Using discrete event simulation to optimize nucleic acid testing process for coronavirus disease 2019 (COVID-19)

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Background: The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory coronavirus-2 (SARS-CoV-2) has placed enormous diagnostic burden on hospitals and testing laboratories. It is thus critical for such facilities to optimize the diagnostic process to enable maximum testing on minimum resources. The current standard of diagnosis is the detection of the viral nucleic acid in clinical specimens.

Methods: In order to optimize the laboratory's nucleic acid testing system for COVID-19, we performed a Discrete-Event-Simulation using the Arena Simulation Software to model the detection process based on the data obtained from the First Affiliated Hospital of Guangzhou Medical University (FAHGMU). The maximum of total time that specimens spent and the equipment consumption was compared under different scenarios in the model.

Results: Seven scenarios were performed to simulate actual situation and improved situations. We analyzed conditions that adding a new nucleic acid extraction system (NAES), shifting a member from night duty to morning duty, using specimen tubes containing guanidine isothiocyanate (GITC), then tested the maximum testing capacity in the current number of technicians. In addition, the costs including personal protective equipment (PPE) and testing kits was calculated.

Conclusions: A work schedule based on specimen-load improves efficiency without incurring additional costs, while using the specimen tubes containing GITC could reduce testing time by 30 min. In contrast, adding new NAESs or polymerase chain reaction (PCR) instruments has minimal impact on testing efficiency.

Keywords: Coronavirus disease 2019 (COVID-19); nucleic acid detection; discrete event simulation (DES); process optimization

Introduction

On Mar 11th 2020, the World Health Organization (WHO) declared the coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory coronavirus-2 (SARS-CoV-2) to be a pandemic (1). COVID-19 can manifest as mild respiratory disease or as severe pneumonia, potentially resulting in multi-system failure and death (2-4). As of September 9th 2021, WHO has reported over 200 million confirmed cases, with mortality of more than 4.5 million deaths (5).

COVID-19 has placed tremendous burden on healthcare systems around the world. Medical facilities not only have to contend with the surge of COVID-19 cases, they also have to manage exposure risks from staff and visitors to other non-COVID-19 patients. The risk of nosocomial infections is high, particularly if some of them are asymptomatic or presymptomatic SARS-CoV-2 carriers (6). Moreover, due to rapid transmission and high mutation frequency, multiple variants of the SARS-CoV-2 Virus have emerged, which have escape effects on current vaccines and antiviral drugs (7). Therefore, virus nucleic acid testing still plays a critical role in detecting positive cases and blocking the spread of viruses. According not only to "*Diagnosis and Treatment Scheme of COVID-19 (Revised Edition 8)*" published by China Center for Disease Control and Prevention on May 11th 2021, but also to "*Laboratory testing for coronavirus disease 2019 (COVID-19) in suspected human cases*" published by WHO on Mar 20th 2020, the diagnosis of COVID-19 is mostly based on real-time quantitative polymerase chain reaction (RT-qPCR) test positive on SARS-CoV-2 nucleic acid (8,9). Many hospitals have instituted a policy to screen prospective in-patients and their accompanying members for COVID-19 prior to being admitted (10). However, the capacity of their testing settings does not account for such a large number of tests. This has placed a big burden on many hospital's testing facilities and resulted in long wait-times for these prospective patients. Reducing the test time and optimizing the testing process is thus important to prevent these patients from waiting and increasing the risk of transmission to others in the hospital. Moreover, an optimized testing process can also help to utilize important resources such as personal protective equipment (PPE), testing equipment, and man-power efficiently. Utilizing the minimum resources to do maximum detection will help prevent and control nosocomial infection and community transmission.

Given the reasons above, this study set out to optimize the COVID-19 laboratory testing process using a simulation software. Discrete event simulation (DES) is a commonly used modeling approach to improve the efficiency of a particular process (or system), including in hospital and laboratory settings (11). Nucleic acid detection in clinical specimens can be considered as a discrete event (12,13), and hence can be modeled using DES. We used the data derived from the laboratory testing of the First Affiliated Hospital of Guangzhou Medical University (FAHGMU) in the simulation to find the optimal scheme of the testing process. FAHGMU is one of the 30 provincial designated hospitals for COVID-19 treatment in Guangdong Province, China. As it is also the State Key Laboratory of Respiratory Disease and National Clinical Research Center for Respiratory Disease, it treats a large number of patients with respiratory symptoms, providing a suitable dataset for the simulation purpose. We present the following article in accordance with the CHEERS reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1496/rc).

