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Plum blossom has been depicted in the traditional Chinese artistic motif as a symbol of endurance, resilience, and diligence in the face of hardship for centuries. It is one of the few plants which bloom in the face of cold, harsh winter. Each petal symbolizes one of the five blessings: longevity, prosperity, health, honour, and good living.

May these flowers bloom miraculously against the barren winter landscape, and give people hope in the new year.

May the pandemic due to COVID-19 viruses vanish speedily.
Humankind is right now experiencing the worst pandemic in more than 100 years with over 1.5 million deaths as of early December 2020. While the global scientific community is earnestly looking for new treatments and effective vaccines, the vast amount of research on various aspects of COVID-19 in just 12 months has been phenomenal. Be that as it may, there remain lots of unknowns up till now in areas from immunology to genetics associated with the infection.

When we were invited by the Editorial Board of the Hong Kong Medical Diary to be guest editors for this commemorative anniversary issue on COVID-19, we agreed without hesitation and came up with a list of hot topics that have been frequently asked. We are indeed privileged to have a panel of experts from various disciplines to share their areas of expertise in this issue. Dr Kelvin To has written an excellent article on the various immunological aspects of the virus. These would carry important implications for herd immunity and, to a certain extent, vaccine development. Professor Ivan Hung compared the clinical presentations of two reinfe cted cases respectively reported in Hong Kong and the U.S.A. and discussed the clinical implications. As for diagnostics, Dr David Lung has provided an up-to-date review of the use of saliva in the diagnosis of COVID-19. Hong Kong has done exceptionally well in term of mortality figures when compared to other developed countries. Dr Kenny KC Chan has come up with a comprehensive review of the current management of COVID-19 patients in the intensive care units in public hospitals in Hong Kong. From the public health perspective, Dr Dennis Ip and Prof Benjamin Cowling have successfully used simple terms to explain a much hear-ted-of term for the past year, the basic reproduction number, in Hong Kong and the U.S.A. and discussed the clinical implications. For the lifestyle section, Dr Peter Gruenewald, a doctor working in the U.K., has kindly shared, in his resourceful article, ways to enhance resilience during this time of high stress. Dr Gruenewald was initially scheduled to contribute this article for the August 2020 issue. However, he came down with COVID-19, and fortunately, he recovered and agreed to contribute his article for this issue.

Both of us would like to express our sincere appreciation to all the contributing authors for their precious time and great effort. We would like to thank Prof Richard Yu, who has contributed a fabulous cover photo with a meaningful caption. Last but not least, we would like to thank the editorial team of FMSSH for assembling this memorable issue on COVID-19 in such a short time! We hope you will enjoy reading this issue and we much welcome your precious feedback. We wish your new year be filled with excellent health and great success.
COVID-19 Re-infection, Two Contrasting Cases, and Many More to Come

Prof Ivan Fan-ngai HUNG
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INTRODUCTION

As of 1st December 2020, COVID-19 pandemic has affected over 66 million patients, with more than 1.5 million deaths in 191 countries. Similar to other respiratory infections, COVID-19 reinfection should happen when neutralising antibodies decline one to two months after the acute infection. In August 2020, we reported the world’s first COVID-19 reinfection by a phylogenetic distinct SARS-coronavirus-2 (SARS-CoV-2) strain confirmed by whole genome sequencing. Subsequently, another case of SARS-CoV-2 reinfection was reported in Nevada, U.S.A. Despite the involvement of a young healthy male patient in both cases, the outcome was very different. Here we compare the presentation of the two cases of COVID-19 reinfection and the implications.

THE PATIENT FROM HONG KONG

The patient was a 33-year-old Caucasian male residing in Hong Kong. He enjoyed good past health. His first COVID-19 infection took place in March 2020 when he presented with cough and sputum, sore throat, fever and headache for three days. He was confirmed to have positive SARS-CoV-2 RT-PCR assay on his oropharyngeal saliva. He was hospitalised for 16 days, during which he remained asymptomatic. The patient was discharged following two negative SARS-CoV-2 RT-PCR assays on nasopharyngeal and throat swabs taken 24 hours apart.

During the second episode, the patient returned to Hong Kong from Spain via the United Kingdom and was tested positive by SARS-CoV-2 RT-PCR on the oropharyngeal saliva specimens collected during the first episode in March and during the second episode in August. Genomic analysis showed that the first viral genome belongs to a clade/lineage different from the second viral genome. The first viral genome belongs to GISAID clade V, Nextstrain clade 19A, and Pangolin lineage B.2 with a probability of 0.99. The second viral genome belongs to GISAID clade G, Nextstrain clade 20A, and Pangolin lineage B.1.79 with a probability of 0.70. The two genomes differ by 24 nucleotides, in which 14 were non-synonymous mutations resulting in amino acid changes. The difference in the amino acids between the two genomes are located in the spike protein (at the N-terminal domain, subdomain two and upstream helix), membrane protein, nucleocapsid protein, non-structural proteins (NSP3, NSP5, NSP6, NSP12), and accessory proteins (ORF3a, ORF8 and ORF10). Blast search revealed that the first viral genome was most closely related to strains from the U.S.A. or England collected in March and April 2020. The second viral genome was most closely related to strains from Switzerland and England collected in July and August 2020.

THE PATIENT FROM WASHOE COUNTY, NEVADA, USA

The patient was a 25-year-old Caucasian male residing in Washoe County, Nevada, U.S.A. He also enjoyed good past health. He was first diagnosed to have COVID-19 in late March 2020. He developed upper respiratory tract symptoms of sore throat, cough and headache, with gastrointestinal manifestations as well, including nausea and diarrhoea. The patient undertook isolation at home, and all symptoms resolved after one month in late April. However, in late May, his symptoms returned with fever, headache, dizziness, cough, nausea and diarrhoea. His condition further deteriorated and was found to be hypoxemic, requiring hospitalisation and oxygen support. Chest radiography confirmed viral pneumonia with patchy, bilateral, interstitial opacities. The patient’s IgG and IgM against SARS-CoV-2 were tested positive.

Comparing the two nasopharyngeal specimens positive for SARS-CoV-2 taken 48 days apart, both specimens belonged to the clade 20C with the five hallmark single nucleotide variants (SNVs) (3037C-T, 14408C-T, 23403A-G, 1059C-T and 25563G-T). The first specimen had five...
further SNVs compared with the reference genome. The second specimen had six additional SNVs and a mutation at position 14,407, adjacent to the SNV 14408C-T. Six SNVs were shared between the first and second specimens. The first specimen had four additional SNVs not seen in the second specimen, whereas the second specimen had seven SNVs not seen in the first specimen. These pieces of evidence suggested that the patient had a reinfection of COVID-19.

**DISCUSSION**

Despite both cases being proven COVID-19 reinfection, the presentation of the second episode in the two patients was very different. The first patient reported from Hong Kong showed a much milder presentation at the second time, and the patient remained asymptomatic during the second episode. During SARS-CoV-2 infection, neutralising antibody develops in most patients. In the Hong Kong patient, although anti-SARS-CoV-2 antibody was not detected initially during the second episode, the low residual titre of antibody might have partially controlled the virus. Since neutralising antibodies target the spike protein, variations in the spike protein may render the virus less susceptible to neutralising antibodies which had been induced during the first infection. Further serological studies are required to determine whether these amino acid differences in the spike protein of the SARS-CoV-2 strains between the first and second infection are responsible for the reinfection. During the second episode, IgG against SARS-CoV-2 was not detected until 5 days after hospitalisation. One possibility is that he did not mount an antibody response after the first infection. Previous studies have shown that antibody response was not detected in some patients until 2-3 weeks after onset of symptoms. Another possibility is that he indeed mounted an antibody response after the first infection, but the antibody titre decreased below the detection limit of the assays. This waning of the antibody level is well described. In one study, IgG against SARS-CoV-2 was not detected until 5 days after hospitalisation. Another implication of the rapid decline in antibody titers is that seroprevalence studies may underestimate the true prevalence of the infection.

In contrast, the second patient reported from the U.S. showed increased severity in his second infection, with radiographic evidence of pneumonia and requiring oxygen support. This phenomenon could be explained by a higher dose of virus or a more virulent virus acquired during the second time. A more likely explanation would be caused by the immune response of antibody-dependent enhancement, by which specific Fc-bearing immune cells become infected with virus binding to specific antibodies. The important difference between the first and the second patient was that the first patient acquired the second infection five months apart, by which time the patient’s IgG and neutralising antibody against SARS-CoV-2 were undetectable. In contrast, the second patient acquired the second infection only two months later. Although the IgG titre was not measured during the first infection, it was likely that the patient still had a high level of positive IgG against SARS-CoV-2 developed during the first infection and hence resulting in the antibody-dependent enhancement which was manifested as pneumonia and worsened symptoms compared to the first episode.

Despite the difference in the clinical outcome of the two patients, the reinfecion carries several important implications. First, it is unlikely that herd immunity can eliminate SARS-CoV-2. IgG antibody will start to fall after a few months, and SARS-CoV-2 will continue to mutate. COVID-19 will likely continue to circulate in the human population similar to influenza virus and other human coronaviruses. Secondly, it is highly unlikely that COVID-19 vaccines will provide lifelong protection; repeated, possibly annual vaccination similar to influenza vaccination will be required to boost the immunity. The viral antigens of the COVID-19 might also be changing every year according to the ‘antigenic drift’ theory. Patients who have developed antibodies against COVID-19 via natural infection will also need to be vaccinated. Further studies on the immunological response after reinfection will be vital for the research and development of a more effective vaccine.

**References**

MCHK CME Programme Self-assessment Questions

Please read the article entitled “COVID-19 Re-infection, Two Contrasting Cases, and Many More to Come” by Prof Ivan Fan-ngai HUNG and complete the following self-assessment questions. Participants in the MCHK CME Programme will be awarded CME credit under the Programme for returning completed answer sheets via fax (2865 0345) or by mail to the Federation Secretariat on or before 31 January 2021. Answers to questions will be provided in the next issue of The Hong Kong Medical Diary.

Questions 1-10: Please answer T (true) or F (false)

1. As of 1st December 2020, COVID-19 pandemic has resulted in more than 1.5 million deaths.
2. Reinfection of COVID-19 has to be confirmed by whole genome sequencing of the comparing samples.
3. Reinfection of COVID-19 always results in mild symptoms in the second episodes.
4. The patient with reinfection from Hong Kong was symptomatic during the second episodes.
5. The patient from Hong Kong acquired the infection locally for both episodes.
6. There were 24 nucleotides differences between the first and second SARS-CoV-2 isolated from the oropharyngeal saliva samples.
7. The patient from US had more severe symptoms during the second episode of COVID-19 infection.
8. The patient from US failed to develop IgG antibody against SARS-CoV-2 during the second episode of COVID-19 infection.
9. The rapid decline in COVID-19 antibody for the first patient from Hong Kong might have led to reinfection.
10. The worsened symptoms during the second episode in the US patient could be related to the immune response of antibody-dependent enhancement.

