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Escalating infection control response to the rapidly evolving epidemiology of the Coronavirus disease 2019 (COVID-19) due to SARS-CoV-2 in Hong Kong

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Abstract (word count 250)

Background: To describe the infection control preparedness for Coronavirus Disease (COVID-19) due to SARS-CoV-2 [previously known as 2019-novel coronavirus] in the first 42 days after announcement of a cluster of pneumonia in China, on 31 December 2019 (day 1) in Hong Kong.

Methods: A bundle approach of active and enhanced laboratory surveillance, early airborne infection isolation, rapid molecular diagnostic testing, and contact tracing for healthcare workers (HCWs) with unprotected exposure in the hospitals was implemented. Epidemiological characteristics of confirmed cases, environmental and air samples were collected and analyzed.

Results: From day 1 to day 42, forty-two (3.3%) of 1275 patients fulfilling active (n=29) and enhanced laboratory surveillance (n=13) confirmed to have SARS-CoV-2 infection. The number of locally acquired case significantly increased from 1 (7.7%) of 13 [day 22 to day 32] to 27 (93.1%) of 29 confirmed case [day 33 to day 42] ($p<0.001$). Twenty-eight patients (66.6%) came from 8 family clusters. Eleven (2.7%) of 413 HCWs caring these confirmed cases were found to have unprotected exposure requiring quarantine for 14 days. None of them was infected and nosocomial transmission of SARS-CoV-2 was not observed. Environmental surveillance performed in a patient with viral load of $3.3x10^6$ copies/ml (pooled nasopharyngeal/ throat swab) and $5.9x10^6$ copies/ml (saliva) respectively. SARS-CoV-2 revealed in 1 (7.7%) of 13 environmental samples, but not in 8 air samples collected at a distance of 10 cm from patient's chin with or without wearing a surgical mask.

Conclusion: Appropriate hospital infection control measures could prevent nosocomial transmission of SARS-CoV-2.

INTRODUCTION

A novel coronavirus, a beta-coronavirus, SARS-CoV-2, was recognized in a cluster of patients with community acquired pneumonia in Wuhan, Hubei Province, China, since December 2019 [1]. With the establishment of high speed rail within China and international travel, this novel coronavirus has been rapidly disseminated to all provinces of China and 25 countries in Asia-Pacific region, North America, Europe, and South America within one months of its discovery [2]. Similar to the other beta-coronavirus such as severe acute respiratory syndrome-associated coronavirus (SARS-CoV) and Middle East respiratory syndrome-associated coronavirus (MERS-CoV), the SARS-CoV-2 is postulated to be originated from bats and transmitted to the intermediate hosts before jumping to human, causing community and nosocomial pneumonia [3-5]. Before 11 February 2020, the disease caused by this novel coronavirus was temporary named as the 2019 novel coronavirus (2019-nCoV) disease. On 11 February 2020, the World Health Organization renamed the disease as the Coronavirus Disease 2019 (COVID-19) while the virus was classified as SARS-CoV-2 by the International Committee on Taxonomy of Viruses (ICTV). Up to 17 February 2020, a total of 71,429 were infected globally, including 70,635 (98.9%) cases in China. Except for 3 patients who died in Philippines, Japan, and France, 1772 deaths were reported in China with a crude mortality of 2.5% [6]. Two healthcare workers (HCWs) were succumbed as a result of nosocomial acquisition of SARS-CoV-2 in China. In Hong Kong, eight HCWs were died in

the outbreak of SARS-CoV in 2003 [3]. Referring to the experience of SARS-CoV, it is important for us to prepare and response to this emerging infectious disease with proactive infection control measures to prevent importation and nosocomial transmission of SARS-CoV-2 in Hong Kong. Here, we reported our infection control preparedness in the first 6 weeks with admission of 42 confirmed cases after official announcement of a cluster of pneumonia of unknown etiology in Wuhan, Hubei Province, by National Health Commission, China.

