Project number: T11-705/14-N

RESEARCH GRANTS COUNCIL
THEME-BASED RESEARCH SCHEME (TRS)

Completion Report on Funded Project

Project start date: *1 January 2015*
Project completion date: *30 June 2020*

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1. Project Title: Viral, Host and Environmental Determinants of Influenza Virus Transmission and Pathogenesis

2. Names and Academic Affiliations of Project Team Members[#]

Project team member	Name / Post	Unit / Department / Institution	Average number of hours per week spent on this project in the current reporting period
Project Coordinator (PC)	Prof JSM Peiris	School of Public Health, HKU	10
Co-Principal Investigators	Prof BJ Cowling	School of Public Health, HKU	10
	Prof Yi Guan	School of Public Health, HKU	10
	Prof David SC Hui	Dept of Medicine & Therapeutics, CUHK	8
	Prof Yuguo Li	Dept of Mechanical Engineering, HKU	8
	Prof John M Nicholls	Dept of Pathology, HKU	5
	Prof Leo LM Poon	School of Public Health, HKU	10
	Prof Wenwei Tu	Dept of Paediatrics & Adolescent Medicine, HKU	8
	Dr Hui-ling Yen	School of Public Health, HKU	12
	Prof Guang Zhu	Division of Life Science, HKUST	8
	Dr Huachen Zhu	School of Public Health, HKU	12

Co-Investigators	Dr Michael CW Chan	School of Public Health, HKU	8
	Prof Matthew TV Chan	Dept of Anaesthesia & Intensive Care, CUHK	2
	Prof Benny Chow	Centre for Housing Renovations, CUHK	2
	Prof DY Jin	School of Biomedical Sciences, HKU	3
	Dr Tommy TY Lam	School of Public Health, HKU	8
	Dr Suki MY Lee	HKU Pasteur Research Pole, School of Public Health, HKU	8
	Dr Chris KP Mok		6
	Dr Sumana Sanyal		6
	Prof PC Sham	Centre for PanorOmic Sciences (*formerly known as Centre for Genomic Sciences*), HKU	1
	Prof PC Shaw	School of Life Sciences, CUHK	5
Collaborators	Prof Donald Milton	School of Public Health, University of Maryland, US	N.A.
	Prof James McDevitt	Dept of Environmental Health, Harvard School of Public Health	N.A
	Dr Elodie Ghedin	NYU College of Global Public Health	N.A
	Prof Michael Katze	Dept of Microbiology, University of Washington, US *(not working in UW anymore and no collaboration with TRS project since Feb 2018)*	N.A
	Dr Yi-Wu Chung	Genomics Research Center, Academia Sinica, Taipei	N.A
	Prof Michael Matthay	School of Medicine, University of California, San Francisco	N.A
	Prof Frank Mckeon	Dept of Biology and Biochemistry, University of Houston (since 2016)	N.A
	Dr Hongjie Yu	Director, Division for Infectious Diseases, China CDC	N.A
	Dr Yuelong Shu	Director, WHO Collaborating Centre for Reference and Research on Influenza, Beijing	N.A
	Prof Edward Holmes	School of Life and Environmental Sciences and Sydney Medical School, University of Sydney	N.A
	Prof Charles J Russell	St Jude Children's Research Hospital, Memphis	N.A
	Dr Zifeng Yang	Guangzhou Institute of Respiratory Disease, The First Affiliated Hospital of Guangzhou Medical University	N.A
	Prof GM Leung	WHO Collaborating Centre for Infectious Disease Epidemiology and Control	N.A

	Dr WH Seto	WHO Collaborating Centre for Infectious Disease Epidemiology and Control	N.A

Please highlight the approved changes in the project team composition and quote the date when the RGC granted approval of such changes. For changes in the project team composition, please submit a separate request, together with the justification and the curriculum vitae of the new member(s), to the RGC three months prior to the intended effective date of the change.

3. Project Objectives

Summary of objectives addressed/achieved:
Please refer to the list of publications and copies of publications at **Appendices I-II** for the publication nos. indicated below.)

