

Research Assessment Exercise 2020
Impact Case Study

University: The University of Hong Kong (HKU)

Unit of Assessment (UoA): 03 - Clinical Medicine

Title of case study: Discovery of novel coronaviruses with public health significance

(1) Summary of the impact

The coronavirus (CoV) research team at the University of Hong Kong have pioneered the discovery of novel/emerging CoVs. The discovery of ancestral viruses of SARS-CoV and MERS-CoV and other animal CoVs (e.g. BatCoV-HKU2 and PDCoV-HKU15) have led to timely identification, diagnosis, clinical management, vaccine development and control of new CoV epidemics. The discovery of HCoV-HKU1 has enabled diagnosis and clinical management of respiratory infections caused by this previously unknown virus through the development of diagnostic tests which are now used in hospitals and laboratories worldwide, with over €300M investment in R&D and over 2500 worldwide clinical customers for products such as FilmArray in 2018 [A].

(2) Underpinning research

Key University of Hong Kong (HKU) Department of Microbiology researchers:

Professor KY Yuen, Chair of Infectious Diseases (1992 - present)

Professor PCY Woo, Clinical Professor (1997 – present)

Professor SKP Lau, Clinical Professor and Head of Department (2001- present)

During the SARS epidemic in 2002-2003, researchers at HKU Department of Microbiology were the first in the world to discover SARS CoV (a novel lineage B *Betacoronavirus*) and developed rapid diagnostic tests (3.1). We also discovered its intermediate animal hosts in civets and its ultimate ancestral virus in Chinese horseshoe bats. Since then, we have taken a leading position in the discovery of novel CoVs, including HCoV HKU1 and nearly 30 CoVs in bats and other animals, a number of which later proven to be closely related to emerging CoVs causing new epidemics (3.2, 3.3).

For HCoV HKU1, we showed that it is an etiological agent of respiratory tract infections associated with significant morbidity and mortality (3.2), developed novel diagnostic tests for this virus, and showed that novel genotypes can emerge through recombination. For bat CoVs, we discovered bat coronavirus HKU4 and HKU5 (belonging to a novel lineage C *Betacoronavirus*) five years ahead of MERS epidemic caused by the closely related MERS CoV (3.4); and more recently bat CoV HKU25 which is genetically even closer to MERS CoV, providing clues to its evolutionary path and origin. Our extended works on MERS-CoV included discoveries on mechanisms of renal pathogenesis and effective antiviral treatment. In 2006, our team also discovered BatCoV HKU2 and predicted its emergence potential for interspecies transmission based on its unique spike protein. The virus was recently proven to have crossed species barrier and cause fatal epidemics in swine in China (3.5). For avian CoVs, we have discovered novel viruses which led to a major change in taxonomy by the ICTV with the introduction of a completely new genus, *Deltacoronavirus*. We detected avian-to-swine interspecies transmission resulting in diarrheal epidemics of porcine CoV HKU15 in swine in various countries.

Together with our discoveries of many other animal CoVs, we have laid down an unprecedented detailed phylogenetic map and evolutionary model for CoVs, with bat CoVs being the origins of *Alphacoronavirus* and *Betacoronavirus* and avian CoVs being the origins of *Gammacoronavirus* and *Deltacoronavirus* (3.6). As for lineage A *Betacoronavirus* which is an exception to this model, we have discovered a novel rodent CoV HKU24, with rodents as the likely origin of this unique CoV lineage.