METHODS

Epidemiology and infection control preparedness for SARS-CoV-2 in Hong Kong

With reference to the infection control preparedness plan for emerging infectious disease in Hong Kong [7], a series of proactive infection control measures were activated in the Hospital Authority, a governing body of all 43 public hospitals responsible for 90% of inpatient service in Hong Kong, immediately after the official announcement of a cluster of pneumonia of unknown etiology in Wuhan, Hubei Province, by National Health Commission, China on 31 December 2019 (denoted as day 1). The key measures include a bundle of early recognition, isolation, notification, and molecular diagnostic for all suspected cases [8]. Active surveillance was performed upon patients' presentation to hospital according to a set of clinical and epidemiological criteria, which was adjusted during the evolution of SARS-CoV-

2 in China and Hong Kong (Table 1). All suspected cases were isolated in airborne infection isolation room (AIIR) for contact, droplet, and airborne precautions. Suspected cases were notified to Centre for Health Protection, Department of Health, and Hospital Authority. Enhanced laboratory surveillance was also conducted to widen the scope of screening (Table 1), but the patient could also be cared in AIIR as far as possible. Otherwise, patient should be cared in a ward with 1 metre spacing between patients.

The upper respiratory specimens including nasopharyngeal aspirates, or flocked swab, and throat swab were collected for all cases under the categories of active and enhanced laboratory surveillance, while the lower respiratory specimens such as sputum, endotracheal aspirates, or bronchoalveolar lavage were collected for rapid molecular diagnostic test if available. The molecular diagnostic test was simultaneously performed by Public Health Laboratory Service, Centre for Health Protection, and Queen Mary Hospital, The University of Hong Kong during the initial phase of the preparedness with a turnaround time of 4 to 8 hours, depending on the number of specimen per batch. With the increasing number of test, molecular diagnostic test was performed by 7 microbiology laboratories in 7 regional hospitals, including Queen Mary Hospital, in Hong Kong since 1 February 2020 (day 33).

Epidemiology of confirmed case was analyzed. Imported case was defined as patients with travelling history to the affected areas 14 days before symptoms onset, while local case was defined as patient had no history of travel to the affected areas 14 days before onset of

symptoms. Enhanced infection control measures with clearly illustration of the choice of personal protective equipment (PPE) were enforced (Table 2). Regular open staff forums were held along with face-to-face education sessions to provide "right-on-time" infection control updates and address staff concern, if any. Practical training sessions of using PPE were performed by hospital infection control team. Hand hygiene compliance assessments were conducted regularly in our hospitals.

Investigation for possible nosocomial transmission of SARS-CoV-2

Upon laboratory confirmation of patient with SARS-CoV-2, infection control team would immediately follow up to identify HCWs and patients with unprotected exposure, which was basically following the contact tracing protocol of avian influenza A H7N9 in Hong Kong [9]. Briefly, close contact referred to those with unprotected exposure, which was defined as HCWs who had provided care for the patient with inappropriate PPE, and patients who had stayed within the same cubicle of the index case regardless of the duration of exposure. Close contact with unprotected exposure required to be quarantine for 14 days since last exposure, and followed by medical surveillance of 14 days after completion of quarantine period. During medical surveillance, they would be advised to wear surgical mask in the hospital and community.

Laboratory diagnosis of SARS-CoV-2

Clinical specimens including nasopharyngeal aspirates, nasopharyngeal swabs, throat swab, saliva, sputum, endotracheal aspirates, or bronchoalveolar lavage were first mixed into 2 mL of viral transport medium (VTM) and 250 μL of the samples were subjected to nucleic acid extraction by the eMAG extraction system (bioMérieux, Marcy-l'Étoile France), with elution volume of 55 μL.

