020 the Ro factor is ca 0.7-0.9 in the major industrialised nations in the northern hemisphere despite their best efforts to track and trace people who have been infected with the virus despite quarantining the vast bulk of the population. The number of deaths in care homes is now in decline and the numbers in the wider population is now declining steadily and has reached manageable proportions (typically less than 100 deaths per day).

Sweden which has a less strict lock-down has had fewer people infected and until recently had fewer deaths in their population but, importantly, has kept their economy running. This serves to cast doubt on the benefits and/or effectiveness of the lock-down applied in the UK i.e. it has been an invaluable mechanism to slow or prevent the spread of the virus in the community but it has never eradicated the virus. There are more factors at play than person to person transmission but of course it was intended to 'flatten the curve' and was not intended to eradicate the virus.

It is worth cautioning the use of 'number of death' statistics because many of these patients did not die at the time that they were infected. They were infected many weeks previously.

In addition [18] the BAME populations appear to be suffering a disproportionately high number of deaths due to the virus e.g. Pakistani origin patients were 3.29 times more likely to die of the virus. This conceivably illustrates that exposure to sunlight is a significant factor in the etiology of SARS-COV-2 infection. Patients with non-Caucasian skin-types require different levels of sunlight to stimulate the production of vitamin D which plays a role in their immune response to viral infection.

Sunlight is commonly associated with the production of vitamin D which plays a role in the immune response [19] however over 100 medical conditions respond to the effect of sunlight which indicates that the beneficial effect of sunlight may not be solely due to the effect of vitamin D but also to the effect of sunlight upon other metabolic processes i.e. that sunlight functions as a photomodulator/ photoactivator of a wide range of metabolic processes [20]. Accordingly if people shelter in their homes, and/or use other means to prevent their exposure to sunlight, they predispose themselves to adversely low levels of vitamin D and greater predisposition to infection [21-23]; and Prietl *et al.* [24] illustrated that low levels of vitamin D are associated with the occurrence of upper respiratory tract infections (URTI) including influenza, COPD and asthma. Perhaps therefore vitamin D supplementation could be of value in preventing the onset of SARS-COV-2 type infections and/or as a way of stimulating immune function in those who are more severely affected.

2. KEY FACTORS WHICH INFLUENCE THE COURSE OF THE INFECTION

This leads to the issues discussed by Ewing in his recent paper [25] which is now extended in this paper. When patients are infected with SARS-COV-2 this brings to bear a number of issues:

(i) Why does the supply of cytokines and other related immune function proteins fail to act upon the virus?

In cases of SARS-COV-2 infection the lungs are infected and inflamed which steadily reduces oxygen saturation, and leads to acidosis and hypoxia. As the infection worsens the body responds by expressing cytokines and other immune proteins. However the patients who are most severely affected by the virus are those with pre-existing medical conditions which are accompanied by elevated levels of acidity in the blood

and consequently lower levels of essential minerals, in particular magnesium and zinc. This is significant because cytokines require magnesium to function [26]. As cytokines are relatively inactive in a magnesium deficient context the body responds by supplying more cytokines and/or the prevailing levels of cytokines accumulates – the so-called 'cytokine storm'.

Seeking an explanation for this we look for precedents and note that in the treatment of pre-eclampsia [27] in vivo $MgSO_4$ treatment substantially reduced maternal TNF-α and IL-6 production i.e. the immunomodulatory effects of concern were mediated by magnesium. Moreover there are many studies and/or medical papers which recognise that magnesium plays a significant role in the immune response [28,29] e.g. Mannon *et al* [30]. have used sodium bicarbonate to stimulate anti-inflammatory pathways and the immune response i.e. the immune response can be altered by adjusting intercellular pH therefore the combination of sodium bicarbonate (oral or, in particular by iv injection) and Magnesium Sulphate can reasonably be expected to combat the cytokine storm.