COVID-19 Re-infection, Two Contrasting Cases, and Many More to Come

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PRECAUTIONS RELATING TO INDICATION

- Since available information on the efficacy and safety of this drug in connection with the SARS-CoV-2 infection is extremely limited, careful determination should be made as to need for administration considering the latest information.
- In line with the majority of use in clinical trials to date, in principle remdesivir should be used for SARS-CoV-2 infections in severe patients whose oxygen saturation is ≤ 94% (room air), requiring supplemental oxygen, under ECMO introduction, or under invasive mechanical ventilation.

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In Hong Kong, the product is conditionally approved with very limited safety, efficacy, and quality data for public health emergency to safely local animal medical need and the registration status is subject to be reviewed by the Pharmacy and Poisons Registration of Pharmaceutical Products and Substances (Certification of Clinical Trial/Preclinical Test) Committee. The product can only be supplied to designated institutions.


Reference: 1. VEKLURY Hong Kong Prescribing Information (Version: RCV4-MAY20 v6.0).

VEKLURY® Abbreviated Prescribing Information (Version: RCV4-MAY20 v6.0)
Presentation: Remdesivir concentrate for solution for infusion 100 mg/20 mL. Each vial contains 100 mg of remdesivir. Colourless to clear yellow solution. Remdesivir powder for concentrate for solution for infusion 100 mg. Each vial contains 100 mg of remdesivir. White to off-white to yellow solid. Indications: SARS-CoV-2 Infection. In principle remdesivir shall be used for SARS-CoV-2 infections in severe patients where oxygen saturation is ≤ 94% (room air), requiring supplemental oxygen, under ECMO introduction, or under invasive mechanical ventilation. Dosage: Adults and pediatrics with body weight ≥ 40 kg. Single dose of remdesivir 200 mg IV injection on Day 1 followed by once-daily doses of remdesivir 100 mg IV injection from Day 2. Pediatrics with body weight between 30 kg and <40 kg. One dose of remdesivir 5 mg/kg IV injection on Day 1 followed by remdesivir 2.5 mg/kg IV injection from Day 2. Solution for concentrate for infusion is not recommended for pediatric between 3 kg and <30 kg. Treatment duration: Within the optimal duration of treatment has not been established. As a guide, for patients who are on ECMO or invasive mechanical ventilation, the duration of treatment is up to 10 days. For patients who are not on ECMO or invasive mechanical ventilation, duration of treatment is up to 5 days or until Day 10 if no symptomatic improvement is observed. Liver impairment has been recommended for adults, infants, children and adolescents with eGFR <50 mL/min/1.73 m² and term newborns (7 to 28 days) with serum creatinine levels ≥ 0.5 mg/dL. Hepatic impairment: Not recommended for patients with ALT levels ≥5 times the Upper Limit of Normal Range. Should be administered only if the therapeutic benefits outweigh the risks for patients with ALT levels ≥ 5 times the Upper Limit of Normal Range. Contraindications: Hypersensitivity to the active substance or to any of the excipients. Warnings and Precautions: Patients should be closely monitored by appropriate clinical and laboratory monitoring during treatment with remdesivir. Laboratory values should be monitored on a daily basis. If any adverse drug reactions are observed, treatment should be continued only if it is determined that the therapeutic benefits outweigh the risks. Kidney and liver function tests should be performed daily before and during administration and the patient’s condition should be carefully monitored. The patient’s condition should be carefully monitored for infusion reactions and administration should be immediately discontinued and appropriate measures should be taken if any abnormalities are observed. Adverse reactions: Information on the safety of remdesivir is extremely limited, and such information is still being collected. Clinically significant adverse reactions include acute renal impairment, hepatic impairment and infusion reactions (hypotension, nausea, vomiting, sweating and tachycardia). Drug interactions: In vitro studies have shown that remdesivir is a substrate for CYP2C9, CYP2D6 and CYP3A4, as well as P450 and Kpp, and, in addition, is an inhibitor of CYP2C9, CYP2D6 and CYP3A4. IATP1B1, DAP1B1, BSEP, MRP4 and Ntcp. No clinical drug-drug interaction studies have been conducted. Before prescribing, please consult full prescribing information which is available upon request. Veikaly is a registered trademark of Gilead Sciences, Inc., or its related companies.
Immunological Response of SARS-CoV-2 Infection

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INTRODUCTION

Coronavirus Disease 2019 (COVID-19) pandemic has devastated the world in 2020. The number of COVID-19 cases has surpassed 62 millions, with over 1.4 million deaths as of 30th November, 2020. COVID-19 has also led to severe disruption in the socioeconomic activity. The World Bank has forecasted a 5.2% reduction in global GDP in 20201.

COVID-19 is caused by a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was first identified during a pneumonia outbreak in Wuhan in December 2019. Epidemiological studies showed that SARS-CoV-2 infection has a lower case-fatality rate than that of 2003 SARS-CoV, but can transmit much more efficiently between humans2. Seroprevalence studies showed that neutralising antibody against SARS-CoV-2 are not found in blood specimens collected before 2020 in Hong Kong3.

Understanding the immune response for COVID-19 is important for clinical practice. First, the correct interpretation of serology results requires a good understanding of the antibody kinetics during infection. Second, although SARS-CoV-2 can infect different organs and can directly cause tissue damage, many complications of COVID-19 are related to the dysregulated inflammatory response or immune-mediated damage. Third, understanding the immune correlates of protection is critical for risk assessment and for determining the immunogenicity of vaccines.

CYTOKINE AND CHEMOKINE RESPONSE

Similar to other infections, SARS-CoV-2 infection is accompanied by elevated levels of cytokine and chemokines. Studies have shown that the cytokine/chemokine pattern in patients with critical illness is distinct from those with moderate disease severity [4]. Critically ill patients (those who died, required mechanical ventilation or ICU admission) had increased levels of all types of cytokines, including those from type 1 (against virus or intracellular bacteria, such as IFN-γ), type 2 (allergic or anti-helminth immunity, such as IL-5) and type 3 (against fungi or extracellular bacteria, such as IL-17) immunity. Critically ill patients also demonstrated persistently elevated levels of cytokines, while those with less severe disease demonstrated a progressive reduction in cytokine levels after day ten post-symptom onset.

Although the cytokine and chemokine levels are elevated among COVID-19 patients, the level is much lower than in other inflammatory conditions. A meta-analysis showed that the level of IL-6 is much lower among COVID-19 patients than patients with cytokine release syndrome, sepsis or acute respiratory syndrome unrelated to COVID-193. This observation is important and suggests that the use of different cytokine inhibitors should be carefully evaluated.

ANTIBODY RESPONSE (HUMORAL IMMUNITY)

How Long Does it Take for Antibodies to Develop After Infection?

During the first week of symptom onset, only <50% of COVID-19 patients have detectable anti-SARS-CoV-2 antibody. The seropositive rate increases to over 95% two weeks after symptom onset6,7. Although some studies showed that IgM seroconversion is earlier than IgG, others showed similar timing in seroconversion7,8. Hence, antibody testing is not recommended for the diagnosis of COVID-19 during the acute phase of the illness, but it is useful to document infections in a retrospective manner during the convalescent phase of the illness.

What are the Different Types of Antibody Assays?

Antibodies against specific viral proteins can be measured using enzyme immunoassays, flow-cytometry based assays, or lateral flow assays. The advantage of these assays is that these can be performed in most clinical laboratories, or even at the point of care. But the disadvantage is that these methods cannot differentiate between antibodies that can protect cells from infection and those that merely bind to the viral proteins without neutralising effect.

On the other hand, neutralisation assays measure the antibodies that can protect cells from SARS-CoV-2 infection. Hence neutralisation assays are considered to be the gold standard for determining protective antibody response9. However, neutralisation assays are technically demanding, and neutralisation assays with live virus require biosafety level 3 facilities.

Studies have shown that serum collected before the COVID-19 pandemic contains antibodies against...
different SARS-CoV-2 proteins due to the cross reaction with proteins from other human coronaviruses, including 229E, OC43, HKU1 and NL63\textsuperscript{10}. However, antibodies against the surface spike protein and nucleocapsid protein are mainly found in COVID-19 patients\textsuperscript{9}. Hence, current antibody assays usually target the spike protein (either the entire spike protein, or only the receptor binding domain [RBD]) or the nucleocapsid protein. Furthermore, antibodies against the ORF8 and ORF3b are also detected at higher levels among COVID-19 patients than controls\textsuperscript{11,12}, but their roles in antibody testing require further evaluation.

**What is the Duration of Antibody Response?**

There is conflicting data regarding the duration of antibody response among recovered COVID-19 patients. While some studies showed a rapid decline in antibody titers\textsuperscript{15-16}, others showed sustained antibody response for a few months\textsuperscript{17,18}. IgA and IgM decrease more rapidly than IgG\textsuperscript{19}. The rapid decline in antibody levels in some patients may be due to the defective T follicular cell differentiation and the lack of germinal centre formation in the lymph nodes\textsuperscript{20}.

Understanding the longevity of antibody response is important for several reasons. First, a rapid decline in antibody response may render recovered COVID-19 patients to be susceptible to reinfection. This was documented in our previous patient with reinfection, for whom neutralising antibody was not detected at the beginning of the second episode\textsuperscript{21,22}. Second, if vaccine-induced antibody response is short-lasting, vaccination will need to be repeated. Third, seroprevalence studies are widely used to estimate the true burden of COVID-19 infection. If many recovered patients are seronegative due to antibody decay, the estimation of the burden of disease would be falsely low.

**What are the Factors Associated with Antibody Response?**

Several factors affect the antibody response. Patients with severe disease have a higher antibody response, while mildly symptomatic or asymptomatic patients have the poorest antibody response\textsuperscript{16,23,24}. Disease severity is also a major factor associated with the duration of antibody detection. In one study, 40% of asymptomatic patients become seronegative during the early convalescent phase\textsuperscript{25}.

Age also plays an important role in the antibody response. Adults have been shown to have higher neutralising antibody titer than children\textsuperscript{26}. One study showed that adult patients generate antibodies against both nucleocapsid protein and spike proteins, while pediatric patients generate much weaker antibody response against the nucleocapsid protein than the spike protein\textsuperscript{27}.

Symptom duration correlates with the sustainability of antibody titers. Those who recover more quickly are more likely to have sustainable titers of antibodies, while who takes longer to recover is more likely to have decline in antibody level\textsuperscript{28}.

**Does Antibody Titre Correlate with Protection?**

It is generally believed that a higher antibody titre correlates with protection. During an outbreak involving a fishing vessel, three members with pre-existing neutralising antibody were not infected, while 88% of people without pre-existing neutralising antibody were infected\textsuperscript{28}.

The S protein receptor binding domain (RBD) is responsible for binding to the host cell surface receptor. Hence, antibodies against the spike protein are considered to be most important for protection. Antibody against the spike protein RBD correlates well with neutralising antibody titre\textsuperscript{29}. Although the N terminal domain (NTD) of the spike protein does not bind to the host cell receptor, monoclonal antibodies against NTD have also been found to have neutralising activity\textsuperscript{30}. Monoclonal antibodies against either the RBD or NTD have been shown to be protective in animal studies\textsuperscript{30}.

