Detecting the COVID-19

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Abstract

The COVID-19 pandemic has created huge damage to society and brought panics around the world. Such panics can be ascribed to the seemingly deceptive features of the COVID-19: compared to other deadly viral outspreads, it has medium transmission and mortality rates. As a result, the severity of this virus was deeply underestimated by the society at the beginning of the outbreak. Based on this, in this review, we define the viruses with features similar to those of COVID-19 as the Panic Zone viruses. To contain those viruses, accurate and fast diagnosis followed by effective isolation and treatment of patients are pivotal at the early stage of virus breakouts. This is especially true when there is no cure or vaccine available for a transmissible disease, which is the case for current COVID-19 pandemic. As of April 2020, more than one hundred kits for the COVID-19 diagnosis on the market are surveyed in this review. It is of critical importance to rationally use these kits for the efficient management and control of the Panic Zone viruses. Therefore, we discuss guidelines to select diagnostic kits at different outbreak stages of the Panic Zone viruses, COVID-19 in particular. While it is of utmost importance to use detection kits with low false negativity at the early stage of an outbreak, the low false positivity gains its importance at later stages of the outbreak. Finally, since a massive attack from a viral pandemic requires a massive defense from the whole society, we urge both government and private sectors to research and develop affordable point-of-care (POC) detection kits, which can be used massively by the general public (and therefore called as massive POC) to contain Panic Zone viruses in future.

Keywords: *Diagnosis, Detection Kits, RT-PCR, Immunoassay, False Negative, False Positive, Sensitivity, Point-of-care (POC)*

1. Background

Since the beginning of the 21st century, our world has been facing unprecedented crises of deadly viruses like Zika, Ebola, SARS, MERS, and so forth. The epidemics of these viral diseases were sparked either by the evolution of pre-existing viruses or by the emergence of new viral species. Such diseases have already caused colossal damage to the society. Loss of lives struck the most, but the consequences aftermath were equally dreadful: the psychological wellbeing of survivors and socio-economic fallout were rather distressing. Now, in December 2019, the world was hit by yet another virus known as SARS-CoV-2 (or COVID-19).
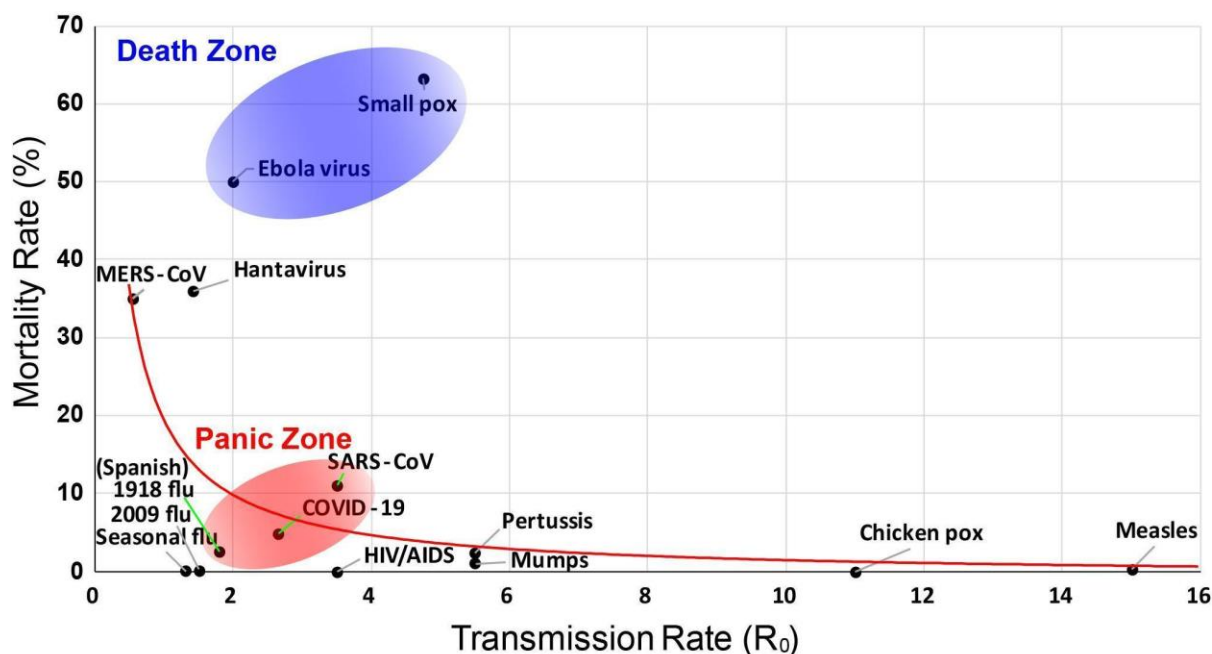
Figure 1. *Viruses with high transmission rates (R_0) are less fatal. R_0 is the reproduction rate of a virus, which measures its transmissibility[1]. Solid curve represents an inverse fitting between the mortality rate and the R_0, which has been proposed as the trade-off principle between the virulence and transmissibility of virus[2]. The inverse function fits well except for the two viruses in the Death Zone (blue), which is defined to have a rather high mortality rate. The Panic Zone contains viruses with medium levels of transmission and mortality rates. The data used here are taken from references[3–6].*

1.1. The Panic Zone viruses

Compared to other viruses, COVID-19 has a medium reproduction rate (R_0=2.65*) and a medium mortality rate of 5.7%*[7] (*subject to change). Such mediocre characteristics give a rather deceiving impression of this virus. When the virus first started in China, it did not draw immediate attention to the public due to its seemingly "benign" appearance. Indeed, compared to the Death Zone viruses which include Ebola and smallpox (Figure 1), this disease was considered merely as another type of influenza even among health professionals. However, the virus soon revealed its damaging nature. Staying untreated, the disease spread out quickly to overwhelm the health systems in a society. This eventually caused panics in the general public. People rushed to see doctors even if they developed very mild or even unrelated symptoms, which overran hospitals. This is because in modern society, the production system of healthcare

supplies is profit driven. Decisions regarding the management of disease can no longer be made based solely on scientific grounds. Unless a disease poses a specific risk to a wide population, its mere presence in a localized area or population may not be significant from a business perspective. As a result, necessary resources such as PPE (Personal Protective Equipment) are in short supply to fight pandemic diseases promptly. Due to these reasons, the diseases in the Panic Zone often wreck huge collateral damages due to its paralyzing role for the whole society.

