Feasibility for SARS-CoV-2 Tests in the Hospital: An Exposure Analysis of Critical Control Points Approach

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Research

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Abstract

Objective Goal of this work is to assess the feasibility to perform COVID-19 RNA tests within hospitals and communities experiencing SARS-CoV-2 virus outbreaks, to ultimately provide recommendations for hospitals with so-called fever clinics. In China, these specialised clinics within a hospital, specifically receive outpatients who have fever symptoms.

Methods A team with expertise in the Exposure Analysis of Critical Control Points (EACCP) framework first identified potential infection routes during the testing for SARS-CoV-2, then constructed and tested flow diagrams, which were confirmed under actual conditions, demonstrating the feasibility to be carried out in hospitals with fever clinics. The team determined critical control points to mitigate the exposure risks at each control point.

Findings The sampling and inactivation steps of clinical samples in fever clinics appeared to be associated with particularly high risk levels of exposure to SARS-CoV-2. Moderate levels of exposure were associated with storage and transportation of samples for inactivation; Low risk levels were associated with the transportation, storage and detection steps after inactivation.

Conclusion To minimise risks of infection for personnel, optimised processes to carry out SARS-CoV-2 RNA tests in hospitals with fever clinics in China are proposed. The high risk of SARS-CoV-2 exposure during procedures preceding testing are the sampling and biological inactivation, which can be reduced by using full personal protective equipment and the use of BSL2 facilities in fever clinics or mobile BSL2 platforms. The implementation of the Exposure Analysis of Critical Control Points framework could facilitate rapid responses to outbreaks of emerging infectious diseases.

Introduction

Infectious diseases have shaped the course of human history, and continue to do so, with new emerging diseases being a threat more than ever to mankind. The COVID-19 outbreak in Wuhan, China, which became a global pandemic later - caused by the SARS-CoV-2 - caught local and global health-care communities unaware and unprepared [1 2]. By May 13th 2020, the outbreak had been associated with at least 6,170,474 confirmed, probable or suspected cases - reported in 188 countries/regions - and 372,099 deaths (https://coronavirus.jhu.edu/map.html). Already before SARS-CoV-2, other emerging infectious diseases outbreaks, such as SARS in 2003, presented extraordinary challenges to health-care systems and governments around the globe. One of the challenges is to test thousands of samples every day to excluded suspected patients, which is a very important marker for the management of an outbreak- especially in the communities of big cities which are transportation hubs, such as Wuhan in China, where the majority of SARS-CoV-2 cases were diagnosed first [3 4]. Highly pathogenic viruses such as SARS-CoV-2 are usually tested in Centers for Disease Control (CDC) and other authorized agencies with the biosafety level 3 (BSL3) protection during outbreaks [5]. In contrast to this, such tests are often not authorised to be carried out in hospitals even if BSL2 facilities are available. However, long distances

between hospitals with COVID-19 patients and authorized agencies that conduct tests requires the samples to be stored and transported under appropriate conditions, for two main reasons: (a) to reduce infection risks of personnel handling the samples, and (b) to avoid degradation of nucleic acids, which was one of the main reasons for false negatives of SARS-CoV-2 RNA tests at the beginning of COVID-19 endemic in Wuhan [6]. Fortunately, nearly all of the hospitals with fever clinics are equipped with Biosafety level 2 (BSL2) facilities to perform molecular biology tests, including PCR, reverse transcription PCR and real-time PCR. The use of BSL2 laboratories in hospitals to carry out RNA tests during a pandemic would greatly support the management of both, patients but also the outbreak itself. These RNA tests results are crucial for a proper scientific management of a huge number of patients which might have contracted the virus ("suspected cases") that have to be screened in a timely fashion every single day during the outbreak. In addition, the testing and results are also critical in the determination whether a patient has recovered and/ or is still shedding viruses.

According to guidelines from the "Office of the National Health Council Office of the National Administration of Chinese Medicine" (ONCONACM) [7], procedures that do not propagate biological material (e. g. the cultivation of pathogens or production of viruses) such as antigen tests, sera tests, RNA extraction and samples inactivation, can be carried out in the BSL2 lab with BSL3 individual protection. Departments of laboratory medicine in Chinese hospitals generally carry out lots of diagnostic tests using biochemical or immunological methods, or molecular biology, microbiology and cell biology techniques, with clinical diagnostic testing in the same facility; here, a high number of clinical staff is present at the same time, making it potentially dangerous for an infectious agent to be handled. In this case, all of the personnel would be required to wear BSL3 protection due to pathogen transmission risks, which might present a logistical and financial burden, especially due to the shortage of personal protective equipment (PPE) during outbreaks. Therefore, one of the main reasons preventing SARS-CoV-2 tests to be carried out in a hospital laboratory are the potential SARS-CoV-2 exposure risks in this setting. In clinical laboratories of Chinese hospitals, a substantial number of diagnostic tests are carried out on a regular basis where the biological material has been inactivated first prior to the test. An example is the testing for tuberculosis which is performed in BLS2 laboratories; here, the samples from patients where an infection with *Mycobacterium tuberculosis* is suspected, is inactivated by heat first before the Ziehl-Neelsen acid-fast staining procedure is performed, thus not risking any infection of the operator [8].