**Will Antibody-based Treatment Work?**

Monoclonal antibody therapy is a promising treatment strategy. Several studies showed that monoclonal antibodies targeting the surface spike protein of SARS-CoV-2 reduce viral load and improve outcomes in animal models\textsuperscript{30,31}. A phase 2 clinical trial showed that fewer out-patients treated with monoclonal antibody LY-CoV555 required hospitalisation or visited the emergency department than those treated with placebo\textsuperscript{32}.

One potential problem with monoclonal antibody therapy is the emergence of escape mutants. Mutations in the RBD and NTD of the spike protein have been shown to confer resistance to monoclonal antibodies\textsuperscript{33}. Recently, in a patient with severe disease, we have identified the emergence of a mutation located at the epitope of the target of a monoclonal neutralising antibody\textsuperscript{34}. Therefore, several groups have used a cocktail of antibodies for treatment\textsuperscript{35}.

**Autoantibodies**

In addition to antibodies against SARS-CoV-2, autoantibodies are also found in many COVID-19 patients, and some autoantibodies have been found to be associated with disease severity. Higher titres of antiphospholipid autoantibodies are associated with more severe respiratory disease\textsuperscript{36}. Autoantibodies are also believed to play a role in pediatric multisystem inflammatory syndrome (PIMS) (also known as multisystem inflammatory syndrome in children [MIS-C])\textsuperscript{37}.

**T CELL IMMUNITY**

T cell immunity is identified among patients without prior SARS-CoV-2 infection. CD4+ T cells against SARS-CoV-2 epitopes can be identified in 20-60% of healthy blood donors\textsuperscript{37,39}. After infection, T cell immunity is induced. However, by the end of the second week
after symptom onset, only about 50% and 25% of patients develop T cell response against nucleocapsid protein and RBD, respectively. Furthermore, there is functional impairment of both CD4 and CD8 T cell subsets during the acute phase.

SARS-CoV-2-reactive CD4+ T cells can be found in almost all recovered COVID-19 patients, including those who were asymptomatic or mildly symptomatic. The duration of T cell immunity appears to be long-lasting.

T cell response is associated with disease severity. A lower frequency of naïve CD8 or CD4 T cells are associated with more severe disease. Patients with severe disease had robust CD4 T cell activation, while those with less severe disease had less CD4 T cell activation. Mild disease is associated with a coordinated CD4 and CD8+ T cell response. However, the uncoordinated response was found in patients older than 65 years.

OTHER IMMUNE CELLS AND COMPLEMENT ACTIVATION

During acute infection, the frequency of natural killer cells, monocytes, and dendritic cells are reduced. The function of dendritic cell is impaired. The complement pathways have been triggered during infection, and are associated with lung injury. The triggering of the complement pathways has been associated with severe disease. Patients with severe disease have higher levels of C5a. The anti-C5aR1 antibody has been shown to ameliorate lung damage in animal models.

DOES INTERFERON PLAY A ROLE IN IMMUNE RESPONSE AGAINST SARS-CoV-2?

Interferon is a key antiviral cytokine. Interferon β inhibits viral replication in airway cell lines. SARS-CoV-2 suppresses interferon β response in order to replicate in host cells. The importance of interferon during COVID-19 is well illustrated by patients having autoantibodies or genetic defects that affect the function of type I interferon. Autoantibodies against type I interferons are found in 10% of severe patients but not among asymptomatic or mildly symptomatic patients. Genetic defects in the type I interferon-related pathways are also present at a higher frequency among severe cases than those with milder illness.

TREATMENT MODALITIES TARGETING THE IMMUNE SYSTEM

Several drugs targeting the host immune system have been evaluated in clinical trials. The most successful is steroid-based therapy. In a large randomised controlled trial in England, the incidence of death was significantly lower among severe patients receiving intravenous dexamethasone 6 mg once daily than those receiving usual care. In a subsequent meta-analysis conducted by the World Health Organization, several corticosteroids have been shown to reduce mortality, including dexamethasone, hydrocortisone, and methylprednisolone.

Interferon β-1b, as part of a triple combination therapy with lopinavir-ritonavir and ribavirin, shortens the duration of symptoms in COVID-19 patients. Inhaled nebulised interferon β-1a has also been shown to achieve faster recovery in a phase 2 randomised controlled trial. However, intravenous interferon β-1a was not beneficial.

Tocilizumab is an anti-IL-6 receptor antibody. Early use of tocilizumab in the first two days of ICU admission was shown to reduce the risk of mortality. However, no benefits were shown in two randomised controlled trials. Anakinra, an IL-1 receptor antagonist, has been used in a case series of 8 patients with haemophagocytic lymphohistiocytosis and these patients showed improvement.

CONCLUSION

COVID-19 is a novel disease. Despite intensive research, there are still many unknowns on this disease. Further research on the immunology of COVID-19 will have a major impact on diagnostics, patient management and vaccine development.

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18. Hachim A, Kavian N, Cohen CA, Chin AWH, Chu DKW, Mok CKP, et al. Protein and RBD, respectively. Furthermore, there is still many unknowns on this disease. Further research on the immunology of COVID-19 will have a major impact on diagnostics, patient management and vaccine development.


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The portable, easy-to-use BD Veritor™ Plus System provides reliable COVID-19 (SARS-CoV-2) results in 15 minutes.

Results in 15 minutes

“How much confidence can I have in this result?”

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<th>Positive % Agreement (PPA)</th>
<th>Negative % Agreement (NPA)</th>
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<td>BD Veritor System for Rapid Detection of SARS-CoV-2 with 84% PPA¹</td>
<td>BD Veritor System for Rapid Detection of SARS-CoV-2 with 100% NPA¹</td>
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98.2%¹ Probability that the negative result is correct**  
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For more information please contact
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References:
* CDC, accessed July 21, 2020 @https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covidview/index.html. ** The negative predictive value is the probability that persons with a negative test result truly do not have the disease. *** The positive predictive value is the probability that persons with a positive test result truly have the disease.

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Current Status of COVID-19 Vaccine

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) first emerged in Wuhan, China in December 2019, rapidly spreading to 216 countries and territories and declared a pandemic by the World Health Organization (WHO) on March 11, 2020, with more than 60 million confirmed cases and 1.4 million deaths worldwide by the end of November 2020.1 This SARS-CoV-2 is a perfect pandemic virus with higher reproduction number and case fatality rate than seasonal influenza virus, hence cannot be just treated as a “simple flu”. Moreover, the incubation period is longer with infectivity begins days before symptoms onset and many cases are asymptomatic yet infectious resulting in difficulties in interrupting transmission.

There is currently no effective treatment, with only non-pharmacological strategies to control the spread of SARS-CoV-2 virus. However, measures such as social distancing, border restrictions, quarantine and isolation carry an enormous negative impact on health, economic, environmental and social changes.2 The current hope to restore global norms is the development of an effective pandemic vaccine, compressing the usual development timeline from 10 – 15 years to 1 – 2 years by bypassing the conventional stepwise approach of vaccine development. Such compression of the timeline demands the development of multiple vaccine platforms and strategies simultaneously because there is so much uncertainty regarding vaccine efficacy and safety, demanding an approach as diverse as possible to increase the chance of success.

WHAT ARE THE CURRENT COVID-19 VACCINE CANDIDATES?

In less than 12 months since the identification of the SARS-CoV-2 virus, 44 vaccine candidates were undergoing clinical evaluation, and over 154 vaccine candidates in pre-clinical evaluation.3 The speed of COVID-19 vaccine development is unprecedented, as compared to no suitable vaccine developed for MERS and SARS 6 years and 17 years after their first outbreaks, respectively. It usually takes more than a decade, and over USD 500 million investment in developing a vaccine, and up to 93% vaccine candidate tested in pre-clinical animal studies would not have been not able to be registered as a final product for clinical use.4 Multiple vaccine production platforms for these COVID-19 vaccines are being pursued, and we have chosen one each from some of these platforms which provide leading vaccine candidates being tested in phase III. Table 1 summarises the different types of production platforms that were being applied in the development of COVID-19 vaccines.

1. Inactivated Vaccine – PiCoVacc

Developed by Sinovac (Beijing, China), it is an inactivated vaccine using the CN2 strain of SARS-CoV-2 virus, β-propiolactone to inactivate and alum as adjuvant. Pre-clinical studies have demonstrated that the vaccine could induce SARS-CoV-2-specific neutralising antibodies in mice, rats and non-human primates. Challenge study showed protection in vaccinated rhesus macaques in terms of a decline in viral load and in histopathological changes in the lungs, with no infection enhancement or immuno-pathological exacerbation observed.5 This vaccine is currently undergoing phase III study involving 8,870 subjects and is estimated to be completed in October 2021.

2. Non-replicating Viral Vector Vaccine – University of Oxford/AstraZeneca Vaccine (Cambridge, United Kingdom)

It is a chimpanzee adenovirus-vectored vaccine (ChAdOx1 nCoV-19) expressing the SARS-CoV-2 spike protein. A phase I/II single-blind randomised controlled clinical trial conducted in the U.K. demonstrated that the vaccine induces both humoral and cellular immune responses, with homologous boosting which increased antibody responses. Local and systemic reactions were more common but were significantly reduced by prophylactic paracetamol.6 A phase III clinical trial involving 30,000 subjects is ongoing, and is estimated to be completed in October 2022. Nevertheless, there was a six-day pause on trial for the investigation of an adverse reaction after a participant received the vaccine. Although there was no official release of information on the adverse reaction, some media outlet reported that the participant developed transverse myelitis after receiving the vaccine.7 The trial was resumed after having been evaluated by an independent safety review committee. With regards to vaccine efficacy, 99% (208 out of 209) analysable participants had neutralising antibody responses 14 days after the booster dose, and T cell responses peaked at 14 days after a standard dose of the vaccine.8 Latest update released by AstraZeneca on November 23, 2020 also
reported that vaccine efficacy of 90% could be achieved by giving half dose first followed by a full dose and was superior to the 62% efficacy of giving two full doses at least one month apart. However, this preliminary result has been criticised, and another phase III clinical trial will be started to re-evaluate the efficacy.

3. Lipid Nano-particle Formulation with Nucleic Acid Vaccine – BNT162b1, BNT162b2 and mRNA-1273

Developed by BioNTech (Germany) and licensed to Fosun Pharma (Shanghai, China) with Pfizer (New York, USA), the two BNT vaccines are lipid nanoparticle–formulated, nucleoside-modified RNA vaccines encoding for either the trimersed SARS-CoV-2 receptor-binding domain (BNT162b1) or the membrane-anchored SARS-CoV-2 full-length spike protein (BNT162b2). In principle, a lipid coat encases the nucleic acid segment coding for the viral antigen of interest so that it could enter the host cells. The viral nucleic acid, which will not be incorporated into the human genome, will then be translated into the viral protein and expressed on the host cells, which triggers the host’s immune response. In a phase I/II clinical trial involving 195 healthy adults, both vaccines reported having mainly local injection site reactions, such as pain, redness and swelling, as well as mild systemic reactions such as fever. A lower incidence of adverse reactions was observed in older adults aged between 65 and 85. No severe systemic reactions have been reported. The two vaccine candidates were able to elicit dose-dependent SARS-CoV-2-neutralising antibody titres, peaked at 7 to 14 days after the second dose. Younger adults, aged between 18 and 55, generate higher antibody titres than older adults aged between 65 and 85. Nevertheless, all subjects had similar to or higher antibody titres than those of SARS-CoV-2 convalescent serum samples. mRNA-1273 is another RNA vaccine developed by Moderna (Massachusetts, USA) which also announced in November 2020 the first interim analysis of 95 participants in the phase III trial, the COVE study, co-conducted with the National Institute of Allergy and Infectious Diseases. Ninety and five of these participants who received placebo and the vaccine respectively contraceted COVID-19, therefore a vaccine efficacy of 94.5%.