In the Panic Zone, SARS was most recently contained by means of massive syndromic surveillance, prompt isolation of patients, and strict quarantine of all contacts. By interrupting all human-to-human transmissions, SARS was effectively eradicated in 2003[8]. Although there are striking similarities between SARS and COVID-19, the difference in the virus characteristics will ultimately determine whether the same measures for SARS will also be successful for the current COVID-19 outbreak. COVID-19 differs from the SARS in terms of infectious period, transmissibility, clinical severity, and extent of the community spread. Although COVID-19 has lower transmissibility than SARS[9], many more COVID-19 patients have mild symptoms that contribute to the rapid spread of the virus as these patients are often missed and not isolated.

1.2. The early detections

It is generally true that for a rapidly transmitting disease with no cure or vaccine available, the most effective way to curb its spread is to isolate patients. The first step to achieve this is to identify these patients using detection kits. Never before is a virus detection system so critical to contain a viral outbreak as dangerous as COVID-19. As shown in Figure 2, for the five countries with similar age distribution and hospital resources, the more extensive the early tests on the COVID-19, the lower the overall mortality rates in a country. Indeed, Korean and Germany did a substantial number of the tests right at the beginning of the COVID-19 outbreak. Correspondingly, their death rates are among the lowest so far (Figure 2, inset). This confirmed the importance of the early testing to curb the spreading of the COVID-19.

In this survey, we first describe the COVID-19 outbreak briefly. Given the importance of the diagnosis for this deadly pandemic disease, we then survey the detection kits used for the COVID-19. Next, we propose and discuss guidelines to use various kits during different stages of the COVID-19 outbreak. We then wrap up by extending these guidelines to potential outbreaks from other viruses in the Panic Zone. Finally, we propose the research and development of affordable point-of-care (POC) diagnosis kits that can be used massively (massive POC) to battle these viral pandemics in the future.
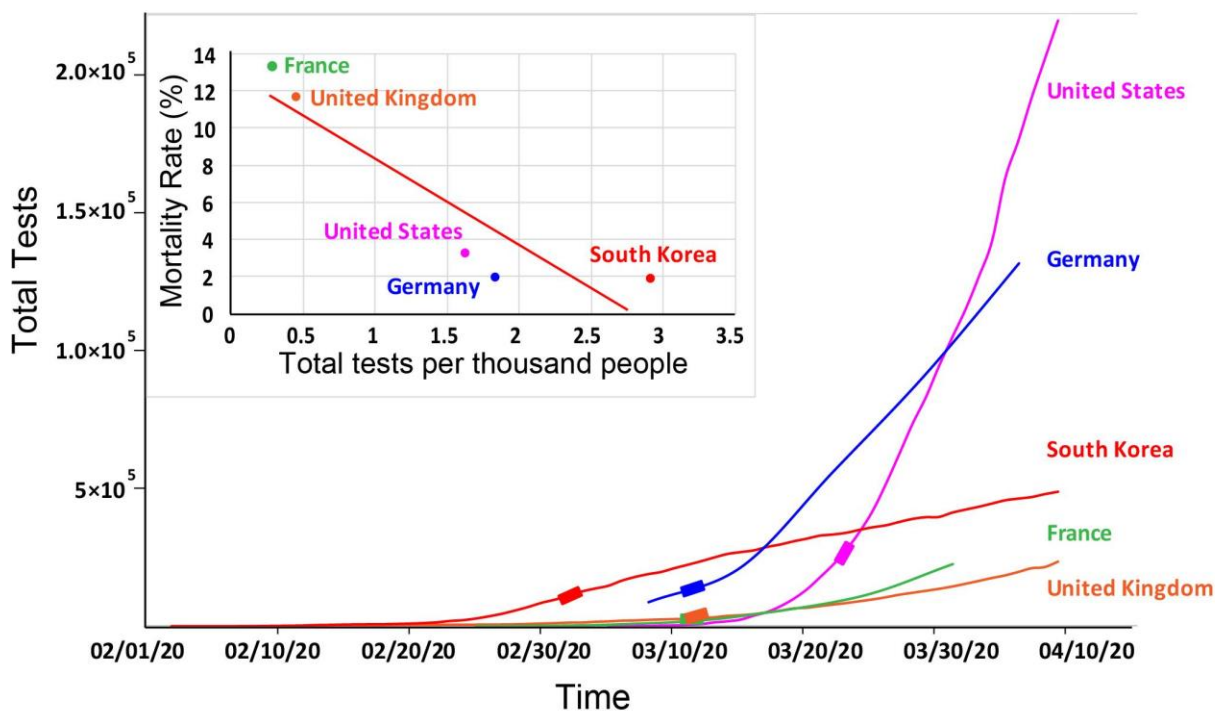
Figure 2. *Critical importance of the early detection in the COVID-19 outbreak. Total COVID-19 daily tests are shown for 5 countries with similar medical resources and age distributions. Inset shows the death rates as of 04/08/2020 vs the number of the early detections per thousand population performed during 03/04/2020 - 03/26/2020. The early detection data for each country[10] are taken from different periods (marked by stretches) to reflect the timing of the outbreak in Asian, Europe, and North America (~2 weeks apart). The inset data are linearly fit (r=-0.914), which indicates a decent negative correlation between the early detection and mortality rate.*