HACCP (Hazard Analysis and Critical Control Points) was originally developed for food production systems [9], but has been successfully adapted to manage and mitigate the exposure risks associated with detection of pathogens in clinical settings. It is increasingly being used to reduce the risks related to emerging infectious diseases and other health threats [10 11]. Since its use is both, low-technology and comparably inexpensive, the framework may be particularly useful in addressing the risks associated with emerging infectious disease in areas where the capacity of existing health-care systems is insufficient to cope with the impact of a health crisis such as an epidemic [12 13]. The framework's methods encourage the use of interdisciplinary expertise while enabling the rapid generation of evidence-based recommendations to assess the feasibility carrying out SARS-CoV-2 RNA test in the hospital with

fever clinic. It therefore offers the potential to manage risks when the rapid control of an outbreak is essential, especially with infection rates for healthcare workers at the early stage of the COVID-19 outbreak being rather high. Here we bring the concept of EACCP (Exposure Analysis and Critical Control Points) forward that could be used to assess the exposures in an infectious disease area. The framework of EACCP is based on the HACCP. In the present study, we evaluated the EACCP and its feasibility regarding SARS-CoV-2 exposures risks posed by diagnostic procedures and generated recommendations for carrying out SARS-CoV-2 RNA tests in hospitals based on EACCP framework.

In our work, we devised a process for each step to test SARS-CoV-2 RNA and evaluated the feasibility of the process to be carried out safely in hospitals. An infection exposure risk assessment of each step was generated, and the critical control points were detailed in our procedure. At the same time, the requirements for PPE were established and recommendations formulated for clinics and for mobile testing facilities. We then evaluated their potential for the EACCPs framework, as a response tool during outbreaks of emerging infectious diseases. Here, exposure, i.e. the close contact to patients possibly infected with SARS-CoV-2 in order to obtain samples, poses a high risks of direct transmission between humans. Other possible sources for direct or indirect transmission of SARS-CoV-2 virus were identified during various procedures associated to sampling, sample storage and transport, as well as inactivation. Finally, we evaluated the potential use of our assessments to be implemented in the EACCP framework as a response tool during an outbreak of an emerging infectious disease.

Methods

In conducting our EACCP, we adapted the guidance (HACCP) contained within an annex to the Codex Alimentarius Commission's General Principles of Food Hygiene [11 14]. Although this guidance refers to 12 steps in the analysis, we disregarded later steps in the process because for our procedure, implementing of the recommended control measures or establishing the subsequent on-the-ground monitoring, is not required (Fig. 1). We used a seven-step process which is similar to the one used for highly pathogenic avian influenza [13]. The seven steps are: (i) Assemble a team with appropriate expertise in EACCP; (ii) identify clinical samples from the potential COVID-19 patients for RNA tests; (iii) construct flow diagrams illustrating the system of care; (iv) test and confirm the accuracy of each flow diagram; (v) list potential virus exposure associated with each step in each flow diagram and conduct a virus exposure analysis; (vi) determine critical control points; and (vii) establish critical limits for each critical control point.

Team

The international and multidisciplinary nature of the problems posed by SARS-CoV-2 virus meant that we - i.e. the members of the research team - were obliged to conduct our analysis via a mixture of online meetings and email exchanges. The research team included experts in emergency medicine, laboratory medicine, HACCPs protocols, medical microbiology, virology, epidemiology, biosafety and others. The team members were drawn from 12 different institutional departments spread across multiple institutes and hospitals within China, USA and United Kingdom. Our analysis began when team members from the

Shanghai Jiaotong University held a series of small online meetings. The progress made in these meetings was then shared with a wider group of team members for comment and feedback.