Methods

Our model was based on current laboratory testing process for SARS-CoV-2 nucleic acid in FAHGMU. In response to the COVID-19 outbreak, the hospital established a special laboratory testing group for SARS-CoV-2 nucleic acid detection. The group works 24 hours a day, 7 days a week. There are three shifts daily, with work hours from 6:00 to 14:00, 14:00 to 22:00, and 22:00 to 6:00, respectively. Members are assigned to work in one of two specific rooms in the laboratory. There are four members on duty at 6:00 to 14:00 shift work hours on every Monday and Tuesday, with three in the inner room and one in the outer room. On remaining days, three members are on duty, with two in the inner room and one in the outer room. There are 28 members in the group, to ensure that everyone works 1 day and has 2 days off. One member only works at 6:00 to 14:00 on Monday and Tuesday. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Ethics approval for this study was not required because it is not a clinical trial or animal experiment. We built a simulation model based on real sample size rather than humans, so no ethical issues were involved in the test. Informed consent from each research participant was not required because certain personal information was also not involved.

COVID-19 nucleic acid detection kit (fluorescent PCR method) produced by Daan Gene Co., Ltd. were utilized
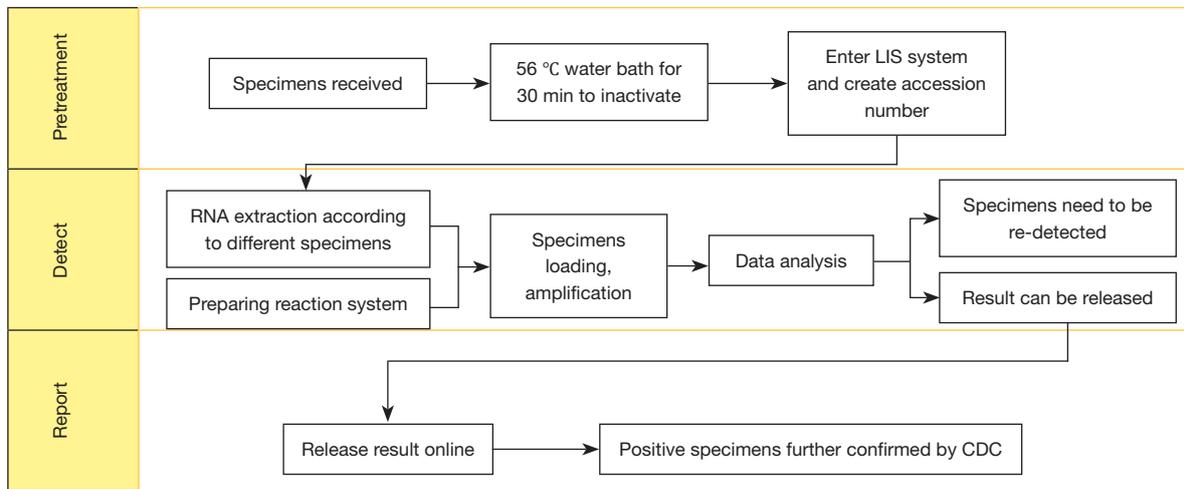
Figure 1 The process of RT-qPCR test for SARS-CoV-2. After receipt, the clinical specimens were first inactivated at 56 ℃ for 30 min, then registered on LIS and coded with an accession number. Subsequently RNA extraction was performed on specimens, and the reaction system was prepared. Then nucleic acid amplification was carried out. Finally, the results were read and reported back on LIS. LIS, Laboratory Information System; CDC, Chinese Center for Disease Control and Prevention; RT-qPCR, real-time quantitative polymerase chain reaction; SARS-CoV-2, severe acute respiratory coronavirus-2.

for laboratory testing. The analytical sensitivity of the kit is 500 copies/mL. In clinical evaluation, the positive coincidence rate of the kit was 97.64%, the negative coincidence rate was 99.71%, and the overall coincidence rate was 98.84%.