Before the identification of SARS-CoV-2, a pan-coronavirus PCR with modification so as to detect 23 coronavirus known to be present in human, animals, and bats was used [8, 10]. Subsequently, real-time PCR targeting the E gene of the SARS-CoV-2/ SARS-like coronavirus was performed by using the LightMix Modular SARS and Wuhan CoV E-gene mix (TIB Molbiol, Berlin, Germany) and the LightCycler Multiplex RNA Virus Master kit (Roche Diagnostics, Mannheim, Germany). Briefly, a 20 μL reaction contained 10 μL of RNA templates, 4 μL of 5x RT-qPCR reaction buffer, 0.5 μL of LightMix reagent mix, 0.1 μL of 200x RT enzyme and 5.4 μL nuclease free H_2O. Thermal cycling was performed at 55 °C for 5 min for reverse transcription, followed by 95°C for 5 min and then 45 cycles of 95°C for 5 s, 60°C for 15 s and 72°C for 15 s on the LightCycler 480 II system (Roche Diagnostics, Mannheim, Germany). The SARS-CoV-2 RNA loads in patient and environmental samples were determined by an in-house developed real-time RT-PCR assay targeting the SARS-CoV-2 RdRp gene [11].

Environmental surveillance for SARS-CoV-2

Air samples for SARS-CoV-2 RNA were collected for the first confirmed case in Hong Kong by an air sampler, SAS Super ISO 180 model 86834 (VWR International PBI S.r.l., Milan, Italy) with modification as previously described [12, 13]. Briefly, the air sampler was perpendicularly positioned at a distance of 10 cm at the level of patient's chin, and 1000 litres of air at a rate of 180 litres of air per minute was collected for each culture plate containing 3 mL of VTM. The patient was instructed to perform 4 different manoeuvres (normal breathing, deep breathing, speaking 1, 2, and 3 continuously, and coughing continuously) while putting on and putting off the surgical mask (comply with ASTM F2100 level 1 standard). The VTM was transferred to the laboratory within 2 hours and was subjected to RT-PCR for the detection of SARS-CoV-2.

Swab samples (Oxoid transport swabs, Copan Italia, Italy) from the patient's environment including bench, bedside rail, locker, bed table, alcohol dispenser, and window bench, before and after collection of air samples, were collected for SARS-CoV-2 RT-PCR. Briefly, swab samples covering a mean surface area of 9 cm^2 (3 cm x 3 cm) and then submerged into 2 mL VTM. The VTM were further centrifuged at 13,000 x g for 1 min and 1 mL of the supernatant was used for nucleic acid extraction.

The nasopharyngeal flocked swab, throat swab, and saliva of this patient were collected on the day of environmental surveillance and subjected to viral load assay.

This study was approved by the Institutional Review Board of The University of Hong Kong/Hospital Authority Hong Kong West Hospital Cluster.

Statistical Analysis

The Fisher's exact test was used to compare independent categorical variables between groups. All reported p values were two-sided. A p value of <0.05 was considered statistically significant. Computation was performed using the SPSS Version 15.0 for Windows.

RESULTS

Epidemiology and infection control preparedness for SARS-CoV-2 in Hong Kong

Up to 10 February 2020 (day 42 after official announcement of a cluster of pneumonia of unknown etiology in Wuhan, Hubei Province), a total of 1275 patients fulfilled the clinical and epidemiological criteria for active and enhanced surveillance upon presentation to our public hospitals, of which 42 (3.3%) of 1275 patients confirmed to be a case of SARS-CoV-2 in Hong Kong (Figure 1). There were 20 male and 22 female with a median age of 59 years (range 22-91 years). Nine of them were resident in mainland China (7 from Wuhan, 1 from Shenzhen, and 1 form Zhuhai), arriving by high speed train (n=6), by flight (n=2), and by bus (n=1). The remaining 33 patients were Hong Kong resident. Five of them had history of

travel to mainland China in the past 14 days before onset of symptoms. Exposure to wet or seafood market was reported in 2 patients. The first patient was confirmed on 21 January 2020 (day 22). From day 22 to day 32, only 1 (7.7%) of 13 confirmed cases was locally acquired. The number of locally acquired case significantly increased to 27 (93.1%) of 29 confirmed case from day 33 to day 42 ($p<0.001$, Fisher's Exact test). There were 8 family cluster involving 28 patients. One (2.4%) patient died and 4 (9.5%) patients remained in critical condition requiring mechanical ventilation as at day 42.

