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COVID-19 isolation strategies: What have we learned

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A B S T R A C T

Since the start of the COVID-19 pandemic, infection prevention and control policies have significantly differed between different public health organization and have been complicated by the emergence of new data on Variants of Concern (VOC). Here, we try to highlight the different strategies for isolating patients with COVID-19 and point-out the evolution of such strategies over time, mainly for mildly or moderately severe SARS-CoV-2 infected patients.

Since the emergence of the Coronavirus disease 2019 (COVID-19) pandemic in December 2019, the healthcare systems across the globe had the challenge of maintaining the provision of basic healthcare, while coping with the unexpected surge of sick COVID-19 patients. Some of the healthcare systems has been overwhelmed with major negative impact of COVID-19 patients care and inability to maintain the basic health care necessity [1–4] as well as impact on the healthcare workers themselves [5]. One of the key issues has been to minimize the impact of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) on the healthcare work forces through minimizing nosocomial and community transmission. Since the beginning of the pandemic the infection prevention and control policies/guidance as it relates to managing HCWs and isolating suspected and infected patients with COVID-19 has significantly differed between different public health organization and has been complicated by the rapid changes related to the emergence of new data on Variants of Concern (VOC) with higher transmission abilities. Here, we try to highlight the different strategies for isolating patients with COVID-19 and point-out the evolution of such strategies over time, mainly for mildly or moderately severe SARS-CoV-2 infected patients.

1. PCR-based strategy

PCR-based strategy was used early on at the time of the disease emergence and patients were kept in isolation till they have repeated negative SARS-CoV-2 PCR results. The World Health Organization (WHO) recommended to have clinical recovery with negative SARS-CoV-2 RT-PCR results on two consecutive samples taken at least 24 h apart [6]. The recommendations were based on previous experience with the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) [6]. Subsequent studies had examined the dynamics of SARS-CoV-2 detection by PCR. The mean and median duration of positive PCR in patients with SARS-CoV-2 were 28.9 and 31 days, respectively [7] with no positive viral cultures. In a large study of 3497 samples of respiratory, stool, serum, and urine origin showed the median duration of positive PCR in stool, respiratory, and serum samples of 22 days (IQR: 17–31, 18 (IQR 13–29) and 16 (IQR: 11–21) days, respectively [8]. Respiratory samples of those with severe disease and mild disease showed positivity for 21 (IQR: 14–30) and 14 (IQR: 10–21) days, respectively [8]. Another study of 414 throat swabs, viral loads slowly decreased to the lower limits of detection at 21 days post symptoms with no difference based on disease severity [9]. Thus, patients with severe disease had longer duration of positivity duration compared to moderate and mild disease. However, the duration of positive PCR was highly variable. One study showed no difference in time to culture conversion by variants or vaccination status [10]. In vaccinated patients, Omicron variant was associated with a mean duration of positive rt-PCR of 9.87 days compared to 10.9 days for Delta infections and had a shorter clearance of 5.35 days vs. 6.23 days, for the Omicron and delta variants, respectively [11]. PCR-based strategy has shown that positive PCR tests may last for a longtime despite recovery as well as evidence of non-infectiousness of the patient. Thus, the sole dependence on PCR as a strategy for discontinuation of isolation precautions especially for the majority of the patient is not recommended and would result in increased cost and unnecessary isolation days. It is important to note however that many countries did not have sufficient capacity so moved

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to a symptom-based strategy for patients' isolation.

