Review Article

Coronavirus Disease 2019 (COVID-19): The Singapore Experience. A Review of the First Eight Months

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Abstract

As of 27 October 2020, there have been 57,980 confirmed cases of COVID-19 in Singapore, with 28 fatalities. To summarise the Singapore experience in managing and containing COVID-19 based on available published data and from relevant sources, a review of literature using research databases such as PubMed and OVID Medline, along with non-peer-reviewed articles and other sources, was conducted with the search terms 'COVID-19' and 'Singapore'. Research conducted in Singapore has provided insight into the clinical manifestations and period of infectivity of COVID-19, demonstrated evidence of pre-symptomatic transmission, linked infection clusters using serological tools, and highlighted aspects of hospital-based environmental contamination. It has also provided guidance for diagnostic testing and has described immune and virologic correlates with disease severity. Evidence of effectiveness of containment measures such as early border control, rigorous contact training, and calibrated social distancing measures have also been demonstrated. Singapore's multipronged strategy has been largely successful at containing COVID-19 and minimising fatalities, but the risk of re-emergence is high.

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Introduction

Singapore reported its first imported case of COVID-19 on 23 January 2020[1] and its first COVID-19 deaths on 21 March 2020.[2] The WHO declared COVID-19 to be a pandemic on 11 March 2020;[3] as of 27 October 2020, there have been more than 42 million confirmed cases and 1.1 million deaths across 200 countries and territories.[4]

Methods

We reviewed the peer-reviewed literature using PubMed and Ovid MEDLINE, and search terms 'COVID-19' and 'Singapore'. We also reviewed published data and policy documents from government-based resources and media releases.

Epidemiology and Transmission

As of 27 October 2020, there were 57,980 confirmed cases of COVID-19 in Singapore, with 28 fatalities,

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yielding a case-fatality ratio (CFR) of 0.05%.[5] The CFR is among the lowest in the world. Figures 1–3 detail the epidemiological distribution of COVID-19 cases in Singapore.

From January to May 2020, 580 (1.0%) cases were imported, initially from China and subsequently from the Southeast Asia region, India, Europe and the United States. With restrictions on international travel worldwide, the number of imported cases fell drastically by the first week of April. As nationwide control measures were introduced, in particular the "circuit breaker" from 7 April, the number of community cases started to fall over time. Incidentally, the foreign worker dormitories started to report new cases from early April and brought about a large wave of infection in Singapore till September, contributing to 94.3% of all reported cases in Singapore (Fig. 1). From end of June till 27 October 2020, more international flights are arriving into Singapore and Singapore has picked up another 612 imported cases of which 54% are from India, 17% from Indonesia and 8% from the Philippines. All these imported cases were isolated on arrival in designated facilities (under 14-day Stay-Home-Notice) and were not implicated in any transmission in Singapore.

Singapore residents made up 1,986 (3.4%), foreign workers (long-term and work pass holders) 55,901 (96.4%), and 93 (0.2%) were foreign visitors.

Among Singapore residents, children and young people up to 19 years old made up only 6.7%; the vast majority (85.0%) was well distributed across the 20 to 69 years age group; and 8.3% were 70 years and older (Fig. 2). Incidence rate among Singapore residents was the highest among the 20–29 years (66.4 per 100,000) and 50–59 years (65.5 per 100,000) age groups. Children and young people up to 19 years old were much lower at 15.5 and 17.6 per 100,000, respectively (Fig. 3). There was conscious effort to prevent infection among the vulnerable younger and older segments of the population.

Among the foreign cases, the vast majority were male. 75.3% were aged 20–39 years old, 19.1% were 40–49 years, and 5.2% were 50 years and older (Fig. 2).

Unlike SARS-CoV, there is evidence of pre-symptomatic transmission of SARS-CoV-2, with identification of several clusters of infection in Singapore in which pre-symptomatic transmission implicated secondary infection.[6] There has also been evidence of asymptomatic transmission in several cases in Singapore although the exact percentage of transmissions attributable to asymptomatic infection warrants further study. Pre-symptomatic and asymptomatic transmission can be key drivers of infection and pose a significantly greater challenge to eradication and containment efforts, as well leading to an underestimation of disease prevalence.[7]

Clinical Features

The first 18 patients diagnosed in Singapore presented with symptoms of a mild respiratory tract infection.[8] Of these 18 patients, 13 (72%) had a fever on presentation, while 15 (83%) had cough. Two presented with dyspnoea (11%) and 11 with sore throat (61%), while 3 patients (17%) had diarrhoea. Among these 18 patients, 6 individuals eventually required supplemental oxygen, while 2 required intensive care.[8] Clinical characteristics of COVID-19 patients in Singapore in comparison to other countries are detailed in Table 1.

A Singapore study by the National Centre for Infectious Diseases (NCID) of 788 patients has generated predictive models to determine the risk of COVID-19 in patients, with clinical signs of elevated body temperature and respiratory rate being the strongest predictors of COVID-19, in addition to the absence of sore throat and sputum production,[13] corroborating with the study by Guan et al.[14] Over a 2-week period, clinicians have also found self-reported olfactory and taste disorders (OTD) in about one-fifth (22.7%) of COVID-19 patients, with the authors concluding that self-reported OTD had high specificity as a screening criterion for COVID-19 in an Asian cohort.[15] Patients with COVID-19 appeared to have higher odds of OTD compared to those positive for other respiratory viruses.[15] Routine screening in patients with new-onset OTD can thus improve case detection during a COVID-19 outbreak.

Approximately 80% of patients with COVID-19 disease have mild symptoms or are asymptomatic, with 15% requiring oxygen and 5% requiring critical care.[16] A definition for severe COVID-19 infection in Singapore, adapted from the Report of WHO-China Joint Mission on COVID-19, has been formalised by the NCID, listed in Table 2.[17] Clinicians across hospitals in Singapore have also identified a list of risk factors[18] for progression towards severe COVID-19 disease, listed in Table 3.