(3) References to the research

- 3.1 Peiris, J. S. M., et al. Coronavirus as a possible cause of severe acute respiratory syndrome. The Lancet 361.9366 (2003): 1319-1325. DOI: [10.1016/s0140-6736\(03\)13077-2](https://doi.org/10.1016/s0140-6736(03)13077-2)
- 3.2 Woo, Patrick CY, et al. Characterization and complete genome sequence of a novel coronavirus, coronavirus HKU1, from patients with pneumonia. Journal of virology 79.2 (2005): 884-895. DOI: [10.1128/JVI.79.2.884-895.2005](https://doi.org/10.1128/JVI.79.2.884-895.2005)
- 3.3 Lau, Susanna KP, et al. Severe acute respiratory syndrome coronavirus-like virus in Chinese horseshoe bats. Proceedings of the National Academy of Sciences 102.39 (2005): 14040-14045. DOI: [10.1073/pnas.0506735102](https://doi.org/10.1073/pnas.0506735102)
- 3.4 Woo, Patrick CY, et al. Comparative analysis of twelve genomes of three novel group 2c and group 2d coronaviruses reveals unique group and subgroup features. Journal of virology 81.4 (2007): 1574-1585. DOI: [10.1128/JVI.02182-06](https://doi.org/10.1128/JVI.02182-06)
- 3.5 Zhou, Peng, et al. Fatal swine acute diarrhoea syndrome caused by an HKU2-related coronavirus of bat origin. Nature 556.7700 (2018): 255-258. DOI: [10.1038/s41586-018-0010-9](https://doi.org/10.1038/s41586-018-0010-9)
- 3.6 WOO, Patrick CY, et al. Discovery of seven novel Mammalian and avian coronaviruses in the genus deltacoronavirus supports bat coronaviruses as the gene source of alphacoronavirus and betacoronavirus and avian coronaviruses as the gene source of gammacoronavirus and deltacoronavirus. Journal of virology, 2012, 86.7: 3995-4008. DOI: [10.1128/JVI.06540-11](https://doi.org/10.1128/JVI.06540-11)

Key research grants:

- Theme-based Research Scheme: Molecular basis for interspecies transmission and pathogenesis of Middle East Respiratory Syndrome Coronavirus (PI, Professor PCY Woo; HK\$35,620,000; 01/11/2015-31/10/2020)
- NSFC/RGC Joint Research Scheme: Understanding the evolution and interspecies transmission of betacoronaviruses by structural and biophysical approaches (PI, Professor KY Yuen; HK\$1,098,911; 01/01/2015-31/12/2018)

(4) Details of the impact

Impacts include: commerce, health and welfare

Main beneficiaries: industry, patients and the public

Our discovery of novel coronaviruses, identification of its animal source and development of its diagnostic tests has had considerable global economic and health impacts.

Impacts on commerce and industry

Based on our discoveries (3.2), numerous commercial rapid diagnostic kits have incorporated HCoV-HKU1 in their panels for respiratory infections, including FilmArray Respiratory panel (bioMérieux), ViroReal (Ingenetix), FTIyo Respiratory pathogens 16, 21(plus) & 33 (Fast Track Diagnostics), FTD Respiratory pathogens 21(plus) & 33, NxTAG® Respiratory Pathogen Panel (Luminex Corporation) and so on. Taking bioMérieux as an example, molecular biology had grown progressively from 5% in 2013 to 23% in 2018 of total sales, which was successfully driven by the FilmArray line [Ai]. A strong increase in sales from 31% in 2013 to 44% in 2017 and 2018 was observed in the Americas region, especially in the FilmArray line [Ai]. The number of FilmArray installed base has increased from 6100 in 2017 to 8200 units in 2018 while the number of customers also grew from 1900 to 2600 [Ai, B]. The company has invested €186M in 2013 and up to €327M in 2018 in R&D, reflecting the contribution by the intensified activities with FilmArray line [Ai]. An increase with 310 workforces in 2013 to 800 workforces in 2018 reflected the importance of commercial team expansion to support the growth of the FilmArray line [Ai]. An R&D breakthrough was reported in April 2017 concerning the development of FDA cleared and CE marked BIOFIRE FILMARRAY respiratory panel 2 Plus which is able to test 18 viruses and 4 bacteria, including HCoV-HKU1 and MERS-CoV, within 45 minutes to facilitate rapid diagnosis [Aii].