2. The COVID-19 outbreak

2.1. Covid-19 Timeline

In December 2019, a cluster of pneumonia cases were reported in Wuhan, China[11]. The causative agent of that disease was unknown until January 7, 2020, when the Chinese authorities confirmed that they have identified a new virus and named it 2019-nCoV (later called as COVID-19, CoronaVirus Disease 2019, by the WHO) since the virus shared ~80% genome from the SARS-CoronaVirus[12]. On January 11, the first death caused by this virus was reported in China. This disease was highly contagious. The WHO declared a Public Health Emergency of International Concern (PHEIC) within a month after the first case. On March 11, WHO declared COVID-19 as a pandemic disease.

2.2. Clinical characteristics of COVID-19

Based on current epidemiological researches, the clinical characteristics for this disease appeared in 1-14 days after the infection and most patients developed symptoms within 3-7 days[13]. The common symptoms include fever, coughing, and body weakness. A few patients developed nasal congestion, running nose, pharyngalgia, myodynia, and diarrhea. In severe

cases, by the end of the first week, the disease can develop into dyspnea and/or hypoxia. In deadly cases, the disease can quickly progress to acute respiratory distress syndrome, septic shock, coagulation disorders, and multiple organ failure[13]. It's noteworthy that patients with high viral loads may have low or insignificant fever during the infection. Some children and neonates did not have typical symptoms, but they presented with gastrointestinal symptoms such as vomiting and diarrhea or presented with depression or shortness of breath[14]. The elderly and patients with chronic underlying diseases had poor prognosis[15].

2.3. Epidemiology of COVID-19

People are generally susceptible to COVID-19 at all ages. The infection is transmitted by droplet (direct inhalation of droplets from the sneeze, cough, or talking of an infected person) or contact (contacting the virus deposited on the object surface, which then enters the body via the mouth, nose, eyes, or other mucous membrane[16]). Study showed a higher viral load in the nasal cavity than the throat, suggesting the nasal sampling is a more effective approach to detect the virus. There was no difference in the viral load between symptomatic and asymptomatic patients[17], the latter of which can also transmit the disease[18]. Guan et al. reported that some patients were tested positive for COVID-19 in stool and urine samples[13].

3. Diagnosis of the COVID-19 infection

As discussed in the Introduction, in the absence of effective therapeutic drugs or vaccines for COVID-19, it is essential to detect the disease at an early stage and immediately isolate infected patients. Currently, there are three methods in clinical practice to diagnose COVID-19, which are summarized below.

3.1. Chest CT Imaging

Studies showed that chest CT images contained characteristic features for COVID-19 patients. The hallmarks of these CT images include ground glass opacities, crazy-paving pattern, consolidative opacities, septal thickening, and the reverse-halo sign[19–22]. These features demonstrate a highly organized pattern of pneumonia[20]. Unlike these features, nodules, cystic changes, bronchiectasis, pleural diffusion, and lymphadenopathy are less common[22].

Despite such features, the Centers for Disease Control (CDC) in the US does not currently recommend CT to diagnose COVID-19. Laboratory testing of the virus remains the reference standard, even if the CT findings are suggestive of COVID-19 infections[23]. This is because features of the chest imaging from COVID-19 patients may overlap with other infections caused by influenza, H1N1, or SARS-CoV[24,25].

However, studies on the sensitivity of CT imaging over RT-PCR (which is considered as the reference standard for laboratory testing of COVID-19) showed that CT imaging is more sensitive and rather reliable in detecting COVID-19 infections. Fang et al. studied 51 patients with COVID-19 symptoms based on their clinical manifestations and epidemiological histories[26]. They found that the chest CT scan was more sensitive (98%) than the RT-PCR method (71%). This study was limited by the number of subjects involved. However, another study involving more than 1000 patients reached similar conclusions[27]. Among 1014 patients, 59% were RT-PCR positive, from which 97% showed positive CT features. In addition, 75% of RT-PCR negative patients showed positive CT features. To further validate this, Ai et al. studied multiple RT-PCR testing and serial CT imaging in a selected group. They found 60 - 93% people who

were RT-PCR negative showed initial positive CT images consistent with COVID-19 infections. From the patients in the recovery stage, 42% showed improvement in CT features before their RT-PCR results turned negative.

According to these diagnostic studies, RT-PCR assays were not as sensitive and reliable as CT images. The false negative results from RT-PCR assays can be detrimental to the control of the COVID-19, especially at the beginning of the outbreak. The caveat for the CT scans is that at an early stage of infection, the lungs of a patient may not develop damaging features that can be picked up by CT scans, increasing its false negative rate. In addition, the COVID-19 CT features share similarities with other viral pneumonia, resulting in false positive detections. Nevertheless, given the rapidly spreading of the COVID-19, the priority is to identify any suspicious case for isolation and proper treatment. In the context of emergency disease control, some false-positive cases may be acceptable. It is the false negative cases, due to the poor sensitivity of methods, that present a threat to public health at the beginning of an outbreak. In some cases, chest CT imaging showed positive COVID-19 infection while RT-PCR testing was negative[26]. A combination of clinical symptoms, epidemiologic history, and CT imaging of a patient is instrumental to identify COVID-19 infections at the time when chemical detection kits are in short supply.