Paediatric populations seem less affected by COVID-19; only 2.4% of reported cases in China,[14] 1% of cases in Italy[21] and 1.7% in the United States[22] were paediatric patients. The disease in children largely appears to also be mild and self-limiting.[23,24] Nonetheless, a small proportion of children have severe (2.5%) or critical (0.2%) disease,[16] with concerns about hyperinflammatory shock resembling atypical Kawasaki
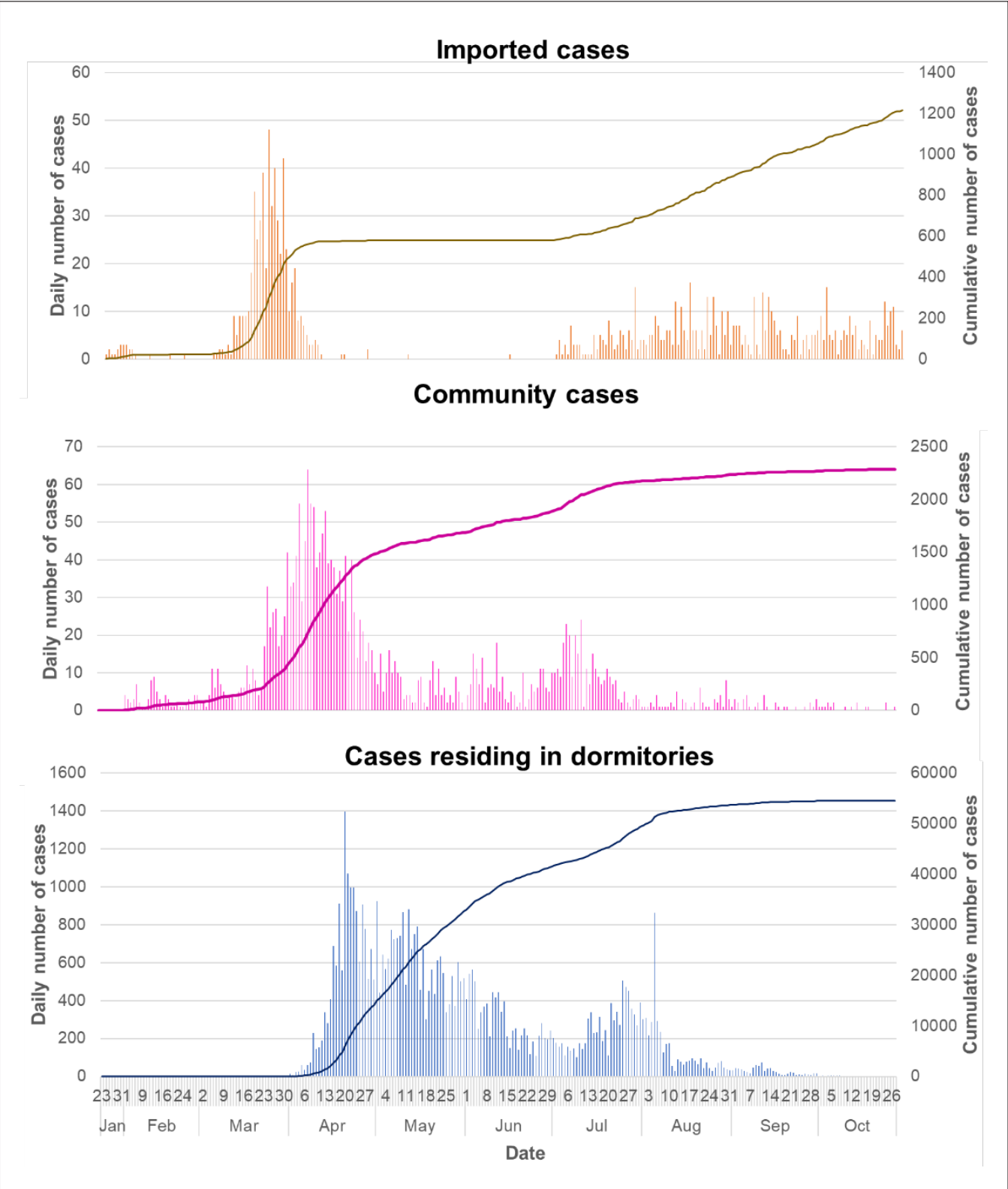
Fig. 1. Epidemiological curve of COVID-19 cases in Singapore as of 27 October 2020.
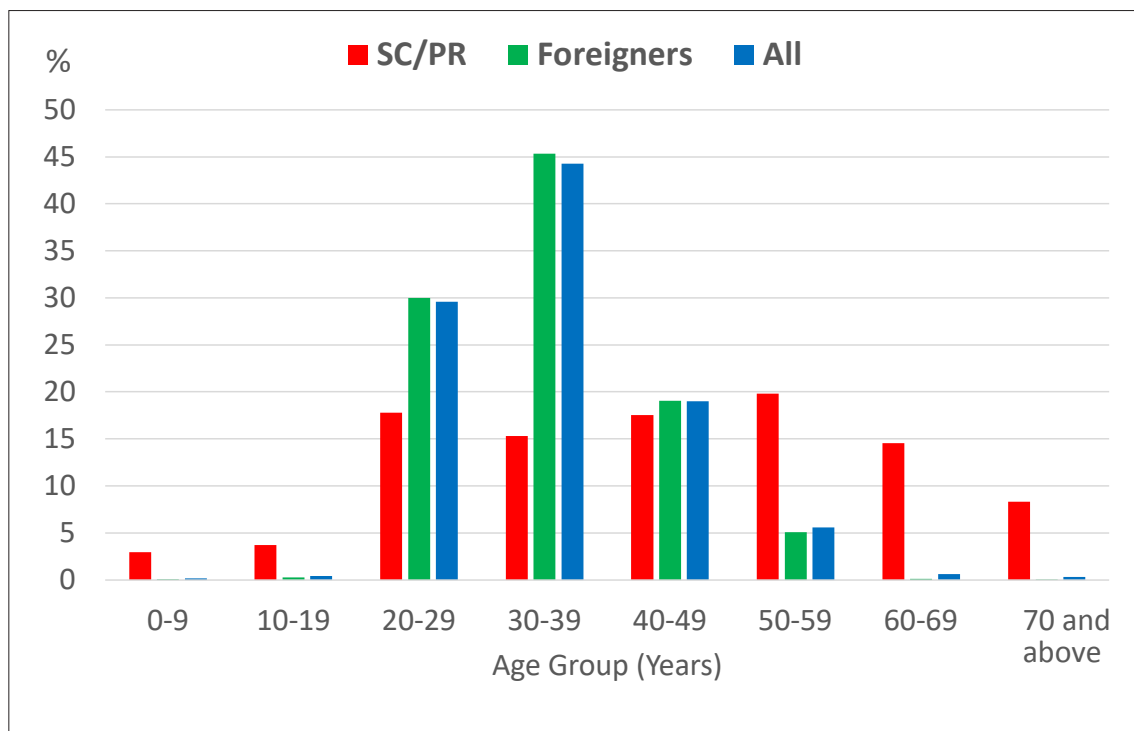
Fig. 2. Age distribution (%) of all COVID-19 cases in Singapore as of 27 October 2020.
SC: Singapore citizen
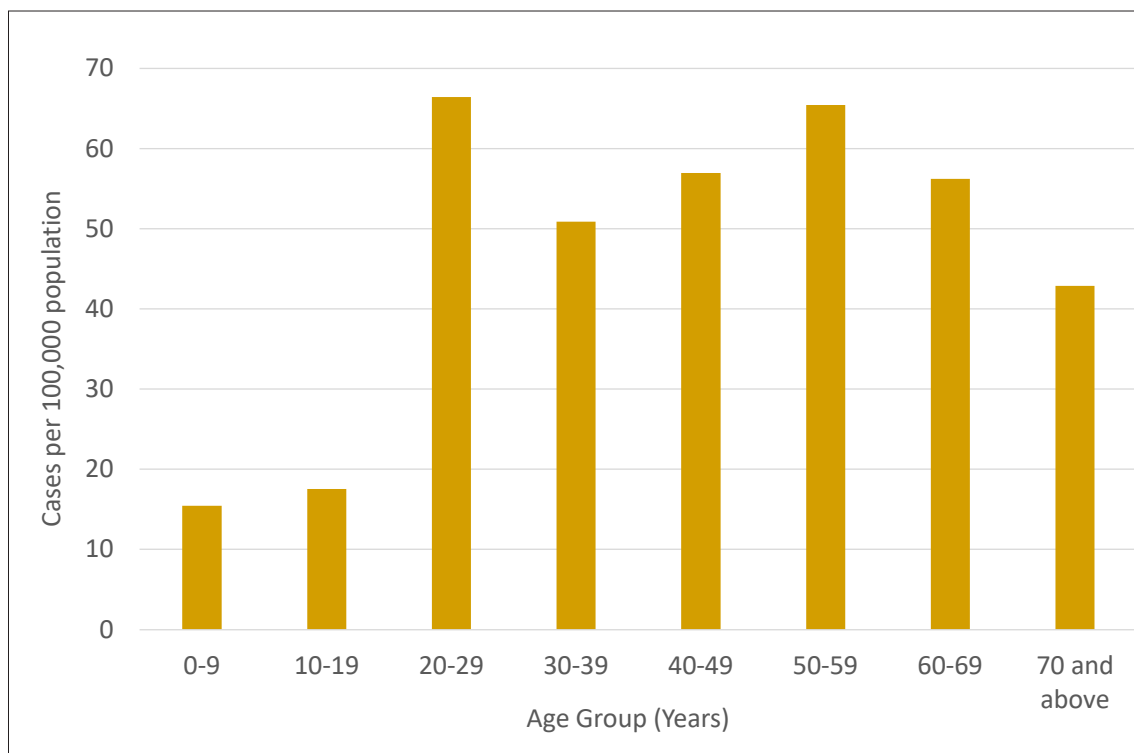PR: Singapore permanent resident

Fig. 3. Age-specific incidence rates of COVID-19 cases among Singapore residents as of 27 October 2020.

