Abstracts for Poster Presentation: Commissioned Research on COVID-19

COVID-1-32
Molecular Epidemiological Study of COVID-19 Cases in Hong Kong

Dr Haogao GU[1], Dr Daniel CHU[1], Prof Malik PEIRIS[1], Dr Vijaykrishna DHANASEKARAN[1], Prof Leo POON[1]
[1]School of Public Health, The University of Hong Kong, Hong Kong SAR, China

Introduction and Project Objectives: Hong Kong uses an elimination strategy with intermittent use of public health and social measures and stringent travel regulations to control SARS-CoV-2 transmission. So far, there were 4 waves of COVID-19 in this city. We conducted a near real-time molecular epidemiology study to understand the transmission dynamics of SARS-CoV-2 in our community in this period.

Methods: SARS-CoV-2 genomes in respiratory samples collected from local and imported COVID-19 cases were deduced using Illumina sequencing technology. About 20% of Hong Kong cases were studied. The deduced genomes were analysed by in-house analytical pipelines.

Results: We revealed the effects of fluctuating control measures on the evolution and epidemiology of SARS-CoV-2 lineages in Hong Kong. Our analyses on imported cases identified a vast number of SARS-CoV-2 variants, such as VOCs Alpha and Delta. Our results on these imported cases justify for the use of stringent follow-up control measures on inbound passengers and crew to prevent introduction of new SARS-CoV-2 variants from other regions in the studied period. Despite numerous importations, only three introductions were responsible for the majority of locally-acquired cases, two of which circulated cryptically for weeks while less stringent measures were in place. We also studied several major COVID-19 transmission events in different settings and identified the first reverse zoonotic transmission, reinfection case and in-flight transmission. In addition, our sequencing results also helped to reveal genetic relationships between COVID-19 cases, thereby providing evidences to epidemiologically link or delink cases in outbreak investigations.

Conclusion: Our molecular epidemiological investigations on COVID-19 cases can inform epidemiological investigations. Our study helps to understand the transmission dynamic of SARS-CoV-2 in a densely populated city and identifies risk factors that facilitate SARS-CoV-2 transmission. Such analyses also provide critical information to relevant stakeholders for developing evidence-based COVID-19 control policy and practice.

Project No.: COVID190205

COVID-2-37
Effectiveness of Remdesivir and in Combination with Dexamethasone among Hospitalized COVID-19 Patients in Hong Kong

Dr Carlos WONG[1], Ms Kristy LAU[2], Mr Ivan AU[2], Ms X XIONG[2], Dr Eric LAU[3], Prof Benjamin COWLING[3]
[1]Department of Family Medicine and Primary Care, Department of Family Medicine and Primary Care, The University of Hong Kong, Hong Kong SAR, China, [2]Department of Pharmacology and Pharmacy, The University of Hong Kong, Hong Kong SAR, China, [3]WHO Collaborating Centre for Infectious Disease Epidemiology and Control, School of Public Health, The University of Hong Kong, Hong Kong SAR, China

Introduction and Project Objectives: Evidence on the significant benefits of remdesivir and its combination with dexamethasone on mild-to-moderate COVID-19 patients is insufficient. Our research aims to investigate the disease progression, various clinical outcomes, changes in viral load, and duration of hospital stay associated with early remdesivir treatment as well as introducing remdesivir on top of dexamethasone among COVID-19 patients.

Methods: A territory-wide retrospective cohort of >10400 patients hospitalized with confirmed COVID-19 infection from 21st January 2020 to 31st January 2021 in Hong Kong SAR, China was analyzed. Early remdesivir treatment was evaluated using 352 patients who had initiated remdesivir within the first two days of admission, and 1,347 patients without early remdesivir treatment as controls at a 1:4 matching ratio. In addition, 466 patients with remdesivir use before or co-initiated with dexamethasone and 1078 patients who had received remdesivir after dexamethasone or only received dexamethasone treatment were selected to examine optimal timing of remdesivir initiation on top of dexamethasone use. Propensity-score matching or weighting were used to minimize residual confounding, and balance baseline covariates between exposure and non-exposure groups. Cox regression models estimated hazard ratios (HR) of event outcomes, while linear regression models examined the treatment effects on hospital length of stay (LOS).

Results: During a 14-day median follow-up, early remdesivir treatment was associated with significantly shorter time to clinical improvement (HR=1.14, 95%CI 1.01-1.29, p=0.038) and positive IgG antibody (HR=1.50, 95%CI 1.31- 1.70, p<0.001), lower risk of in-hospital death (HR=0.58, 95%CI 0.34-0.99, p=0.045), significant shorter hospital LOS among survivor (-2.56 days, 95%CI -4.86 to -0.26, p=0.029), in addition to achieving low viral load quicker (HR=1.51, 95%CI 1.24-1.83, p<0.001). Among hospitalized patients receiving dexamethasone within 13-day median follow-up, initiation of remdesivir prior to or co-initiated with dexamethasone had shorter time to clinical improvement (HR=1.23, 95%CI 1.02-1.49, p=0.032) and positive IgG antibody (HR=1.22, 95%CI 1.02-1.46, p=0.029), lower risk of

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in-hospital death (HR=0.59, 95%CI 0.36-0.98, p=0.042), as well as shorter hospital LOS by 2.65 days among survivors when compared with those receiving remdesivir after dexamethasone or non-remdesivir users.

Conclusion: For hospitalized COVID-19 patients with the moderate disease but not requiring oxygen therapy on admission, early remdesivir treatment could be a potentially effective choice. Among hospitalized patients receiving dexamethasone, early or co-initiation of remdesivir with dexamethasone demonstrated significant clinical benefits, and was associated with shorter time to clinical improvement and positive IgG antibody, lower risk of in-hospital death, in addition to significantly shorter length of hospital stay.

Project No.: COVID190210

COVID-3-39
Stability of SARS-CoV-2

Dr Alex CHIN[1], Prof Leo POON[1]
[1]*School of Public Health, The University of Hong Kong, Hong Kong SAR , China*

Introduction and Project Objectives: SARS-CoV-2 (formerly named as 2019-nCoV) is a novel human coronavirus and is the causative agent for COVID-19 pandemic. At the early stage of the virus emergence, little is known about the properties of this novel virus. Therefore, the objectives of this project are to understand the viral stability in different environmental conditions and on surfaces of different materials. In addition, we aim to determine the virus stability on several specially designed surfaces and to validate the methods to decontaminate the contaminated surfaces.

Methods: SARS-CoV-2 cultured from VeroE6 cells was used to determine the virus stability in buffer at different conditions and on surfaces of different materials. In addition, the effectiveness of different disinfectants against SARS-CoV-2 was tested. The infectivity of the virus was determined by TCID50 assay in BSL-3 laboratory.

Results: We demonstrated that the stability of SARS-CoV-2 decreases at higher temperature. A 30 min incubation at 56°C or a 5 min incubation at 70°C is sufficient to reduce the infectivity of the virus by at least 99.9%, while the virus remains extremely stable at 4°C up to 14 days. On the other hand, the virus remains stable in a wide range of pH. We also demonstrated that the virus are more stable on smooth surfaces, such as stainless steel, plastics and glass, than on rough surfaces, such as tissue paper and clothes. Strikingly, the infectious virus remains detectable on the surface of a surgical mask even after 7 days incubation at room temperature. With the findings above, we further demonstrated the feasibility of disinfecting the masks with heat treatment, enabling reuse of the masks in case of extreme shortage in supply. In addition, we demonstrated several metal alloys and surface coatings containing copper or copper compounds that are effective in reducing the infectivity of the virus on their surfaces. These materials could be applied on the common touch surfaces to reduce the risk of fomite transmission of the virus. Furthermore, we demonstrated that common disinfectants including household bleach, ethanol, chlorohexidine, benzalkonium chloride, etc at their working concentrations are effective in inactivating the virus within 5 min.

Conclusion: With the findings above, we gain more understandings on the properties of this novel respiratory virus and the effective ways in inactivating it. These could contribute to the determination of the control measures against the disease.

Project No.: COVID190116

COVID-4-63
A Novel Linker-Immunodominant Site (LIS) Vaccine Targeting the SARS-Cov-2 Spike Protein Protects against Severe COVID-19 In Syrian Hamsters

Dr Bao-zhong ZHANG[1], Dr Xiaolei WANG[1], Prof Jiandong HUANG[1]
[1]*The University of Hong Kong, Hong Kong SAR, China*

Introduction: The Coronavirus Disease 2019 (COVID-19) pandemic is unlikely to abate until sufficient herd immunity is built up by either natural infection or vaccination. We previously identified ten linear immunodominant sites on the SARS-CoV-2 spike protein of which four are located within the RBD.

Methods: We designed two linker-immunodominant site (LIS) vaccine candidates which are composed of four immunodominant sites within the RBD (RBD-ID) or all the 10 immunodominant sites within the whole spike (S-ID). They were administered by subcutaneous injection and were tested for immunogenicity and in vivo protective efficacy in a hamster model for COVID-19.

Results: We showed that the S-ID vaccine induced significantly better neutralizing antibody response than RBD-ID and alum control. As expected, hamsters vaccinated by S-ID had significantly less body weight loss, lung viral load, and histopathological changes of pneumonia.

Conclusion: The S-ID has the potential to be an effective vaccine for protection against COVID-19.

Project No.: COVID190117

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COVID-5-66

One Health Investigation of Exposure to SARS-2-Related Coronaviruses in Trafficked Sunda Pangolins (Manis Javanica)

Brian M. WORTHINGTON[1,2,3], Portia WONG[4], Kishoree K. KUMAREE[1,2,3], Tracey PRIGGE[4], Kar Hon NG[1], Paolo MARTELLI[5], Shelby MCILROY[4], Yunshi LIAO[1], Marcus H.-H. SHUM[1], Elliott F. MIOT[1,6,7], William Y.-M. CHEUNG[1,2,3], Helen C. NASH[8], WIRDATETI[9], Gono SEMIADI[9], Caroline DINGLE[4], Oliver G. PYBUS[10,11], Edward C. HOLMES[12,13], Gabriel M. LEUNG[1,13], Yi GUAN[1,2,3,13], Huachen ZHU[1,2,3,13], Timothy C. BONEBRAKE[4], Dr Tsan Yuk LAM[1,2,3,6,13]

[1]State Key Laboratory of Emerging Infectious Diseases, School of Public Health, The University of Hong Kong, Hong Kong SAR, China, [2]Guangdong-Hongkong Joint Laboratory of Emerging Infectious Diseases, Joint Institute of Virology (Shantou University/The University of Hong Kong), China, [3]EKIH (Gewuzhikang) Pathogen Research Institute, China, [4]Division of Ecology & Biodiversity, School of Biological Sciences, The University of Hong Kong, Hong Kong SAR, China, [5]Ocean Park Corporation, Hong Kong SAR, China, [6]Centre for Immunology & Infection Limited, Hong Kong SAR, China, [7]HKU-Pasteur Research Pole,The University of Hong Kong, Hong Kong SAR, China, [8]Department of Biological Sciences, National University of Singapore, Singapore, [9]Research Center for Biology, Indonesian Institute of Sciences (LIPI), Indonesia, [10]Department of Zoology, University of Oxford, United Kingdom, [11]Department of Pathobiology and Population Sciences, The Royal Veterinary College, United Kingdom, [12]Marie Bashir Institute for Infectious Diseases and Biosecurity, Charles Perkins Centre, School of Biological Sciences and Sydney Medical School, University of Sydney, Australia, [13]Laboratory of Data Discovery for Health Limited, Hong Kong SAR, China

Introduction and Project Objectives: Early in the COVID-19 pandemic, Sunda pangolins (Manis javanica) involved in illegal wildlife trade in mainland China were identified as hosts of SARS-2-related coronaviruses (SARS2r-CoVs).