Objectives*	Percentage achieved	Remarks**#
1. Understanding the viral, host and environmental determinants of influenza virus transmission between humans, and from animals to humans	100%	• Epidemiological research based on household and other studies [24-45, 53, 54, 86, 91, 94, 107, 110, 119, 139,145, 149] • Hospital cross-infection studies continued [55, 56,126,151] • Evolution, epidemiology, clinical and pathogenesis studies on zoonotic influenza e.g. H7N9; H10N8; H5N6; swine influenza [1-7, 9-15, 84, 88, 93, 108, 121, 128, 132, 152] • Developing and applying methods for virus phenotyping, characterization and risk assessment of zoonotic viruses e.g. Ex vivo and organoid cultures, ferrets. [16-23, 130,131] • Viral quasi-species in transmission in humans and ferrets published and ongoing [46, 47] • Ferret aerobiology [47, 51]. • Correlates of protection and vaccine immunity [96, 111, 121,123,125,134,135,137,141,142] • Response to COVID-19 pandemic [114, 115,148, 150]
2. Understanding the viral and host determinants of pathogenesis of severe influenza	100%	• Pathogenesis of acute lung injury [3,64-70, 87, 95] • Glycan array developed and being validated with currently relevant viruses • TLR10 cellular localization and ligand identification studies completed [57] • Tree-shrew animal model studies completed [104] • Gamma-delta T/NK-cell studies continued [58-63,143, 146] • Molecular virology, structural biology and cell biology [71-77, 78, 79, 90, 98, 100, 103, 112, 117, 120, 129,133,136,138,144]. • Novel vaccine strategies [154]

3. Develop evidence based interventions to reduce transmission and novel therapeutic strategies targeting the host	100%	• Studies in the mock hospital room to investigate hospital cross-infection are now complete and the data analysis is ongoing. • Studies on aero-biology and other factors contributing to transmission of avian influenza viruses within live poultry markets or public places and interventions to reduce such transmission [48-50, 83, 89, 97, 109]. • Basic research on vaccines and antivirals [80, 81, 82, 99, 101]. • Interventions for control of human influenza [102, 106]
4. To foster development of the next generation of researchers of international stature	100%	Staff in place. Research postgraduates and post-doctoral fellows being trained.

* *Please highlight the approved changes in objectives and quote the date when the RGC granted approval of such changes.*

** *Please provide reasons for significantly slower rate of progress than originally planned.*

6. Research Highlights and Outputs

6.1 What are the most exciting research accomplishments of the project?

(Please list five or more of the team's best research accomplishments, such as journal and conference papers, software codes, research infrastructure, etc. For each item, please clearly justify how it has achieved international excellence (e.g. best paper award, invited presentation, citations, product licensed to industry, etc.))

Since the start of the TRS program in 2015, the project team has so far published **154** peer-reviewed international papers cited **4,801** times (h-index=**28**), 70 (45%) being in journals with impact factor >6, 22 (14%) being with impact factor >10. These include Nature (2) (IF: 42.78); Science (2) (IF: 41.06), Nature Medicine (1) (IF: 30.6), Nature Genetics (1) (IF: 29.35), Nature Microbiology (1) (IF: 14.17), Nature Communications (2) (IF: 12.35), Lancet Infect Dis (1), (IF: 21.37), Lancet Respiratory Medicine (2) (IF: 19.3), Sci Transl Med (1) (IF: 16.3), Cell Host Microbe (3) (IF: 15.75), Signal Transduct Target Ther (1) (IF: 13.49), Eur Respir J (3) (IF: 11.81), Nucleic Acid Res (1) (IF 11.5), Small (1) (IF: 10.86), PNAS (2) (IF: 9.68), Trends Microbiol (1) (IF: 9.19), Lancet Child Adolescent Health (1) (IF:8.4), Clinical Infectious Diseases (9) (IF: 8.22), Clinical Chemistry (1) (IF8.6); Emerg Infect Dis (14) (IF: 8.22), Cell Reports (1) (IF:7.8), Clin Translational Immunology (1) (IF: 7.27), J Autoimmunity (2) (IF: 7.54), Eurosurveillance (4) (IF: 7.20), Frontiers in Immunology (7) (IF: 6.43), mBio (1) (IF:6.8), Emerging Microbes and Infections (4) (IF: 6.03).

Please refer to the list of publications at **Appendix I** for the reference numbers cited in the text below.

Five best research accomplishments:

A. Analysis of zoonotic and pandemic risk:

Systematic characterization of influenza viruses to assess zoonotic and pandemic threat is a critical aspect of pandemic preparedness. Work done as part of this TRS has made major contributions towards this goal. As a key illustration, we have developed and characterized human lung airway organoid cultures which provide data with human and avian influenza viruses that are highly correlated with that observed in ex vivo human bronchus cultures, we had pioneered for characterization of influenza viruses previously **[21]**[published in Lancet Respiratory Medicine, cited 31 times so far]. These organoids have all the different cell types present in the human bronchus but these cultures can be maintained indefinitely in culture. This is a **major advance in investigating virus-host interactions and for risk assessment of zoonotic influenza or other respiratory viruses**. Other work has built around this theme. We compared the virus tropism and innate host responses of these H5N6 viruses (both human and bird isolates) with that of HPAI H5N1 and 2009 pandemic H1N1 (H1N1pdm) using ex vivo cultures of human nasopharynx, bronchus and lung. Human H5N6 virus replicated as efficiently as H1N1pdm and with higher replication competence than HPAI H5N1 in human bronchus and had ability to infect human nasopharynx ex vivo cultures suggesting better adaptation to the human upper airways than conventional H5N1 viruses. Thus H5N6 viruses may pose a significant public health threat [16]. We evaluated the replication of human and avian H9N2 influenza viruses in the human respiratory tract using ex vivo respiratory organ cultures and found that although H9N2 viruses infected the human upper and lower respiratory tract, they had decreased ability to release virus from the bronchial epithelial cells possibly due to a weak neuraminidase (NA) cleavage of carbon-6-linked sialic acid (Sia) rather than carbon-3-linked Sia [18]. The tropism and replication competence of avian influenza A H7N9 in the human respiratory tract has been assessed to enhance risk assessment of the pandemic threat posed by these viruses [130]. These human ex vivo lung models have also been used to investigate seasonal influenza B viruses [131].

Impact: The ex vivo cultures of the human respiratory tract as a method of risk assessment (a method pioneered by us) is now accepted as part of the newly launched WHO “Tool for Pandemic Risk Assessment” (TIPRA). A member of this TRS (JSMP) has been involved as a core member in the development of WHO TIPRA and other team members (including YG and HZ) are involved in ongoing WHO/TIPRA risk assessment exercises.

B: Aerobiology of influenza virus transmission and refining the ferret animal model for investigating influenza virus transmission. A major objective of our TRS project was to assess the transmission dynamics and aerobiology of influenza transmission in ferrets as an experimental surrogate for understating transmission between humans. Investigating the airborne particle sizes mediating transmission of influenza has proved to be a challenge. Through the close synergy

between virologists and engineers fostered as part of this TRS, we have designed a novel approach to size-fractionate the aerosols that pass from infected donor ferrets to recipients. We now demonstrate that the airborne transmissibility of the pandemic H1N1 virus inoculated ferrets decreased gradually after initial infection, with airborne transmission efficiency at 100%, 66.7%, 33.3% detected on days 1, 3, 5 post-inoculation. Transmission was mediated by airborne droplets in the range of 2.9-7.9um, consistent with the quantity and size of virus-laden particles released by the donor ferrets. Airborne transmission by donors was most efficient prior to symptom onset and may continue for at least five days after inoculation. Multiple virus gene segments enhanced airborne transmission potential of a swine-origin H1N2 influenza virus among ferrets by increasing the release of virus-laden particles in air **[51]** [Published in PNAS in 2018; cited 30 times]. We believe that this model will become the "gold-standard" for investigating influenza transmission in the ferret model and we are exploring the possibility to extend this approach to humans (pilot studies commenced).
Impact: Our global leadership in this area is demonstrated by our organizing a TRS supported small-group workshop of key opinion leaders and practitioners in the field held in June 2017. Key experimental variables were discussed and identified and these have now been published with a view to standardising the application of the ferret animal model for influenza research **[22].** As a follow-up, we are organizing a benchmarking exercise between laboratories by sharing identical standard virus strains for a comparative assessment of outcomes.

C. Transmission of seasonal influenza viruses within families. The use of household transmission studies to elucidate influenza virus transmission was a major focus of our TRS. The success of this work program is highlighted and summarised in a review entitled "Household transmission of influenza viruses" [28] [Published I Trends in Microbiology, 2016, cited 40 times]. Individuals research projects based upon these household transmission studies include the following.
Viral shedding in influenza A virus infections matched closely with the dynamics of clinical illness. In contrast, viral shedding in influenza B virus infections increased as early as 2 days prior to symptom onset and persisted for 6-7 days after onset with a bimodal pattern. Our results suggest that while clinical illness profiles may serve as a proxy for clinical infectiousness in influenza A virus infections, patients may potentially be infectious even before symptom onset or after clinical improvement in influenza B virus infections. Influenza B behaves fundamentally differently from influenza A in transmission patterns, an important finding and contrary to current assumptions **[24].** This paper was selected as "Editor's Choice" with accompanying editorial in Clinical Infectious Diseases. In a follow up study we found evidence that infected persons with higher viral loads and presence of fever were correlates of higher infectiousness **[25].** Few studies have previously investigated the epidemiological and virological characteristics of asymptomatic and pauci-symptomatic influenza. Using data from our community based studies we showed that the mean levels of influenza viral RNA shedding was approximately 1-2 log10 copies lower and duration of viral RNA shedding was shorter in paucisymptomatic and asymptomatic than in symptomatic cases **[26].** Using household-level data from known-index studies of virologically confirmed influenza A infection, the relationship between an individual's infectiousness and their symptoms was quantified. We found that the presence of respiratory symptoms in an index case does not influence transmission probabilities, with the exception of child-to-child transmission where the donor has phlegm or a phlegmy cough **[27].** Oseltamivir treatment within 24 hours of onset of illness was associated with shorter duration of self-reported illness symptoms but we did not find any association of oseltamivir treatment with duration of viral shedding (by polymerase chain reaction) or with the risk of secondary household transmission **[30].** Thus, the intuitive expectation that antiviral treatment may reduce transmission is not supported by the epidemiological data.
There are few data on the comparative epidemiology of influenza B Victoria- and Yamagata-lineage viruses. Data from the index patients and their household contacts showed that for Victoria-lineage