The laboratory testing procedure and the time required for each process is as follows: upon receipt, the clinical specimens are firstly inactivated at 56 ℃ for 30 min, then registered on the Laboratory Information System (LIS) with a coded accession number. This process takes 5 min for each sample (*Figure 1*). Subsequent processes will then differ according to specimen types. Sputum samples will be treated with dithiothreitol (DTT) for 10 min. Stool samples will need to be resuspended for 2 min, followed by drawing off the supernatant, which needs an extra 2 min. Nucleic acid extraction will then be performed on liquefied sputum, stool supernatant, the original swab and urine specimens. Nucleic acid extraction reagent should be added to every specimen (1.5 min each) before extracting on the nucleic acid extraction system (NAES) (DAAN GENE, Smart 32). There are 3 NAESs, the highest throughput of which is 32 specimens (25 min). After extraction, the nucleic acid solution is transferred to 96-well-plates for RT-qPCR. Nucleic acid amplification is carried out in a RT-qPCR instrument (Applied Biosystems, 7500). As a positive control and a negative control are needed in every plate, the highest throughput is 94 specimens each

instrument per 2 h run. There are a total of three qPCR instruments. All the steps mentioned above are conducted by members in the inner room. Members in the outer room are in charge of analyzing the results after amplification using a remote computer and report the results back on the LIS system. Results analysis takes 5 min for each plate and LIS-reporting takes 20 s for each specimen. In addition, members in the outer room are supposed to prepare reaction systems for amplification, which takes 30 s for each specimen. In the end, positive specimens should be sent to Chinese Center for Disease Control and Prevention (CDC) for further re-detection. In the best-case scenario, the time from sample receipt to result for sputum specimens is 192 min 50 s, stool specimens is 186 min 50 s, swabs/urine specimens is 182 min 50 s.

After 4 months of operation, the number of daily specimens has stabilized and shows a temporal trend. The maximum specimen number is on Monday, and decreases progressively through the week. In a single day, specimens will be delivered by 8:00, and peaking at nearly 10:00. The number of specimens will increase again at 14:30, reaching the second peak for the day at 16:00. The number is relatively low at other times, ranging from 0 to 5 samples per hour. We collected a dataset of clinical specimens from Apr 13th to Apr 19th, as there was no vacation or special days in the week before and after, making it representative

Table 1 The characteristics of scenarios

Scenario	Based on	Changes
1	The current operating status of the inspection group	None
2	Scenario 1	Adding a NAES
3	Scenario 2	Shifting the duty of one member in the inner room from 22:00-to-6:00 to 6:00-to-14:00
4	Scenario 3	Using specimen tubes containing GITC
5	Scenario 3	Adding an RT-qPCR instrument
6	Scenario 5	Infinite NAESs and RT-qPCR instruments. Improving specimen number
7	Scenario 6	Using specimen tubes containing GITC

The scenarios and characteristics are presented. Scenario 1 was based on the current operating status of the inspection group without changes. Others were based on previous scenarios. NAES, nucleic acid extraction system; GITC, guanidine isothiocyanate; RT-qPCR, real-time quantitative polymerase chain reaction.

of a normal work week. Data we collected consisted of received time and approval time, representing the time that specimens are received, and results are reported, respectively. Furthermore, the time intervals were counted.

Apart from time, we also considered equipment usage. Every member on duty has to don PPE. For ease of calculation, we converted these consumptions into costs in USD. Every member in the outer room needs a surgical mask ($0.41), a pair of disposal shoes covers ($0.56), a disposal hat ($0.28). Moreover, every member in the inner room needs an extra single-use protective clothing for medical use ($25.07), an N95 mask ($1.94), anti-skid shoe covers ($1.90), and an operating gown ($4.05). To sum up, a member in the outer room costs $1.25, and a member in the inner room costs $34.21. Kits and consumables for nucleic acid extraction and RT-qPCR were also calculated. One specimen cost $10.28.

We used Arena Simulation Software v14 (Rockwell Automation, Milwaukee, WI, USA) to model the nucleic acid detection process. Received time was categorized into half-hour arrival rates and then inputted to the model, by which we got the time distribution curve of specimen receipt number. The simulation began from 0:00 on Monday with no specimens in the model and maintained until all the specimens received on Sunday had been reported on LIS. New specimens for the next week were not considered. The work schedules of members might differ according to simulation scenarios.

The first outcome of our simulation was the total time that specimens spent in the model. Because we focused model running condition with high system load, comparison among scenarios was based on a maximum of total time. In view that specimens entered the model randomly at half-hour arrival rates, the amounts of specimens and the precise arriving time of a certain specimen in the model were somehow random, so replications were needed to ensure result validity. We believed a 95% confidence interval (CI) of less than 1% of the mean would make the results persuasive. After preliminary experiments, 95% CI of the total time was less than 1% of the mean in the basic scenario with 25 replications. So, we performed 25 replications and analyzed the mean and 95% CI of results as a final result in every scenario. The costs consisting PPE and testing kits were also calculated and analyzed with 25 replications.

