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One world, one health
Joseph Sriyal Malik Peiris

The past year has underscored the threat that emerging viruses pose to global health. The 2021 John Dirks Canada Gairdner Global Health award recognizes the contributions of Joseph Sriyal Malik Peiris and Yi Guan toward understanding the origins and options for control of newly emerging infectious disease outbreaks in Asia, notably zoonotic influenza and severe acute respiratory syndrome (SARS). Nicole Neuman of Cell corresponded with Malik Peiris about his path to studying emerging infectious diseases and the challenges of this work. Excerpts of their exchange are included here.

Nicole Neuman: What brought you to the field of virology? What is the motivation to study different viruses throughout your career?
Malik Peiris: When I was in junior high school in Sri Lanka, we had an English reading assignment and the book was “Pasteur and Modern Science” by Rene Dubos. I was fascinated by the life of Pasteur and his logical approach to conceptual problems such as “spontaneous generation”, the germ theory of disease, and the practical applications of vaccination to prevent infectious diseases. That inspired me to become a researcher and ignited an interest in infectious diseases. When I finished high school, I really wanted to be a chemist, like Pasteur, but was prevailed on by my grandfather, who was a medical doctor, to try medicine first. Thus I entered medical school (1967) and after graduation completed a few years of clinical practice. But my interest in research and infectious disease persisted. I therefore joined the Department of Microbiology at the Faculty of Medicine of my alma mater, University of Peradeniya, Sri Lanka, in 1974. This choice was also reinforced by professor of microbiology Chubby Arseculeratne, whose success illustrated to me that it was possible to do good research even in a setting with limited resources. Initially, my passion was for immunology, but to my dismay, there was already someone earmarked to train in immunology. Professor Arseculeratne wanted me to do virology because there was no virology established at the university and indeed relatively little virology in Sri Lanka overall. I was dismayed because what I had learnt of clinical virology up to that time was that viral diagnosis took weeks, by which time the patient most likely had recovered or succumbed. I was however comforted by new developments in “rapid viral diagnosis” being developed in Europe by Phillip Gardner (Newcastle upon Tyne) and others.

I went to Oxford for my postgraduate training in virology at the Dunn School of Pathology, University of Oxford, with James Porterfield who worked on arboviruses. He gave me the challenge of investigating a new observation that had been made by Scott Halstead who showed that antibodies could enhance replication of dengue viruses. Understanding the mechanisms and antigenic specificity of this phenomenon formed the basis of my doctoral thesis—a very exciting and productive time. Upon completion of my PhD (1980), rather than taking up a post-doctoral fellowship, I wanted to get my certification as a clinical virologist. This I did, in Birmingham with Tom Flewett (discoverer of...
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rotaviruses) and in Newcastle upon Tyne with Dick Madeley, where Philip Gardner had previously demonstrated the feasibility of rapid viral diagnosis.

After successfully completing my membership of the Royal College of Pathology, UK, I returned to Sri Lanka to set up a virology laboratory from scratch. In retrospect, I think that period (1982–1988) was the period of my career I am most proud of. I was able to successfully set up a virology research unit in a lab that had no cell culture or virology capacity hitherto and in spite of minimal local funding. I was fortunate to have funding from the Wellcome Trust and the US National Institutes of Health via a program called BOSTID. We did some interesting work on the epidemiology of arboviruses and diarrheal pathogens in Sri Lanka, and in collaboration with an excellent parasitologist, Kamini Mendis, developed the first available monoclonal antibodies reactive to Plasmodium vivax malaria, and helped define antigen specificities that could be targeted to develop “transmission blocking immunity”. We trained a number of graduate students who are now excelling within Sri Lanka and in other parts of the world (including at NIH in Bethesda, Maryland, USA).

