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Review of Research on Covid-19

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ANNOUNCEMENT

- The 2019 International Conference on Quality of Life was held at Kyoto Pharmaceutical University from Sept 28-29, 2019. Further information can be found at http://as4qol.org/icqol/2019/
- We have moved to continuous publication. Beginning January 2019 the editing committee has decided to adopt a continuous publishing model for Journal publication. Individual articles will be released online as they become ready, allowing a steady stream of informative quality articles. We will also be moving to a calendar year issue cycle. In traditional terms, each volume will encompass a single year and consist of a single issue. Publishing on a just-in-time basis allows authors to present their results in a timely fashion, and our readers, students, and colleagues to access our content and cite articles more quickly and free from the restrictions of a predefined timetable. As a result of these changes, the look and style, as well as the function, of the Journal will be different, and hopefully improved.
- The 2019 International Meeting on Quality of Life was held recently. Proceedings as well as photos and other information can be found at http://as4qol.org/icqol/

JAS4QoL

Wisdom (Philosophical) Note

Review of Research on Covid-19

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1. Introduction

In late 2019, doctors in Wuhan, China, started seeing patients with a novel, severe respiratory disease. Experience with the SARS epidemic earlier this century led the doctors and scientists to recognize that this disease was caused by a newly observed corona virus. This virus, called Covid-19 virus or SARS CoV 2, was quickly isolated and its genetic material (RNA) sequenced, showing its phylogenetic relationship with other corona viruses. Results strongly suggest that the Covid-19 virus is a mutant form of an animal virus which crossed the animal-human transmission barrier. Since its first recognition in Wuhan, the virus has spread throughout the world, rapidly causing a pandemic and causing havoc with normal human life.

In this time of upheaval, grief and uncertainty due to the Covid-19 pandemic, we can hope for progress towards prevention, successful treatments and an acceptable post-pandemic future as a result of research by the world's medical scientists and clinicians. This report will attempt to summarise these efforts.

Before describing scientific and medical approaches to the pandemic, it is useful to consider the structure of the virus. As shown in Figure 1, an individual virus particle (virion) is made up of a number of components. The essence of the virus is the genetic material, called the viral genome, in this case a strand of RNA (shown in the figure as RNA and N protein). The genome is surrounded and protected by structural proteins. A virus particle is not able to reproduce by itself and needs to invade a host cell to access the cellular machinery required for replication. A surface protein called the spike protein is responsible for entry of the virus into human cells, particularly cells of the respiratory system. Particles of Covid-19 virus are also surrounded by a lipid (fatty) bilayer which makes them easily destroyed by the action of detergents and organic solvents (as in soaps and hand sanitisers). The abbreviation Covid-19 strictly refers to the disease but is used interchangeably in this review to refer to the disease or the virus causing the disease.

2. Summary of approaches to the Covid-19 pandemic

2.1 Development of rapid and reliable tests for Covid-19.

Monitoring and controlling the Covid-19 pandemic is facilitated by the ability to determine who is infected with the virus, how long the infection

