Executive Summary: COVID-19
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The Executive Summary is produced weekly and contains in-depth analysis.
International SOS publishes a COVID-19 Daily Case Summary.

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Today's Executive Summary focuses on COVID-19 illness.

VIRAL PNEUMONIA, ARDS, CYTOKINE STORM AND DEXAMETHASONE

As reported last week, on Tuesday 16 June, an Oxford University study showed dexamethasone, an immune dampener, to be the first drug to significantly reduce the risk of death among severe COVID-19 cases.

Preliminary results showed that dexamethasone lowered the death risk from 40% to 28% for patients on ventilators, and from 25% to 20% for those requiring supplemental oxygen over 28 days. There were no substantial side effects.

Dexamethasone did not help mild COVID-19 cases without any breathing issues.

What is "Acute Respiratory Distress Syndrome" (ARDS)

ARDS is a life-threatening illness in which the lungs are severely inflamed. Swelling throughout the lungs causes capillaries to leak fluid causing the alveoli (air sacs) to collapse or fill with fluid. This prevents the oxygenation of the blood in the lungs.

Symptoms include shortness of breath, faster respiratory and heart rates, and dangerously low blood oxygen levels. ARDS has many different causes, including pneumonia, sepsis and inhalation injuries.

COVID-19 Pneumonia & ARDS

While most people with COVID-19 suffer a minor, acute respiratory infection, some develop a severe viral pneumonia. Autopsy data shows inflammation, diffuse alveolar damage (DAD) and alveolar fluid accumulation consistent with acute respiratory distress syndrome (ARDS).

However, several features of COVID-19 pneumonia distinguish it from typical ARDS; the patients may have very low blood oxygen levels without being excessively short of breath, sometimes described as "happy hypoxemia". This suggests a failure of the body's homeostatic O2-sensing system (HOSS).

Cytokine storm

Cytokines are small proteins released by many different cells in the body. When released by white blood cells, they normally coordinate the body's response against infection and trigger inflammation. The name "cytokine" is derived from the Greek words for cell (cyto) and movement (kinos).

A cytokine storm is a physiological reaction in which the immune system causes an uncontrolled and excessive release of cytokines. Normally, cytokines are part of the body's immune response to infection, but their sudden release in large quantities can cause multisystem organ failure and death.

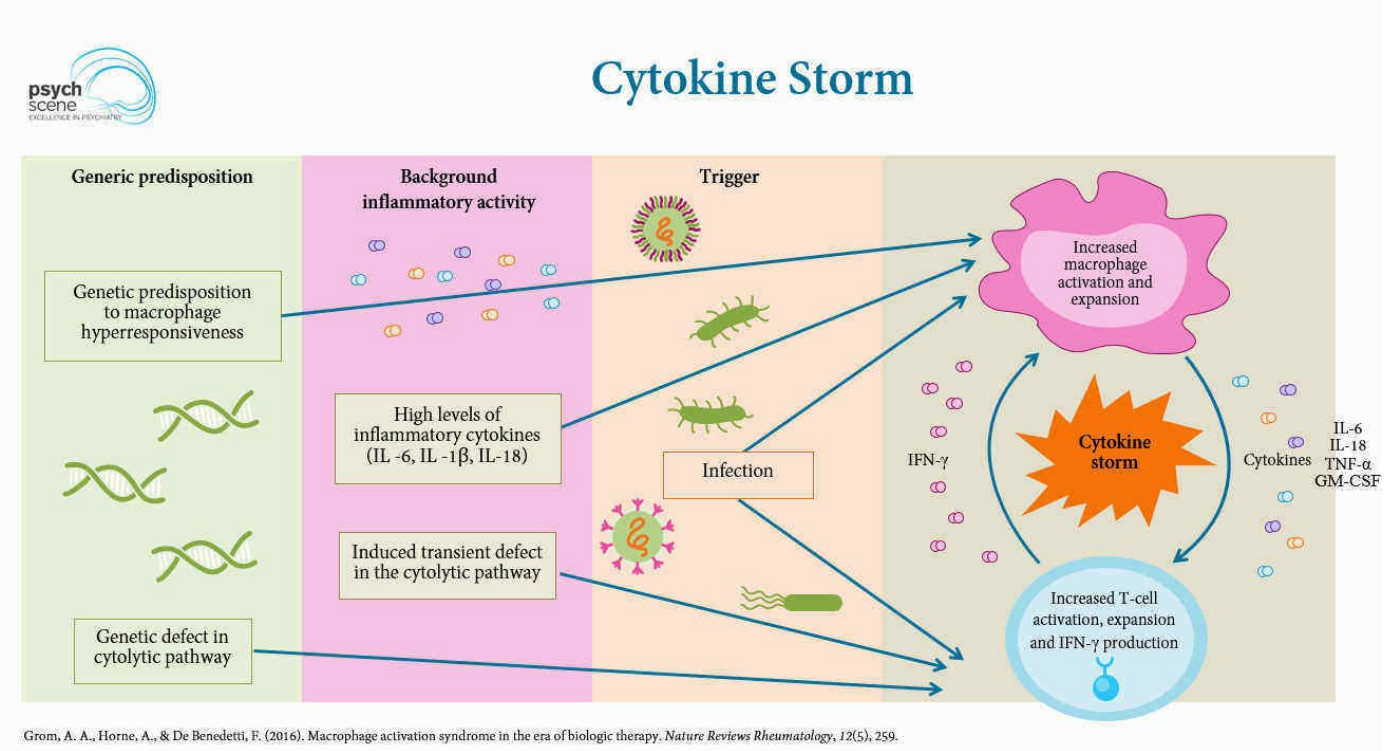
In general, the sudden release of cytokines causes blood vessels to leak, allowing immune cells to get into organs, potentially driving organ failure. Cytokine storms can also cause blood clotting. In influenza infections, cytokine storms are also tied to aberrant glucose metabolism, researchers reported recently, based on experiments in mice.