3.2. Nucleic acid based methods

After identification of the COVID-19 virus for this pandemic outbreak, the COVID-19 genome was quickly sequenced[28], from which unique sequences have been identified for COVID-19 diagnosis. Reverse transcriptase-polymerase chain reaction (RT-PCR) is a nucleic acid amplification assay that has been used routinely for the detection of RNA viruses in clinical settings[29]. In RT-PCR, reverse transcriptase is first used to convert RNA to its complementary DNA, which is amplified by PCR (polymerase chain reaction). There are variants of RT-PCR method that share the same mechanism while differing in the detection strategy. For example, real time RT-PCR reads fluorescent signals in real time during PCR[30] to quantify the target, whereas nested RT-PCR uses two sets of primers to avoid non-specific PCR amplification[31].

The COVID-19 genes targeted for detection so far include the RdRP gene, Nucleocapsid (N) gene, E gene, Spike protein (S gene), and ORF1ab gene. Chu et al. used two different one-step real-time RT-PCR approaches to detect ORF1ab and N genes of the viral genome[32]. This assay showed a high dynamic range of 0.0002-20 $TCID_{50}$ (50% tissue culture infective dose) per reaction and the detection limit below 10 RNA copies per reaction. Later, WHO developed a technical guidance including the protocols from different countries to aid COVID-19 diagnosis[33]. In the US, CDC developed a real time RT-PCR diagnostic kit with detection limits as low as 4-10 RNA copies per μl. Scientists from Germany used the E gene for the first-line screening and the RdRP gene for confirmatory testing. This method further increased sensitivity to detect as low as 5.6 RNA copies per reaction for the E gene and 3.8 RNA copies per reaction for the RdRP gene. In Hongkong, the N gene was used as the first-line screening while the ORF1b as the confirmatory testing. In France, two RdRP genes were used for initial screening followed by the confirmatory E gene testing. In Japan, nested RT-PCR was used, which significantly reduced the non-specific target amplification, leading to decreased false-positive results. In general, the sensitivity of these assays ranges from 3.8 to 10 RNA copies per reaction, with high specificities.

High-throughput sequencing presents another confirmatory method to detect COVID-19. However, the application of high-throughput sequencing in clinical diagnosis is limited because of its equipment dependency and high cost. Zhang et al. demonstrated a point-of-care (POC) testing based on CRISPR-based SHERLOCK[34] to detect synthetic COVID-19 RNA fragments[35]. They utilized isothermal DNA amplification method and targeted the ORF1ab and S genes with a detection limit as low as 10 copies/µl.

In the public health emergency, highly sensitive methods are desirable. Although studies have shown that RT-PCR may be less sensitive than CT imaging, its specificity makes it superior to other methods to detect COVID-19 or other viruses. It is of critical importance to rationally choose specific diagnostic methods to battle outbreaks of viral diseases. Any negligence or compromise in the diagnosis may lead to devastating consequences. Wang et al. suggested combining RT-PCR with other methods as well as epidemiological history of patients to diagnose COVID-19 infection more credibly[36]. Indeed, the Chinese authority has adopted this approach to diagnose COVID-19 in Wuhan by combining RT-PCR with CT scans[27]. Studies also showed that the sensitivity of RT-PCR varies with the specimen types. To et al. revealed that the saliva samples were more promising to be used in RT-PCR[37] while Yam et al. concluded that testing more than one specimen could significantly maximize the sensitivity of the RT-PCR testing[38]. These findings suggest it is rather important to apply nucleic acid based kits with optimized conditions to maximize their diagnosis potency.

Table 1 lists the nucleic acid based kits used for the diagnosis of COVID-19. The sensitivity of those kits ranges from 100-1000 copies/mL.

3.3. Immunoassays

Immunoassay is another established method to diagnose diseases. This method detects serum antibodies generated in patients who have been exposed to the COVID-19. These antibody tests are important in detecting infections with few or no symptoms.

In the COVID-19 infection, studies have shown that the seroconversion in the patient-generally starts after a week of the first symptom[39]. In a study of post symptomatic patients, Amanat et al. detected high IgA and IgM immune responses[40]. Using recombinant viral proteins, this immunoassay could detect antibodies as early as 3 days after the development of the first symptom. Liu et al. reported that the accuracy of the ELISA for IgG and IgM antibodies was more than 80%[41]. The efficacy of the immunoassay also depends on the specificity of the antigens used to capture the antibodies from the patients. Between the spike (S) proteins and nucleocapsid (N) proteins, the sensitivity of the S proteins is higher for the antibody capture. Among various spike proteins, the S1 protein has shown more capabilities to bind to COVID-19 antibodies[42]. In a comparative study, both ELISA and colloidal gold immunochromatographic kits showed equal sensitivity with 100% specificity for the COVID-19 detection[43].

Several immunoassay kits are already on market for emergency detection of COVID-19 specific antibodies **(see Table 2)**. However, the major problem of this method is that it only works for post-symptomatic patients who must have an immune response to the COVID-19. At this stage, some patients may already be critically ill. Nevertheless, immunoassays are faster[44] and cheaper than the RT-PCR methods. They can be used for rapid screening of the COVID-19 infection. It also has a unique advantage of identifying individuals who have strong immune responses against the virus and therefore, can serve as potential donors for therapeutic and research purposes.

4. Ideal characteristics of diagnostic methods

Diagnostic testing has become indispensable for diagnosis, prognoses, and monitoring the progress of different diseases. Efficient diagnostic testing is an important intervention for outbreak management and control. WHO has developed the ASSURED criteria as a benchmark to decide if a test efficiently addresses the needs for disease control: **A**ffordable, **S**ensitive, **S**pecific, **U**ser-friendly, **R**apid and robust, **E**quipment-free and **D**eliverable to end-users[45]. It's ideal to have all the criteria fulfilled in a single test. In practice, however, testing methods can rarely fit all the ASSURED criteria. In pandemic outbreaks for example, rapid and sensitive methods are dearly needed at the beginning of the outbreak. But many kits available require qualified laboratories and personnel for testing. In such a case, accommodation of the ASSURED principles must be taken to facilitate the testing.