viruses, the risk of within-household infection among household contacts aged ≤15 years was significantly higher than that for older household contacts, while for Yamagata-lineage viruses, the risk of infection did not differ by age. The two lineages exhibited similar characteristics in viral shedding and clinical illness **[29].** The mechanisms underlying these epidemiologic differences deserve further investigation. Given our expertise in household transmission studies, our team was invited to collaborate in the analysis of household transmission of influenza virus in Nicaragua. We showed that oseltamivir treatment of index patients did not appear to reduce household transmission and that transmissibility of influenza B virus was higher than that of influenza A virus among children **[107].**
Impact: Co-PI BJC led the preparation of the WHO Guidance document entitled:
World Health Organization. (2019). Non-pharmaceutical public health measures for mitigating the risk and impact of epidemic and pandemic influenza: annex: report of systematic literature reviews. World Health Organization. https://apps.who.int/iris/handle/10665/329439. License: CC BY-NC-SA 3.0 IGO.

D. Pathogenesis of acute lung injury. Acute lung injury is the final pathogenic pathway leading to adverse or fatal outcomes following influenza as well as other severe viral respiratory diseases (e.g. COVID-19). Host responses play a role in the development of acute lung injury caused by pathogenic influenza viruses and antivirals alone may not ensure a successful outcome. We developed an in vitro model of acute lung injury and compared the extent to which avian influenza A/H5N1, H7N9 and seasonal influenza A/H1N1 viruses impair alveolar fluid clearance and protein permeability. We demonstrated that virus-induced soluble mediators play a dominant role in such a phenotype. Impaired alveolar fluid clearance was associated with the down regulation of sodium and chloride transporters in the alveolar epithelium, highlighting these molecules as a key drugable target for therapeutic intervention in such disease. We find that viruses such as H5N1 and H7N9 associated with adverse clinical outcomes manifest markedly greater impairment of alveolar fluid clearance than seasonal influenza viruses. We demonstrated that these effects are prevented or reduced by bone marrow-derived mesenchymal stromal cells (MSC) in vitro and in vivo in mice experimentally infected with influenza A/H5N1, showing the feasibility of a novel therapeutic approach to treating patients with acute lung injury caused by pathogenic viruses **[64].** [Published in PNAS 2016; cited 86 times]. We found that umbilical cord MSCs were more efficient that bone –marrow derived MSC in restoring impaired alveolar fluid clearance and protein permeability of A(H5N1)-infected human alveolar epithelial cells **[95].**
We have also showed that MSC therapy improves survival in a mouse model with bleomycin induced lung fibrosis. The alleviation of pulmonary fibrosis by human MSCs was mediated by the PD-1/programmed death-ligand 1 pathway **[65].**
Impact: This is one of the projects selected for taking forward towards therapeutic application under the auspices of the Centre for Infection and Immunity, under the InnoHK scheme.

E. Response to the emergence of SARS-CoV-2 The expertise and infrastructure developed as part of this program led to important and highly cited contributions in response to COVID-19 in 2020. A study initiated under TRS to investigate the size and infectivity airborne particles released by influenza infected individuals also included some with acute respiratory infections infected with seasonal coronaviruses. In this study we also investigated the effectiveness of wearing surgical masks on the release of such airborne infectious particles. We showed that both large (>4μm) and small (<4μm) airborne particles was released by seasonal coronavirus infected patients and that the release of these particles was markedly reduced by the wearing of surgical masks. This had seminal influence on the policy of universal masking for control of spread of COVID-19 **[114]** (published in Nature Medicine in 2020; cited 539 times already and one of the most downloaded research papers among Nature journals soon after it was published).
Within days of the identification of a novel coronavirus as the cause of COVID-19, we developed, validated and shared one of the earliest WHO recommended RT-PCR protocols for detecting