The phenomenon became more widely known after the 2005 outbreak of the avian H5N1 influenza virus, also known as "bird flu", when the high fatality rate was linked to an out-of-control cytokine response.

In 2006, six healthy young men were left in intensive care with multiple organ failure as a result of an out-of-control cytokine immune response during a preclinical trial of a new kind of drug, theralizumab. This reaction happened just 90 minutes after receiving a dose of the drug.

Cytokine storms can be caused by a number of infectious and non-infectious etiologies, especially viral respiratory infections such as H5N1 influenza (bird flu) and SARS. Other causes include the Epstein-Barr virus, cytomegalovirus, and group A streptococcus, as well as non-infectious conditions such as graft-versus-host disease, multiple sclerosis and pancreatitis.

Graphic of cytokine storm: Psych Scene



Grom, A. A., Horne, A., & De Benedetti, F. (2016). Macrophage activation syndrome in the era of biologic therapy. *Nature Reviews Rheumatology*, *12*(5), 259.

Cytokine storms and COVID-19

COVID-19 can cause cytokine storms. Their occurrence may also explain why some people have a severe reaction to SARS-CoV-2 while others only experience mild symptoms.

They could also be the reason why younger people are less affected, as their immune systems are less developed and so produce lower levels of inflammation-driving cytokines.

Genetics may play a role in determining which COVID-19 patients develop cytokine storms. Some studies looking broadly for genetic variants associated with COVID-19 severity are underway.

Dexamethasone

Dexamethasone "dampens" the immune system explaining why it seems to be helpful in severe COVID-19.

Dexamethasone is one of the glucocorticoids, a subgroup of steroid hormones also sometimes called corticosteroids, and the synthetic counterpart of the natural glucocorticoid cortisol.

Cortisol, dexamethasone, and other similar molecules regulate the immune system by entering a cell's nucleus and suppressing expression of genes that encode inflammatory cytokines and increasing expression of the gene that encodes Annexin A1, a protein that limits immune system overreactions.

Dexamethasone (and the weaker glucocorticoid, prednisone) are used to treat many conditions including allergies, asthma, some forms of cancers and autoimmune diseases. Dexamethasone is often prescribed for sepsis and ARDS in the intensive care unit (ICU). Dexamethasone has a half-life of more than 36 hours allowing it to be given in a single intravenous dose. This simplifies treatment in the ICU.