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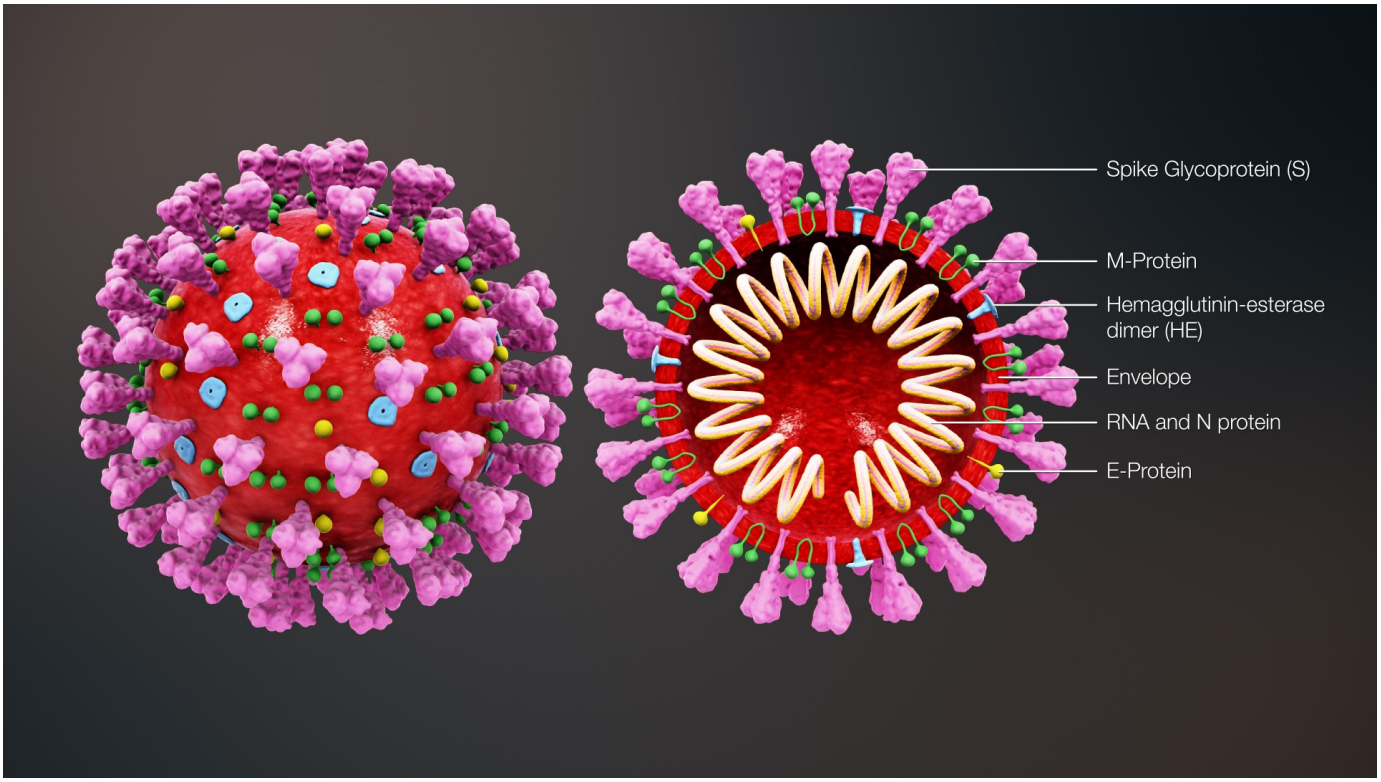

Figure 1. 3-D medical animation still shot showing the structure of a coronavirus.[3]

lasts, how readily the infection (virus) is transmitted from person to person etc. The ideal test for Covid-19 measures the viral load and is rapid, such that it is reasonable to request that the person being tested stay in place while the test is being read. Appropriate advice on the next steps can then be given to the person before they re-enter the community (*e.g.* self isolation or quarantine if the test is positive, depending on the legislation in place at the time). Extensive testing is even more essential because of the existence of pre-symptomatic and asymptomatic transmission.

The first test kits developed use a technique called RT PCR, with thermal cycling, to measure viral particles on nasal swabs. In essence, a section of the viral RNA specific for Covid-19 is converted to a corresponding DNA sequence (by reverse transcriptase, RT) which is then amplified by the polymerase chain reaction (PCR) so that it can be readily observed and quantified. Unfortunately this test takes hours rather than minutes and requires specialised equipment. Backlogs have meant that after providing a test sample, days may pass before a result is communicated to the patient, days in which a person positive for the virus could have spread virus in the community. More recently, an RT PCR test has been developed and is being marketed by Abbott Laboratories and other companies. In this test, amplification is isothermal (not requiring thermal cycling) and results are available after a few minutes. A further advantage is that the equipment required is simpler and more widely available (*e.g.* Abbott Laboratories ID NOW platform). With this test, the result and clinical advice can be provided before the patient leaves the clinic.

A second type of test for the virus is called "antigen testing". These tests use antibodies raised in the laboratory against a protein component of the virus to detect the viral protein, usually in saliva. These tests are simpler than the RNA tests and are capable of being massively upscaled. It should be noted that both types of test for the virus described above measure fragments of viral RNA or protein as well as intact viral particles, so that a positive test does not prove the presence of intact virus.