4. Recombinant Protein Subunit (Trimeric) Vaccine with Adjuvant – NVX-CoV2373

Developed by Novavax (Maryland, USA), the NVX-CoV2373 is a recombinant SARS-CoV-2 nanoparticle vaccine consisting of the trimeric full-length SARS-CoV-2 spike protein with a mutation at S1/S2 cleavage sites to stabilise the S2 subunit in a prefusion conformation, mixed with an adjuvant called Matrix-M. Animal study has demonstrated that NVX-CoV2373 with Matrix-M1 protected against SARS-CoV-2 challenge with no evidence of vaccine-associated enhanced respiratory disease. In a phase I/II clinical trial, NVX-CoV2373 appeared to be safe, and was able to elicit immune responses that exceeded levels in convalescent serum from symptomatic COVID-19 patients. Novavax has announced that a phase III clinical trial has been initiated in late September, targeting to recruit 10,000 healthy adults.

WHAT COULD WE EXPECT FROM THE CURRENT COVID-19 VACCINE CANDIDATES

The ideal COVID-19 vaccine should interrupt transmission so that we can resume life before the COVID-19 era. However, it will require a vaccine that could generate not only high titre of neutralising antibody in blood, but also long-lasting respiratory mucosal immunological memory. Studies in COVID-19 survivors have demonstrated that although all patients developed seroconversion, their antibody titres can wane significantly as early as 1 – 2 months post-symptom onset. Experience from SARS survivors in 2003 showed that there was a significant reduction in patients with detectable SARS-CoV IgG three years after Infection and no memory B cell responses were detectable six years after infection, suggesting that antibody responses to SARS-CoV wane significantly over time. On the contrary, memory T cell responses have been reported to have a significantly better longevity. Therefore, the development of the ideal COVID-19 vaccine should not only be focused on the short-term development of neutralising IgG antibodies, but also whether long term effective T and B immunological memory could be generated. All the current vaccines do not offer data on the durability of the immune response beyond the immediate post-vaccination time points; hence the need for revaccination every year or so remains uncertain.

Alternatively, the vaccine given intranasally may generate adequate mucosal immunity to reduce transmission. Studies in animal coronaviruses, SARS-CoV and MERS-CoV have demonstrated that intranasal but not subcutaneous vaccination protected mice from human coronaviruses through airway memory CD4 T cell responses. MERS vaccine animal studies have also shown that intranasally administered vaccines were superior over intramuscular ones in terms of neutralising efficacy. Nevertheless, the current COVID-19 vaccines that have entered phase III clinical trials are all to be given parenterally. Currently, one intranasally administered vaccine candidate in the COVAX co-developed by the University of Hong Kong State Key Laboratory for Emerging Infectious Diseases, Xiamen University and Wantai Biopharmaceutical Company of Mainland China has been approved for non-phase III human clinical trial.

The currently available phase III COVID-19 vaccine candidates, including those being mentioned above,
may only prevent the disease in individuals but not interrupting transmission, the latter requiring a high vaccine coverage rate of perhaps 70 – 80% of the global population. However, the next generation COVID-19 vaccines coming into phase III trials that could generate much higher neutralising antibodies titre and memory T cells at the mucosal level to stop viral replication in the nose within 1 – 2 days of infection may be able to reduce transmission more effectively.

**OTHER VACCINATION STRATEGIES – CONCEPT OF THE TRAINED INNATE IMMUNE MEMORY**

Innate immune memory is a recently recognised component of immunological memory induced by several live attenuated human vaccines, including the BCG vaccine. It mediates non-specific protective responses to heterologous infections in addition to pathogen-specific adaptive immune memory. Through transcriptional, epigenetic and metabolic reprogramming of myeloid progenitors in the bone marrow, the BCG vaccinated individuals demonstrated enhanced pro-inflammatory cytokines secretions from their monocytes when stimulated in-vitro by unrelated bacterial and fungal pathogens. Studies have also explored whether BCG can offer a level of protection from COVID-19, in an attempt to explain why regions explored whether BCG can offer a level of protection from COVID-19, in an attempt to explain why regions

**DISTRIBUTION OF THE VACCINE – THE ART OF THE SCIENCE**

The three-staged goals of COVID-19 vaccination include (i) to maintain core community activities, (ii) to reduce disease severity, and (iii) to reduce transmission, all of which begin within each country and expand globally. Otherwise, safe international travel will not be possible. Apart from the development of a safe and effective COVID-19 vaccine, ensuring the vaccine being available to all people around the world is equally important in order to enable resumption of global travels and activities. Lower-income countries may not be able to afford these vaccines, and higher-income self-financing countries may not be able to secure adequate vaccine supplies through bilateral deals with manufacturers.

### Table 1. Summary of different types of vaccine platforms (Excerpted from Jeyanathan M et al 20)

<table>
<thead>
<tr>
<th>Vaccine Platforms</th>
<th>SARS-CoV-2 antigens</th>
<th>Neutralising Antibody</th>
<th>CD4 + T cells</th>
<th>CD8 + T cells</th>
<th>Phase III COVID-19 Vaccine Candidate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inactivated virus</td>
<td>Multiple viral antigens</td>
<td>Strong induction</td>
<td>Tx1 or Tn2 response depending on adjuvant</td>
<td>Weak response</td>
<td>PiCoVacc</td>
</tr>
<tr>
<td>Non-replicating viral vector (ChAd)</td>
<td>S protein</td>
<td>Unimpeded as no pre-existing viral vector immunity</td>
<td>Tx1 response</td>
<td>Potent response</td>
<td>ChAdOx1 nCoV-19</td>
</tr>
<tr>
<td>m-RNA based vaccine</td>
<td>S protein or RBD (mRNA encapsulated in lipid nanoparticle)</td>
<td>Unimpeded as no pre-existing viral vector immunity</td>
<td>Tx1 or Tn2 response depending on adjuvant</td>
<td>Depends on the choice of adjuvant and formulation</td>
<td>BNT162b1 and BNT162b2 mRNA-1273</td>
</tr>
<tr>
<td>Protein subunit vaccine</td>
<td>S protein or RBD</td>
<td>Strong induction</td>
<td>Tx1 or Tn2 response depending on adjuvant</td>
<td>Weak response</td>
<td>NVX-CoV2373</td>
</tr>
<tr>
<td>Virus-like particle</td>
<td>Multiple viral antigens</td>
<td>Strong induction</td>
<td>Tx1 or Tn2 response depending on adjuvant</td>
<td>Weak response</td>
<td>Phase I in Canada</td>
</tr>
</tbody>
</table>

ChAd – chimpanzee adenovirus; RBD – receptor binding domain; S – spike
vaccination coverage would improve to cover high-risk individuals, including the elderly aged over 65 years old or those with co-morbidities. Children were not included in the initial phase for vaccination because of much milder diseases as well as the relative lack of paediatric subjects having been included in the current vaccine trials. To interrupt transmission in the community, the whole population, including children, may need to be vaccinated ultimately.

A global collaboration, known as the Access to COVID-19 Tools (ACT) Accelerator, aimed to accelerate the development and production of, as well as to ensure equitable access to, COVID-19 tests, treatments, and vaccines. The COVAX was launched in April by the WHO, the European Commission and France in response to this pandemic, and is one of three prongs of the ACT Accelerator that focuses on vaccine development with the commitment to, upon successful vaccine development, provide innovative and equitable access to COVID-19 vaccines to every place across the globe regardless of their financial capabilities. The initial aim is to have 2 billion doses available by the end of 2021, which should be adequate to protect high risk and vulnerable people, as well as frontline healthcare workers. Hong Kong has adopted a two-pronged approach to securing vaccines: buying directly from manufacturers and joining the global COVAX Facility. Furthermore, logistical challenges on the implementation and distribution of the vaccines shall be considered, since some vaccines discussed above might become available in 2021. Careful analysis of phase III clinical trial data will be needed to guide the establishment of each country’s priority list of vaccine recipients, including the elderly aged over 65 years old or those with co-morbidities. Children were not included in the initial phase for vaccination because of much milder diseases as well as the relative lack of paediatric subjects having been included in the current vaccine trials.

CONCLUSION

Thanks to the global efforts in combating the COVID-19 pandemic, an effective and safe COVID-19 vaccine might become available in 2021. Careful analysis of phase III clinical trial data will be needed to guide the government and our expert panel in choosing safe and effective vaccines for the people of Hong Kong. In addition to healthcare and essential workers, high-risk citizens should be prioritised for vaccination when the vaccine becomes available to the market as soon as a safe and efficacious vaccine is available. The uncertainty of much milder diseases as well as the relative lack of paediatric subjects having been included in the current vaccine trials might need to be vaccinated ultimately.

References

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ESBL: extended-spectrum β-lactamase; KPC, Klebsiella pneumoniae carbapenemase.

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1. TRADE NAME: ZAVICEFTA. 2. PRESENTATION: Powder for concentrate for solution for infusion 3g ceftazidime/0.5g avibactam. 3. INDICATIONS: Indicated in adults for: (a) complicated intra-abdominal infection (IAI); (b) complicated urinary tract infection (cUTI), including pyelonephritis; (c) hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP). 4. DOSAGE: 3.5g Q8H for 2 hours. Refer to full PI for duration of therapy. 5. CONTRAINDICATIONS: Hypersensitivity to active substances, to any of the excipients or to any cephalosporin antibacterial agent. Severe hypersensitivity (e.g., anaphylactic reaction, severe skin reaction) to any other type of β-lactam antibiotic agent (e.g., penicillins, monobactams or carbapenems). 6. WARNINGS & PRECAUTIONS: Hypersensitivity reactions; clostridium difficile-associated diarrhea; in patients with renal impairment; nephrotoxicity; direct amphotericin test (DAQT or COOMbs test) serum conversion and potential risk of haemolytic anemia; in patients with controlled sodium diet. Ceftazidime may interfere with copper reduction methods (Benedict's, Fehling's, Clinistix) for detection of glycosuria leading to false-positive results. Ceftazidime does not interfere with enzyme-based tests for glycosuria. (Please refer to the full Prescribing Information for details). 7. INTERACTIONS: Probendecol and chloramphenicol. Concurrent treatment with high doses of cephalosporins and nephrotoxic medicinal products such as aminoglycosides or potent diuretics (e.g., furosemide) may adversely affect renal function. 8. PREGNANCY AND LACTATION: Should only be used during pregnancy only if the potential benefit outweighs the possible risk. Ceftazidime is excreted in human milk in small quantities and a decision must be made whether to discontinue breast feeding or to discontinue/avert treatment from ceftazidime/avibactam therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman. 9. SIDE EFFECTS: Very Common: Clostridium difficile associated diarrhea. Common: Candidiasis (including vulvovaginal candidiasis and oral candidiasis), eosinophilia, thrombocytopenia, thrombocytopenia, headache, dizziness, diarrhea, abdominal pain, nausea, vomiting, anorexia, anemia, leuco cytopenia, leukopenia, neutropenia, increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, gamma-glutamyltransferase increased, blood lactate dehydrogenase increased, rash, maculopapular, urticaria, pruritus, infusion site thrombosis, infusion site phlebitis, pyrexia. Reference: HK PRI (version date/LDF date) OCT 2018

Date of preparation: MAR2019 Identify number: ZAV0319

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INTRODUCTION

The pandemic of COVID-19 begins at the end of December 2019. The first case was reported in Hong Kong on 22 January 2020, and by the end of October 2020, there were more than 5,300 confirmed cases. Although the majority of the COVID-19 patients had mild disease, a number of them developed a severe illness and required intensive care. Furthermore, the management of this novel disease has evolved rapidly along with ongoing research around the world. This article summarises the intensive care of COVID-19 patients in the context of Hong Kong, as at the time of this writing.