Dexamethasone's biological pathways overlap with that of COVID-19 pathology and cytokine storms

From Medium.com: "On the biochemical level, glucocorticoids easily diffuse through the host cell membranes and bind to the glucocorticoid receptor in the cell cytoplasm. This receptor binding triggers a cascade of reactions that end up suppressing pro-inflammatory cytokines IL-1, IL-2, IL-6, IL-8, TNF, and IFN-gamma. Importantly, five of these are linked to COVID-19 severity.

Moreover, one of the primary culprits of COVID-19 the cytokine storm is the overactivation of macrophages, which is also inhibited by glucocorticoids. A 2019 cell culture study has also shown that dexamethasone rescued human alveolar (air sacs) cells from destruction by pro-inflammation cytokines."

The future for dexamethasone in COVID-19

We await further studies on the use of dexamethasone in severe COVID-19 cases. It is, as always, likely that more case studies will be needed to validate the utility of corticosteroids earlier in the disease process as well as their use, dosage and frequency in established infections, both for those with pre-existing conditions and those without.

STUDY OF PROPHYLACTIC STEROIDS TO PREVENT CYTOKINE STORM

This interventional, non-randomised study investigates whether prophylactic (preventive) treatment with short-term steroids administered to high-risk COVID-19 patients can prevent a cytokine storm and progression to respiratory failure.

- Patients will be admitted to a regular room in the hospital (not ICU)
- Methylprednisolone 80 mg will be given intravenously daily for five days
- Patients will be monitored closely with vital signs taken every four hours to ensure their respiratory and cardiovascular status does not deteriorate.

COVID-19 CAN STRIKE THE BODY ANYWHERE FROM THE BRAIN TO THE TOES

Here we examine some of the COVID-19 affects on various organ systems.

A take home message is that people with comorbidities need to be even more carefully isolated from potentially infected persons compared to the otherwise healthy population.

KIDNEYS

Some patients suffering severe COVID-19 show signs of kidney damage, even those previously who had no underlying kidney problems. Abnormalities include high levels of protein in the urine and abnormal kidney function tests. The kidney damage is, in some cases, severe enough to require dialysis.

Early reports indicated that up to 30% of patients hospitalized with COVID-19 in China and New York developed moderate or severe kidney injury.

How does COVID-19 damage the kidneys?

There are various theories:

- Coronavirus might target kidney cells
- Too little oxygen can cause kidneys to malfunction
- Cytokine storms can destroy kidney tissue
- COVID-19 causes blood clots that might clog the kidneys

Coronavirus kidney damage: a serious sign

Organ systems such as the heart, lungs, liver and kidneys rely on and support one another's functions, so when COVID-19 causes damage in one area, other organs may be at risk. Kidney damage in patients with COVID-19 is a possible warning sign of a serious, even fatal course of the disease.

COAGULATION / BLOOD CLOTS

COVID-19 has been associated with clots in large vessels, causing strokes and even amputations. Inflammation and possible blocking of smaller vessels and capillaries may cause some of the pulmonary and renal damage and be involved in "COVID toes" areas of painful red inflammation of the feet.

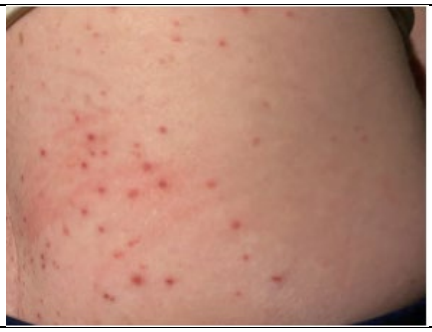
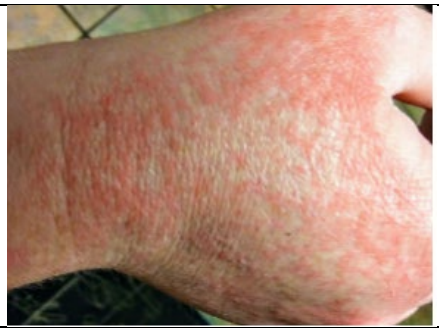
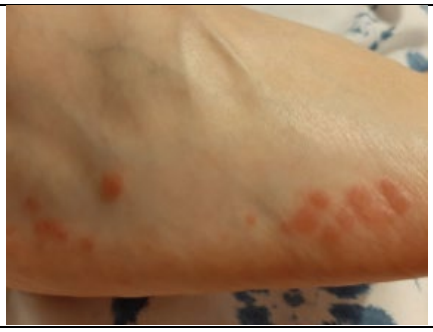
There are several theories about how these blood clots form:

- Activation of coagulation pathways during the immune response to infection results in overproduction of pro-inflammatory cytokines leading to multi-organ injury

- An interaction between the virus and the blood vessel walls (vasculitis / endothelitis)

SKIN

DermNet NZ, a world-renowned resource of skin disease information, describes several types of rashes caused by COVID-19.

		
Exanthem associated with COVID-19	Rash associated with COVID-19	Rash on feet associated with COVID-19

Much like anosmia (the loss of sense of smell) such rashes and other signs of developing infection are not specifically diagnostic, but need to be considered in the context of the patient's possible exposure to the virus. If COVID is suspected, the patient must be isolated and tested, and contact tracing started, if indicated.

Multisystem inflammatory syndrome in children (MIS-C)

MIS-C is condition of children where different organs can become inflamed, including the heart, lungs, kidneys, brain, skin, eyes, or gastrointestinal organs. The cause of MIS-C is unknown, however it seems to be linked to SAR-CoV-2 infection or exposure. MIS-C can be serious, and occasionally fatal, however most children recover.

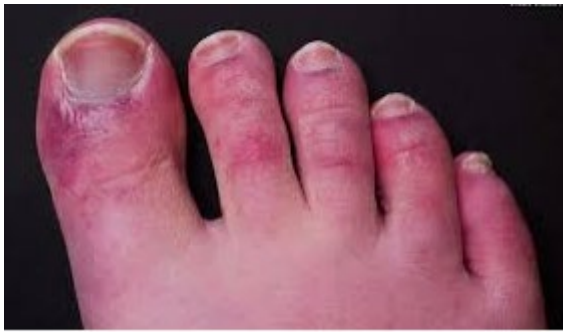
Some of these cases resembled a rare inflammatory illness of children called Kawasaki Disease which causes blood vessels to become inflamed or swollen throughout the body. Kawasaki disease is sometimes called mucocutaneous lymph node syndrome because it also affects glands that swell during an infection (lymph nodes), skin, and the mucous membranes inside the mouth, nose and throat. Kawasaki disease can present with high fever and peeling skin.

Fortunately, as is the case for MIS-C syndromes, Kawasaki disease is usually treatable, and most children recover from Kawasaki disease without serious problems.

COVID toes

DermNZ describes “COVID toes” as areas where there are digital infarcts resulting in black crusted lesions on the tips of toes (or fingers), which are described as like pernio/chilblains or frostbite.

IMAGE COVID TOES: Livescience.com



BRAIN

Neurologic symptoms have been noted in many COVID-19 cases. Apart from a temporary loss of smell (anosmia) previously noted, and altered sensations of taste, most of the neurological effects seem to only occur in very severe cases of COVID-19. However, current evidence suggests these may be long-lasting and potentially devastating.

Regarding more severe neurological sequelae, early in the New York outbreak, COVID patients were passing out before they were hospitalized, some had unusual movements, some headaches, some dizziness, and some had strokes. There have also been reports of patients with Guillain-Barre syndrome. Neurologic symptoms, i.e., impaired-consciousness and delirium, suggest SARS-CoV2 entry and spread in neocortex of the brain.

It is unclear if these effects are due to virus entering the brain; are possibly hypoxic "knock-on" effects of a severe virus attacking the body; are specifically direct effects of this virus attacking the brain; relate to induced vasculitis / endothelitis; are part of a hyper-immune / cytokine storm response; or a combination of some or all of the above. Also, given the relative prevalence of the symptom of anosmia, it is possible that the virus could enter the brain via the olfactory nerve or the olfactory lymphatic vessels.

PSYCHIATRY

The MERS-CoV outbreak in 2012, also precipitated neuropsychiatric symptoms as a result of an immunological reaction.