Methods: Using a combination of virological and wildlife forensics tools, we investigated 89 Sunda pangolin carcasses seized by Hong Kong authorities during anti-smuggling operations in the territory conducted in 2013 (n=1) and 2018 (n=88). Swabs, organ tissues, and blood or other body fluids were collected from each animal during post-mortem examination. We aimed to examine the virome of these animals, to determine any previous exposure to SARS2r-CoVs, and to approximate the origin of these animals from wild populations throughout Southeast Asia.

Results: Several pangolin individuals were found to be seropositive or borderline seropositive using a double-antigen bridging assay to detect anti-SARS-CoV-2 spike antibodies. SARS-CoV-2 specific RT-qPCR and conventional RT-PCR with universal CoV primers was performed on >500 swab and tissue samples, though none of the samples tested positive. Putative seropositive individuals were determined to have originated from populations in Borneo, Java, and Sumatra, indicating that natural exposure to SARS2r-CoVs may be common due to the shared ecology of pangolins, bats, and potentially other host species, or this may indicate infection acquired during the illegal trafficking of these animals.

Conclusion: Our ongoing work aims to characterize the virome of these animals and to further investigate their origins. As wildlife trade has become a major focus of efforts to prevent the future emergence of novel pathogens, One Health approaches incorporating the expertise of multiple and diverse stakeholders are needed to investigate the origins and cross-species transmission of SARS2r-CoVs.

Project No.: COVID190223

COVID-6-67

Cytokine Profile in COVID-19 Patients

Prof Rita NG[1], Prof. Lowell LING[2], Prof. CK WONG[3], Prof. Grace LUI4, Prof David HUI[4], Prof Zigui CHEN[1], Dr Wai Tat WONG[2], Dr Eugene TSO[5], Dr Kitty FUNG[6], Dr Veronica CHAN[5], Ms Apple YEUNG[1], Prof Paul CHAN[1]

[1]Department of Microbiology, The Chinese University of Hong Kong, Hong Kong SAR, China, [2]Department of Anaethesia and Intensive Care, The Chinese University of Hong Kong, Hong Kong SAR, China, [3]Department of Chemical Pathology, The Chinese University of Hong Kong, Hong Kong SAR, China, [4]Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong SAR, China, [5]Department of Medicine and Geriatrics, United Christian Hospital, Hong Kong SAR, China, [6]Department of Pathology, United Christian Hospital, Hong Kong SAR, China

Introduction and Project Objectives: The pathogenesis of coronavirus disease 2019 (COVID-19) is yet to be fully understood. Cytokine storm that played a critical role in other severe viral infections could be an important determining factor in SARS-CoV-2 infection as well. However, studies on longitudinal cytokine profiles in patients across the whole severity spectrum of COVID-19 are lacking.

Methods: We conducted a prospective observational study on adult COVID-19 patients admitted to two Hong Kong public hospitals. All cases were laboratory confirmed infection and were classified into mild (without pneumonia), moderate (pneumonia) or severe/critical (oxygen support) according to their clinical symptoms and severity. Profiling of 40 cytokines was performed on blood samples taken during early phase (within 7 days of symptom onset) and late phase (8 to 12 days of symptom onset). The difference in early and late cytokine profiles among patient groups with different disease severity were delineated, and associations between cytokines and clinical endpoints in critically ill patients were examined.

Results: A total of 40 adult patients (mild = 8, moderate = 15, severe/critical = 17) hospitalized with COVID-19 were included

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in this study. We found 23 cytokines correlated with disease severity, as proinflammatory Th1-related cytokines (IL-18, IP-10, MIG and IL-10) and ARDS-associated cytokines (IL-6, MCP-1, IL-1RA and IL-8) were progressively elevated with increasing disease severity. Furthermore, 11 cytokines were consistently different in both early and late phases, including 7 (GRO-α, IL-1RA, IL-6, IL-8, IL-10, IP-10 and MIG) that increased and 4 (FGF-2, IL-5, MDC and MIP-1α) that decreased from mild to severe/critical patients. IP-10, followed by IL-8 and IL-6, were the best performing early biomarkers to predict disease severity. Among critically ill patients, MCP-1 predicted the duration of mechanical ventilation, highest norepinephrine dose administered and length of intensive care.

Conclusion: Cytokine profile varied across different severity of COVID-19 over time. Th1 response and ARDS-associated cytokines were elevated in patients with increasing severity of COVID-19. IP-10 was the best performing early biomarker to predict severity. MCP-1 level at ICU admission was related to days on mechanical ventilation, highest dose of vasopressor and length of ICU stay.

Project No.: COVID190107

COVID-7-68
Hidden SARS-CoV-2 Infection in Hong Kong before Massive Vaccination

Dr Siaw BOON[1], Prof Martin WONG[2], Dr Danny LEUNG[3], Prof Zigui CHEN[1], Prof Christopher LAI[1], Prof Rita NG[1], Ms Wendy HO[1], Dr Kitty FUNG[4], Dr Junjie HUANG[2], Dr Barry WONG[4], Prof Paul CHAN[1]

[1]Department of Microbiology, The Chinese University of Hong Kong, Hong Kong SAR, China, [2]School of Public Health and Primary Care, The Chinese University of Hong Kong, Hong Kong SAR, China, [3]Department of Chemical Pathology,The Chinese University of Hong Kong, Hong Kong SAR, China, [4]Department of Pathology, United Christian Hospital, Hong Kong SAR, China

Introduction and Project Objectives: Asymptomatic and mild SARS-CoV-2 infections are common. Delineating the prevalence of hidden (unrecognized) infection is essential to inform the extent of outbreak and provide a basis to evaluate mitigation strategies.

Methods: We conducted a prospective cross-sectional study from April 2020 to April 2021, following each major wave of COVID-19. Adults in the general population were recruited to estimate the prevalence of unidentified infection in Hong Kong. Evidence of SARS-CoV-2 infection was based on SARS-CoV-2 IgG detection by ELISA based on spike protein, and followed by confirmation with an electrochemiluminescence immunoassay based on the receptor binding domain (RBD) of spike protein.

Results: A total of 4,198 citizens aged ≥18 years who had not been diagnosed as having COVID-19 were recruited, including 903 (22%), 1,046 (25%) and 2,249 (53%) subjects following the three major waves, respectively. The proportion of participants aged 18-39, 40-59 and ≥60 years was 32%, 39% and 29%; with 60% female. 58% stayed in Hong Kong all along since November 2019; whilst 50% had received SARS-CoV-2 RNA tests with negative results. Only 4% reported ever contact with confirmed cases, and 5% had been isolated or quarantined. Up to 67% did not recall of any illnesses; whilst 18%, 5% and 9% had experienced respiratory symptoms, gastrointestinal symptoms, or both, respectively, prior to testing. As a result, six subjects were confirmed to be positive for anti-SARS-CoV-2 IgG. All except one subject had been tested one or more times for using deep-throat saliva, but were all negative.

Our findings estimated an adjusted prevalence of unidentified infection of 0.15% (95% C.I. 0.06% to 0.32%).

Extrapolating these findings to the whole Hong Kong, there were less than 1.9 unidentified infections for every recorded confirmed case. The overall prevalence of SARS-CoV-2 infection in Hong Kong before the massive rollout of vaccination was less than 0.45%.

Conclusion: The prevalence of unidentified SARS-CoV-2 infection was very low, implying the success of the pandemic mitigation by stringent isolation and quarantine policies even without complete city lockdown. More than 99.5% of the general population remain naïve to SARS-CoV-2, highlighting the urgent need to achieve a high vaccine coverage.

Most of the unidentified cases had received PCR test using deep-throat saliva, but were all negative. While they might not be tested at the right time, the possibility of false-negative should not be neglected; since deep-throat saliva has been shown to carry a false-positive rate of up to 31%.

Project No.: COVID190108

COVID-8-95
Effect of Cigarette Smoke on Airway Epithelium in the Pathogenesis of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection

Dr Rui CHEN[1], Dr Kenrie Pui-Yan HUI[2,3], Dr Yingmin LIANG[1], Mr Ka-Chun NG[2], Mr Man-Chun CHEUNG[2], Mr Pak-Hin CHU[1], Prof John Malcolm NICHOLLS[4], Prof Mary Sau-Man IP[1], Dr Michael Chi-Wai CHAN[2,3], Dr Judith Choi-Wo MAK[1,5]

[1]Department of Medicine, The University of Hong Kong, Hong Kong SAR, China, [2]School of Public Health, The University of Hong Kong, Hong Kong SAR, China, [3]Centre for Immunology and Infection, The University of Hong Kong, Hong Kong SAR, China, [4]Department of Pathology, The University of Hong Kong, Hong Kong SAR, China, [5]Department of Pharmacology & Pharmacy, The University of Hong Kong, Hong Kong SAR, China

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Introduction and Project Objectives: The coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become a worldwide pandemic with over 219 million cases and over 4.5 million deaths1. It was reported that smoking-related chronic obstructive pulmonary disease (COPD) might be a crucial risk factor for COVID-19 patients to develop severe condition2,3. Cigarette smoking was also associated with the negative progression and adverse effect of COVID-194. Patients with smoking history showed more severe symptoms of COVID-19 in comparison to the non-smokers4. However, the role of CS-induced airway epithelial cell injury, which acts as the first barrier in the pathogenesis of SARS-CoV-2 infection, remains poorly understood.

Methods: Primary human airway epithelial cells were differentiated under air-liquid interface culture. Well-differentiated human airway epithelial cells were then exposed to cigarette smoke medium (CSM) before infection with SARS-CoV-2. The infection susceptibility, morphology, and the expression of proteins related to immune response, ciliated and goblet cell markers were evaluated.

Results: Despite no change in the replication of SARS-CoV-2 after medium (as control) or CSM exposure, an aggravated immune response was observed, with the upregulation of interleukin (IL)-6, IL-8, tumour necrosis factor (TNF)-α and interferon (IFN)-stimulated gene 15. In addition, CSM worsened SARS-CoV-2-induced airway epithelial cell injury, resulting in severe motile ciliary disorder and disruption of epithelial tight/adherens junctions.

Conclusion: The current findings suggest that smoking may lead to greater immune response and cell damage in SARS-CoV-2-infected airway epithelium. This study provides us better understanding of the pathogenesis of SARS-CoV-2 infection in smokers.

Acknowledgement: This study was supported by Commissioned Research on COVID-19 of the Health and Medical Research Fund (COVID190201), Hong Kong SAR, China.

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Project No.: COVID190201

COVID-9-99

Assessing Novel Coronavirus Antibodies for Specificity and Function during Clinical Infection and Community Asymptomatic Cases

Dr Niloufar KAVIAN[1], Miss Asmaa HACHIM[1], Miss Carolyn COHEN[1], Prof Malik PEIRIS[1], Prof Leo POON[1], Dr Sophie VALKENBURG[1]
[1]*HKU-Pasteur Research Pole, School of Public Health, The University of Hong Kong, Hong Kong SAR, China*

Introduction and Project Objectives: Several serology tests for diagnoses of SARS-CoV-2 infection are currently in use which primarily assess Spike (S), and on occasion Nucleocapsid (N) antibodies. Most vaccines in use are Spike focused and inactivated whole virion vaccines are in limited use. Serology to detect infection is dependent on the retention of specific responses which have waning over time, contain antigenic changes, and specificity is dependent on low cross-reactivity with existing antibody responses.

