

CHAPTER 7

Flying The Flag

Diagnosed with COVID-19, many faced fear and anxiety, yet we saw courage and selflessness in so many of our patients as they willingly volunteered to participate in the COVID-19 studies, donating their blood and respiratory samples so that we could learn about the novel pathogen. Patients often told us that they wanted to do something to help, and perhaps even contribute to finding a cure or a vaccine. Many patients returned to the hospital to donate convalescent blood samples months after they recovered, allowing us to study the long-term immune response to infection. It was humbling to have the support of our patients – it truly made all the hard work worthwhile.

**JENNY LOW AND
SHIRIN KALIMUDDIN**

Senior Consultant and Consultant,
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In June 2020, SGH clinicians and Duke-NUS Medical School scientists published one of Singapore's earliest COVID-19 scientific papers¹, detailing the host response to severe disease. Many more publications have followed since, and SGH continues to contribute to scientific understanding of COVID-19, especially in the area of vaccine and therapeutic development. Yet, this success was not pure serendipity.

Infectious Diseases (ID) physicians Shirin Kalimuddin² and Jenny Low³ described the efforts that bore much research fruit in the pandemic.



¹ Ong EZ et al. A dynamic immune response shapes COVID-19 progression. *Cell Host Microbe* 2020;27: 879.

² Dr Shirin Kalimuddin, Consultant, Department of Infectious Diseases, is a recipient of a Transitional Award from the National Medical Research Council (NMRC).

³ Dr Jenny Low, Senior Consultant, Department of Infectious Diseases. She is an established clinician-scientist whose work is supported by the NMRC.



PREPARE YOUR UMBRELLA BEFORE IT STARTS TO RAIN

The SARS crisis of 2003 taught us that we needed to be better prepared for the next big outbreak. During SARS, the healthcare system was overwhelmed by clinical workload and the challenges of an epidemic that few had anticipated. Faced with more pressing tasks at hand, little resources were dedicated to basic research. As a result, precious opportunities to learn about the new illness through research were lost. This deficiency weighed heavily on the mind of ID physician Tan Ban Hock⁴, then a consultant with the Department of Internal Medicine (DIM). When the Department of Infectious Diseases (DID) was formally constituted in 2008, a conscious effort was made to build research capability within the department.

Drawing upon lessons from SARS and the H1N1 pandemics, a prospective “Novel Pathogens Research Protocol” was developed by Ban Hock and Jenny, the latter then a budding clinician-scientist. Under this umbrella protocol, patients in SGH could be recruited prospectively, and their samples collected systematically, during any infectious disease outbreak. In 2016, the protocol allowed the rapid recruitment of patients during the Zika outbreak. The protocol, which had been developed in peacetime and was hence subjected to lengthy reviews by the Institutional Review Board (IRB)⁵, allowed for a plug-and-play approach the moment COVID-19 landed on our shores. By November 2020, more than a hundred COVID-19 patients in SGH had been recruited via the protocol. Data and samples collected have led to new insights into COVID-19 pathogenesis and the host immune response to the virus.

Alone we can do so little; together we can do so much

Unlike the Edward Jenners and Alexander Flemmings of the past, researchers of today can no longer work in silos. Almost all of SGH’s COVID-19 research output has been the result of multi-institutional collaborations with academia and with partners, both locally and overseas. We partnered Duke-NUS and industry to lead the first-in-human trials of a COVID-19 self-replicating mRNA vaccine and a novel therapeutic monoclonal antibody⁶.

⁴ Dr Tan Ban Hock, Senior Consultant, Department of Infectious Diseases. He was the first Head of Department.

⁵ The IRB is a body that reviews, approves and audits all research in an academic institution for compliance with national regulations and ethics guidelines.

⁶ The writers refer to clinical trials of the vaccine produced by Arcturus Pharmaceuticals, as well as of the monoclonal antibody produced by Tychan Pte Ltd. Dr Jenny Low was the lead investigator for both.

We were also an active participating site in several multinational COVID-19 clinical trials⁷. Yet, many of these collaborations began long before the start of the outbreak.

Since the establishment of Duke-NUS Medical School in 2005, SGH has built and maintained strong collegial ties with the Programme in Emerging Infectious Diseases, one of the school's signature research programmes. Over the past decade, ground-breaking translational research on re-emerging viruses (such as dengue and yellow fever) impressed funders and led to the establishment of the Viral Research and Experimental Medicine Centre (VIREMICS) at the SingHealth Duke-NUS academic medical centre. This Centre has played a pivotal role supporting clinical trials and research throughout this COVID-19 outbreak. These established links enabled both clinical and bench researchers to dive into their critical roles even before Singapore's first COVID-19 patient.