THE BURDEN ON HOSPITAL SERVICE AND INTENSIVE CARE

At the beginning of the pandemic, many western countries encountered an unprecedented ICU demand. For European countries, the average ICU occupancy was 11% of the total hospital occupancy.1 So far, Hong Kong’s epidemic curve of COVID-19 had peaked at the end of July 2020. We encountered the highest number of simultaneously hospitalised patients in early August, reaching more than 1,200 patients. The ICUs saw their peak patient load in the first week of August, amounting to 51 patients, comprising 4% of all the hospitalised COVID-19 patients.

Up till the end of October 2020, 214 adult patients in Hong Kong had received ICU service for their COVID-19. Two-thirds were male. Their median ICU length of stay was nine days, and the crude hospital mortality was 17%. One-third of them were younger than 60 years, and one-third of them were older than 70 years. The hospital mortality for those ICU-treated and younger than 60 years, 60 to 70 years and more aged than 70 years were 1.3%, 18%, and 36% respectively. In a meta-analysis of reported overseas data before June 2020, the in-ICU mortality of COVID-19 was 41.6%, which was higher than the usual mortality from other forms of viral pneumonia.2 The mortality rates as reported in the study have fallen as the epidemic progresses, possibly as a result of the adaptation of the healthcare system to the epidemic, in the form of resource provision and of mounting experience among ICU staff.3

TRIAGE OF COVID PATIENTS

As ICU care provides a reasonable chance of survival, its availability becomes a critical issue in the battle against COVID-19. ICU beds were doubled in many overseas hospitals to cope with the surge of patients.4 Currently, there are around 18,000 acute hospital beds in Hong Kong, of which about 300 are ICU beds, and approximately 200 are intermediate care beds. The number of critical care beds is 7.1 per 100,000 population and is the lowest among the well-developed regions in Asia.5

There were suggestions to plan and allocate resources using the assumption that 1 in 5 hospitalised adult COVID-19 patients would require ICU admission.6 Such target is unrealistic in the short term, and some form of triage has to be exercised during an uncontrolled outbreak. The triage policy has to be fair for patients with or without COVID-19. Careful weighing of the benefits and risks involved in ICU admission is required while striving to guarantee a fair distribution of available resources. A recommendation was published recently, outlining the crucial factors to consider during a triage. They included the patient’s usual functional state, the severity of any pre-existing disease, the number of organ failure and the predicted probability of survival with ICU care.4

MEDICAL MANAGEMENT

Respiratory Support

Oxygen supplement is the mainstay of respiratory support for COVID-19 patients. In the RECOVERY trial, 24% of the patients did not require oxygen upon their randomisation, while 60% received oxygen, with or without non-invasive ventilation, and 16% required invasive mechanical ventilation.7 In the Oxygen-ICU study, it was found that targeting oxygen therapy at a SpO2 level of 94-98% was associated with lower ICU mortality than a level of 97-100%.8 As such, the author would recommend oxygen to be started only when SpO2 is less than 94% and targeting a SpO2 of 94-98%.

High flow nasal cannula (HFNC) is an emerging form of respiratory support where heated, humidified and oxygen-enriched air, typically at an oxygen concentration of 30-100%, is delivered to patient’s nostrils at a flow rate of 30-60 litre per minute. With its simplicity, HFNC can be done in settings where nursing care is less intensive, or there is a shortage of ventilators. In a prospective multicentre observational study, 47% of COVID-19 patients could be weaned from HFNC.9 The main concern on the use of HFNC is the possibility of aerosol generation, which might spread the disease
within the hospital. However, a systematic review found no direct study using COVID-19 patients or virus particles to study the risk of aerosolisation. As such, the risk of SARS-CoV-2 aerosolisation with HFNC remained undetermined. The author only had experience with HFNC in recovering COVID-19 patients who were extubated and had developed neutralising antibodies. Non-invasive ventilation (NIV) has also been used for COVID-19 patients and could provide more respiratory support than HFNC. However, in a post-hoc analysis of the LUNG SAFE study, NIV use was independently associated with increased ICU mortality. Also, the guideline of the European Respiratory Society and American Thoracic Society does not make any recommendation on the use of NIV for de novo acute respiratory failure (ARF). To the author’s knowledge, no COVID-19 patient in Hong Kong received NIV in ICU for ARF in their early phase of the disease. As our mechanical ventilators and other ICU resources had never been exhausted by COVID-19, our mortality of the severe COVID-19 cases was not higher than that of the acute respiratory distress syndrome in general. The therapeutic role of NIV is probably limited in the COVID-19 unless there is a shortage of mechanical ventilators. Another concern about NIV is the risk of aerosolisation. Negative pressure room with adequate air change is required if NIV is to be used. Invasive mechanical ventilation using a lung-protective strategy remained the mainstay of support for patients with severe ARF. Components of lung protection include: using a tidal volume of 4-6 ml per kg ideal body weight, keeping a plateau pressure of less than 30 cm H2O, minimising the driving pressure, and tolerating a higher than normal PaCO2 if the arterial pH is greater than 7.15. The setting of PEEP had been a subject of debate at the beginning of the epidemic, as two different types of lung mechanics, namely “L-type” and “H-type”, were described. However, subsequent studies showed no apparent evidence for different types of ARF in COVID-19 and most ICU specialists would set a PEEP level to minimise the driving pressure and to achieve adequate oxygenation (SpO2 88-95%) with a safe level of inspired oxygen concentration. After the PROSEVA trial, mechanical ventilation in the prone position has been used as an adjunct for severe ARF patients, especially during the early period of ARF. In particular, prone positioning had been shown to improve the PaO2/FIO2 (P/F) ratio in COVID-19 patients. Therefore, it should be considered for mechanically ventilated patients with inspired oxygen concentration greater than 60% and a P/F ratio less than 20 kPa.

Having seen the improvement of oxygenation from prone positioning in mechanically ventilated patients, people started to ask awake non-ventilated COVID-19 patient to turn prone and see if their oxygenation improves. A systematic review of reported case series confirmed the improvement in oxygenation with awake prone positioning. However, in a randomised control trial of awake prone positioning for patients receiving HFNC, such treatment only resulted in a one-day delay in intubation, but could not reduce the need for intubation. For the sickest COVID-19 patients, extracorporeal membrane oxygenation (ECMO) is the ultimate life support that we could offer. The hospital mortality was 39% according to an international ECMO registry. To the author’s knowledge, Hong Kong provided ECMO to nine COVID-19 patients, and the hospital mortality was greater than 70%. This poor outcome could be due to case selection, as the median age of the patients in the registry was only 49, while all of the Hong Kong ECMO patients were 60 or above.

**Other Organ Support**

COVID-19 patients are prone to thrombosis, and a meta-analysis consisting of mostly western population and a small number of Chinese patients found that the pooled incidence of pulmonary embolism was 23.4%. Patients in ICU should receive routine low molecular weight heparin (LMWH) as pharmacological thrombosis prophylaxis, and the author routinely provides mechanical prophylaxis in addition to the LMWH.

Acute kidney injury is also common in severe COVID-19 patients. For those treated in the ICU, around 20% received renal replacement therapy (RRT). In the Hong Kong cohort, 19% of the ICU COVID-19 patients received RRT, and the crude mortality for those having received RRT was 56%.

Moreover, restrictive fluid intake should be attempted to improve oxygenation. Full nutritional support should be provided according to international recommendations. Use of omega-3 lipid may be considered, and physical activity should be promoted to preserve muscle mass and function.

**Anti-Viral Therapy**

The most widely used anti-viral therapy for COVID-19 in local ICUs was the combination of Interferon, Lopinavir-Ritonavir (Kaletra), and Ribavirin. However, reports were finding no therapeutic effect with Kaletra and Ribavirin, while the role of interferon required further study. The most promising anti-viral therapy is Remdesivir, and it has been used in a few ICU patients in Hong Kong. However, the clinical effect was difficult to appreciate with too few patients.

Virus neutralisation may also be achieved by infusion of convalescent plasma harvested from patients having recovered from COVID-19. Again, a small number of ICU patients in Hong Kong were treated with convalescent plasma, and no remarkable clinical effect could be seen in this small cohort. A recent phase II trial showed no benefit in moderately ill COVID-19 patients. It was not a surprise as most of the patients were antibody positive at the peak of their acute respiratory failure. It could be the immune response, rather than the viral replication, causing the profound disease.

**Immunomodulation**

After the RECOVERY trial, Dexamethasone 6 mg daily for up to 10 days is the most accepted treatment for
COVID-19 patients requiring oxygen supplement. The 28-day mortality was dropped by 12% for mechanically ventilated patients. In a meta-analysis, corticosteroids were associated with lower 28-day mortality in the critically ill. This finding agreed with the hypothesis that the host's immune response plays a significant role in the deranged physiology.

It was observed that COVID-19 patients might deteriorate rapidly, with a clinical picture similar to the cytokine release syndrome. As such, Tocilizumab, an interleukin-6 receptor antibody, was used in several sick COVID-19 patients in Hong Kong. Retrospective observation studies had found lower mortality in patients receiving Tocilizumab. However, such benefit was not seen in prospective trials.

Extracorporeal blood purification may have a role in controlling the cytokine release syndrome. Some ICU patients had received haemo-adsorptive therapy, where blood was exposed to medical devices which could absorb cytokines. Cytosorb (Cytosorbents, Germany) and oXiris (Baxter, US) are two such devices that are available in Hong Kong. From the author’s experience, there was an association between improvement in oxygenation and the use of such therapy. However, it is uncertain if such transient physiological improvements could be translated into a survival benefit. The main advantage of blood purification from pharmacological immunosuppression is a lower risk of nosocomial or opportunistic infection.