Methods: We have defined the antibody landscape of the SARS-CoV-2 response after infection. We evaluated the anti-SARS-CoV-2 antibody profiles to 15 antigens by cloning and expressing open reading frames (ORFs) in mammalian cells and screened antibody responses from COVID-19 patients using the Luciferase Immunoprecipitation System (LIPS). We assessed responses in patient plasma and a large set of pre-pandemic samples to define cut-offs, and calculated assay sensitivity and specificity.

Results: The LIPS technique allowed us to detect antibody responses in COVID-19 patients to 11 of the 15 SARS-CoV-2 antigens, identifying novel immunogenic targets. We found that antigens ORF3b and ORF8 allow detection of antibody early in infection in a specific manner and revealed the immunodominance of the N antigen in COVID-19 patients. Antibodies that target non surface proteins can mediate Fc receptor functions, we therefore assessed ORF8-specific antibodies in patients for FcR binding to mediate cellular cytotoxicity and phagocytosis function.

Conclusion: These studies provide novel insights for SARS-CoV-2 replication, immunogenicity to identify key targets for specific diagnostics for breakthrough infections.

Project No.: COVID190115

COVID-10-110

Nowcasting COVID-19 Transmission Dynamics, Severity, and the Effectiveness of Control Measures

Prof Benjamin COWLING[1], Dr Peng WU[1], Prof Joseph Tsz Kei WU[1]
[1]*WHO Collaborating Centre for Infectious Disease Epidemiology and Control, School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China*

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Introduction and Project Objectives: The disease Coronavirus Disease (COVID-19), caused by the virus Serious Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), was first recognised in December 2019 in a cluster of cases of atypical pneumonia linked to a wet market in Wuhan. Since then, infections have spread regionally across and outside China to the rest of the world, with over 146 million confirmed cases reported by 26 April 2021. The objectives of this study are: (1) To estimate the reproductive number in real-time throughout the epidemic, using a variety of data sources; (2) To estimate the "hospital fatality risk" and the "symptomatic case fatality risk" in real-time throughout the epidemic, using a variety of data sources, and (3) To estimate the impact of control measures on the COVID-19 epidemic such as isolation, quarantine, school closures, travel restrictions, and other social distancing measures and behavioural changes.

Methods: We use data from a variety of data sources, including: (1) Detailed reports on COVID-19 cases from Centre for Health Protection; (2) Detailed clinical information on COVID-19 patients from Hospital Authority; (3) Aggregate rates of hospitalisation rates for a variety of conditions to be obtained in December 2020, and (4) Community prevalence of illness over time from separately-funded surveys. Statistical and mathematical models will be used to estimate the incidence of infections, severity of infections, and the impact of control measures.

Results: Throughout the pandemic, we have been estimating the daily reproductive number in real time via our dashboard (https://covid19.sph.hku.hk), and found that the behaviour of the reproductive number was closely linked with the implementation of social distancing measures and border controls. Based on serological samples during March 2020, we estimated an infection rate of 0.76% (0.03%, 1.49%). Using the infection rate, we estimated the infection fatality risk up until the end of March 2020 to be 0.35% (0.17%, 2.14%). Finally, we found a substantial reduction in the reproductive number and number of cases of COVID-19 in Hong Kong related to the implementation of various social distancing measures, working from home and border closures.

Conclusion: As the COVID-19 pandemic continues in Hong Kong and the rest of the world this study provides important information on its epidemiology and control locally.

Project No.: COVID190118

COVID-11-112

Longitudinal Study of COVID-19 Seroprevalence in Health Care Workers in Comparison to the General Community

Prof Benjamin COWLING[1], Ms Wey Wen LIM[1], Prof J. S. Malik PEIRIS[1]

[1]*School of Public Health, The University of Hong Kong, Hong Kong SAR, China*

Introduction and Project Objectives: Healthcare workers (HCWs) are at increased risk of emerging infectious diseases due to the potential for occupational exposures, particularly during the early phase of an outbreak or pandemic. As HCWs are essential to a fully functional healthcare system, the surveillance of emerging infectious diseases among HCWs is important to protect both HCWs and patients who are under their care.

Methods: We collected blood samples at 6-month intervals from healthcare workers in Hong Kong to estimate the seroprevalence of COVID-19 in healthcare workers (HCWs), a group that has elevated occupational exposure to COVID-19. When vaccines were made available in Hong Kong, we extended the study to collect post-vaccination blood samples from volunteer HCWs to assess the immunogenicity of COVID-19 vaccines. We tested the blood samples for antibodies to SARS-CoV-2 using an ELISA to detect antibodies that bind to the receptor binding domain of the spike protein, testing ELISA-positive samples for neutralising antibodies with a surrogate virus neutralisation (sVNT) assay, and then a plaque reduction neutralisation test (PRNT) with live SARS-CoV-2 virus.

Results: From June 18, 2020, to July 20, 2021, 1,729 HCWs were screened and 1,472 HCWs consented to participate in this study. Each of them provided at least one blood sample during the first 3 rounds of this study or after receiving the first or second dose of COVID-19 vaccine. Occupational exposure to COVID-19 patients in our cohort is high in general, but we only identified three seropositive samples and our estimate of the cumulative incidence of infection was 0.4% (95% CI = 0.1%, 1.1%). Antibody responses to BNT162b2 (BioNTech) were substantially greater than antibody responses to CoronaVac (Sinovac) at one month after the second dose.

Conclusion: By measuring levels of binding and neutralising antibodies against the SARS-CoV-2 virus, the seroprevalence of COVID-19 is estimated to be low in HCWs in Hong Kong despite high levels of occupational exposure. A simple comparison of mean neutralising levels of post-vaccination neutralising antibody titers in HCWs that were fully vaccinated in our cohort with published immunogenicity and efficacy data of available COVID-19 vaccines indicates that the vaccine efficacy of both the mRNA and inactivated vaccines in Hong Kong should be relatively high, particularly for the mRNA vaccine. Continuous follow-up of this cohort in the future will provide additional information on waning in antibody titers over time.

Project No.: COVID190119

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COVID-12-117

A Novel CRISPR-based Point-of-Care Test for Rapid Detection of SARS-CoV-2 Infection

Dr Shui-Shan LEE[1,2], Dr Grace Chung-Yan LUI[1,3], Dr Ross Ka-Kit LEUNG[1]

[1]Stanley Ho Centre for Emerging Infectious Diseases, The Chinese University of Hong Kong, Hong Kong SAR, China, [2]JC School of Public Health and Primary Care, The Chinese University of Hong Kong, Hong Kong SAR, China, [3]Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong SAR, China

Introduction and Project Objectives: Rapid and reliable point-of-care (POC) testing for SARS-CoV-2 is an important component of the control strategy against the COVID-19 epidemic. Field application of conventional RT-PCR technology in rapid testing is often limited by the need of transporting samples to designated laboratories, installation of special analyzer and the laborious operations. Antibody-based POC testing is fast but detection is deferred because of the delay in host response following virus replication. Sensitivity is a concern for antigen testing and the low viral load setting in asymptomatic or mild cases. CRISPR-Cas system is a promising means for POC testing for viral infection, by virtues of its rapidity, affordability and reliability. The aim of this project is to study the feasibility of implementing a novel POC test for rapid detection of SARS-CoV-2, with the objectives of (a) developing a novel CRISPR-based lateral flow assay (LFA); (b) evaluating its performance in the detection of SARS-CoV-2; and (c) assessing the practicability of its use in healthcare setting.

Methods: Representative sequences of the coronavirus family were collected from literature and public databases. Short sequences of around 200bp emulating SARS-CoV-2 gene targets and the corresponding guide RNAs were designed. A LFA-CRISPR-based detection kit was designed and testing protocol was developed. The performance of the new system was evaluated by conducting mock virus testing in different institutions and environment.

Results: The synthesis of SARS-CoV-2 gene target and its guidance RNA has been successfully completed. A novel lateral flow dipstick based on fluorescence quantitative PCR by CRISPR-Cas technologies was established. A 2-step CRISPR-based POC test kit was fabricated and evaluated. Mock virus testing was performed in multiple facilities in Mainland China and Hong Kong. There were a total of 171 true positives, 5 false positives, 171 true negatives and 3 false negatives, giving a sensitivity of 98% and specificity of 97%.

Conclusion: The novel detection kit is potentially useful for enhancing the efficiency of SARS-CoV-2 diagnosis, complementing strategy for controlling the spread of the epidemic. The high specificity and sensitivity, the anticipated low cost for mass production, and the simple operation without requiring complex instruments are the advantages of the system. The practicability and impacts of LFA-CRISPR-based tests for SARS-CoV-2 infection in healthcare settings would be assessed in near future.

Project No.: COVID190102

COVID-13-123

Public Compliance with Disease Prevention and Public Health Measures to Control COVID-19

Prof Elsie YAN[1], Prof Wing Leung, Daniel LAI[2], Dr Wan Ping, Vincent LEE[1]

[1]The Hong Kong Polytechnic University, Hong Kong SAR, China, [2]Hong Kong Baptist University, Hong Kong SAR, China

Introduction and Project Objectives: Disease prevention measures (DPM) such as wearing face masks, social distancing, and vaccination are effective in controlling the spread of COVID-19. This study applied the Health Belief Model to identify facilitators of and barriers to DPM adoption.

Methods: A two-wave longitudinal telephone survey was conducted with 1225 and 1003 participants successfully interviewed in December 2020 and June 2021. Descriptive and logistic regression analyses were conducted to examine patterns of and factors associated with DPM adoption.

Results: Baseline adoption of DPM was high: 94.4% wore face masks in public areas; 88.4% avoided touching their eyes, nose, and mouth; 82.1% performed hand hygiene; 81.5% used alcohol-based hand rub; 74.6% practiced social distancing; and 39.7% tested for COVID-19 on a voluntary basis. Perceived benefits, perceived barriers, self-efficacy, encouragement from significant others, perceived acceptability, and COVID-19 related disruptions in daily life were associated with individuals' adoption of DPM at baseline. At 6-month follow-up, 48.8% demonstrated sustained or increased adoption of DPM. Sustained or increased adoption was associated with greater perceived benefits and obstacles of DPM. At baseline, 42% of the participants indicated intention to vaccinate, 31.5% showed vaccine hesitancy and 26.5% reported refusal. Intention to vaccinate at baseline was associated with male gender, older age, being employed, exposure to previous pandemic (such as SARS and swine flu), high perceived susceptibility, poor knowledge about COVID-19, lack of concerns about vaccine safety, acceptance of government prevention measures, encouragement from significant others, and high self-efficacy. At 6-month follow-up, 23.4% of the participants indicated that they received vaccination. Vaccination uptake at 6-month follow-up was not associated with intention to vaccinate at baseline. Major reasons cited for vaccination uptake were "required by work" (12.8%), "safeguard personal health (15.8%), "safeguard family's health" (15%), and "respond to government appeal" (9.9%). Older age, baseline exposure to COVID-19,

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baseline perceived susceptibility, baseline acceptance of government prevention measures, having family and friends who had been vaccinated were associated with actual vaccination up-take.

Conclusion: Based on these findings, we recommend promoting the benefits of DPM thereby encouraging citizens' continual DPM adoption. In order to encourage fellow citizens to get vaccinated, efforts should be made to promote the benefits of vaccination, especially in terms of safeguarding individuals' and their families' health. Amicable arrangements should be made to encourage individuals to accompany needed families and friends to vaccinate.