SARS-CoV-2 cited over 400 times so far **[115]** [published in Clinical Chemistry in 2020, cited 402 times; patent application filed]. These reagents and controls were shared with over 140 laboratories in over 70 countries during the early phase of the outbreak to allow them to start testing for SARS-CoV-2. A number of countries made their first detection of SARS-CoV-2 using our reagents, prior to commercial tests becoming available. We were identified as one of the WHO Reference laboratories for the diagnosis of SARS-CoV-2 infections.
Other important work in response to the COVID-19 pandemic includes the development of what is now regarded as the best animal model for SARS-CoV-2, i.e. the hamster **[150]** [published in Nature in 2020, cited 223 times] and antivirals for SARS-CoV-2 [148] [cited 301 times already].

For an overall narrative of the overall research publications please see **Appendix IV.**

6.2 What was the added value of the TRS funding, rather than standard project grant funding?
(For example, could this work have been achieved with other funding scheme, such as the General Research Fund or Collaborative Research Fund? If not, why?)

The TRS project allowed us to plan and execute a integrated and cohesive research program of a scale, output and impact that could not be achieved by individual RGC GRF grants or even CRF grants. The certainty provided by sustained funding for a 5-year period allows us to develop infrastructure (both software and hardware) that could not be attempted with GRF or CRF funds. Examples of these include the following. The household transmission cohort could not be set up and funded in any other way and its impact has been well revealed in this TRS. The Biosafety level 3 team could be funded and sustained in a way that would be impossible with short term funding. It takes years to train a technician to work competently in biosafety level 3 facilities. The availability of such a trained team paid ample dividends during the COVID-19 crisis (SARS-CoV-2 is a biosafety level 3 pathogen). The availability of core funding from TRS allowed a rapid and highly productive research response to the emergence of SARS-CoV-2 as described above. Similarly, the Area of Excellence grant that preceded this TRS similarly allowed us to similarly make an excellent research response to the emergence of the 2009 H1N1 influenza pandemic as well as the emergence of avian influenza A H7N9.
I would like to emphasise that in my view, TRS/AoE type funding is absolutely critical for Hong Kong to make a meaningful impact on the global research stage and such funding should be markedly enhanced in future.

6.3 If the project has not met its original objectives, why?

We would respectfully submit that the project has fully met, and even exceeded original objectives, especially when our contributions to COVID-19 are considered.

6.4 (a) Peer-reviewed journal publication(s) arising <u>directly</u> from this project:
(Please attach a copy of the publication and/or the letter of acceptance if not yet submitted in the previous progress report(s). All listed publications must acknowledge RGC's funding support by quoting the specific grant reference. Please mark the symbol "#" next to the publications involving inter-institutional collaborations)
Please refer to **Appendix I** for the list of peer-reviewed publications and **Appendix II** for copies of publications not yet submitted in previous reports.

(b) Recognised international conference(s) in which paper(s) related to this project was/were delivered:
<u>(Please attach a copy of each conference abstract)</u>
Please refer to **Appendix V** for the list of international conference papers and **Appendix VI** for the list of conference abstracts.

(c) RGC funding should have been acknowledged in all publication(s)/conference papers

listed in (a) and (b) above. If no acknowledgement has been made in any of the publications/ papers, please indicate and provide explanations. NIL

6.5 To what extent this project has strengthened inter-institutional collaborations and other partnerships?
Please refer to **Appendix VII** for details.

6.6 Research students trained (registration/awards):
Please refer to **Appendix VIII** for the list of research students trained.

6.7 Specific products (e.g. software or netware, instruments or equipment developed):

- We developed diagnostic tests for detecting pandemic H1N1 and avian H7N9 for WHO.
- Software package: ggtree [1] is a software package for annotation of phylogenetic trees.

