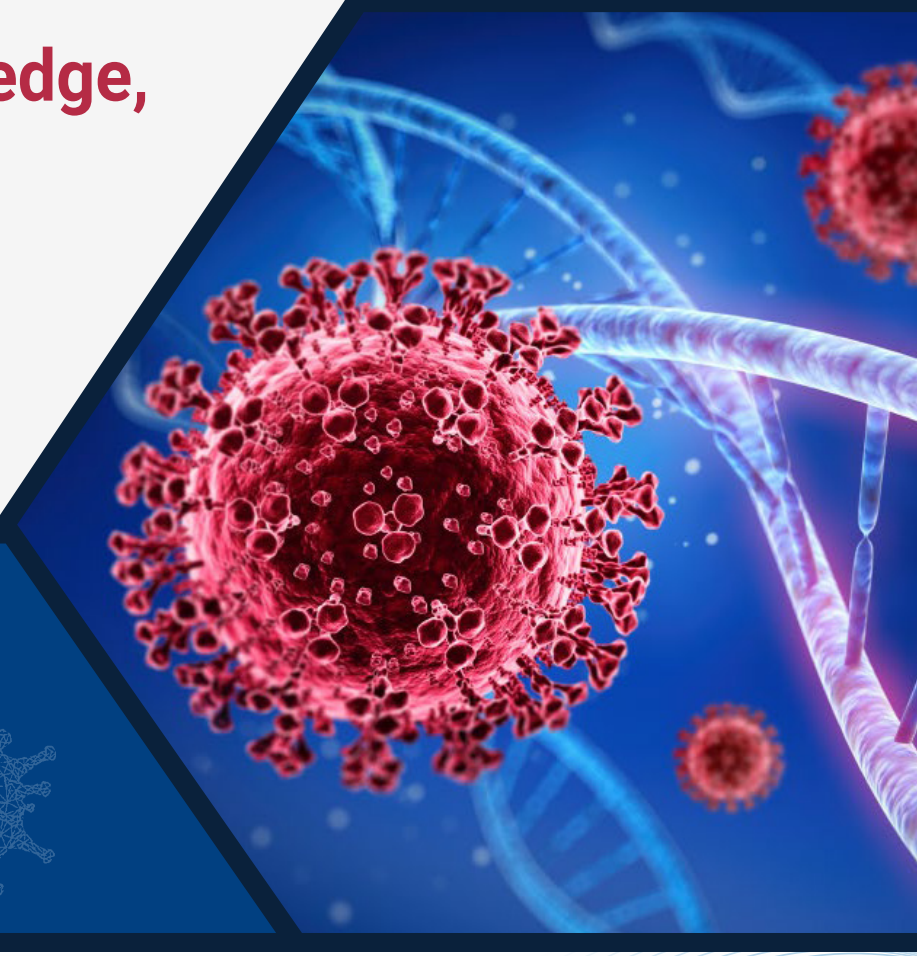
NUS National University of Singapore | Yong Loo Lin School of Medicine

12 Jan - 21 Feb 2022
7 - 9 pm SGT (GMT+8)
Monday & Wednesday

COVID-19:
Biomedical Insights Into An Evolving Epidemic

Translating Knowledge, Saving Lives



COURSE COMPENDIUM

FOREWORD

Titled "COVID-19: Biomedical Insights Into An Evolving Epidemic (Translating Knowledge, Saving Lives)", the educational webinar series was launched by the Department of Microbiology and Immunology at Yong Loo Lin School of Medicine, National University of Singapore, with the aim to discuss insights on recent SARS-CoV-2 discoveries and breakthroughs, as well as lessons learnt in the past two pandemic years. Through engaging lectures and dynamic discussions by a team of international experts, the webinar series featured a wide range of topics on the biology and biomedical research behind the COVID-19 pandemic.

Field leaders introduced the science behind SARS-CoV-2 transmission, zoonosis, virus evolution, epidemiology and modelling, before shifting gears to focus on the viral life cycle and genetics; infectious disease clinicians elaborated on COVID-19 disease pathology and clinical management of disease progression; a panel of key specialists presented crucial advances in the understanding of immune responses and microbiome features in the context of long COVID and paediatric infections; other field experts analysed recent, and sometimes controversial, developments in SARS-CoV-2 vaccines, treatments, diagnostics and clinical trials. Importantly, new technological innovations in the field of artificial intelligence as applied to diagnostics and therapy were also highlighted.

The series concluded with a stimulating panel discussion among coronavirus experts on the new normal, living with COVID-19 and hopes for the future as we learn from the mistakes and successes of the current scourge. We are deeply grateful to the Victor and William Fung Foundation for the strong support of this initiative at the NUS Yong Loo Lin School of Medicine, and thank them for their philanthropy, which has helped inform, update and train medical students, clinicians, and researchers through this timely educational webinar series. We are pleased to share the highlights of the webinar series in this book, and hope that you will have an enriching time reading them.

Associate Professor Kevin SW Tan
Programme Director
Head, Department of Microbiology and Immunology
Healthy Longevity Translational Research Programme
Vice-Dean, Graduate Studies
Yong Loo Lin School of Medicine, National University of Singapore

Associate Professor Pablo Bifani
Co-Programme Director
Department of Microbiology and Immunology
Research Director, Infectious Diseases Translational Research Programme
Yong Loo Lin School of Medicine, National University of Singapore

Dr Rajesh Chandramohanadas
Co-Programme Director
Faculty Scientist EII, Pathogen Biology Program
Rajiv Gandhi Centre for Biotechnology
Kerala, India

In July 2020, we launched a 16-hour long educational series on COVID-19 (BIEE1) based on the urgent need to carefully examine and discuss on-going basic research on this devastating pandemic. Based on positive feedback and requests, we organized a follow-up series, that coincided with a year after the start of the pandemic. The 18-hours long certificate course (BIEE2) was held in January 2021 and addressed pertinent aspects of the pandemic in the 6 months since the first series. BIEE2 involved a wider selection of top scientists from around the world and provided up-to-date knowledge of virus biology and the on-going pandemic. It was successfully organized, and the feedback was better than that for BIEE1. On overall satisfaction, BIEE2 scored 4.66/5 (BIEE1 scored 4.44); improving understanding to the science of COVID-19, BIEE2 scored 4.62/5 (BIEE1 scored 4.33); on likelihood of recommending similar webinars to peers, BIEE2 scored 4.74/5 (BIEE1 scored 4.44). Many participants highlighted how much the course had contributed towards a better understanding of the complex scientific aspects of COVID-19, and several indicated a new appreciation for the work of frontline healthcare workers and researchers. BIEE2's global reach and impact was evidenced in the demographics of the attendees, many of whom took the course from South America, Europe or Asia. For the healthcare professionals and policymakers who attended, it was hoped that the unique scientific depth provided by the lessons had helped them make well-informed decisions based on scientific rigour.

In May 2021, we witnessed a global resurgence of COVID-19, despite high hopes of the rollout of various efficacious vaccines. Breakthrough infections and the rise of the Delta variant (B1.617 mutant), first identified in India, had many countries walking on a knife's edge. Many nations were caught off guard by this turn of events. Conversely, many new innovations (diagnostic, preventive and therapeutic) were borne out of this global affliction. Clearly, there is much to learn from recent events. BIEE3 seizes this opportunity to provide a comprehensive educational series to share new knowledge with a global audience.

Overview

Research and efforts to develop diagnostics, vaccines and therapeutics for SARS-CoV-2 have surpassed any historical research initiative, condensing years of investigation and development into a single year. Here, we provide an update on the biology and biomedical research on SARS-CoV-2 pandemic including epidemiology of the outbreak, prediction models, virus variants, structure and biology, pathophysiology including newly appreciated complications, immunology, therapies (drug and antibody-based), and vaccine development.

Objectives

The aim of this short course is to provide a comprehensive overview and update of diverse on-going biomedical research on COVID-19 and its etiological agent, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), including impact of leading vaccine and therapeutic efforts, pathophysiology, and clinical management. This course will feature and shed light on new and often controversial developments in epidemiology, virus mutations, pathogenesis, treatment and prevention (vaccines).

Target audience

Healthcare professionals, graduate/undergraduate students, research staff, MBBS research track students.

Schedule

Webinars were held on Mondays and Wednesdays from 19:00 to 21:00 hrs (GMT +8), with two presenters per session, between January 12th to February 21st 2022.

Requirements

Basic Life Science background and/or clinical training.

Opening lecture
Moderators: Wanni CHIA; Amanda BIFANI; Matthew TAY

01	DATE	TOPIC	LECTURERS
	12 Jan	**Opening Lectures**	David HEYMANN (LSHTM)
		Global situation of COVID-19 pandemic: where are we today? A discussion on the evolution of COVID-19 from SARS and MERS, its current epidemiology, differences between herd immunity and population immunity, living with endemic SARS-CoV-2 and the concept of Access to COVID Tools (ACT) Accelerator focusing on its value in the COVID-19 pandemic.	
		COVID 19 resiliency – A destination or a dream? The journey undertaken by Singapore, since January 2020, to fight the deadly COVID-19 pandemic. The 4 critical time points in the COVID-19 journey and insights gained from them: (1) the beginning of the pandemic, (2) development of vaccines and therapeutics as a major game changer, (3) rise of Delta-variant and finally (4) the present era of Omicron emergence. What is Singapore's approach to living with COVID-19?	Kenneth MAK (MOH)

Part I: Epidemiology of a pandemic
Chairs: Kevin TAN & Pablo BIFANI

02	DATE	TOPIC	LECTURER
	17 Jan	**Epidemiology: origin and spread of COVID-19** A review of the origins and spread of SARS-CoV-2 including: the role of bats as a common natural reservoir for viruses; the crucial role of serological tests in identifying origins of the outbreak; different hypotheses on the origins of SARS-CoV-2; risk of zoonosis, spill-over and spill-back events, and the challenges that we should be prepared for in case of future outbreaks. Three different scenarios applicable to emerging zoonotic viruses, the importance of serology in outbreak investigation and the origin of the Omicron variant are also covered.	Linfa WANG (Duke-NUS)

03	DATE	TOPIC	LECTURER
	17 Jan	**SARS-CoV-2: emergence of variants** SARS-CoV-2 genetic epidemiology: tracking of the emergence and global impact of different SARS-CoV-2 variants. The importance of genomics and genetic epidemiology in the present pandemic is discussed, along with the topics covering advances in the field of genomics, sequencing the virus, and molecular fingerprints of viruses.	Vinod SCARIA (IGIB)

04	DATE	TOPIC	LECTURER
	19 Jan	**SARS-CoV-2: Updates on virology** A detailed overview on coronavirus biology and disease mechanisms, with emphasis on the viral structure, entry mechanisms, replication and therapeutic strategies.	Gagandeep KANG (CMC)

05	DATE	TOPIC	LECTURER
	19 Jan	**Leveraging on technology for outbreak predictions of COVID-19** Prediction models used to evaluate the evolving COVID-19 pandemic, especially considering the more infectious viral variants. The relevance of technology to develop mathematical models. The history of mathematical modelling for predictions.	Alex COOK (NUS)

Part II: Immunopathology

Chair: Veronique ANGELI & Haiyan LIU

06	DATE	TOPIC	LECTURER
	24 Jan	**COVID-19 Clinical and pathophysiologic manifestations** An overview of risk factors for mortality, severity and inflammatory aspects of disease, several case-based examples of affected organs in the body, post-COVID conditions, incidence and the current scenario pertaining to the Omicron variant.	Jyoti SOMANI (NUH)

07	DATE	TOPIC	LECTURER
	24 Jan	**Immunological aspects of COVID** Updates on the global and local COVID-19 situation and an overview of symptomatic, radiological and laboratory characteristics of COVID-19. Exploring the met and unmet needs in biology, etiology and epidemiology of COVID-19: rapid detection and point-of-care tests, COVID-19 therapeutics including small molecules and monoclonal antibodies, preventative strategies and lastly, the challenges of ensuring variant-specific long-lasting immunity.	Laurent RENIA (NTU/A*STAR)

08	DATE	TOPIC	LECTURER
	26 Jan	**Gut Microbiome in Long COVID and vaccine immune response** The role of the gut microbiome in the risk and severity of COVID-19: looking at the gut microbiome in development of long COVID-19 and the impact of gut microbiome on vaccine response. Key questions on the cause of higher susceptibility, and reasons for different outcomes of the disease and durability of vaccine protection are explored.	NG Siew Chien (CUHK)

09	DATE	TOPIC	LECTURER
	26 Jan	**COVID-19 in children** The concept of systems-immunology: tracing of concomitant immunological events, to infer how the system functions in people of different age groups, during an infection or during a response to a vaccine. An introduction to the work of COVID Human Genetic Effort Consortium, observations regarding the Type-I IFN response to SARS-CoV-2 infection, immune system profiling of patients, and long COVID in children are also discussed.	Petter BRODIN (KI)

Part III: Antibodies and vaccines

Chair: Nicholas GASCOIGNE & Ruklanthi de ALWIS

10	DATE	TOPIC	LECTURER
	7 Feb	**Vaccine updates: RNA and viral vector vaccines** The global burden of COVID-19 and the availability of vaccines against SARS-CoV-2 virus. Topics covered include: various approaches to vaccine development in the context of COVID-19, the human immune response to vaccines that arise once the vaccine is injected into the body, the rationale of booster dose administration, safety and immunogenicity of different COVID-19 vaccines as a booster following two doses of AstraZeneca and Pfizer vaccines and some data from the preclinical trial using self-replicating mRNA vaccine being developed by Arcturus and Duke-NUS, Singapore.	Eng Eong OOI (Duke-NUS)

11	DATE	TOPIC	LECTURER
	7 Feb	**Vaccine updates: inactivated virus and subunit vaccines** Updates on leading vaccines in clinical use are given, with a focus on inactivated and protein subunit vaccines. The importance of vaccines in building herd immunity, the basic reproductive number (R0), the vaccination rates required to obtain herd immunity, the requirement for a higher percentage of vaccination rates, a review of vaccine platforms and how to combat the challenges faced with the Omicron variant are also discussed.	Lianpan DAI (IM-CAS)

12	DATE	TOPIC	LECTURER
	9 Feb	**Antibodies and COVID-19** The advancements in COVID-19 antibody research, exploring insights from recent reports, data from labs, and collaborative networks. Measuring antibodies in patients with COVID-19 and vaccines, and generating antibodies for COVID-19 diagnostics and therapeutics.	Paul MACARY (NUS)

13	DATE	TOPIC	LECTURER
	9 Feb	**Neutralising Antibodies against SARS-CoV-2: Implications for vaccines and therapies** The role of neutralising antibodies against SARS-CoV-2. A review of available assays to measure its titer, correlation of protection by vaccines, breakthrough infections and monoclonal neutralising antibodies in the prevention and therapy of SARS-CoV-2 infection.	Stephen KENT (U. Melb)

Part IV: Treatment, diagnostics and new innovations

Chair: Rajesh CHANDRAMOHANADAS & Benoit MALLERET

14	DATE	TOPIC	LECTURER
	14 Feb	**SARS-CoV-2: diagnostics, overview and advances** An update on the various diagnostic tests currently available for COVID-19 detection, including point of care testing (POCT), role of antigen rapid tests (ART) and optimal sampling for the SARS-CoV-2 detection, correlation of the diagnostic tests with infectiousness, variant typing and immunological correlates of protection against COVID-19.	Shawn VASOO (NCID)

15	DATE	TOPIC	LECTURER
	14 Feb	**Novel AI-based COVID-19 Diagnosis: Video, Audio, Cardio** A review of new developments and innovations on COVID-19 diagnosis through novel artificial intelligence (AI) methods, focusing on the use of audio for COVID-19 detection, and the challenges involved.	Björn SCHULLER (ICL)

16	DATE	TOPIC	LECTURER
	16 Feb	**Innovations in Treatment: Harnessing Digital Medicine to Re-Imagine COVID-19 Therapy Development and Beyond** Current innovations for COVID-19 treatment and the future of artificial intelligence (AI) technology in drug development. Looking at the history of technology and AI in therapy & pandemic preparedness, with examples of AI deployment and the challenges faced with using AI to address drug development. Furthermore, approaches used to further harness AI to optimise drug development for effective combinations, and neural networks and drug development studies are discussed.	Dean HO (N.1)

17	DATE	TOPIC	LECTURER
	16 Feb	**COVID-19 Treatment** An update on the wide range of treatment modalities available for COVID-19 based on ongoing randomized control trials (RCT), including monoclonal antibodies (mAb), antiviral drugs and immune modulators in treatments for COVID-19, and finally, vaccines as best prevention against COVID-19.	David LYE (NCID)

Panel discussion

Moderators: Kevin TAN; Pablo BIFANI

18	DATE	TOPIC	PANELISTS
	21 Feb	**Panel Discussion** **The New Normal: A moving target?** A panel discussion on COVID-19 and the global new normal. A review of epidemiology, transmission, pathology, antibodies, vaccines, and treatment of COVID-19.	David LYE, Paul MACARY, Jyoti SOMANI, Yik Ying TEO (NUS) and Linfa WANG

Professor David HEYMANN

Professor
London School of Hygiene & Tropical Medicine

01 TOPIC
Global situation of COVID-19 pandemic: where are we today?

Professor David Heymann is a medical epidemiologist and Professor of Infectious Disease Epidemiology at LSHTM. From 1989 to 2009 he held various leadership positions in infectious diseases at WHO, and in 2003 headed the WHO global response to SARS as executive director of communicable diseases. In 1976, after spending two years working in India on smallpox eradication, he was a member of the CDC (Atlanta) team to investigate the first Ebola outbreak in DRC and stayed on in sub-Saharan Africa for 13 years in various field research positions on Ebola, monkeypox, Lassa Fever, malaria and other tropical diseases.

Professor Heymann has published over 250 peer reviewed articles and book chapters. He is editor of the Control of Communicable Diseases Manual, and an elected member of the UK Academy of Medical Sciences and the US National Academy of Medicine. In 2009 he received an honorary CBE for services to global health.

Associate Professor Kenneth MAK

Director of Medical Services
Ministry of Health, Singapore

01 TOPIC
COVID-19 resiliency – A destination or a dream?

Associate Professor Kenneth Mak is Director of Medical Services at the Ministry of Health (MOH) Singapore and oversees the provision of all health services in Singapore. Since the beginning of the COVID-19 pandemic, he also advises Singapore's Multi-Ministry Taskforce as well as other governmental agencies in crafting the overall strategy for managing public health responses to combat the spread of COVID-19.

As the Deputy Director of Medical Services (Health Services Group) in MOH previously (2015 - 2019), Associate Professor Mak worked closely with the Regional Health Systems and healthcare institutions in Singapore on care integration, as well as on Singapore's long-term healthcare transformation strategy. Associate Professor Mak was trained as a general surgeon with subspecialty interests in hepatobiliary and pancreatic surgery, as well as in trauma surgery. He maintains his clinical practice as a Senior Consultant surgeon in the Department of Surgery, at Khoo Teck Puat Hospital, Singapore.

Professor Linfa WANG

Professor
Duke-NUS Medical School, Singapore

02 TOPIC
Epidemiology: origin and spread of COVID-19

Professor Linfa Wang is an internationally recognized expert in the field of zoonotic diseases, bat immunology and pathogen discovery. He holds a PhD degree (University of California, Davis USA) and a Bachelor's degree (East China Normal University, Shanghai China). In 1990, he joined the Commonwealth Scientific and Industrial Research Organization (CSIRO), Australian Animal Health Laboratory (AAHL) where he played a leading role in identifying bats as the natural host of the Severe Acute Respiratory Syndrome (SARS) virus. Joining Duke-NUS in 2012, his recent research achievements include developing antibody-based serological tests to detect SARS-CoV-2, and the early and successful culture of the virus from an infected patent's sample. His team also works with local and international partners to develop new broad-spectrum vaccines and therapeutics against COVID-19 variants and pre-emergent sarbecoviruses.

Professor Wang is a member of multiple WHO committees on COVID-19. He holds several honorary positions and memberships and has received numerous awards. He has published more than 500 scientific papers in journals such as Science, Nature, New England Journal of Medicine, and Lancet. He also serves on various editorial boards and is currently the Editor-in-Chief of the Virology Journal.

Dr Vinod SCARIA

Principal Scientist
CSIR-Institute of Genomics and Integrative Biology, India

03 TOPIC
SARS-CoV-2: emergence of variants

Dr Vinod Scaria is a clinician turned computational biologist, involved in creating novel methods and resources for analysis and annotation of genomes, and understanding the functional impact of genomic variations. He is also the co-founder of the Genomics for Understanding Rare Disease: India Alliance Network (GUaRDIAN), one of the largest networks of clinicians and researchers in India working on rare genetic diseases. His team established the COVID-19 Open Research, Data and Resources initiative to provide open access to genomic, epidemiological data-sets, and protocols pertaining to the COVID-19 epidemic in India.

Dr Scaria received the CSIR Young Scientist Award for Biological Sciences in 2012 and he is a Kavli Frontiers of Science Fellow of the US National Academy of Sciences, an elected Fellow of the Royal Society of Biology and an elected Fellow of the Royal Society of Public Health. He has published over 150 papers and is also an editorial board member of many reputable international journals.

Professor Gagandeep KANG

Professor
Christian Medical College, Vellore, India

04 TOPIC
SARS-CoV-2: Updates on virology

Professor Gagandeep Kang is Professor of Microbiology, at the Wellcome Trust Research Laboratory, Division of Gastrointestinal Sciences at the Christian Medical College (CMC) in Vellore. She is a leading microbiologist and virologist and has been instrumental in advancing hospital- and community-based infectious diseases and vaccine research, particularly in children, informing policy-making in India. She is a member of several advisory committees for WHO, mainly related to the research and use of vaccines. She serves or has served on the scientific advisory or strategic committees of several national and international institutions.

Professor Kang has published over 400 papers in international and national journals and is on multiple journal editorial boards. She is the first Indian woman to be elected as a Fellow of the Royal Society and also to the Fellowship of the American Academy of Microbiology. She is also the only physician-scientist to receive the Infosys Award in Life Sciences.

Associate Professor Alex COOK

Vice Dean (Research)
NUS Saw Swee Hock School of Public Health

05 TOPIC
Leveraging on technology for outbreak predictions of COVID-19

Associate Professor Alex Cook is Vice-Dean (Research) at the NUS Saw Swee Hock School of Public Health. He works on infectious disease modelling and statistics, including dengue, influenza and other respiratory pathogens, and on population modelling to assess the effect of evolving demographics on non-communicable diseases such as diabetes. In collaboration with government agencies, research by his multidisciplinary team has contributed to national policy making where (1) their projections of the future burden of diabetes in Singapore was cited in the Committee of Supply when the Minister of Health declared 'war' on diabetes, (2) their evaluation of the impact of school closure on hand, foot and mouth disease transmission supported the government's relaxation of that policy, (3) close collaborations with the National Environment Agency led to the development of a real time dengue forecasting algorithm that is routinely used as part of Singapore's vector control programme, (4) they have been working closely with Singapore's Ministry of Health on analytics for the COVID-19 outbreak throughout the pandemic.

Dr Jyoti SOMANI

Senior Consultant
Division of Infectious Diseases
National University Hospital

06 TOPIC
COVID-19 Clinical and pathophysiologic manifestations

Dr Jyoti Somani graduated from medical school in 1991 and attended the University of Chicago Hospitals for her Internal Medicine Residency and the first year of her Infectious Disease Fellowship. She completed her fellowship at Emory University. Dr Somani was in the US Indian Health Service (1998-2000), then became an Assistant Professor of Infectious Disease at Emory University (2000-2004). From 2004-2008, she worked on a HIV and Leadership Training Program for doctors in Chennai, India. She also spent time in private practice in Atlanta (2008-2012) and subsequently, the Australian Embassy clinic and Siloam Hospitals in Jakarta (2012-2014).

In 2014, Dr Somani joined the General Medicine Department at Khoo Teck Puat Hospital, Singapore. She then moved to NUHS as a Senior Consultant for the Division of Infectious Diseases and as the Clinical Director of the ASP program (2019). She is also Director of the NUH Epidemiology Unit and Chair of the Infection Control Committee. She is passionate about rational use of antibiotics and is highly interested in infections related to transplants, especially haematology and HSCT.

Professor Laurent RÉNIA

Professor
Lee Kong Chian School of Medicine, Nanyang Technological University

07 TOPIC
Immunological aspects of COVID

Professor Laurent Rénia is currently Professor of infectious diseases and Director of the Respiratory and Infectious Diseases Program at the Lee Kong Chian School of Medicine, NTU and a senior fellow at the A*STAR ID Labs. He obtained his PhD in 1991 from University Pierre et Marie Curie in Paris (France) and did his post-doctoral at New York University. He obtained a permanent position as a research scientist at the French National Institute of Health (INSERM) in 1993. Between 2001 and 2006, he became Director of the Department of Immunology at the Institut Cochin. He joined A*STAR as a senior principal investigator in the Singapore Immunology Network (A*STAR) in 2007 and eventually became its Executive Director (2013-2020). In 2020, he founded the A*STAR ID Labs as its Executive director. His scientific interests cover the immunology of infectious disease and newly emerging viruses. He has published more than 350 articles and book chapters.