This is further supported by noting that the first line treatment of SARS-COV-2 patients is the use of electrolytes and/or fluids [31] and also that the use of magnesium [32] with vitamins B12 and D have been shown to have a positive effect upon older SARS-COV-2 patients.

(ii) Do they have sufficient lung capacity to deliver O_2?

In the most affected categories patients have reduced lung capacities by virtue of their obesity which reduces their ability to inhale and supply O_2. Accordingly, an infection such as SARS-COV-2 will reduce their effective lung capacity still further and oxygen saturation declines.

(iii) What happens if the inflammation caused by the infection reduces the supply of O_2 to a critical level?

In such cases the prevailing medical dogma and standard operating procedures is that the patient should be give support by CPAP or, in the most severe cases be treated using ventilators. The evidence illustrates that CPAP has been a valuable intervention in some patients although there is no way of knowing whether the patient would have recovered without CPAP i.e. there was no placebo group against which the results and/or outcomes could be compared. The evidence in favour of ventilators is much less clear. Ca. 40-60% of patients placed on ventilators have succumbed to the infection and died which suggests that ventilators are not having the expected levels of success treating SARS-COV-2 [33].

Moreover it has now been recognised that the administration of dexamethasone can reduce the inflammatory response in the lungs and thereby reduce the number of deaths in those who are ventilated [34]. If so, is the inflammatory response due to the viral infection, the onset of acidosis, or is it due to the potentially allergic (or other) effect of the ventilator?

(iv) Can they absorb the O_2 being delivered i.e. do they have sufficient haemoglobin and/or is the haemoglobin able to absorb O_2?

The use of ventilators is based upon the assumption that the problem lies with the physical capacity and/or capability of the lungs to supply of O_2 to the alveoli where it is absorbed by haemoglobin however many of the those in the 'at-risk' category have low levels of haemoglobin [35]. Moreover the absorption of oxygen by haemoglobin declines under increasingly acidic conditions which is the case in those in the 'at-risk' category.
The successful use of ECMO [36] indicates that both issues – of lung capacity and the ability of the blood to absorb O_2 - must both be taken into account.

Moreover, what is the long-term effect on the patient's mental and physical health of being treated by ventilator i.e. if they survive?

(v) Is the heart able to circulate O_2 through the lungs?

The diabetic and obese patient encounters a range of diabetic comorbidities which often involve cardiac testing. Excess strain on the heart as it pumps blood with elevated viscosity (thickness) leads to strain on the cardiac musculature; a range of pathological indications; elevated blood pressure; etc. Moreover, the function of cardiac musculature is dependent upon the supply of O_2 in order to function. The heart has the greatest oxygen consumption by comparison with all other human organs. If it does not get sufficient oxygen a

condition known as ischaemia (ischaemic heart disease) develops. Pathologies which contribute to this condition include coronary heart disease and atherosclerosis. This is significant because if the heart is not supplied with oxygen it will be increasingly less able to pump blood around the blood vessels and through the lungs. In effect slowing the rate at which oxygen can be absorbed by haemoglobin.

(vi) Can the accumulation of CO_2 be removed?

Consequently impaired heart function leads to the accumulation of CO_2 in the blood and inter and extra-cellular mediums. The main mechanism for removal of CO_2 is via the lungs so reduced lung function leads to acidosis.

(vii) Does the accumulation of CO_2 hinder the absorption of O_2?

The autonomic nervous system works most effectively at a neutral pH (pH 7.35). At this level there is a balance/equilibrium between the levels of essential minerals and transition metals. In order to neutralise excess acidity in the body the body (i) exudes a bicarbonate-rich bile from the pancreas and (ii) converts CO_2 into HCO_3. Failure to maintain the pH in the range 7.0-7.35 leads to acidosis which adversely influences the prevailing levels of Mg and Zn, and reduces the immune response.

CO_2 is one of the main contributors to acidosis. Others include the consumption of acidified beverages, red meat, stress, and the accumulation of excess body fat. The enzyme carbonic anhydrase metabolises CO_2 into HCO_3 which is alkaline. Carbonic anhydrase requires Zn in order to function so increased levels of acidity in the blood severely impacts upon the removal of CO_2 via the lungs.