6.8 Other education activities and/or training programmes developed:

- The HKU-Pasteur courses below brought together Hong Kong and international students in small group discussions with international world-leading researchers:
  - 12th HKU-Pasteur Virology Course, 12-24 July 2015
  - 8th HKU-Pasteur Immunology Course, 22 November - 4 December 2015
  - 13th HKU-Pasteur Virology Course: "Bats and viruses", 10-22 July 2016
  - 9th HKU-Pasteur Immunology Course: "Quantitative Immunology", 19 – 31 March, 2017
  - 14th HKU-Pasteur Virology Course: "Viral, Host and Environmental Determinants of Influenza Virus Transmission and Pathogenesis", 6-14 July 2017
  - 8th HKU-Pasteur Cell Biology Course, 14-23 March 2018
  - Croucher Summer Course on Emerging Viral Infections – The One-Health Approach, 1-7 July 2018
  - 10th HKU-Pasteur Immunology Course, 3-14 December 2018
  - 10th HKU-Pasteur Immunology Course Anniversary Symposium, 14 December 2018
- "Little Dr Flu": An outreach program introducing Primary School students in Hong Kong to science and to infectious diseases initiated as part of the KE / community outreach activities of the TRS. Since 2013, over 1,640 students from 21 primary schools and 1 secondary school have visited our laboratory through the "Little Dr. Flu" program. (MC)
- Virtual Keystone Symposia: Preparing for the next pandemic: the emerging infectious disease threat, Jan 28, 2019.

6.9 Please highlight any deliverables indicated in the project implementation timetable endorsed by the RGC which have not been covered or achieved as per sections 6.1 to 6.8 above, and explain/ elaborate. NIL

Project Management

6.10 Please elaborate how the PC has played his/her role in coordinating and managing the project. In addition to holding the meetings of the management team (see above) for resource allocations, the PC has also coordinated and monitored the progress of different projects within the overall grant

with regular discussions with the Co-PIs and Co-Is and through hosting the following research activities:

- regular TRS seminars (see **Appendix IX**), presenting the latest project research findings and allowing a forum for the Co-PIs, Co-Is, PDFs and students to meet and discuss research activities;
- regular lab meetings (weekly) as well as a journal club at which the research students and post-doctoral fellows present their work and discuss recent relevant research publications

7. Awards and Recognition

7.1 Have any research grants been awarded that are directly attributable to the results obtained from this project?

The work from the TRS has enabled TRS researchers to secure funding from competitive international funding agencies to extend and build upon research generated from TRS.

- PI (BJC), TRS "Control of Influenza: Individual and Population Immunity" (Amount: HK$55.555M)
- PI (JSMP) Centre of Infection and Immunity (C2I), InnoHK project funded by Innovation and Technology Commission, a major initiative of the Hong Kong Special Administrative Region Government to develop Hong Kong as the hub for global research collaboration (Amount HK$ 540 million).
- Co-Investigators (HY, JSMP), EU CORDIS grant "Delta Flu - Avian influenza in a changing world" (Amount: HK$2.5M)
- PI (BJC), Major Grant for randomized clinical trial for vaccination from US CDC for Research on the Epidemiology, Vaccine Effectiveness and Treatment of Influenza and Other Respiratory Viruses in Southeast Asia and the Western Pacific. **(**Amount: HK$40M)
- NIH – Surveillance Project on Avian and Swine Influenza (Amount: USD 1.235M)
- NIH - Development of methods and their application for the investigation of the animal sources of human infection with MERS CoV (Amount: USD1.27M)

7.2 Have any project team members participated as invited speakers in or organisers of international conferences as a result of this project?

- Board member (BJC), Antiviral Group Committee Member (HY) of ISIRV (International Society for Influenza and Other Respiratory Diseases).

Leveraging on the theme and focused expertise arising from the TRS we have co-organised two pivotal international meetings (see below):

- Co-Chaired and Organized the Keystone Symposium on "Framing the Response to Emerging Virus Infections" held on 14-18 October 2018 at the University of Hong Kong
- Co-PI (BJC) serving on the Scientific Committee for the Options X for the Control of Influenza to be held on 28 August to 1 September 2019 in Singapore

7.3 Have any project team members taken leadership positions in editorial boards, scientific and professional organisations?

- TRS investigators serve/have served as editors (HY, Antiviral Research) (BJC, Editor in Chief, Influenza and Other Respiratory Viruses; Editor, Epidemiology and Infection) or serve on editorial boards of Lancet Infectious Diseases (JSMP), Emerging Infectious Diseases (BJC); Current Opinion in Virology (JSMP), PLoS Med (JSMP); Antiviral

Research (HY, DH), PLoS One (BJC, HY, MC, YG), Influenza and Other Respiratory Viruses (BJC); Virus Evolution (LLMP); International Journal of Clinical and Experimental Pathology (MC); International Journal of Clinical and Experimental Medicine (MC); Open Journal of Respiratory Medicine (MC)