Investigation for possible nosocomial transmission of SARS-CoV-2

Upon epidemiological investigation of 42 confirmed cases, 36 patients were directly admitted to AIIR, while 6 patients were initially cared in the non-AIIR facilities. 413 HCWs caring these patients before confirmation of SARS-CoV-2, eleven (2.7%) HCWs were found to be close contact with unprotected exposure requiring quarantine for 14 days. None of them was infected with SARS-CoV-2 by the end of the quarantine. Nosocomial transmission was not observed in the hospitalized patients.

Environmental surveillance for SARS-CoV-2

While the viral load of the first confirmed case was 3.3 x 10^6 copies per mL in the pooled nasopharyngeal and throat swab and 5.9 x 10^6 copies per mL in saliva, respectively, on the day of environmental sample, the air samples were all undetectable for SARS-CoV-2 RNA when the patients were performing 4 different manoeuvres (normal breathing, deep breathing, speaking 1, 2, and 3 continuously, and coughing continuously) while putting on and putting off the surgical mask. The viral load of window bench was 6.5 x 10^2 copies per mL of VTM before the collection of air samples, while the other environmental samples collected before and after the air sampling were undetectable for SARS-CoV-2 RNA. The environmental and air samples were collected by an experience infection control nurses, who worn full PPE including N95 respiratory, face shield, cap, gloves, and gown, and was in close contact with the confirmed case for a total of 63 minutes. She had completed 14 days of medical surveillance without developing fever or respiratory symptoms.

DISCUSSION

The emergence of novel coronavirus associated pneumonia posed a global threat and challenges to the community as well as the healthcare system. In response to this unprecedented outbreak, which had already produced a higher number of infected case and mortality as compared with outbreak of SARS-CoV in 2003 within the first 6 weeks of its declaration [2, 3], a rapid infection control response is essential to contain and mitigate the risk of nosocomial transmission and outbreak. With reference to experience in the outbreak of SARS-CoV, almost 60% of nosocomial acquisition of SARS-CoV was HCWs [4], it is critically important to implement a proactive infection control measures, which must be

planning ahead. In Hong Kong, as a cosmopolitan city of 1,104 square-kilometers with a population of 7.45 million in Southern China, we are at a high risk of importation of infected case from mainland China. Therefore, we had progressively stepped up our infection control measures by widening the clinical and epidemiological criteria of surveillance for early recognition and isolation of index case according to the evolving of epidemic. In particular, patient who had visited a hospital in Mainland China was introduced as one of an epidemiological criterion for surveillance on day 17 of our preparedness, even though SARS-CoV-2 was only confined in Wuhan, Hubei Province not until day 20 [2]. This criteria of hospital visit was included because it was previously known as a risk factors for SARS acquisition in China [14]. Under the surveillance program, of 42 cases of SARS-CoV-2 identified in Hong Kong, 36 of them were immediately isolated in AIIR upon admission. During the outbreak of SARS, the median time between index patient admission and patient isolation was 4.5 days (1 to 13 days) in the review of literature [4].