2. Time-based strategy

Other studies relied on advanced viral cultures to evaluate the infectiousness of patients with persistent positive PCR. In the case of mild to moderate disease, SARS-CoV-2 was not routinely isolated in cultures after 10–12 days from the time of the onset of symptoms. These studies showed that the positive SARS-CoV-2 PCR does not correlate with viral replication. In one study of mostly mildly symptomatic patients, among 130 positive cultures the positivity rate was 74% in the first week compared to 20% in the second weeks ($p = 0.002$) [12]. In addition, the positivity rate was 6% (95% CI: 0.9–31.2%) at day 10 of symptoms and zero after day 12 [12]. In another small study of 26 samples with positive cultures, there was no growth after 8 days of onset of symptoms and there was a reduction in the odd ratio of positivity of 37% reduction with each day post symptoms [13]. In much smaller study of nine patients, SARS-CoV-2 PCR was positive for 28 days post development of symptoms and no positive viral cultures after 8 days [14,15]. One study compared Delta and Omicron variants and found that the time to culture negativity was a median of 6 days (interquartile 50 range of 4–8 days) [16]. In symptomatic patients, viral culture was positive in 7 (77.8%) of those with RT-PCR positive and RDT negative vs. 165 (88.2%) of those who had both RT-PCR and RDT positive tests [17]. Thus, it was recommended to have 10 days of isolation for mildly symptomatic patients. This period had recently changed to five days by certain organization such as the US CDC with the recent emergence and widespread of Omicron [18]. In a small study of infected vaccinated patients who had Omicron, culture was positive in 17% beyond day 5 from symptom onset and the last day of positivity was day 12 [19].

3. Symptom-based strategy

Symptom-based strategy had utilized both time-based in combination with resolution of symptoms. So far, the WHO recommends 10 days of isolation after symptom onset with the addition of at least three days without symptoms (without fever and/or without respiratory symptoms) and of 10 days for asymptomatic patients [20] and similar guidelines were used by the US CDC [21]. Recently, the US CDC had shortened the duration of the isolation of COVID-19 cases who are asymptomatic or without fever for 24 h to five days followed by five days of wearing a mask when around others [22]. One study showed that PCR based strategy caused an extra 166 days of hospitalization and additional cost of $415,000 [23]. However, a mathematical model had suggested that not shorten the outbreak duration but decrease the number of infected individuals [24]. In addition, the implementation of isolation for one day post-fever decreased secondary attack rate from 79% to 71% with possible benefit from isolation for six days [24].

4. Antigen-based strategy

Since the emergence of COVID-19 in late December 2020 more than 400 rapid diagnostic testing (RDT) have been made available commercially and are based on antigen detection [25]. As of December 2021, only 28 RDTs have been granted authorization under the EUA by the US FDA, while the EU have registered more the 140 RDT kits for use. For these kits to receive US FDA or WHO EUA they must have 80% sensitivity and 97–98% specificity compared to PCR testing [26,27]. They are widely available over the counter and are used extensively by patients. Most available RDT based on lateral flow immunoassays and detects SARS-CoV-2 Nucleocapsid (N) protein [28,29].

Current strategies for RDT use for COVID-19 include symptomatic cases, asymptomatic high-risk contacts and finally for asymptomatic individual who plans to be in a high risk gathering like travel or attending a sport game in the stadium [30]. All antigen based RDT are approved for use in symptomatic individuals while some are approved for asymptomatic individuals with the majority requiring testing twice over a 3 days period. Such antigen-based testing had been used in rural areas with fast turn-around time with reduction in the cases of COVID-19 cases [31] and this depends on the antigen-test being used and its validity compared with the PCR test as other antigen tests did not show high sensitivity [32]. In one recent study of the use of antigen-based strategy among 480 HCWs with mild disease, 173 (36%) had positive rapid antigen test for SARS-CoV-2. However, the utility of rapid antigen in other patients with severe disease was not tested [33]. The emergence of SARS-CoV-2 variants may have an impact on viral dynamics. In a small study of 14 vaccinated Omicron infected patients, the use of RDT was associated with 100% sensitivity and 86% specificity on day 4–6 from diagnosis compared to SARS-CoV-2 culture and a negative predictive value of 100% and positive predictive value of 50% [19].