Project No.: COVID190216

COVID-14-132
SARS-CoV-2 Replication and Immune Response Induced in the Respiratory Epithelial Cells of Paediatric and Adult

Dr Renee WY CHAN[1,2,3,4], Dr Kin Pong TAO[1,2,3,4], Dr Joseph GS TSUN[1,2,3,4], Dr Kenrie PY HUI[5], Prof Gary WK WONG[1], Dr Michael CW CHAN[5], Prof David SC HUI[6], Prof Paul K S CHAN[7], Dr Kate C C CHAN[1], Prof Hugh Simon LAM[1], Prof Albert M LI[1,2]

[1]Department of Paediatrics, The Chinese University of Hong Kong, Hong Kong SAR, China, [2]Hong Kong - Hub of Paediatric Excellence, The Chinese University of Hong Kong, Hong Kong SAR, China, [3]Laboratory for Paediatric Respiratory Research, Li Ka Shing Institute of Health Sciences, The Chinese University of Hong Kong, Hong Kong SAR, China, [4]CUHK-UMCU Joint Research Laboratory of Respiratory Virus & Immunobiology, The Chinese University of Hong Kong, Hong Kong SAR, China, [5]School of Public Health, The University of Hong Kong, Hong Kong SAR, China, [6]Department of Medicine & Therapeutics, The Chinese University of Hong Kong, Hong Kong SAR, China, [7]Department of Microbiology, The Chinese University of Hong Kong, Hong Kong SAR, China

Introduction: SARS-CoV-2 infection ranges from asymptomatic infection to fatality. The majority of laboratory-confirmed cases are adults, while children cases comprise a small percentage with a milder clinical course. Thus, a direct comparison of the susceptibility and immune response between adults and children allows a better understanding of their clinical outcomes and their role in disease transmission.

Objectives: To compare the virus replication kinetics in the respiratory epithelial cells and the immune response in paediatric and adult subjects' nasal epithelial lining fluid hypothesized that there are intrinsic differences between the respiratory cells originated from children and adults, and therefore their susceptibility to SARS-CoV-2 infection. Moreover, the mucosal antibody response in the COVID-19 patients may have a role in the milder disease outcome in children compared with adults.

Method: Primary human nasopharyngeal epithelial cells (dHNPEC) were obtained from healthy children and adults for cell isolation and air-liquid interface differentiation. These in vitro cell cultures were subjected to SARS-CoV-2 virus infection. The viral replication kinetics between paediatric and adult cells were compared at 1, 24, 48, 72 and 96 hours post-infection. In addition, the mucosal antibody response specific to SARS-CoV-2 Spike protein in paediatric and adult COVID-19 patients was assessed by collecting their nasal epithelial lining fluid (NELF) longitudinally from disease onset every week until the 4th week. The SARS-CoV-2 specific IgA level and the neutralization potency were measured by ELISA and surrogate ACE2 - SARS-CoV-2 receptor binding domain assay, respectively.

Results: Effective replication of the SARS-CoV-2 was observed in the dHNPEC. Significant increase in viral titer in paediatric dHNPEC between 1-to-72 hpi (median log10TCID50/ml = 2.71 vs 6.96, p = 0.0394) and in adult's dHNPEC between 1-to-96 hpi (median log10TCID50/ml = 3.08 vs 6.39, p= 0.0253) were detected by Friedman test followed by Dunn's multiple comparisons test. No differences in the viral load between paediatric and adult dHNPEC were significant. A higher percentage of paediatric patients (n=33) possessed SARS-CoV-2 Spike protein 1 (S1) specific immunoglobulin A (IgA) than adult patients (n=18) in their NELF in the first nine days after diagnosis. S1-specific IgA was induced early in asymptomatic paediatric patients (n=14) than symptomatic patients (n=19). The IgA and IgG levels correlated positively with the surrogate neutralization readout. Within the first week of diagnosis, higher S1-specific antibodies in NELF and plasma and lower viral loads were detected in paediatric than adult patients with mild disease.

Project No.: COVID190112

COVID-15-135
How High is the Risk of Environmental Contamination and Airborne Infection of the SARS-CoV-2 Virus?

Prof Chi-tim HUNG[1], Prof Eng-kiong YEOH[1], Prof Kin-fai HO[1], Dr Dominic TSANG[2], Dr Raymond Wai-man LAI[3], Dr Kai-ming CHOW[4], Dr Richard XU[5], Dr Kai-lu WANG[1]

[1]School of Public Health, The Chinese University of Hong Kong, Hong Kong SAR, China, [2]Public Health Laboratory Centre, Department of Health, Hong Kong SAR, China, [3]Department of Microbiology, Prince of Wales Hospital, Hospital Authority, Hong Kong SAR, China, [4]Department of Medicine & Therapeutics, Prince of Wales Hospital, Hospital Authority, Hong Kong SAR, China, [5]Department of Rehabilitation Science, The Hong Kong Polytechnic University, Hong Kong SAR, China

Introduction and Project Objectives: This study aims to detect the presence of SARS-CoV-2 virus in the air and environment at frequently visited places of hospitals admitting COVID-19 patients, find out the risk factors affecting the presence of virus

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particles in the air and environment, and explore the potential of airborne transmission for SARS-CoV-2.

Methods: The study comprises of two parts. In part 1, bi-weekly surveillance was conducted in eight hospital areas through swabbing inanimate surfaces and collecting air samples for SARS-CoV-2. In part 2, a longitudinal study was conducted to follow COVID-19 patients for up to 10 days to detect presence of SARS-CoV-2 at surfaces and air inside the isolation room daily.

Results: In part 1, among the 2150 samples tested, only 2 air samples and 1 surface sample in outpatient areas were positive for SARS-CoV-2. All other samples including inpatient areas other than the COVID-19 isolation rooms and medical staff areas were negative. In part 2, 3291 samples were collected during 348 patient-days of follow-up. Around 5.0% of the samples were positive, including 6.6% of surface samples and 2.1% air samples, and 6.7% of samples in isolation room, 1.0% of samples in anteroom, and zero outside the anteroom. Environmental or air contamination was associated with pre-existing cardiovascular or respiratory conditions, cough or fever on day of sampling, CT value of the latest PCR test on respiratory tract samples, time since last disinfection of cubicle and lower environmental temperature.

Discussion: The findings showed at low to medium epidemic intensity under prevailing precautions for preventing COVID-19 transmissions, the risk of SARS-CoV-2 contaminating general hospital environment is low. This does not apply to the isolation room and anteroom where COVID patients are staying. Patients with pre-existing conditions, fever, cough and higher virus load would pose higher risk for environmental contamination. Six-hourly or more frequent environmental disinfection and higher room temperature could reduce the level of air contamination. Presence of coughing on day of sampling was associated with higher risk of finding virus in the air, but the virus was not consistently detected in the post-cough samples. Additional engineering measures in addition to negative pressure ventilation might be considered to further reduce contaminations in the vicinity of the patient.

Conclusion: Air and surface samples near the patient could contain virus. While prevailing measures seemed adequate for general hospital environment, additional engineering measures to further reduce chance of transmission in the isolation room might be considered.

Project No.: COVID190101

COVID-16-137
Utilization of CRISPR/cas9-Modified Lactobacillus Casei as an Oral Vaccine for Treating and Preventing COVID-19 Infection

Prof Yiu Wa KWAN[1], Mr Eddie Chung Ting CHAU[1], Miss Tsz Ching KWONG[1], Mr Pak Ting HAU[1], Prof Andrew ML CHAN[1], Prof Xiaoqiang YAO[1], Prof George Pak-Heng LEUNG[2], Prof William Chi-Shing TAI[3], Dr Shun Wan CHAN[4], Prof John SL TAM[3]

[1]School of Biomedical Sciences, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, China, [2]Department of Pharmacology and Pharmacy, The University of Hong Kong, Hong Kong SAR, China, [3]Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hong Kong SAR, China, [4]Department of Food and Health Sciences, Faculty of Science and Technology, Technological and Higher Education Institute of Hong Kong, Hong Kong SAR, China

Introduction: COVID-19 is a highly infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Receptor binding domain (RBD) of the Spike (S) protein of SARS-CoV-2 is vital in binding to the angiotensin converting enzyme 2 (ACE2) receptor of human cells and facilitates viral entry. The mucosal delivery of vaccines for mass immunization is an explicit goal of the World Health Organization (WHO) to deal with global pandemic. In this project, we utilized CRISPR/cas9 gene-editing procedures (with bio-containment features) to manufacture recombinant Lactobacillus casei (an edible probiotic) which expressed sufficient quantities of individual antigenic epitopes of RBD of the S protein of SARS-CoV-2, and triggered immune responses, in vivo, after oral consumption.

Project Objectives:

1. To manufacture recombinant Lactobacillus casei using gene-editing CRISPR/cas9 procedures to express the antigenic epitopes of RBD of the S protein of SARS-CoV-2.
2. To evaluate the optimum dosing regiments of oral administration of recombinant L. casei and the generation of high-titre antibodies against the S protein in the serum of golden Syrian hamsters after oral consumption.

Methods: Antigenic epitopes (receptor binding motif (RBM), B-cell and T-cell epitopes) of the RBD of the S protein of SARS-CoV-2 were designed and constructed using DNA sequences predicted based on computational predictive algorithms, and inserted into the genome of L. casei using CRISPR/cas9 techniques (with bio-containment features). The growth rate (at 37oC) of individual type of recombinant L. casei was monitored and compared every hour by measuring the optical density of the bacterial culture medium (MRS) at 600 nm (OD600) using an automated spectrophotometer / incubator.

Results: All three antigenic epitopes of the RBD of the S protein of SARS-CoV-2 were successfully constructed and inserted into the genome of L. casei using CRISPR/cas9 procedures. The growth rate (37oC) of individual recombinant L. casei was "inversely correlated" with the size of the epitope expressed, i.e. RBM (~26.2 kDa, slowest growth) > B-cell epitope (~5.1 kDa) ≥ T-cell epitope (~3.5 kDa, fastest growth).

Conclusion: Our results illustrated that we have successfully constructed and inserted the antigenic epitopes of the RBD

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of the S-protein of SARS-CoV-2 into the genome of L. casei. It remains to be determined about the efficacy of these recombinant probiotics (administered alone or in combination) after oral consumption in triggering the immune responses against challenge of different variants of SARS-CoV-2 in golden Syrian hamster – a gold standard model for SARS-CoV-2 related research.

Project No.: COVID190219

COVID-17-140
Understanding Transmission Risk of SARS-CoV-2 in A&E and Patient Rooms

Louise YUNG[1], Dr Ling Yan LEUNG[3], Steven MORRELL[1], Dr Kwok Hung LEE[3], Min Whui FONG[1], Nikki FUNG[1], Ms Pan CHENG[2], Prof David SC HUI[4], Prof Colin GRAHAM[3], Benjamin COWLING[1], Prof Yuguo LI[2], Dr Hui-Ling YEN[1]
[1]School of Public Health, The University of Hong Kong, Hong Kong SAR, China, [2]Department of Mechanical Engineering, The University of Hong Kong, Hong Kong SAR, China, [3]Accident and Emergency Medicine Academic Unit, The Chinese University of Hong Kong/Prince of Wales Hospital, Hong Kong SAR, China, [4]Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong SAR, China

Introduction and Project Objectives: To evaluate the exposure risk of SARS-CoV-2 virus in the hospital setting, an environmental surveillance was conducted at the Accident and Emergency (A&E) Department of a teaching hospital in Hong Kong from 7 April 2020 to 30 March 2021. This will be followed up by a multi-route modelling using patient care activity data in the second stage of the study. The used multi-route model has been evaluated using the two-bus outbreak of COVID-19 in Hunan in early 2020, in which some limited data of human behaviour at the time of infection became available. The airborne transmission was found to predominate while fomite transmission was negligible in the outbreak.