At the same time, we enhanced the infection control measures by implementation of standard, contact, droplets, and airborne precautions for suspected or confirmed cases. We stepped up the use of PPE among HCWs in performing aerosol generating procedures (AGPs) even though for caring patients without clinical features and epidemiological exposure risk in the general wards. Performance of AGPs such as endotracheal intubation, open suctioning, and use of high flow oxygen had been shown to be associated with the risk

factors for nosocomial transmission of SARS-CoV among HCWs [15]. In addition, provision of surgical mask to all HCWs, patients, and visitors in clinical areas was implemented since day 5. Although wearing surgical mask alone was not clearly associated with protection of person from acquisition of SARS-CoV, wearing surgical mask by either HCWs or patients had shown to reduce the risk of nosocomial transmission of influenza pandemic [16, 17]. The combination of hand hygiene with facemasks was found to have statistically significant efficacy against laboratory-confirmed influenza in the community as illustrated in a systematic review and meta-analysis [18]. Hand hygiene among HCWs and patients were promoted and enforced during the epidemic of SARS-CoV-2 [19, 20]. With all these measures, we could maintain zero nosocomial transmission of SARS-CoV-2 since the importation of first confirmed case since day 22 in Hong Kong.

The mode of transmission of SARS-CoV-2 deserves further investigation. Opportunistic airborne transmission had been implicated in SARS-CoV [21]. World Health Organization recommends the use of airborne precautions whenever applicable in addition to standard, contact, and droplets precautions [22]. In this connection, we demonstrated a pilot experiment in an attempt to examine the exhaled air of a confirmed patient, who had moderate level of viral load in the respiratory specimens, with or without wearing a surgical mask in the AIIR. It was interesting to note that RNA of SARS-CoV-2 was undetectable in the air samples but present in an environmental sample. We may not be able to make a definite conclusion based on the

analysis of a single patient. However, it may help to reassure our staff that the exhaled air may be rapidly diluted inside the AIIR with 12 air change per hour, or probably the SARS-CoV-2 may not be predominantly transmitted by airborne route. The presence of environmental contamination by SARS-CoV-2 highlighted the importance of transmission via direct or indirect contact. For SARS-CoV, it retained its viability in smooth surface for over 5 days at temperatures of 22-25°C and relative humidity of 40-50% [23].

Transmission within family remained a concern as 66% of confirmed cases diagnosed in Hong Kong were spread within their family members. One family clusters constituted a total of 11 cases, most probably transmitted during their gathering for hot pot, where using of utensil and chopstick contaminated by saliva may occur. Saliva was shown to be positive for SARS-CoV-2 in 11 of 12 patients at a median of 3.3 x 10^6 copies per mL at the time of presentation [24]. In this family cluster, asymptomatic patient was retrospectively diagnosed in a 91-year-old lady. Along with our recent report of asymptomatic case in a pediatric patient [25], asymptomatic infection could occur in the age of extremities. The transmissibility of infection among asymptomatic patient deserves further investigation.

With the implementation of active and enhanced surveillance with progressive widening of screening criteria during the evolution of epidemic, we could recognize most of the confirmed case upon hospitalization and achieved zero nosocomial transmission in HCWs and patients within the first 6 weeks. However, our surveillance program may be challenged

by the patients with mild symptoms. In the early publications, fever and cough were reported in 87% and 80% of patients, respectively, at the time of presentation [1, 25-30]. With the presence of locally acquired case, epidemiological criteria may no longer be useful for admission screening. Vigilance in hand hygiene practice, wearing of surgical mask in the hospital, and appropriate use of PPE in patient care, especially performing AGPs are the key infection control measures to prevent nosocomial transmission of SARS-CoV-2 even before the availability of effective antiviral agents and vaccine.

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Conflict of interest.

All authors report no conflicts of interest relevant to this article.