The basic scenario was defined as the current operating status of the testing group without any changes (*Table 1*). Comparing simulation outcomes of the basic scenario and empirical data allowed us to assess the validity of the model.

The data was displayed as mean, 95% CI, and max value. One-way analysis of variance (ANOVA) tests were performed and $P<0.05$ was considered statistically significant.

Results

Scenario 1: the basic scenario and validity

The results of the basic scenario were set out in *Table 2*. The average number of specimens in 25 replications was 2,399.20±27.62 (not presented in the table), and the average total time was 3.9086±0.02 h. While the mean of time intervals of 2,391 specimens detected from Apr 13th to Apr

Table 2 The simulation results of the different scenarios

Scenario	The average number of specimens[1]	Total time (h)[2]			Max extraction number[3]	Max amplification number[3]	The QLMWT (h)[4]	Cost ($)[5]
		Average	Half width (95%)	Max value				
1	2,399.20	3.9086	0.02	5.7723	42	79	The queue that adding nucleic acid solution to the plates, 0.7500	26,195.27
2	2,415.16	3.8474***	0.02	5.7558	26	81	The queue that adding extraction reagent, 0.6471	26,359.33
3	2,400.60	3.7024****	0.01	4.8965	29	93	The reporting queue, 0.5194	26,209.66
4	2,404.72	3.2007****	0.01	4.1188	25	99	The queue that preparing reaction system, 0.5468	27,261.99
5	2,382.32	3.5311####	0.01	4.2969	27	69	The reporting queue, 0.4139	26,021.74
6	3,088.20	3.7294####	0.03	5.9580	36	76	The queue that adding extraction reagent, 1.0833	33,278.19
7	3,350.04	3.3201####	0.01	6.5219	35	80	The queue that adding nucleic acid solution to the plates, 1.4667	37,376.92

[1], in our simulations specimens entered the model randomly at half-hour arrival rates, therefore the amounts of specimens in the model were somehow random. Accordingly, 25 simulation replications were performed to get an average number of specimens. [2], the time intervals between received time and result reporting time of each specimen. In order to access the condition of a maximum load, comparisons among scenarios were based on a maximum value. [3], the maximum number that the NAESs and PCR instruments operated once. If the max extraction number is over 32 or the max amplification number is over 94, the NAESs and PCR instruments have overloaded, respectively. [4], the QLMWT indicates the step with the largest load, and the time that the longest-staying specimen spent in this step are followed. The unit is h. [5], the total cost is summed up, including PPEs for members and kits and consumables for specimens. ***, compared to Scenario 1, $P<0.001$; ****, compared to Scenario 1, $P<0.0001$; ####, compared to Scenario 4, $P<0.0001$. QLMWT, queue with the longest max waiting time; NAES, nucleic acid extraction system; PCR, polymerase chain reaction; PPE, personal protective equipments.

19th in FAHGMU, was 4.2784±0.11 h. Since the difference between simulated time and empirical time is negligible, the validity of our model had been confirmed. The max total time was 5.7723 h, meaning the specimen staying longest in the model in 25 replications spent 5.7723 h. The queue with the longest max waiting time (QLMWT) was the queue that adding the nucleic acid solution to the plates, and the time was 0.7500 h. It is worth mentioning that we had set the NAESs to boot up every 10 min and the PCR instruments every 50 min. As we had 3 NAESs and 3 PCR instruments and they cost 25 min and 2 h for each run, respectively, they had nearly reached their maximum frequency load. Therefore, they would not overload as long as the maximum extraction number and maximum amplification number were less than 32 and 94, respectively, which was their highest throughput. The maximum extraction number was 42 in this scenario, signifying the NAES had already overloaded.

As mentioned above, PPEs cost $1,531.49 for the whole week. A total of 2,399.20 specimens had been tested in the week, so $24,663.78 would be paid for them. The total cost was $26,195.27.

Scenario 2: adding a new NAES

In the basic scenario, the model had been overloaded, as the NAESs had processed more than 32 specimens at one time. Therefore, one more system was needed, and their running intervals should be accordingly reduced to 7min to reach the max frequency.

Scenario 2 in *Table 2* provides an overview of the results. After we added one more NAES, the maximum extraction number was reduced to 26. However, the average and maximum total time remained similar to Scenario 1. The QLMWT was the queue that adding extraction reagent with the time of 0.6471 h. The cost of PPEs was still $1,531.49 per week.