Methods: In response to the COVID-19 pandemic, in addition to the routine infection control guideline, the A&E Department has adopted enhanced measures according to Hospital Authority Communication Kit –Coronavirus disease 2019 (Hospital Authority, 2021). In addition, the A&E Department has designated areas for gown up and gown down respectively.

Results: From 39 sampling events, a total of 2216 surface samples and 339 air samples (paired with 339 negative control) were collected from 77 surfaces and 3 air sampling sites. Three surface samples were tested positive for the N-gene of SARS-CoV-2 RNA, resulting in a surface positive rate of 0.135% (3/2216). The sampled surfaces are classified into "patient area" (N=1189), "healthcare worker area" (N=531), and "patient-healthcare worker area" (N=496) based on the accessibility to patients and healthcare workers. None of the air samples was tested positive. The three positive surface samples were collected from the area accessible by both the health care worker and the patients (the wall next to the resuscitation room and the floor of triage area) and from the patient waiting area with limited access by health care workers (door handle of male washroom), suggesting a higher risk of contamination of patient accessible surfaces. The cycle threshold values of the three positive samples ranged from 36.7-38.4, indicating that the samples are likely non-infectious. During the study period, a total of 283 SARS-CoV-2 infected patients have visited or have been diagnosed at the A&E Department of this teaching hospital.

Conclusion: Overall, our results suggest that the risk of exposure to SARS-CoV-2 at the A&E Department has remained low, possibly due to the success of infection control measures.

Reference:
Hospital Authority: Hospital Authority Communication Kit – Coronavirus disease 2019: https://www.ha.org.hk/haho/ho/pad/Comkit.pdf. Last version 7.12 updated 23 September 2021.

Project No.: COVID190113

COVID-18-142
Identification of Lingnan Chinese Medicines against COVID-19 Infection

Miss Xiaoyang WANG[1], Mr Hung Chun LEE[1], Dr Shengying LIN[1], Mr Ho Hin CHAN[1], Mr. Wai Lun TANG[1], Dr Sheyne Sta. Ana CHOI[1], Dr Ka Wing LEUNG[1], Dr Sarah Elizabeth WEBB[1], Prof Andrew L. MILLER[1], Prof Karl Wah-keung TSIM[1]
[1]Division of Life Science, Center for Chinese Medicine and State Key Laboratory of Molecular Neuroscience, The Hong Kong University of Science and Technology, Hong Kong SAR, China

Introduction and Project Objectives: Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the causative agent of the acute respiratory disease (COVID-19), has resulted in millions of deaths worldwide since its outbreak in Dec 2019. Numerous efforts have been made globally to develop effective prevention and treatment therapeutics. In China, the use of traditional Chinese medicine (TCM) has been reported to have good efficacy in the clinical treatment of the viral infection. Intriguingly, TCMs derived from Lingnan region (Southern China) have long been used in clinical applications due to their efficacious antiviral activity.

Methods: Here, a screening platform of anti-SARS-CoV-2 infection has been established targeting an extensive library of Lingnan TCM herbs/single molecules. Those shown to have promising efficacy will be developed further, using well-established pharma drug trial procedures, for consideration as novel herbal prescriptions. During infection by SARS-CoV-2, the

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spike (S) protein of the virus recognizes angiotensin-converting enzyme 2 (ACE2) on the host cell surface, and this triggers viral entry via endocytosis. In addition, we propose that two-pore channels (TPCs; a family of pleiotropic cation channels) might mediate endocytosis of SARS-CoV-2 into host cells as they have been shown to do for Ebola and MERS-CoV viruses. Once inside the host cells, non-structural proteins, such as 3CL protease, enable viral replication and proliferation, leading to the widespread pathogenic damage that is characteristic of this disease. Thus, the S-protein, ACE2, 3CL protease and TPCs are the target proteins we are using for screening Lingnan TCMs both in vitro and in vivo.

Results: In total, over 300 TCM products (both water and ethanol extracts), and over 200 phytochemicals have been subjected for screening so far, from which over 40 hits have been identified. We have shown that the identified TCM extracts/phytochemicals can significantly inhibit the host cell entry of SARS-CoV-2 pseudovirus in a dose-dependent manner. In addition, these TCM herbs have an excellent safety record from their historical usage, which suggests they can be "fast-tracked" for clinical application.

Conclusion: Thus, over the last 12 months, we have established a multi-target screening platform and successfully identified several potent herbs/phytochemicals for subsequent drug development and/or clinical application.

Project No.: COVID190213

COVID-19-149
The Impact of COVID-19 on Physical Wellbeing of Survivors

Prof Siu Ngor FU[1]
[1]*The Hong Kong Polytechnic University, Hong Kong SAR, China*

Introduction: The coronavirus disease 2019 (COVID-19) has infected > 219 millions of people worldwide. Although Hong Kong has a relatively low number of confirmed cases, it is not uncommon for COVID-19 survivors to experience various extents of cognitive, physical and psychosocial sequelae. Importantly, a few overseas studies also reported a high prevalence of fatigue in these survivors although factors related to such fatigue remain unclear.

Project Objective: (1) To assess the incidence of fatigue of COVID-19 survivors when discharge from hospitals; and (2) to determine factors predicting fatigue in these survivors.

Methods: Potential COVID-19 survivors were referred by their physicians from four local hospitals at discharge. These survivors were contacted and consented participants were invited to undergo assessments in the respective hospitals or on a university campus. All participants completed a battery of biopsychosocial tests including fatigue assessment scale, quadriceps strength and spirometry tests, functional evaluations using 6- minute walk and 30-second sit-to-stand tests, cognitive test using Chinese auditory verbal learning test. Descriptive analysis was used to summarize the findings. Factors affecting fatigues were analysed by a logistic regression model with age, gender, body-mass index post-COVID time, comorbidity, and education level being entered into first level.

Results: Ninety-four participants (age range: 24 to 88 years; 59.2% females; mean duration of COVID: 4.72±2.8 months) were assessed. Fatigue was reported in 45% of participants with 4% experience severe fatigue. Those reported fatigue had significantly lower forced vital capacity (FVC) (p=0.016) and a trend of reduced forced expiratory volume (FEV1) (p=0.051) and lowered normalized torque (left and right) of the quadriceps muscles (p=0.069). The regression model showed that COVID-19 survivors with lower FVC (odds ratio: 0.382, p=0.084), and quadriceps torque (odds ratio= 0.979, P=0.016) were more likely to have clinically significant fatigue.

Discussion: While up to 45% of COVID-19 survivors experience clinically significant fatigue, the mechanisms underlying post-COVID-19 fatigue remains unclear. Our findings suggest that self-perceived clinically significant fatigue at discharge from hospitals is characterized by poor forced vital capacity and poor lower limb strengths. Structured rehabilitation programs targeting the restoration of lung function and lower limb muscle strengths of COVID-19 survivors are warranted to reduce their fatigue, and enhance their ability in performing activities of daily living.

Project No.: COVID190222

COVID-20-151
Development of an Enzyme-Linked ImmunoSorbent Assay Detecting Antibodies against a Novel Secreted Antigen of SARS-CoV-2

Joy-Yan LAM[1], Kelvin Kai-Wang TO[1], Kwok-Yung YUEN[1], Kin-Hang KOK[1]
[1]*Department of Microbiology, The University of Hong Kong, Hong Kong SAR, China*

Introduction and Project Objectives: A novel human coronavirus, known as SARS-CoV-2, has infected millions of individuals globally since December 2019. Currently, early molecular diagnosis of human SARS-CoV infection mainly depends on the quantitative reverse-transcription-polymerase (RT-qPCR) and sequencing preformed in laboratory. There are also commercially available COVID-19 antigen rapid tests, and most of them are detecting spike or nucleoprotein in the format of lateral flow assay. In January 2020, we first reported that one of the main differences between SARS-CoV-2 and other human pathogenic coronaviruses is the presence of an uncharacterized orf8 viral protein (EMI, 2020). We further

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demonstrated that orf8 is a secreted viral protein as exemplified by the detection of secreted orf8 in COVID-19 patients' serum using Liquid Chromatography–Mass Spectrometry, and the detection of overexpressed orf8 in the supernatant of cultured lung epithelial cells (mBio, 2020). Therefore, we hypothesized that SARS-CoV-2 orf8 protein is an immunogenic secreted protein and the detection of its antibodies in patients may be an alternative for early diagnosis of COVID. In this project, we aimed to develop an accurate assay for the detection of orf8 antigen or anti-orf8 antibody in the serum samples of COVID-19 patients.

Methods: We optimized the recombinant orf8 protein production using human Expi293 expression system. Highly purified orf8 protein was used for the development of ELISA-based anti-orf8 antibody detection in serum samples of COVID-19 patients. In addition, we used the peptide library to identify the linear B cell epitopes of SARS-CoV-2 orf8 protein from COVID-19 patients.

Results: We characterized the SARS-CoV-2 orf8 as a novel immunogenic secreted protein and utilized it for the accurate diagnosis of COVID-19 (mBio, 2020). Extracellular orf8 protein was detected in cell culture supernatant and in sera of COVID-19 patients. In addition, using our optimized home-made ELISA, we demonstrated that orf8 was highly immunogenic in COVID-19 patients, who showed early seropositivity for anti-orf8 IgM, IgG, and IgA. Furthermore, we identified the most immunogenic linear epitope of orf8 protein from COVID-19 patients (EMI, 2021).

Conclusion: We hypothesized that orf8 secretion during SARS-CoV-2 infection facilitates early mounting of B cell response. It is evidenced by the early seropositivity for anti-orf8 antibodies in this study. Our optimized ELISA detecting anti-orf8 IgG antibody can be further developed for the serological test and diagnosis of COVID-19.

Project No.: COVID190120

COVID-21-153
Long Term Immunological Response and Longitudinal Seroepidemiology of SARS-CoV-2 in Hong Kong

Dr Kelvin TO[1], Prof Ivan Fan-Ngai HUNG[1], Dr Owen Tak-Yin TSANG[2], Dr Lu LU[1], Dr Kwok-Hung CHAN[1]
[1]Department of Microbiology, The University of Hong Kong, Hong Kong SAR, China, [2]Department of Medicine and Geriatrics, Princess Margaret Hospital, Hong Kong SAR, China

Introduction and Project Objectives: COVID-19 patients usually develop antibody response against SARS-CoV-2 within 2-3 weeks after symptom onset. For recovered COVID-19 patients, antibody status is useful for assessing the risk of reinfection, because seropositive patients have a much lower risk of reinfection. Furthermore, since SARS-CoV-2 antibodies can be detected in blood for several months, antibody test is useful for retrospective diagnosis for patients who were not diagnosed during the acute stage of infection. Serological surveillance is therefore an important tool in revealing the true burden of COVID-19. In this study, we monitored the long term kinetics of anti-SARS-CoV-2 antibodies among recovered COVID-19 patients, and we conducted serosurveillance to determine the burden of subclinical infection in Hong Kong.

Methods: The long term antibody response of COVID-19 patients was determined using binding antibody tests against the spike protein (including the receptor binding domain [RBD]) or nucleoprotein (N), surrogate virus neutralization test (sVNT), and conventional virus neutralization test (cVNT) and at 2, 6 and 12 months post symptom-onset (MPSO). For the serosurveillance study, sera from the general population were first screened using a binding antibody assay or sVNT, and seropositivity was confirmed using the cVNT.