Table 1. Clinical features of COVID-19 patients in Singapore in comparison to other countries, in the initial stages of the pandemic

Clinical signs and symptoms on presentation No. (%)	Singapore: Young et al.[8] (n=18)	China: WHO-China Joint Mission Report[9] (n=55,924)	Italy: Marta et al.[10] (n=44)	United States: Kujawski et al.[11] (n=12)	Korea: COVID-19 National Emergence Response Centre[12] (n=28)
Fever	13 (72)	49,157 (88)	40 (91)	2 (29)	9 (32)
Cough	15 (83)	37,860 (68)	15 (34)	8 (67)	5 (18)
Malaise	–	21,307 (38)	2 (5)	5 (42)	3 (11)
Myalgia	–	8277 (15)	–	–	4 (14)
Dyspnoea	2 (11)	10,401 (19)	10 (23)	1 (8)	–
Rhinorrhoea	1 (6)	–	–	1 (8)	–
Sore throat	11 (61)	7773 (14)	–	1 (8)	9 (32)
Headache	–	7605 (14)	–	3 (25)	3 (11)
Diarrhoea	3 (17)	2069 (4)	3 (7)	1 (8)	–

Table 2. Definition of severe COVID-19 infection

Definition of Severe COVID-19 Infection (adapted from Report of WHO-China Joint Mission on COVID-19)[18]

- Patients fulfilling any of the following criteria:
- Dyspnoea, respiratory rate > 30 breaths/min, P/F ratio < 300mmHg, lung infiltrates > 50% of lung fields in 24 to 48 hours
- Admission to an intensive care unit (ICU)
- Current receipt of mechanical invasive or non-invasive ventilation
- Current receipt of intravenous vasoactive medications to maintain mean arterial pressure > 65mmHg
- Myocarditis/myocardial dysfunction secondary to SARS-CoV-2

Available at: http://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf

disease or toxic shock syndrome being reported in France[25] and the United Kingdom,[26] although no such cases have occurred in Singapore to date.[24] Studies have reported an increased risk of coagulative abnormalities in patients with severe COVID-19 disease, with patients exhibiting increased clot waveform analysis patterns consistent with hypercoagulability.[27] Thus far, only 2% of 102 patients in Singapore who have ever been to ICU have reported presence of deep venous thrombosis (DVT) and an incidence of pulmonary embolism at 5.9%,[28] which appears lower compared to what has been reported.[29] Data from Singapore also reported an incidence of ischaemic myocardial damage at 5.9% and ischaemic cerebrovascular accidents at 4.9%[27] as compared to other studies demonstrating rates of myocardial ischaemia to be 19.6%[30] and cerebrovascular accidents to be 1.6% in COVID-19 patients.[31]

Neurological complications were rare in Singapore given that the demographic of the outbreak was skewed towards young individuals with mild or asymptomatic illness. Nonetheless, a wide spectrum of conditions has been reported, including acute disseminated encephalomyelitis, acute ischaemic stroke and transient ischaemic attacks, cerebral venous sinus thromboses and autonomic neuropathy.[32]

Diagnosis

The mainstay of diagnosis of COVID-19 in Singapore is via nucleic acid detection using polymerase chain reaction (PCR) testing, with the collection of virus samples done via throat or nasopharyngeal swabs. The latter demonstrated greater efficacy in detection according to a swab audit done by NCID, with a higher

Table 3. Classification for persons at low versus high risk of disease progression

LOW RISK	HIGH RISK
Age < 30 years	Age ≥ 30 years, particularly age > 50 years
No chronic comorbidities	Chronic comorbidities (chronic lung, heart or kidney disease, HbA1c > 7.2%, immunosuppression)
Normal body mass index (BMI)	Obesity, if age < 60 years[20]
Reassuring clinical features, including: • No dyspnoea • Respiratory rate ≤ 20 breaths/min • Normal SpO_2 (≥ 95% on room air) • Not requiring oxygen therapy	Concerning clinical features, including: • Dyspnoea • Respiratory rate > 20 breaths/min • Abnormal SpO2 (< 95% on room air) • Requiring oxygen therapy
Normal chest X-ray	Chest X-ray showing features of pneumonia
Reassuring laboratory results* including:[19] • CRP ≤ 60mg/L • LDH ≤ 550U/L • Lymphocytes ≥ 1 x 10^9/L • Neutrophils ≤ 3 x 10^9/L	Concerning laboratory results[19] including: • CRP > 60mg/L • LDH > 550U/L • Lymphocytes < 1 x 10^9/L • Neutrophils > 3 x 10^9/L

*Certain risk stratification factors may be non-modifiable (e.g. age), whereas others are dynamic (e.g. evolving clinical features, radiology or laboratory results). Repeat labs are recommended at intervals (e.g. 2–3 days) for patients with concerns for clinical deterioration or when there is worsening of disease. Please note that these cut-offs are based on aggregate data from Singapore COVID-19 cases and there may be some variability in normal reference ranges between laboratories.

clinical sensitivity than nasal (middle turbinate) or saliva samples.[33] Extrapolated data from the performance of PCR from individual sites, however found that middle turbinate samples combined with throat swabs had a similar performance to nasopharyngeal samples combined with throat swabs, as shown in Table 4.

Limitations of this testing modality include inadequacy of sample collections, throat discomfort and nasal trauma, risk of exposure to the healthcare provider, and inherent limitations of PCR itself.[34] At NCID, active case detection of suspects in the early course of illness combined with daily sequential sampling of upper respiratory tract specimens over 2 days as part of an

Table 4. Diagnostic yields of various swab modalities for COVID-19[33]

Sample Site	Sensitivity (%)*+#			
	Day of illness < 8	Day of illness > 8	Upper Respiratory Tract Infection	Pneumonia
Single site	95	70	92	70
Oropharynx	88	67	88	61
Combination of nasopharynx and oropharynx	98	83	96	83
Combination of oropharynx and mid-turbinate nasal	98	77	94	78

* Sensitivity refers to the proportion of individuals infected with COVID-19 who are found to have a positive test result.

+ Specificity: 100%, refers to the proportion of individuals not infected with COVID-19 who are found to have a negative test result.

Other sampling sources showed lower sensitivity, including mid-turbinate alone and saliva (alone or in combination with mid-turbinate).

evaluation algorithm[35] detected most COVID-19 cases, 67 out of 70 (95.7%) cases.[36] While PCR testing for viral RNA is heavily employed in Singapore, viral RNA detection by PCR does not equate to infectiousness or viral viability. A surrogate marker of 'viral load' with PCR is the cycle threshold (Ct) value, with a low Ct value indicating a high viral RNA amount and vice versa. In a multicentre cohort of 73 COVID-19 patients in Singapore, when the Ct value was 30 or higher, no virus could be isolated, suggesting non-viable virus.[37] A new rapid serological coronavirus detection test allowing for rapid detection of neutralising antibodies (NAbs) has been developed in Singapore and is believed to be the first in the world,[38] subsequently being used to link two different clusters of infection among churches in Singapore. Sero-epidemiological studies to determine levels of COVID-19 infection among healthcare workers and the community have commenced.[39]

Serum antibody testing in Singapore for anti-SARS-CoV-2 immunoglobulin M (IgM) yielded detection of IgM in 17.9% of patients in the first week of illness, increasing to 39.3% in the second week of illness before declining to 35.7% and 7.1% in the third and after the third week of illness respectively. Anti-SARS-CoV-2 IgG was detected in 7.7% of patients in the first week of illness, 26.9% of patients in the second week of illness, and 50% of patients in the third week of illness, before declining to 15.4% after the third week.[37] Higher antibody levels were found in more severely ill patients; they were not associated with baseline Ct values from respiratory samples, duration of viral shedding, age or comorbidities.[37] Serological testing is thus potentially more useful in the later phase of the illness and needs to be interpreted in the appropriate medical context; it is not ready for prime time use in point-of-care-testing (POCT) diagnosis. Further data is needed to clearly define the role of rapid antigen tests for COVID-19.[40]

Laboratory studies that can be used to augment diagnosis include complete blood counts, inflammatory markers, cytokine and enzyme levels. In an analysis of haematological parameters among 96 COVID-19 patients in Singapore, lymphopaenia was observed in 28% of patients,[19] lower than the patients in China[14] and Italy.[10] Lymphopaenia featured prominently in COVID-19 patients in intensive care, with a nadir absolute lymphocyte count of 0.4 x 10^9/L, while neutrophilia has also been seen in critically ill patients. Thrombocytopaenia and leukopaenia were detected in a significant number of patients in Singapore as well, although again lower compared to that of patients in China[14] and Italy.[10] A systematic review and meta-

analysis of all published studies up to 15 March 2020 showed that on meta-regression, ICU admission was predicted by raised leukocyte count ($P<0.0001$), raised alanine aminotransferase ($P=0.024$), raised aspartate transaminase ($P=0.0040$), elevated lactate dehydrogenase (LDH) ($P<0.0001$) and increased procalcitonin ($P<0.0001$). Acute respiratory distress syndrome (ARDS) was predicted by elevated LDH ($P<0.0001$), while mortality was predicted by raised leukocyte count ($P=0.0005$) and elevated LDH ($P<0.0001$).[18]

False positive dengue IgM results have been found in COVID-19 patients in Singapore,[41] which further complicates differentiation between COVID-19 and dengue fever. Primary care physicians have described the challenges on the ground dealing with a dual outbreak of dengue and COVID-19 and have argued for a reliable POCT for COVID-19.[42]

Radiological tests that can help augment diagnosis of COVID-19 include chest X-ray (CXR) films and computer tomography (CT) scans of the chest. Radiological evidence of pneumonia was the overall strongest predictor of COVID-19 in modelling studies done by NCID.[13] Radiological findings in Singapore have included X-ray features of pneumonia such as consolidation,[43,44] CT features of consolidation with ground-glass opacities,[45] ground-glass opacities with subpleural reticular bands, and an anterior-posterior gradient of lung abnormalities resembling that of ARDS, as well as 'crazy paving'[45] in keeping with other studies in China[46] and the United States.[47] Nonetheless, COVID-19 is known to also present with normal imaging findings, particularly early in the disease course.[44]

Disease Course, De-isolation and Decanting

Analysis of the first 18 cases in Singapore has found that higher viral shedding occurred at the early stage (within the first week) of the illness, whereby the virus was more transmissible.[8] Viral load was not significantly correlated with disease severity. Based on another analysis of 766 patients in Singapore, by day 15 of illness onset, 30% of COVID-19 patients are PCR-negative by nasopharyngeal swab, rising to 68% by day 21, 88% by day 28, and 95% of all patients by day 33.[48] Age was not a key factor in determining speed of viral clearance, although patients aged less than 30 years appeared to have longer viral clearance.