Impacts of Healthcare services and Patients Benefit

Our discovery of lopinavir-ritonavir and interferon- β 1b as effective antiviral treatments for MERS in a non-human primate model [B] was included in the World Health Organization MERS-CoV Global Summary and provided the scientific basis for their use in patients during MERS outbreaks in the Middle East and South Korea and an ongoing multicentre double-blind randomized controlled trial (MIRACLE trial, NCT02845843, sponsored by King Abdullah International Medical Research Center, which aims to transform lab results into products that improve the quality of life). During the Korean outbreak in 2015, South Korea MERS rapid response team together with Centre for Infection Diseases, National Medical Centre, Seoul, recommended our type 1 interferon plus lopinavir/ritonavir combination as the first-line regimen in the published antiviral treatment guideline for MERS [B, C].

Some of the top ten US hospitals use Filmarray and all private hospitals in HK/Macau are equipped with Filmarray systems in clinical routine [D]. These commercial assays assist clinicians to reduce the misuse of antibiotics during treatment of respiratory infections and facilitate patient management and implementation of infection control measures (patient allocation, antibiotics stewardships, etc.) [Ai]. As for CoV-HKU2, Swine Health Information Centre has set a high priority for research and development of rapid diagnostic and serological tools for swine samples in US [E].

Impact on health policy

The tracking of SARS origin in animals has provided a crucial example to guide public health measures in segregating the animal carriers with humans, prompt tracking and control of animal-to-human transmission of emerging pathogens like MERS-CoV. As a result, continuous surveillance of animal viruses and identifying potential emerging zoonotic viruses was incorporated as public health policies with government funding [Fi-ii]. This notwithstanding, our experience in antiviral treatment for coronavirus infections has formed the scientific basis with impact on disease control by international public health organizations, e.g. Public Health England and the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) [G].

When MERS-CoV was discovered, it was most closely related to BatCoVs HKU4 and HKU5, the only two members in Lineage C *Betacoronavirus* [H]. Based on the available epidemiological and genome data of HKU4 and HKU5, camels were later found to be the immediate animal source of MERS coronavirus, while bats may be a possible ancestral origin [H]. Our discovery of BatCoV HKU25 further fills the evolutionary gap between bats and camels. These findings were important in guiding public health measures in the Middle East such as laboratory diagnosis of suspected cases at border control, avoiding camel-to-human transmission and continuous hunt for ancestral bat viruses [Fi-ii, Ii-ii]. Without our founding works on SARS and bat coronaviruses, the rapid identification and accurate diagnosis of MERS-CoV after its emergence in 2012 and prompt implementation of public health policies made in late 2013 to control its transmission would not have been possible [Fi-ii, Ii-ii].

Our discovery of BatCoV HKU2, which did not receive much attention until when it caused fatal epidemics in piglets in China (our paper was cited in Nature, 3.5), facilitated the discovery of this novel swine disease agent by enabling identification of bat origin and rapid detection of infected piglets, with no further reports of massive outbreaks since 2018. This has led to a new policy by the National Institutes of Health and Swine Health Information Center in US with research and development funding on CoV-HKU2 [E, 3.5]. Our discovery of porcine CoV HKU15 (PDCoV), has similarly facilitated the early recognition and control of new diarrheal epidemics in swine population in various countries, and minimized economic loss in the agricultural industry [E].

Impacts on education and public understanding of science

Our team members have served in various societies and hospital/government committees (K.Y. Yuen, S.K.P. Lau, P.C.Y. Woo) with direct influence on international/local public policies, including member of the coronavirus section of International Committee on Taxonomy of Viruses (ICTV) (P.C.Y. Woo) [Ji-ii], consultant/advisor to the Hong Kong government such as Department of Health and Center for Health Protection (K.Y. Yuen, S.K.P. Lau, P.C.Y. Woo) [Fi-ii, Ii-ii], which in turn