- Serve on Scientific Advisory Boards of major international research institutions: Doherty Institute for Infection and Immunity, Melbourne (JSMP); Imperial College London HPRU in Respiratory Infections (BJC)
- Scientific Advisory Board of major international grants (EU FP7 project PREPARE, JSMP
- Member, WHO Working Group for Influenza Diagnosis (LLMP).
- Member of biannual WHO Influenza Vaccine Strain Selection meetings (advising on zoonotic/pandemic influenza vaccines) (YG and others)

7.4 Any documentary proof of the application of technologies arising directly from this project?

- We developed diagnostic tests for detecting pandemic H1N1 and avian H7N9 for WHO
- Software package: ggtree [1] is a software package for annotation of phylogenetic trees
- Contribution to the development and implementation of the WHO "Tool for Influenza Pandemic Risk Assessment (TIPRA)"
- Contribution to biannual WHO Meetings on "Antigenic and genetic characteristics of zoonotic influenza viruses and development of candidate vaccine viruses for pandemic preparedness"
- Co-PI BJC led the preparation of the WHO Guidance document entitled World Health Organization. (2019). Non-pharmaceutical public health measures for mitigating the risk and impact of epidemic and pandemic influenza: annex: report of systematic literature reviews. World Health Organization. https://apps.who.int/iris/handle/10665/329439. License: CC BY-NC-SA 3.0 IGO

7.5 Other awards and recognitions as a result of this project (please specify):

- TRS members have been identified by Clarivate Analytics as "Highly Cited Researchers" repeatedly since 2014 (YG, JSMP) and 2015 (LLMP)
- Fellow by Distinction, Faculty of Public Health, UK (LLMP, YG, JSMP, JTW, BJC)
- Croucher Senior Research Fellowship (BJC, LLMP)
- Nature's Science stars of East Asia (JSMP)
- Elected Fellow of American Academy of Microbiology 2016 (JSMP)
- Elected Foreign Associate of The National Academy of Sciences, USA (JSMP)
- Founding Fellow of the Academy of Sciences of Hong Kong (JSMP)
- Honorary Fellow of the Hong Kong College of Community Medicine (JSMP)
- TRS team members promoted to grade of Full Professor (BJC, LLMP)
- HKU Outstanding Researcher Award 2016-17 (BJC, LLMP)
- HKU Outstanding Young Researcher Award 2015-16 (HCZ)
- Two TRS members (JSMP & YG) were awarded a highly prestigious international Award, the 2021 John Dirks Canada Gairdner Global Health Award for their contributions to global public health.

8. Impacts

8.1 What are the current and expected impacts of the project on the long-term development of Hong Kong (social or economic development, e.g. patent, technology transfer, collaboration

with external organisations, etc.)?

Please refer to **Appendix X** for details.

8.2 Others (please specify):

NIL

9. Sustainability of the Project

9.1 Whether there are new ideas evolved directly from this project?

There were many new ideas arising from this project. Some of these were highlighted in the major research highlights summarised in Section 6.1 above.

Specifically, these include

a) The use of human airway organoid cultures for risk assessment of zoonotic viruses for pandemic threat. Further development is being followed up by an Government InnoHK funded Centre of Infection and Immunity
b) The novel method for size fractionating airborne infectious particles to understand particle size that mediates airborne transmission. This is now been extended to COVID-19 and to human influenza
c) Identification of downregulation of sodium and chloride transporters as the mechanism underlying the pathogenesis of acute lung injury following virus infections, providing therapeutic targets for intervention. This is being followed up by an Government InnoHK funded Centre of Infection and Immunity
d) A novel strategy of development of attenuated influenza vaccines based on manuscript ref 154. Patent for novel broad-reactive live attenuated "universal vaccine" for influenza has been filed in 2021. Recombinant viruses expressing alpha-1,3-galactosyltransferease and uses thereof (Application number: PCT/CN2021/071079)

9.2 Whether there are new projects evolved directly from this project?

- PI (BJC), TRS "Control of Influenza: Individual and Population Immunity"
- PI (JSMP), Centre for Infection and Immunity, a InnoHK project funded by Innovation and Technology Commission, Government of the Hong Kong Special Administrative Region.

9.3 Whether there are new collaborations developed directly from this project?

Please refer to Appendix VI for details on collaborations established which directly pertain to this project.

9.4 Please give details on how much money and from which sources has been obtained/requested for the specific purpose of continuing the work started under this project.

- PI (BJC), TRS "Control of Influenza: Individual and Population Immunity" (Amount: HK$55.555M)
- PI (JSMP) Centre of Infection and Immunity (C2I), InnoHK project funded by Innovation and Technology Commission, a major initiative of the Hong Kong Special Administrative Region Government to develop Hong Kong as the hub for global research collaboration (Amount HK$ 540 million).