Process

In the analysis, a systematic approach that allows for the synthesis of expert opinion is combined with the available knowledge. This might provide clarity in the otherwise extremely complex topic of public health. In our early meetings we concentrated on defining the most important exposure operations - in terms of the risk of exposures to pathogen material- and then created initial flow diagrams representing the pathways that could be used for sampling and RNA tests in the hospitals (Fig. 2). The diagrams were then shared with the other team members - with involvement of further colleagues, so that a wider group of experts could comment on them - before they were reviewed and simplified. Experts from the fields of medicine, biosafety, and molecular biology, as well as infectious medicine and medical microbiology provided their views on the flow diagrams. This review and a final critical analysis by an international panel of experts led to further modifications to - and simplifications of - the diagrams.

We considered an exposure to be a process - within a hospital with patients possibly infected by SARS-CoV-2 - that could lead to human exposure to the virus or provide the opportunity for transmission of the SARS-CoV-2 to another person. During the evaluation of the likely exposure scenarios, we grouped the exposures into high-, medium- and low-risk categories. Following the validation of each flow diagram, the research team determined appropriate critical control points - i.e. the points at which there is an opportunity to reduce or eliminate the risks of virus exposure. The team then created so-called critical limits, for each identified critical control point, on the basis of expert knowledge (Fig. 1), followed by the validation via an analysis of the relevant published data on the epidemiology, prevention and control of COVID-19 and the current relevant recommendations from the World Health Organization (WHO) [15].

Feasibility of implementation and recommendations for procedures

We used the results of the analysis to evaluate the feasibility of implementation of our procedure and to develop recommendations to carry out COVID-19 RNA tests in the hospitals. On 19th April.2020, Chinese government announced and required Grade A hospitals to carry out SARS-CoV-2 RNA test; the grade A hospitals in Shanghai (eg. Shanghai General Hospital) have already carried out SARS-CoV-2 RNA test since 20th April 2020. The patients for testing were sampled at fever clinic and stored with agents that could inactivation SARS-CoV-2, then delivered to the BSL2 room for test following the requirements of UN2814.

Results

Exposure analysis

Our assessment of the feasibility for SARS-CoV-2 RNA tests in the hospital within hospital settings affected by SARS-CoV-2 virus, revealed multiple exposure practices linked to the sampling, storage, transportation, inactivation and transport for subsequent analysis of samples from potential COVID-19 patients (Table 1 and Fig. 2). We believe that, if managed poorly, each of these operations presents an unacceptable level of risk of transmission of the virus.

Table 1
Summary of the Exposure Analysis of Critical Control Point (EACCP) assessment for the COVID-19 RNA detection in the hospital with fever clinics in China

Potential exposure by critical control point	Level of concern about Exposure		Individual protection level	Feasibilities	CCPs	PPE and Key requirements
	Samples	Surface of Sampling tubes				
1. Sampling	High	Medium	BSL3	Currently Available	Yes	- Face mask - Medical protective clothing - Glove - Goggle - Faceshield
2. Sample storage for transport	Medium	Medium	BSL 2	Currently Available	Yes	- Faceshield - Box - Glove - Goggle - Medical protective clothing
3. Sample transport for disinfection	Medium	Medium	BSL 2	Currently Available	Yes	- UV- and heatproof box - Disinfectant (70% ethanol) - Goggle - Faceshield - Medical protective clothing

CCPs: critical control points; PPE: personal protective equipment.

BSL 3: Biosafety Level 3; BSL 2: biosafety level 2.

Potential exposure by critical control point	Level of concern about Exposure		Individual protection level	Feasibilities	CCPs	PPE and Key requirements
	Samples	Surface of Sampling tubes				
4. Sample disinfection	High	Medium	BSL 3	Not available	Yes	- BSL2 platform - Class II BSC - Temperature controllable heater - Goggle - Faceshield - Medical protective clothing
5. Sample test	Low	Low	BSL 2	Currently available	No	- Surgical face mask - Medical isolation garment - glove
CCPs: critical control points; PPE: personal protective equipment.						
BSL 3: Biosafety Level 3; BSL 2: biosafety level 2.						

All the operations that we categorized as high-risk involved potential exposures to SARS-CoV-2: the sampling, and inactivation procedures (Fig. 2). The practices identified as medium-risk were the storage and transportation of samples for disinfection (Table 1). All of the other activities and practices linked to operation after the inactivation of the samples were deemed to present a lower level of risk of the transmission of the virus.