In the multicentre cohort study by Young et al., the virus could also not be isolated or cultured after day 11 of illness, suggesting that although prolonged viral RNA detection may persist in some patients, such patients are likely to be non-infectious.[37] The same study also highlighted the virus' lack of viability when its Ct value

was more than 30, allowing for earlier discharges.[37] To preserve hospital capacity and prevent straining of the healthcare system, right-siting of care is crucial. NCID and public healthcare institutions have developed clinical criteria that would allow clinically stable patients to be transferred to community care facilities for isolation and monitoring, freeing up hospital beds for other patients.

An observational cohort study found that a major deletion in the SARS-CoV-2 genome within the open reading frame 8 (ORF8) region was associated with seemingly milder clinical symptoms.[49] Severe infections were associated with earlier seroconversion and higher peak IgM and IgG levels, with levels of inflammatory cytokines such as IP-10, IL-6, and VEGF-A being significantly correlated with disease severity.[37]

Management

Treatment of COVID-19 is mainly supportive, with most patients not requiring additional treatment. Supplemental oxygen therapy should be given promptly to hypoxaemic patients to keep saturations above 94%.[17] In Singapore, non-invasive ventilation is not routinely recommended due to concerns of droplet aerosolisation, while high-flow nasal cannulae may be associated with high failure rates.[50] Therefore, early intubation and mechanical ventilation is considered upon detection of impending respiratory failure, with internationally established ventilatory protocols being employed for patients who develop COVID-19 associated acute respiratory distress syndrome.[50] These involve the use of lung protective ventilation, judicious administration of fluids, neuromuscular blockade and prone ventilation if deemed appropriate. In addition, holistic ICU management including early mobilisation and prevention of nosocomial infection should be continued.[50] There have been calls to categorise patients according to variations in lung compliance and clinical phenotype (type 'H' and type 'L' phenotype), and tailor ventilator management accordingly[51], although this is not routinely practiced across all ICUs in Singapore.

Early prone ventilation of awake, non-intubated patients appears to lead to rapid improvements in oxygenation and was well tolerated in a case series of 10 such patients in Singapore; only 1 patient eventually required intubation.[52] Consequently, prone position was adopted for use in patients in the general wards meeting suitable criteria.

Mortality rates for COVID-19 in Singapore are low. In a single-centre case series in Singapore,[53] 22 COVID-19 patients admitted into ICU had an overall ICU mortality rate of 9.1%, while in patients requiring intermittent mandatory ventilation (IMV), ICU mortality was 15.4%, sharply lower than other rates in China (49%),[14] Italy (26%)[54] and the United Kingdom (43.2%).[55] Possible reasons for the disparity could be due to lower risk profiles of patients in Singapore, less pressure on ICU capacity, and sufficient ICU resources.[52]

Interim recommendations from the COVID-19 therapeutic workgroup and Chapter of Infectious Diseases, Academy of Medicine Singapore, have recently been updated and include a treatment algorithm for COVID-19 as shown in Fig. 4. The latest guidelines recommend remdesivir or dexamethasone for patients meeting eligibility criteria, and that patients be enrolled into a clinical trial if off-label use of medications is considered.[17]

Remdesivir is a novel nucleotide analogue RNA polymerase inhibitor that has shown activity against MERS and SARS coronaviruses in animal studies.[56] Despite an early trial failing to demonstrate clinical benefit, likely due to suboptimal recruitment,[57] a multicentre trial (ACTT-1) has shown evidence of remdesivir shortening recovery in hospitalised COVID-19 patients (11 vs 15 days, $P<0.001$), although no significant 14-day mortality difference was noted and minimal benefit was observed on patients receiving mechanical ventilation.[58] Results from ACTT-2 involving the addition of baracitinib to remdesivir are pending. The Health Sciences Authority (HSA) conditionally approved remdesivir for treatment of COVID-19 in Singapore on 10 June 2020, for adult patients with $SpO_2 < 94\%$ room air, or those requiring oxygen supplementation, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO), for treatment up to 10 days, or as part of a clinical trial.[17] Lopinavir-ritonavir and hydroxychloroquine have both been removed from management guidelines due to a lack of effectiveness[59] and associated increased mortality[60] respectively.

Steroids were initially recommended only to be used in COVID-19 patients if there were other indications such as exacerbation of asthma or refractory septic shock,[61] due to concerns about super-infections and delayed viral clearance. A subsequent large-scale randomised controlled trial (RECOVERY) showed that low dose dexamethasone cut deaths by a third among critically ill COVID-19 patients.[62] Based on data from the RECOVERY trial, corticosteroids (dexamethasone 6mg or equivalent for up to 10 days) for patients with more severe COVID-19 (receipt of supplemental oxygen or mechanical ventilation) is now recommended in guidelines in Singapore[17] with appropriate monitoring of side effects.
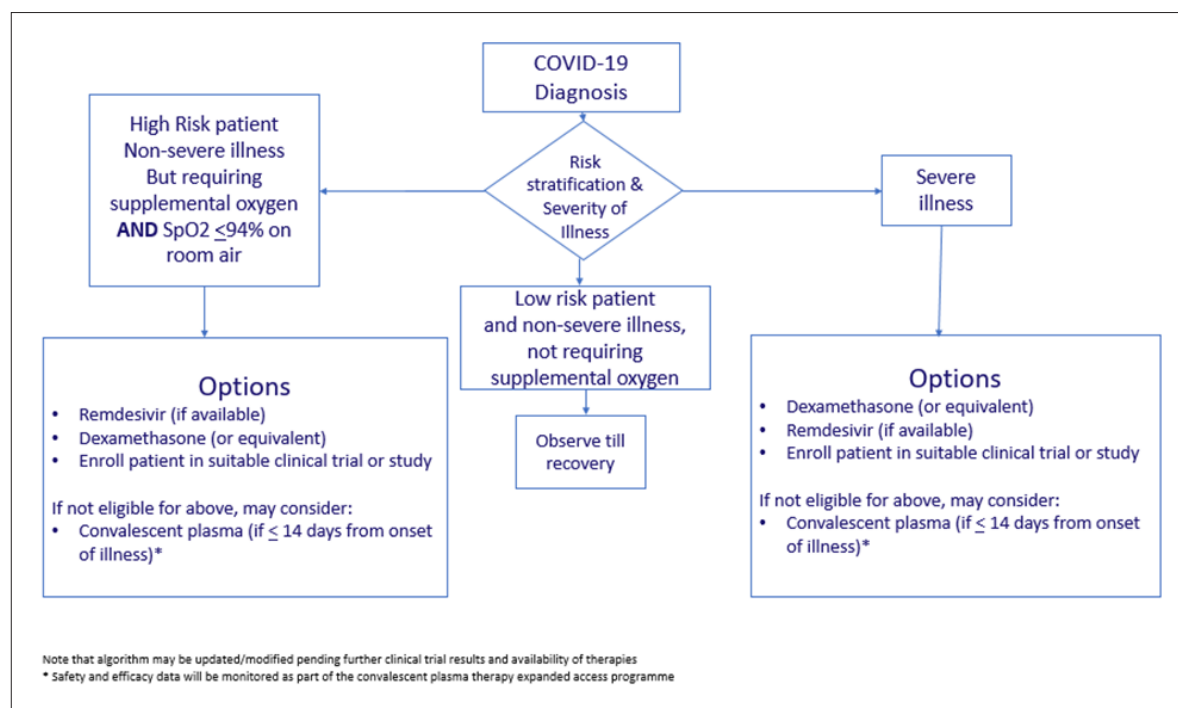
Fig. 4. NCID treatment algorithm for COVID-19, version 4.0.