By 1988, the political situation in Sri Lanka was becoming dire, with constant interruptions to work because of insurgent activities. I then moved back to my old lab at Newcastle upon Tyne, UK, as a clinical virologist. Sadly, arboviruses were not a major public health problem in the UK and I worked on viruses relevant in the immunocompromised host (i.e., herpesviruses). In 1995, I took up the challenge of setting up a clinical virology unit at the Queen Mary Hospital and the University of Hong Kong. I pioneered the application of rapid viral diagnosis, including rapid diagnosis of respiratory pathogens. There was skepticism of the relevance of diagnosing respiratory viruses, because in 1995 we had no antivirals to treat these infections. It was fortuitous that 1997 saw the emergence of “avian flu” H5N1 in Hong Kong and the rapid respiratory virus diagnostic service proved its weight in gold! This led me to focus my future research on influenza viruses at the animal-human interface. In this I was inspired and mentored by Robert Webster who helped obtain research funding from NIAID for work on avian influenza viruses in Hong Kong. That is where I joined my colleague (and fellow Gairdner Prize awardee), Yi Guan.

Thus, my motivation to study different viruses has been driven by my environment, context, and opportunity. One may think this is a tortuous path to the “focus” of research in one’s career, but I learnt a lot along the way. But from 1997 on, my focus has been on emerging respiratory viruses at the animal-human interface—avian and swine influenza, human influenza, SARS, MERS, and more recently COVID-19.

NN: What is the biggest challenge you have overcome during your research of unknown viruses, for example your studies of SARS?

MP: There are many challenges in dealing with emerging infectious diseases. Over 70% of newly emerged infections arise from animals with pathogens crossing species barriers to humans. This means that such spillover events cannot be anticipated, managed, or adequately responded to by the human health sector alone or within the laboratory. It requires a truly multidisciplinary effort involving collaboration between the animal health, environmental health, human health, and laboratory sectors—i.e., a “One Health” response. This may be difficult to achieve in practice because of professional and administrative “silos” —we are more comfortable in our own comfort zones. But my own experience has been that such interdisciplinary collaborations have been extremely fruitful and rewarding.

My initiation into One Health began long before this became a fashionable phrase, when I was working in Sri Lanka, investigating the first massive Japanese encephalitis outbreak in that country in 1985. Prior to that, I was primarily a “lab person”. But to understand this outbreak, I had to work with clinicians, veterinarians, entomologists, and environmentalists, and thoroughly enjoyed the experience. I have been comfortable working across disciplines ever since, and indeed that is what I have been doing, whether it is with influenza or coronaviruses (SARS, MERS, and now COVID-19). For example, the work done by Yi Guan, myself, and our team in collaboration with our Department of Agriculture showed that H5N1 viruses were being imported into Hong Kong from 1999 onward, and clearly showed that these viruses were circulating in the wider region. But the region failed to heed these warnings, until 2004 when suddenly 10 Asian countries woke up to the fact that H5N1 viruses were circulating within their borders. In many (not all) places, this delay meant that it was almost too late to eradicate it. Early attention may well have prevented the much larger impact of these viruses, to the poultry industry as well as to human health. While pathogen adaptation is one key factor in these zoonotic species-jumps, the reason why such events are increasing in recent decades is primarily due to human behavior and activities. For example, changes to livestock production, environmental degradation and encroachment, the pet animal trade, international travel and trade, climate change, human behavior, and others.

While surveillance at the animal-human interface is important, it is also important to “risk assess” what we find, to identify which viruses we need to focus on or respond to before they become pandemics. For example, over the past three decades, we have seen the emergence of avian influenza H5N1, H5N6, H5N8, H7N9, H9N2, and others. We also see swine influenza viruses undergoing rapid change and evolution. Which of these should we focus on in terms of preemptive pandemic preparedness? As COVID-19 illustrates, responding after a pandemic has started is always “behind the curve”. In the field of influenza, we have made some progress toward a
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systematic and structured risk assessment framework, for example the IRAT or TIPRA frameworks for risk assessing animal viruses for pandemic threat. But for other groups of viruses, including coronaviruses, we are far behind. That, I think, is the “grand challenge”.