10. Statistics on Research Outputs

(Please ensure the statistics in this section are consistent with the information presented in other sections of this report.)

	Peer-reviewed journal publications	Conference papers	Scholarly, books, monographs and chapters	Patents awarded	Other research outputs (please specify)	
No. of outputs arising directly from this research project	154	147	0	1	Type	No.
					NIL	0

11. Public Access of Completion Report

(PCs of projects funded in 2010/11 academic year or onwards are required to release the completion reports to the public through the RGC website. Completion reports containing information such as abstracts in non-technical terms, objectives, research output including the list of conference papers / publications / journals and research findings and contact information of PCs should be open to public access.)

Please specify the information, if any, that cannot be provided for public access and give the reasons.

Information that cannot be provided for public access	Reasons
NIL	

12. The Layman's Summary

(describe in layman's language the abstracts and research impact of the project.)

Project Abstract

Influenza is a major threat to global public health. Hong Kong is situated at an epicenter of pandemic emergence. Pandemic influenza arises from animals at unpredictable intervals and can spread worldwide within weeks. Seasonal influenza is a predictable yearly occurrence that is associated with significant morbidity and mortality.

We established a multi-disciplinary influenza research program which has contributed to public health responses locally and globally. We have investigated the viral, host and environmental factors that allow animal viruses to adapt to humans. We have helped improve risk-assessment of animal viruses for pandemic or zoonotic threat, contributed to enhancing global pandemic preparedness and provided evidence-based interventions to contain emerging threats. We have worked with local Government Departments to reduce the threats of avian influenza outbreaks in Hong Kong. We investigated the factors that pre-dispose to transmission of seasonal influenza viruses in humans by studies of influenza transmission within families and within hospital settings. These studies have helped provide understanding

of the mechanisms of influenza transmission and allowed evidence based interventions that can reduce influenza virus transmission within the community and within hospitals. Importantly, this understanding in regard to modes of airborne transmission and the role of non-pharmaceutical interventions helped to inform public health policy in response to the COVID-19 pandemic.

Through studies of influenza in the community and by vaccine trials we have provided a better understanding of the immune mechanisms that protect against influenza and investigated new approaches to influenza vaccine development for both seasonal influenza epidemics and pandemics. We have investigated how influenza viruses cause severe pneumonia and acute lung injury and are pursuing novel therapeutic approaches for treating patients with severe influenza disease. The expertise and teams established as part of this project contributed significantly to the global response to the COVID-19 pandemic.

This program is an inter-disciplinary collaborative project involving The University of Hong Kong, the Chinese University of Hong Kong and the Hong Kong University of Science and Technology. It enhances global public health, provides high quality research, intellectual property, real-time data to inform local, national and global health policy, trains the next generation of scientists and helps maintain and enhances Hong Kong's world-leading status in influenza research.

Research Impact

TRS members and the team have / are:

a) Designated as WHO Collaboration Centre for Infectious Disease Epidemiology and control,
b) Designated as WHO H5 reference laboratory; and Control;
c) Designated as WHO Reference laboratory for providing confirmatory testing for COVID-19
d) Provided real-time data on emerging viral pathogens such as avian influenza H7N9 and H5N6 viruses to WHO, FAO and other international agencies for risk assessment and pandemic vaccine response.
e) Provided submissions to the Legislative Council of Hong Kong on the subject of the "Study of the Way Forward for the live poultry trade in Hong Kong."
f) Organised three pivotal international conferences and workshops on the themes of Respiratory virus transmission and Emerging Virus Infections (including the Keystone Symposium "Framing the Response to Emerging Virus Infections" in Hong Kong) and in scientific advisory board to organise Control of Influenza X to be held in Singapore.
g) Advice Hong Kong Food and Environmental Hygiene Department on modifications implemented in live poultry markets in Hong Kong so as to further reduce zoonotic risk.
h) Participated in biannual WHO Influenza vaccine strain selection meetings;
i) Contributed to development and evaluation of WHO "Tool for Influenza Pandemic Risk Assessment" and take part in regular risk assessment activities.
j) Speakers / organizers of WHO and FAO meetings; training courses in infectious disease outbreak response, working groups
k) Participated in WHO missions / country visits / training visits / expert committees
l) Participate as invited expert in the WHO IHR Emergency Committee on COVID-19

m) Board Member: International Society for Influenza and Other Respiratory Diseases; Editor in Chief, Influenza and Other Respiratory Diseases Journal; Editor, Antiviral Research
n) Serve on SABs of Major International Research Institutes (Institut Pasteur, Paris; Peter Doherty Institute for Infection and Immunity, Australia) and major International Research Programs