INFECTION CONTROL MEASURES

Last but not least, infection control is of utmost importance for COVID-19. After the SARS epidemic in 2003, Hong Kong’s hospitals and ICUs have developed an excellent infection control practice for highly infectious disease. So far, no hospital personnel contracted COVID-19 during their work. Mask, cap, eye protection, full-length gown and gloves are the standard personal protective equipment when managing COVID-19 patients who are still infectious. When an aerosol-generating procedure is contemplated, an N95 mask and full-face shield will be used to avoid inhalation of aerosols and minimise deposition of aerosols onto one’s face. Intubation and cardiopulmonary resuscitation are standard ICU procedures that carry the highest risk. The Adult ICU of Queen Mary Hospital has produced videos demonstrating the practice of CPR and intubation of COVID-19 patients. You may also find the CPR and intubation protocol of the Prince of Wales Hospital ICU online.

CONCLUSION

There are very few specific therapies for COVID-19 disease, but with proper ICU care, the mortality is not more than other forms of ARDS. It is believed that the high mortality rate seen at the beginning of the pandemic is due to inadequate healthcare resources to cover the vast number of patients. Having a low number of beds and a continuously high occupancy rate, Hong Kong’s ICUs are at risk of collapse if a major outbreak occurs. Thanks to the excellent public health measures, an overwhelming surge of patients has not happened. Before the availability of an effective vaccine, everyone must continue with the highest vigilance for COVID-19.

References


### Dermatology Quiz

**Dr Lai-yin CHONG**

MBBS(HK), FRCP(Lond, Edin, Glasg), FHKCP, FHKAM(Med)

Specialist in Dermatology & Venereology

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**Questions**

1. What is your diagnosis and differential diagnoses?
2. What are the possible underlying causes?
3. What is your treatment for these lesions?
4. Currently, what important disease should be watched out?

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Fig 1: Painful erythematous swollen fingers.
**FIT FOR THE NEEDS OF ASIANS**

**Prefered P2Y1 inhibitors in 2018 Chinese Expert Consensus on Antithrombotic Therapy for Special Populations with ACS in the following populations:**

For details of the recommendations and other information stated in this consensus, please refer to the full publication in Chinese:

**Presentation:** Clopidogrel is a thiolated tablet. Indications: Prevention of arterial thrombotic events in (i) adult patients suffering from myocardial infarction (from a few days until less than 30 days), non-ST segment elevation myocardial infarction (from a few days until less than 30 days), non-Q-wave myocardial infarction (from a few days until less than 30 days), or unstable angina (from a few days until less than 30 days); (ii) adult patients suffering from stroke/TIA (from a few days until less than 30 days); (iii) adult patients suffering from peripheral arterial disease or established atherothrombotic disease (from a few days until less than 30 days); (iv) adult patients suffering from transient ischaemic attack (from a few days until less than 30 days); (v) adult patients suffering from acute coronary syndrome. Chin J Cardiol 2018;46:255-266. **Reference:** Specifically Coordinated Prevention and Treatment at Thrombolysis of Chinese College of Cardiology in Multinational. Multinational Consensus on the Management of Acute coronary Syndrome. Chinese Journal of Cardiology. Chinese expert consensus on antiplatelet therapy for special patients with acute coronary syndrome. Chin J Cardiovasc Dis 2018;46:399-399. **Legal Classification:** Full prescribing information is available upon request. APH/HeE 2018/08.**

---

**Clopidogrel in DAPT for Special Populations with ACS**

<table>
<thead>
<tr>
<th>Contraindications</th>
<th>Low platelet counts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersensitivity to clopidogrel or excipients</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Severe hepatic impairment</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Active pathological bleeding such as peptic ulcer &amp; intracranial haemorrhage</td>
<td>Contraindicated</td>
</tr>
</tbody>
</table>

**Dosage:**

- **Adults and elderly:** 75mg once daily. For patients with UA/NQWMI, loading dose 300mg, followed by 75mg once daily (with ASA 75mg-325mg daily). Since higher doses of ASA were associated with higher bleeding risk, recommended dose of ASA ≤100 mg. For patients with UA/NQWMI who had undergone PCI, the recommended loading dose was 300mg (clopidogrel) plus 300mg (ASA), followed by 75mg clopidogrel plus 75mg ASA once daily.

- **Patients with ACS:** The recommended loading for therapy should be DAPT on clopidogrel plus aspirin for 7 days. For ACS patients with moderate hepatic disease who may have bleeding diatheses, clopidogrel should be discontinued 7 days prior to surgery. Patients who may be at risk of increased bleeding from the following patients should be considered suitable candidates for clopidogrel use: patients with renal impairment; patients with moderate hepatic disease who may have bleeding diatheses. Not recommended.

- **Patients with STEMI receiving thrombolytic therapy should initiate DAPT as soon as possible.** clopidogrel should be discontinued 7 days prior to surgery. Patients who may be at risk of increased bleeding from the following patients should be considered suitable candidates for clopidogrel use: patients with renal impairment; patients with moderate hepatic disease who may have bleeding diatheses. Not recommended.

**Undesirable effects:**

- **75 mg x 14’s; 300 mg x 30’s.**

---

**Thrombolytic therapy in STEMI**

- **For ACS patients with a history of renal failure (eGFR <30 mL/min), clopidogrel (75mg) plus aspirin (75-100 mg) is recommended.**

- **For ACS patients with renal function abnormality and absolute bleeding, clopidogrel (75mg) plus aspirin (75-100 mg) is recommended.**

- **For ACS patients with concomitant use of ARB, clopidogrel (75mg) plus aspirin (75-100 mg) is recommended.**

- **For ACS patients with severe renal failure and acute gout arthritis, clopidogrel (75mg) plus aspirin (75-100 mg) is recommended.**

- **For ACS patients with a high risk of GI bleeding (including the elderly and patients with atrial fibrillation), clopidogrel (75mg) plus aspirin (75-100 mg) is recommended.**

- **For ACS patients with concomitant use of ARB and aspirin, clopidogrel (75mg) plus aspirin (75-100 mg) is recommended.**

---

**Presentation:** Clopidogrel is a thiolated tablet. Indications: Prevention of arterial thrombotic events in (i) adult patients suffering from myocardial infarction (from a few days until less than 30 days), non-ST segment elevation myocardial infarction (from a few days until less than 30 days), non-Q-wave myocardial infarction (from a few days until less than 30 days), or unstable angina (from a few days until less than 30 days); (ii) adult patients suffering from stroke/TIA (from a few days until less than 30 days); (iii) adult patients suffering from peripheral arterial disease or established atherothrombotic disease (from a few days until less than 30 days); (iv) adult patients suffering from transient ischaemic attack (from a few days until less than 30 days); (v) adult patients suffering from acute coronary syndrome. Chin J Cardiol 2018;46:255-266.
Use of Deep Throat Saliva for the Diagnosis of Coronavirus Disease 2019 in Adults and Children in Hong Kong

Dr David Christopher LUNG
Department of Pathology
Queen Elizabeth Hospital / Hong Kong Children's Hospital

INTRODUCTION

Hong Kong has been adopting precision measures to control the Coronavirus disease 2019 (COVID-19) pandemic, which mainly consist of universal masking, social distancing, border control, liberal laboratory testing, mandatory isolation, contact tracing and quarantine of contacts. The mainstay of laboratory diagnosis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is by reverse-transcriptase polymerase chain reaction (RT-PCR), where nasopharyngeal swab (NPS) or nasopharyngeal aspirate (NPA), with or without a throat swab was initially used as a standard specimen type in Hong Kong. However, the collection of nasopharyngeal specimens (NPsp) results in patient discomfort and is considered an aerosol generating procedure (AGP), which poses risks to healthcare workers. Moreover, the supply of personal protective equipment (PPE) was very limited during the earlier phase of the pandemic. These constraints limit large-scale testing. Hence there was a need to explore alternative and more convenient specimen types.

Deep throat saliva (DTS) has been demonstrated to be a reliable specimen type for influenza and different respiratory viral infections. DTS is easy to collect, does not cause any patient discomfort and allows conservation of PPE. Hong Kong is the first place in the world to use DTS as a convenient specimen for extensive screening of COVID-19. In February 2020, the World Dream Cruise sat dock at the Kai Tak cruise terminal, and self-collected DTS was used to screen more than 1,800 crew members and passengers. This outbreak created the first ever opportunity in the world for DTS to be used for mass screening of COVID-19.

SCIENTIFIC BASIS OF THE USE OF DTS FOR THE DIAGNOSIS OF SARS-CoV-2

Angiotensin-converting enzyme 2 (ACE2) receptors are known to be the functional receptor of SARS-CoV and SARS-CoV-2, and a recent study showed high expression of ACE2 receptors in the mucosa of the oral cavity. A Chinese rhesus macaque model demonstrated that epithelial cells of the salivary gland ducts are early targets for SARS-CoV soon after infection and infected epithelial cells act as a significant source of virus in saliva. SARS-CoV-2 was first demonstrated to be present in saliva in a local study, in which the virus was found in saliva in 11/12 (91.7%) COVID-19 confirmed cases and the live virus was also recovered from the viral culture. Another study conducted by the same group demonstrated that posterior oropharyngeal saliva (POPS) sample had the highest viral load near the presentation of infection and declined steadily afterwards.

Since there is limited data on the performance of saliva in the initial phase of the epidemic, early morning DTS was collected to enhance the yield. While POPS is a more precise description of the anatomical origin of DTS, the two terms are interchangeable. The posterior oropharynx is the meeting point of secretions from the following anatomical sites:

- posterior nasopharynx
- salivary glands
- upper and lower respiratory tracts

A recent study of the viral shedding pattern of POPS showed that there is a diurnal variation of viral shedding, with the viral load being the highest in the early morning but POPS could still be taken at any time throughout the day. To facilitate all-day collection of POPS, patients are instructed to refrain from eating, drinking and teeth-brushing for at least 2 hours before obtaining POPS regardless of the actual collection time.