Table 1. Surveillance program for early recognition of patient with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in Hong Kong

Active surveillance for imported case [a] (from 31 December 2019, day 1) [b]		
A.	**Clinical criteria (evolving with time)**	**Remark**
1.	Presented with fever and acute respiratory illness, or pneumonia (from day 1 to day 23)	Prepare for the importation of index patient to Hong Kong
2.	Presented with fever or acute respiratory illness or pneumonia (with effect from day 24)	
B.	**Epidemiological criteria (evolving with time) [c]**	
1.	Travel history to Wuhan, Hubei province, People's Republic of China within 14 days before onset of symptoms, irrespective of any exposure to wet market of seafood market (from day 1 to day 16)	Prepare for the importation of index patient to Hong Kong
2.	Patient had either one of the following within 14 days prior to the onset of symptoms: (a) visited Wuhan (regardless of whether the individual had visited wet markets or seafood markets there); or (b) visited a medical hospital in Mainland China; or (c) had close contact with a confirmed case of the novel coronavirus while that patient was symptomatic (from day 17 to day 20)	In response to the evolving epidemic with increasing number of confirmed case in Wuhan
3.	Patient had either one of the following within 14 days prior to the onset of symptoms: (a) visited Hubei Province (regardless of whether the individual had visited wet markets or seafood markets there); or 2 (b) or 2 (c) listed above (with effect from day 21)	In response to spread of nCoV-209 beyond Wuhan
Enhanced laboratory surveillance to identified imported and locally acquired case (starting from 13 January 2020, day 14, and evolving with time) [d]		
C.	**Patient with pneumonia**	**Remark**
1	(a) With unknown causes (not responding to treatment in 3 days); or (b) requiring ICU care; or occurring in	In response to the evolving epidemic

	clusters; or (c) who is a healthcare worker (from day 14 to day 21)	with increasing number of confirmed case in Wuhan, and other parts of China
2.	Point C1 or any inpatient with pneumonia and travel history to Mainland China within 14 days before onset of symptoms (from day 22)	
3.	Community acquired pneumonia without travelling history (from day 32)	In response to the confirmed local case in Hong Kong

[a] Application for Accidental and Emergency Department (AED), outpatient clinics, and day centers to prevent importation of patient with of novel coronavirus. Patient fulfilling clinical and epidemiological criteria is to be isolated in airborne infection isolation room, reported to Centre for Health Protection, Department of Health, and tested for novel coronavirus by reverse transcription polymerase chain reaction (RT-PCR); [b] day 1 denoted the day of official announcement of a cluster of pneumonia in Wuhan, Hubei Province by National Health Commission of the People's Republic of China; [c] epidemiological criteria has been updating according to the spread of the novel coronavirus; [d] serving as safety net to detect infected patient without a clear epidemiological exposure.

Table 2. Enhanced infection control measures to prevent nosocomial transmission of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in Hong Kong