Control points and limits

We identified 4 critical control points- i.e. 4 points at which there is an opportunity to adopt measures to reduce the risks of exposure. For each such point, following extensive consultation and cross-referencing with the existing literature, one or more potential exposure risks were identified. We then established one or more sets of recommendations to increase the feasibility to reduce the exposure risk presented by each identified step (Table 1). All of the critical control points identified, could be assigned to one of five categories: sampling from patients potentially suffering from COVID-19, sample storage, transportation

for inactivation, or inactivation. The recommendations that we made for each critical control point derive from a combination of basic exposure control, but also to keep SARS-CoV-2 RNA material intact for reliable subsequent analysis, such as (i) employing BSL-3 protection for the healthcare workers who take samples from the patients and inactivate samples in order to reduce exposure risk and (ii) avoiding physical, chemical and biological factors that might lead to RNA degradation. After, analysing existing literature and SARS-CoV-2 RNA tests recommendations, we suggest procedure-related changes that could reduce the false negative due to RNA degradation. Several of the recommendations we made include fundamental aspects of infection prevention and control - e.g. the correct and proper use of full personal protective equipment, appropriate storage and transportation, and the appropriate disinfection operation using UV, heating equipment and followed by use of appropriate disinfectants for inactivation, the materials of transport boxes or sample containers; most importantly, RNA degradation inhibitors should be prepared and ready prior to sampling.

Discussion

In the present study based on the EACCPs framework, assessed the feasibility for implementation of new or optimized processes, and made recommendations for the protection of health workers and other staff in health facilities as well as the wider public from the risks of exposures that occurs during the sampling of sputum, oropharyngeal swabs, bronchoalveolar lavage fluid (BALF), blood or feces of (suspected) COVID-19 patients for SARS-CoV-2 RNA tests. During this analysis, we identified 4 critical control points associated with the sampling, storage, transportation, and inactivation of the samples from COVID-19 susceptible patients; also, the required individual BSL3 protection measures for these operations identified. The first three (sampling, transportation and storage) have been all already available in [fever] clinics in hospitals in China; furthermore, the majority of clinical laboratories of hospitals are equipped with BSL2 facilities providing the possibility to conduct RNA tests.

Our analysis took the state of the art and present knowledge described in the published literature and guidelines published by the Chinese national or international organizations associated with the inactivation of SARS-CoV-2 for RNA tests into account. The framework allows for a rapid identification of the risks associated with a known exposure. The existing conditions that prevents SARS-CoV-2 tests to be conducted in the laboratories of clinics are mainly resulting in the potential SARS-CoV-2 exposure to all staff, with some not even involved in the testing for COVID-19. In order to establish a safe, robust and reliable testing procedure, one of the most critical control points would be to avoid a down-process risk completely, by inactivation of the samples before sending them for the test. Therefore, we propose that the inactivation of the SARS-CoV-2 samples should be performed in the fever clinics BSL2, mobile BSL2 facilities (Fig. 3) or the sampling tubes with inactivation agents. To summarize: in order to effectively combat any infectious disease outbreak in the future, BSL2 facilities (or higher) -whether in hospitals or mobile facilities- with individuals equipped with BSL3 protection, should be used for sample inactivation.

Besides the general requirement to establish BSL2 facilities, a 56℃ heating system or preloaded sampling tubes including agents for inactivation of samples inside of tubes or bottles are required; in

addition, disinfectants (such as 70% ethanol) for disinfection outside of the tubes or bottles or inside or outside of box for transportation, and UV violet for surface disinfection, are also needed. It is well established that a heat treatment of 56℃ for a duration of 60 min or UV violet radiation for 15 min are both able to deactivate SARS-CoV-2 viruses or reduce its infectivity to very low level [16]. In addition, suitable individual protection equipment also provides a sufficient protection to the risk of exposure. After inactivation (e.g. by heat treatment), the samples can now be transferred for RNA tests into a standard BSL2 molecular laboratory, commonly found in many hospitals with infection medicine. As the samples are inactivated and present no or minor risk of transmission, it is not required to perform the tests exclusively by the CDC or other authorized agencies; if the test could be performed in the hospital itself, this would massively accelerate the screening for suspected COVID-19 cases during an outbreak. More than 1716 local healthcare workers were infected by SARS-CoV-2 in the hospital till Feb. 14th 2020, 87.5% of them in Wuhan (Mar 8th 2020 reports from ONCONACM). This is likely to have happened due to SARS-CoV-2 transmissions allowed by insufficient protection at the beginning of endemic; soon thereafter, there were more than 42600 healthcare workers supporting Wuhan and no infections occurred among them due to sufficient protection (Mar 8th 2020 reports from ONCONACM). This suggests that appropriate individual protection is sufficient to avoid the risk of exposure during various procedures with patients and patient samples, and also shows potential feasibility carrying out the screening in the hospitals. It has been suggested that samples inactivated by heating should result in lower positive test results and might increase the Ct value [17]. Another report showed that the agents inhibiting RNA degradation during sampling could prevent negative test results of COVID-19 patient samples [18]; this implies that, for COVID-19 RNA tests, the choice of proper inactivating procedures is crucial for high accuracy of test results.