It takes a village

During the outbreak, COVID-19 research in SGH progressed at a relentless pace. The clinical trial evaluating the antiviral remdesivir took less than four weeks from conception to site initiation, something unheard of in peacetime. Author lists on publications and reports in the media often fail to acknowledge the large team of individuals working faithfully behind-the-scenes to make research possible.

It is not possible to name everyone, but we would be remiss not to give significant credit to the Clinical Research Coordinators (CRCs) from DID (Natalie Lee⁸, Christina Titin⁹ and Sam Huizhen¹⁰), teams from the SGH Clinical Trials Research Centre, SingHealth Investigational Medicine Unit, and the SGH Research Office.

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⁷ SGH was a site in the remdesivir studies sponsored by the international pharmaceutical giant, Gilead. The site principal investigator was Dr Shirin Kalimuddin.

⁸ Natalie Lee, Clinical Research Coordinator, Department of Infectious Diseases.

⁹ Christina Titin, Clinical Research Coordinator, Department of Infectious Diseases.

¹⁰ Sam Hui Zhen, Clinical Research Coordinator, Department of Infectious Diseases.

During the outbreak, many people stepped up to serve, often venturing out of their comfort zones and going beyond the call of duty. Despite stressful work conditions and heavy clinical volumes, staff were ever ready to assist the research teams. Clinical research was made even more challenging given the strict infection control protocols in place. Consent forms could not be removed from the isolation rooms, and samples had to be meticulously wiped down and triple-bagged before they were transported out. Without the assistance of dedicated clinical staff, it would have been almost impossible to carry out research in the isolation ward (IW).

Junior doctor Shivani Durai¹¹ volunteered to assist with COVID-19 research (something beyond her clinical duties), and spent long hours in the IW recruiting patients and collecting research specimens. Shivani explained why she volunteered. “I felt deeply moved when I saw a vast majority of my friends selflessly fighting on the frontlines. I thus decided to work in research to tackle the disease and hopefully make a difference. I believed that was the right thing to do as a doctor and as a fellow Singaporean.”

¹¹ Dr Shivani Durai, Senior Resident, Department of Obstetrics and Gynaecology.

Research Coordinator Natalie Lee shared her thoughts. “It was truly a once-in-a-lifetime experience. Being on the frontlines during the pandemic as a Clinical Research Coordinator highlighted the importance of research where time was of the essence. That made me see the importance of the role I played. Working amidst the chaos, with fast changing rules, while ensuring that all precious research samples were collected and research protocols were adhered to – it was challenging yet extremely thrilling. Even though everyone was overwhelmed, we helped each other out whenever we could, so no one would be left behind.”

Her colleague Christina Titin added. “The period from April to May 2020 when we had many patients in the remdesivir trials was an extremely busy time. We delivered drugs to the ward and ensured that nurses administered them on time. Moreover, we had to make sure that all tests and assessments were done according to the clinical trial protocol, not forgetting the piles of data that needed to be entered. I was thankful for the colleagues around, who lifted our spirits. Check-ins like ‘Are you ok?’ from people around felt so comforting.”



Staff donating blood for COVID-19 research into antibodies following vaccination. The study began in 2021.

One memorable experience was having to recruit healthcare workers for a COVID-19 related study. At first, my colleague and I had difficulty publicising our study. But with a stroke of luck, news of our study spread by word of mouth and suddenly we had nurses from wards 68 and 67, staff from outpatient clinics, even doctors from the labs calling us and expressing interest. We felt like we had won the lottery. We were overjoyed and grateful, knowing that they did it with the pure intention of helping with research. Moments like these make me feel like our efforts have paid off. It has been a tough year, but it has also been one of the most rewarding.

Sam Hui Zhen, Clinical Research Coordinator, Department of Infectious Diseases

MEDICAL STUDENT EDUCATION – NOT LEFT TO LANGUISH

When the first case was confirmed in Singapore, we grappled with the dilemma of whether to continue the medical student clinical postings; at what scale, which posting; how to continue safely, and how to craft a robust surveillance system to track the well-being of the students. Maintaining constant, open and timely communication with the medical schools helped us feel our way forwards. It was imperative to keep all stakeholders, including the students, updated on the latest measures.

For a start, all incoming clinical electives for the period January 2020 to August 2020 were cancelled. This was to ensure the safety of inbound students.