Scenario 3: shifting a member from night duty to morning duty

In the two scenarios above, the QLMWT were both queues that were handled by members in the inner room, indicating that members in the inner room could be at stretched.

Given that the number of specimens peaked during the day but stayed low at night, we wondered if the model could bear more load when shifting the duty of one member in the inner room from 22:00-to-6:00 to 6:00-to-14:00.

The change was made based on Scenario 2 and the results are presented as Scenario 3 in *Table 2*. Though the average total time had little difference, the max total time had reduced nearly 1 to 4.8965 h. The time the sample stays in the detection system was effectively shortened The QLMWT had become the reporting queue and the time was 0.5194 h, which was completed by members in the outer room. Remarkably, in spite that the max total time had reduced nearly 1 h, the cost stayed consistent as no new people taking part in.

Scenario 4: replacing virus transport medium with specimen tubes containing GITC

Specimen tubes containing guanidine isothiocyanate (GITC) have the ability to inactivate virus, therefore 30 min for inactivation could be saved using this kind of tubes. We simulated the scenario that reduced the inactivating process based on Scenario 3, and the results have been displayed as Scenario 4 in *Table 2*.

Compared with Scenario 3, the average and maximum total time in Scenario 4 was reduced by approximately 30 min. The maximum extraction number and amplification number had little difference, and the QLMWT is now the queue that prepares the reaction system, which was operated by members in the outer room.

However, specimen tubes containing GITC are $0.42 higher than normal virus transport medium, increasing the total weekly costs to $27,261.99.

Scenarios 5-7: the maximum load capacity without new people

The RT-qPCR instruments had nearly overloaded or were already overloaded in the scenarios above, therefore a new RT-qPCR instrument was needed and the results of the simulation based on Scenario 3 had been presented as Scenario 5 in *Table 2*. Running intervals had decreased to 35 min.

As now members of the model could bear the load of nearly 2,400 specimens a week in spite of overloaded NAESs and RT-qPCR instruments, we simulated infinite systems and instruments and improved the specimen number to explore the test capacity of this model with current people. It turned out that when the number of specimens in 1 week surged to 3,000 (Scenario 6, *Table 2*), the model with current people had reached its maximum load. The maximum time waiting in the queue was 1.0833 h spent in the queue that adding extraction reagent.

Considering the specimen tubes containing GITC could reduce the total time by 0.5 h, we simulated the model without an inactivating process. The results (Scenario 7, *Table 2*) revealed that once the number of specimens exceeded 3,300, the max total time would surge to over 6.5 h. The NAESs were overloaded, while the RT-qPCR machines could still bear the load. The addition of the nucleic acid solution to the plates was the longest queue with a time of 1.4667 h.

Discussion

As the COVID-19 pandemic are developing continuously, several countries including the US, UK and China, are calling for improved detection capabilities in order to better manage existing health resources and reduce risks of transmission (14-16). However, the improvement of testing capacity is currently more focused on the improvement of diagnostic methods, and there is a lack of good guidelines for the optimization of workflow in the local laboratories of healthcare institutions. We did the simulations to estimate the impact of certain measures to reduce possible trial and error costs. To explore the maximum detection loading capacity with minimum resources, we performed 7 scenarios with different working schedules or resources.

As the number of the specimens peaked at 10:00 and stayed quite low at night, we shifted a member from night duty to morning duty, which reduced the max total time by nearly 1 h. It proves that shifting working schedule corresponding to specimen quantity pattern is useful to improve work efficiency, while the costs stay the same. Among the tested scenarios, we found that most of the QLMWTs were those operated by members in the inner room, except for Scenario 3 and Scenario 5. It may be explained by the fact that though there were more members in the inner room, they were still taking on more pressure. Since the workload is heavier in the morning and in the inner room, clinical laboratories should figure out a better work pattern based on the specimens numbers, especially for those who have limited test resources.

Comparing Scenario 1 with Scenario 2, we found that adding new NAESs gave little contribution to reducing the max total time. The effect of adding new RT-qPCR instruments were similar, comparing Scenario 4 and

Scenario 5. It seems that a new NAES or machine makes no significant difference in the max total time. That could be because we had set the NAESs and RT-qPCR instruments to their max frequency load. As the time of each run was fixed, new NAESs or RT-qPCR instruments would not help to reduce the max total time.

One unanticipated result was that the specimen tubes containing GITC could save 30 min of the total time of each specimen by skipping the inactivating process but had no influence on the following processes. However, the extra costs should be paid for each specimen.