Professor Siew Chien NG

Professor
Department of Medicine and Therapeutics
The Chinese University of Hong Kong

08 TOPIC
Gut Microbiome in Long COVID and vaccine immune response

Professor Siew Chien Ng is Professor at the Department of Medicine and Therapeutics, Assistant Dean (Development) and Associate Director for the Centre for Gut Microbiota Research, Faculty of Medicine, the Chinese University of Hong Kong. She is also Director for the Microbiota I-Center. Professor Ng's research interests focus on epidemiological, genetics and microbiota studies in inflammatory bowel diseases (IBD) as well as COVID-19. She leads large scale epidemiological and genomic research in IBD across Asia-Pacific. Her team was the first to discover a link between gut dysbiosis and COVID-19 infection and disease severity.

In 2017, Professor Ng established Asia's First Microbiota Transplantation (FMT) & Research Centre and the first longitudinal intestinal microbiota transplantation registry in Asia. She has won multiple awards and accolades including the Croucher Senior Medical Research Fellowships Award, Sir Francis Avery Jones Visiting Professorship and Award, Joanna David B. Sachar Professorship and Highly-cited Researchers by Clarivate in 2020 and 2021.

Professor Petter BRODIN

Professor of Pediatric Immunology
Science for Life Laboratory, Department of Women's and Children's Health
Karolinska Institutet

09 TOPIC
COVID-19 in children

Professor Petter Brodin is Garfield Weston Chair of Neonatology and Professor of Paediatric Immunology at Imperial College London, as well as Professor of Pediatric Immunology at the Karolinska Institutet. He is a pediatrician specialising in pediatric immunology, with notable research focused on COVID-19 in children, severe and long COVID.

Professor Brodin has won multiple awards and accolades including Göran Gustavsson award, Swedish Royal Academy of Science (2020) and EMBO Young Investigator (2019). He is an expert in experimental technologies and computational analysis for profiling immune systems using mass cytometry, mRNA-sequencing and integrative multiomics analyses.

Professor Eng Eong OOI

Professor
Duke-NUS Medical School, Singapore

10 TOPIC
Vaccine updates: RNA and viral vector vaccines

Professor Eng Eong Ooi was trained in medicine at the University of Nottingham and then completed his PhD studies at the Department of Microbiology, National University of Singapore. He holds a concurrent appointment in the SingHealth Duke-NUS Global Health Institute, as well as a joint Professorship at the Saw Swee Hock School of Public Health, National University of Singapore.

Professor Ooi co-directs the Viral Research and Experimental Medicine Centre at the SingHealth Duke-NUS Academic Medical Centre (ViREMiCS), which aims to develop molecular endpoints for use in viral disease therapeutic and vaccine trials. In addition, he received the Clinician-Scientist (Senior Investigator) Award by the National Medical Research Council of Singapore in 2010, 2014 and 2019.

Professor Lianpan DAI

Head of Innovative Vaccine and Immunology Research Group
Institute of Microbiology, Chinese Academy of Sciences

11 TOPIC
Vaccine updates: inactivated virus and subunit vaccines

Professor Lianpai Dai is Head of Innovative Vaccine and Immunology Research Group at Institute of Microbiology, Chinese Academy of Sciences in Beijing. His research interest is in the design and development of novel vaccines for important pathogens, and investigating protective immune response mechanisms. His research group is engaged in the research and development of new vaccines, mainly focusing on (1) the structural basis of main antigen proteins of important pathogens, (2) innovative vaccine design and development based on structure, (3) research on protective immune response mechanism, (4) promoting the translation of basic research results into clinical practice.

Professor Dai has undertaken a number of projects from the National Natural Science Foundation of China, the Ministry of Science and Technology, and the Chinese Academy of Sciences. In 2018, he won the Young Scholar Award from the Chinese Society for Immunology (CSI).

Associate Professor Paul MACARY

Director
Life Sciences Institute (LSI)
NUS Yong Loo Lin School of Medicine

12 TOPIC
Antibodies and COVID-19

Associate Professor Paul MacAry received his BSc (Hons) in Molecular Biology from Glasgow University in 1992, his PhD in Immunology from GKT, University of London in 1998 followed by Wellcome Trust postdoctoral fellowship positions in Cambridge University until 2005. Since 2005, he has been an independent investigator in the Department of Microbiology and Immunology at National University of Singapore (NUS). The multi-disciplinary research in his laboratory covers basic research to industrial applications with an emphasis on antibody biology, immune repertoire mapping and protein engineering.

Associate Professor MacAry was a founding member of the Singaporean Society of Immunologists (SgSI) - Singapore's first international learned society (www.sgsi.org.sg/) and the founding scientist for four biotechnology companies – BSCR LTD in Cambridge (2004), Antibody Cradle LTD in Singapore (2012), Singapore MABs LTD (2016) and Gen Y Biologics Pte Ltd (2020). He is also a founding member and Associate Editor of Nature Vaccines (www.nature.com/npjvaccines/), a member of the Faculty of 1000 (https://f1000.com/) and his research has been featured in covering articles on BBC, CNN and Reuters.

Professor Stephen KENT

Professorial Fellow
The University of Melbourne

13 TOPIC
Neutralising Antibodies against SARS-CoV-2:
Implications for vaccines and therapies

Professor Stephen Kent was trained as an infectious disease physician and viral immunologist in Melbourne and the USA. He is a National Health and Medical Research Council Senior Principal Research Fellow. Professor Kent heads a lab studying immunity to HIV, Influenza, COVID-19 and other variable-and-difficult-to-vaccinate-against viruses. Several vaccine concepts tested in his lab have shown sufficient promise to progress into human clinical trials. He remains active in infectious diseases clinical medicine at the Alfred Hospital and Melbourne Sexual Health Centre.

Professor Kent has published over 300 scientific papers and is well recognised for his studies of T cell and antibody immunity to HIV and influenza. He has given over 100 invited talks and seminars on his research. He has also won multiple awards for his research and PhD supervision. In addition, he was elected to the Australian Academy of Health and Medical Sciences in 2018.

Dr Shawn VASOO

Clinical Director
National Centre for Infectious Diseases

14 TOPIC
SARS-CoV-2: diagnostics, overview and advances

Dr Shawn Vasoo is Clinical Director at the National Centre for Infectious Diseases (NCID) in Singapore and Senior Consultant in the Department of Infectious Diseases at Tan Tock Seng Hospital. He graduated from NUS in 2001, and completed an Internal Medicine and Infectious Diseases Fellowship at Rush University Medical Center (Chicago), followed by subsequent fellowships in Clinical Microbiology and Orthopedic Infectious Diseases at the Mayo Clinic in Rochester, Minnesota.

Dr Vasoo leads the Infectious Diseases Research Laboratory at NCID, besides caring for patients under the Infectious Diseases Service. He is also an educator with the Lee Kong Chian School of Medicine, Nanyang Technological University, and the Yong Loo Lin School of Medicine at NUS. He serves on several editorial boards including Singapore Medical Journal, BMC Infectious Diseases, Journal of Bone and Joint Infection and Journal of Clinical Microbiology. He has an interest in rapid diagnostics, Gram negative resistance, bone and joint infections and outbreak preparedness.

Professor Björn SCHULLER

Professor
Imperial College, London

15 TOPIC
Novel AI-based COVID-19 Diagnosis: Video, Audio, Cardio

Professor Björn Schuller is a Professor of Artificial Intelligence and the Head of GLAM at Imperial College, London. He is also Full Professor and Chair of Embedded Intelligence for Health Care and Wellbeing at the University of Augsburg, Germany. Additionally, he is Guest Professor at Southeast University in Nanjing, China and a permanent Visiting Professor at Harbin Institute of Technology, China amongst other professorships and affiliations. He is also the co-founding CEO and current CSO of audEERING – an Audio Intelligence company based in Germany.

Professor Schuller has more than 1,000 publications and is currently Field Chief Editor of Frontiers in Digital Health. His work on COVID-19 involves the use of audio processing and deep learning models to detect COVID-19 from recordings of coughing and breathing. He and his team have developed an app that can detect COVID-19 infection via speech with an accuracy rate of over 80%.

Professor Dean HO

Head
NUS Biomedical Engineering

16 TOPIC
Innovations in Treatment: Harnessing Digital Medicine to Re-Imagine COVID-19 Therapy Development and Beyond

Professor Dean Ho is Provost's Chair Professor, Director of The N.1 Institute for Health (N.1), Director of the Institute for Digital Medicine (WisDM), and Head of the Department of Biomedical Engineering at the National University of Singapore. Using his CURATE.AI platform, he has led multiple pioneering interventional studies that have validated the promise of N-of-1 medicine where only a patient's own data is used to personalise their treatment in indications ranging from oncology to digital therapeutics. His team also pioneered the use of IDentif.AI to optimise and prioritise combination therapies for SARS-CoV-2 and antimicrobial resistance applications.

Professor Ho is an elected Fellow of the US National Academy of Inventors (NAI), American Association of the Advancement of Science (AAAS), American Institute of Medical and Biological Engineering (AIMBE) and Royal Society of Chemistry. He is also a recipient of the NSF CAREER Award, Wallace H. Coulter Foundation Translational Research Award, and V Foundation for Cancer Research Scholar Award, among others.

Associate Professor David LYE

Director
Infectious Disease Research and Training Office
National Centre for Infectious Diseases, Singapore

17 TOPIC
COVID-19 Treatment

Professor David Lye is Director of Infectious Disease Research and Training Office at National Centre for Infectious Disease (NCID), Associate Professor at Lee Kong Chian School of Medicine and acting Deputy Executive Director, Programme for Research in Epidemic Preparedness and Response (PREPARE), Ministry of Health, Singapore. He is also Senior Consultant, Department of Infectious Diseases, TTSH and Associate Professor at Yong Loo Lin School of Medicine.

Professor Lye has held more than SGD$12 million in research grant as principal investigator to date. His research interests are in COVID-19, dengue and antimicrobial resistance. He has published more than 290 peer-reviewed manuscripts in journals such as NEJM, Lancet, JAMA, Lancet Respiratory Medicine, Lancet Infectious Diseases, Lancet Global Health as well as Science, Nature Biotechnology, Nature Communications, Science Translational Medicine, Journal of Clinical Investigation and Journal of Experimental Medicine.

Professor Yik Ying TEO

Dean
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TOPIC
The New Normal: A moving target?

Professor Yik Ying Teo is the Dean of the Saw Swee Hock School of Public Health at the National University of Singapore. Trained as a mathematician at Imperial College and completing his MSc and PhD at Oxford in statistical genetics, he returned to Singapore in 2010 after working for four years as a Lecturer in Oxford and concurrently a researcher at the Wellcome Trust Centre for Human Genetics.

Prior to his Deanship, Professor Teo was the Founding Director for the Centre for Health Services and Policy Research, and also the Director for the Center for Infectious Disease Epidemiology and Research. He is presently a member on the Council of Scientists for the International Human Frontier Science Program, as well as a governing board member of the Regional Centre for Tropical Medicine and Public Health Network for Southeast Asia.

Global situation of COVID-19 pandemic: where are we today?

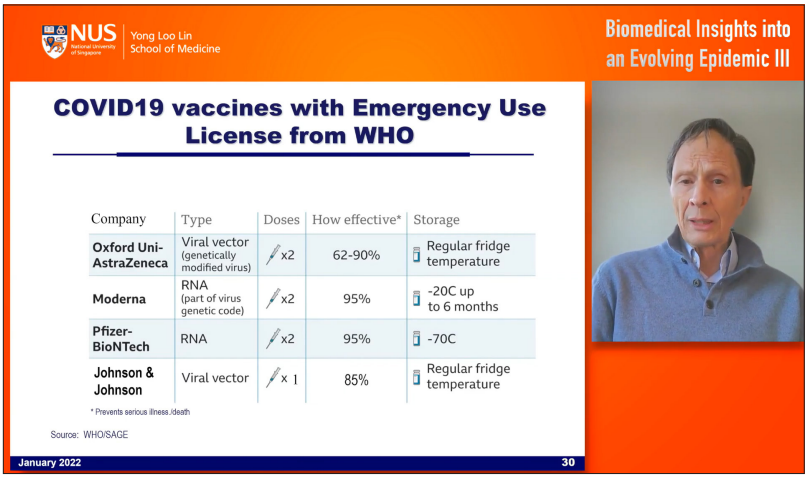
Professor David HEYMANN [SPEAKER'S PROFILE]

Professor David Heymann opened his Keynote address with a discussion on the evolution of COVID-19 from SARS and MERS, its current epidemiology, differences between herd immunity and population immunity, living with endemic SARS-CoV-2 and the concept of Access to COVID Tools (ACT) Accelerator focusing on its value in the COVID-19 pandemic.

To begin, Prof Heymann focused on the comparison between various human coronaviruses endemic to the northern hemisphere with peak infections during winter. These were transmitted from animal reservoirs to humans via intermediary hosts. He particularly emphasized on human coronavirus–OC43 (HCoV-OC43) which transmitted to humans from bovine hosts. Referring to the popular work of Vijgen *et al.* (2005), Prof Heymann highlighted how large-scale genetic sequencing efforts led to the discovery that the bovine coronavirus (BCoV) and HCoV-OC43 share a high degree of genetic similarity, suggesting a relatively recent zoonotic coronavirus transmission event. The 1888 Russian Influenza pandemic was hypothesized to have been caused by an ancestor of HCoV-OC43, that had leapt from cows, and resulted in millions of deaths worldwide before becoming endemic.

Prof Heymann also expanded on two previous coronavirus outbreaks in the modern era. In 2003, Prof Malik Peiris first identified and sequenced the SARS coronavirus in Hong Kong. The SARS outbreak began in November 2002 in the Guangdong province of China and its transmission began from healthcare workers and their family members before evolving into a major outbreak which spread to different parts of the world including Hong Kong, Canada, US, Singapore and Vietnam. He emphasized that the outbreak was successfully controlled since the key participants of the transmission chain – "healthcare workers", cooperated and abided by the WHO recommendations.

Secondly, the MERS outbreak which began in Saudi Arabia in 2012 was first reported by Dr Ali Mohamed Zaki. Although the patients presented SARS-like symptoms, the pathogen's genetic sequence revealed that it was indeed novel. The infection spread across UK and other parts of the world; however, it was effectively contained due to proper control measures with the exception of South Korea. It was later found that the virus was endemic and resided in the nasal passage of camels in the Middle East and Africa, while humans were occasionally infected.



Next, Prof Heymann highlighted that the common factor between the present SARS-CoV-2 and the previous outbreaks is the element of confusion and assumptions due to lack of knowledge among scientists, journalists, health leaders and public regarding this new pathogen. He also stressed on ambiguities related to the use of vaccines encompassing its durability, the need for boosters and their mode of action. Conversely, recent studies have shown that the efficacy of these vaccines do deteriorate and are compromised over time, particularly with the emergence of new SARS-CoV-2 variants. However, the importance of the vaccine and its role in ameliorating the severity of infection and preventing death cannot be understated.

He also emphasized the existing debate between herd immunity and population immunity. The former is defined as the indirect protection of susceptible individuals when a portion of the population is immune. He pointed out the significance of herd immunity threshold, which primarily depends

on the reproductive number. Reaching the herd immunity threshold would ensure that there is no transmission of infection. For example, Rubella and measles are infections showing high reproductive numbers and thus the threshold is also quite high to reach herd immunity. Many infections, including measles, can attain herd immunity and many societies have successfully eliminated such diseases. However, Prof Heymann rightfully raised concerns regarding herd immunity in COVID-19 infection chiefly due to two main factors:

1) Uncertainty about the immune response in naturally occurring infections,
2) Uncertainty about the characteristics of vaccine protection.

Lastly, he rebuffed the data modeling suggesting that herd immunity can be attained if 50-75% of the population gets infected or vaccinated, since vaccine or natural infection does not protect an individual from COVID-19 re-infection. He thus proposed that it is rational to talk about population immunity, which is the percentage of the population that exhibits an immune response to a disease. Natural infection as well as vaccination contribute to population immunity and is measured by random serological surveys that identify antibodies in the serum. Population immunity that has been achieved in the UK, despite the rise in hospitalization post Omicron emergence, has kept the mortality rates low.

Prof Heymann concluded his talk stressing the importance of vision and foresightedness of public health groups. The ACT Accelerator was set up across the world to ensure fair distribution of vaccines, diagnostics and therapeutics. However, he raised concerns about the large funding gap of 23 billion USD that has been generated through COVAX, the vaccine pillar of ACT Accelerator. The objective of the COVAX facility to ensure fair distribution of vaccines was limited by over reliance on certain vaccine suppliers, insufficient funding and bilateral agreements which have resulted in vaccine makers prioritising regulatory approvals in rich countries where the profits are the highest. Thus, the need of the hour is global cooperation across different countries to achieve resource equity in our fight against this unprecedented pandemic.

COVID 19 resiliency – A destination or a dream?

Associate Professor Kenneth MAK [SPEAKER'S PROFILE]

Associate Professor Kenneth Mak in his enriching lecture spoke about the journey undertaken by Singapore, since January 2020, to fight the deadly COVID-19 pandemic. He took us through the 4 important time points in the COVID-19 journey along with insights gained: the beginning of the pandemic, development of vaccines and therapeutics as a major game changer, rise of the Delta-variant and finally the present era of Omicron emergence.

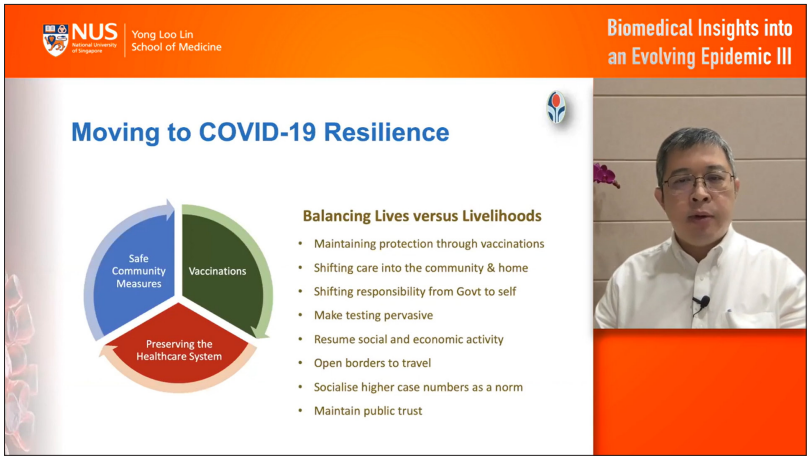
It started with reports of clusters of infection, with atypical symptoms of pneumonia, in the province of Wuhan and Hubei, China. The first imported case of COVID-19 in Singapore was reported on 23rd Jan, 2020, and was then followed with occurrence of local clusters. There was some confusion in the beginning regarding the spread of infection, whether it was air-borne or spread through droplets. From previous insights gained in the battle against SARS, strategies were employed to deal with the COVID-19 situation, and with the availability of different tools, Singapore was aiming for a "zero-COVID" strategy. The first exponential increase was observed among migrant workers housed in dormitory settings of Singapore. Special national efforts had to be undertaken, apart from imposing community restrictions, to contain the rapid spread of infection among the migrant workers. It took months to limit this "outbreak within the outbreak".

Through April-August 2020, the time was effectively used to strategize means for handling the upcoming clusters and preparing for the unseen battle ahead. The ability to test, isolate and quarantine proactively was very helpful in the initial fight against COVID-19 infection. He also shared an important model of "The Hammer and the Dance", a term coined by Tomas Pueyo that became popular among health care administrators as a strategy to control the outbreak. This model suggested that during high community spread, it was important to impose strict lockdowns and circuit breakers to restrict the spread - "the hammer"; and easing measures when the infection was in control alongside tweaking some strategies in the community and having safe distancing measures, to limit local spread of infection - "the dance".

A/Prof Mak highlighted that a major milestone in the battle against the pandemic was reached with the development of therapeutics and vaccines. The national vaccination program was initiated in early 2021, with initial emphasis to strengthen the frontline by vaccinating essential workers and health care professionals. This was followed by the vulnerable population with a higher risk of morbidity and mortality, and then the rest of Singapore, in hopes of developing a greater level of community resilience against the disease. The mRNA vaccines - Pfizer-BioNTech and Moderna were approved on emergency basis and procured early as a part of the national vaccination program. These vaccines have shown very high effectiveness during severe infection. To deal with contraindications associated with mRNA vaccination, other WHO enlisted vaccines including Sinovac/Sinopharm from China were procured to ensure a broader coverage of the vaccination program. According to the latest statistics, around 89.1% of the total population has received at least one vaccine and ~87.4% of the population has been completely vaccinated, thus ensuring 90% of the eligible population (>12 years and above) are protected. However, among the highest vulnerable population of seniors, around 37,000 of them remained unvaccinated. The vaccine coverage was considered satisfactory, if scrutinised through different age groups, with the vaccination program among children (aged 5-11 years) having begun since December 2021. The difference between the severity of infection among the vaccinated vs the non-vaccinated is stark and much higher protection is rendered on those who are vaccinated, in all age groups. It was highlighted that despite similar titres of the virus in the onset of infection, vaccinated individuals were less infectious and showed higher rates of viral clearance compared to the unvaccinated. He rightly pointed out that even with such a high vaccination coverage, the easing of restrictions have been slower in Singapore compared to other countries like the UK, with a view that the chances of re-infection may occur in recovered and vaccinated individuals.

The next big challenge confronting Singapore was the emergence of different variants, especially Delta. With its high transmissibility and the potential for vaccine breakthroughs, it urged us to rethink the concept of herd immunity, where increased vaccination drive was not the answer to prevent infection and spread. This led to the introduction of boosters and to educated decisions on the optimal interval of booster doses. During the surge of cases, A/Prof Mak pointed out that there were two options, starting fresh lockdowns by pulling the brakes or to ride with the waves. Complete lockdowns were proven to be extremely damaging to social wellbeing and the economy, and is not a feasible option in the long term. Thus, testing widely and frequently, and isolating the infected was the best possible strategy going forward. Vaccination-differentiated strategies were introduced to reach out and protect larger segments of the population. Furthermore, self-tests and supervised self-tests were encouraged to identify and isolate affected individuals. More recently, there's been a sharp increase in community cases, partly due to a new variant, Omicron, and due to increased social interactions during the festive seasons. Although the Omicron variant appears to be superior in transmissibility and breaking-through the vaccination than Delta, it causes less severe disease and fatality.

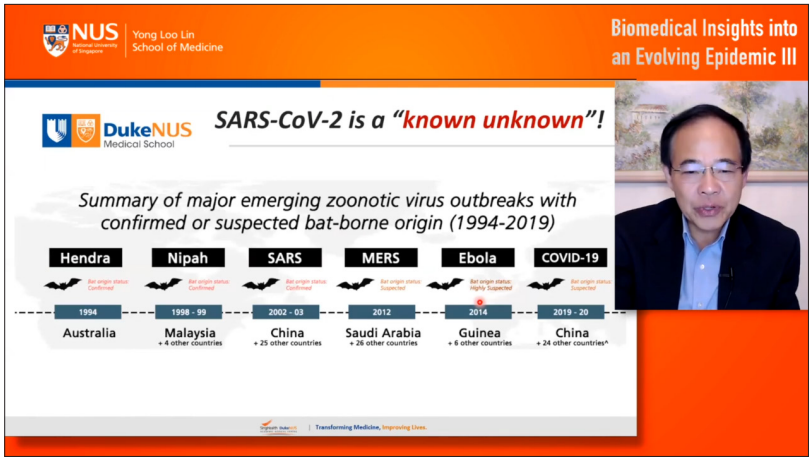
Finally, A/Prof Mak concluded his lecture with Singapore's approach to living with COVID-19. He termed it the transition towards COVID resilience, and that it can be achieved by balancing safe community measures, vaccinations and preserving the health care system, with safeguarding community wellbeing and the economy. In a nutshell, balancing lives and livelihoods as the main philosophy undergirding COVID-resilience.