The situation evolved fast and furious. It was a race to keep up with, and implement, the various guidelines from MOH, SGH and the medical schools. We had to be nimble, consistent and coherent in our response to the evolving situation. Clinical medical education ceased once Singapore went into DORSCON Orange¹². Faculty had to rapidly adapt and provide live-streamed clinical teaching and online lectures. When students were allowed in the wards, we had to carefully manage the numbers to avoid overcrowding. We had to reduce workplace-based assessments. But the academic examinations continued — it was important to maintain the pipeline of junior doctors.

DR TAY SOOK MUAY

Senior Consultant,
Department of Anaesthesiology

She served as Associate Dean for the National University of Singapore Yong Loo Lin School of Medicine, SGH Campus, from 2012 to 2021.

¹² Singapore raised the risk assessment level to DORSCON Orange on 7 February 2020 after the appearance of local cases without links to previous cases or travel history to China.

Organ transplant during the pandemic

For the members of SGH's various transplant teams, closing their programmes was not an option. Transplant specialists Jasmine Chung¹³, Tan Ek Khoon¹⁴ and Terence Kee¹⁵ recounted the uncertainty in February 2020. "As the then Wuhan virus made its way around the world, and as a slew of new work protocols unleashed themselves on us, the first response was to suspend all transplant activity¹⁶.

"SARS veterans among us, however, felt that the SingHealth Duke-NUS Transplant Centre (SDTC) should come together and talk our way through the morass of clinical and ethical conundrums. In 2003, many had witnessed the "second victims" of SARS – patients who presented with advanced cancer or whose diabetes had spun out of control because they had put off consulting a doctor about their symptoms, for fear of catching the virus.

"In February 2020 (an era before virtual meetings), we gathered a few times, usually starting at 7:30am, to discuss the options. We all knew, from bitter experience, that a steady trickle of patients became ineligible just waiting for a transplant – heart candidates sometimes developed a stroke, liver candidates saw their cancers spread, and lung candidates expired from lack of oxygen. Suspending the programme would clearly prolong the wait, and turn the trickle into a torrent. The ethics seemed straightforward in favour of carrying on, but wait. Would the transplanted organ itself bring the virus into the recipient? Would our staff catch the virus operating on an asymptotically infected patient?

¹³ Dr Jasmine Chung, Consultant, Department of Infectious Diseases. She is one of three ID physicians in SGH who serve on the various transplant programmes in SingHealth.

¹⁴ Dr Tan Ek Khoon, Consultant, Department of Hepato-pancreato-biliary and Transplant Surgery.

¹⁵ Dr Terence Kee, Senior Consultant, Department of Renal Medicine. He is also Programme Director, Renal Transplant Programme, SGH.

¹⁶ The Straits Times. Organ transplants, donations hit by COVID-19. 7 June 2020 [Internet]. Available at: www.straitstimes.com/singapore/health/organ-transplants-donations-hit-by-covid-19.

“The proposed way out seemed sensible enough – evaluate a potential donor carefully, and test him/her for the virus several times. This seemed a rational strategy, but it could not be backed by published evidence. The West, always a rich source of evidence, had not yet been hit by the virus, and was carrying on with life as usual. The first two cohorts described by the Wuhan doctors had not included transplant recipients or candidates. The data-driven among us wanted to know the accuracy of the new diagnostic tool, but of course no such information was available. Everyone was learning about the virus.

“Somehow we managed to agree to keep the transplant programme going. It fell upon the Transplant ID team to draw up the protocols. This proved less daunting than imagined – there was little literature to quote, just common sense to exhibit.

“We were glad to have had the support of senior management, and happy when MOH officially allowed most types of transplants to proceed. We went on to contribute to the MOH guidance on transplantation in the pandemic.

“At the end of March 2020, with the nation in DORSCON Orange, and days before the Prime Minister appeared on TV to announce a national lockdown, we were offered organs from a brain-dead donor. SGH’s liver and lung programs put ourselves through the paces of our own protocols, and carried on with the transplants¹⁷.”

The transplant team published their experience in an academic journal¹⁸.

¹⁷ These two transplants went well. Neither recipient caught COVID-19. Both have gone back to leading normal lives.

¹⁸ Chung SJ et al. Practical considerations for solid organ transplantation during the COVID-19 global outbreak: the experience from Singapore. *Transplant Direct* 2020;6:e554.



A GIFT OF LIFE DURING THE PANDEMIC

(excerpts from Singapore Health¹⁹)

In March 2020, Mr Koh Khim Teck became one of the first patients to receive a transplant during the COVID-19 pandemic.

His condition took a turn for the worse when his liver cancer stopped responding to treatment, and a transplant became critical. Mr Koh was able to undergo the life-saving procedure because of revised transplant guidelines developed during the disease outbreak.