facilitated the Department of Health in giving advice on the prevention and management of MERS for the general public, travellers and universities, including good personal and environmental hygiene maintenance, travel advice and proper reporting procedures in the advisory document (Iiii). We have continuously made numerous press releases, conferences, TV and newspaper episodes to the media and public, and hence raised public awareness on CoV transmissions, emergence potential, pathogenesis, personal hygiene and travel advice. We have also held educational seminars, laboratory visits with hands-on experience, and exhibitions on CoVs for various local institutions, with numerous positive written and informal feedbacks from questionnaires and post-event sharing sessions with the beneficiaries (URL: http://www.microbiology.hku.hk/09_KE.html). Participants were particularly impressed by the laboratory visits with hands-on experiments. These KE activities have successfully aroused students' interests in topics concerning infectious disease control and virus discovery. Secondary school teachers and students found the seminars, e.g. "Coronavirus discovery in Hong Kong" and "Early diagnosis of Middle East Respiratory Syndrome", very impressive and helpful as the contents are complementary to the topic "Microorganisms and Humans and Biotechnology" under the Hong Kong Diploma of Secondary Education biology syllabus parts VII & VIII.

(5) Sources to corroborate the impact

[Ai] bioMérieux 2013-14, 16-18 Annual Reports (P. 50 (2013); P.50-51 (2014); P. 6 (2016); P. 7, 29 (2017); P. 6, 7, 33 (2018) and FY2018 Results & 2019 Outlook. Pages 6, 12. (Date of access: 24/09/2019)

[Aii] bioMérieux receives FDA Clearance for BioFire's FilmArray® Respiratory Panel 2 (RP2)-Press Release. Page 1. (Date of access: 25/09/2019)

[B] Chan, Jasper Fuk-Woo, et al. Treatment with lopinavir/ritonavir or interferon-β1b improves outcome of MERS-CoV infection in a nonhuman primate model of common marmoset. The Journal of infectious diseases 212.12 (2015): 1904-1913. DOI: [10.1093/infdis/jiv392](https://doi.org/10.1093/infdis/jiv392).

[C] Chong, Yong Pil, et al. Antiviral treatment guidelines for Middle East respiratory syndrome. Infection & chemotherapy 47.3 (2015): 212-222. Page 5. DOI: [10.3947/ic.2015.47.3.212](https://doi.org/10.3947/ic.2015.47.3.212)

[D] Email Evidence - Sales Information from Senior Manager of bioMérieux China Limited

[E] Swine Health Information Center 2018 Progress Report. (Date of access: 10/08/2019)

[F] Consultancy Service for Enhancing Laboratory Surveillance of Emerging Infectious Diseases for Department of Health: Program on human and animal surveillance of novel and emerging microbes.

i. Consultancy service agreement (not for open access)

ii. Annual Reports 2013-2018 (not for open access)

[G] Decision Support: Treatment of MERS-CoV v.1.0. Public Health England. ISARIC. Page 11, 12, 16, 17, 18, 19. (Date of access: 06/2019)

[H] Woo, Patrick CY, et al. Genetic relatedness of the novel human group C betacoronavirus to Tylonycteris bat coronavirus HKU4 and Pipistrellus bat coronavirus HKU5. Emerging microbes & infections (2012): 1-5. DOI: [10.1038/emi.2012.45](https://doi.org/10.1038/emi.2012.45)

[I] Centre for Health Protection, Department of Health:

i. Middle East Respiratory Syndrome (formerly known as Severe Respiratory Disease associated with Novel Coronavirus). Page 8, 13, 19, 22. (not for open access)

ii. Consensus Summary on Severe Respiratory Disease associated with Novel Coronavirus (not for open access)

iii. Health Advice to School for the Prevention of Middle East Respiratory Syndrome (MERS)

[J] International Committee on Taxonomy of Viruses (ICTV):

i. de Groot, Raoul J., et al. Commentary: Middle East respiratory syndrome coronavirus (MERS-CoV): announcement of the Coronavirus Study Group. Journal of virology 87.14 (2013): 7790-7792. DOI: [10.1128/JVI.01244-13](https://doi.org/10.1128/JVI.01244-13)

ii. Taxonomic proposal to the ICTV Executive Committee. Page 1, 7, 11, 14, 20, 21, 22. (Date of access: 24/09/2019)