In a pandemic outbreak, it is always important to understand the nature of the pathogen before developing efficient diagnostic tests. Translating the tests into the point-of-care (POC)[46] mode can help decision-making and improve the efficiency of the treatment. POC provides rapid and actionable information for patient management and care at the time when it is most needed. Many affordable POC kits such as lateral flow immunoassays[47] are also appropriate for resource-limited settings in middle- or low-income countries where laboratory infrastructure is weak. One example for affordable POC testing is the pregnancy strip test[48] in which pregnancy can be quickly determined at home using paper strips on specimens such as noninvasive urine samples. Due to the requirements of easy usage and cheap price, they often use colloidal gold based immunoassay mechanisms. Such POC testing kits perhaps represent the best solution to fight fast transmitting pandemics.

5. Rationales in choosing diagnostic methods in the COVID-19 outbreak

As stated in the introduction, diagnosis becomes one of the most important approaches to curb a virus outbreak such as COVID-19, which does not have a cure or vaccine. As shown in Figure 3, intervention such as identification of patients for isolation at the early stage before the inflection point of the viral spreading will significantly slow down the transmission of the virus. It will not only delay the time at which the peak occurs, but also reduce the magnitude of the peak population. While decreased peak magnitude directly reduces the burden on hospitals, the delay of the peak gives more time for the public to prepare well for the peak-time challenge. Both are expected to decrease the mortality rate. Such an early intervention heavily relies on the quality and quantity of the detection kits for specific viruses. Since the outbreak of the COVID-19, many diagnostic kits have been developed in different countries (**see Tables 1-3**). With the increase in the number of diagnostic tests, it is difficult for policymakers, laboratories, and other end-users to obtain rational decisions about the selection and use of these tests. As a result, tests have been used unnecessarily and incorrectly, with results misinterpreted. Here, based on the epidemiology of the COVID-19 and the available diagnostic kits on the market, we suggest some guidelines to rationally select kits for efficient disease control and suppression.
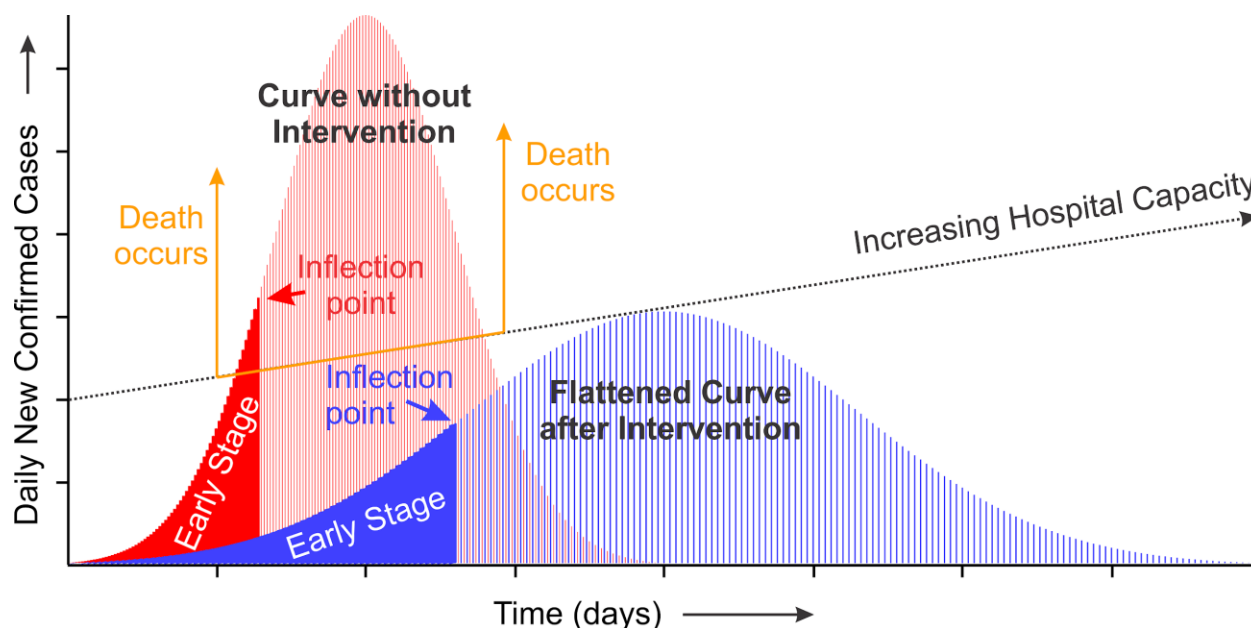
Figure 3. *Intervention of the COVID-19 outbreak. The intervention at an early stage (before the inflection point, which is the point where the half width of a Gaussian peak is equivalent to the sigma of the Gaussian) of a virus breakout is the key to slow down the transmission of the virus. It not only decreases the peak value of newly confirmed daily cases, but also saves the time to increase the hospital capacity, each of which reduces the overall mortality rate.*

Among all current methods, nucleic acid based kits are considered the most reliable because of their high specificity and accuracy. This is not surprising since these methods target unique sequences in the viral genome for identification. Due to these advantages, it becomes a detection of choice at the beginning of a virus outbreak. At this stage, it is critical to identify and isolate all possible patients before the virus enters an exponential growth stage (around the inflection point, see Figure 3). Therefore, it is important to reduce the false negative results of the diagnosis. To achieve this, high sensitivity is a necessity. The PCR amplification used in various RT-PCR kits can detect as low as 100 copies/mL reaction (**see Table 1**), which is equivalent to 0.167 attoMolar (for a reaction volume of 100 microliters). It is noteworthy that high sensitivity is accompanied with increased false positive results. But at the beginning of a virus outbreak, some false positive level may be tolerated. Since there are not so many infected patients at the initial stage of the outbreak, the chance of cross contamination from COVID-19 patients to these false positive cases is small, even if they are isolated together (but well protected by PPE) in spacious locations such as convention centers. When the viral outbreak becomes stronger, false positive cases should be reduced as much as possible due to the increasing cross contamination concerns.