The response and management to the challenge of a pandemic varies from country to country due to resources, governmental structures and compliance of the population, among others. Rapid and accurate diagnoses as well as monitoring of SARS-CoV-2 infections have shown to be crucial for an effective control of the current outbreak [19]. Similar to the Fangcang shelters for the treatment of the diagnosed COVID-19 patients with mild symptoms [20]. It is essential to avoid cross-transmission of disease agents such as other viruses or pathogenic bacteria in the waiting room, prior to sampling for testing. For developed countries like the USA which are often less densely populated compared to China and Korea (Fig. 3 and Table 2), almost every family has a privately owned car. Setting up “drive-through” test sites is convenient for the potential infected person but also reduces the risk of being infected with pathogens, while also presenting a safe solution for the healthcare workers performing the test. For developed countries such as South-Korea that are densely populated, privately owned vehicles are often available; in addition to the "drive through” test sites, additionally hospital-based or mobile platforms are required for efficient testing for those who cannot use a car. In contrast to this, Chinese citizens often do not own a car; therefore it is un-realistic for carrying out “drive through” tests, in order to cover the majority of the population and not just a section of it.

Table 2
Response modes of some countries for text suspected COVID-19 cases.

Countries/District	Modes	Start date
South Korea; USA; United Kingdom;	Mobile BSL2 platform/ “Driven through” test sites	Feb 27,2020
China; Serbia; United Arab Emirates; Brunei; Kingdom of Saudi Arabia	“Fire Eye” mobile BSL2 developed by BGI group	Feb 5, 2020
Germany	Governmentally financed research institutes (eg: Robert Koch Institute)	/
China (Shanghai)	Special Fever Clinic for COVID-19 cases in Zhongshan Hospital	/
China (Shanghai)	Special sampling room for screening the patients in Shanghai General hospital	Apr 20, 2020
China (Zhengzhou)	BSL2 laboratory converted in Fever Clinic in First people’s hospital of Zhengzhou	Feb 13,2020
USA	At home test	Apr 21, 2020
“/” means unavailable		

During the SARS-CoV-2 outbreak hospitals in big cities like Shanghai and Zhengzhou, received hundreds of outpatients in their fever clinics daily; in order to avoid cross-transmission in waiting rooms of the hospitals. Zhongshan hospital in Shanghai set up two separate fever clinics, one specifically for suspected COVID-19 cases. Here, the patients were sampled and samples then sent to CDC or another authorized agency for processing and testing. While, as the designated hospital receiving COVID-19 patients, the Zhengzhou First People’s hospital, converted BSL2 laboratory in fever clinic, so the suspected cases could be tested timely avoiding to wait for the results with longer time after sending out for RNA test. Furthermore, commercial entities started to develop systems to participate in the testing for the SARS-CoV-2 virus; an example is the “Fire eye” mobile BSL2 laboratory platform developed by BGI for the detection of viral RNA, which include the process from sampling to testing. In Germany and the USA, private companies also participate in the testing for the coronavirus, but also governmentally financed research institutes like the Robert Koch Institute in Germany that contributes to testing. In addition, the German government sought the advice of the institute for testing and the containment of the SARS-CoV-2 virus to decrease the number of infections in the population.

Conclusion

In conclusion, our analysis has shown that it is feasible to carry out SARS-CoV-2 RNA tests in the hospitals. Different transmission risks are associated with sampling, sample storage and transportation, as well as with inactivation for subsequent tests of samples from patients potentially suffering of COVID-19. Procedures include sampling (high risk), storage (medium risk) and transportation (medium risk) are being carried out from patient to testing facility. The feasibility to use existing BSL2 tests facilities in hospitals which were widely available in large cities in China during the COVID-19 outbreak, require one crucial step: The inactivation of the samples, a high risk operation, has to be performed in clinics or mobile facilities using BSL2 level equipment, but with BSL3 protection provided for all the operators and other personnel present. This process, if implemented, would massively decrease the test burden for the CDC during the outbreak of COVID-19 and lay a part of the foundations for a thorough preparation for the emergence of the next infectious disease outbreak in the future.