PERFORMANCE OF POPS

Evaluation of the performance of POPS may be challenging since there is the absence of a “gold standard” specimen type and the viral shedding can be intermittent. Therefore, assessment of the performance of POPS is ideally done by head-to-head comparison of paired POPS and NPsp collected simultaneously, expressed by percent agreement or concordance rate. Pooled evaluation of the positive rate of POPS compared with NPsp or comparing non-same day specimens may not be able to truly reflect the performance of POPS. Studies with head-to-head comparison of paired saliva and NPsp are listed in table 1. The PPA can range from 78.9-100% , where the agreement would be higher during the early stage of the disease and discordance usually occur when the viral load starts to drop after seven days of onset of illness. There are also studies demonstrating that the performance of saliva may be inferior to NPsp. The variation in performance could be due to different practices in collecting saliva and analysing pooled saliva data from different stages of the disease. POPS has been evaluated on different platforms and showed promising results.
**Table 1: Studies comparing the performance of Saliva (Summarised by author)**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Method</th>
<th>Number of subjects</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wollie et al.18</td>
<td>Saliva</td>
<td>70 patients with COVID-19</td>
<td>Day 1-5: 81% saliva vs 71% NPS positive, Higher viral RNA generally detected in saliva</td>
</tr>
<tr>
<td>Wong et al.8</td>
<td>Deep throat saliva</td>
<td>299 matched pairs from 44 symptomatic COVID-19 patients</td>
<td>PPA (overall): 85.2%, PPA (&lt;7 days): 96.6%</td>
</tr>
<tr>
<td>Leung et al.9</td>
<td>Deep throat saliva</td>
<td>95 matched pairs from 62 patients, including 29 confirmed patients</td>
<td>PPA (overall): 78.9%, Discordant pairs favour DTS</td>
</tr>
<tr>
<td>Yee et al.11</td>
<td>Saliva</td>
<td>300 patients recruited, 97 confirmed COVID-19</td>
<td>PPA: 82.4% (PPA: 83.3%; PPA (Paed): 93.8%)</td>
</tr>
<tr>
<td>Rao et al.19</td>
<td>Early morning saliva</td>
<td>217 COVID-19 positive in quarantine centre</td>
<td>Concordance: 45.6%, Detection rate of saliva was higher than NPS</td>
</tr>
<tr>
<td>Pasomsub et al.12</td>
<td>Saliva collected before NPS</td>
<td>200 patients</td>
<td>Agreement: 97.5%</td>
</tr>
<tr>
<td>Procop et al.10</td>
<td>Enhanced saliva specimen collected prior to NPS collection</td>
<td>224 patients</td>
<td>PPA: 100%</td>
</tr>
</tbody>
</table>

*PPA: Positive percentage agreement

**USE OF SALIVA FOR DIAGNOSIS OF COVID-19 IN PAEDIATRIC PATIENTS**

The use of saliva for the diagnosis of COVID-19 has also been explored in the paediatric age group. One Singaporean study involving 18 children concluded that saliva was not useful in diagnosing COVID-19 in children.16 The sensitivity of saliva was calculated based on positive NP results, and no percentage of agreement was stated in the study. The study also stated that in around 12% of children had delayed saliva collection.

Another study reviewed both adult and paediatric data, and the performance of saliva remained good in both young and older children. The saliva PPA reached 83.3% in children aged 4-10 years and 81.8% in older patients between 11-18 years.11 A study conducted in Hong Kong, including seven paediatric patients demonstrated fair categorical concordance in children, but the sample size was relatively small. Before having more comprehensive data, POPS should only be used in children who are able to obey the command.

**CONCLUSION**

Saliva is currently recognised as an acceptable specimen for the diagnosis of SARS-CoV-2 PCR in Hong Kong and other regions.17 It is a convenient tool for mass screening, especially in community outbreak settings, outpatient settings, surveillance of high-risk groups, elderly homes or schools. Collection of POPS is simple and non-invasive, allows self-collection and return, ease to distribute specimen bottles as plain bottles are sufficient and viral transport medium is not required unless there is delay in specimen processing, allowing POPS collection kits to be distributed by automatic vending machines.

To ensure the diagnostic yield of POPS, the following measures should be ensured:

1. Standard and clear instruction sheets, including video demonstration, should be provided to patients.
2. Abstain from eating, drinking and rinsing of mouth at least 2 hours prior to specimen collection.
3. Avoid collection of POPS before bedtime.
4. Collect sufficient volume and remind patient to spit at least 3-5 mouthfuls of POPS into the spout bottle.
5. Direct supervision may be necessary, especially for young children, whose compliance to instructions cannot be ensured.

**References**

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Non-inferior to meropenem in 28-day all-cause mortality in ITT population

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Favourable 28-day all-cause mortality for the subgroups of vHAP and previous failure of antibiotics for current nosocomial pneumonia episode

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Using $R_0$ to Inform Public Health Policy for the 2019 Novel Coronavirus (COVID-19) Pandemic

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BACKGROUND

A wide variety of human respiratory viruses cause acute respiratory infections in all ages. Most infections are mild and self-limiting, and typically referred to as “common colds”. Some infections can cause more serious disease requiring hospitalisation. From time to time, viruses jump from non-human animals to humans, causing zoonotic infections. If these infections are able to spread efficiently from one human to another, a global pandemic may result. Considerable effort has been made to plan for the risk of influenza pandemics, with the number of cases increasing exponentially. Conversely, when $R_0$ is < 1, each case can only transmit the disease to less than one individual on average, and the infection would be expected to die out from the population. Because of chance events, it might still be possible to have small outbreaks even when $R_0$ is < 1, but a sustained epidemic would not occur. This threshold concept of $R_0$ provides an assessment of inherent transmissibility of an infection, and the potential difficulty in controlling its spread. An infection with $R_0$ just above one could be easier to control than an infection with a much higher $R_0$.

When $R_0$ is > 1, each infected individual would, on average, infect more than one new person, and the disease would be expected to spread through the susceptible population as an epidemic, with the number of cases increasing exponentially. Conversely, when $R_0$ is < 1, each case can only transmit the disease to less than one individual on average, and the infection would be expected to die out from the population. Because of chance events, it might still be possible to have small outbreaks even when $R_0$ is < 1, but a sustained epidemic would not occur. This threshold concept of $R_0$ provides an assessment of inherent transmissibility of an infection, and the potential difficulty in controlling its spread. An infection with $R_0$ just above one could be easier to control than an infection with a much higher $R_0$.

A related concept is the effective reproductive number, $R_t$ at time $t$. Similar to the basic reproductive number, the $R_t$ represents the average number of secondary infections produced by a typical case of the infection, but $R_t$ can vary over time because of the implementation of public health measures or because of the accumulation of immunity in the population either as a consequence of natural infections or because of the use of effective vaccines. The objective of public health measures is to reduce $R_t$ below 1. For example, suppose $R_0$ were estimated to be 2, meaning that each individual infects on average two other persons. In that case, the objective of public health measures could be to reduce transmission by at least 50% so that $R_t$ is brought below 1, and the epidemic will then gradually fade out. If $R_0$ were greater, we might determine that more stringent public health measures are needed to control an epidemic.

During the course of an evolving epidemic, the effective reproduction number can be estimated by the product of the basic reproductive number and the fraction of the host population that is remaining susceptible ($x$), as in the following formula:

$$R_t = R_0x$$

For example, for an infection with a $R_0$ of 6 in a population where one-third of the population has become immune, the effective reproductive number would be reduced to 4. This leads to the important concept that transmissibility of an infection can...
Effectively be reduced by rendering a significant proportion of the population immune. With a larger number of people being immune in a population, the likelihood of contact between an infectious case and a susceptible person will be lower, thus effectively breaking the chain of transmission and reducing the potential of a sustaining epidemic. This concept has been referred to as “herd immunity”, where a substantial proportion of immune individuals in a population is also protecting the whole population against an epidemic. A simple calculation of the threshold required to achieve herd immunity is provided by the formula

\[(R_0 - 1)/ R_0 \text{ or } 1 – 1/ R_0\]

THE PRINCIPLES BEHIND THE CALCULATION OF R0 AND RT

A detailed exploration of the technical aspect of how the calculation of R0 is beyond the scope of the present article, as although the concept of R0 is very intuitive, its calculation is much less straightforward. The two broad approaches for estimating R0 included individual level modelling (ILM) and population level model (PLM). For ILM, detailed individual-level contact tracing data obtained at the very start of an epidemic is used. Such contact tracing included the tracing and laboratory testing for the ascertainment of infection status of all the contacts once an individual is diagnosed, so as to identify all secondary and tertiary cases as the infection is spreading in the population. The R0 is then calculated by averaging over the number of secondary cases caused by many diagnosed individuals.

Population level models, which are being more commonly employed, use population-level data of cumulative incidence in the community without actual tracking of individuals. Basing on a number of individual-level assumptions, such as the mass-action principle of infectious spread and time independent infection rates, mathematical models are constructed using Ordinary Differential Equations to describe the dynamics of the expected population size in different disease stages of the infection (susceptible, infectious, and recovered, etc). Population level parameters in terms of disease transmissibility and progression rates are obtained by fitting the model to population-level data, with a threshold parameter obtainable from bifurcation analysis of the mathematical model.

It is important to be aware that R0 values obtained from different ILMs using contact tracing data do not necessarily agree with those obtained from PLM based on mathematical models, as the former calculates the value of R0, whilst the latter calculates the value of a threshold parameter; how parameters generated from population-level data are related to the individual-level processes is generally unknown. The accuracy of ILMs, in particular, depends on the extensiveness and efficiency of contact tracing, the accuracy of laboratory test employed for diagnosis, and the ease of recognition of the infection as dictated by its clinical profiles.

On the other hand, it is important to remember that R0 is not an intrinsic variable of the infectious agent but being affected by a large number of factors, including the rate of contacts of individuals in the population, the probability of the infection being successfully transmitted during a contact, and the average duration of infectiousness, including periods of asymptomatic infectiousness, the population size, and the rate of recovery or death. These factors may explain the wide variability of estimates reported for the same infection by different researchers, as they can be very different in different localities, and continuously changing over the course of an epidemic. Moreover, the use of different models for the estimation of R0 may also play a role in the discrepancies observed among different studies, thus making their direct comparison being less straightforward.

For instance, in the case of COVID-19, the World Health Organization (WHO) had initially estimated the R0 to range between 1.4 and 2.5. Other early studies have estimated the R0 to range from 2 to 3.5. Two reviews of early studies in China have reported mean estimates of R0 of 3.28 (ranging between 1.4 to 6.49) and 3.38 (ranging between 1.90 to 6.49). Another work argued that there is global convergence of R0 reported across many nations to a value 4.5. In fact, there is no single true value of R0, and we would expect the R0 in Hong Kong to be relatively higher than many other locations because of the high population density and population mixing in Hong Kong.

UNDERSTANDING R0 AND RT IN RELATION TO COMMUNITY EPIDEMICS

In previous epidemics of different emerging infectious diseases, the basic reproductive number has been estimated and employed for various different purposes. One such use of R0, as in the case for the 1918 pandemic influenza, was for quantifying and understanding the relative infectious risk and transmissibility associated with a novel pathogen, in comparison with some known and better understood pathogens. Such comparison, though potentially useful in enhancing our understanding of an emerging pathogen, is necessarily retrospective until the epidemic has run at least part of its course for sufficient incidence data to be accumulated. On the other hand, the evaluation and comparison of the changing R0 before and after the application of some putative control measures would help to assess the potential impact, and the required magnitudes of different control measures or their combinations, for bringing the R0 to less than the threshold of unity. Such comparison may inform policy decision and practical guidelines in a more objective manner.

POTENTIAL CONTRIBUTION OF R0 AND RT IN THE SETTING OF THE EVOLVING COVID-19 PANDEMIC

Estimation of R0 and Rt has been critical in guiding public health responses to the COVID-19 pandemic. The School of Public Health at the University of Hong Kong has been providing daily updates on the local Rt values on a dashboard at https://covid19.sph.hku.hk. Fig.1 shows the estimated Rt for the period from late January through to early November 2020, covering Hong Kong’s first three waves. Our earliest estimate of Rt was approximately 2.5 on 24 January 2020; this may already be lower than R0 because people had
Kong’s large third wave began in early July, but this was preceded by a considerable rise in $R_t$ in late June, at a time when physical distancing measures had been mostly relaxed. Re-introduction of these measures in the second half of July was effective in bringing $R_t$ back below one by the start of August. $R_t$ rose above 1 in early November, corresponding to the start of the fourth local wave.