Blood tests for antibodies in patient blood (which are produced by immune system cells when the virus is present) are in development and have already been utilised in some studies. Antibodies are measured by an ELISA, a type of test which is carried out extensively in pathology laboratories and which requires simple and widely available equipment. The test requires a preparation from the virus (or a recombinant protein based on the virus), likely to be related to the spike protein, which will bind to antibodies in the blood of the patient. Point-of-care tests for antibodies, which require only a drop of blood, are also being developed. Detailed analysis of the immune response and how it may be manipulated is also in progress.

Some tests for Covid-19 have proved inaccurate and further test improvement is likely over the next weeks and months. Tests with a significant percentage of false negative results are potentially dangerous if they result in infectious patients being returned to the community. Tests for virus and tests for antibodies are complementary and both have important uses in managing individual patients and in providing data for government decision-making.

2.2 Epidemiology

Medical epidemiologists study the spread of a pathogen or toxin (*e.g.* a virus, a bacterium or a chemical) through the community. Their studies, including advanced computer modelling, are informed by testing and are important in advising governments about actions which should be taken to limit the spread of the pathogen. Major efforts are being undertaken to trace the source of infection of individual patients (person to person transmission). This tracing is much more difficult because of pre-symptomatic and asymptomatic transmission which has been demonstrated.

Epidemiologists also study which groups in the community are more or less susceptible. In the present instance it is clear that older patients are much more likely to die than younger patients, leading to recommendations about isolation, especially for over 70's and younger people at risk because of compromised immune systems or other health problems.

The antibody test mentioned above will be useful in population studies to show how far the virus has penetrated into the community. Preliminary results suggest that many people have been exposed to the virus and gained immune protection without knowing they had contracted the virus. Herd immunity may eventually develop if a high percentage of the population has been exposed to the virus and retain immunity into the future. At this stage, it is not known how long immunity will persist in recovered patients.

In another development, the nucleic acid sequence of the virus is being determined in virus isolated from a large number of patients. Many mutant forms of Covid-19 have already been found which help epidemiologists to track the arrival of the virus in a region or country and its subsequent spread. Note that most mutant forms will retain their infectivity since the sequence changes will mostly be in non-critical positions.

2.3 Clinical treatments.

Clinicians responsible for treating patients admitted to hospital with severe symptoms of Covid-19 disease (severe respiratory problems) are able to alleviate the immediate symptoms by providing oxygen and ventilation of the lungs. CT scans of the lungs have been found to be a powerful tool for monitoring of disease severity and progression. As the disease progresses, other organ failures may occur and require management. We know that many people recover from the acute disease emphasizing the importance of hospital care.

Experience will show which other treatments and already approved medications will alleviate symptoms and allow recovery. For example, it is now known that formation and breakdown of blood clots in the lungs is a feature of the advanced disease. Potentially, clinicians will be able to control blood clotting and clot lysis using well established drugs such as anticoagulants and tissue plasminogen activator (tPA). Experience will also show clinicians how to deal with co-morbidities. A major challenge is to learn why some patients experience very mild disease while other patients, sometimes young and otherwise healthy, deteriorate rapidly and pass away.

2.4 Treatment of patients with immune serum and immunoglobulins

The blood of patients who have recovered from Covid-19 contains antibodies and immune system cells which are highly likely to destroy the virus if infused into the blood of seriously ill Covid-19 patients. The preparation of immunoglobulins from serum of recovered Covid patient blood donors has great potential for treatment of severely ill patients. The process of preparing immunoglobulins and using them in patients is very well established worldwide and is an important activity of CSL Behring and several other companies. Treatment with immunoglobulins from convalescing patients seems likely to be an important

component of clinical care. Preparations are expected to become available relatively soon, pending approval by FDA, TGA and other agencies.

2.5 Testing of already approved drugs for efficacy against Covid-19 infections.

Drugs being mentioned include hydroxychloroquine, ivermectin and anti- HIV drugs. Testing of numerous compounds *in vitro* against the virus is happening now, in cell culture using cells which internalise the virus and allow it to replicate. Some promising results are being obtained which must be followed by clinical trials. For example, remdesivir developed by Gilead Sciences, is an inhibitor of replication of RNA viruses such as Ebola virus. Clinical trials have commenced using remdesivir for treatment of Covid-19 patients. Trials can be completed faster for drugs already approved for other conditions.