A systematic review and meta-analysis of the neuropsychiatric manifestations of SARS1 and MERS CoV revealed that during the acute illness, common symptoms included confusion (27.9%), depressed mood (32.6%), anxiety (35.7%), impaired memory (34.1%) and insomnia 41.9%.

In the post-illness stage, depressed mood (10.5%), insomnia (12.1%), anxiety (12.3%), irritability (12.8%), memory impairment 18.9%, fatigue 19.3%, traumatic memories (30.4%) and sleep disorder (100%) were frequently reported.

The meta-analysis indicated that in the post-illness stage the point prevalence of post-traumatic stress disorder was 32·2%, depression 14·9% and anxiety disorders 14·8%.

It is not yet clear to what extent the psychiatric sequelae are induced by the primary infection or the consequence of living with debilitating effects of COVID-19.

VOMITING AND DIARRHOEA

An article in the British Journal "Gut", describes evidence from China which showed that of patients presenting with gastrointestinal issues, such as diarrhoea, nausea and vomiting, more than a quarter of them may not have any respiratory symptoms.

Angiotensin Converting Enzyme 2 (ACE2), the protein which allows coronavirus to infect a wide range of human cells, is present in both the lung and the gastrointestinal tract. This could explain why some patients with COVID-19 present with gastrointestinal symptoms.

THE "LONG TAIL" OF COVID-19

Do some patients have COVID-19 symptoms for six weeks or longer? There are no formal studies.

WEIRD AS HELL

As reported in the Guardian, Professor Paul Garner developed COVID-19 in March 2020. "Initially he felt 'a little bit off.' Days later, he found himself fighting a raging infection. It's like being 'abused by somebody' or 'clubbed over the head with a cricket bat. The symptoms were weird as hell,' he said. His symptoms included loss of smell, heaviness, malaise, tight chest and racing heart. At one point, Garner thought he was about to die. He assumed his illness would swiftly pass. Instead it went on and on – a rollercoaster of ill health, extreme emotions and utter exhaustion – for more than seven weeks.

"Prof Tim Spector of King's College London, estimates that a small but significant number of people are suffering from the 'long tail' form of the virus."

The Financial Times reported that "data from Professor Tim Spector's symptom-tracking app, which has been downloaded by more than three million people globally, indicated that about 10% of people still had symptoms at 25 days, and 5% were still ill a month later…. 'Someone urgently needs to be doing studies on these people,' said Prof."

POST-VIRAL SYNDROME?

On 11 June, The Washington Post detailed four people whose COVID-19 had lasted more than 60 days.

The article goes on to say:

"Post-viral syndromes have been associated with numerous viruses in the past, but until the pandemic, they were considered relatively rare. In the case of COVID-19, researchers are unsure whether people with extended symptoms are simply facing a long recovery, or whether their illness will come to resemble something like chronic fatigue syndrome, a complex illness characterized by profound exhaustion and sleep problems, or other conditions that can last for years, or a lifetime."

RECENT STUDIES ON IMMUNITY

Two recent studies show an early loss of humoral (antibody-based) immunity, with the second study suggesting that the loss is quicker in those who have had asymptomatic infection. Both studies contrast with another recent study showing long-lasting humoral immunity.

Yet another new study suggests protection from cellular immunity in the absence of antibodies

EARLY LOSS OF HUMORAL IMMUNITY

Two studies published this week suggest that people may lose their IgG antibodies within weeks or months after recovering from COVID-19.

The first recent study (non-peer reviewed – published in MedRix) found that 10% of nearly 1,500 COVID-positive patients registered undetectable antibody levels within weeks of first showing symptoms, while a minority lost their antibodies two to three months after recovering from the infection. This scenario was more common among those who tested positive but were asymptomatic.

The second recent study (published 18 June in Nature Medicine) found that of people who had tested positive, 40% of those who had been asymptomatic had undetectable levels of IgG two to three months after the infection, compared to 13% of the symptomatic patients.

LONGER LASTING HUMORAL IMMUNITY

A study in March 2020 (now published in the Clinical Journal of Infectious Diseases) indicated that COVID-19 antibodies remain stable in the blood of most infected people almost two months after diagnosis, and possibly longer.