Results: Long term antibody response among recovered laboratory-confirmed COVID-19 patients: The seropositive rates declined for all antibody assays at 6 or 12 MPSO. Among different antibody assays, anti-RBD IgG has the highest seropositive rate at all time points (>95%). The seropositive rates of sVNT or cVNT were lower than those of anti-RBD IgG at 6 (about 90%) and 12 MPSO (about 80%). Most patients were seronegative for IgM against spike or N proteins at 6 or 12 MPSO. Quantitative analysis showed that there was a gradual decline in the levels of antibodies in all assays between 2 and 12 MPSO. For sVNT and cVNT, the decline of antibody titers occurred mainly from 2 to 6 MPSO. General population serosurveillance study: Before April 2021, no serum specimen tested positive by both binding antibody assay/sVNT and cVNT. However, in April 2021, 2% of the serum specimens tested positive by both sVNT and cVNT.

Conclusion: The decline in antibody level among COVID-19 patients suggests that these patients should receive COVID-19 vaccine to prevent reinfection. Results from the serosurveillance study suggests that the rate of subclinical COVID-19 infection in Hong Kong remain low before April 2021. The seropositive individuals since April 2021 may be related to COVID-19 vaccines rather than subclinical infections.

Project No.: COVID190124

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COVID-22-155

Psychological Trauma and Unsafe Behaviour during the COVID-19 Pandemic: a Mixed-Method Study of People's Emotion, Knowledge, Attitude and Behavior

Prof David SHUM[1], Dr Judy Yuen-man SIU[2], Dr Yuan CAO[1]
[1]Department of Rehabilitation Sciences, The Hong Kong Polytechnic University, Hong Kong SAR, China, [2]Department of Applied Social Sciences, The Hong Kong Polytechnic University, Hong Kong SAR, China

Introduction: Everyone in Hong Kong has been affected by the COVID-19 pandemic in various ways, such as health, employment, education and social aspects. It is important to conduct a population-wide study to fully gauge the impact of this virus on citizens in Hong Kong.

Project Objectives: To examine Hong Kong residents' current level of psychological trauma, knowledge and attitudes about COVID-19, behaviours regarding infection prevention, reasons of not adopting appropriate preventative actions, such as receiving COVID-19 vaccination.

Methods: A mixed-method design was used. First, a telephone survey was carried out among 3011 adults in Hong Kong, one year since the beginning of the pandemic, to investigate their level of psychological trauma, compliance with preventative measures, effect of reading news reports on COVID-19, vaccine acceptance and willingness to participate in voluntary testing (phase 1). Logistic regression analyses were used to determine the association between demographic variables of interest, PTSD, the Prevention Score, vaccine acceptance and engagement in voluntary testing. Second, with a phenomenology approach, 31 older adults were interviewed for deeper understanding of their experiences, such as receiving vaccination (phase 2). A comprehensive analysis of qualitative data was conducted based on the framework of Critical Medical Anthropology.

Results: The prevalence of possible post-traumatic stress disorder was found to be 12.4%, lower than that reported by earlier studies. Socio-demographic correlates of psychological trauma and health-protective behavior were also found. Respondents were generally compliant with routine preventative measures, but less than half had accepted vaccination and voluntary testing. The qualitative findings further revealed struggles experienced among older adults at four social-levels according to the Critical Medical Anthropology framework: (1) individual (trust and confidence, social support networks), (2) micro-social (stigma of healthcare providers), (3) intermediate-social (government), and (4) macro-social levels (cultural stereotypes, civic and collective responsibility, economic) factors.

Conclusion: Socio-demographic factors, such as educational level, affected both psychological trauma and engagement in health-protective measures. Furthermore, deciding to receive COVID-19 vaccination is a complex decision and experience for older adults. These results have implications for the design of governmental policies to help manage the effects of the pandemic and to prevent future outbreaks.

Project No.: COVID190217

COVID-23-161

Investigation of Hong Kong's Early Detection, Assessment and Response (S-EDAR) System to the New Emerging Infectious Disease Outbreak COVID-19

Prof EK YEOH[1], Prof Marc Ka-chun CHONG[1], Prof Vincent Chi-ho CHUNG[2], Prof Dong DONG[2], Prof Chi Tim HUNG[1], Prof Eman Yee-man LEUNG[2], Prof Eliza Lai-yi WONG[1], Prof Samuel Yeung-shan WONG[2], Prof Joey Zu-yao YANG[2], Prof Johnson Zixin WANG[2]
[1]JC School of Public Health and Primary Care & Centre for Health Systems and Policy Research, The Chinese University of Hong Kong, Hong Kong SAR, China, [2]JC School of Public Health and Primary Care, The Chinese University of Hong Kong, Hong Kong SAR, China

Introduction and Project Objectives: To investigate how Hong Kong's system of early detection, assessment and response (S-EDAR) to COVID-19 outbreak can be enhanced.

Methods: A formative evaluation is used with a two-stage design. In Stage 1, we assessed S-EDAR in Hong Kong and evaluated its effectiveness and implementation by literature reviews, comparative case study in 6 Western Pacific jurisdictions, key informant interviews, system dynamics modelling and expert workshops. In Stage 2, we develop an enhanced S-EDAR informed by international expert input and the feasibility and applicability in the local context from a Delphi survey. The study settings/participants include:

- Six regional case studies in Hong Kong, Japan, Malaysia, South Korea, Shanghai, and Singapore;
- Over 35 local key informants including policy makers, healthcare administrators and professionals, chairpersons of business organizations, and general public/patients;
- Over 17 local and international experts;
- SARS-CoV-2 infection surveillance and control data from the Centre of Health Protection and Hospital Authority

Results:

1. Scoping reviews

There was adequate empirical evidence for the effect of physical distancing at individual level and of partial/full lockdown in reducing transmission, but not for individual interventions including workplace/business closure. We analysed the implementation barriers and facilitators by the Consolidated Framework for Implementation Research.

2. Comparative case study

The key lessons highlight the need for an on-going surveillance

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system, broaden screening, comprehensive preparedness plans and regular drills, information technology, capacity for testing, contact tracing, isolation and quarantine. Measures should be proportionate to the stages of the outbreak to reduce socio-economic impacts. Relaxation of measures should be based on risk assessment, implemented in stages, and reversible when needed.

3. System dynamics modelling
The simulation suggests that both PCR-polymerase chain reaction(with a 7-day quarantine) and rapid antigen test screening to inbound travelers are unable to control the local outbreak if the travel volume returns to the level in 2019. Nevertheless, if the travel volume can be kept as a low level such as the level before the entry ban of all countries, screening can still work well.

4. Enhanced S-EDAR based on WHO guidelines, key informants and experts

We propose an enhanced S-EDAR with three components:1) Preparedness plan and resilience system for public health emergencies, 2)Readiness, and3)Response system with implementation strategies at government, healthcare and community levels.

Conclusion: The enhanced S-EDAR will equip the health system with instruments that have the capacity to capture the dynamic and complex context in preventing and controlling future pandemic threats.

Project No.: COVID190105

COVID-24-175
Role of Gastrointestinal Tract and Gut Microbiota in Pathogenesis of Coronavirus Disease 2019 (COVID-19): A Missing Site for Viral Replication & Transmission

Prof Siew Chien NG[1]
[1]*Department of Medicine & Therapeutics, The Chinese University of Hong Kong, Hong Kong SAR, China*

Introduction and Project Objectives: Although there is mounting evidence suggesting that the gastrointestinal tract is involved in COVID-19, role of GI tract and gut microbiota in pathogenesis of this disease remain unknown. We aim to quantify SARS-CoV-2 viral load in feces of COVID-19 patients, evaluate gut bacterial and viral microbiota in COVID-19 patients and its association with disease severity and outcomes, determine the effect of COVID-19 on gut inflammation and ACE2 expression, and explore gut microbes regulating ACE2 expression to decrease disease risk for severe COVID-19.

Method: 50 patients with COVID-19 hospitalized with laboratory-confirmed SARS-CoV-2 infection, 30 patients hospitalized with community-acquired pneumonia (pneumonia controls), and 30 healthy individuals (healthy controls) were recruited. The pneumonia patients with COVID-19 had stool and plasma sample collected in three sampled time until discharge. After discharge, 20 patients were followed, and one stool sample was collected at 1 week, 2 months and 6 months respectively. The pneumonia patients without COVID-19 and healthy controls have stool collected only once at recruitment. Specimen was subjected to laboratory tests including COVID-19 load, fecal bacterial and viral profiling, inflammatory markers profiling and ACE2 expression detection.

Result: 73.3% patients had SARS-CoV-2 nucleic acid detected in feces at hospitalization (median 3.86×103 copies per mL inoculum). 46.7% patients showed active SARS-CoV-2 infection with strikingly higher coverage the 3′ vs 5′ end of SARS-CoV-2 genome in their fecal viral metagenome profile, even after disease resolution. Patients with COVID-19 had disturbed bacterial and viral microbiota, compared with healthy controls ($P < 0.05$), which persisted up to 6 months after recovery. Several gut commensal bacteria with known immunomodulatory potential such as Faecalibacterium prausnitzii, Eubacterium rectale and bifidobacteria and two Pepper-derived RNA virus species (RNA virus) were underrepresented in patients. Depletion of these bacterial and viral taxa associated with more severe disease as well as elevated concentrations of inflammatory cytokines and blood markers ($P < 0.05$).

Conclusion: Our study showed prolonged and active SARS-CoV-2 virus in the gut of patients with COVID-19, even after recovery, which highlights the importance of long-term coronavirus and health surveillance and the threat of potential fecal-oral viral transmission. We for the first time identified several biomarkers of gut bacterial and viral microbiota specific to COVID-19 cases, and elucidate their associations with disease severity and host immune response. This will open up potential therapeutics to modulate the gut microbiota to reduce severity and complication of COVID-19 infections.

Project No.: COVID190111

COVID-25-189
Workplace Safety towards SARS-CoV-2 among Non-Healthcare Workers in Hong Kong, Nanjing and Wuhan: Prevention, Response and Sustainability

Prof Shelly Lap-ah TSE[1], Dr Priscilla Ming Yi LEE[1], Dr Dongming WANG[2], Miss Yan Li[3], Mr Shuyuan YANG[1], Prof Shoulin WANG[3], Dr Janice Ying Chui LAU[4], Prof Tangchun WU[2], Prof Hongbing SHEN[3], Prof Xiaoming JI[3], Prof Weihong CHEN[2]
[1]*Jockey Club School of Public Health and Primary Care, The Chinese University of Hong Kong, Hong Kong SAR, China,* [2] *School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, China,* [3]*School of Public Health Nanjing, Nanjing Medical University, China,* [4]*Stanley Ho Centre for Emerging Infectious Diseases, The Chinese University of Hong Kong, Hong Kong SAR, China*

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Introduction and Project Objectives: There has been no validated tool to assess the performance of workplace prevention measures towards respiratory infectious diseases in non-healthcare work settings, especially for the COVID-19. This study aimed to develop a new tool to measure workplace safety towards infection control and prevention of COVID-19 in a variety of non-healthcare industries from cities of China with different socioeconomic development.

Methods: In this cross-sectional study during 07/2020 to 04/2021, 6684 non-healthcare workers were recruited from Hong Kong, Nanjing and Wuhan of China and responded a standard questionnaire containing information of prevention measures implemented by companies and individual workers towards infectious control, particularly SARS-Cov-2 and COVID-19. All participants were randomly stratified into two sub-samples of equal sample size as the training sample and validation sample. The workplace safety towards SARS-Cov-2 and COVID-19 index was developed and validated using exploratory factor analysis (EFA) and confirmatory factor analysis (CFA). The robustness of the index was further verified by the actual uptake of SARS-Cov-2 testing.