**CONCLUSIONS**

In conclusion, ongoing estimation of $R_0$ and $R_t$ can help to inform public health policy in an evolving epidemic by the objective guiding and impact assessment of changing implementation and magnitude of different public health measures. Caution needs to be exercised; however, when comparing $R_0$ or $R_t$ across different settings as they may vary from one location to another due to different population and local factors.

### Acknowledgments

The authors thank Tim Tsang, Eric HY Lau, Peng Wu, Tiffany WY Ng, Jessica Y Wong, Dillon C Adam, Faith Ho, Huizhi Gao, Zoe Xiao and Cattiriona Murphy.

### References

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Techniques to Enhance Well-being in the COVID-19 Era

Dr Peter GRUENEWALD

It is easy to feel daunted by the COVID-19 pandemic: constant reporting of the number of infections and fatalities; fear of infection, illness and death; shielding in the case of increased risk, if suffering from obesity, heart disease, hypertension or being immune compromised. Social distancing and lockdown can have an enormous impact on our relationships, bringing about potentially tense relationships at home, increase in domestic violence, and experiences of profound isolation, with a sense of detachment from other human beings, community and nature. Alcohol consumption increases, diets may be less balanced, screen time may be increased, exercising reduced. Jobs are being lost; the financial livelihood of individuals and families are at risk.

Being affected by increasing levels of stress, anxiety, and depression can, in turn, affect the functioning of our immune system, making us potentially more vulnerable to infections.

Research into the field of stress and resilience has shown that the psycho-physiological impact of stress and anxiety on the autonomic nervous system balance, inflammation and the hypothalamic-pituitary-adrenal axis has a profound immune-modulating impact and may influence the outcome of viral infections (cytokine response and appropriate levels of corticosteroids).1

Emotion regulation and the ability to shift from negative (anxiety, fear, sadness, frustration etc.) to positive emotions (courage, engagement, passion, compassion, care, appreciation etc.) promotes flexibility, adaptability rhythm, and dynamic balance of the autonomic nervous system, with an increasingly positive impact on developing physical and emotional, mental and spiritual resilience whilst facing pressure, through for example enforced change and/or adversity.2 This may in turn have a positive impact on acute and chronic inflammation parameters, such as immunoglobulin levels, T-cell activity and cytokine response.3

Predisposition to the negative impact of stress and extreme emotions is not just genetically predisposed, but also determined by a preverbal and precognitive exposure to toxic stress or trauma, defined as adverse childhood events during pregnancy and also during the time of early attachment.4 The earlier the adverse experience during the development of the child, the more physiological is the response to stressful events later on in life.

An effective, evidence-based and practical approach to developing adaptive resilience and reducing the negative effect of so-called negative emotions, such as stress and anxiety, should therefore not be purely based on psychological interventions, such as cognitive behaviour therapy based exercises, but should include body awareness (mindfulness, breathing and relaxation techniques) to effectively create optimal and flexible adaptation of levels of arousal to inner and environmental challenges.5

One of the particularly helpful technique in this context is the resonant frequency training or coherence training, a breathing technique with simultaneous focus on positive emotional states.6

This audio-guided breathing technique deploys slow diaphragmatic breathing at a pace of approximately 5.5 breathing cycles per minute, whilst simultaneously focusing on a positive feeling, such as appreciation. During this exercise, the breathing rhythm is, with the help of an audio-breath pacer, being rhythmically aligned with blood pressure rhythm and heart rate variability (HRV), creating a resonance phenomenon that leads to a significant increase in the amplitude of heart rate variability during the exercise and beyond. HRV is a measure for the rhythm, flexibility, dynamic and balance of the autonomic nervous system and has been a predictor for ill health and all-cause mortality in middle-aged and older people. Optimising heart rate variability through paced breathing and/or HRV biofeedback has also been shown to improve mental and emotional health, through reducing negative stress, improving mood, reducing anxiety.7,8,9,10

It is important to note that the resonant frequency training creates a physiological state of autonomic balance between stimulation (sympathetic) and relaxation (parasympathetic), comparable with the physiological state underpinning flow and engagement, when we are simultaneously alert and mobile (sympathetic) and relaxed and laid back (parasympathetic). Training body and mind repeatedly (1x to 2x daily for 10 to 15 minutes) into this state of autonomic balance will allow to access this resourceful state on demand in challenging circumstances, i.e. when exposed to pressure. This will allow to prevent being fixed in a physiological fight or flight response or conversely in a freeze and flow response, allowing for optimal adaptation and health promotion, even when exposed to short- or long-term pressure.

This psycho-physiological approach to stress management and developing of physical and emotional resilience should be supplemented by techniques that enhance the capacity to shift from negative to positive emotional states.
Mindfulness-based exercises, such as nature observation\textsuperscript{11} and active listening\textsuperscript{2,13,14} can be very helpful here, as are exercises that lift subconscious negative emotions into our consciousness, in order to neutralise them.\textsuperscript{15} Gratitude journaling has also shown to be highly effective in regard of accessing positive emotional states as resources for physical and emotional resilience and health.\textsuperscript{16,17,18,19}

Finally, using positive self-talk\textsuperscript{20,21} and mental rehearsing\textsuperscript{22} can help create clear goals, vision and purpose in order to build resilience and protect health\textsuperscript{23}.

The guided breathing technique (resonant frequency training – coherence training) and the breath pacers are made available on www.bestfutureself.org.

All other evidence-based techniques being referred in this can be found in my ‘Manifesting Your Best Future Self. Building Adaptive Resilience.’ available on Kindle and Amazon.

References
13. Nancy Kline, Time to Think: Listening to Ignite the Human Mind (London: Cassell, 2002). The power of effective listening is recognized as the essential tool of good management.
20. Shad Helmstetter, “What to say when you talk to yourself,” Park Avenue Press (2011)
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**The Hong Kong Neurosurgical Society Monthly Academic Meeting – To be confirmed**

**Facebook Live**

**HKFMS Foundation Meeting**

**FMSHK Executive Committee Meeting**

**Facebook Live**

**Certificate Course on Lower Urinary Tract Symptoms (LUTS) management**
- Session 1 - Palliative Home Care in the Eye of Family Care
- Session 2 - Hospital at Home Care Focus on Pain Control
- Session 3 - Legal Aspects of End of Life Care
- Session 4 - Urinary Tract Symptoms (LUTS) management
- Session 5 - Peripheral Nerve Injury
- Session 6 - Urological Trauma
- Session 7 - Urinary Tract Infections
- Session 8 - Urinary Tract Symptoms (LUTS) and Mortality (Falls And Fractures)
- Session 9 - Urinary Tract Symptoms (LUTS) and Incontinence
### Calendar of Events

<table>
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<th>Date / Time</th>
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| **13 WED** 7:30 AM | The Hong Kong Neurosurgical Society Monthly Academic Meeting –To be confirmed | CME Accreditation  
College: 1.5 points  
College of Surgeons of Hong Kong  
Enquiry: Name: Dr Calvin MAK  
Tel: 2595 6456  
Fax: No.: 2965 4061 |
| **16 SAT** 2:00 PM | Facebook Live  
Symposium on End of Life Care (3-session)  
Session 1 - Palliative Home Care in the Eye of Family Physicians  
Session 2 - Hospital at Home and End of Life Care: Focus on Pain Control  
Session 3 - Legal Aspect of End of Life Care  
Organiser: HKMA-Hong Kong East Community Network  
Speaker: Session 1: Dr Patrick Hung-wai CHAN; Dr Luke Chiu-yee TSANG; Dr Henry Wing-ming KONG  
Session 2: Dr Charles CHAN Fei  
Session 3: Ms Olivia LEUNG | Ms. Candice Tong  
2861 1979  
1 CME Point |
| **21 THU** 7:00 PM | HKFMS Foundation Meeting  
Organiser: The Federation of Medical Societies of Hong Kong  
Venue: Council Chamber, 4/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong | Ms. Nancy CHAN  
Tel: 2527 8898 |
| **21 THU** 8:00 PM | FMSHK Executive Committee Meeting  
Organiser: The Federation of Medical Societies of Hong Kong  
Venue: Council Chamber, 4/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong | Ms. Nancy CHAN  
Tel: 2527 8898 |
| **23 SAT** 2:00 PM | Facebook Live  
Certificate Course on Lower Urinary Tract Symptoms (LUTS) management  
7. LUTS and heart disease (CHF)  
8. LUTS and Mortality (Falls And Fractures)  
9. LUTS and incontinence  
Organiser: Hong Kong Medical Association  
Hong Kong Elderly Welfare Foundation  
Speaker: Dr CHU Wing-hong  
Dr John Tai-hung WONG  
Dr Cecilia Willy CHEON / Dr Toby CHAN | HKMA CME Dept.  
2527 8452  
2 CME Points |

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### Medical Conscience

The Medical Conscience is formed by a group of medical professionals with common beliefs in the virtues as professionals and values as citizens of Hong Kong. We uphold the values of peace, liberty, and justice.

A group of us met on 20 December 2019 and resolved to establish an organisation. We named ourselves Medical Conscience the very same day and formed our first Council. We received our Certification of Registration on 8 January 2020. As of today, we have over 300 Members.

As doctors and medical professionals, we strongly insist that beliefs and convictions, whether religious, political or otherwise shall in no way come between our patients and us in harm’s way. We must treat every single patient equally and wholeheartedly to the furthest of our capabilities.

We take it upon ourselves as our moral duties to advise society on medical and health care issues, including crisis and policies. We shall provide volunteer services if we consider it necessary.

We shall do all we can to provide mentoring to students of our professions in order to nurture virtuous generations of our peers.

In November, we successfully became a Member of the Federation of the Medical Societies of Hong Kong. This, to me, is a landmark of our acceptance into the wider Medical community.

Dr David Lam  
Chairman, Medical Conscience
Answers to Dermatology Quiz

Answers:

1. Chilblains (Pernio), also known as “蘿蔔仔” in Cantonese. The differential diagnoses should include frostbite (凍瘡), erythromelalgia, Raynaud’s phenomenon, acrocyanosis and thrombo-ischaemic diseases.

2. Majority of chilblains are idiopathic due to an abnormal vascular response to cold exposure (non-freezing temperature), especially in humid conditions, causing itching or painful erythematous, swelling and blistering on hands and feet. Most frequently it occurs in young and middle-aged women and children. In chronic chilblains, it may be secondary to systemic diseases such as myeloproliferative diseases, paraproteinaemia, antiphospholipid syndrome, Raynaud’s disease, lupus erythematosus, etc.

3. Chilblains usually resolve spontaneously within one to three weeks when the weather returns warmer. Preventive measures for recurrence include limiting exposure to cold and dressing warmly.

4. Chilblains-like lesions are now known as one of the cutaneous signs of SARS-CoV-2 infection (also known as “COVID toes”). One should therefore have a high index of suspicion of this disease if the patients also have anosmia /ageusia, fever or flu-like symptoms and signs.

Dr Lai-yin CHONG
MBBS(HK), FRCP(Lond, Edin, Glasg), FHKCP, FHKAM(Med)
Specialist in Dermatology & Venereology
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