CELLULAR IMMUNITY DESPITE NO ANTIBODIES

A recent study (non-peer reviewed – published in MedRix) found that in eight members of seven households with at least one known positive COVID-19 case, six of the eight household members had blood samples with measurable T-cell responses, but no measurable antibodies.

The study concludes:

1. "Exposure to SARS-CoV-2 can induce virus-specific T-cell responses without seroconversion. T-cell responses may be more sensitive indicators of SARS-CoV-2 exposure than antibodies….

2. "Our results indicate that epidemiological data relying only on the detection of SARS-CoV-2 antibodies may lead to a substantial underestimation of prior exposure to the virus."

A VIEW FROM THE LABORATORY: PROFESSOR JOHN OXFORD

High cortisol levels correlate with greater risks of death from COVID-19

Prof Dhillon at the Imperial College has published (The Lancet, Diabetes and Endocrinology) the first data to show that cortisol levels are marks of severity of the illness and can be used to identify patients who are more likely to need intensive care.

This is an observational study of 515 patients and 403 had confirmed COVID-19. The COVID-19 patients with a baseline cortisol level of 744 or less, survived an average of 36 days. Patients with levels over 744 nmol/l survived only 15 days. The point here is that this simple marker can be used along with oxygen saturation levels to identify patients who need to be admitted immediately.

The physiological stress from surgery and acute illness increase serum cortisol levels. This in turn initiates changes in metabolism, cardiovascular function and immune regulation. The group theorised that severe infection could trigger mimicry to adeno corticotropic hormones. The authors, not unexpectedly, note that a prospective study will now need to be done.

Do asymptomatic patients have weaker immune response to virus?

This data from Chongqing, China is detailed but the number of patients investigated is low at 37 (Nature Medicine). These were picked from a group of 178 people with infection, 22 females and 15 males, aged 8-75 years. They had a median shedding time of 19 days compared to 14 days for a group of 37 symptomatic patients.

Firstly, levels of IgG were significantly lower in the asymptomatic group. They also had lower levels of 18 pro and anti-inflammatory cytokines. We can speculate that these patients had a weaker immune response to COVID-19.

They also recorded that IgG levels began to reduce after 2-3 months in these asymptomatic patients. Finally, they discuss the potential risks of so-called immunity passports and strongly suggest the continuation of public health interventions and widespread testing, as well as investigating the other immune response parameters of asymptomatics.

On a personal note I would say that a lot of weight is placed here on antibody quantities. In other infections there may be a similar phenomenon. In general, I would expect IgG response to diminish after a few weeks. I would urge

the authors to begin testing for T-cell responses (CD_4 and CD_8 cells), not just to the "S" or spike protein but to internal proteins of the virus which may be shared by epidemic B Coronaviruses. Influenza shares internal proteins throughout the wide flu family and the concept of Universal Influenza Vaccine is derived from this observation.

Identification of genetic factors in COVID-19 disease, (NEJM, D. Ellinghaus *et al*, June 17th)

For four or more years, virologists have used molecular biology "Knowledge of Tools" to investigate, find and exploit a human gene controlling virus virulence. There have just been a handful of papers, one of the first from the Sanger (Wellcome Trust) Institute which produced the early human genome analysis in laboratories on the main road between London and Cambridge. An interferon gene set contributed to virulence of pandemic influenza A (H1N1) and was more commonly found in Han Chinese.

This group analysed data from 1,980 patients from seven hospitals in Italy and Spain. In the final analysis, 835 patients, and 1,255 controls were included. They analysed 8.5 million single nucleotide polymorphisms and conducted a meta-analysis of the group. In essence, they identified the potential involvement of the ABO blood group system with the involvement of a gene cluster 3 21.31.

In retrospect, the involvement of genes for blood group would not seem unlikely. What seemed unlikely until recently is the pathology of the infection involving blood clotting. They showed higher risk in blood group A and a protective effect of blood group O.

More Immunity:

Probably we are all a little prejudiced but a paper in "Science" wakes everyone up, and another in NEJM.