A lack of viable organs and a long waitlist already made it hard for patients to get a suitable organ. With the virus outbreak, the concerns of infection added to the risks associated with a transplant. But for SGH transplant specialists, closing the service was not an option.

“COVID-19 could last for months or even one to two years. If we do not think and plan ahead, patients may fall off the waitlist and die from disease progression,” said Dr Jasmine Chung.

Nevertheless, patients are often willing to take the risk. According to transplant surgeon Prema Raj²⁰, 83% of patients who are on the wait list expressed willingness to continue with the transplantation during the pandemic²¹.

“The key is speaking to patients because they are the ones who are sick; they are the ones who will receive the organs. For someone who has end-stage lung disease or end-stage liver cancer, the potential for a change in life is tremendous. So once we know our patients are keen, we physicians have to make it as safe as possible for them,” said Dr Raj.

¹⁹ This story was first published as “A gift of life during the pandemic”, in Singapore Health Nov/Dec 2020, a SingHealth patient education newsletter.

²⁰ Dr Jeyaraj Prema Raj, Senior Consultant, Department of Hepato-pancreato-biliary and Transplant Surgery. He is also Director, Liver Transplant Programme, SGH and Director, SingHealth Duke-NUS Transplant Centre.

²¹ For the survey on wait list candidates’ attitudes to transplantation during COVID-19, see Tan EK et al. Waitlisted transplant candidates’ attitudes and concerns toward transplantation during COVID-19. *Ann Transplant* 2020;25:e926992.



STILL OPERATING

When the virus first touched down in SGH, we scrambled to equip our Operating Theatre (OT) on-call team with protective gear, knowing that they would be at the frontline managing the airway of suspect cases requiring intubation. We were fortunate to have SARS veterans among our anaesthesiologists and nurses who provided valuable advice and initiated on-the-spot training for the young doctors going on-call that same night.

With the immediate concerns addressed, we next focused on the main principles to prioritise the safety of our patients and staff in the face of a new unknown, a potentially deadly pathogen. These principles were: segregation by location, segregation by workflow, and protective equipment.

Segregation by location

The Urology Centre's OT were a natural choice for an isolation OT complex due to their distance from the major OT complex. Unfortunately, there were limitations, mainly because of their size. Surgeons and anaesthesiologists of all disciplines were invited to view the site for suitability for their specialty-specific needs. We carried out in-situ simulation to see if the Urology OT would be able to accommodate cardiac surgery and obstetric surgery, among others. With the support of the Medical Board, we re-configured the entire Urology OT complex as the isolation operating facility for SGH.

Segregation by workflow

This was a key aspect of our management. First, we had strict criteria to screen patients deemed to be at risk of having the virus. Then we had a workflow to keep suspect patients separate from other patients. We also had a workflow to segregate staff caring for suspects from those caring for other patients.

All patients were screened for travel and contact history, as well as the presence of signs and symptoms of the infection. There were numerous calls to our ID colleagues to seek advice on risk stratification. Sometimes we had lengthy debates on the suitability of using the isolation OT for the patient in question.

Developing and then promulgating the isolation OT activation workflow were critically important because all processes were new. Efficiency fell, mainly because equipment had to be brought from other OTs. There were also new factors that needed to be accounted for, such as the availability of security escorts²². Our staff found the team brief and debrief very useful. In the early days, a coordinator (usually the Anaesthesiology consultant on-call that day) was assigned to guide staff and to facilitate the smooth running of the case. In situ simulation helped us to identify unanticipated problems; we uncovered many small details that we might otherwise have overlooked.

Protective equipment

As anaesthesiologists, we knew that our daily work with the airway involved the highest risk of exposure to respiratory secretions, an obvious source of virus. The department was quickly fitted with N95 masks and our Powered Air-Purifying Respirator (PAPR) super-users spent days training every member of staff in the use of the different models available in SGH. Emphasis was also placed on safe doffing of personal protective equipment (PPE), in order to prevent transmission to our colleagues and patients.

As the virus made its way around the world, we saw more and more countries go into lockdown as their healthcare systems were ravaged by the surge in COVID-19 patients. This heralded a supply chain issue for Singapore as we faced delays in the shipment of necessary medical supplies. April 2020 was a particularly intense period when we had to source for alternative supplies while worrying about an upswing in the number of critically ill patients. The Sterile Supplies Unit (SSU), under the leadership of nurse Goh Meh Meh²³, came up with ways to sterilise single-use consumables, in the event that this became necessary. Pharmacy and nursing performed weekly stock checks to make sure that we had the drugs we needed. Our technicians used their intimate knowledge of our equipment to come up with innovative solutions to utilise existing resources to replace what we lacked. This was a commendable multi-disciplinary effort – so many people came up with ways to get around problems you'd never thought would emerge!