Several small-scale studies[63] have highlighted the potential effectiveness of convalescent plasma as a therapeutic modality for COVID-19, although evidence remains inconclusive. A protocol for collection of convalescent plasma from recovered COVID-19 patients for the treatment of severely ill COVID-19 patients has been developed by NCID, Tan Tock Seng Hospital (TTSH) and HSA, with 6 patients being treated so far with convalescent plasma as of 27 October 2020.

Evidence regarding possible worsening of COVID-19 disease when non-steroidal anti-inflammatory drugs (NSAIDs) are used remains inconclusive.[64] Consumption of angiotensin-receptor blockers (ARBs) and angiotensin-converting-enzyme (ACE) inhibitors may be continued without fear of exacerbation of COVID-19 disease.[65]

Despite the increased risk of venous thromboembolism,[29] available evidence for routine full anticoagulation in COVID-19 patients remains limited. A study in China had demonstrated decreased mortality in severely ill COVID-19 patients treated with anticoagulation;[66] however, given that most patients in ICUs receive thromboembolic prophylaxis, it is important to further investigate if such data remained generalisable to all COVID-19 patients. Current recommendation in Singapore is to use thromboembolic prophylaxis in COVID-19 for all critically ill patients or those with severe disease.[17]

Global organisations such as GAVI aim to ensure global equitable access to COVID-19 vaccines via initiatives such as the COVAX programme, of which Singapore is a co-chair. Several countries such as Russia, China and the United States are actively developing and evaluating COVID-19 vaccines in various capacities and stages, of which several have been promising.[67] The Duke-NUS Medical School in Singapore has partnered with Arcturus Therapeutics to develop a COVID-19 vaccine in Singapore (LUNAR-COV19) and it is currently undergoing Phase I/II clinical trials.[68] Despite such efforts, preventive treatment for COVID-19 remains unavailable and is likely to remain so until there is established evidence of widespread efficacy and tolerability.[69]

Hospital Containment Strategies

Transmission of COVID-19 among healthcare workers has been reported in other countries such as China[70] and the United States,[71] leading to infections and deaths among healthcare workers.[70] Hospitals in Singapore promptly implemented outbreak response measures in line with Disease Outbreak Response System Condition (DORSCON) Yellow alert responses and according to regularly updated circulars from the Ministry of Health. Staff from different hospitals were segregated to reduce the risk of cross-contamination across hospitals, while

large department staff meetings were cancelled in favour of videoconferencing. Temperatures of staff were measured twice daily with digital oral thermometers, and recorded and monitored via a web-based form. Pregnant and immunocompromised staff were re-assigned from caring for COVID-19 patients.

Specific measures were required for business-as-usual and outbreak-related work across all specialties. Radiology departments implemented new workflows to cope with the increased requirement for shorter turnaround times for CXR reports, with separation of radiologists into teams covering inpatients, outpatients, and emergency department attendees. Active use of technological adjuncts to improve multidisciplinary collaborative efforts was also encouraged.[72] Interventional radiologists developed new methods to maximise workload optimisation and allow for service segregation.[73] Patients with end-stage renal disease requiring dialysis were also managed according to infection control principles, including designation of several dialysis centres as the national dialysis centre for patients on home quarantine, and contact tracing.[74] Infection control precautions were adopted by centres practising gastrointestinal endoscopy, including postponement of elective procedures and deferment of more extensive diagnostic sampling.[75] Clinicians at the Institute of Mental Health developed a protocol to allow for the safe and clean use of electroconvulsive therapy with calibrated infection control precautions such as decontamination and batching patients by location.[76]

To cope with the increased influx of COVID-19 patients, elective surgeries were reduced, and operating rooms segregated, with certain rooms with negative pressure environments reserved specifically for suspected COVID-19 patients. Increased frequency of disinfection was also carried out with hydrogen peroxide or ultraviolet-C irradiation. Routine pre-operative assessments and post-operative visits were suspended and replaced with teleconsultations. Patients with acute respiratory illness were advised to postpone non-emergency surgeries till 6 weeks after illness onset.[77] Awake intubation procedures were discouraged due to the risk of aerosolisation of the virus while regional anaesthesia was encouraged where possible. The use of plastic tents or screens for intubation or extubation procedures has been innovated by clinicians as potentially low-cost, accessible and disposable methods of reducing contamination by respiratory secretions.[78]

Comprehensive programmes for the use of personal protective equipment (PPE) were instituted for staff, with refresher training for the use and maintenance of the powered air-purifying respirator (PAPR) also conducted. Current guidelines in Singapore on PPE are in concordance with the United States Center for Disease Control and Prevention (CDC), which recommends gloves, gown, respiratory protection (e.g. disposable N95 respirators) and eye protection (e.g. goggles or disposable face shields), without shoe covers.[79] Designated areas for donning and removal of PPE were introduced, and visual aids to guide staff on correct usage of PPE were also set up. Given the risk of scarcity of PPE, particularly N95 respirators, in a prolonged global pandemic, there is a need for practices to extend the use of or reuse each respirator. Studies have shown that most healthcare personnel can tolerate wearing N95 respirators for up to 8 to 12 hours,[80] although practically most healthcare workers will use the respirators for up to 4 hours at a time due to the need for breaks. Healthcare professionals were trained extensively on practices to reuse N95 respirators, such as hand hygiene, ensuring adequate seal checks, avoiding contact with the outer surfaces of the respirator, and storage of the respirator to avoid contamination and preserve integrity.[81] Nonetheless, a case study in Singapore found that 41 healthcare workers, exposed to aerosol-generating procedures done on a positive COVID-19 patient on the ward for at least 10 minutes at a distance of less than 2 metres, led to none of the healthcare workers being infected with SARS-CoV-2, in spite of the fact that the staff were wearing surgical masks rather than N95 respirators.[82] A study in Singapore also showed the absence of contamination of PPE among healthcare workers who used PPE for an extended period of time, with no contamination of N95 respirators and disposable face visors after patient care, although in 1 instance SARS-COV-2 nucleic acid was found on the front surface of a healthcare worker's shoe.[83]

In addition to robust PPE training, early detection, active surveillance, and outbreak management are key to reducing potential healthcare-associated transmission. Ground-level reporting and compliance for healthcare workers with acute respiratory illness during the SARS-CoV-2 outbreak was strengthened, with a centralised reporting system set up.[84] Fast-track systems at fever screening centres were set up for staff, with close surveillance of staff with potential exposure to SARS-CoV-2 via occupational health clinic reviews and daily phone monitoring.[85] These measures have helped to prevent infection among frontline healthcare workers.[84]

ICUs have enhanced infection control practices, such as the provision of clean scrubs during duties and instituting mandatory showering after each shift.[86] Isolation teams were allowed a 2-week off-duty observation period if manpower was deemed available. Intubation was typically done only by the most skilled person using rapid sequence intubation technique to minimise aerosolisation,

with exhalation filters attached to bag-mask ventilators. Disposable bronchoscopes were also used on several occasions to provide bronchoscopy services safely.[86]

Sinks, toilets and air vents have been shown to be main areas of contamination by COVID-19 patients in hospitals.[87] To minimise nosocomial transmission, increased frequency of disinfection and cleaning of potentially contaminated surfaces was carried out by environmental services within hospitals with appropriate cleaning agents such as 0.5% hydrogen peroxide or 62-71% ethanol.[88] At the height of the outbreak, over 400 confirmed cases from NCID were managed in TTSH in wards specially configured with suction fans that exhausted air out to augment air exchange and create negative pressure.