Abbreviation

Exposure Analysis of Critical Control Points (EACCP); Hazard Analysis and Critical Control Points (HACCP); personal protective equipment (PPE); Office of the National Health Council Office of the National Administration of Chinese Medicine (ONCONACM).

Declarations

Ethics approval and consent to participate

Not Applicable.

Consent for publication

All authors contributed significantly to the work, and saw the manuscript and approved to submit to the journal.

Competing interests

The authors declare no conflicts in interests.

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Authors' contributions

The study was conceived and designed by ZLC and TTF. The data were acquired by MQG, JG, YHZ, LBZ, YXW, QTL, and XKG; interpreted by ZLC, TTF initiated the study and ZLC coordinated and oversaw the study. The manuscript was drafted by TTF, ZLC. SL, MYL, NT and QTL revised for intellectual content and approved for publication by TTF, SL, MYL, JG, MQG, LBZ, QTL, YHZ, YXW, XKG and ZLC.

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Availability of data and material

Not Applicable.

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Figures

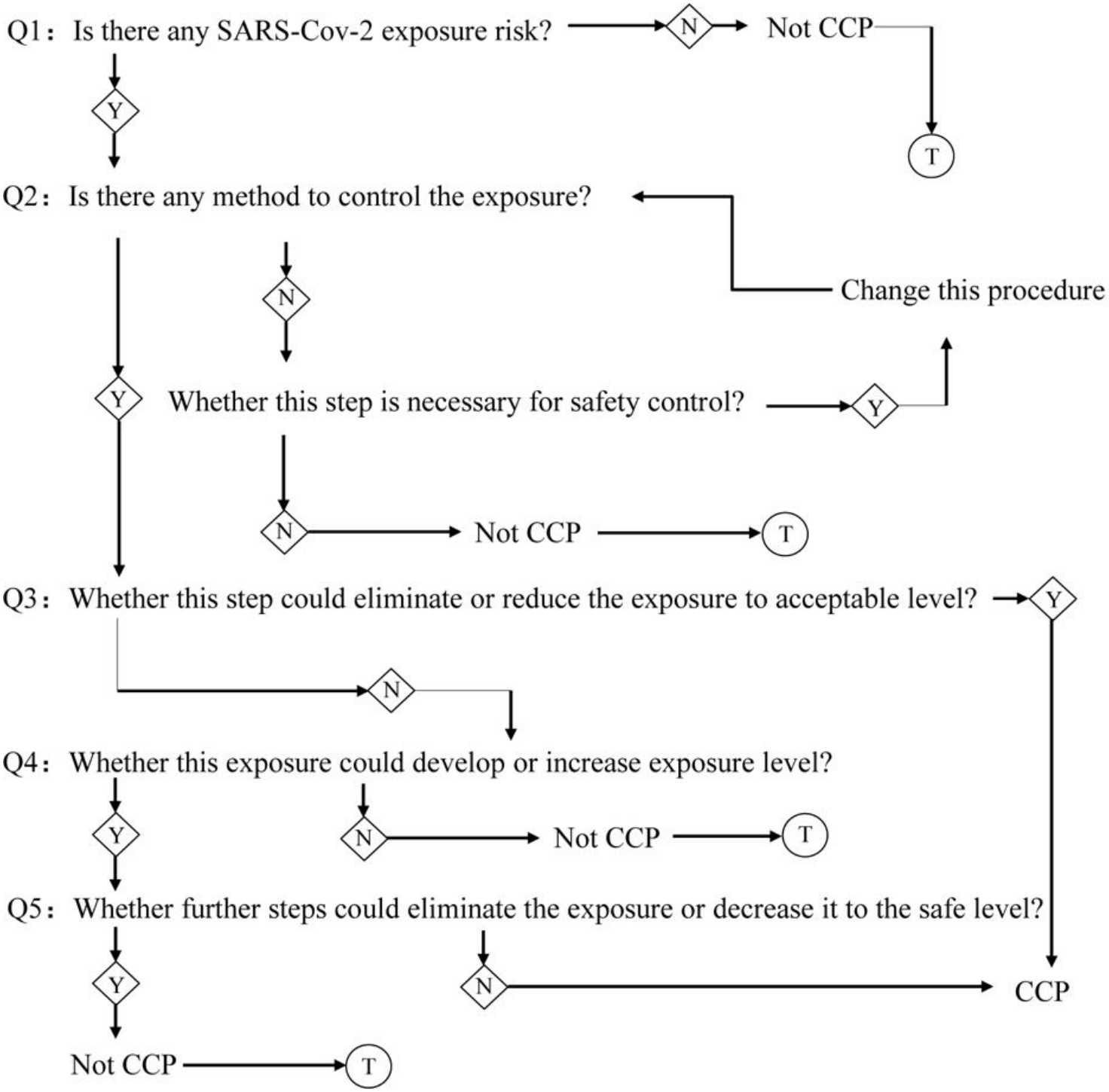

Figure 1

The critical control points decision tress. (N: no, Y: yes, CCP: critical control point, T: terminated).