Results: We identified 14 variables in a newly developed "Workplace safety towards SARS-Cov-2 & COVID-19 index (WSSC index)", with three sub-indices named "Workplace's implementation of occupational safety and health prevention measures", "Company's management of occupational safety and health" and "Worker's exposure prevention behavior and awareness". The new WSSC index obtained a good internal consistency reliability (Cronbach's alpha coefficients ranged: 0.76-0.91), good composite reliability (composite reliability ranged: 0.70-0.95) and satisfactory fit of the model (GFI=0.95; SRMR=0.05; RMSEA=0.07). We further performed stratified analysis according to cities and the index remained stable. Workers with higher scores of the WSSC index were more likely to uptake virus testing. A higher score of this novel index indicates better awareness of workplace safety towards prevention and control of COVID-19.

Conclusion: "Workplace safety towards SARS-Cov-2 & COVID-19 index" is a novel and validated tool to horizontally measure the awareness of workplace safety towards SARS-Cov-2 & COVID-19 among non-healthcare workers across industries and cities of China with different layers of socioeconomic development. Whether the tool is valid for longitudinally monitoring is under testing.

Acknowledgment: this study is funded by Health and Medical Research Fund (Reference number: COVID190104). We appreciate the Hong Kong Federation of Trade Unions-Occupational Safety and Health Association for their support. Please contact shelly@cuhk.edu.hk

Project No.: COVID190104

COVID-26-203
Characterization of the Distribution of Aerosols Released from Drainage Ventilating Pipe of Public Housing Buildings

Dr Polly LEUNG[1], Dr Kwok Wai MUI[1], Dr Ling Tim WONG[1], Dr Yang ZHOU[1]
[1]*The Hong Kong Polytechnic University, Hong Kong SAR, China*

Introduction and Project Objectives: Occurrence of COVID-19 cases in public house building suggested that aerosols released from drainage vent pipe at building rooftop can be a potential route for transmission of SARS-CoV-2. However, there is a lack of comprehensive studies on the spatial distribution of aerosols discharged from drainage vent.The project aims to characterise the spatial distribution of aerosols released from the drainage vent pipe at the rooftop and the top floor residential units, and to identify the key contributing factors influencing the distribution of aerosols. The ultimate goal is to develop of a risk assessment model for exposure to SARS-CoV-2.

Methods: The project employs computational fluid dynamic (CFD) simulation and mathematical modelling supported by onsite measurements to characterise distribution of aerosols discharged from the draining vent pipe. Four representative types of public housing blocks in Hong Kong will be studied. Tracer gas will be released by gas doser at the drainage vent discharge on the rooftop. Tracer gas will be tracked by wireless sensors placed at various sites on rooftop. Key contributing parameters, such as wind speed and height of vent pipe, that influencing the spatial distribution of aerosols in residential units on the first to third floors below the rooftop will be identified.

Results: So far, five public building blocks of cruciform type have been studied. The wind speed on the day of field measurement was 1.5 – 2.0 m/sec, which was regarded as low wind speed. When tracer gas was released at the vent discharge near the rooftop edge, tracer gas was detected at on the first and third floors (37/F and 35/F) below the rooftop, but not the second floor (36/F). This could be a result of turbulence effect. Similar result patterns were obtained when tracer gas was released at 1 m, 1.5 m or 2 m above ground level. However, when the tracer gas was released near the rooftop centre, tracer gas were detected at lower concentrations in the on 37/F and 35/F.

Conclusion: Aerosols discharged from the drainage vent pipe at the rooftop could reach the three floors below the rooftop. A turbulence effect was observed, and height of drainage vent pipe to as high as 2 metres did not have much influence on the distribution of aerosols. However, when source of aerosols was near the centre of the rooftop, lower aerosols concentration were detected at the three floors below the rooftop.

Project No.: COVID190203

Abstracts for Poster Presentation: Commissioned Research on COVID-19

COVID-27-208
Incident Mental Morbidity and Web-based Psychological treatment in COVID-19 (A WMH-COVID-19 study)

Dr Dun Ping Arthur MAK[1], Prof Yeung Shan Samuel WONG[2], Prof Chiu Wa Linda LAM[1], Dr. Ben YIP[2], Prof Eliza WONG[2], Prof Pim CUIJPERs[3]
[1]Department of Psychiatry, The Chinese University of Hong Kong, Hong Kong SAR, China, [2]JC School of Public Health and Primary Care, The Chinese University of Hong Kong, Hong Kong SAR, China, [3]Faculty of Behavioural and Movement Sciences, Vrije Universiteit Amsterdam, The Netherlands

Introduction and Project Objectives: The COVID-19 pandemic brought about unprecedented challenges in mental health care burden and care delivery in infection survivors, healthcare workers, quarantine camp confinees, and the general public. This study aims to (i) estimate the enduring mental health care burden and costs from COVID-19; (ii) test and implement web-based psychological treatment for depressive and anxiety disorders

Methods: PHASE 1 - 1-year web-based cohort study measuring mental morbidity (anxiety, depression, PTSD) and burden at baseline, 6 months and 12 months. Four samples include: (i) 500 COVID19 patients via hospital database (ii) 1000 Penny Bay quarantine camp confines (iii) 1500 representative public healthcare workers from major acute hospitals in Hong Kong (iv) 2500 persons via randomly selected household addresses through the Census and Statistics Department.

Progress and preliminary Results: Recruitment has been completed for health-care workers, and is ongoing for the other groups (71%, 90%, 51% registered for public, quarantined, and survivors groups).

To date (October 2021), of the 4283 survey baseline respondents, 50% were screened positive for at least one mental disorder (generalized anxiety: 39.7%, depression: 35.5%, suicidal thoughts or behaviours: 16.7% and PTSD: 13.7%). The figures were similar in healthcare workers, COVID 19 survivors, quarantine camp confinees and the general public. 38.3% of the COVID-19 survivors were screened positive for subjective cognitive impairment up to a year since index infection. The 6-month and 12-month waves of follow-up survey will track changes in mental health statistics and needs in these 4 groups.

PHASE 2 – web-based psychological treatment: The first 150 respondents with significant anxiety and depressive symptoms are randomized to receive either a web-based 2-month cognitive behavioral therapy-based psychological treatment or control (educational materials).

Progress: Recruitment is on-going, with 42 participants randomised (21 treatment, 21 control) to date. Ratings of depression, generalized anxiety, acute stress disorder and post-traumatic stress disorder symptoms and health-related quality of life will be obtained via self-report questionnaires.

Expected outcomes: It is hypothesized that web-based psychological treatment will result in a 50% reduction in PHQ-ADS score compared to control intervention at both 6 and 12 weeks from baseline.The proposed study estimates the incidence and associated burden of common mental disorders from COVID-19. It also provides web-based psychological treatment as an accessible and cost-effective solution to the escalating mental morbidity, which will serve as a model ready to serve the mental health needs of the population in the post-COVID-19 era.

Project No.: COVID190212

COVID-28-212
Discovery and Mechanistic Evaluation of Antiviral Treatment Options for Coronavirus Disease 2019 (COVID-19) Through Structure-based Drug Discovery and Drug Repurposing Approaches

Dr Jasper Fuk-Woo CHAN[1], Dr Richard Yi-Tsun KAO[1], Dr Kong-Hung SZE[1], Dr Shuofeng YUAN[1], Dr Hin CHU[1]
[1]Department of Microbiology, The University of Hong Kong, Hong Kong SAR, China

Introduction and Project Objectives: The Coronavirus Disease 2019 (COVID-19) pandemic is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel betacoronavirus first identified in patients with pneumonia in Wuhan, China, in late 2019 that quickly disseminated worldwide. Antiviral treatments for COVID-19 remain limited. This project aims to find rapidly available COVID-19 treatment options using our established high-throughput drug compound library screening and in-silico structure-based screening platforms, and to thoroughly assess the selected drug candidates' anti-coronaviral activities and mechanisms in-vitro, in ex-vivo organ tissue culture, and in-vivo models.

Methods: Drug discovery programmes were conducted by (i) high-throughput screening of drug compound libraries using automated robotic screening platform assisted by manual testing, and (ii) in-silico structure-based virtual screening of chemical libraries, followed by molecular docking and molecular dynamics simulations targeting the key viral enzymes and viral components of SARS-CoV-2. Top hit drug compounds with in-vitro anti-SARS-CoV-2 activity were further prioritized by their pharmacological properties and translational potentials for evaluation in our established COVID-19 ex-vivo organ tissue culture and/or Syrian hamster models. Mechanistic evaluation of selected drug compounds was performed to provide insights for drug analogue optimization.

Results: In a library of drugs encompassing approximately

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12,000 clinical-stage or clinically-approved small molecules, we identified 100 molecules that inhibit SARS-CoV-2 replication. Of these, 13 exhibit effective concentrations commensurate with achievable therapeutic doses in patients, including the antimycobacterial clofazimine, the PIKfyve kinase inhibitor apilimod, and numerous cysteine protease inhibitors. In particular, the orally available clofazimine possesses broad-spectrum anti-coronaviral activities against SARS-CoV-2 and other human-pathogenic coronaviruses. Mechanistically, clofazimine inhibits spike-mediated cell fusion and viral helicase activity. Prophylactic or therapeutic clofazimine resulted in reduced viral loads and inflammation in the respiratory tract of SARS-CoV-2-infected hamsters. Combination of clofazimine and remdesivir exhibited in-vitro and in-vivo antiviral synergy. Moreover, our in-silico screening and phenotypic antiviral evaluations identified numerous other anti-SARS-CoV-2 drug compounds, including recombinant interferons and lopinavir that are available for clinical evaluation.

Conclusion: Based on the novel findings in this project, clinical trials to evaluate the effect of clofazimine and other identified anti-SARS-CoV-2 drug compounds for treating COVID-19 patients have been started. The antiviral mechanisms of actions reported in this project provide novel insights for drug analogue optimization and development of anti-coronaviral drug compounds.

Project No.: COVID190121

COVID-29-219

Single-dose Intranasal Administration of an NSP16-deficient SARS-CoV-2 as a Candidate Live Attenuated Vaccine Provide Sterilizing Immunity in Hamsters and K18-hACE2 Mice

Dr Zi-Wei YE[2], Mr Chon Phin ONG[1], Mr Kaiming TANG[2], Ms Yilan FAN[1], Prof Kwok Yung YUEN[2], Dr Guang Sheng LING[1], Dr Shuofeng YUAN[2], Prof Dong-yan JIN[1]

[1]School of Biomedical Sciences, The University of Hong Kong, Hong Kong SAR, China, [2]Department of Microbiology, The University of Hong Kong, Hong Kong SAR, China

Introduction and Project Objectives: Live attenuated vaccines can induce mucosal and sterilizing immunity against SARS-CoV-2 that the existing mRNA, adenoviral vectored and inactivated vaccines fail to elicit. The aim of our project is to harness the infectious molecular clone to construct a candidate stain for a live attenuated vaccine against SARS-CoV-2.

Methods: An NSP16-deficeint recombinant SARS-CoV-2 was constructed on the infectious molecular clone on a bacterial artificial chromosome (BAC).

Results: We designed and created a candidate live attenuated vaccine strain of SARS-CoV-2 in which the NSP16 gene encoding 2′-O-methyltransferase is catalytically disrupted by a substation at amino acid 130, in which aspartate (D) was replaced by alanine (A). This virus containing this D130A point mutation, designated d16, was severely attenuated in hamsters and K18-hACE2 transgenic mice, whereby it established an asymptomatic and non-pathogenic infection. A single dose of d16 vaccinated intranasally resulted in sterilizing immunity in both upper and lower respiratory tracts of hamsters, hence eliminating viral spread in a contact-based transmission model. It also robustly induced humoral and cell-mediated immune responses, therefore providing complete protection against lethal challenge with SARS-CoV-2 in the K18-hACE2 transgenic mouse model. The neutralizing antibodies elicited by d16 effectively cross-reacted with several SARS-CoV-2 variants including the δ variant. Importantly, secreted IgA was detected in the nasal wash of vaccinated mice.