Another important issue is trying to understand common pathways of viral “emergence” so that we can use generic measures of risk reduction. For example, the demonstration that live poultry markets are a major amplification site of avian influenza viruses allowed us to use market management interventions such as rest days or “day-only” poultry markets and demonstrate major reduction in virus amplification in these markets associated with these interventions. Similarly, understanding that wild-game animal markets were the interface for spillover of SARS coronavirus 1 to humans in 2003 (work done by my colleague Yi Guan) led to the closure of these markets and very likely prevented reemergence of SARS-CoV-1 in 2004. Furthermore, understanding that many zoonotic avian influenza viruses emerge by the genetic reassortment of influenza viruses from aquatic birds and terrestrial (e.g., chicken) poultry provides an option to reduce such emergence by separating the marketing chains of aquatic and terrestrial birds.

Once a spillover event has taken place, the major problem is recognizing that an unusual event has occurred. Many diseases, e.g., viral pneumonia or viral respiratory infections, are common disease syndromes and it is difficult to recognize that there is a new pathogen afoot. This is why alerting clinicians, epidemiologists, veterinarians, and microbiologists is so crucial. Even when an unusual outbreak is recognized, it is often difficult to know which patients to investigate. Then, there is the tremendous pressure for “results” in “identifying the cause”. This can lead the unwary to jump to wrong conclusions. You really need to be very careful, systematic, and disciplined to avoid these pitfalls.

These were the problems we faced in Hong Kong, when we heard of an unusual severe respiratory disease circulating in Guangdong Province, Southern China in February 2003. There are thousands of people crossing between Guangdong and Hong Kong every day. It was inevitable that this unusual disease would spill over into Hong Kong. In collaboration with the Hospital Authority of Hong Kong, we were able to set up a surveillance system of all severe viral pneumonia with undetermined etiology in Hong Kong with a recent travel history to Guangdong. We identified those who were negative for known viruses and tried different techniques to seek a novel pathogen in the others. At that time, NextGen sequencing was not yet readily available. We had several “molecular fishing” approaches which I set up with my colleague Leo Poon. We screened the specimens with “broad range” RT-PCR and PCR primers that span across viral families. We also set up viral culture to isolate an unusual virus. We tried all the conventional cell lines used to grow respiratory viruses with negative results. We then started to use other cell lines available in the laboratory that were not routinely used for culture of respiratory viruses, and we managed to isolate viruses from two patient specimens. Using a panel of paired sera from other suspected SARS patients, we demonstrated that all these patients seroconverted to the new virus while control sera did not. That strongly suggested that the virus we had growing in culture was the cause of the new disease, which had been named by the World Health Organization (WHO) as severe acute respiratory syndrome (SARS). We then went on to identify the virus a novel coronavirus, SARS-coronavirus. We also generated a partial genome sequence of the virus that allowed us to develop and deploy diagnostic RT-PCR tests for the infection within days of the partial viral genome becoming available. We were sharing our data in real time with the WHO laboratory network of labs across the world coordinated by WHO to investigate this new disease. However, there were many other claims of alternative etiologies, chlamydia, human metapneumovirus being some of these false leads. We were rapidly able to show the clear association between the new virus and the disease SARS. In parallel, two other labs in the USA (CDC) and Germany (Dr. Christian Drosten) also found a novel coronavirus in patients with suspected SARS.

From there, we were then able to quickly define the virological, clinical, and pathological features of this illness and understand how transmission could be interrupted. It was fortuitous that SARS-CoV-1 viral load in the upper respiratory tract was low in the first few days after symptom onset but increased later in the illness. This meant that transmission was not common in the first few days after symptom onset. This allowed early diagnosis and patient isolation to interrupt transmission in the community and bring the global outbreak under control. The containment of SARS in 2003 was a great triumph for global public health and it was a privilege to have worked with many other researchers, public health professionals, and WHO in this effort. In contrast, we reported very early (February 2020) that SARS-CoV-2, though a closely related virus, had a very different viral load profile in the upper respiratory tract, and we predicted that this disease was unlikely to be contained by the same measures that worked with SARS. Sadly, this was the case.