Epidemiology: origin and spread of COVID-19

Professor Linfa WANG [SPEAKER'S PROFILE]

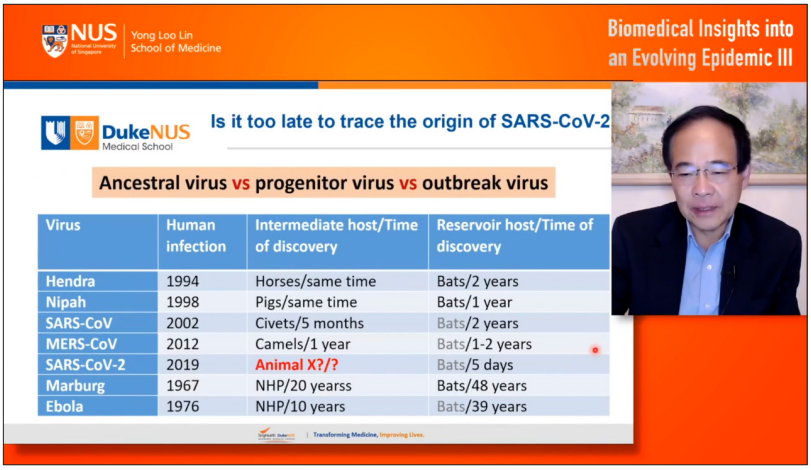
Professor Linfa Wang, in his lecture, addressed several key aspects and questions pertaining to the origin and spread of SARS-CoV-2 including: the role of bats as one of the most common natural reservoirs for viruses including SARS-CoV-2 and other coronaviruses; the crucial role of serological tests in identifying origins of the outbreak; different hypotheses on the origins of SARS-CoV-2; risk of zoonosis, spillover and spillback events and finally, the challenges that we should be prepared for in case of future outbreaks.



He elaborated on three different scenarios applicable to emerging zoonotic viruses - "known knowns", "known unknowns" and "unknown unknowns". Emergence of SARS in 2002-2003 was the "unknown unknown", since it was the first time in modern times that we saw such high lethality and human-to-human transmission caused by a coronavirus of animal origin. Prof Wang rightly pointed out that emergence of SARS-CoV-2 in 2019 could however be classified as "known unknown". He highlighted that major emerging zoonotic virus outbreaks like Hendra (1994) in Australia, Nipah (1998-99) in Malaysia, SARS (2002-03) in China, MERS (2012) in Saudi Arabia, Ebola (2014) in Guinea and COVID-19 (2019-20) in China had confirmed or suspected bat-borne origins. Alpha- and beta- groups (genera) of the Coronavirus family mainly infect mammals, of which, around half of the virus species are bat-borne. Prof Wang affirmed that bats act as a special viral reservoir based on host genetics and immunology but are not the only natural reservoir.

Next, Prof Wang highlighted the importance of serology in outbreak investigation. Tracing the antibody immune response during an infectious disease outbreak is equally important to polymerase chain reaction (PCR) and next generation sequencing for viral detection. Although detection using serology is less definitive, antibodies can persist for a longer time after infection, in both humans and animals. He also emphasized that serological information has a very important role for origin studies in different viral infections like Hendra, Nipah, SARS, MERS and COVID-19. Prof Wang, along with his team, has developed a surrogate virus neutralization test based on antibody-mediated blockage of ACE2 receptor and spike protein. The test allows rapid detection of SARS-CoV-2 neutralizing antibodies without using live viruses. The FDA-approved COVID Pass (cPass™) kit was developed based on SARS-CoV-2 neutralization test and is now being used in different contexts of COVID-19 including contact tracing, assessing vaccine efficacy, to determine the specificity of immune responses during infection, origin tracing and "spillback" studies.

Speculations exist about the time and origin of SARS-CoV-2 emergence in the human population, the major point of debate being whether it is a natural or a man-made virus or an accidental laboratory release. However, there isn't enough evidence to ascertain the origin and emergence of SARS-CoV-2 because the theories have been highly politicised. In contrast, the investigations regarding the origin and evolution of SARS-CoV in 2002-03 were performed freely, undergirded by unbiased global collaborations. The investigative team, including Prof Wang, responsible for investigations on the origins of SARS-CoV-2 showed that bats were the natural reservoir for SARS-like coronaviruses with a genome identity of 88-92% to SARS-CoV-2. He affirmed that SARS-CoV-2 is not a man-made virus and is improbable that it accidentally leaked from the lab. He mentioned that it is possible to search the origin of the virus, at a later time after the initial outbreak. However, for SARS-CoV-2, we may have already missed the opportunity to identify the intermediary host.



Shortly after the identification of the strain of coronavirus from Wuhan, scientists showed that bat coronavirus RaTG13 strain is roughly 96% identical to SARS-CoV-2, making it convincing that the virus has a natural origin. Scientists globally claimed that in order to investigate the true geographical origin for SARS-CoV-2, it is important to look beyond China, for two primary reasons: bat diversity is higher in South-East Asia and bat surveillance is much better within Chinese borders. Also, many novel viruses closely related to SARS-CoV-2 were circulating in different regions of South-East Asia including Thailand, Cambodia, Laos and others. The immune relatedness of these viruses was traced with the help of serology and antibody neutralization and not through phylogenetic analysis. Discussing about the furin cleavage site, Prof Wang highlighted that although this site seems unique for SARS-CoV-2, partial sequences of this site exist in four other bat-borne coronaviruses. This once again supports the theory that SARS-CoV-2 has evolved from pre-existing bat-borne viruses and is of natural origin. Weighing on zoonotic transmission, Prof Wang enlightened us with the concept of "spillover" (forward zoonotic transmission from animals to humans) and "spillback" (reverse zoonotic transmission from humans to animals). Thus, during the scenario of viral transmission, it is passed from a natural reservoir (e.g., bats) to humans via an intermediary host (e.g., some other animal) through a spillover event, where the virus may undergo mutation, and through spillback event, infects other animals (e.g. mink). But it is also possible that the amplifying host may not be a farm animal and instead the host may be another wildlife/bat that can serve as a reservoir for a future spillover event (SARS-CoV-3, -4 and so on). Prof Wang remarked that another predominant animal reservoir for coronaviruses is the white-tailed deer (around 40% sero-positive for SARS-CoV-2 using cPass™) in the USA, indicating another spillback event.

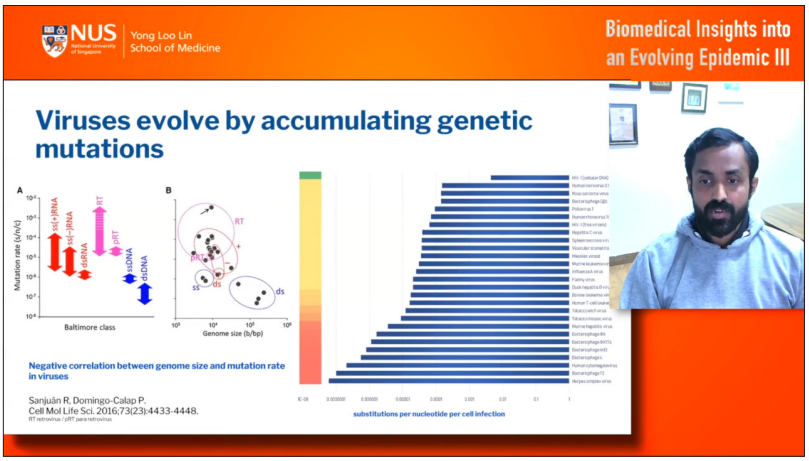
Finally, Prof Wang shared that it is too early to have any conclusive statement regarding the origin of Omicron variant, which harbours multiple mutations. The beta subgroup of coronaviruses is the most dangerous since they include emerging zoonotic viruses. However, Prof Wang predicted that the highly transmissible and lethal subgenus of sarbecovirus with ACE2 binding site would be the likely origin for SARS-CoV-3 infection with a hot spot in South-East Asia. He wrapped up his lecture with the concept of "Dream Vaccine", which will be the third-generation vaccine and would provide pan-protection from the sarbecoviruses, through cross-clade immunity.

SARS-CoV-2: emergence of variants

Dr Vinod SCARIA [SPEAKER'S PROFILE]

Dr Vinod Scaria gave an enriching lecture on SARS-CoV-2 genetic epidemiology with a focus on tracking of the emergence and global impact of the different SARS-CoV-2 variants. He introduced the concept of genomics and genetic epidemiology and discussed its importance in the present pandemic. He further delved into the applications of genomics and explained ways to use it for deciphering viral origin and evolution, differentiating clinically overlapping presentation of reinfections and reactivation, and providing early warning signals for public health interventions. Subsequently, he covered areas of molecular contact tracing using genomic fingerprinting. Dr Scaria pointed out that there have been significant advancements in the field of genomics over the last two decades due to high throughput sequencing, cost efficiency and reduced turnaround time. With such rapid developments, it is not surprising that the traditional tools of microbe isolation and observation are being replaced with genome sequencing directly from biological samples, facilitating its molecular characterization. Thus, instead of using traditional microbiological tools, *Wuhan Hu 1*, the first genome of SARS-CoV-2, was detected and characterised through direct sequencing of the bronchoalveolar fluids from an infected patient (Wu *et al.*, 2020).

Next, Dr Scaria highlighted the importance of sequencing the virus. This is primarily because viruses evolve by accumulating genetic mutations, and the rate of mutations is inversely correlated to its genome size. The rate of mutations provides useful insights into the evolution, epidemiology and spread of virus. SARS-CoV-2, being an RNA virus, is prone to mutate at faster rates compared to DNA viruses. The early genomes from the Wuhan cluster had very few mutations that accumulated at a constant rate with time.



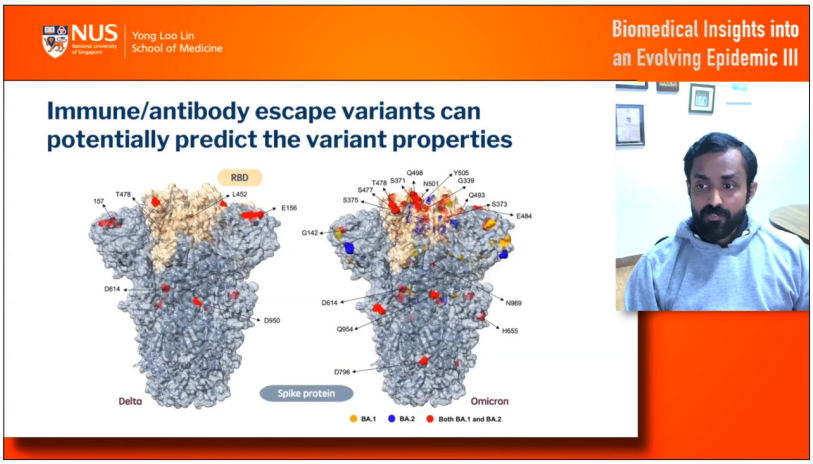
Delineating the concept of molecular fingerprints of viruses, Dr Scaria explained the possibility of tracking viral evolutions since the mutations accumulate on a previous genomic background over time. Thus, by taking a cross-section of the samples at any given point, it is expected to find relatively similar proportions of each of the genomes with fingerprints. However, specific genetic fingerprints could be predominant in some time points compared to others. This predominance of a particular virus subtype at a given time point is called an emergence event and is characterized by two factors:

- Host factor: A super spreader host that transmits a particular fingerprint to many individuals and thus accumulating a greater proportion of that variant at a given time.
- Transmission: A variant may harbour higher potential for transmissibility than others at a given time point. For instance, the Omicron variant has a higher transmissibility than its predecessors.

These fingerprints in the genome are identified by genome sequencing, a multi-step process which involves isolation of RNA, sequencing, and further in-depth analysis of the genomic data to identify genetic variations in the virus. Dr Scaria explained the concept of clustering different viruses based on their mutations and fingerprints, which are referred to as lineages or clades of the virus. Such clusters would have a common genetic fingerprint and therefore could signify a common lineage and close relationship between the members. With large number of genomes available in the public domain, there are multiple resources and systems which put together such clusters on a global scale. Commonly used cluster architecture systems are NextStrain lineage system which follows the year of origin to name the lineages and PANGO, which is a dynamic system of nomenclature

factoring in the ancestor of the lineage. Since the rate of substitutions are largely constant for a virus, such approaches can help in identifying the time of origin of a particular lineage or the most common ancestor for a lineage to shed light on how a virus came into a population and spread across geographical barriers. These approaches have also been used widely to identify cryptic transmission of the virus in the early phase of the pandemic.

Further, he emphasized on the importance of high throughput sequencing for the detection and surveillance of SARS-CoV-2. One of the first large-scale high throughput assays was the COVIDseq assay developed by Illumina, which was carried out on clinical samples at the Institute of Genomics and Integrative Biology, which could process 750-3000 samples per day. The sequence analysis of the SARS-CoV-2 genome was also required to keep up with such high throughput data in a comprehensive computational timeline. COVIDSeq was adopted in mid-2020 for surveillance in seven Indian states as part of the *IndiCovGEN* consortium. As part of this programme, a new lineage of SARS-CoV-2 in India was identified which was named the I/A3i. Dr Scaria explained the concept of haplotype maps, the fingerprint of the genome. Since the virus evolves at a constant rate, it was possible to roughly map the transmission chain of events from an outbreak and analyse its spread across the country. Significant proportion of the early cases in India could be traced to many such outbreak events across the country. The WHO has now classified SARS-CoV-2 strains as 'variants of interest' - with mutations of known functional impact and 'variants of concern' - with increased transmission and virulence; to enable efficient public health response.



He next spoke about the applications of diagnostics in improving disease prediction and early diagnosis. One of the key features is to design optimal primers and probes that are used in the RT-PCR for molecular diagnosis of the virus. Genomic mutations pose significant challenges as they could adversely affect primer binding and efficiency, which in turn will hinder the virus detection. Over 50 odd, standardised primers/probes are now being used across the world.

Dr Scaria concluded his talk by stressing the importance of genomics to differentiate clinically overlapping conditions like reinfections as well as reactivation and to identify variants which could cause breakthrough infections among the vaccinated. Lastly, he underlined the importance of global data sharing to provide warning signals when variants of concerns are identified, through federated systems which countries can operate on a common platform.

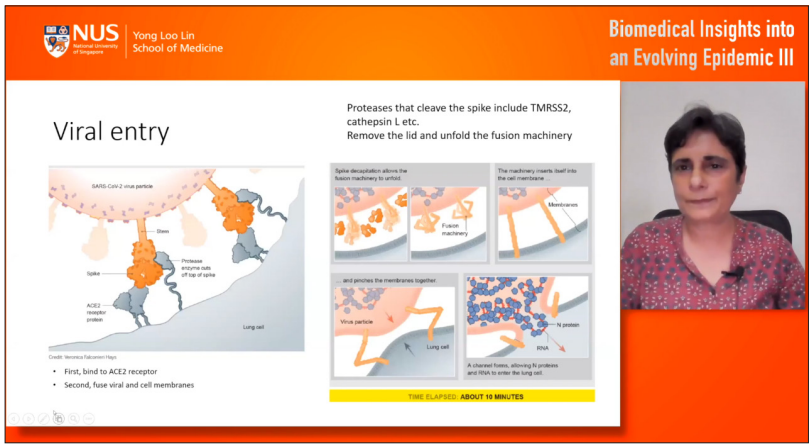
SARS-CoV-2: Updates on virology

Professor Gagandeep KANG [SPEAKER'S PROFILE]

In her talk, Professor Gagandeep Kang gave a detailed overview on coronavirus biology and disease mechanisms, with emphasis on the viral structure, entry mechanisms, replication and therapeutic strategies.

She set the stage by describing various members of the coronavirus family and their classifications. Coronaviruses belong to the family coronaviridae which are enveloped, single-stranded positive-sense RNA viruses grouped into four genera (alpha, beta, delta and gamma) and primarily infect birds and mammals. SARS-CoV-2 belongs to the subgenus Sarbecovirus, which is an out-stem of the Betacoronavirus genus. SARS-CoV-2 is related to many other coronaviruses infecting humans, most closely to SARS-CoV which emerged in 2002-2003. She talked about the origins of human coronaviruses, which were first identified by June Almeida, in 1966 and were coined so based on their 'crown' like structure. Historically, coronaviruses were postulated to cause enteric infections leading to diarrheal diseases owing to their potential to infect mucosal surfaces and were later found to be associated with respiratory diseases. While infections caused by coronaviruses have remained relatively mild in the past, the three recent outbreaks, SARS-CoV, MERS and SARS-CoV-2, have established a trend of increasing virulence and lethality.

The first instance, in recent times, of severe infections were reported with Severe Acute Respiratory Syndrome (SARS) in 2002-2003, where roughly 8000 people were affected globally with a 10% fatality rate. Prof Kang highlighted that the virus became infectious only after the person presented with symptoms. Thus, it was possible to establish proper control measures to effectively break the transmission chain by isolating such patients. Investigations highlighted zoonotic transmission from bats to humans via an intermediary host, civet cats. Another severe infectious disease, Middle East Respiratory Syndrome (MERS), was first reported in Saudi Arabia in 2012, and exists until today. MERS revealed zoonotic transmission from bats to camels and then to humans. Although it infected fewer people, it had a much higher fatality rate compared to SARS, in addition to poor infection control due to the presence of asymptomatic cases.



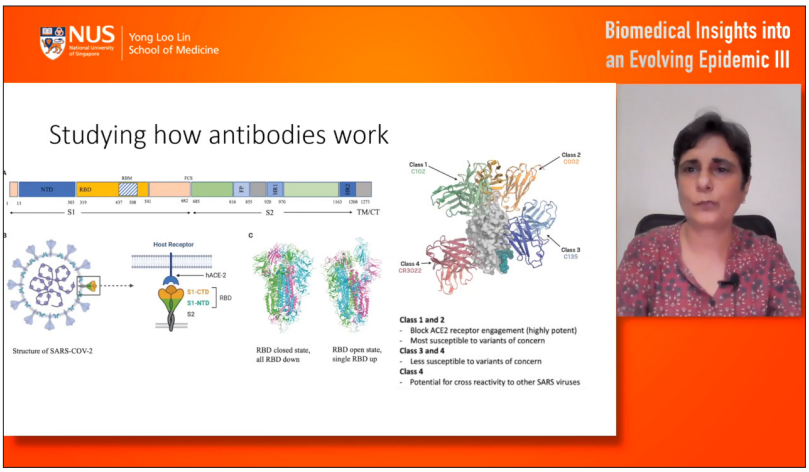
Prof Kang pointed out that the SARS-CoV-2 genome spans ~30kb of single stranded RNA which encompasses 13 genes, translating to 27-30 different viral proteins, thus implicating a "clever" viral strategy to make multiple proteins from a single strand. Of these, the structural proteins include the Nucleocapsid, Spike, Envelope and Membrane proteins, which are important for genome packaging, orchestrating the host-entry, determining the viral shape and CoV assembly. She further expanded on the viral cycle, which includes its attachment and entry into the host; followed by replication, packaging new genetic material and finally escaping the cell. The first step in infection is viral entry facilitated through the binding of spike proteins to the angiotensin-converting enzyme 2 (ACE2) which functions as a receptor for the virus, resulting in fusion of viral and host cell membranes. The spike protein of SARS-CoV-2 consists of two domains, S1 and S2. S1 contains the Receptor Binding Domain (RBD) and engages with the host receptor, while S2 mediates membrane fusion. Activation of the spike protein requires cleavage of the protein at two points, first at the boundary of S1 and S2, and then at S29, allowing fusion of viral and cellular membranes. The S29 cleavage is facilitated by cell surface transmembrane serine protease 2 (TMPRSS2). This results in the release of the viral genome into the host cell. It has been reported

that the virus may have other entry mechanisms, whereby it enters the host cell through endocytosis (e.g. Omicron variant). Prof Kang emphasized that the knowledge of "multiple paths of entry" within the host is critical for designing potential therapeutic strategies aimed at blocking its entry.

She described two strategies employed by the virus for synthesizing multiple proteins. First is through open reading frame 1 (ORF1), which lacks stop signals resulting in two giant polyproteins that are further cleaved to make 16 distinct functional proteins, and the second strategy is the use of discontinuous transcription, which allows multiple sub-genomic RNAs to be constituted for translation or virion packaging. Unlike other RNA viruses, and because of its large genome, it has a unique proofreading exonuclease N (ExoN), which serves to edit genes to ensure high fidelity.

Prof Kang asserted that recombination in coronaviruses is an inherent part of the replication cycle (linked to discontinuous transcription), which is the key driver of inter-species spread. The proteins that are made by the ribosomes begin to remodel cells into a virus making factory. One key stealth mechanism employed by the virus is the formation of replication-transcription complexes derived from rough endoplasmic reticulum that are anchored by nsp3/4/6 proteins and are used to hide signatures of viral replication from the innate immune system. Viral RNA made in the vesicles leave via molecular pores for translation to new viral proteins or are packaged into new particles. Viral genomic RNA is then encapsulated with the nucleoprotein which stabilizes it and thus can travel to viral assembly sites where it associates with the membrane and undergoes budding, resulting in progeny virions that are released by the infected cells. Another prominent mechanism of survival and replication in the host is achieved by suppressing the host response through inhibition of type-1 interferons and pattern recognition receptor, RIG-I.

Subsequently, Prof Kang vividly described various therapeutic strategies against SARS-CoV-2. The first, preventing viral entry, is reflected in the use of monoclonal antibodies as well as vaccines targeting the spike protein. For example, monoclonal antibodies such as 'Sotrovimab' can neutralize both Delta and Omicron variants efficiently, while emerging data suggests that several other monoclonals are not effective against Omicron. The second strategy is encouraging production of defective viruses as exemplified by antiviral drugs such as Molnupiravir, which inhibits viral reproduction by promoting widespread mutations during the replication of viral RNA leading to error accumulation in a process referred to as 'error catastrophe' or 'lethal mutagenesis'. Another strategy entails shutting down the virus completely, by drugs like Remdesivir, a nucleoside analogue which inhibits the RNA-dependent RNA polymerase (RdRp) resulting in stalling and inhibition of viral replication. Lastly, reducing the hyper-immune response of host cells by using drugs like Tocilizumab and other steroids.



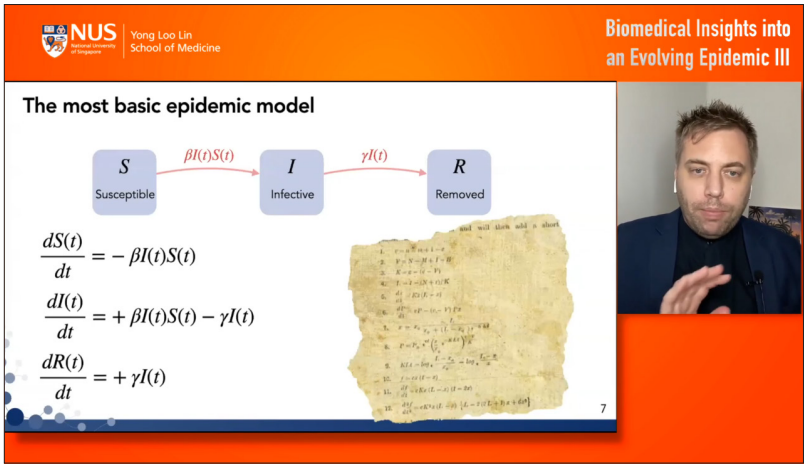
The lecture concluded with Prof Kang reflecting upon the current COVID-19 vaccines, most of which are based on inducing neutralizing antibodies against the spike proteins or virus envelope. Previous studies with MERS and SARS had demonstrated the importance of spike protein stabilization, to achieve potent neutralizing antibodies. The spike protein was stabilized by introducing two proline residues into the gene sequence, which has been applied by both Moderna and Pfizer/BioNTech vaccines. Knowledge of the types of antibodies that are generated in response to different vaccines is crucial for understanding the longevity of the immune response and will guide intervention strategies.

Leveraging on technology for outbreak predictions of COVID-19

Associate Professor Alex COOK [SPEAKER'S PROFILE]

Associate Professor Alex Cook discussed the significance of prediction models used to evaluate the evolving COVID-19 pandemic, especially considering the more infectious viral variants. He emphasised the relevance of technology to develop mathematical models, which provide useful predictions that can be effectively communicated with policy makers to guide government response and prevent public health systems from being overwhelmed.

To build mathematical models for the pandemic, simple reflections (duration of the infection, risks involved) from the overall epidemic system are used as smaller fragments or "building blocks". Simple equations can represent these small fragments which in turn generate an ensemble of equations from which a complex dynamic of the system can emerge. He rightly pointed out that simplified models reflect complex realities and that both are not the same. These models can be used to represent or reflect reality.



Further, A/Prof Cook shared that mathematical modelling for predictions dates back some 100 years. Dr Ronald Ross's hallmark work on malaria vectors published in British Medical Journal, in 1915 had a significant component of mathematical modelling and complex pathometric equations. For illustrating a very basic epidemic model, we discreetly assign the population into basic units, Susceptible(S), Infective(I) and Removed(R). The equation is generated as we move through each unit sequentially, very similar to the flow of the pandemic. This conceptual model of disease is thus reflected using several mathematical equations, to describe how people move from one state to the next. Thus, by representing the epidemic to the mathematical form, insights into the basic reproduction number (R_o) which is the expected number of cases directly generated by one case in a population where all individuals are susceptible to infection, can be gained. Conceptually, a model is prioritized by looking at the value of R_o in real life and extrapolated forward to make predictions. However, the final prediction model formulated by A/Prof Cook and colleagues is far more complex, since an array of variables had to be accounted for, which encompassed age (a key determinant of severity), symptomatic and asymptomatic cases, variable rates of vaccination, decreasing immunity with time and number of deaths or ICU admissions.