With the frenetic competition at the moment, and retractions from some pretty high-powered journals, is even "Science" a safer haven? I am not sure I know the answer, but I liked the paper trying to deal with B and T cell responses. M. Leslie *et al.* appear to show that COVID-19 infected people "harbour T-cells" that may help them recover. Similar cells were also found in people who had not been infected with COVID-19, indicating a potential cross reactivity with epidemic coronaviruses like OC43 which have circulated each year in the world but produce mild common cold symptoms.

These patients had helper T-cells recognising the virus S (spikes) protein. Killer cells were also detected in these patients. A potential lesson for vaccinologists is **not to only concentrate on the "S" protein** because the immune response is wider.

There is a **whole virus vaccine** under development at the pharma group Sinovax in China and this vaccine would contain all virus proteins and could be very immunogenic. Certainly, whole virus influenza vaccines are the most powerful for influenza. We can speculate that one reason why the symptoms are restricted to, say, 30% of infections is that prior contact with epidemic mild coronaviruses and T memory contribute. This is a helpful sign, which is the sort of optimistic (and perhaps realistic) summary.

Also, to note is that there is no indication of abnormal T-cell response, which could point to vaccine induced enhancement. Perhaps we can begin to place that worry to one side, at least for the moment!

Lungs from post-mortems can be unrecognisable

In a parliamentary discussion a pathologist, Prof Mauro Giacco from King's College London, described complete disruption of the lung architecture. These autopsies were performed on patients after 30-40 days in intensive care. Large amounts of virus persisted in the lungs alongside unusual fused cells. There is massive thrombosis. The fused cells are very large, are COVID-19 virus antigen positive and contain 10-15 nuclei. This is not a disease caused by a virus which kills cells.

On a personal note, the fused cells are also characteristic of viruses such as Respiratory Syncytial Virus (RSV) a common cold infection of children. With RSV the pathology is also complex, and an early vaccine made 50 years ago enhanced infection of immunised children.

But the pathology data, the relative absence of super infecting bacteria such as pneumococcus and the unique x-ray and CT scan photos point to a 'cytokine storm' and immune based pathology. However, this does not abrogate the use of vaccines and antivirals. Just the opposite: prepare and obviate disease in a patient before reaching 'auto immune-' stage.

Rapid diagnosis of COVID-19 from urine, blood, saliva and mouth swabs

Just published in PLOS ONE (a real reviewing journal, referring back to our analysis last week of unreviewed papers). L. Lamb of the Beaumont Health System, Michigan describes in a short paper the problems of the regular PCR test which requires a laboratory and excessive equipment. There is a modification called RT-LAMP which belies its complicated name (loop-mediated isothermal amplification) for a simple relatively cheap and speedy technology. It is well established for a range of other viruses. A result was achieved in 30-45 mins and did not detect other coronaviruses and gave a result very similar to RT PCR.

I would say that this is a "keep an eye open" method and a final decision will be whether it can be used on a very large scale. It is not like urine 'dip tests' for diabetes and for pregnancy, which rely on colour-metric paper. A piece of equipment is needed but the authors say, "it is not expensive". It does sound to have potential for a factory and a largish GP's clinic for example. What caught my eye is that the test picks up COVID-19 RNA in urine and blood which poses the question of a viraemia following infection or is the RNA only 'overflow' from the main seat of infection? In short, one could wonder whether the blood banks are at risk of contamination, even a very small risk.

Finally: Some good news from the four nations of the UK

The Chief Medical Officers in England, Scotland, Wales and Northern Ireland agreed today to reduce the threat of COVID-19 from Level 4 (COVID-19 virus in general circulation, transmission is high and rising exponentially) to level 3 (COVID-19 virus is in general circulation).

The message from the Department of Health and Social Care notes that there has been a steady decrease in cases in all four nations and this continues. Localised outbreaks are still liable to occur. "We have made progress against the virus thanks to the efforts of the public and we need the public to continue to follow the guidelines carefully to ensure this progress continues."

I would add that a major effect has been made by 50,000 or so HCW throughout the four nations, many of whom have put their lives at risk!

Regardless, we all recognise that aside from the medical aspects, all countries have to evaluate the economic consequences of mass quarantine versus the negative effects more infected patients and the delayed treatment of some.

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