In considering what drugs may work, it is valuable to know the mode of action of the drug concerned and hence the possible mode of action against Covid-19. This virus is similar to other corona viruses that have been studied extensively, such as SARS-CoV and MERS-CoV. The Covid-19 genome (RNA) encodes 16 non-structural proteins, four main structural proteins and several accessory proteins (see Ref. 1). Studies completed with other corona viruses are likely to be informative. For a virus particle to enter a susceptible cell, the Covid-19 spike protein is first activated by a cell surface protease TMPRSS2, then binds to a particular cell receptor (the ACE2 receptor) and is internalised. The virally encoded proteins interact with numerous cellular proteins to achieve viral replication, assembly of new viral particles and release of the expanded number of viruses from the cell. Thus there are numerous targets for drug design and development and numerous possibilities that pre-existing drugs may be effective.

2.6 Numerous approaches to producing a vaccine

A vaccine is a preparation containing an immunogen that when injected into a person leads to an immune response which prevents the replication of the virus and thus prevents the disease. The spike protein on the surface of the virus is the most obvious contender as an immunogen. If an antibody and/or cellular response can be produced by cells of the human immune system against a preparation of the spike protein, subsequently any Covid-19 virus that is taken up into a person (*e.g.* by breathing in viral particles) would be confronted by a primed immune system and destroyed.

There are many different types of immunogen. Using the spike protein as an example, one approach is to produce the spike protein or a component of the spike protein in cell culture (as a recombinant protein) and to inject this as the vaccine (optionally together with other vaccine components called adjuvants which stimulate the immune response). A recent article in *Science* listed 47 vaccine candidates under initial testing by various scientists around the world (see Ref. 2). Hopefully these will be consolidated into a small number of the most promising candidates after initial rounds of testing.

One difficulty that has to be overcome is to avoid inappropriate and dangerous immune responses being induced by a vaccine. Hence, extensive safety and efficacy testing both in experimental animals and then in humans is essential. For these reasons, a vaccine suitable for protection of the population against Covid-19 is still a year or more away.

2.7 Developing new antiviral drugs against Covid-19

Because the sequences of the virally encoded proteins were rapidly determined from the genome sequence, key non-structural proteins can be made in the laboratory as recombinant proteins. Recombinant proteins can then be purified and serve as targets for drug development. The next step may be to determine the three dimensional structure of the protein target. Already, structures have been determined for at least two essential viral proteins, the RNA polymerase which is required to copy the viral genome and a protease which processes the protein products of translation of the viral genome in the human cell. Knowing the structure makes it possible to design compounds, called inhibitors, which can bind to the viral protein and prevent its action. These inhibitors are drug leads. Drug development is also assisted by prior work on related viruses like SARS CoV and HIV. Progress towards potent and selective inhibitors of the RNA polymerase and the main protease is likely to be rapid but the time required to have a fully tested and approved drug is still years rather than months.

3. Conclusion

A number of approaches to alleviate the Covid-19 pandemic have been discussed as well as longer term solutions. It seems possible that, when the pandemic has run its course, Covid-19 will continue at a low level in the community and be controlled by a vaccine and selective drugs developed as a consequence of the pandemic. How rapidly the properties of the virus may change as a result of mutations remains to be seen. Changes may lead to weakening of vaccine efficacy, development of drug resistance and/or to a strengthening or weakening of the virus' infectivity. The Covid-19 pandemic has highlighted once again the possibility that future viruses may cross the animal human barrier with devastating consequences. Such events are rendered more likely by increases in world population and destruction of wild animal habitat.

4. References

1. Genotype and phenotype of Covid-19: Their roles in pathogenesis. L. Mousavizadeh et al, *Journal of Microbiology, Immunology and Infection*, available online March 31, 2020.
2. Vaccine designers take first shots at Covid-19. J. Cohen et al, *Science*, issue of April 3, 2020. Vol. 368, Issue 6486, pp. 14-16.
3. 3D medical animation still shot showing the structure of a coronavirus. https://www.scientificanimations.com/coronavirus-symptoms-and-prevention-explained-through-medical-animation/