For the Delta variant, projections were made with prior evidence of severity, growth rate and size during the peak of the infection (October 2021), although considering a major uncertainty related to the future growth in terms of government policies and public behaviour. For the Omicron variant, the uncertainty criteria is much more challenging and include effectiveness of vaccines, cross protection along with the transmissibility and severity of the disease.

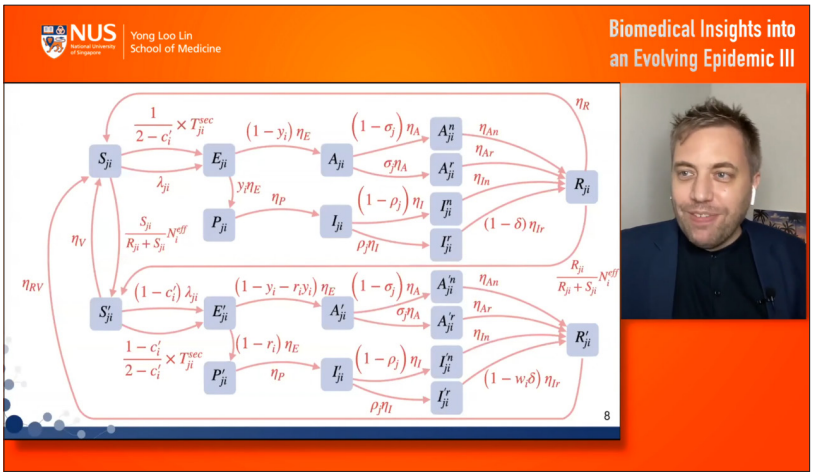
Subsequently, A/Prof Cook addressed the issue on how technology can be useful for better mathematical modelling leading to improved understanding of COVID-19 epidemiology. He delineated a specific technology, which is required for measuring contact within individuals to better understand outbreaks. This technology, pertaining to massively recording and accessing contacts between individuals, is novel to the COVID-19 pandemic. Singapore was the first country that developed and introduced to its population an application, called *Trace Together,* to potentially capture contacts between individuals. A/Prof Cook and his team conducted a research study in Singapore's foreign

worker dormitories using this technology in the first half of 2021. Antithetically, the number of affected cases shot up sharply after the lockdown. There were almost two simultaneous epidemics occurring at that time, one among the foreign workers and the other in the general community. A dominating number of infected cases were reported among the foreign workers residing in the dormitories, which have a very high population density. During the lockdown and few months after that, they were locked in their respective rooms except for special purposes like doctor visits. Thus, by the end of the wave most of the foreign workers were affected. Eventually, strict restrictions were imposed on them from the fear of spread from dorms to the community, community to the dorms and within the dorms. Thus, it was necessary to assess the risk of spread within dorms using objective measurements of their network structure and degree of contacts. Hence, a device was designed which would automatically send and receive messages allowing the policy makers to identify exposed individuals.

BluePass, manufactured by D'Crypt (like the Trace Together token or application) are devices for contact tracing that are worn on the wrists and send out radio signals for identification with timestamping features. This involved a long-drawn data extraction process, consenting and questionnaires, and server upload. Workers were compensated through a drink reimbursement. It was originally planned for 500 BluePass datasets to be collected. However, 30% of the apps failed within a few months of being issued. Thus, oversampling had to be done to get around 1000 extractions and this recorded around 86 million events.

From the BluePass records, contacts were classified as long term (regular) or short term (transient) based on duration [sustained (>1 hour) or non-sustained] and time of contact (daytime or night-time). The studies showed that there were significant differences between overall number of contacts between different dorms, which mirrored the dorm outbreaks in the first wave. It was observed that there were times of the day, especially during shift changes, when the risk was much higher. Also, when considering daytime interactions, the cumulative risk was greater among the transient than regular contacts. Further, it was discovered that despite low connections between the dorms, the infection within certain dorms was still not contained. This was due to the contacts between men from different rooms in the same block, which was a result of government mandated lockdown of the entire block. A/Prof Cook stressed that quarantine strategies should thus be developed considering mathematical modelling data, to increase effectiveness in fighting the pandemic.

Finally, A/Prof Cook wrapped up his lecture with several important insights. He showed that there is a clear trade off with the degree of intrusiveness of data captured using different technologies and this leads to better or worse outcomes in terms of control and learning about infection spread. Less information undoubtedly means less impact while more intrusive data gathering gives a clearer picture about the epidemiology but may not contribute towards epidemic control measures.



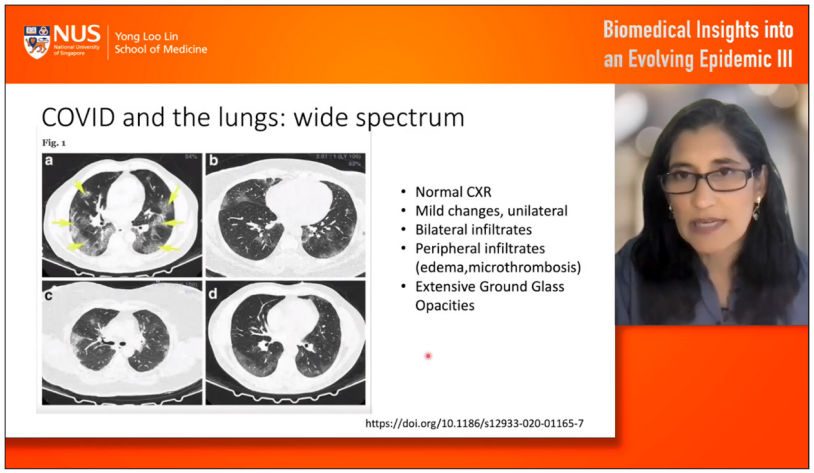
COVID-19 Clinical and pathophysiologic manifestations

Dr Jyoti SOMANI [SPEAKER'S PROFILE]

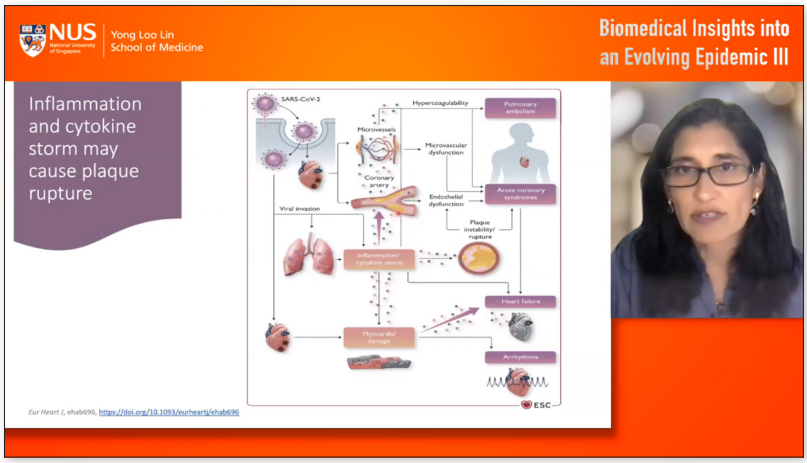
In her illuminating lecture, Dr Jyoti Somani described the clinical manifestations and pathophysiology of COVID-19. It entailed a brief overview of risk factors for mortality, severity and inflammatory aspects of disease, several case-based examples of affected organs in the body, post-COVID conditions, incidence and lastly concluding remarks on the current scenario pertaining to the Omicron variant.

To begin, she highlighted that individuals with cardiovascular diseases (32%) were at the highest risk of developing a severe disease, followed by those with diabetes (30%) and chronic lung disease (18%). Other risk factors for COVID-19 encompassed cancer, kidney and liver disease, obesity, sickle cell disease, immunocompromised conditions including transplant patients and pregnancy. Secondly, the risk for COVID-19 death increased with age, especially after the age of 65 despite their vaccination status, and, importantly, outweighed all assessed comorbidity conditions. Additionally, citing a study done across 465 health care facilities in the United States, the presence of four or more risk factors increased the probability of ICU admission, having a respiratory failure or death.

Dr Somani illustrated the myriad manifestations of COVID-19 transcending beyond lungs and traversing neurologic, thromboembolism, cardiac, endocrine, dermatological, gastrointestinal, renal, and hepatic organ systems. She further described complex case-based phenotypes, for instance, how, in one case study, acute COVID accelerated progressive liver disease and elevated liver enzymes. The lungs presented with unilateral and bilateral infiltration, edema, microthrombosis and extensive ground glass opacities.



Mechanistically, SARS-CoV-2 infects the bronchial epithelial cells, type I, and type II alveolar pneumocytes and capillary endothelial cells. This increases the dead space ventilation, diffusion barrier and right-to-left shunt in the alveoli, resulting in loss of compensation for hypoxia and difficulty in oxygenating the lungs. Dr Somani further elaborated that diffuse alveolar damage was the hallmark of COVID-19 lung pathology with lung fibrosis developing after 14 days and presence of neutrophil-rich pneumonia in severe cases. Referring to her cases, she shed light on concerning trends of post-COVID lung fibrosis or COVID-associated organizing pneumonia which consists of tissue granulation and proliferation of fibroblasts within the lung parenchyma and occurs ≥4 weeks post-acute COVID-19. With regards to the kidney, citing comparisons from a study done in the USA, she stated that acute kidney injury was more likely in severe COVID, where only ~33% of hemodialysis patients recovered kidney function within the first 90 days of discharge in Singapore. Some in-vitro studies have reported fibrosis and SARS-CoV-2 replication in kidneys. Referring to the cardiovascular complications of the disease, Dr Somani pointed out that the response comprised of increased blood pressure and heart rate, poor diabetic control, and renal damage. She further shared her experience of observing increasing numbers of COVID-19 cases with myocardial infarction or stroke. Thereafter, Dr Somani characterized probable causes of COVID-related diabetic ketoacidosis as insulin resistance owing to the inflammatory state, direct viral damage, or indirect effects on beta cells of the pancreas causing impaired insulin secretion. Another complication of COVID-19 is intracerebral haemorrhage (ICH), which is rare (0.25%) and can be caused due to arterial hypertension, haemorrhagic transformation of ischemic stroke, or anticoagulation therapy. It was reported that the median timeline from the onset of COVID-19 symptoms to developing ischemic stroke was 16 days with a median age of 69. While citing the differences in clinical manifestations



between influenza and COVID-19, she shared findings of a recent study which reported higher likelihood of stroke in COVID-19 than in influenza with an odds ratio of 7.6.

Thereafter, Dr Somani emphasised WHO's definition of long COVID, as the condition which is either a new onset or a persistent condition from a previous illness and lasts for about three months from the onset of the disease. Common symptoms of long COVID are fatigue, shortness of breath and cognitive dysfunction. Quoting a study on linked electronic health records of 273,618 COVID-19 survivors between Jan 2020-Dec 2020, she reported the incidence of "any" long-COVID feature varied from 46.42% in the 10- to 21-year age group to 61.05% in the age group above 65 years. Additionally, 63.64% of hospitalization and 73.22% of the ICU cases progressed to long COVID. In another study, long COVID risk was half when comparing breakthrough infections in vaccinated vs unvaccinated population, suggesting that vaccinated individuals are protected from long COVID. Referring to existing data, Dr Somani commented that the pathophysiology of long COVID was not very different from the primary disease. However, she highlighted the micro-clot model in long COVID-19 patients, where large anomalous fibrin(ogen) amyloid deposits (micro-clots) are present in plasma and are resistant to the body's ability to dissolve the coagulated blood.

Concluding her insightful lecture, Dr Somani described the clinical picture and pathophysiology of the Omicron variant as being five times more infectious than the wild type SARS-CoV-2, presenting lower viral loads than Delta and exhibiting immune evasion strategies. Moreover, current data suggests that the Omicron variant is less severe and replicates faster than all other SARS-CoV-2 variants in the ex-vivo human bronchus but less efficiently in the lung parenchyma. Furthermore, Omicron efficiently entered cells independent of TMPRSS2 pathway, via endocytosis. As a final point, she raised the question; if Omicron doesn't replicate well in the lungs, would we see less coagulopathy and inflammatory complications and less post-COVID-19 sequalae in future? Dr Somani concluded her lecture with emphasis on the importance of vaccines in reducing the risks of severe COVID-19 and severe manifestations, and on mitigating the challenges associated with post-COVID sequelae – "tsunami of chronic conditions".

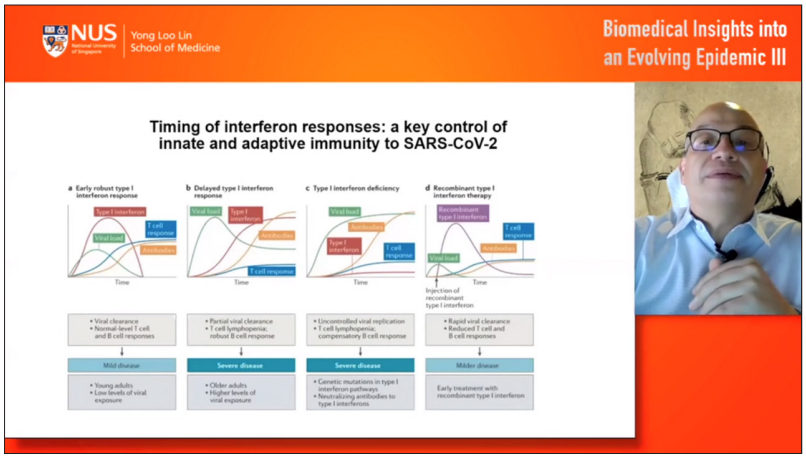
Immunological aspects of COVID-19

Professor Laurent RÉNIA [SPEAKER'S PROFILE]

Professor Laurent Rénia gave an enlightening lecture delineating immunological aspects of COVID-19. He provided a glimpse of the global and local COVID-19 situation, with over 320 million confirmed cases and about 5.5 million confirmed deaths worldwide, and over 291,000 cases and 843 deaths reported in Singapore. Thereafter, he gave an overview of symptomatic, radiological and laboratory characteristics of COVID-19, with an emphasis on blood tests showing decreased white blood cells (lymphopenia), and an increase in C-reactive protein. In his lecture, Prof Rénia discussed the partially met and unmet needs with regards to biology, etiology and epidemiology of COVID-19 by elaborating on rapid detection and point-of-care tests, COVID-19 therapeutics including small molecules and monoclonal antibodies, preventative strategies and lastly, the challenges of ensuring variant-specific long-lasting immunity.

In his talk, Prof Rénia delved deeper into the immune responses during natural infection. He noted a strong pro-inflammatory profile during the acute phase of COVID-19 infection, where severity of the disease was associated with higher pro-inflammatory signatures and asserted the use of corticosteroids to dampen their impact. Prof Rénia highlighted the impairment of type I interferon (IFN) in severe COVID-19, a key marker essential to control viral infections. He further described the impact of the virus on innate immunity in two ways, first, by limiting the production of interferon alpha and beta in infected cells, and second, by preventing interferon response to interferons; thereby abrogating their primary immune response. Additionally, this enlisted a cascade of events comprising depletion of resident alveolar macrophages which serve to maintain lung homeostasis, increase in inflammatory macrophages, monocytes, neutrophils and eosinophils into the lungs, which leads to dysregulated inflammation characterized by uncontrolled secretion of pro-inflammatory mediators, also known as the "cytokine storm". Prof Rénia asserted that critical COVID-19 was a combination of i) defects in early control of Type I and type III IFN and ii) impaired control of inflammatory response (cytokine storm).

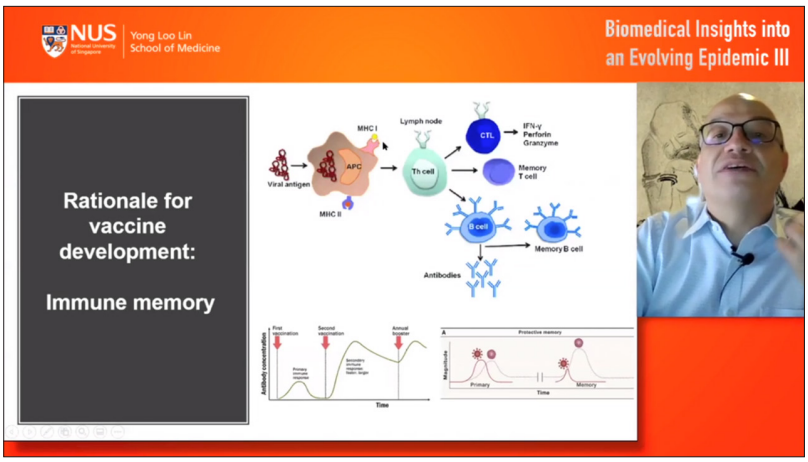
Prof Rénia also outlined the two major components of adaptive immunity in SARS-CoV-2 immune response. First being the seroconversion or development of antibodies, which recognize viral antigens and prevent virus entry into host cells and second being the repertoire of T cells which comprise CD4 T cells, that assist in making the antibodies by stimulating the cells and CD8 T cells which act as killer cells and destroy infected cells. Lastly, memory B cells act as the immune memory and rapidly mobilize B cells during subsequent infections. After a COVID-19 infection, almost 90% of the individuals seroconvert by 10 days post-symptom onset. The spike and N proteins are immunodominant and circulating neutralizing antibodies (NAb) develop in most infected people. However, severe cases with high virus load showed higher antibody levels, where some subsets (with low fucosylated Fc) antagonize type I IFN production and favour pro-inflammatory responses by macrophages. Elaborating more about T cell immunity, Prof Rénia stated that the main targets of CD4 and CD8 T cells are spike, M, nucleoprotein, ORF3a and NSP3 viral proteins. Additionally, circulating as well as local SARS-CoV-2 specific CD4 and CD8 T cell responses are associated with less severity and cross-reactive memory T cells are linked to aborted infection.



Next, he described four different scenarios signifying the timing of IFN response as a key control for innate and adaptive immunity to SARS-CoV-2. These include, a) early robust type I IFN response which is instrumental in viral clearance and initiating normal T

and B cell responses leading to mild disease; b) delayed type I IFN response results in severe course with partial viral clearance and T cell lymphopenia; c) type I IFN deficiency causes uncontrolled viral replication, T cell lymphopenia and compensatory B cell response leading to severe disease; and lastly, d) early injection of recombinant type I IFN would result in rapid viral clearance and milder disease course. Citing a recent study by Cromer *et al.*, he underlined that SARS-CoV-2 reinfection was not frequent due to two main factors – long-lived immune memory or immune boosting post reinfection.

Next, he elucidated various antibody-based therapies constituting convalescent plasma, intravenous immunoglobulins (IV-IG) and animal polyclonal antibodies, where therapeutic human monoclonal antibodies (from convalescent patient or humanized mouse) appeared to be the most promising.



Prof Rénia wrapped-up his lecture by weighing on the principle of vaccination and benefits of downstream immune response. He narrated the salient features of an ideal vaccine as being able to establish long lasting immune response against field pathogens, immunogenicity in all individuals, eliciting minimal side-effects, ease of manufacture, economical and stable at room temperature. Lastly, he addressed the burning questions of SARS-CoV-2 infection regarding vaccine effectiveness which in turn depends on a plethora of factors comprising host, demography, vaccine access, immunity, and viral variants. Hence, he remarked, while there is still no sign of achieving herd immunity, the need of the hour is an improved version of the COVID-19 vaccine (vaccine 2.0) that would confer long-lasting immunity.

Gut Microbiome in Long COVID-19 and vaccine immune response

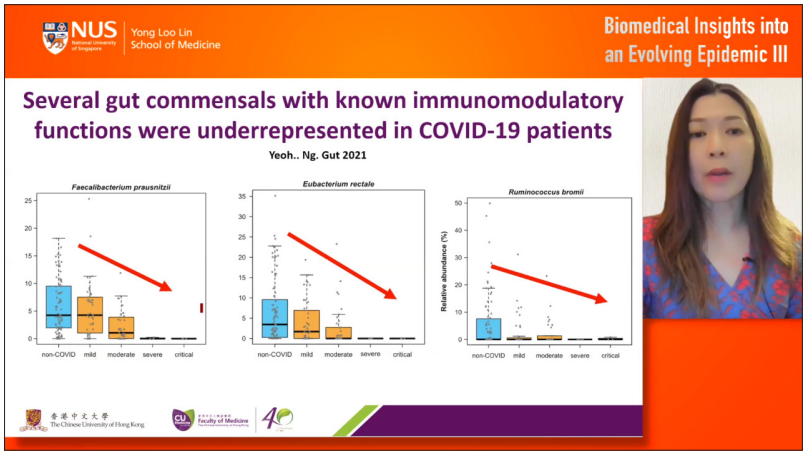
Professor Siew Chien NG [SPEAKER'S PROFILE]

Professor Siew Chien Ng presented an insightful lecture on topics spanning the role of the gut microbiome in the risk and severity of COVID-19, to the association of gut microbiome in development of long COVID-19 and the impact of gut microbiome on vaccine response. With over 5.5 million deaths and more than 326 million cases reported worldwide, she posed several key unanswered questions including the cause of higher susceptibility in some cases, reasons for different outcomes of the disease and durability of vaccine protection.

Prof Ng highlighted that COVID-19 is not just a respiratory disease but also impacts the human gut. The viral entry receptor, ACE2, is highly expressed in the human gut and widely distributed across lungs, kidneys, and liver. Notably, epithelial cells of the large and small intestines express these receptors abundantly. She emphasized work during the early stages of the pandemic, where SARS-CoV-2 was detected in a myriad of clinical specimens ranging from faeces, blood, urine, nasal swabs and even in stool samples from patients without any gastrointestinal (GI) symptoms.

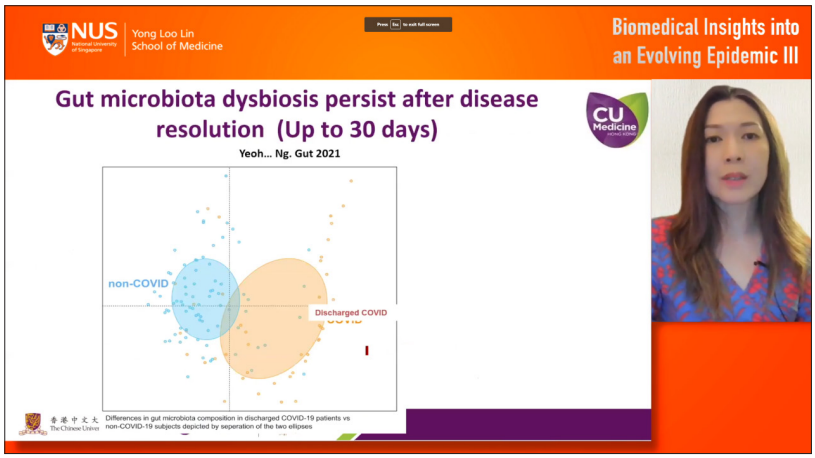
Prof Ng, along with her colleague in Austria, studied the impact of SARS-CoV-2 on other organ systems besides the lungs. Their findings showed that in patients with COVID-19, GI symptoms (diarrhoea, vomiting and abdominal pain) were common and viral detection in the stool samples was also observed in asymptomatic carriers. Additionally, SARS-CoV-2 RNA was detected in the gut of severe cases. Viral genome analysis using shotgun sequencing on stool samples showed that there was active replication of the virus in the gut. Moreover, it was intriguing to observe active viral particles a few days post disease resolution, the implications of which are still unknown.

From microbiome analyses, Prof Ng's group observed beneficial bacteria providing host immunity and synthesizing short chain fatty acids in the gut microbiome of patients with inactive SARS-CoV-2 viral activity. Conversely, opportunistic pathogens causing secondary infection or bacteriemia were more abundant in the gut of patients with active SARS-CoV-2 activity. Also, she implicated a potential threat of faecal-oral viral transmission. Speaking about detection assays, Prof Ng highlighted that SARS-CoV-2 PCR on stool samples is safe and accurate and has been extensively implemented for elderly and young children.