All patients and visitors presenting to the hospital were screened using a questionnaire designed to assess infection risk. Patients fulfilling criteria for suspected SARS-CoV-2 infection were isolated, referred to an infectious disease specialist, and tested for the virus on-site. Thermal scanners at entry points into hospitals were set up to screen for febrile visitors. Visitors were asked screening questions at points of entry and exit to hospitals, and numbers were also restricted.[89]

A multinational, multicentre study showed a significant association between the prevalence of physical symptoms and psychological outcomes during the COVID-19 outbreak.[90] As such, resources to better help staff cope with the increased work demands, such as reading materials, a counselling helpline, and various peer support strategies were set up involving direct communication channels with senior clinicians and divisional heads.[91] Psychotherapists have also been assisting with efforts to deal with mental health issues among healthcare professionals. Strategies to ensure medical education is continued among medical students and professionals were also adopted.[92]

Public Containment Strategies

At the start of the outbreak, the risk of an imported COVID-19 outbreak in Singapore was deemed to be considerable due to close travel links with China, with 3–4 million Chinese visitors to Singapore annually. A multipronged strategy involving rigorous contact tracing, effective isolation and quarantine of COVID-19 positive patients and identified close contacts, border controls, community education on necessary precautions was employed to contain the outbreak. Several days after COVID-19 was first reported in China, the Ministry of Health developed a case definition for COVID-19 and close contacts of COVID-19 patients for use in Singapore[93] and advised all medical practitioners to be vigilant in their clinical practice. The importance of heightened vigilance

among clinicians was demonstrated in the early phases of the outbreak, in which approximately one-quarter of cases were detected through enhanced surveillance among hospitalised patients with pneumonia and through practitioners' clinical discretion.[94] Upon formation of the first cluster of infection on 4 February, the Ministry of Health raised the DORSCON level from Yellow to Orange soon after. Between the period of 2 January to 29 February, the spread of COVID-19 appeared to have been slowed, even though local transmission of cases occurred.[94] Rigorous manual contact tracing efforts were augmented with digital technology such as smartphone applications and tokens (TraceTogether) and check-in systems (SafeEntry), and were lauded by several leading epidemiologists.[95]

Border controls were implemented early, with temperature screenings eventually covering all inbound flights. A travel ban on short-term visitors was later imposed as the number of imported cases continued to rise with importations from multiple countries across the world. Mandatory 14-day stay-home notices were being issued to all travellers returning to Singapore initially from high-risk areas, but later expanded to all countries. Such efforts to minimise the numbers of imported cases have shown success in reducing imported cases to zero by the end of April.[96]

Compulsory wearing of face masks by the public was instituted by the government on 15 April as it emerged that asymptomatic and pre-symptomatic transmission was possible, and that there was sufficient evidence supporting the effectiveness of face mask use against COVID-19 transmission.[96]

Primary healthcare settings have been instrumental in the national defence against COVID-19.[97] The Public Health Preparedness Clinic (PHPC) scheme, which consolidates the primary care clinic response to public health emergencies, was activated early in the outbreak. COVID-19 testing capabilities were expanded to all government polyclinics and more than 200 PHPCs via the Swab and Send Home (SASH) programme, where patients would be tested in a swab-equipped clinic and sent home while waiting for the results, thereby reducing hospital admissions.[98] The criteria for SASH are depicted in Table 5.

The SASH scheme enhanced case-finding in primary care, reduced demand for dedicated ambulance services, and assisted with alleviating patient loads at emergency departments. In addition, all patients with symptoms of acute respiratory illness were issued medical certificates (MC) of sick leave for 5 days' duration, with patients legally obligated to stay at home throughout the period of the MC.

Table 5. Swab-and-Send-Home (SASH) criteria

Swab-and-Send-Home (SASH) Criteria

Patients fulfilling any of the following criteria:
• Community acquired pneumonia, not requiring admission
• Acute respiratory illness of any duration
  ◦ With relevant contact or travel history
  ◦ Stayed in a foreign worker dormitory
• Prolonged febrile acute respiratory illness ≥ 4 days, with body temperature ≥ 37.5°C
• Clinical discretion

Public health expertise and mathematical modelling[99] have helped to inform strategies like social distancing and staying at home as far as possible to contain the outbreak by way of a circuit breaker as the number of cases in Singapore started to escalate in late March and early April 2020. These measures were accompanied by strict enforcement. Progressively, there has been a decline in the number of cases in Singapore. Since the large outbreak of the disease among foreign workers living in cramped dormitories, the situation has been brought largely under control due to a combination of strict safe distancing measures and rigorous testing. Unlike SARS-COV-1, higher viral loads were detected much earlier in COVID-19 disease, while asymptomatic and mild infections did not contribute extensively to the chain of infection of SARS-CoV-1 as compared to SARS-CoV-2. This has informed prevailing contact tracing protocols to include this aspect. It has also underscored the importance of public health behaviours in combating transmission by way of wearing masks in public, social distancing and personal hygiene. As an aside, an unintended but favourable secondary outcome of these measures has been the plunging influenza rates in Singapore.[100]

Lessons learnt from previous outbreaks including SARS-CoV in 2003, had led to a boost in healthcare infrastructure, including the setting up of NCID, and regular pandemic preparedness exercises. These had helped to prepare Singapore to take on the challenges of COVID-19, including ensuring adequate stockpiling of PPE, aggressive testing, isolation of cases, and detailed contact tracing. Initial containment efforts were lauded by the WHO but were upended by the extensive outbreak among foreign workers living in cramped dormitories. This was further amplified by evolving knowledge that asymptomatic or pre-symptomatic infections could drive cross-contamination. However, a major concerted effort to contain the dormitory outbreak, coupled with enhanced public health measures including mandatory wearing of face masks and social distancing, have paid off. As borders continue to open, Singapore has to remain vigilant of possible weak links in its defences, while striving to maintain prevailing public health measures without giving in to fatigue. Lockdowns are unlikely to be a long-term solution due to economic and social costs, and other measures, including social distancing and ongoing efforts to test at-risk groups, are among interventions needed to ring-fence vulnerable patients such as nursing home residents.

Conclusion

In conclusion, this review summarises the available knowledge surrounding COVID-19 and showcases the efforts of Singapore and international research collaborations across diverse sectors including public health, infection control, therapeutics, diagnostics and vaccines. The pandemic is expected to last for a prolonged period, and comprehensive strategies and measures are required to keep the outbreak under control and keep fatalities to a minimum. Given the considerable uncertainty regarding COVID-19, local clinicians remain on a learning curve, and more research and data will guide and inform future practice.

REFERENCES

1. Ministry of Health, Singapore. Confirmed imported case of novel coronavirus infection in Singapore; multi-ministry taskforce ramps up precautionary measures. 23 January 2020. Available at: https://www.moh.gov.sg/news-highlights/details/confirmed-imported-case-of-novel-coronavirus-infection-in-singapore-multi-ministry-taskforce-ramps-up-precautionary-measures. Accessed on 29 March 2020.

2. The Straits Times, Singapore. Singapore reports first two coronavirus deaths: A 75-year-old Singaporean woman and 64-year old Indonesian man. 22 March 2020. Available at: https://www.straitstimes.com/singapore/singapore-reports-two-covid-19-deaths-health-minister-gan. Accessed on 29 March 2020.

3. World Health Organization, WHO Director Genera's opening remarks at the media briefing on COVID-19 – 11 March 2020. Available at: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020. Accessed on 29 March 2020.

4. World Health Organization, Coronavirus Disease (COVID-19): Weekly Epidemiological Update – 27 October 2020. Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports. Accessed on 28 October 2020.

5. Ministry of Health, Singapore. Situation Report, 27 October 2020. Available at: https://www.moh.gov.sg/docs/librariesprovider5/local-situation-report/20201027_daily_report_on_covid-19.pdf. Accessed on 29 October 2020.

6. Wei WE, Li Z, Chiew CJ, et al. Presymptomatic transmission of SARS-CoV-2 — Singapore, January 23–March 16, 2020. MMWR Morb Mortal Wkly Rep 2020;69:411-5.

7. Huff HV, Singh A. Asymptomatic transmission during the coronavirus disease 2019 pandemic and implications for public health strategies. Clinical Infectious Diseases, ciaa654

8. Young BE, Ong SWX, Kalimuddin S, et al. Singapore 2019 Novel Coronavirus Outbreak Research Team. Epidemiologic features and clinical course of patients infected with SARS-CoV-2 in Singapore. JAMA 2020;323:1488-1494. Erratum in: JAMA 2020:323:1510.

9. Report of the WHO-China Joint Mission on coronavirus disease 2019 (COVID-19). 16-24 February 2020. Available at: https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf. Accessed on 28 March 2020.

10. Colaneri M, Sacchi P, Zuccaro, et al. and COVID19 IRCCS San Matteo Pavia Task Force (2020). Clinical characteristics of coronavirus disease (COVID-19) early findings from a teaching hospital in Pavia, North Italy, 21 to 28 February 2020. Euro Surveill 2020;25:2000460.

11. Kujawski SA, Wong KK, Collins JP, et al. Clinical and virologic characteristics of the first 12 patients with coronavirus disease 2019 (COVID-19) in the United States. Nat Med 2020;26:861-8.

12. COVID-19 National Emergency Response Center, Epidemiology and Case Management Team, Korea Centers for Disease Control and Prevention (2020). Early epidemiological and clinical characteristics of 28 cases of coronavirus disease in South Korea. Osong Public Health and Research Perspectives 2020;11:8-14.