Due to the extensive amplifications, isothermal amplification-based methods (**see Table 1**) usually have superior sensitivities albeit with increased false positive levels. Therefore, at the beginning of an outbreak, isothermal amplification may be used first. However, this method usually involves many testing steps, therefore, it is more complex to run. Due to the same reason, its development and approval also take time, which makes the technique difficult to be adopted at the beginning of an outbreak. With easy performance and fast approval, PCR based kits still remain the gold standard at the beginning of a viral outbreak.

Another way to reduce the false negativity in nucleic acid based testing is to perform CT scans. As discussed in Section 3.1, it can be more sensitive to diagnose COVID-19 using CT scans. The caveat for the CT scan is its relatively low specificity (false positive results), which may be tolerated at the initial stage of an outbreak. However, positive CT scans only show for patients at the later stage of their COVID-19 infections, which limits its use for early stage screening. The method is still valuable to quickly screen serious cases from mild ones. Due to limited testing kits and over-burdened clinical resources, many patients with mild symptoms have been self-isolated first. When their conditions deteriorate, it becomes important to streamline life-threatening cases as soon as the patients are sent to the hospital. Due to the fast performance and interpretation of CT scans within tens of minutes as demonstrated in China for example, these patients can be quickly identified, followed by appropriate treatment to save lives.

Immunoassays work well only after the human body develops antibodies to fight viruses. Therefore, these kits are not appropriate to detect infection cases at the early stage of an infection at which patients may be asymptomatic. Given that asymptomatic patients also transmit COVID-19[18], it is not recommended to use immunoassays at the beginning of the pandemic. In the current COVID-19 breakout, we have often seen that during the exponential increase stage of the disease (around the inflection point, **see Figure 3**), there have been insufficient number of nucleic acid based kits to test all suspicious cases. Current strategy to solve this issue is rather impassive. The precious testing kits are reserved only for more serious cases. For the patients with light symptoms, they were sent home for self-isolation. The immunoassay can be used to test those patients after their symptoms lasted about one week. Since these tests are cheaper, faster, and easier to perform[47] with respect to nucleic acid based methods, they can be quickly and massively conducted by staff at drive-through stations.

In the future, the high-throughput, microarray-based testing may be able to address the bottleneck diagnosis problem caused by shortage of testing kits. In such a method, thousands of tests can be run simultaneously on a chip[49]. For this method, the time limiting step becomes the sample collection, which must be performed one-at-a-time. The other direction to resolve the bottleneck testing problem is to develop affordable POC kits as discussed in section 4. These kits can be performed at home for self-isolated people with mild symptoms. If they are tested positively by the POC kits, their conditions will be closely monitored for further medical treatments or other interventions. The inherent properties of these POC kits (cheap, fast, and easy-to-use) afford their massive usage by the general public to fight with pandemic outbreaks. We therefore name such an approach as massive POC strategy. Given there is no such massive POC product on the market for the COVID-19 yet, research and development on the affordable POC kits are dearly needed at this stage for virus detections.

6. Conclusions and Perspectives

In summary, like other viruses in the Panic Zone, the COVID-19 has caused unexpected damage to society. During the outbreak of the COVID-19, most studies have focused on the potential causes and epidemiology of the virus while the information on the epidemic prevention is obscure. From the data we have collected so far, it is imperative to carry out the diagnosis to isolate and treat patients at the early epidemic stage of the viruses in the Panic Zone. This is especially important for the virus without a cure or vaccine. The burden of accurate and rapid diagnosis falls on the detection kits used for the COVID-19, which include nucleic acid based methods and immunoassays. Given the epidemiology of the COVID-19 and the features of

available detection kits, it is crucial to reduce false negative results at the expense of some false positive level during the early stage of the outbreak. It becomes important to reduce the false positivity in later stages of the outbreak. Although nucleic acid based detection kits, RT-PCR in particular, offer best solutions so far to these requirements because of their high sensitivity and specificity, immunoassays can well supplement the detection armory due to their cheaper price, simpler operation, and faster detection time. The use of immunoassays is especially useful at the later stages of the virus outbreak when patients already develop symptoms for a while or when nucleic acid based testing kits are unavailable or not enough due to mass inflow of patients to hospitals for example. We believe a massive attack from a Panic Zone viral outbreak requires a massive defense from the whole society. The best approach to deal with this massive attack is the development of cheap, fast, and easy-to-use point-of-care (POC) detection kits that can be used in a massive fashion by the general public. We therefore call such kits as massive POC kits. In the future, intensive research and development on the massive POC testing kits for Panic Zone viruses therefore should be encouraged both by government and by private sectors.