Describing the gut microbiota further, she reported that it regulates immunity to maintain natural defence against bacterial and viral infections. Furthermore, the gut secretes metabolites into the lumen, which activates the immune system, including dendritic cells and macrophages, to generate an adequate immune response. Prof Ng defined 'gut dysbiosis' as an imbalance of gut microbiota associated with unhealthy outcomes and possible infections, including COVID-19. Their study on microbial profiling of faecal samples from healthy and COVID-19 patients by metagenomic sequencing showed that the gut microbiome was significantly altered among COVID-19 patients. Correlating gut microbiome composition and disease severity, Prof Ng mentioned that several gut commensals with known immunomodulatory functions were underrepresented in COVID-19 patients. Reduction of these beneficial bacteria in the gut was invariably related to more severe and critical disease. *Faecalibacterium prausnitzii*, an anti-inflammatory bacterium producing short-chain fatty acids, was persistently depleted even after recovery. Several species of bacteria that are depleted in COVID-19 are associated with increased inflammatory marker (IFN, TNFs etc) concentration.

Thereafter, Prof Ng delineated the characteristics of long COVID or post-acute COVID-19 syndrome (PACS), whereby some patients develop subacute or sustained COVID-19 symptoms which can last up to six months post recovery. Primary symptoms include fatigue, joint pain, shortness of breath, mental health illness (anxiety, depression, PTSD, sleep disturbances), chest pain, thromboembolism and chronic kidney diseases, hair loss and others. Probable reasons behind this condition are either remnant undetectable viral particles or exaggerated immune response causing cell damage, as a physiological consequence of critical care. Prof Ng specified that about 75% of COVID-19 patients suffer from such symptoms post recovery. Studies on the COVID-19 patient cohort from Hong Kong revealed that alterations in the gut microbiota composition, including lower levels of the commensals and dysbiosis, persisted up to 30-45 days post recovery. She opined that gut microbiome analysis can help in predicting the likelihood of long COVID.



Prof Ng reasoned that gut dysbiosis is associated with cases that are more likely to develop severe disease, such as the elderly, comorbid, diabetic and obese population. Citing the study by her group, she reported that faecal sample in patients with COVID-19 showed underrepresentation of pepper mild mottle virus (RNA virus), multiple bacteriophage lineages and environmental derived eukaryotic DNA viruses. Faecal virome in SARS-CoV-2 infection harboured more stress, inflammation and virulence- associated genes including those involved in DNA repair, metabolism and virulence. Despite the strong associations between dysbiotic gut microbiota and severity and chronicity of COVID-19 symptoms, Prof Ng stated that at the moment, it is still unknown whether there is a causal link between SARS-CoV-2 and the microbiome (the chicken and egg analogy).

A possible remedy to improve the gut flora is through prebiotics, probiotics and other dietary approaches. A unique microbiome immunity formula (SIM01) was developed using big data analysis and machine learning to be tested in clinical studies, since there were no existing treatment strategies. It was observed that patients who received SIM01 supplement had almost complete symptom resolution by week 2. Secondly, the concentration of pro-inflammatory cytokines in the blood was significantly reduced in the test group. A similar result in terms of rapid resolution of COVID-19 was observed in two patients who were given faecal microbiota transplantation.

Describing the impact of gut environment on vaccine response, Prof Ng mentioned that microbial dysbiosis can cause a blunted vaccine response. Vaccine immune response depends on the immune system and different aspects of the vaccine including its formulation, dose, and route of administration. However, what remains largely unknown is the impact of gut microbiota on the vaccine response. Factors among the gut microbiota like antibiotic treatment, use of probiotics, and environment are crucial players in vaccine response. Studies undertaken on high and low responders after second dose of COVID-19 vaccines show some specific bacterial species - *Bifidobacterium adolescentis*, are associated with higher antibody response to COVID-19 vaccine.

Making concluding remarks regarding future directions and clinical implications, Prof Ng reiterated that the gut is a potential reservoir of recurrent disease or immune cell stimulation. Follow-up studies of patients with and without COVID-19, for up to 5 years, are currently being undertaken in Hong Kong, which aims to identify the onset of any chronic or severe disease post recovery and understand the implication of COVID-19 in the population to ensure personalized treatment for such individuals.

COVID-19 in children

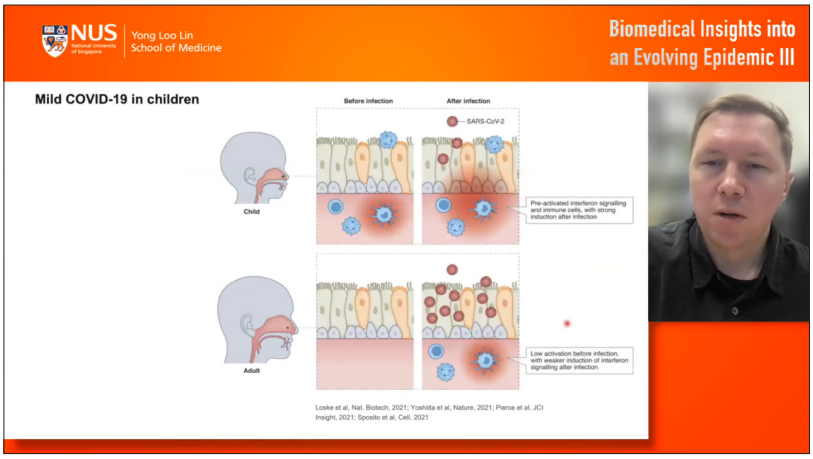
Professor Petter BRODIN [SPEAKER'S PROFILE]

Professor Petter Brodin introduced the concept of systems-immunology, in which the focus is switched from individual components of the immune system to how they communicate with one another and respond collectively during a challenge. By tracing these concomitant immunological events, it is possible to infer how the system functions in people of different age groups, during an infection or during a response to a vaccine. Talking about SARS-CoV-2 infection, Prof Brodin emphasized the remarkable heterogeneity in disease presentation ranging from mild to severe, to multisystem inflammatory syndrome (MIS), and finally to long COVID.

Prof Brodin is a member of the COVID Human Genetic Effort Consortium, which extensively shares information to derive a better understanding of the disease with special focus on cases having rare presentations like young children developing severe pneumonia or MIS. Two significant studies came out from this collaborative effort with the striking finding that the main determinant of severe pneumonia in acute COVID-19 infection is the response mediated by Type-I interferons (IFN). SARS-CoV-2 is sensed by host innate immune sensors such as the toll like receptors (TLR) 3/7, which in turn activate a cascade of signalling pathway leading to the production of IFN and reducing viral replication. Rare affected young adults, showing severe symptoms of pneumonia, were seen to have inborn defects in immunity, thus leading to very low IFN production. He further stressed that a larger group of individuals had neutralizing autoantibodies to inactivate and inhibit Type-I IFN, developed from a previous infection.

Thereafter, he shared a few observations regarding the Type-I IFN response to SARS-CoV-2 infection. Firstly, early IFN responses to viral infection can be useful for viral clearance thus preventing severe manifestations, as seen in younger adults. Next, in elderly cases, abrogation of type-I responses may lead to sharp increase in viral load causing massive inflammatory response and a cytokine storm, resulting in severe pneumonia. Finally, in rare cases of IFN deficiency, the virus replicates without any host immune resistance. Sharing insights on IFN therapy, he underlined the challenges regarding administering recombinant IFN, which has to be given when the patient is still asymptomatic.

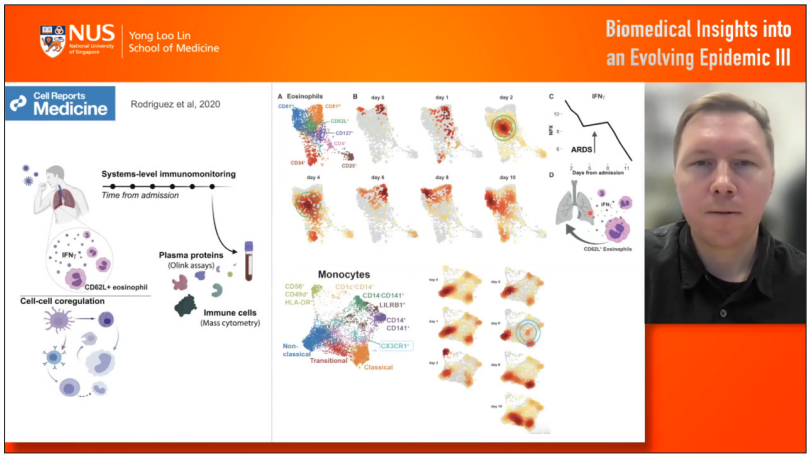
Furthermore, Prof Brodin highlighted that apart from the IFN response, viral replication is also inhibited by inflammasome formation. The inflammasome is a protein complex, which gets triggered by viral infection and other cellular stresses leading to production of pro-inflammatory cytokines like IL-1 and IL-18. If uninhibited, this could result in a hyperinflammatory response - cytokine storm. Using single cell data analysis by mass cytometry, Prof Brodin and his colleagues reported that patients with severe COVID-19 infection, had increased eosinophils before developing Acute Respiratory Distress Syndrome (ARDS). Moreover, cells expressing the fractalkine receptor - CX3CR1, which can travel from the blood stream to inflammatory tissue, had a similar expansion in the monocytes before developing ARDS. Treatments comprising IL-6 inhibition and preventive therapies using steroids have shown promising results. However, once the hyperinflammatory loop is triggered within the lung alveolus, it is difficult to stop the cycle. Additionally, Prof Brodin and his colleagues are working on developing fractalkine receptor CX3CR1 blockers as a useful therapeutic strategy to combat the disease.



Prof Brodin noted that although MIS is seen in children, this age group generally presents with milder symptoms due to pre-activation of IFN signalling and immune cells post infection,

unlike in adults. However, in 2020, Europe witnessed a rise in severe cases in children, which was initially presumed to be Kawasaki disease. Kawasaki disease is a vasculitis syndrome caused by viral infections and is considered as one of the most common causes of acquired heart failure in children. Severe cases of Kawasaki-like disease occurred almost ~30 times more frequently than normally observed in Italy. The presentation differed from the typical Kawasaki disease as the children were older, had severe abdominal pain, presented with severe heart failure and shock. This condition was subsequently termed Multisystem inflammatory syndrome in children (MIS-C) and is known to occur one to two months after a mild to moderate SARS-CoV-2 infection. Most children developing MIS-C remain asymptomatic during COVID-19 infection.

Prof Brodin and his colleagues performed an immune system profiling of patients with different clinical presentation (SARS-CoV-2, MIS-C, Kawasaki Disease) vs healthy children. Their study showed that the hospitalized patients had a severe cytokine storm when compared to other infected adults. There is a contrasting hyperinflammation in MIS-C vs Kawasaki disease. Various cytokines drive MIS-C and Kawasaki disease, the latter predominantly driven by IL-17. Standard treatment involves steroids, and for more severe cases IL1-R antagonists are administered, since inflammasome formation is more critical in this disease. Autoantibodies from MIS-C and Kawasaki diseases were profiled against 9000 different human proteins, which showed that they targeted a range of different proteins (~100). Interestingly, one such target that came up was the casein kinase, broadly expressed in different tissues and is induced by SARS-CoV-2 infection. To determine why autoantibodies are generated, it was observed that T cells are activated by super antigens in MIS-C. Notably, the SARS-CoV-2 spike protein has a superantigen motif which cross links with T cells, providing a mechanistic basis for the autoimmunity-like pathology. However, it is currently unclear why most of the superantigen mediated immune activation takes place several months post infection.



The observation that children exhibit a longer persistence of viral particles in their stool samples compared to adults may serve as a link between the development of MIS-C and those children who predominantly experience a mild infection. Another research group reported that patients who developed MIS-C have disruption of intestinal tight junctions including leakage of bacterial products and cleaved spike protein S1 in the blood stream. This perhaps indicates that super antigenic stimulation of T cells occurs repeatedly by secretion of spike proteins from the gut into the blood stream linking viral persistence to MIS-C. Thus, it can be hypothesized that children are more likely to develop milder infections as they have a higher threshold for tolerating viral persistence before mounting a strong systemic inflammatory response than adults.

Finally, Prof Brodin wrapped up his lecture with a brief overview of long COVID. The number of children that present with post-acute COVID-19 syndrome is few, however children reporting persistent fatigue, anosmia (partial or complete loss of the sense of smell) is far greater. It has been reported that ~30% of patients with symptoms of severe long COVID, show postural orthostatic tachycardia syndrome (POTS). He concluded his lecture with an energy-allocation hypothesis to explain mild COVID-19 and MIS-C in children and shared evidence that viral persistence in the gut is one of the probable causes for long COVID.

Vaccine updates: RNA and viral vector vaccines

Professor Eng Eong OOI [SPEAKER'S PROFILE]

Professor Eng Eong Ooi spoke about the global burden of COVID-19 and the availability of vaccines against SARS-CoV-2 virus. He described the various approaches to vaccine development in the context of COVID-19: these vaccines could be classified as chemically inactivated (Sinopharm, Sinovac, Bharat Biotech), recombinant subunit (Novavax), DNA- or RNA-derived (Moderna, Pfizer, Arcturus-Duke-NUS) or recombinant viral vectors (AstraZeneca, J&J, Sputnik V). Prof Ooi then lucidly explained the human immune response to vaccines that once the vaccine is injected into the body, it triggers genes associated with immune cells and subsequently the lymph nodes, where B cells are activated, mounting an antibody response while simultaneously triggering the formation of memory cells (B and T cells).

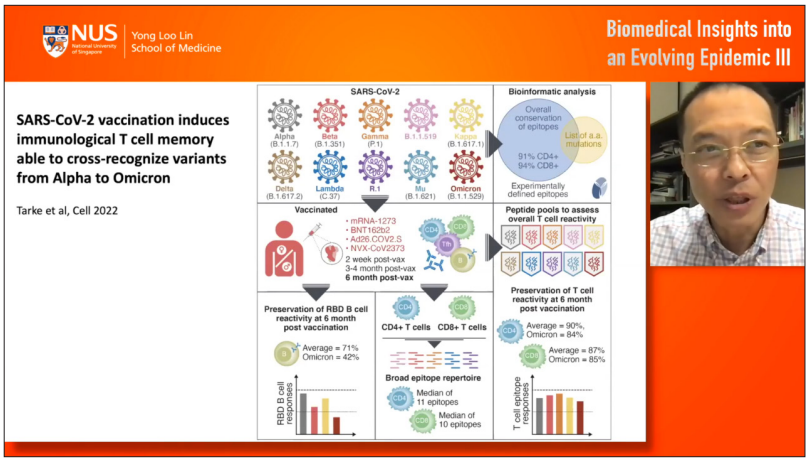
Thereafter Prof Ooi discussed the rationale of booster dose administration as it is observed that the immunity against SARS-CoV-2 virus gradually wanes after the regular two-dose vaccine regimen. To further elaborate, he drew lessons from the yellow fever vaccine, which is one of the best-known vaccines globally. He demonstrated that the antibody, as well as the T cell response, against yellow fever vaccine virus (live attenuated) depends on the duration of the viral load, genes triggering the antibody response and activation of the memory T cells. Furthermore, drug-mediated removal of the live viral vaccine failed to increase the viral load in the body concomitant with dampening of the humoral and cellular response and minimal neutralizing antibody titer. This suggested that persistence of the live viral vaccine was key to developing a robust immune response. Prof Ooi then reasoned that whether it is necessary to receive repeated vaccine doses to protect against COVID-19 depended on whether we choose to have protection against the symptomatic infection or against hospitalization. To explain this, Prof Ooi presented data from a US CDC study, which showed that vaccine "effectiveness" was highest for symptomatic infection at 94% for three doses of Pfizer vaccine and decreased steadily to 86% for two doses of Pfizer vaccine (<180 days) and 76% for two doses of Pfizer vaccine (>180 days). However, the third dose of Pfizer vaccine, did not produce any significant difference in the hospitalization rate (94% for 3 doses, 90% for 2 doses (<180 days) and 81% for 2 doses (>180 days) showing that the third dose would be helpful in reducing the symptomatic infection only.

Next, Prof Ooi examined the safety and immunogenicity of seven COVID-19 vaccines as a booster following two doses of AstraZeneca and Pfizer vaccines. Here he highlighted that booster doses of mRNA vaccines could lead to a significant increase in antibody titers at days 7 and 28. He further emphasized that even a single dose of Pfizer or Moderna vaccine could provide significant protection against SARS-CoV-2 infection, beginning as early as day 12. To reiterate this finding, Prof Ooi cited the work of Kalmuddin *et al.* (2021) where the titer of different antibodies (IgG, IgA, IgM, neutralizing) were measured against the spike protein in healthcare workers in Singapore. It was observed that the titers of IgG, IgA and IgM binding antibodies were negligible at day 7 and increased dramatically on day 10. In contrast, only 20% and 15% of the subjects developed sufficient neutralizing antibodies inhibiting the RBD-ACE2 binding and neutralizing live virus on day 10. To understand this further, he explained that the binding antibodies act by degranulating the natural killer cells and releasing cytokines which increases steadily from day 0, to days 10 and 21. He then went further to highlight the importance of T cell-mediated immune response in early protection against the SARS-CoV-2 infection. These results suggested that binding antibodies and T cell responses are responsible for early protection against COVID-19 and call for circumspection on the prevailing notion that neutralizing antibodies are absolutely required for protection.

Lastly, Prof Ooi presented data from the preclinical trial using self-replicating mRNA vaccine being developed by Arcturus and Duke-NUS, Singapore. He reported that in post exposure to SARS-CoV-2, the mice that were vaccinated demonstrated 100% survival while those administered with placebo showed 100% death. He further explained that since this vaccine triggers both the antibody and T cell response, it is imperative to test the importance of the humoral versus the cellular responses. To demonstrate this, vaccine administered mice were infected with SARS-CoV-2 virus. It was observed

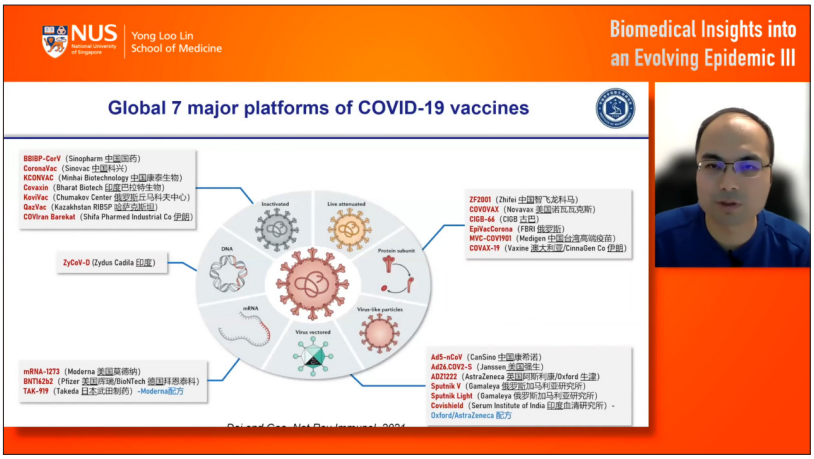
that removal of T cells resulted in higher viral loads in the organs as compared to removal of B cells, suggested that T cells play a critical role in protecting against COVID-19 infection. He further demonstrated that in a group of healthcare workers (Singapore and UK) that were seronegative throughout the pre-pandemic and pandemic era, adequate amount of T cells was observed in the body. This signifies that T cells are important in protecting against SARS-CoV-2 infections. He proposed that people who have completed the 2-dose vaccination regime and have been exposed to SARS-CoV-2, would have had a good protection from SARS-CoV-2 and its variants since both arms (B and T cells) of the immune response would have been adequately activated.

Prof Ooi concluded his lecture with key lessons learnt from SARS-CoV-2 infection and vaccination: neutralizing antibodies are not absolutely imperative for protecting against COVID-19, and more critically, that T cells play an equally important role in conferring protection against COVID-19.



Vaccine updates: inactivated virus and subunit vaccines

Professor Lianpan DAI [SPEAKER'S PROFILE]



Professor Lianpan Dai gave an informative talk on the current advancements on some of the leading vaccines in clinical use, with a focus on inactivated and protein subunit vaccines.

Prof Dai began his talk emphasising the importance of vaccines in building herd immunity. Using a mathematical measure known as the basic reproductive number (R0), the vaccination rates required to obtain herd immunity in a population can be determined. He further stressed the requirement for a higher percentage of vaccination rates, as new SARS-CoV-2 variants have emerged, encouraging for more vaccination drives.

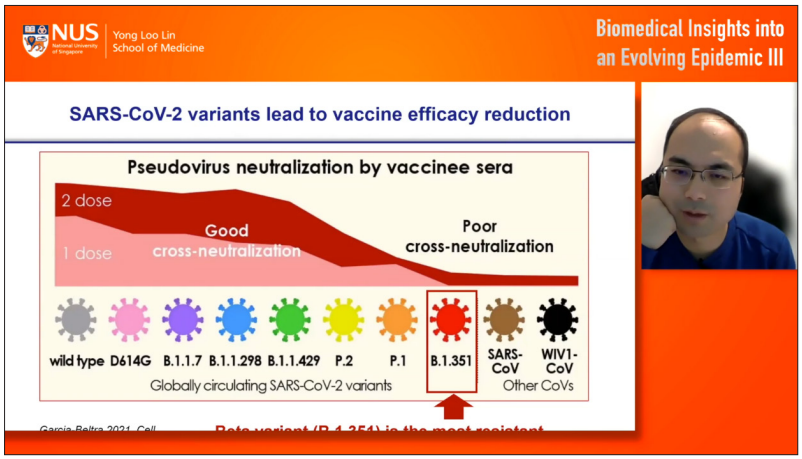
Prof Dai introduced the two arms of vaccine immune responses, while focusing on B cell responses. He stated that B cell responses triggered by various approved vaccines is highly correlated with SARS-CoV-2 protection through recruitment of neutralising antibodies. Thus, knowledge of the vaccine target becomes imperative. The spike (S) protein of SARS-CoV-2 virus mediates the entry of the virus through a receptor binding domain (RBD) and can both be major targets for vaccines. To aid the understanding of the highly dynamic process of viruse binding and entry, Prof Dai showed an animated video, highlighting the conformational changes that occur in the S protein, allowing the virus to fuse with the host cell wall, releasing viral RNA into the cell. He introduced the various vaccine types, including inactivated vaccines consisting of whole virus with chemically inactivated RNA. He explained that the process of spike proteins binding to ACE2 receptors results in a stable structure that is important for vaccine design. Various strategies are used to stabilize the S protein, including a mutation known as S2P, for mRNA vaccines (Moderna and Pfizer). The last group is one that uses the RBD, and requires engineering to increase the immunogenicity for higher efficacy.

Prof Dai focused on two of the seven vaccine platforms. The first is that of inactivated vaccines. There are currently 11 approved COVID-19 inactivated vaccines globally, with the two most widely used from Sinopharm and Sinovac, and a third from Bharat Biotech. Clinical trials of two vaccines from Sinopharm indicated an efficacy of 72.8% and 78.1%. In comparison, data from Sinovac showed an efficacy of 83.5% (Turkey) and an effectiveness of 65.9% (Chile). Prof Dai then illustrated that BBV152 (Bharat Biotech) uses imidazoquinoline, a Toll-like receptor 7/8 agonist, which enhances the T cell response, unlike the vaccines from Sinopharm and Sinovac. However, the efficacy for the Delta variant with BBV152 is dramatically reduced.

Prof Dai next discussed on the second platform; protein subunit vaccines. There are 12 vaccines approved globally, including Novavax, a vaccine approved to be used in Singapore in the near future. Prof Dai then focused on ZF2001, a protein subunit vaccine in which he participated in its development at Zhifei Longcom Institute, China. To initiate this vaccine design, Prof Dai and his team leveraged on the prototype vaccine for MERS, focusing on the RBD. This was done with an aim to recruit potent neutralising antibodies for enhanced responses. Two forms of RBD were observed, a dimer and a monomer. However, it is unknown which form was better for the vaccine, so both forms were assessed through *in vivo* experiments. Using MERS mice cohorts, the RBD dimer significantly enhanced neutralizing antibodies compared to the monomer. This discovery led the team to determine the crystal structure revealing that the RBD binding motif is fully exposed, which is important for ACE2 engagement, postulating that this structure would indeed induce a good

neutralising response. Further structural analysis of the N and C terminus of the RBD inspired the team to engineer the dimer to connect the N and C terminus. This newly engineered dimer elicited enhanced immunogenicity.

Prof Dai and his team used the same design to develop vaccines against SARS-CoV-2, their pre-clinical data illustrated high immunogenicity with the RBD dimer for both SARS-CoV-2 and SARS. Collaborating with Zhifei Longcom, a pilot trial produced high yields of antigen generation for both MERS-RBD-dimer and SARS-CoV-2-RBD-dimer (ZF2001). Pre-clinical trials for ZF2001 showed protection in mice and in non-human primates, reverting any lung injury occurred during infection. ZF2001 successfully passed phase 1 and 2 clinical trials, with minimal safety concerns, indicating this vaccine is well tolerated. Further data showed that 2 doses of ZF2001 achieved 93% neutralising antibodies, while 3 doses achieved 100% (ages below 60) and was also effective (94.7%) in ages above 60. Prof Dai then highlighted a multi-national phase 3 clinical trial that was performed in 5 countries using ZF2001 in December 2020, observing high efficacy in symptomatic (81.4%) and severe (92.4%) cases. Finally, Prof Dai highlighted that this vaccine was already in use in 4 countries.