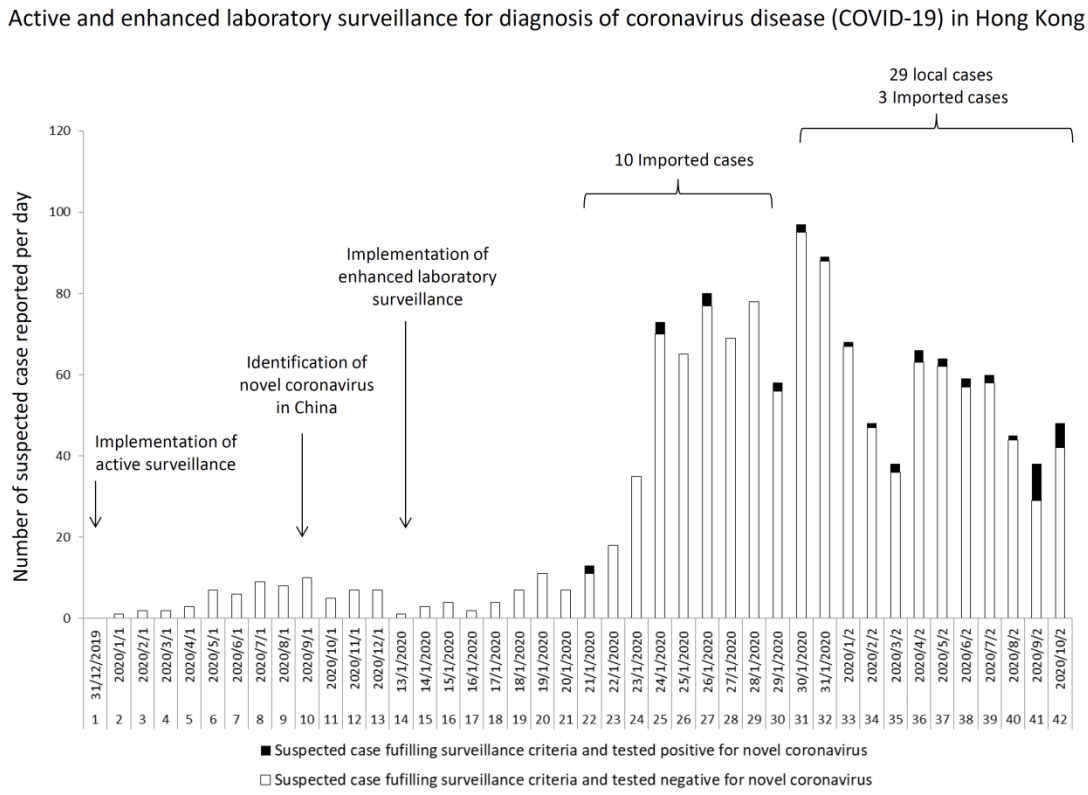
	Caring for suspected or confirmed SARS-CoV-2 [a]	**Triage station** [b]	**Aerosol generating procedures** [c]	**Other wards or patients areas** [d]	**Other area with no direct patient contact**
Hand hygiene	Required	Required	Required	Required	Required
Choice of mask	N95 respirator	N95 respirator [e]	N95 respirator	Surgical mask	Surgical mask
Isolation gown	AAMI level 3 [f]	AAMI level 1 or 3 [f]	AAMI level 1 or 3 [f]	Standard precautions +/- transmission based precautions	Not required
Disposable gloves	Required	Risk assessment	Required		Not required
Eye protection	Goggles / face shield	Eye visor / goggles / face shield	Goggles / face shield		Not required
Hair cover	Optional	Optional	Optional		Not required

[a] suspected or confirmed case of novel coronavirus 2019 is cared in airborne infection isolation room; [b] including triage stations of emergency rooms and outpatient clinics; [c] aerosol generating procedures included endotracheal intubation, cardiopulmonary resuscitation, bronchoscopy, and open suction of respiratory tract, sputum induction, use of nebulizer therapy, non-invasive positive pressure ventilation, and high frequency oscillatory ventilation; [d] including outpatient clinics, radiological facilities, physiotherapy, occupation therapy, and day centers; [e] surgical mask could be used as an alternative based on risk assessment; [f] AMMI, Association for the Advancement of Medical Instrumentation PB70:2003 is to define the liquid barrier performance and classification of protective apparel and drapes intended for use in health care facilities (https://www.fda.gov/medical-devices/personal-protective-equipment-infection-control/medical-gowns); AAMI level 1 isolation gown is used when small amounts of fluid exposure is anticipated while AAMI level 3 isolation gown is used when large amounts of fluid exposure is anticipated;

Figure legend

Figure 1.

Active and enhanced laboratory surveillance for diagnosis of novel coronavirus in Hong Kong



Note. Both calendar date and day after official announcement of a cluster of pneumonia in Wuhan, Hubei Province by National Health Commission of the People's Republic of China on 31 December 2019. From day 1 to day 20, pan-coronavirus PCR with modification so as to detect 23 coronavirus known to be present in human, animals, and bats was used. From day 21 onwards, real-time PCR targeting the E gene of the SARS-CoV-2 / SARS-like coronavirus was performed by using the LightMix Modular SARS and Wuhan CoV E-gene mix (TIB Molbiol, Berlin, Germany) and the LightCycler Multiplex RNA Virus Master kit (Roche Diagnostics, Mannheim, Germany).

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