Whilst the use of iv saline solution will likely have some beneficial effect, the author suggests that the use of iv HCO_3 would reduce levels of CO_2 and be more effective, more rapidly. Moreover, in the ICU context, there is likely to be an immediate need to introduce Mg and Zn in order to stimulate the patient's immune response and to stimulate the activity of Carbonic Anhydrase to eliminate CO_2.

(viii) How does this explain the occurrence of blood clots?

Werring D *et al.* reported the occurrence of blood clots and ischaemic stroke in 6 SARS-COV-2 patients in the age range 53-85 years [37]. It is an issue which perplexes yet obesity is the consequence of elevated levels of blood lipids and fats, and results in acidosis. It accompanies and/or leads to the onset of clotting in atherosclerosis [38]. Moreover, it is widely known that increased levels of acidosis accompany blood clot formation, especially so in the trauma context [39,40].

The successful use of saline and electrolytes in most patients illustrates that the fundamental problem – that of acidosis – is associated with hypoxia, pulmonary inflammation and/or infection, and death.

(ix) SARS-COV-2 increases predisposition to diabetes.

People with chronic type 2 diabetes and obesity are most at risk [41,42]. This occurs because their greater body mass, in particular around the abdominal areas, influences the function of their diaphragm and hence their ability to inhale. Consequently, they have lower effective lung capacity, their supply of oxygen to the blood is inhibited, they have lower levels of haemoglobin and hence are less able to absorb oxygen, and they become vulnerable when exposed to infections which further reduce their effective lung capacity. It creates acidosis and hypoxia.

This will inevitably influence those with type 1 diabetes, in particular those who are not otherwise physically fit, and it will make those who are otherwise healthy at greater risk of becoming diabetic, because acidosis reduces the rate at which pre-pro-insulin is genetically expressed, the storage of the zinc-hexamer in the pancreas, the metabolism of insulin with its reactive substrate the insulin receptor protein, and the prevailing levels of chromium in the smooth muscles.

If zinc levels get too low the conversion of CO_2 to HCO_3 – performed by Carbonic Anhydrase - is no longer able to proceed. The seriousness of this situation in which the body's existence is challenged requires that it absorbs Zn stores from the pancreas in order to reduce CO_2 levels and thereby regulate the body's intercellular pH however the consequence of this is that the pancreas becomes less able to store insulin and as a result the patient shows signs of diabetes [43,44].

Finally, this virus is now circulating widely around the world therefore it is now almost inevitable that further rounds of infection will occur. What are the implications for medicine in 2020/21? Can it ever be possible to return to the pre-SARS-COV-2 models of healthcare in which the patients routinely attend primary or secondary care consultations? If you wish to have a consultation with your doctor you will need to wear a face-mask but this is a relatively minor inconvenience. Of greater concern is whether people will wish to work in the healthcare professions if this predisposes them, and their families, to greater risk of infection. How many doctors and nurses will retire from the medical profession earlier than normal retirement dates? How will this influence medical protocols? For example how will be patients be screened in scanning equipment? Will they need to be cleaned after every patient? This will drive up costs yet again! Will social distancing become the norm in clinics and hospitals and erode work efficiency?

There is a clearly now, more than ever before, a need for accurate Remote Online Technology Platforms which enable the patient to consult their doctor or to be tested and/or treated remotely [45]. There is now, more than ever, the need for radical and disruptive technologies which allow healthcare to be provided remotely.

3. CONFLICT OF INTEREST DECLARATION

Graham Ewing is Chief Executive of Mimex Montague Healthcare Limited – a company devoted to the commercialisation of the first comprehensive way of screening and treating the patient using a precise and sophisticated mathematical model of the relationship between sense perception, brain function, the autonomic nervous system and physiological systems, and cellular and molecular biology (known by the brand name 'Strannik').

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