Table 1: Kits based on nucleic acid detection

Authorization	Manufacturer	Mechanism	Target	LOD	Time
4/7/2020*	InBios International, Inc	RT-PCR	E, N, ORF1ab	12.5 GE/rxn	-
-	1drop Inc	RT-PCR	RdRP, E	8 cp/rxn	~2 h
^λ	3B BlackBio Biotech India Ltd	RT-PCR	RdRP, E, N	-	-
4/6/2020*	Gnomegen LLC	RT-PCR	N (N1, N2)	8 GE/rxn	-
4/3/2020*	Co-Diagnostics, Inc	RT-PCR	RdRP	600 cp/spl	-
4/3/3030*	ScienCell Research Laboratories	RT-PCR	N (N1, N2)	500 cp/uL	-
4/3/2020*	Luminex Corporation	RT-PCR	ORF1ab, N	75 GE/uL	-
4/2/2020*	Becton, Dickinson and Company	RT-PCR	N (N1, N2)	40 GE/mL	-
4/1/2020*	Ipsum Diagnostics, LLC	RT-PCR	N, RP	8.5 cp/µL	-
3/30/2020*	QIAGEN GmbH	RT-PCR	-	500 cp/mL	-
3/30/2020*	NeuMoDx Molecular, Inc	RT-PCR	Nsp2, N	150 cp/mL	-
3/27/2020*	Abbott Diagnostics Scarborough, Inc.	Isothermal amplification	RdRP	125 GE/mL	5-13 min
03/2020$	Rendu Biotechnology	Isothermal amplification	-	-	-
***	Promedical	Lateral Flow Immunoassay	-	-	-
03/2020#	Vision Medicals	PCR (Clinical Sequencing Assay)	-	-	-
3/13/2020*	Thermo Fisher Scientific, Inc.	real time RT-PCR	S, N	10 GE/rxn	4 h
2/29/2020*	Wadsworth Center, New York State Department of Public Health's (CDC)	real time RT-PCR	RP	25 cp/rxn	-
03/2020#	3D Medicines	RT-PCR	-	-	-
€	A*Star Tan Tock Seng Hospital of Singapore	RT-PCR	-	-	-
3/18/2020*	Abbott Molecular	RT-PCR	RdRP, N	100-200 cp/mL	-
02/2020#	Anatolia Geneworks	RT-PCR	-	-	-
**	ARUP Laboratories	RT-PCR	-	-	-
03/2020#	AUSDiagnostics	RT-PCR	-	-	-
3/25/2020*	Avellino Lab USA, Inc.	RT-PCR	Rnase P (RP)	55 cp/µL	1-2 days
-	Beijing Applied	RT-PCR	ORF1ab, N, E	1000 cp/mL	90 min
3/26/2020*, 3/2/2020#, 1/2020$	BGI Genomics Co. Ltd.	RT-PCR	ORF1ab	100 cp/mL	-
-	BGI Wuhan Biotech Co., Ltd	RT-PCR	ORF1ab	100 cp/mL	90 min
3/23/2020*	BioFire Defense, LLC	RT-PCR	ORF1ab, ORF8	330 cp/mL	50 min
-	Bioneer	RT-PCR	-	-	-
**	BioReference Laboratories	RT-PCR	-	-	-
2/4/2020*	Centers for Disease Control and Prevention's (CDC)	RT-PCR	N1, N2. RP	4-10 cp/µL	-
3/20/2020*	Cepheid	RT-PCR	N2, E	250 cp/mL	45 min
03/2020	CerTest BioTec	RT-PCR	-	-	-
02/2020****, #	Co-Diagnostics	RT-PCR	-	-	-
03/2020#	Credo Diagnostics Biomedical	RT-PCR	-	-	-
-	Daan Gene Co., Ltd., Sun Yat-sen University	RT-PCR	ORF1ab, N	500 cp/mL	110 min
03/2020****, #	DiaCarta	RT-PCR	-	-	-

Authorization	Manufacturer	Mechanism	Target	LOD	Time
****	Diagnostic Solutions Laboratory	RT-PCR	-	-	-
3/19/2020*	DiaSorin Molecular LLC	RT-PCR	ORF1ab, S	500 cp/mL	1-1.5 h
-	Diatherix Eurofins	RT-PCR	-	-	-
03/2020#	Genetic Signatures	RT-PCR	-	-	-
03/2020#	Genomica/PharmMar Group	RT-PCR	-	-	-
3/16/2020*	Hologic, Inc.	RT-PCR	-	10^{-2} TCID50/mL	-
*	Integrated DNA technologies/Danaher	RT-PCR	-	-	-
€	JN Medsys	RT-PCR	-	-	-
#, Ψ	Kogene Biotech	RT-PCR	-	-	-
3/16/2020*	Laboratory Corporation of America (LabCorp)	RT-PCR	Rnase P (RP), N	6.25 cp/µL	-
*	LGC, Biosearch Technologies	RT-PCR	-	-	-
3/27/2020*	Luminex Molecular Diagnostics, Inc.	RT-PCR	ORF1ab, N gene, E	1.5 cp/µL	4 h
-	Maccura Bio-tech Co.,	RT-PCR	ORF1ab, N, E	-	2 h
3/30/2020*	NeuMoDx Molecular	RT-PCR	-	-	-
3/20/2020*, 2/2020#, 3/26/2020ʎ	Novacyt/Primerdesign	RT-PCR	-	-	-
02/2020#	OsangHealthCare	RT-PCR	-	-	-
3/24/2020*	PerkinElmer, Inc.	RT-PCR	ORF1ab, N	20 cp/mL	-
3/20/2020*	Primerdesign Ltd.	RT-PCR	-	0.33 cp/µL	-
3/17/2020*	Quest Diagnostics Infectious Disease, Inc.	RT-PCR	N1 and N3	136 cp/mL	-
3/23/2020*, 3/2020#	Quidel Corporation	RT-PCR	pp1ab	0.8 cp/µL	75 min
3/12/2020*	Roche Molecular Systems, Inc.	RT-PCR	E	-	3 hrs
-	SANSURE Bio-tech Co., Ltd	RT-PCR	ORF1ab, N	200 cp/mL	90 min
02/2020#, $$	See Gene	RT-PCR	-	-	-
-	Shanghai Bio Germ	RT-PCR	ORF1ab, N	1000 cp/mL	90 min
-	Shanghai GeneoDx Biotech Co., Ltd	RT-PCR	ORF1ab, N	500 cp/mL	90 min
-	Shanghai ZJ Bio-tech Co., Ltd.	RT-PCR	ORF1ab, N, E	1000 cp/mL	90 min
2/2020#, $$, $$$	SolGent	RT-PCR	-	-	-
03/2020#	Systaaq Diagnostic Products	RT-PCR	-	-	-
03/2020#	TIB MolBiol Synthesalabor	RT-PCR	E	-	-
-	Ustar	RT-PCR	ORF1ab, N	-	90 min
-	Wuhan Easydiagnosis	RT-PCR	ORF1ab, N	-	75 min
3/23/2020*	Mesa Biotech Inc.	RT-PCR and colorimetry	N	100 cp/rxn	30 min
3/19/2020*	GenMark Diagnostics, Inc.	RT-PCR, electrowetting and sensing	-	10^5 cp/mL	2 h
**	Fulgent Genetics/MedScan laboratory	Sequencing	-	-	-