Interpreting RDT result is dependent on the scenario of testing. A positive result in a high probability symptomatic person or high-risk contact indicates a confirmed test. But false negative rates are high and negative test should be repeated within 3 days to confirm negativity. One study showed that few negative RDT was associated with low RNA level but with a positive viral culture [34]. An additional study showed that such discordant samples showed viral replication in cultures in 10.53% of samples compared to 56.52% of true positive samples [35]. A study showed that antigen-based RDTs detected 100% of infection in 15 cell culture-positive samples ($n = 15$) and were 66.7% effective in distinguishing viable samples from those with subgenomic RNA. In addition, discordant samples with positive RT-PCR but negative RDT were actually culture negative [36]. Based on the sample, it was found that nasopharyngeal swabs were more sensitive than nasal swabs using RDT with 100% and 98.7% sensitivity, respectively [37]. The sensitivity of the RDT is also dependent on the manufacturer of the test [38]. It is interesting to note that the performance of RDT was not different between the Delta and Omicron variants [39].

5. What about critical patients and immunocompromised patients?

It is recommended that those patients get isolated for a period of 10–20 days. Prolonged viral cultures were documented in case reports after 10 days of symptom onset [40] and another study showed positive cultures up to days 43 and 95 [41,42] and for 7 weeks in a patient with agammaglobulinemia [43]. In another case series of 13 immunocompromised patients, 3 (23%) had positive viral cultures on days 7, 11 or 16 [44]. Based on these small studies, there is a need to have larger studies of immunocompromised patients to assess the best time for de-isolation and the use of a test-based, symptom-based approach, or a combination for the de-isolation of immunocompromised patients [44].

It is important to point that viral culture is the gold standard to ascertain that detected viruses are or are not replicating [45]. However, these are not routinely done in clinical practice thus limiting the utility of this strategy for routine clinical use. In addition, virus culture and the variability in virus isolation techniques for SARS-CoV-2 alone can account for some differences among studies. Furthermore, the sample assessed is often ~50 μL with or without an eluate. Negativity in such a small sample for virus culture does not confirm that live virus is not being shed in a more complex scenario of the infection site.

In conclusion, early in the emergence of any respiratory pathogen it is very important to develop clinical research coupled with virologic research to ascertain the longevity of viral shedding to inform clinicians on the duration of the needed isolation. The pros and cons of the different strategies are shown in Table 1. The use of antigen testing in clinical settings especially for discontinuation of isolation had not been validated and further studies are required. PCR based strategy proved to show prolonged positivity and this might not correlate with positive cultures and to show intermittent positivity as well [7,46]. There is a dichotomy between what isolation would be scientifically warranted

Table 1
Pros and Cons of different isolation strategies.

Strategy	Pros	Cons
PCR-based	Gold standard test High sensitivity and specificity (>95%)	Expensive Usually requires HCW for testing Identify asymptomatic and non-infectious False negative may occur due to technique or transportation Does not differentiate infectious and non-infectious individuals
Antigen-based	Can be POCT Relatively cheaper Faster results Negative tests after infection identifies non-infectious Do not require specialized laboratory technique Can be utilized for mass testing	Miss asymptomatic contacts Multiple antigen -based tests with different sensitivity (mean of 56.2%)
Symptom-based	Easy to calculate and rely-on for quick management of a large number of infected individuals	Miss asymptomatic contacts Does not allow viral dynamic testing May not be used at initial emergence of pandemics May not shorten the outbreak duration*

POCT: point of care test; HCW: Healthcare worker; * see text for explanation.

versus that which is practical or palatable given the large numbers of infected patients and/or healthcare workers. It is important to note however that many countries did not have sufficient capacity so moved to a symptom-based strategy for patients' isolation. In addition, the emergence of variants of concern such as Omicron may change the viral dynamics and the transmission. With continued emergence of variants of concerns and in the event of future emergence of viruses, it is important to have studies of viral kinetics with longitudinal sampling, PCR testing, measuring viral Ct values, antigen testing as well as assessing viral viability [47].

CRediT authorship contribution statement

Jaffar A. Al-Tawfiq: Conceptualization, Methodology, initial writing of the manuscript. **Ziad A. Memish:** Writing – original draft, Both authors finalized and approved the final draft and the revision.

Declaration of competing interest

None.

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