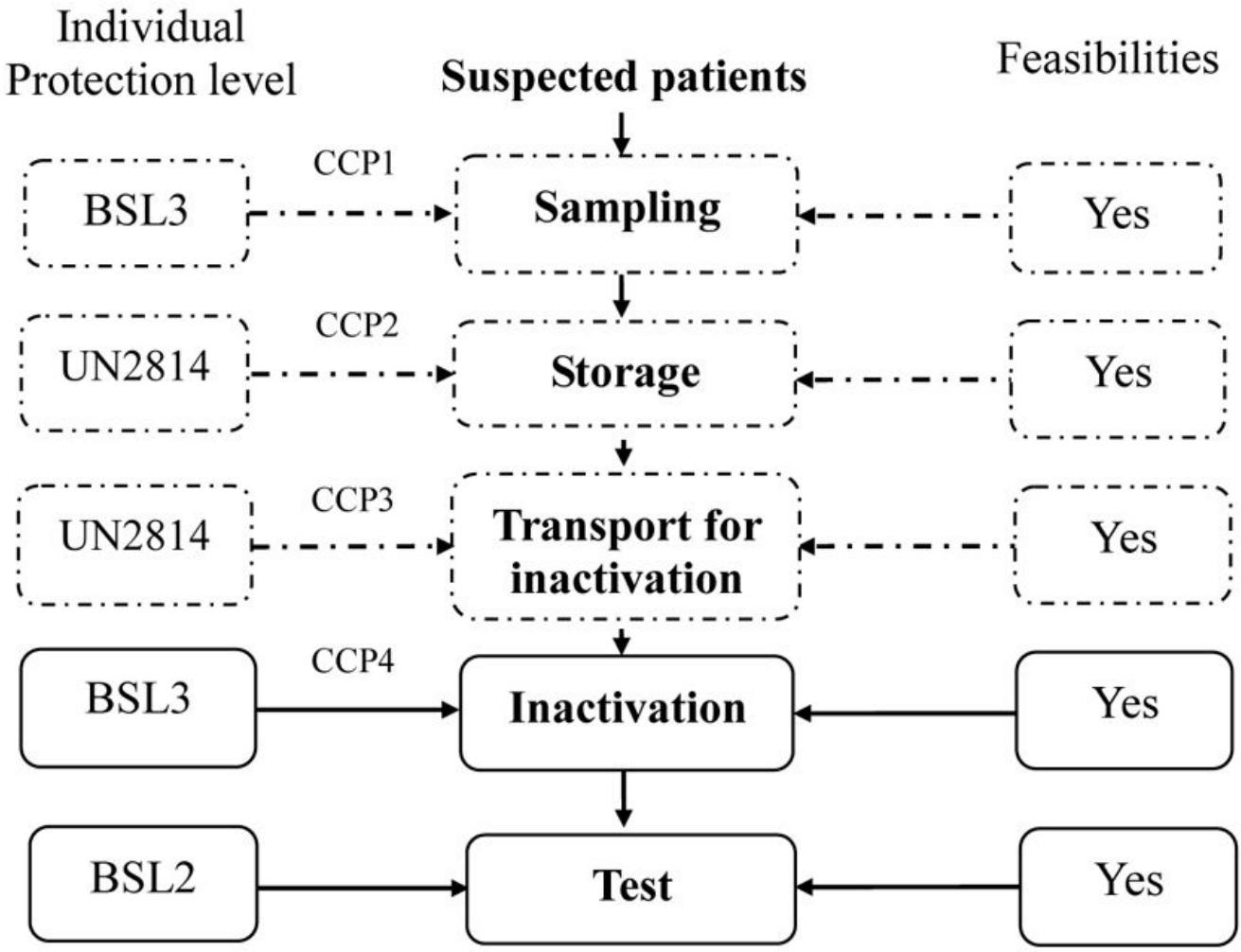

Figure 2

The flow chart about the COVID-19 susceptible samples for test. The dash line showed is the all the operation should be taken in fever clinic the red one could be taken in BSL2 platform.