²² Security escorts were needed to clear the path and manage the lifts so that no one would inadvertently come into contact with a patient/suspect being transported. Read more about this process in Chapter 1.

²³ Goh Meh Meh, Deputy Director Nursing, oversees the SSU which cleans and sterilises tools and equipment used for surgery.

In spite of the pandemic, then, OT life went on. Patients still had fractures, cancer, and needed surgery. With solid plans in place, we were able to confidently and simultaneously care for suspects as well as business as usual (BAU) patients (the latter in our main OT complex). While many elective operations were postponed during the Circuit Breaker²⁴ to allow manpower to be diverted to the migrant worker dormitories²⁵, time-sensitive operations such as cancer surgery were allowed to proceed.

But there was an air of impermanence. One day we had to resume full services, and return the Urology OT to the urologists. This would not be possible as long as COVID-19 lurked in some dark corner. The critical problem was that operating rooms were positively-pressured, meaning air was always pumped out of the operating room. This meant that cases/suspects could not be operated on there while life continued outside.

Our colleague Hairil Abdullah²⁶ chewed on this problem and came to the rescue. Teaming up with a local biomedical incubator, he created a System of Portable AnteRoom for Containment (SG-SPARC).

With SG-SPARC, we were able to safely co-locate the isolation OT within the major OT complex without worry of disease transmission. Units of the device are now placed at the doors of a few of our operating theatres, enabling anyone with confirmed or suspect COVID-19 to undergo surgery without risk to the staff.

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She was the Infection Prevention Liaison Officer (IPL) in the Division of Anaesthesiology and Peri-operative Medicine.

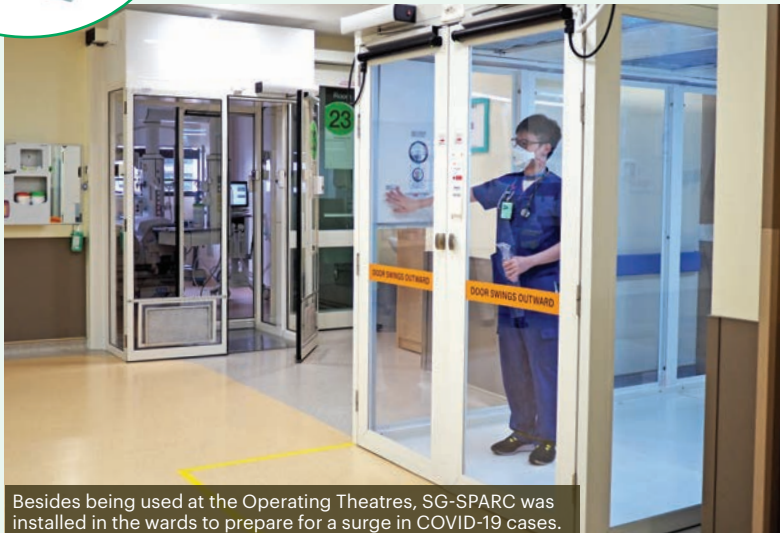
²⁴The Circuit Breaker lasted from 7 April to 1 June 2020, when the population was required to stay home.

²⁵For details of SGH Campus' operations at the dormitories, see Chapters 8 and 9.

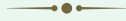
²⁶Dr Hairil Abdullah, Senior Consultant, Department of Anaesthesiology and Director, Perioperative Services.

NEGATIVE PRESSURE ISOLATION ROOMS IN AN HOUR

SG-SPARC is a portable negative pressure anteroom system that, in one hour, transforms a room into a negative pressure isolation room. The box-like SG-SPARC, with its double interlocking doors, can be installed at the entrance. After installation, all gaps are sealed. The negative pressure system allows air to come out of the room where the patient is but prevents contaminated air aerosols from flowing into the corridor. A high efficiency particulate absorbing (HEPA) filter cleanses the air before expelling it to the exterior. Air that is sent back to the patient's room is also HEPA-filtered first, so that only clean air enters the patient's room.



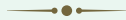
Besides being used at the Operating Theatres, SG-SPARC was installed in the wards to prepare for a surge in COVID-19 cases.



*The single most important lesson
I have learnt from this
pandemic is that people
are our biggest asset.*

*There is an incredible amount of
talent, creativity, resilience and
dedication amongst our staff.*

*We can only achieve what we set out
to do when we galvanise everyone
towards a single cause, remembering
that patients are at the heart of all
we do.*



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