**NN:** How have your experiences in different viruses have helped with your work on SARS-CoV-2?

**MP:** Since my research has been on emerging respiratory virus diseases (influenza, SARS, MERS), there are many common themes that cut across all these viruses that are relevant to COVID-19. For example, the animal-human
interface, understanding the determinants of the spillover of viruses from animals to humans, how viruses adapt to transmission in humans, how these viruses cause severe respiratory disease, and most importantly, how these viruses are transmitted. Over 10 years ago, we identified the question of how respiratory viruses are transmitted as a big knowledge gap. Although there were many dogmas in this field, the scientific evidence base was weak. Therefore, a group of us put forward a large 5-year consortium research proposal to the Research Grants Committee of Hong Kong to better understand influenza virus transmission, both between humans and from animals to humans. This project was very fruitful and provided a knowledge base to address the questions of the transmission respiratory viruses in general, including COVID-19, when it arose. For example, work done as part of this program by my colleague Ben Cowling had shown that in people infected with seasonal coronaviruses and with influenza, wearing surgical masks reduces the release of infectious airborne respiratory droplets produced by breathing or coughing. Although this study was done with “seasonal” coronaviruses rather than SARS-CoV-2, the information was a vital part of the evidence base in support of “universal masking” as a measure for reducing COVID-19 transmission, given the observation that pre-symptomatic transmission was important in COVID-19 transmission. Also, as part of this consortium, my colleague Hui-ling Yen developed an innovative methodology to fractionate infectious airborne respiratory droplets so that she was able to define the size of airborne respiratory droplets that transmit influenza in experimental animal models. This work is now being extended to SARS-CoV-2 and to humans. She also demonstrated that hamsters are an excellent experimental model for investigating transmission of SARS-CoV-2. So, our research directions over the years have been an ideal training ground for responding to SARS-CoV-2.

NN: How do you balance your life and research?

MP: Work-life balance with the type of work I do is very challenging. Indeed, one of my regrets is that I did not spend more time with my young and growing family, my wife, daughter, and son. Time passes quickly with children as they develop and grow and time lost cannot be regained. Thankfully, they understand this commitment. They are now settled and doing well in their chosen professions. My “plan” was that 2020 would be the year that I would commence fractional working so that my wife and I could have more time to spend with our son and daughter, who are in different parts of the world. Well, that did not turn out as planned. COVID-19 saw to that. Not only was fractional working not possible but international travel is on hold. I hope things will gradually change in 2021, with the rollout of safe and effective vaccines—truly a remarkable demonstration of the potential of science.

NN: Thanks so much for sharing your experiences with us, and congratulations on your Gairdner Award. Do you have any closing thoughts for our readership?

MP: What our research group has been able to achieve has been due to excellent collaborations with many partners too numerous to mention. However, Dr. Rob Webster (St. Jude’s Children’s Hospital, Memphis) and the WHO need special mention as well as research funding from NIAID (CEIRS); the Research Grants Council of Hong Kong; the Health and Medical Research fund, Hong Kong; and others.

Thinking of the future, COVID-19 has clearly shaken the foundations of modern social, economic, and political systems. Many decades ago, Rene Dubos warned that “—at some unpredictable time and in some unforeseeable manner, nature will strike back”. An event such as this pandemic was highly predictable and even the likely target pathogens were identified, but investment in both research and public health capacity was too little and too late. The underlying causes for these emerging viral disease outbreaks still exist and they are mostly driven by human activities. So, the need to prepare much better for future epidemics and pandemics should no longer be in question. But will the commitment remain after the acute crisis has passed? It was transient after SARS.

There are even greater but more insidious crises with potential for even greater catastrophes than those posed by COVID-19. These include climate change, environmental pollution, and loss of biodiversity. I hope our experience with COVID-19 can be used to push for more aggressive action to confront these threats, which require even more radical changes in our behavior and lifestyles. Our current model of “economic growth” risks rupturing the limits of planetary sustainability. In nature, nothing grows forever—the human species is no exception.