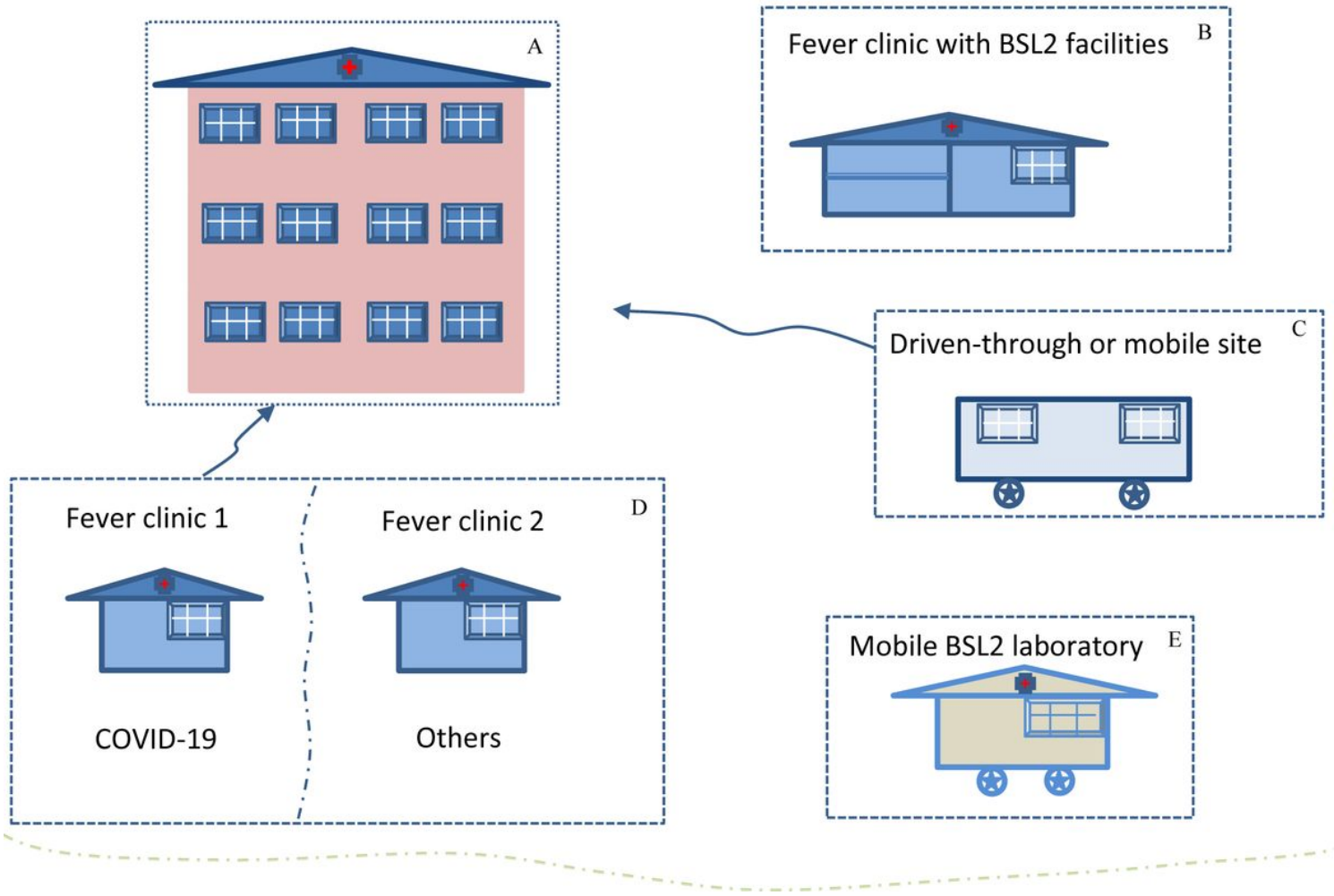

Figure 3

Different response modes of some countries to screen and/or test suspected COVID-19 cases. (A) represents the CDC or other authorized agencies for SARS-CoV-2 RNA testing; (B) represents the fever clinic with BSL2 facilities like that in the First hospital affiliated with Zhengzhou University; (C) represents the mobile platform or “Drive-through” test sites to enroll COVID-19 patients for RNA tests in USA and Korea; (D) represents the two fever clinics placed as in the Zhongshan hospital affiliated with Fudan University in Shanghai, one is for suspected COVID-19 patients, another is for patents with fever symptoms caused by other reasons; (E) represent the mobile BSL2 laboratory screening suspected COVID-19 cases both from sampling to test.