However, despite this breakthrough, there remains a challenge with the emergence of SARS-CoV-2 variants. One of the variants of concerns (VOC) is the B.1.351 (Beta), a highly vaccine-resistant variant. The use of ZF2001 against this variant elucidated different outcomes between two groups (short interval and long interval between the second and third doses). Results showed larger neutralisation activity in the long interval group, and this holds true for other variants tested. Prof Dai concluded that a good interval between doses would therefore enhance vaccine performance.

Prof Dai briefly discussed other protein subunit vaccines. Novovax uses the S-2P strategy through liposome technology and an adjuvant to further enhance immunogenicity. Although this vaccine can initiate high neutralising antibodies, it can also produce high reactogenicity (typical side effects), which could be a trade-off. Clinical trials of Novavax shows an overall high efficacy specifically with the alpha variant. Clover SCB-2019 is another subunit protein vaccine which uses stabilised S-trimer strategy with two potential adjuvants, AS03 (GSK) or CpG1018 (Dynavax).

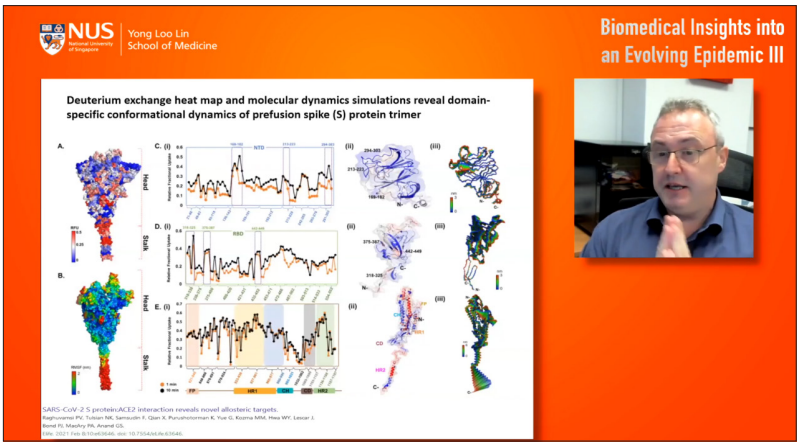
Prof Dai concluded his talk with a possible counter measure to combat challenges faced with the Omicron variant and with waning immunity. This included administering boosters or use of a mix-and-match method of vaccines. For the future of COVID-19 regiments, Prof Dai believes the platform, the antigen used, the administration routes, the dosage and the dose intervals all need to be considered for effective vaccine candidates.

Antibodies and COVID-19

Associate Professor Paul MACARY [SPEAKER'S PROFILE]

Associate Professor Paul MacAry delivered an enlightening talk on the advancements in COVID-19 antibody research, drawing insights from recent reports, data from his own lab, as well as from within his collaborative network.

A/Prof MacAry structured his talk into two parts. Firstly, measuring antibodies in patients with COVID-19 and vaccines and secondly, generating antibodies for COVID-19 diagnostics and therapeutics.

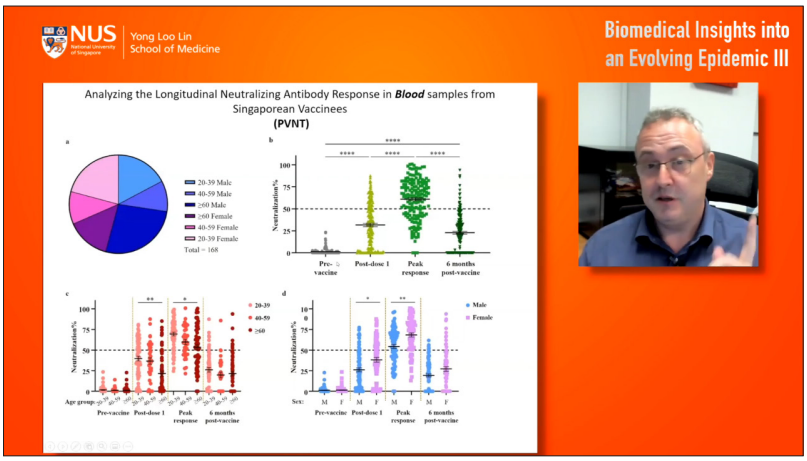


Before delving into these two lecture components, A/Prof MacAry emphasized that for every antibody project, there is the need to first identify the antigen. His lab focused on building mammalian and insect expression systems in order to express important components of the virus (spike trimers, recombinant ACE2 receptors and components derived from variants). At the start, A/Prof MacAry was interested in observing how the viral spike protein interacts with its target receptor, ACE2. Data observed early on only illustrated a classic structural snapshot of a protein interaction, as analyzing the whole protein complex was challenging. Thus, A/Prof MacAry used hydrogen deuterium exchange mass spectrometry (HDXMS), a method used to observe dynamic protein interactions. The trimeric spike protein has two principal domains (S1 and S2). S1 contains the receptor binding domain (RBD), which directly engages with ACE2. The S1 domain is linked to the S2 domain, which includes the stalk that attaches the S-trimer to the surface of the viral membrane allowing fusion with the host membrane. Upon incubating a protein with deuterium (heavy water), water molecules present on the protein will get replaced with deuterium. Subjecting the protein to mass spectrometry, a specific pattern would be observed at a steady state and therefore, alterations in the protein structures could be derived from the pattern observed. Hence, for SARS-CoV-2, utilizing this method would aid in revealing dynamic interactions of the whole spike trimer and ACE2 over time.

HDXMS reveals that the whole S-trimer is not static, contrary to conventional structures reported. He stated that most proteins are constantly in flux (moving or waving). Looking at the deuterium exchange on the S-trimer, the part of the protein that is interchanging (moving) is revealed to be the stalk (S2 domain). Upon binding of the S-trimer to ACE2, the stalk was stabilized. Interestingly, with this, distal allosteric effects occur, opening up pockets that are now accessible for proteolytic processing. These two pockets were at the S1 and S2 junction, leading to new target areas for therapeutics.

A/Prof MacAry moved on to discuss the nature of antibody responses in vaccinated populations. He shared data on antibodies from the breast milk of vaccinated mothers. IgG antibodies (S-trimer specific) were present from day 7 up to several weeks post vaccination, in breast milk. Interestingly, IgA (spike specific) antibodies were also present in breast milk. In addition, he stated that these antibodies have good cross reactivity (binding events) with SARS-CoV-2 variants, including the Delta and Beta variants.

A/Prof MacAry then elaborated on the effects of neutralizing antibody responses on vaccinated groups in Singapore. The data observed is based on pseudo-virus neutralization tests, with a cohort



(168) ranging in ethnicity, gender and age-group. The study focused on individuals with the Pfizer mRNA vaccine prior to vaccination (dose 1), post dose 1 (day 21), the peak response (day 60-90) and after 6 months. There was a good neutralizing response up to the peak, with a reduction at 6 months. A/Prof MacAry observed that individuals above 60 years of age required 2 doses of vaccines for a good neutralizing response, and that women responded better than men in this Asian cohort. A/Prof MacAry then confirmed through a technology known as quartz crystal microbalance, that utilizing and working with a single RBD recombinant is sufficient and analogous to the spike trimer (3 RBD) when assessing RBD-ACE2 interaction. The technology measures binding events in the presence or absence of neutralizing antibodies, in order to assess if ACE2 will bind to the recombinant RBD on the chip. Thus, antibodies (from serum or plasma) that block spike-ACE2 interactions, or any other viral proteins, can be assessed. The challenge remains, though, of comparing neutralization studies from multiple groups. A/Prof MacAry explained that with this technology, the readout of ACE2 binding inhibition can be converted to an IC50 using WHO references to build standard curves. He then focused on using this assay to assess for the variants of concerns. The data illustrated that a high number of individuals responded with good neutralizing responses for all the variants up until the peak, including the Delta and Beta, however this response dropped dramatically at 6 months. Demographic data were similar as observed before.

He next focused his talk on Omicron, the current variant of global concern. In this variant, the RBD has a higher number of mutations, but still binds perfectly to ACE2. Neutralizing response at the peak time for Omicron shows a marked reduction in the same cohort studied, however, a booster aids in achieving a better response, but not reaching up to that of other variants.

Next, A/Prof MacAry discussed the different ways in which antibodies could be utilized. In COVID-19 diagnostics, there are lateral flow tests (ART kits), which captures the viral nucleocapsid instead of the highly variable spike protein. A/Prof MacAry stated that to a degree, the nucleocapsid protein is better conserved compared to spike protein, allowing the flow tests to also detect Omicron, however, this depends on the test being used. Antibody therapies for COVID-19 include using hyperimmune globulins (antibodies from a recovered COVID patient), but trials have been disappointing. Antibody cocktails and monoclonal antibodies are also being used and have shown good responses.

Lastly, A/Prof MacAry shared some methods to define good neutralizing antibodies from moderate or weak ones. The data obtained aims to analyze the moderate to weak antibodies more closely and to evaluate the defenses in their binding determinants. Solely looking at RBD is not sufficient and weak antibodies bind at a slightly distal patch to the RBD. Strong neutralizing antibodies stabilize the spike protein in a pre-fusion state.

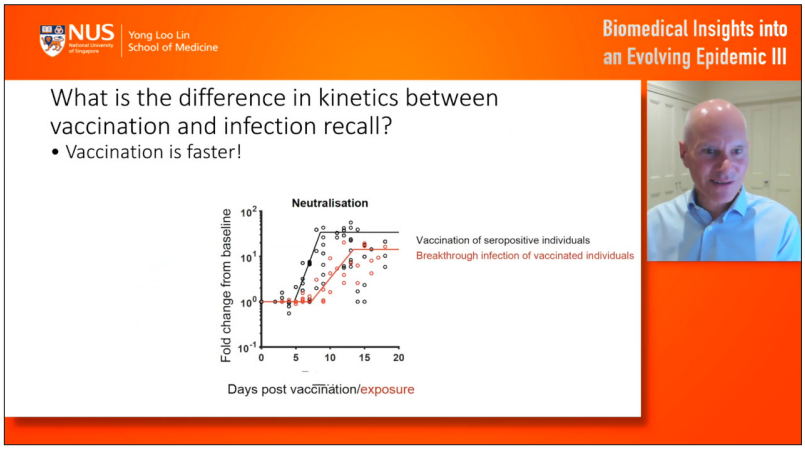
A/Prof MacAry concluded his talk by emphasizing that there are a lot of effective therapeutic antibodies which work well against the variants including Delta. However, and worryingly, most currently deployed antibodies show very poor neutralizing activity against Omicron.

Neutralising Antibodies against SARS-CoV-2: Implications for vaccines and therapies

Professor Stephen KENT [SPEAKER'S PROFILE]

Professor Stephen Kent gave an informative update on the role of neutralising antibodies against SARS-CoV-2, touching on current available assays to measure its titer, correlation of protection by vaccines, breakthrough infections and monoclonal neutralising antibodies in the prevention and therapy of SARS-CoV-2 infection.

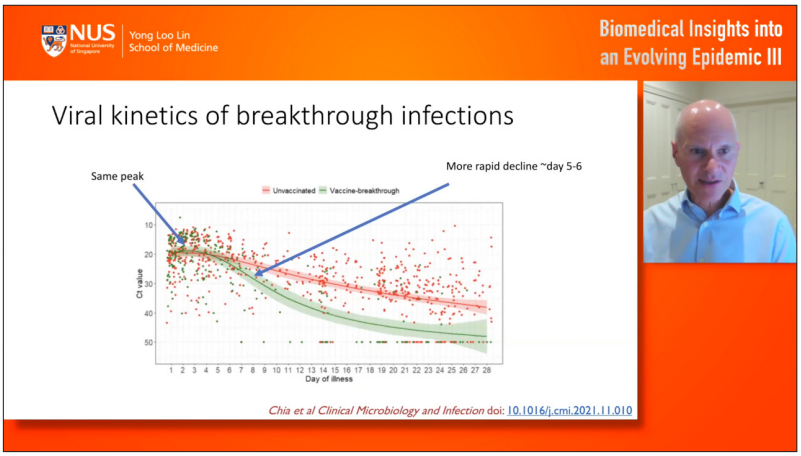
Prof Kent initiated his talk by stating that the germinal centers of the lymph nodes are the site of neutralising antibody (NAb) production. He elaborated that as the viral antigens interact with various immune cells, B cells are activated, producing a wide range of antibodies, including NAb, a subset that can inhibit the entry of the virus into the cell. On examining the germinal centers of the tonsil gland of a COVID-19 recovered patient, his group demonstrated $CD4^+$ T follicular helper cells (TFH) are the chief cells that generates NAb. Next, Prof Kent introduced the various assays that are currently available to measure NAb. Such assays include non-cell and non-virus based (ACE2-RBD inhibitor assays) and cell-based assays (e.g., Live SARS-CoV-2). According to Prof Kent, the cell-based assays are more robust and reliable than the non-cell based ones, since they mimic the *in vivo* immune environment. He further discussed two main cell-based assays; single cycle assays, which involve co-incubation of the pseudovirus carrying SARS-CoV-2 Spike protein and the cells, or the limiting dilution type (SARS-CoV-2) assay where antibodies are incubated with the virus. Lastly, Prof Kent made specific remarks on the SARS-CoV-2 surrogate virus neutralization assay (Tan *et al.*, Singapore) as it is simple, reproducible and robust, based on the NAb mediated blockage of the interaction between ACE2 and RBD. Next, he stated a paradoxical yet interesting finding, that severe COVID infection produces stronger NAb responses. This was possibly due to the prolonged infection causing the germinal centers to produce NAb exponentially. He then shared an intriguing observation, that upon vaccination, minimal NAb are produced in the mucosal surfaces (throat, saliva, lungs, and tears), which could be the basis of unrecognized infection transmitting through the eyes in vaccinated people.



In the next part of his talk, Prof Kent demonstrated that NAb are well correlated with protection from infection by vaccines. He presented data from a study and discussed the "Khoury curve", which depicted the NAb titers in vaccinated and convalescent groups and compared with seven different commonly administered vaccines. The reported mean neutralization level from phase 1 and 2 trials and the protective efficacy from phase 3 trials for 7 vaccines, as well as the protection observed in a seropositive convalescent cohort, were compared and results illustrated that the NAb titres correlated well with vaccine efficacy. He also assured that a booster dose (mRNA vaccine) administered to those that have completed a two-dose regimen of less efficacious vaccines, now have levels of NAb comparable to those that have completed the three doses regimen of mRNA vaccines, emphasizing that a three-dose vaccination is imperative for protection from SARS-CoV-2 infection. Moving on, Prof Kent discussed that the cut-off level of NAb required for 90% protection against the SARS-CoV-2 infection is approximately 1:150, with a much lower titre required for protection against severe disease. He mentioned that for influenza, haemagglutination titre is 1:40 (for 50% protection). Therefore, drawing a comparison, like annual vaccination for influenza, a six-monthly vaccination regime may be required to maintain the NAb tire for protection against SARS-CoV-2.

Therefter, Prof Kent discussed the "point of care" (POC) test developed by his team, which could measure the RBD-ACE2 NAb from whole blood. This test could be utilised in the future without the need for laboratory-based tests and could offer a rapid turnaround time. The POC test was compared against the gold standard microneutralization assay and a high correlation was observed. He then stated that approximately 50% of the immunity provided by NAb is lost in a span of 3 months. To support this statement, he presented data depicting the titre of NAb against different vaccines in symptomatic infection portraying 50% immunity decay every 3 months. However, he highlighted that once a third dose is administered, the NAb rises and immunity is boosted up to 100%. Lastly, he demonstrated that the neutralising immunity against the variants (Delta and Beta) was much lesser as compared to the ancestral and alpha SARS-CoV-2 virus.

Next, Prof Kent presented the predictive model data for protection against the Omicron virus. He revealed that AstraZeneca and Pfizer provided minimal protection against Omicron infection which increased upon administering the booster dose. Whilst for severe Omicron infection, AstraZeneca and Pfizer provided 40% and 80% protection respectively, which increased to 100% after booster dose. These data reiterate two vital points, firstly, the type of vaccine administered is important and secondly, the administration of a booster dose is critical for protection against the variants.



Prof Kent then focused on "breakthrough COVID", which is defined as occurrence of COVID infection despite being vaccinated. This depended on the type and number of vaccines administered, as well as the time elapsed after vaccination. He further enlightened that breakthrough COVID is mild to moderate in severity and fewer "long COVID" cases are encountered, but it is highly transmissible, driven by rapid viral replication. Citing a study by Chia *et al.*, he illustrated that the unvaccinated and the breakthrough infections show similar Ct value (viral peak) at the beginning, but unlike the unvaccinated group, the Ct values of breakthrough COVID patients declines rapidly in 5-6 days. There is an ongoing debate that the cause of the rapid decline of breakthrough infections in 5-6 days could be due to cross reactive T cells or due to humoral immunity. To prove his stand, Prof Kent demonstrated that the levels of CD4+ and CD8+ T cells fail to increase in the first 5-6 days, instead the levels of NAb, B cells and plasmablasts increased steadily, elucidating that in controlling the breakthrough infection, NAb and not T cells play a major role. (Note: this is a debated topic. For evidence supporting a major role for T cells in COVID-19, please refer to summaries by Professors Laurent Renia and Ooi Eng Eong).

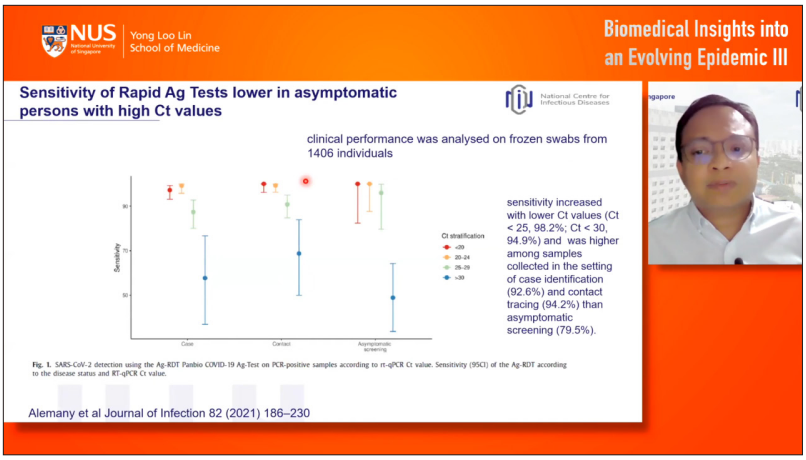
In the last part of his talk, the speaker touched on monoclonal antibodies (mAb) in the treatment and prevention of SARS-CoV-2 infection. He presented data from a clinical trial demonstrating the utility of mAb, where upon administration of Regen-COV to 750 household contacts of SARS-CoV-2 positive cases, only 1.5% compared to 7.8% from the placebo group, caught symptomatic COVID-19 infection. He further stated that mAb has little/no utility in protecting against Omicron positive cases, hence the FDA has banned the use of certain mAbs in USA. Finally, he presented the Australian guidelines for the usage of Sotrovimab (commercial mAb), which states it should be administered as early as possible to immunosuppressed patients, patients not on oxygen therapy, age >55 years and with multiple risk factors groups (diabetic, obese, chronic kidney disease, CHF, COPD and moderate to severe asthma).

SARS-CoV-2: diagnostics, overview and advances

Dr Shawn VASOO [SPEAKER'S PROFILE]

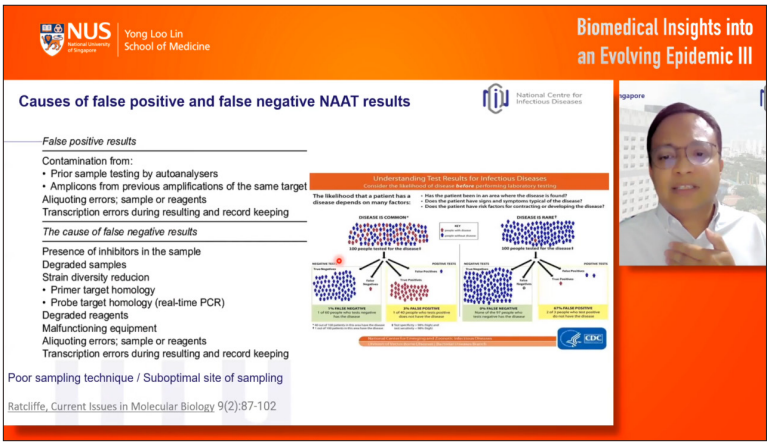
Dr Shawn Vasoo provided an excellent and insightful update on the various diagnostic tests currently available for COVID-19 detection. He gave an overview of point of care testing (POCT), role of antigen rapid tests (ART) and optimal sampling for SARS-CoV-2 detection, correlation of the diagnostic tests with infectiousness, variant typing and immunologic correlates of protection against COVID-19.

Dr Vasoo opened his talk sharing various traditional approaches (detection of viral nucleic acids, antigens and host antibodies) and novel methods including mass spectrometry (MALDI-TOF) and biosensors (volatile organic compounds) for COVID-19 diagnosis. Viral nucleic acids can be detected by RT-PCR assays which are known as nucleic acid amplification tests (NAAT). PCR is the mainstay for diagnosis of SARS-CoV-2 infection, versatile and quick to set up once the viral sequence is known. He updated that there were supply chain issues at the peak of the pandemic, which spurred innovations like isothermal approaches (loop-mediated isothermal amplifications) and direct sample processing (removing the preanalytical step). Unfortunately, the gains in the reduction in the turnaround time (TAT) can result in reduced overall sensitivity. He then commended various "home grown" advances like, phosphate-buffered saline and minimal essential medium as potential alternatives to viral transport media as well as the Fortitude kit 3.0 (MIRXES) and RESOLUTE 2.0 (Advanced MedTech) *in vitro* diagnostic kits. Currently all the various COVID-19 rapid molecular tests that are available are CLIA-waived for emergency usage and these tests are rapid (TAT less than an hour) and could be performed at POC by the patient or his physician.



Thereafter Dr Vasoo described ART that are currently available as self-test kits, POCTs or laboratory-based tests. These tests detect the presence of the specific viral antigen known as the nucleocapsid protein. They are less expensive and rapid with a TAT of 15-30 minutes. Multiple studies have corroborated and validated that while ART are best for symptomatic patients with low Ct value (high viral load) and close contacts of COVID-19 positive patients, it is least sensitive for asymptomatic cases with high Ct value (low viral load). Note: The Ct (cycle threshold) value refers to the number of PCR cycles required for detection of the virus. A high Ct value correlates to low viral load and conversely, low Ct value is indicative of high viral load.

The positive predictive value (PPV) of the diagnostic tests describes the probability of a patient with a positive test to be truly infected with the viral pathogen. It is influenced by the specificity of the test, prevalence of the infection, stage of illness and the sampling site. He further apprised that in a population with low prevalence rate, even a highly specific test could show increased false positive results thus, decreasing the PPV. Stage of illness influences the PPV of a test, as the viral RNA genome and protein shed maximally in the first week of illness (high PPV) and thereafter decreases steadily. Nasopharyngeal swab provides the highest sensitivity for the test followed by the throat, midturbinate and saliva. Combining nasopharyngeal and throat or midturbinate and throat samples, within 7 days of illness, could increase the overall sensitivity. Furthermore, false positive results could arise due to contamination or transcription errors that could be mitigated by repeated extractions and re-running the assay, alternative specimen (stool), performing serology, and evaluating the patient's clinical features. False negative results could be attributed to poor sampling technique, suboptimal samples or technical errors and could be minimized by repeating or deep sampling. He then highlighted a pertinent fact that PCR performed in the first few days of illness could detect more than 90% of



cases, however repeated testing is advised in highly suspicious negative cases. He shared that while there are no international standards for Ct cut-offs, in his experience, a Ct value of less than 25 was a good general guide for COVID positivity (infectious) and a value of greater than 30 was a guide for low transmissibility.

Moving on, Dr Vasoo elucidated the effectiveness of various tests in determining the infectiousness for COVID-19. While viral culture remains the gold standard, it has low sensitivity, long TAT and is tedious to perform. ART could be the best marker for infectivity, but its sensitivity is variable and false negative results could be generated due to viral mutations. Real time PCR provides Ct values that may give an indication of viral load and infectivity but, several analytic variables affect the Ct values. Lastly, viral RNA intermediates, such as the subgenomic RNA (sgRNA), have been evaluated for infectivity in animal models, but with limited support in human data. There is evidence that some humans shed sgRNA over long period of time, probably indicating infectivity.