Table 2: Kits based on immunoassay

Authorization	Manufacturer	Mechanism	Target	LOD	Time
***	Beijing O&D Biotech	Colloidal gold	-	-	-
***	Jiangsu Macro & Micro-Test Med-Tech	Colloidal gold	IgG IgM	-	-

***	Nantong Diagnos Biotechnology	Colloidal gold	-	-	-
***	Zuhai Livzon Diagnostics	Colloidal gold	IgG IgM	-	15 min
***	Assure Tech	Immunoassay	IgG IgM	-	-
***	Autobio Diagnostics	Immunoassay	-	-	-
***	Beijing Decombio Biotechnology	Immunoassay	IgG IgM	-	-
***	Beijing Diagreat Biotechnologies	Immunoassay	IgG IgM	-	-
***	Beijing Kewei Clinical Diagnostic Reagent	Immunoassay	IgG IgM	-	-
***	Beroni Group	Immunoassay	IgG IgM	-	-
***	BioMedomics	Immunoassay	IgG IgM	-	-
-	BiOSCiENCE	Immunoassay	IgM IgG	-	30 min
***	BTNX	Immunoassay	IgG IgM	-	-
4/1/2020*	Cellex	Immunoassay	IgG IgM	-	-
***	ChemBio Diagnostic System	Immunoassay	IgG IgM	-	-
***	Core Technology	Immunoassay	IgG IgM	-	-
***	Diazyme Laboratories	Immunoassay	IgG IgM	-	-
***	Eachy Biopharmaceuticals	Immunoassay	IgG IgM	-	-
-	Eagle Bioscience	Immunoassay	IgG, IgM	-	-
-	Guangdong Hecin	Immunoassay	IgM	-	-
***	Guangzhou Wondfo	Immunoassay	-	-	15 min
***	Hangzhou AllTest Biotech	Immunoassay	IgG IgM	-	-
***	Hangzhou Biotest Biotech	Immunoassay	IgG IgM	-	-
***	Hangzhou Clongene Biotech	Immunoassay	IgG IgM	-	-
***	Hangzhou Testsealabs Biotechnology	Immunoassay	IgG IgM	-	-
***	Healgen Scientific	Immunoassay	IgG IgM	-	-
-	INNOVITA (Tangshan)	Immunoassay	IgG IgM	-	15 min
***	Lifeassay Diagnostics	Immunoassay	IgG IgM	-	-
***	Medical Systems Biotechnology	Immunoassay	IgG IgM	-	-
***	Nanjing Liming Bio-Products	Immunoassay	IgG IgM	-	-
-	Nanjing Vazyme	Immunoassay	IgM, IgG	-	10 min
***	NanoResearch	Immunoassay	IgG IgM	-	-
***	Nirmidas Biotech	Immunoassay	IgG IgM	-	-
***	PCL	Immunoassay	IgG IgM	-	-
***	PharmaTech	Immunoassay	IgG IgM	-	-
***	SD Biosensor	Immunoassay	IgG IgM	-	-
***	Shenzhen Landwind Medical	Immunoassay	IgG IgM	-	-
02/2020#	Snibe Diagnostics	Immunoassay	IgG IgM	-	-
***	Telepoint Medical Services	Immunoassay	IgG IgM	-	-
***	Tianjin Beroni Biotechnology	Immunoassay	IgG IgM	-	-
-	Xiamen innoDx Bio-tech	Immunoassay	IgG IgM	-	-

Table 3: Kits based on 'not identified' mechanism

Authorization	Manufacturer	Mechanism	Target	LOD	Time

-	Biological Technologies Co., LTD	-	-	-	-
-	(Chongqing) Bio-tech, Co., Ltd	-	-	-	-
-	Health Technology Co., Ltd	-	-	-	-
-	Bio-tech Co., Ltd	-	-	-	-
-	Medical Technology Co., Ltd	-	-	-	-
-	Biotechnologies (Hangzhou) Ltd	-	-	-	-
-	Biomedicine Co., Ltd.	-	-	-	-

*US EUA Authorized, **US EUA Planne,***US Notified FDA under section IV.D, ****US EUA Submitted, #European Union Conformity Marked, $The National Medical Product Administration Authorized China, $$Korea Ministry of Food and Drug Safety, $$$Philippines Food and Drug Administration, €Singapore Health Sciences Authority, personal authorization for clinical use, ΛEUA India, ΨKorea Centers for Disease Control and the Korea Food and Drug Administration

-Data Not Available

References for kits in table 1-3: https://www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-use-authorizations#coronavirus2019;
http://ph.china-embassy.org/eng/sgdt/t1760281.htm;
https://www.modernhealthcare.com/safety/coronavirus-test-tracker-commercially-available-covid-19-diagnostic-tests;
https://www.finddx.org/covid-19/pipeline/;

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