13. Sun Y, Koh V, Marimuthu K, et al. National Centre for Infectious Diseases COVID-19 Outbreak Research Team. Epidemiological and clinical predictors of COVID-19. Clin Infect Dis 2020;71:786-92.

14. Guan WJ, Ni ZY, Hu Y, et al. China Medical Treatment Expert Group for Covid-19 (2020). Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020;382:1708-20.

15. Wee LE, Chan YFZ, Teo NWY, et al. The role of self-reported olfactory and gustatory dysfunction as a screening criterion for suspected COVID-19. Eur Arch Otorhinolaryngol 2020;277:2389-90.

16. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. JAMA 2020;323:1239-42.

17. National Centre for Infectious Diseases, Singapore. Interim Treatment Guidelines for COVID-19, version 4.0 dated 31 August 2020. Available at: https://www.ams.edu.sg/view-pdf.aspx?file=media%5C5798_fi_466.pdf&ofile=Interim+Treatment+Guidelines+for+COVID-19+v4+(31+Aug+2020)_Final.pdf. Accessed on 19 September 2020.

18. Zhang JJY, Lee KS, Ang LW, et al. Risk factors of severe disease and efficacy of treatment in patients infected with COVID-19: A systematic review, meta-analysis and meta-regression analysis. Clin Infect Dis 2020:ciaa576.

19. Fan BE, Chong VCL, Chan SSW, et al. Hematologic parameters in patients with COVID-19 infection. Am J Hematol 2020;95:E131-4.

20. Ong SWX, Young BE, Leo YS, et al. Association of higher body mass index (BMI) with severe coronavirus disease 2019 (COVID-19) in younger patients. Clin Infect Dis 2020:ciaa548.

21. Parri N, Lenge M, Buonsenso D. Coronavirus Infection in Pediatric Emergency Departments (CONFIDENCE) Research Group. Children with Covid-19 in pediatric emergency departments in Italy. N Engl J Med 2020;383:187-90.

22. CDC COVID-19 Response Team. Coronavirus disease 2019 in children - United States, February 12-April 2, 2020. MMWR Morb Mortal Wkly Rep 2020;69:422-26.

23. Kam KQ, Yung CF, Cui L, Tzer R, Mak TM, Maiwald M, et al. A well infant with coronavirus disease 2019 with high viral load. Clin Infect Dis 2020;71:847-9.

24. Li J, Koh CT, Chia YC, et al. Comparative analysis of symptomatic and asymptomatic SARS-CoV-2 infection in children. Ann Acad Med Singap 2020;49:530-7.

25. Toubiana J, Poirault C, Corsia A, et al. Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study. BMJ 2020;369:m2094.

26. Riphagen S, Gomez X, Gonzalez-Martinez C, et al. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet 2020;395:1607-8.

27. Tan CW, Low JGH, Wong WH, et al. Critically ill COVID-19 infected patients exhibit increased clot waveform analysis parameters consistent with hypercoagulability. Am J Hematol 2020;95:E156-8.

28. Unpublished ICU cohort data, personal communication, Phua SH (Department of Respiratory and Critical Care, TTSH).

29. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. Blood 2020;135 :2033-40.

30. Bonow RO, Fonarow GC, O'Gara PT, et al. Association of coronavirus disease 2019 (COVID-19) With myocardial injury and mortality. JAMA Cardiol 2020;5:751-3.

31. Merkler AE, Parikh NS, Mir S, et al. Risk of ischemic stroke in patients with coronavirus disease 2019 (COVID-19) vs patients with influenza. JAMA Neurol 2020;77:1-7.

32. Koh JS, De Silva DA, Quek A, et al. Neurology of COVID-19 in Singapore. Journal of the Neurological Sciences 2020;418:117-8.

33. Sutjipto S, Lee PH, Tay JY, et al. nand National Centre for Infectious Diseases COVID-19 Outbreak Research Team (2020). The effect of sample site, illness duration, and the presence of pneumonia on the detection of SARS-CoV-2 by real-time reverse transcription PCR. Open Forum Infectious Diseases 2020;7:335.

34. Winichakoon P, Chaiwarith R, Liwsrisakun C, et al. Negative nasopharyngeal and oropharyngeal swabs do not rule out COVID-19. Journal of Clinical Microbiology 2020;58:e00297-20.

35. Tay JY, Lim PL, Marimuthu K, et al. De-isolating coronavirus disease 2019 suspected cases: A continuing challenge. Clin Infect Dis 2020;71:883-4.

36. Lee TH, Lin RJ, Lin RTP, et al. National Centre for Infectious Diseases COVID-19 Outbreak Research Team. Testing for SARS-CoV-2: Can we stop at two? Clin Infect Dis 2020:ciaa459.

37. Young BE, Ong SWX, Ng LFP, et al. Singapore 2019 Novel Coronavirus Outbreak Research team. Viral dynamics and immune correlates of COVID-19 disease severity. Clin Infect Dis 2020:ciaa1280.

38. Tan CW, Chia WN, Qin X, et al. A SARS-CoV-2 surrogate virus neutralization test based on antibody-mediated blockage of ACE2–spike protein–protein interaction. Nat Biotechnol 2020;38:1073-8.

39. Three National-Level Seroepidemiological Studies to Determine Level of COVID-19 Infection in Singapore. NCID. Available at: https://www.ncid.

sg/News-Events/News/Documents/SEROEPIDEMIOLOGICAL%20 STUDIES_FOR%20RELEASE%20FINAL_UPDATED.pdf. Accessed on 28 October 2020.

40. Scohy A, Anantharajah A, Bodéus M, et al. Low performance of rapid antigen detection test as frontline testing for COVID-19 diagnosis. J Clin Virol 2020;129:104455.

41. Yan G, Lee CK, Lam LTM, et al. Covert COVID-19 and false-positive dengue serology in Singapore. Lancet Infect Dis 2020;20:536.

42. Lam L, Chua YX, Tan DHY. Roles and challenges of primary care physicians facing a dual outbreak of COVID-19 and dengue in Singapore. Family practice 2020;37:578-9.

43. Liew JRP, Lim YD, Liew JYC, et al. Clinics in diagnostic imaging (207). Coronavirus disease 2019 (COVID-19) atypical pneumonia. Singapore Med J 2020;61:363-9.

44. Zhou JC, Hui TC, Tan CH, et al. Chest Radiography in Coronavirus Disease 2019 (COVID-19): Correlation with Clinical Course. Ann Acad Med Singap 2020;49:456-61.

45. Lim ZY, Khoo HW, Hui TCH, et al. Variable computed tomography appearances of COVID-19. Singapore Med J 2020;61:387-91.

46. Pan Y, Guan H, Zhou S, et al. Initial CT findings and temporal changes in patients with the novel coronavirus pneumonia (2019-nCoV): a study of 63 patients in Wuhan, China. Eur Radiol 2020;30:3306-9.

47. Kooraki S, Hosseiny M, Myers L, et al. Coronavirus outbreak: what the department of radiology should know. J Am Coll Radiol 2020;17:447-51.

48. Position Statement from the National Centre for Infectious Diseases and the Chapter of Infectious Disease Physicians, Academy of Medicine, Singapore – 23 May 2020. Available at: https://www.ams. edu.sg/view-pdf.aspx?file=media%5C5556_fi_331.pdf&ofile=Perio d+of+Infectivity+Position+Statement+(final)+23-5-20+(logos).pdf. Accessed on 30 June 2020.

49. Young BE, Fong SW, Chan YH, et al. Effects of a major deletion in the SARS-CoV-2 genome on the severity of infection and the inflammatory response: an observational cohort study. Lancet 2020;396:603-11.

50. Goh KJ, Choong MC, Cheong EH, et al. Rapid progression to acute respiratory distress syndrome: review of current understanding of critical illness from COVID-19 infection. Ann Acad Med Singap 2020;49:108-18.

51. Marini JJ, Gattinoni L. Management of COVID-19 respiratory distress. JAMA 2020;323:2329-30.

52. Ng Z, Tay WC, Ho CHB. Awake prone positioning for non-intubated oxygen dependent COVID-19 pneumonia patients. Eur Respir J. 2020;56:2001198.

53. Chew SY, Lee YS, Ghimiray D, Tan CK, Chua GSW. Characteristics and outcomes of COVID-19 patients with respiratory failure admitted to a "pandemic ready" intensive care unit – Lessons from Singapore. Ann Acad Med Singap 2020;49:434-48.

54. Grasselli G, Zangrillo A, Zanella A, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy region, Italy. JAMA 2020;323:1574-81.