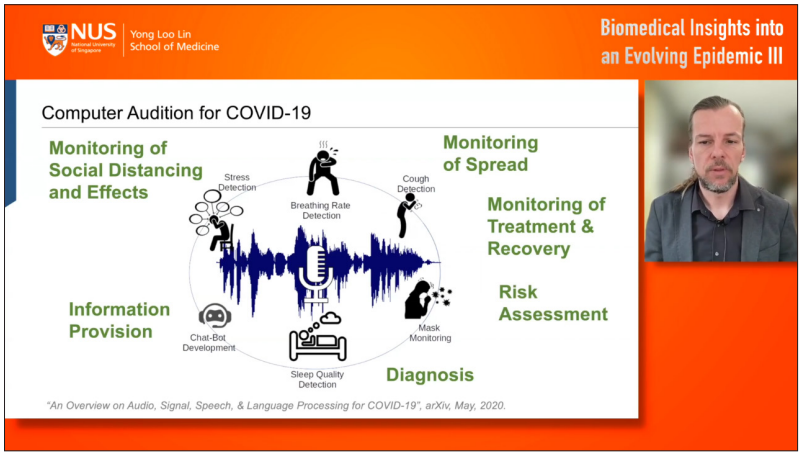
Dr Vasoo reaffirmed that viral RNA peaks 1-2 days before the symptoms appear and persist for 8-10 days but is no longer culturable and thus not transmissible by day 8 (NCID and HKU data). He concluded that testing capacity should be conserved for patients at earlier stages of illness rather than at stages when the patient is no longer infectious. He further emphasized that for vaccine breakthrough, the predicted mean Ct value reached to 30 by day 9 versus day 15 in fully vaccinated and unvaccinated group respectively, highlighting the importance of vaccination in controlling the severe symptoms of SARS-CoV-2 infection. In the context of Omicron, the Ct value reaches 25 by day 7 and 30 by day 10, thereby governing the time-based discharge from isolation. This data guided the government policy for de-isolation in Singapore whereby patients should be discharged at day 14 (unvaccinated) and day 7 (vaccinated). Lastly, for the immunocompromised group, deisolation should be done from day 14-21 and PCR/ART should be used to guide if deisolation must be done before day 14 and after day 21.

In the final part of his talk Dr Vasoo discussed the importance of diagnosis of variants in the context of public health, infection control, prognostication, and possible therapies (most therapeutic monoclonal antibodies are ineffective against the Omicron variant). Currently allele-specific RT-PCR, whole genome sequencing and targeted/Sanger sequencing are approaches to SARS-CoV-2 genotyping. Lastly, immune correlates for protection against COVID-19 are pertinent for procuring vaccine licensure/trials, determining needs for boosters, and guide use of monoclonal antibodies. Presently there are no robust immune correlates and the regulatory bodies have cautioned against the use of antibodies to evaluate a person's level of immunity or protection from COVID-19. Progress is currently in the right direction, as the WHO is setting an international standard for anti-SARS-CoV-2 immunoglobulins.

Dr Vasoo concluded his talk with this thought: although advancements have been made in diagnostic strategies for SARS-CoV-2, there are still uncertainties and unanswered questions for which solutions must be sought.

Novel AI-based COVID-19 Diagnosis: Video, Audio, Cardio

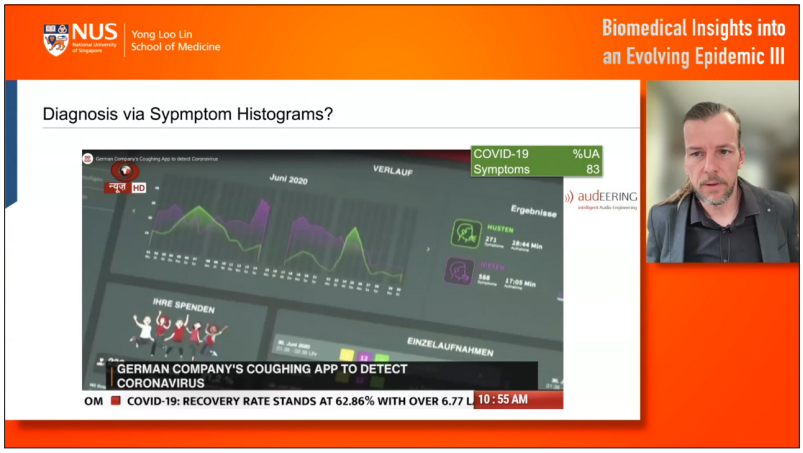
Professor Björn W. SCHULLER [SPEAKER'S PROFILE]



Professor Björn Schuller presented an enlightening talk on new developments and innovations on COVID-19 diagnosis through novel artificial intelligence (AI) methods, focusing on the use of audio for COVID-19 detection.

Prof Schuller introduced video diagnosis as a well-established method to detect other modalities. He illustrated a chest computerized tomography (CT) scan to diagnose COVID-19 (96.1% accuracy). However, images obtained may not be limited to just COVID-19, with evidence of other diseases, rendering this approach prone to human errors and misdiagnosis for COVID-19. In addition, using databases containing CT scans and chest X-rays (CXR) that have low numbers of participants must be interpreted carefully if these are used for machine learning.

Prof Schuller then focused his talk on audio diagnosis, which could detect changes in the voice or coughing, as COVID-19 primarily affects the respiratory tract, impacting vocal production properties. His team demonstrated that computer audition could be used to detect COVID-19 through symptoms, and monitor mask wearing, social distancing, COVID-19 spread and treatment and recovery. The aim was to have a quick real-time and environmentally friendly method (app), which was then tested from speech data obtained from a Wuhan cohort (85% accuracy). Prof Schuller then questioned whether audio diagnosis would be better and more reliable than other established methods (risk assessment, Bluetooth for contact tracing, temperature measurements), or could be used to compliment these methods.



Prof Schuller further explained the use of the app (AI SoundLab) that was initially created for COVID-19 diagnosis through symptom histograms. The navigation page inputs symptoms from a questionnaire, followed by options to record the patient's response overnight (prolonged time) or shorter time periods. Breathing rate and pattern recognition were the targets from audio, with results depicting a good challenge, illustrating a high correlation rate of 0.85 - 0.9. Results obtained from the challenge that were relevant to the risk (age, gender, breathing, having a cold, etc.), had a relatively high accuracy.

Upon the roll-out of the first demonstrator, the app went 'viral'. However, this was short-lived, as a new wave emerged that directly inferred the presence or absence of COVID-19 through the sound of the voice (recording vowel pronunciations). Data collected by volunteers portrayed a positive or negative read-out based on hoarseness of voice, through an app measuring probability. Similar research conducted by several other groups revealed high correlations (90-100%), triggering concerns that these methods may be implementing a 'more' reliable diagnosis than conventional

PCR. The results obtained in his challenge elucidated high reliability, as the study cohort was taken from a hospital, where voice recordings were subjected to similar acoustic conditions throughout the study. Representation from the data had also been evaluated in terms of key sounds from COVID-19 patients who vocalised a certain sentence (in Chinese) that would generate a 3-way classification for COVID-19 recognition, as well as from forced coughing or simply just breathing sounds. He updated that currently many databases have been generated but, the problem lies in the imbalance of more negative participants compared to positive, and that these negative cohorts manifest other symptoms. Another problem that Prof Schuller highlighted was the inability for the database to collect data from the same person with and without COVID-19, thus leading the team to collect data from other sources (social media of politicians and celebrities) before 2019 (pre-COVID-19) and after 2019 (COVID-19). Prof Schuller then mentioned that new databases depicted results with high accuracy and emphasized that tests should be well organized, reproducible and blinded.

Prof Schuller moved on to describe the process of speech-to-pause ratio, where a longer pause (severe breathing difficulties) and fast speech led to the detection of COIVD-19. Other features, such as coughing and breathing, also play a role and, over the next part of his talk, Prof Schuller presented several audio clips to demonstrate these audible features. The use of fundamental frequencies can help detect positive COVID-19 patients as the frequencies are not as periodic and not steady (jittery). Data from vowel speech depicted perturbations in the amplitude (shimmer and jitters), period length and voice segments, to detect positive and negative patients. Data observed from the Cambridge team confirmed reliability, where good results were observed even when comparing asthmatic patients, however, the sample size was very small. In addition, data collected from the challenge initiated with COVID-19 positive cohorts (April 2020), only to realize the need for negative cohorts, collected at a later time (June 2020), speculating that time of the year could have an effect on audio collection. Results (speech-base and coughing) after the challenge showed COVID-19 diagnosis to be above the baseline, though not reaching above 80%. Prof Schuller was hopeful, as more data is still being collected to improve the hardware systems. Prof Schuller then mentioned that artificial intelligence data can also be implemented to augment insufficient data collection, such as adding different noises and changing amplitude and tempo.

Prof Schuller highlighted another study that used humans to detect COVID-19 through audio, and not experts or apps. Unfortunately, the results from this study were disappointing as they were unable to detect COVID-19 patients from audio, but perhaps the subjects might not have gained sufficient experience with this detection system. Thus, currently, humans cannot detect COVID-19 positive patients through audio, and machines can do it better.

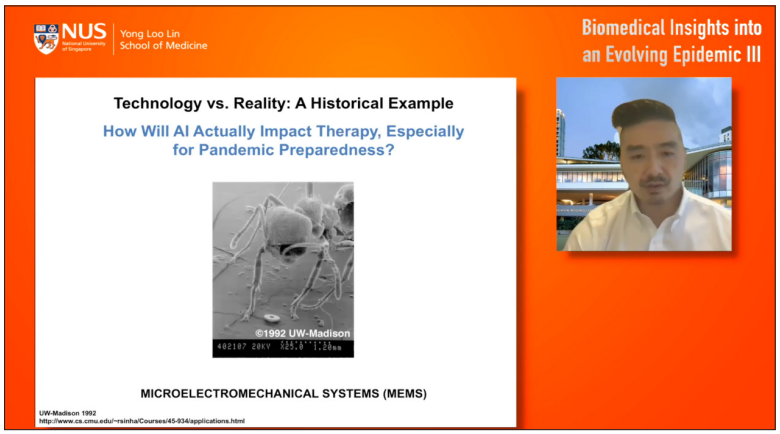
The next part of Prof Schuller's talk discussed the cardio aspect, where heart-rate data was collected over several months through a tracker (Fitbit). Some subjects caught COVID-19 and some did not, and so using an auto encoder, any deviations on heart rate patterns that were observed from this data set could be correlated with the known onset of COVID-19. A useful enhancement would be to incorporate a combination approach with addition of other features, such as a microphone (Amazon's Halo View tracker).

Prof Schuller ended his talk by discussing the current challenges, apart from his on-going large data collection, to improving audio diagnosis. These included ethics, legal and societal impact; trust of results, objective analysis, and sharing of data across groups. Overall, Prof Schuller concluded that there is an agenda that needs to be achieved to improve the system, which includes finding strategies to be more data efficient with new variants and other modalities, combating drifting targets or symptoms and conducting a fair diagnosis across user groups.

Innovations in Treatment: Harnessing Digital Medicine to Re-Imagine COVID-19 Therapy Development and Beyond

Professor Dean HO [SPEAKER'S PROFILE]

Professor Dean Ho gave an engaging talk on current innovations for COVID-19 treatment and shared his views on the future of artificial intelligence (AI) technology in drug development.

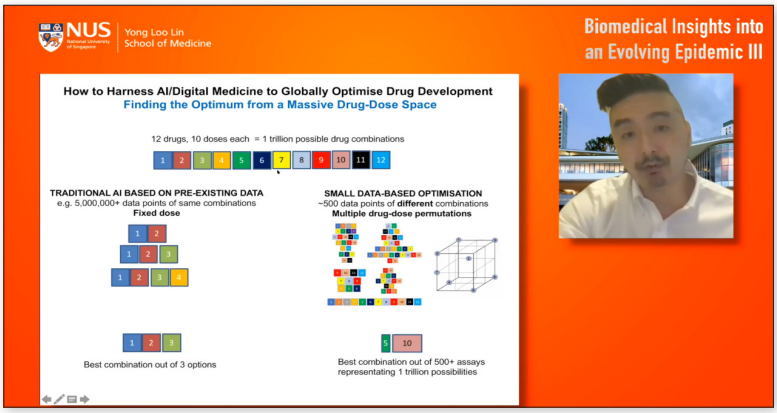


Prof Ho started his talk on the history of technology, posing a provocative question, "how will AI impact therapy, especially for pandemic preparedness?" The aim, back then, in the microelectromechanical systems (MEMS) field, was the potential to find better means to engineer technology in a scalable fashion. When a new technology emerged, the notion was that this technology would change how things were done, however, when the technology became broader deployed, and more in use, the industry discovered unforeseeable challenges, which needed to be surmounted before adoption into society. In the context of medicine, Prof Ho explained that the deployment of a technology, from early development to actual adoption, requires time (e.g., microfabricated device for spinal injury). He highlighted the element of packaging which allows for the original concept of micro-electrical mechanical systems to be actually implementable, in the context of using AI for COVID-19 therapy. Prof Ho further emphasized that technology alone cannot change entire fields (healthcare or COVID-19). Other aspects to consider were expectations and limitations of AI technology, in order to achieve specific goals that were reasonable in the context of drug discovery and development.

Prof Ho moved on to illustrate an example of AI deployment – finding new drugs with AI. In February 2020, the AI-driven repurposed drug, baricitinib, was named a potential treatment for 2019-nCOV acute respiratory disease (early name for COVID-19). Continued research on evaluating its mechanisms, pre-clinical validations and finally, to an emergency use authorization (EUA,) was achieved in a record time of 9 months (November 2020). This was a breakthrough for AI, especially in the context of potential COVID-19 therapies.

Next, Prof Ho highlighted the challenges faced from using AI to address drug development (drug combination designs, lessons from other indications and dosing). He stated that the challenge faced was that of validation of drug combinations for re-purposing therapy, with the greatest concern being urgency, especially for newly emerging pathogens (COVID-19). At this stage, there was uncertainty on which drugs to combine and at what dose. Prof Ho emphasized that even good drugs given at the wrong dose would not yield efficacy. However, re-optimizing the dosage for these compounds could restore their utility, eliminating the misconception that these drugs were unusable. Thus, the entire drug work-flow could be 're-imagined' for administration using AI (identify new targets and optimized dosage). At the drug discovery stage, Prof Ho stated that there are segments that may get overlooked. Initially, AI was first used to find promising drugs for COVID-19 (drug sensitivity) followed by finding effective combinations of drugs (synergistically), but in reality, this would not be sufficient for good clinical outcome.

Prof Ho then elaborated on the approaches used to further harness AI to optimise drug development for effective combinations. When presented with 12 drugs at 10 doses, this results in 1 trillion possible combinations. Thus, feeding big data into an algorithm could be leveraged to make predictions. Additionally, when dealing with intervention, and using AI, working with smaller datasets also had its merits. For this, the data needed to be more specific (prospectively and experimentally) and on a specific disease model, where a whole map of combinations could be attained, leading



to determining the best and worst drug combinations. In other words, therapies that seem to not work on their own, could have unexpectedly positive outcomes when used in combination with other drugs.

Prof Ho explained that when correlating drugs and dosing as the 'input' and efficacy and safety as 'output', a map of second-order correlations could be achieved. This optimisation process generated good potential combinations rapidly and allowed for a dramatic reduction in experimentation time. Ranking of these AI-discovered potential combinations *in vitro* led to further re-optimisation *in vivo* (pre-clinical response) and finally in patients (clinical).

Prof Ho illustrated, in the next part of his talk, how he applied neural networks (IDentif.AI) to drug development studies of over 50 models of diseases. Prof Ho put together a team of experts, ranging from engineers, clinicians, global heath and security experts, healthcare economists, etc, to use a platform of AI, with the aim of applying this knowledge in a pandemic or an outbreak. As healthcare systems and industries would be strained during a pandemic, the urgency to define good successful combinations was imperative. With the help of a field epidemiologist, 12 drugs (in clinical trials at that time) were potentially identified to treat COVID-19. Using a quick live-virus assay (single drug activity assay), clinically relevant doses were administered to prospectively rank the combinations from the best to worst. With the clinicians' help, a few combinations of interest were chosen for re-evaluation and optimisation to increase the robustness of the approach. Results showed that a drug like remdesivir was moderately effective alone, but in combination with other drugs, such as lopinavir, enhanced activity was observed. This led the team to think about different classes of drugs that could be used in combination (e.g., protease inhibitors). In addition, based on the current work, an active IDentif.AI database was generated and made available online. It is used by clinical partners around the world, giving rise to multiple clinical protocols.

In a collaboration with clinicians at NCID and NUH, IDentif.AI 2.0 (re-run of IDentif.AI), was employed to look for new drugs that exist in tablet form against the Beta, Delta and Omicron (IDentif.AI 3.0 - on-going) variants. The optimisation phase was rapid (2-3 weeks) and data generated provided insights into optimal drug combinations, providing clinically useful information for clinicians. In addition, Prof Ho assured that there is strong evidence that *in vitro* AI-driven drug identifications translate well to the clinics. Prof Ho reiterated that to achieve the best possible candidates, we must go beyond the concept of re-purposing or drug sensitivity and look at the entire parameter space. Lastly, beyond COVID-19, this approach could be used for other disease models, including HIV, a highly debilitating disease.

Prof Ho focused the last part of his talk on other indications and factors during the optimisation process for therapeutics. He shared lessons learned from other clinical indications, such as in transplants, where variability between patients, and even within themselves are high. AI was useful for determining optimal dosage (population therapies or personalised) for transplant patients to reduce discharge time. Prof Ho emphasized that the problem of dynamic synergy (role of dose), can now be reconciled for better drug combination design. Lastly, AI-driven analysis of two oncology drugs found to be toxic to a patient, predicted greater efficacy at a 50% dose reduction. The prediction correlated well clinically and the patient resumed an active lifestyle.

To end, Prof Ho concluded that when selecting therapies, the role of dosage must be considered carefully. Furthermore, being able to reconcile both drug selection and dose optimisation from the trillion drug-combo-perimeter spaces, allowed his team to think beyond achieving synergy or solely mechanism of action, and focus on better use of the drug pool. He reminded the participants that AI-driven approaches can contribute significantly to clinically-optimized therapy for infectious diseases, if limitations and expectations of the technology were taken into consideration.

COVID-19 Treatment

Associate Professor David Lye [SPEAKER'S PROFILE]

Associate Professor David Lye gave an excellent update on the wide range of treatment modalities available for COVID-19 based on several ongoing randomized control trials (RCT). Monoclonal antibodies (mAb), antiviral drugs and immune modulators are effective treatments currently available for different stages of COVID-19.

A/Prof Lye firstly emphasized that vaccines provide the best prevention against COVID-19. He further highlighted that vaccines stimulate both humoral (antibody) and cellular immunity (T cell response), which is essential for protection against severe infection.

A/Prof Lye introduced monoclonal antibodies (mAbs) as a prophylaxis and treatment modality for COVID-19. Currently, the only available mAb for pre-exposure prophylaxis is AZD7442 (tixagevimab and cilgavimab; AstraZeneca) which reduces the risk of COVID-19 by 77% (unpublished phase III study). For post-exposure prophylaxis, REGEN-COV (casirivimab and imdevimab; Regeneron), when administered within 4 days of exposure, reduces the risk of COVID-19 by 81%, on par with vaccination protection. Another mAb, bamlanivimab when administered within 7 days of exposure to nursing home residents and staff, reduced the risk of infection by 81%. Lastly AZD7442 provides 71% and 92% protection when administered within 7 days and after 7 days of exposure respectively. A/Prof Lye moved on to discuss the rationale for early treatment of high-risk cases, reasoning that the rate of progression to hospitalization or death is very high in such circumstances. High risk cases include old age, high body weight, pregnancy (in some), diabetes, heart failure, chronic kidney and liver disease, dementia, stroke and cancer. Bamlanivimab and etesevimab showed a 70% reduction in progression to hospitalization and death in COVID-19 high-risk patients and reduced the viral load. Similarly, REGEN-COV (phase II trial) when administered showed a 50% reduction in progression to severe disease and viral load. In another phase III trial, REGEN-COV reduced the progression to hospitalization/death by 71% when administered within 3 days of positive COVID-19 test. In addition, if administered early in seronegative patients, the protection was enhanced to 82%, concluding that mAb provides greater benefit when administered to seronegative patients in the first week of infection. Sotrovimab (GSK-Vir Inc.), AZD7442 (AstraZeneca), BRII-196/BRII-198 (Brii Biosciences Ltd) and regdanvimab (Celltrion, Korea) reduced severe infection by 85%, 50%, 78% and 72% respectively, in different clinical trials. Lastly, A/Prof Lye mentioned high titer convalescent plasma therapy, when administered within 2 days of infection, reduced the progression to severe disease by 52%. Likewise, a RCT conducted by The Johns Hopkins Hospital in children treated with plasma therapy showed a reduction in progression to severe disease.

In the next part of his talk, A/Prof Lye focused on antiviral treatment against COVID-19 infection. One of the first antivirals that was found to be useful in preventing progression to severe COVID-19 infection was remdesivir. When administered intravenously, for three days, it reduced progression by 87%. Molnupiravir was a game changer for COVID-19 treatment as it was the first orally administered antiviral drug. In non-hospitalized patients it reduced the risk of progression to severe disease by 50%. However, it had an efficacy of only 30% and was not suitable for pregnant women. Paxlovid, a 3C-like protease inhibitor (antiviral nirmatrevlvir and anti-HIV ritonavir), if given within first 3 days of high-risk patients, reduced the progression by 88%. Since Paxlovid showed drug interactions, careful monitoring should be done for five days for any adverse drug reactions. For COVID-19 pneumonia

cases that do not require oxygen, no treatment was required. In severe COVID-19 cases, where oxygen was required, remdesivir treatment led to an earlier recovery (5 days), reduced hospital stay, reduced the need of high flow oxygen and mechanical ventilation, and shortened the time on oxygen.

The RECOVERY trial (sponsored by University of Oxford) established the role of dexamethasone in the treatment of critical COVID-19-pneumonia patients, demonstrating that intubated patients showed a benefit of 35%, whilst those on high-flow oxygen, showed a benefit in 18% of cases. Additionally, dexamethasone provided better protection if given in the 2nd week of pulmonary pneumonia. However, A/Prof Lye cautioned that since pulmonary aspergillosis (commonly reported in India) is known to be associated with diabetes and corticosteroids, dexamethasone should be judiciously used in COVID-19 patients at risk of infection with this fungal pathogen.

Next, A/Prof Lye discussed the role of immunomodulators in the treatment of COVID-19. NIH ACTT-2 conducted a double blinded trial with a combination of baricitinib and remdesivir, administered to hospitalized adults. Results obtained showed early recovery by 8 days, reduced mortality in patients requiring low-flow (by 60%) and high-flow oxygen (45%), reduced progression to oxygen and intubation requirement and shortened the time on a mechanical ventilator. In a second independent trial (Elli Lily), baricitinib reduced the overall mortality by 43%, progression to high-flow oxygen, and noninvasive and mechanical ventilation significantly. Baricitinib showed benefits whether it was administered in the first or second week of infection, giving it an edge over remdesivir, and dexamethasone. A third pilot phase II trial demonstrated benefits of baricitinib in reducing mortality in critically ill hospitalized COVID-19 patients on mechanical ventilation or on extracorporeal membrane oxygenation. Several phase III RCTs have shown that tocilizumab is not beneficial in treatment of COVID-19. However, the REMAP-CAP investigators showed that tocilizumab and sarilumab improved survival in critically ill patients with COVID-19 receiving organ support. This was further confirmed by the RECOVERY trial here; tocilizumab reduced mortality by 15% and had benefits in secondary outcomes.

A/Prof Lye then discussed the role of mAb in the treatment of severe COVID-19 pneumonia with or without oxygen supplementation. Contrary, to its success in the early treatment of high-risk cases, the NIH platform trial (ACTIV-3) studied mAb from Elli Lily, Vir-GSK and Brii Bio and concluded that none of these were significant in the primary outcome of early recovery in hospitalized COVID-19 patients. However, a phase III RCT (RECOVERY) surprisingly showed that high dose REGEN-COV reduced mortality by 20% in seronegative COVID-19 patients.

A/Prof Lye concluded his talk by focusing on the treatment modalities available against the SARS-CoV-2 variants, especially Omicron. Amongst all the mAb, only Sotrovimab and AZD7442 have proven efficacious against the Omicron variant. In addition, another mAb, bebtelovimab (Eli-Lilly), received an FDA-EUA (emergency use authorization) approval based on the results of a phase II clinical trial showing that it was effective against Omicron.

The New Normal: A Moving Target?