Conclusion: Our work provides the proof-of-concept for harnessing NSP16-deficient SARS-CoV-2 to develop live attenuated vaccines and paves the way for further preclinical studies of d16 as a prototypic vaccine strain to which new features might be introduced to improve safety, transmissibility, immunogenicity and efficacy.

Project No.: COVID190114

COVID-30-224

The Blended Gaming COVID-19 Training System (BGCTS) with WHO guidelines for Staff in Residential Care Homes: Development and Pilot Testing

Prof Angela Y. M. LEUNG[1,2,3], Mr Terence LAU[1,3], Dr Daphne CHEUNG[1,2,3], Dr Mimi TSE[1,2,3], Dr Doris Y. P. LEUNG[1], Dr Eliza WONG[1,3], Dr Simon LAM[1,3,4], Dr Justina LIU[1,2,3], Prof Alex MOLASSIOTIS[1,2]

[1]School of Nursing, The Hong Kong Polytechnic University, Hong Kong SAR, China, [2]WHO Collaborating Centre for Community Health Services, School of Nursing, The Hong Kong Polytechnic University, Hong Kong SAR, China, [3]Centre for Gerontological Nursing, School of Nursing, The Hong Kong Polytechnic University, Hong Kong SAR, China, [4]Squina International Centre for Infection Control, School of Nursing, The Hong Kong Polytechnic University, Hong Kong SAR, China

Introduction and Project Objectives: Residents in residential care homes are at a high risk of being infected by COVID-19 due to their advanced age, associated co-morbidities, and state of dependence. The price paid for an outbreak in residential care homes is high. This is Phase 1 of a clustered randomized controlled trial. It aims to develop and test the Blended Gaming COVID-19 Training System (BGCTS) which provides infection control training to all staff in RCHs in Hong Kong.

Methods: This is a system development study with cognitive interviews with six RCH staff of different ranks. The cognitive interviews were video recorded and analyzed. The key

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recommendations and comments about the BGCTS system were collected.

Results: The contents of the BGCTS system were developed with reference to the World Health Organization (WHO) guideline 'the COVID-19 Risk Communication Package for Healthcare Facilities'. Animations and games were created by nurses, engineers and infection control specialists. One introductory animation and eight gamified topics were made and the topics include: preparing for COVID-19 at your facility, managing patients with suspected or confirmed COVID-19 at your facility, projecting yourself at work, personal protective equipment, symptoms and means of transmission, coping with stress, and 5 moments for hand hygiene. All the staff considered the BGCTS system as 'informative and motivational' for learning infection control practices. They appraised the animations as 'attractive' and the games as 'interesting and educational'. They have made more than 30 suggestions for refining the system in terms of graphical design, instructions to users, and presentation format and style. These are helpful to convey the key messages of infection control practices to the RCH staff.

Conclusion: The BGCTS system will be revised according to these recommendations and will be evaluated in a randomized controlled trial. The BGCTS is the first of this kind training, addressing the diverse health literacy levels of staff and helping RCH staff to comply with WHO infection control guidelines.

Acknowledgment: The project is funded by Health and Medical Research Fund - Commissioned Research on the Novel Coronavirus Disease (COVID-19), Food and Health Bureau, The Hong Kong SAR government (reference no.: COVID190218).

Project No.: COVID190218

COVID-31-228
Suppression of an Outbreak of COVID-19 Without Lockdown in Hong Kong: the Challenge of Inefficient Testing and Tracing

Dr Hsiang Yu, Sean YUAN[1,2], Prof Colin BLAKEMORE[3]
[1]Department of Biomedical Sciences, City University of Hong Kong, Hong Kong SAR, China, [2]Centre for Applied One Health Research and Policy Advice, City University of Hong Kong, Hong Kong SAR, China, [3]Hong Kong Institute for Advanced Study, City University of Hong Kong, Hong Kong SAR, China

Introduction and Project Objectives: Maintaining effective contact tracing to control COVID-19 is challenging. Rapid growth in the number of infected cases can overload tracing and testing capacity, resulting in failure to trace contacts and delays in confirming an infection until after symptom onset (confirmation delay), hence increasing transmissibility. A substantial outbreak in Hong Kong, which was suppressed with non-pharmaceutical interventions (NPIs), provided an opportunity to assess the impact of overloading contact tracing and of efforts to improve its efficiency.

Methods: Using epidemiological-link (epi-link) data, we calculated the probability and duration of confirmation delay for cases with and without an epi-link, among all 3,148 confirmed cases between 5 July and 15 August 2020. Logistic regression was performed to determine the relationship between the number of recently confirmed infections and the probability of confirmation delay for epi-linked (contact-traced) cases. We estimated the impact on this relationship of targeted testing of at-risk groups.

Results: The probability and duration of confirmation delay were associated with the rise in daily case number during growth of the outbreak. The proportion with confirmation delay among contact-traced cases increased from about 60% to nearly 85% as the number of cases grew from 1 to 50 per day (p-value = 0.003). The subsequent introduction of testing services for at-risk groups substantially reduced the proportion and it did not approach 85% again until the daily number of cases exceeded 125. This 2.5-fold improvement in capacity contributed crucially to suppression of the outbreak.

Conclusion: The number of recently confirmed infections is an indicator of the load on the contact-tracing system, the consequence of which can be assessed by the probability of confirmation delay. Measures to monitor and improve contact-tracing efficiency, alongside social distancing interventions, can enable outbreaks to be controlled without lockdown.

Project No.: COVID190215

COVID-32-229
The Safety of High Flow Nasal Cannula and Conventional Oxygen Therapy for Treatment of Patients with COVID-19 Complicated by Respiratory Failure

Prof David HUI[1], Dr Grace LUI[1], Dr Susanna NG[1], Ms Louise YUNG[2], Prof Yuguo LI[3], Dr Hui-Ling YEN[2]
[1]Department of Medicine & Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong SAR, China, [2]School of Public Health, The University of Hong Kong, Hong Kong SAR, China, [3]Department of Mechanical Engineering, The University of Hong Kong, Hong Kong SAR, China

Introduction and Project Objectives: Patients with COVID-19 may develop respiratory failure requiring supplemental oxygen or ventilatory support but there is concern about aerosol generating procedures causing nosocomial transmission.

Methods: This study performed air samplings and environmental swabs on 16 patients with COVID-19 on oxygen via nasal cannula or filtered Hudson mask or high flow nasal cannula (HFNC) to look for any contamination.

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Results: Among 177 air samples, only one positive sample with NiOSH size fraction > 4μm with CT value 37.1 was detected on an 87 yr old male on 2L of O2 via nasal cannula one day after admission while his respiratory specimen CT value was 17.79.

Among 110 environmental samples collected from bedrails, table, chair, bathroom door handle, bed trunk, window fill, floor, pillows and blankets) on 6 patients whose respiratory specimen CT values were 19.6(IQR 7.3) on the day of collection, positive PCR samples were noted on the floor (CT value 34.1) and right bedrail swabs (CT 36.4) in a 73 yr old lady receiving 2L/min O2 via conventional nasal cannula, 10 days after admission post air sampling while her respiratory specimen CT value was 18.54. In a 68 yr old male receiving 2 L/min of oxygen via conventional nasal cannula without coverage by a surgical mask, the pillow and the blanket swabs were positive (CT values 33.39 and 38.77 respectively) while only the pillow was positive (CT value 36.88) when a surgical mask was covering the nasal cannula.

All air and environmental samples were negative among those receiving oxygen via the Hudson mask with filters or HFNC. No patients with COVID-19 received non invasive ventilation at the hospital as this is regarded by the critical care physicians/ intensivists as risky.

Conclusion: This study has shown that oxygen delivery via conventional nasal cannula may cause air or environmental contamination while a Hudson mask with filters or HFNC appear safe for application in the hospital negative pressure isolation room (supported by HMRF#COVID190110).

Project No.: COVID190110

COVID-33-231

An Open-label Randomized Controlled Trial on Interferon β-1b and Remdesivir Combination versus Remdesivir as Treatment for COVID-19 Infection

Prof Fan Ngai Ivan HUNG[1], Dr Kwok-Cheung LUNG[2], Dr Raymond LIU[3], Dr Ricky ZHANG[1], Dr Kwok-Hung CHAN[1], Prof Kwok-Yung YUEN[4]

[1]Department of Medicine, The University of Hong Kong, Hong Kong SAR, China, [2]Department of Medicine, Pamela Youde Nethersole Eastern Hospital, Hong Kong SAR, China, [3]Department of Medicine, Ruttonjee Hospital, Hong Kong SAR, China, [4]Department of Microbiology, The University of Hong Kong, Hong Kong SAR, China

Introduction and Project Objectives: Previous studies suggested that early antiviral therapy was essential in the treatment of COVID-19 patients. We assessed the efficacy and safety of combined interferon beta-1b, and remdesivir for treating COVID-19.

Methods: We conducted a multicentre, prospective open-label, randomized, controlled trial involving adults hospitalized for COVID-19. Patients were randomly assigned to a 5-day combination of interferon beta-1b 16 million units daily and remdesivir 200mg loading on day 1 followed by 100mg daily on day 2 to 5 (double-group), or to remdesivir 200mg loading on day 1 followed by 100mg daily on day 2 to 5 (single-group) as control (1:1). The primary end-point was the time to complete alleviation of symptoms [National Early Warning Score 2 (NEWS) = 0]. The secondary end-points were the time to negative nasopharyngeal swab (NPS) and deep throat saliva (DTS) SARS-CoV-2 RT-PCR to negative and duration of hospitalization.

Results: Among the 212 treated patients (109 in double-group and 104 in single-group), the median days of treatment commencement from symptom onset was 3 days. The baseline demographics were similar. There was no mortality. Fourteen patients required intensive care treatment, 75 patients required oxygen therapy, 10 patients required high-flow oxygen therapy, 6 patients required ventilator support, 1 patient required extracorporeal membrane oxygenation support and 62 patients received subsequent concomitant stress doses of corticosteroid. The double-group had significantly shorter time to complete alleviation of symptoms (NEWS=0) (4 versus 6.5 days; hazard ratio [HR], 12.54; 95% confidence interval [CI], 0.76-1.04; P<0.0001), negative NPS VL (8.5 versus 12 days; hazard ratio [HR], 11.12; 95% confidence interval [CI], 1.05-1.51; p<0.0001), negative DTS VL (8.5 versus 13 days; hazard ratio [HR], 10.77; 95% CI, 0.91-1.31; p<0.0001), and shorter hospital stay (11 versus 13 days; HR, 9.93; 95% CI, 0.55-0.83; p=0.001) when compared to the single-group. The time to onset of IgG RBD seropositive was also significantly shorter in the double-group (8 versus 10 days; HR, 8.9; 95% CI, 0.61-0.96; p<0.0001) with significantly higher microneutralization antibody titre on day 9 (40 versus 5; HR, 12.3; 95% CI, 0.37-0.51; p<0.0001) in the double-group. Adverse events were self-limited with no difference between the two groups.

Conclusion: Early combination of interferon beta-1b and remdesivir was safe and better to remdesivir alone in alleviating symptoms, shorten viral shedding and hospitalization with earlier seropositivity in COVID-19 patients.

Project No.: COVID190125