55. Richards-Belle A, Orzechowska I, Gould DW, et al. COVID-19 in critical care: epidemiology of the first epidemic wave across England, Wales and Northern Ireland. Intensive Care Med 2020;46:2035-47.

56. Gordon CJ, Tchesnokov EP, Feng JY, et al. The antiviral compound remdesivir potently inhibits RNA-dependent RNA polymerase from Middle East respiratory syndrome coronavirus. J Biol Chem 2020;295:4773-9.

57. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet 2020;395:1569-78. Published correction in Lancet 2020;395:1694.

58. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19 final report. N Engl J Med 2020; NEJMoa2007764.

59. Cao B, Wang Y, Wen D, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. N Engl J Med 2020;3 82:1787-99.

60. Rosenberg ES, Dufort EM, Udo T, et al. Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York State. JAMA 2020;323:2493-502.

61. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Lancet 2020;395:473-5.

62. RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with Covid-19 preliminary report. N Engl J Med 2020;NEJMoa2021436.

63. Shen C, Wang Z, Zhao F, et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. JAMA 2020;323:1582-9.

64. Russell B, Moss C, Rigg A, et al. COVID-19 and treatment with NSAIDs and corticosteroids: should we be limiting their use in the clinical setting? Ecancermedicalscience 2020; 14:1023.

65. Reynolds HR, Adhikari S, Pulgarin C, et al. Renin-angiotensin-aldosterone system inhibitors and risk of Covid-19. N Engl J Med 2020;382:2441-8.

66. Tang N, Bai H, Chen X, et al. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost 2020;18:1094-9.

67. Logunov DY, Dolzhikova IV, Zubkova OV, et al. Safety and immunogenicity of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine in two formulations: two open, non-randomised phase 1/2 studies from Russia. Lancet 2020;396:887-97.

68. ClinicalTrials.gov 22 July 2020. Available at: https://clinicaltrials.gov/ ct2/show/NCT04480957. Accessed on 3 August 2020.

69. Bar-Zeev N, Inglesby T. COVID-19 vaccines: early success and remaining challenges. Lancet 2020;396:868-9.

70. Lai X, Wang M, Qin C, et al. Coronavirus Disease 2019 (COVID-2019) Infection Among Health Care Workers and Implications for Prevention Measures in a Tertiary Hospital in Wuhan, China. JAMA Netw Open 2020;3:e209666.

71. CDC COVID-19 Response Team. Characteristics of Health Care Personnel with COVID-19 — United States, 12 February–9 April 2020. MMWR Morb Mortal Wkly Rep 2020;69:477-81.

72. Kok SSX, Mohamed Shah MTB, Cheong WK, et al. Dealing with COVID-19: initial perspectives of a small radiology department. Singapore Med J 2020;61:375-7.

73. Gogna A, Punamiya S, Gopinathan A, et al. Preparing IR for COVID-19: the Singapore experience. JVIR 2020;31:86975.

74. Khoo BZE, See YP, Koh TJK, Yeo SC. Coronavirus Disease 2019 (COVID-19) and dialysis: the experience in Singapore. Kidney Med 2020;2:381-4.

75. Ang TL, Li JW, Vu CKF, et al. Chapter of Gastroenterologists professional guidance on risk mitigation for gastrointestinal endoscopy during COVID-19 pandemic in Singapore. Singapore Med J 2020;61:345-9.

76. Tor PC, Phu AHH, Koh DSH, et al. ECT in a time of COVID-19. J ECT 2020:10.1097/YCT.0000000000000690.

77. Wong J, Goh QY, Tan Z, et al. Preparing for a COVID-19 pandemic: a review of operating room outbreak response measures in a large tertiary hospital in Singapore. Can J Anaesth 2020;67:732-45.

78. Au Yong PS, Chen X. Reducing droplet spread during airway manipulation: lessons from the COVID-19 pandemic in Singapore. Br Journal Anaesth 2020;125:e176-8.

79. Interim infection prevention and control recommendations for patients with known or patients under investigation for 2019 novel coronavirus (2019-nCoV) in a healthcare setting. Centers for Disease Control and Prevention website. Available at: https://www.cdc.gov/coronavirus/2019-nCoV/hcp/infection-control.html. Accessed March 30, 2020.

80. Radonovich LJ Jr, Cheng J, Shenal BV, et al. Respirator tolerance in health care workers. JAMA 2009;301:36-8.

81. Rebmann T, Alexander S, Bartley J, et al. APIC position paper: extending the use and/or reusing respiratory protection in healthcare settings during disasters. Washington, DC: APIC; 2009.

82. Ng K, Poon BH, Kiat Puar TH, et al. COVID-19 and the risk to health care workers: a case report. Ann Intern Med 2020;172:766-7.

83. Ong SWX, Tan YK, Sutjipto S, et al. Absence of contamination of personal protective equipment (PPE) by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Infect Control Hosp Epidemiol 2020;41:614-6.

84. Wee LE, Sim XYJ, Conceicao EP, et al. Containment of COVID-19 cases among healthcare workers: The role of surveillance, early detection, and outbreak management. Infect Control Hosp Epidemiol 2020;11:1-7.

85. Htun HL, Lim DW, Kyaw WM, et al. Responding to the COVID-19 outbreak in Singapore: staff protection and staff temperature and sickness surveillance systems. Clin Infect Dis 2020;71:1947-52.

86. Liew MF, Siow WT, MacLaren G, et al. Preparing for COVID-19: early experience from an intensive care unit in Singapore. Crit Care 2020;24:83.

87. Ong SWX, Tan YK, Chia PY, et al. Air, Surface Environmental, and Personal Protective Equipment Contamination by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) From a Symptomatic Patient. JAMA 2020;323:1610-2.

88. Kampf G, Todt D, Pfaender S, et al. Persistence of coronaviruses on inanimate surfaces and their inactivation with biocidal agents. J Hosp Infect 2020;104:246-51.

89. Ministry of Health Singapore. Additional precautionary measures in response to escalating global situation. Available at: https://www.moh.gov.sg/news-highlights/details/additional-precautionary-measures-in-response-to-escalating-global-situation. Accessed on 20 April 2020.

90. Chew NWS, Lee GKH, Tan BYQ, et al. A multinational, multicentre study on the psychological outcomes and associated physical symptoms amongst healthcare workers during COVID-19 outbreak. Brain Behav Immun 2020;88:559-65.

91. Wong JEL, Leo YS, Tan CC. COVID-19 in Singapore-current experience: critical global issues that require attention and action. JAMA 2020;323:1243-4.

92. Ashokka B, Ong SY, Tay KH, et al. Coordinated responses of academic medical centres to pandemics: Sustaining medical education during COVID-19. Med Teach 2020;42:762-71.

93. Singapore Ministry of Health. Ministerial statement on whole-of-government response to the 2019 novel coronavirus (2019-NCoV). Singapore: Singapore Ministry of Health; 2020. Available at: https://www.moh.gov.sg/news-highlights/details/ministerial-statement-on-whole-of-government-response-to-the-2019-novel-coronavirus-(2019-ncov). Accessed on 30 March 2020.

94. Ng Y, Li Z, Chua YX, et al. Evaluation of the Effectiveness of Surveillance and Containment Measures for the First 100 Patients with COVID-19 in Singapore — 2 January–29 February 2020. MMWR Morb Mortal Wkly Rep 2020;69:307-11.

95. Niehus R, De Salazar PM, Taylor AR, et al. Estimating underdetection of internationally imported COVID-19 cases. Available at: https://www.medrxiv.org/content/10.1101/2020.02.13.20022707v1.full.pdf. Accessed on 11 November 2020.

96. Chen JI, Yap JC, Hsu LY, et al. COVID-19 and Singapore: From early response to circuit breaker. Ann Acad Med Singap 2020;49:561–72.

97. Lim WH, Wong, WM. COVID-19: notes from the front line, Singapore's primary health care perspective. Ann Fam Med 2020;18(3):259–261.

98. Tan G, Ang H, Manauis CM, et al. Reducing hospital admissions for COVID-19 at a dedicated screening centre in Singapore. Clinical microbiology and Infection: the official publication of the European Society of Clinical Microbiology and Infectious Diseases 2020;26:1278-9.

99. Koo JR, Cook AR, Park M, et al. Interventions to mitigate early spread of SARS-CoV-2 in Singapore: a modelling study. Lancet Infect Dis 2020;20:678-88.

100. Chow A, Hein AA, Kyaw WM. Unintended Consequence: Influenza plunges with public health response to COVID-19 in Singapore. J Infect 2020;81:e68-9.