Panelists: Associate Professor David LYE, Associate Professor Paul MACARY, Dr Jyoti SOMANI, Professor Yik Ying TEO, and Professor Linfa WANG
Moderators: Associate Professor Kevin SW TAN and Associate Professor Pablo BIFANI

The finale of Biomedical Insights Into An Evolving Epidemic III (BIEE3) was in the form of a panel discussion on COVID-19 and the new normal. The discussion was divided into sessions covering the epidemiology, transmission, pathology, antibodies, vaccines, and treatment of COVID-19.

Session I: Epidemiology and Transmission

"COVID is no longer a socially critical disease"

Prof Teo began the discussion by raising a very pertinent point that a huge inequity exists in vaccination status amongst the different countries. Countries like Nigeria and Ethiopia (less than 7% and 8% of the entire population are fully vaccinated, respectively) are lagging behind Singapore, Chile and Portugal, where more than 80-85% have been fully vaccinated. Due to this global inequity, transitioning out of the COVID-19 pandemic will be asynchronous. He also highlighted a rather harsh fact that moving forward, natural selection will be the order of the day, such that, either people will recover well, with natural immunity or succumb to long term COVID-19 consequences.

"The emergence of Omicron makes vaccine inequity less important, because being less virulent, Omicron may act as a natural vaccine"

Prof Teo acknowledged that Omicron is less virulent, more transmissible, leads to lower hospitalization rates and provides protection against reinfection by Delta and other SARS-CoV-2 strains. But the main concern would be the emergence of new virulent and deadlier variants compared to Omicron and other previous variants. Hence, global surveillance for newly emerging variants or sub-lineages of Omicron will be needed in the future. Prof Wang concurred with Prof Teo's comments and pointed out that current available data are from vaccinated countries, which does not reflect the true global picture pertaining to COVID-19 infection and pathogenicity. He cited an animal study by a Hong Kong group, which showed that among the Omicron and Delta variants, the latter is fitter and out-competes Omicron. However, with vaccination, Omicron is fitter than Delta virus. He further added that Omicron exhibits immune escape as it evades the immune system and the three sub-lineages of Omicron (BA.1, BA.2 and BA.3) are still being investigated. Hence, it is too early to declare that COVID-19 has been defeated.

"Living with the Omicron virus"

Prof Wang stated that it is debatable whether Omicron could provide broad protection against other SARS-CoV-2 strains. He cited an animal study (NIH) where mRNA vaccines were administered to a naïve population of mice infected against the ancestral Wuhan virus, Beta, Delta, and Omicron variants. It was observed that even a single dose of vaccine against the ancestral Wuhan virus provided protection against the Beta (10-20%), Delta (5-10%) and Omicron variant (50%). Conversely, if the mice were administered with a vaccine against Omicron, neutralizing antibodies were developed only against the Omicron variant and not against other strains. He warned that if there is a new variant which is antigenically different from the original strain, then the vaccination status, or previous COVID-19 infection, would be unable to protect against such variant. Dr Somani agreed that Omicron is more transmissible, where pathogenicity was high in animal models, however clinically mild symptoms were observed in humans. She echoed Prof Teo's thoughts that Omicron is immune evasive, and the vaccine protection is reduced for this variant. Prof Teo then added that even though Omicron is not as deadly as the Delta variant, if unvaccinated, it may lead to severe infections. Moreover, inaccessible antiviral treatments in poorer countries, would make Omicron not as trivial as it seems. He also added that since new variants usually do not follow previous variants, he cautioned preparedness for the next variant. A/Prof Bifani added that it is possible that the new strain may be derived from the ancestral Alpha strain and not the Omicron variant. A/Prof

MacAry was hopeful that even though Omicron is significantly different from its previous variants (more than 30 mutations, mostly on the receptor binding domain), cross-reactivity against different strains was still observed. This implied that current vaccines might still provide protection against the newer variants that may emerge in the future. On the flip side, A/Prof Bifani stated that though Omicron is mild, mortalities and serious infections seen in the elderly warrants concern.

"Lessons learnt from the last three coronavirus outbreak (SARS, MERS and COVID-19). How can this prepare us better for the next one?"

Prof Wang shared insightful lessons from his experience. Firstly, coronavirus will not be the last zoonotic virus that will infect humans. He advised the audience not to underestimate coronaviruses, as it is difficult to contain. Second, early sensing and detection, international collaborations and containment are still better than developing a rapid vaccine. Finally, a better understanding of immunity against coronaviruses is required, to be well prepared for the next pandemic (SARS-3). He highlighted that the vaccine against the Hendra virus (more lethal than coronaviruses) worked 100% against the Nipah virus as well, even though they are structurally different. In contrast, the first-generation vaccine against the Wuhan strain does not protect against the Omicron variant (differed by only 0.01%), hence, the need for better understanding of immunity against coronaviruses. Prof Teo added that ever since the outbreaks of SARS, MERS and H1N1, the world has focused on global health security in an endeavor to guard against future pandemics. **The Global Health Security Index was introduced in Nov 2019 by USA, which surprisingly revealed that countries ranking high in this index, were least capable of minimizing the impact of COVID-19, resulting in greater infections and higher mortalities. Therefore, in accordance with his thoughts, the lesson to be learned is to understand that apart from policy implementation, social, cultural, behavioral, and political context are key in dictating how countries cope with pandemics.**

Session II: Pathology

"Long term effects of COVID-19"

Dr Somani commented that SARS-CoV-2 causes a tsunami of long-term effects, like chronic lung diseases, cognitive and kidney dysfunctions, diabetes, and mental health problems. A recent study in the United States revealed increased anxiety, depression, post-traumatic stress disorder (PTSD) in not only those who recovered from severe disease, but also those who recovered from mild COVID-19 disease.

"Impact of the clinical experience of COVID-19 on the management and preparedness of future pandemics"

Dr Somani highlighted that even before the pandemic began, developed countries had started focusing on chronic diseases and its prevention. But since the onset of COVID-19, even developing countries had to shift their focus from acute to chronic diseases and its prevention, such as adult vaccinations and preventive screenings. She also added lessons learnt from COVID-19, that other than the elderly, even younger people with risk factors had high mortality rates. Obesity was one of the risk factors and countries like the US and UK, where the obesity rate was high, mortality due to COVID was also quite high. She further reassured that NUH is well prepared for managing long-term effects with the help of MOH.

"Complications from Omicron that causes death"

Dr Somani revealed that the Omicron variant causes slow progressive disease, where patients progressively develop fever, eventually requiring oxygen and may succumb to death. She highlighted that elderly, weak and patients with co-morbid conditions, are more susceptible to severe disease and/or death. In contrast, the Delta variant caused patients to quickly progress to severe complications, oxygen requirement and finally death. A/Prof Lye added that survivors of COVID-19 are at risk of heart attack and stroke. He emphasized that vaccination reduces the long-term side

effects, but not completely. He reiterated that elderly, unvaccinated and those with poor immunity are at high risk of mortality.

"Breakthrough COVID and long-term consequences"

A/Prof Lye highlighted that there is sufficient data to suggest that long COVID will diminish with breakthrough COVID-19. Several studies showed that in vaccinated cohorts, symptoms of long COVID were significantly less, compared to the unvaccinated. Additionally, inflammatory markers in COVID-19 survivors, who were vaccinated are reduced compared to the unvaccinated.

"Safety profiles of the COVID vaccines"

A/Prof Lye informed the audience that the incidence of severe adverse reactions from the mRNA vaccines is quite low (0.07%). The most severe adverse reaction for mRNA vaccines is anaphylaxis (severe allergy) and was reported to be 1 in 100,000 and for inactivated vaccines, like Sinovac, 5 in 100,000, affirming that the safety margin of these vaccines is quite high. Dr Somani commented that the risk of being unvaccinated or vaccinated must be borne by the individual. She also commented that children have milder COVID-19 symptoms, but some data showed adolescent and teenage children do suffer from long COVID-19, emphasizing the need for vaccinations in children. In terms of long COVID, she reaffirmed that vaccination lowers the risk of long COVID, especially for cardiovascular and pulmonary complications., but not for cognitive dysfunction, fatigue, depression etc.

Session III: Antibodies and Vaccines

Prof Bifani moderated this session highlighting the impressiveness in the speed of antibody and vaccine development, including the use of novel technology (mRNA technology), and emphasized the effective use of antibody therapies as front-stage therapeutics compared to small molecule therapies from the past.

"*The future of antibody development for therapeutic purposes for COVID and other diseases"*

A/Prof MacAry initiated this discussion supporting the various spectacular developments and deployment of antibody therapies for COVID-19. He commented on the remarkable speed and turn-around time for antibody therapies used in clinics, with examples like Regeneron's cocktail of antibodies, as an early candidate for the treatment of COVID-19. He further emphasized that the key reason for failed therapies of good neutralising antibodies was their poor delivery to the site of infection. Thus, recent improvements in modifications and formulations of antibody drugs, have successfully enhanced delivery to specific sites. Unfortunately, these treatments have been rendered unusable with the surge of the Omicron variant, with a possible exception of Sotrovimab (GSK and Vir Biotechnology), yet still exhibiting a four-fold reduction in efficacy. He assured that soon enough, B cells extracted from recovered Omicron patients would help in developing the next series of potential antibody therapies. Lastly, A/Prof MacAry highlighted that companies like Pfizer BioNTech and Moderna are generating Omicron-specific vaccines using the mRNA platform, with clinical testing already underway, and only time would tell if these would supersede the current successful vaccines.

"The role of mRNA vaccines for treating other diseases in the future"

A/Prof MacAry explained that such mRNA platforms already existed for other diseases (Moderna – Zika virus) but failed, due to the short duration of its protective response (6 months – 1 year). Interestingly, COVID-19 has taught the industry that even a years' protection could be vital and useful. A/Prof MacAry was hopeful that more mRNA vaccines would be developed in the future. He further emphasized and appreciated that the success of COVID-19 mRNA vaccines involved extraordinary protein engineering designed to translate spike protein in its actual conformation rendering a better immune response.

"Strategy for future preparedness: to have platforms ready to produce mRNA vaccines and antibodies that can be rapidly rolled-out"

Prof Teo shared his thoughts that countries, including Singapore, are setting up necessary technologies to develop candidates prior to a potential crisis but was sceptical if the preparedness would be broad enough to aid every pandemic. Dr Somani added that companies initially used mRNA vaccines for cancer therapies, highlighting additional plans for this technology.

Continuing the discussion, Dr Somani posed a burning question for the other experts regarding trustability of mRNA vaccines and its technology compared to adenovirus vector vaccines (marketed as viral vector vaccines). She explained that viral vectors carry DNA, which when taken up by a cell, transcribes into mRNA. *Her question was: if the community is able to accept DNA vaccines, with the apparent risk of genomic integration, why has there been so much distrust of mRNA vaccine technology, when that risk is eliminated?*

Prof Wang first commented the concern for using high dosage for mRNA vaccines, and the notion of traditional vaccines being 'safer'. Nevertheless, Prof Wang reassured Dr Somani, and the audience, that the benefits outweigh the side-effects for all mRNA vaccines. He further stated that improving mRNA vaccines in the future would remain a challenge. Referring to Dr Anthony Fauci's commentary, Prof Wang explained that SARS laid a foundation for antigen design leading to rapid developments. For other diseases, such as dengue, even though mRNA technology exists, it will not solve antigen design challenges. Prof Wang, who is also a scientific advisory member of the Coalition for Epidemic Preparedness Innovations (CEPI), then underscored the pre-emptive potential of vaccines, highlighting the ambitious goal of the "100-day vaccine". Other concepts, such as the 'vaccine library' and antibody cocktails would be ready pre-clinically, but realistically the high cost remains a concern. He emphasized that even with a ready platform, a lack of knowledge of the protein, renders the platform purposeless, thus the imperative need for pre-emptive 'vaccine libraries' for related viruses.

"The effect of vaccination on long-term COVID?"

A/Prof Lye commented eloquently by stating that persistent inflammation in recovered COVID-19 patients (and not in vaccinated) remains the basis of 'long COVID'. mRNA vaccines are potent and induces an antibody and T cell response, however, in lupus or arthritic patients, symptoms are slightly worsened, but recoverable. Thus, A/Prof Lye shared that, mRNA vaccines do not cause 'long COVID', but an individual's response to the vaccines could contribute to long COVID.

"The use of therapies to prevent or reduce the need for vaccine boosters"

Therapies like Paxlovid and Remdesivir are game changers as A/Prof Lye emphasized, and highlighted that these tablets reduce the risk of severe COVID-19 in high-risk groups by 88%. He stressed that these therapies could save risk groups with other diseases. Furthermore, these antivirals are not affected by the variants, as the target is not the spike protein. However, daily intake of antivirals could render severe side effects, like diarrhoea, nausea, and liver damage. A/Prof Lye re-emphasised that though antivirals are effective for high-risk groups, and a game-changer in terms of availability and usage, it is not a replacement for vaccines, which are cheaper, safer, saves more lives and imperative to evade this pandemic.

"May 2021 BMJ: Vaccines 'likely' responsible for 10 deaths, after vaccinating 30,000. Should we be more open about the possibility of the vaccines causing death, to avoid the perception of hiding adverse effects?"

A/Prof Lye clearly stated that higher vaccination rates are associated with lower cases of mortality in any country. He explained further that a viral vector vaccine (AstraZeneca), could lead to a serious side effect of thrombosis (blood-clots). mRNA vaccines could cause anaphylaxis and myocarditis (in young men), which usually resolve in a few days (95%), thus the mortality from these vaccines

remains low. He reminded the participants that everyday around 10 people die in Singapore from natural causes, further reassuring that these vaccines do not cause excessive death, and although there are recognisable side-effects, the regulators are transparent.

"What is the mechanism by which mRNA vaccines stimulate antibody response as this requires the MHC Class II pathway?"

A/Prof MacAry addressed this question explaining that the mRNA vaccine is introduced into muscle cells which translate the mRNA code into a large complex peptide (spike protein). This makes it a great target for antibody and T cell responses, mimicking a foreign protein from a pathogen.

Session IV: Prevention and Treatment

"The world has moved from deploying vaccines to deploying therapeutics against COVID. Singapore will receive Pfizer Paxlovid this month, and we expect MSD's Molnupiravir to follow shortly. Is this the game changer to end the pandemic, and is there data from other countries that supports this notion?"

A/Prof Lye initiated the discussion and shared that COVID-19 vaccines instead were the game changer and strongly emphasized the need for boosters. He also acknowledged concerns such as vaccine side effects, misinformation from anti-vaxxers, vaccine waning and loss of effectiveness with newer variants. Elaborating on the use of antivirals, he highlighted that these antivirals are for treatment and are not preventive. They are costly and present with side-effects, including Paxlovid (risk for high cholesterol and transplant patients) and Molnupiravir (not effective with other medications and concerns for pregnancy). He explained that the antivirals were considered a game changer to reduce hospitalization and increased availability to the community. Dr Somani further asserted the need for vaccines as the first line of protection for the masses, but highlighted antivirals could play a critical role in patients that do not respond to vaccines (renal transplant and haemodialysis patients on anti-lymphocyte drugs).

"False claims on COVID 19 treatment (from taking anti-parasitic drugs to drinking urine) can cost lives – How can we prevent the spread of misinformation?"

To address this, Prof Teo approached the problem from the perspective of public communications stating that countries with strong participation of scientists and public health experts, and leaders who consult experts prior to public announcements, tend to minimise the spread of misinformation. On the contrary, country leaders who generate 'fake' information are presented with problems. Prof Teo believes and emphasized that ultimately the responsibility lies with the leaders and experts, and that trust by the public would aide to reduce the spread of misinformation. A/Prof MacAry added that scientific journals have a responsibility to be professional and honest. He raised an example of a publication from LANCET 20 years ago showing an association between MMR and autism (despite the study's rejection by all the reviewers), raising scepticism for vaccine usage, especially in the UK. In contrast to Prof Teo, A/Prof MacAry stated that, particularity in the west, there remains a natural distrust to the government, due to the nature of modern communication through social media.

"Amid the high degree of COVID spread, Singapore has decided to open for travellers and loosen its measurements such as routine testing and safe distancing. What is the current prevalence of Omicron vs Delta in the community and the cause of the higher number of deaths seen lately again?"

A/Prof Lye highlighted that since mid-January, Omicron has replaced Delta in Singapore. Even with heightened infection, Omicron infection is milder than Delta, with fewer patients on oxygen and in ICUs. Mortality was high from Delta, including young patients. In comparison, Omicron has a lower mortality rate, and mainly in elderly patients with poor immunity, which may not even be COVID related as they harbour other ailments. Dr Somani agreed and further emphasized that the new concern lies in the delayed care for patients with other issues. She explained that hospitals are strained, and this is the current battle that Singapore faces. **Fortunately, patients with Omicron are**

not severely sick, but those hospitalized have other concerning issues that needs to be attended to. She also highlighted concerns with patients who are unable to be admitted due to the full capacity of hospitals, cautioning that when hospitals are stretched, patients will die.

Parting Thoughts

Prof Yik Ying Teo

Countries and jurisdictions are transitioning their disease management strategies from a pandemic to an epidemic to try to 'live with COVID-19'. This will heavily rely on (1) vaccines, boosters, and natural immunity from infections, with some vaccines being more effective than others, (2) preparedness for the people and the healthcare sector to avoid death, where 2022 will be a pandemic for the unvaccinated and (3) global inequities, hampering a sustained global epidemic response.

Prof Linfa Wang

Having experienced 6 different pandemics or outbreaks, the pandemic preparedness and response for COVID-19 was disappointing in terms of policies and international collaborations. A message for the young clinicians and scientists in the audience is to do better, not only to lead in science, but to create a culture and environment to fight a common enemy, like the virus, together.

Dr Jyoti Somani

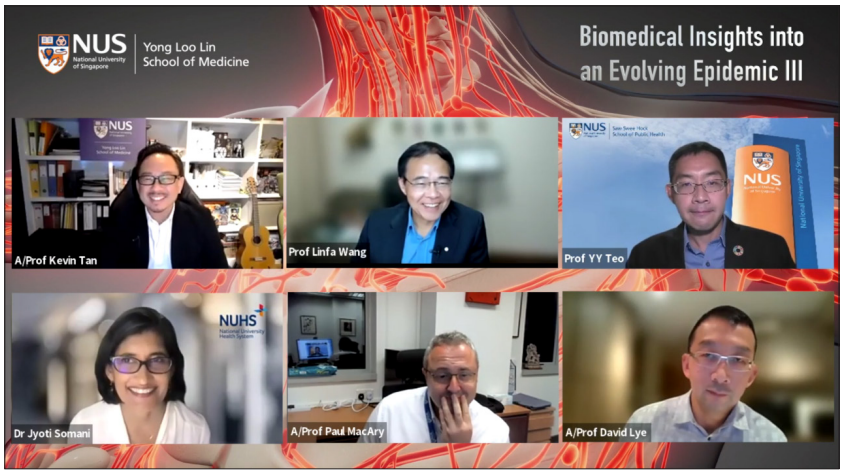
Firstly, a fourth booster should not be administered, except maybe to the immunocompromised. Rather, we need to vaccinate the world. Secondly, the fatigue factor has to be considered early on. Third, health is something we cannot attain overnight. Educating the younger generation and focusing on nutrition is the key. If people were healthier, we would see less impact from COVID-19.

A/Prof Paul MacAry

The world we live in harbours perfect conditions for a pathogen to rip through the global population. The scientific response to the pandemic has been remarkable, with sophisticated modelling of diseases, novel technology for vaccines and therapies, understanding the biology of viruses and advanced AI platforms which helped in aspects like social distancing policies. However, the sociological and political arms still leave a lot to be desired.

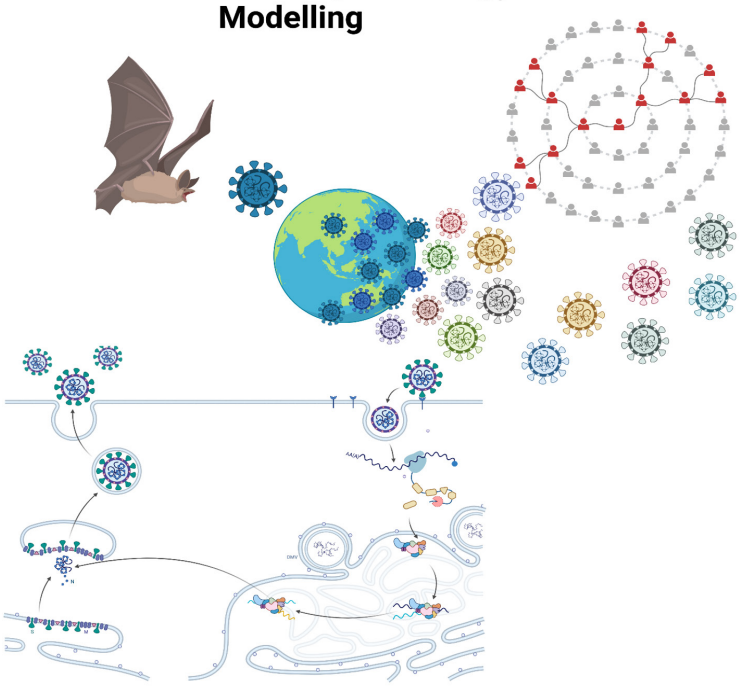
A/Prof David Lye

"2022 is the year we defeat COVID-19, but in any victory in a war we must always be prepared for the next counter offence" and for COVID-19, these are the variants. Variants emerge due to inadequate protection in a population, thus, working on a universal vaccination plan for the world is vital. Some countries do fairly well with vaccinating their population, however, misinformation drives rejection for vaccination in many countries. There are many treatments, however dexamethasone remains the only affordable one. Supporting WHO, a collective effort is needed to make antivirals available for countries in need and for severe patients. Counties that fared well in vaccinations are key role models for other countries to catch up to.

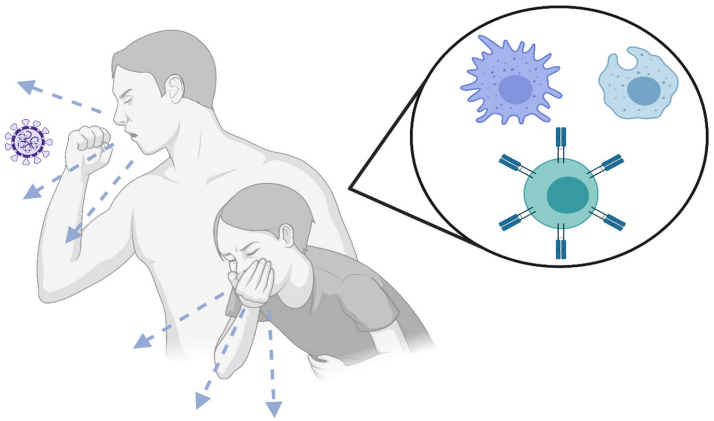


COURSE SUMMARY DIAGRAM

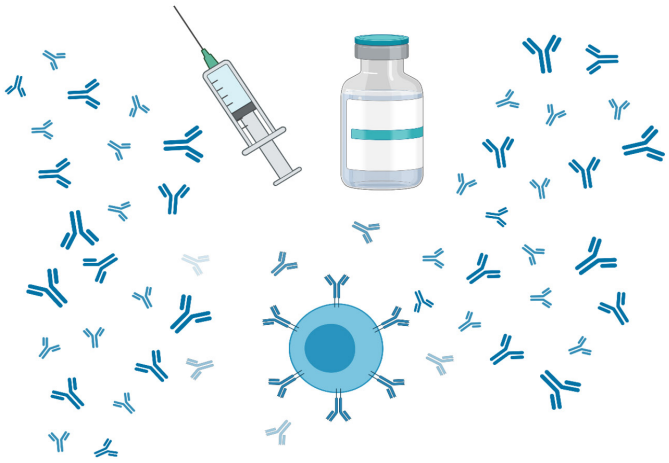
Part I: Epidemiology and Modelling



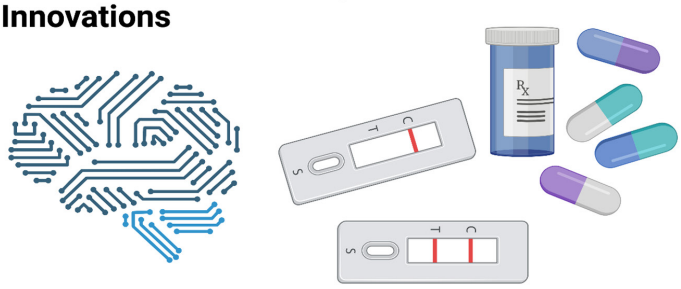
Part II: Immunopathology



Part III: Vaccines and Antibodies



Part IV: Treatment, Diagnostics and New Innovations



ACKNOWLEDGEMENTS

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SPONSORS

Victor and William FUNG FOUNDATION 馮氏 經綸慈善基金

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Published by Department of Microbiology and Immunology, Yong Loo Lin School of Medicine

First edition, May 2022