Although DES is an important tool to allow us to estimate the potential effects of different scenarios, there are certain limitations. Firstly, our data were collected from only 1 week. Although we believed the week we chose was representative, it was sampled from a single week and potential seasonality was unknown. Secondly, bar code printing time and audit time were collected to assess the validity of our model, but more time details among the processes such as waiting time in the reagent preparing queue, were unavailable. This prevented us from fine-tuning the model. Additionally, our model was built based on FAHGMU and testing kits from Daan Gene. However, situations in local hospitals might differ. Here we just provided a simulation approach to explore the maximum throughput with limited laboratory members and facilities. We believe this would be helpful during epidemic outbreak where there is explosive growth in sample size and insufficient resources. Any implementation of measures should adjust to local features.

Footnote

Reporting Checklist: The authors have completed the CHEERS reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1496/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1496/dss

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1496/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1496/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Ethics approval for this study was not required because it is not a clinical trial or animal experiment. We built a simulation model based on real sample size rather than humans, so no ethical issues were involved in the test. Informed consent from each research participant was not required because certain personal information was also not involved.

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References

1. Subspecialty Group of Gastroenterology, the Society of Pediatrics, Chinese Medical Association. Prevention and control program on 2019 novel coronavirus infection in children's digestive endoscopy center. Zhonghua Er Ke Za

Zhi 2020;58:175-8.

2. Zhu N, Zhang D, Wang W, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med 2020;382:727-33.

3. Zhou L, Liu HG. Early detection and disease assessment of patients with novel coronavirus pneumonia. Zhonghua Jie He He Hu Xi Za Zhi 2020;43:167-70.

4. Gorbalenya AE, Baker SC, Baric R, et al. Severe acute respiratory syndrome-related coronavirus: The species and its viruses–a statement of the Coronavirus Study Group. BioRxiv 2020. doi: 10.1101/2020.02.07.937862v1.

5. WHO. WHO Coronavirus (COVID-19) Dashboard. 2021. Available online: https://covid19.who.int/

6. Wong SCY, Kwong RT, Wu TC, et al. Risk of nosocomial transmission of coronavirus disease 2019: an experience in a general ward setting in Hong Kong. J Hosp Infect 2020;105:119-27.

7. Centers for Disease Control and Prevention. SARS-CoV-2 Variant Classifications and Definitions. 2021. Available online: https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-info.html

8. National Health Commission of the People's Republic of China. Diagnosis and Treatment Scheme of COVID-19 (Revised Edition 8). 2021. Available online: https://www.chinacdc.cn/jkzt/crb/zl/szkb_11803/jszl_11815/202111/W020211103288098629939.pdf

9. WHO. Laboratory testing for coronavirus disease 2019 (COVID-19) in suspected human cases: interim guidance, 2 March 2020. 2020. Available online: https://apps.who.int/iris/handle/10665/331329

10. National Health Commission of the People's Republic

of China. Investigation and Management Guideline for Close Contacts of COVID-19 Cases. Available online: https://www.chinacdc.cn/jkzt/crb/zl/szkb_11803/jszl_11815/202003/W020200309540843039285.pdf (Accessed 2020/7/2).

11. Abo-Hamad W, Arisha A. Simulation-based framework to improve patient experience in an emergency department. Eur J Oper Res 2013;224:154-66.

12. Best AM, Dixon CA, Kelton WD, et al. Using discrete event computer simulation to improve patient flow in a Ghanaian acute care hospital. Am J Emerg Med 2014;32:917-22.

13. Hoot NR, LeBlanc LJ, Jones I, et al. Forecasting emergency department crowding: a discrete event simulation. Ann Emerg Med 2008;52:116-25.

14. The State Council of the People's Republic of China. Nucleic acid testing capacity to be improved. 2020. Available online: https://english.www.gov.cn/policies/latestreleases/202008/31/content_WS5f4d0257c6d0f7257693b5cb.html

15. National Institutes of Health. NIH continues to boost national COVID-19 testing capacity: new laboratory and point-of-care tests to enable access and rapid result. 2020. Available online: https://www.nih.gov/news-events/news-releases/nih-continues-boost-national-covid-19-testing-capacity

16. Department of Health and Social Care. Help the government increase coronavirus (COVID-19) testing capacity. 2020. Available online: https://www.gov.uk/guidance/help-the-government-increase-coronavirus-covid-19-testing-capacity