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Editorial

A Push for Real Normal: Mass Screening for COVID-19

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COVID-19 has been the worst pandemic in the last 100 years. The causative agent of this disease, SARS-CoV-2, is highly transmissible in humans. As of August 20, 2021, SARS-CoV-2 has caused 210 million confirmed cases worldwide, resulting in 4.4 million deaths. Different governments have used different strategies to control this pandemic. Some have used a mitigation approach that aims at controlling the number of COVID-19 cases within a manageable number, whereas some have used a suppression approach that aims at reducing the number of COVID-19 cases to a minimum (1). Irrespective of which approach is used for controlling this pandemic, both approaches require comprehensive and accurate public health data to inform policy making or management. With the wide use of quantitative reverse transcription–PCR (RT–PCR) technology, it is now possible to provide accurate and timely laboratory diagnostic test results to public health experts and other stakeholders in a robust manner. This is in sharp contrast to the last influenza pandemic in 2009, in which the diagnosis in many clinical settings was mainly based on clinical observations (2), resulting in an underestimation of actual number of deaths caused by the pandemic influenza A (H1N1) 2009 virus.

Hong Kong thus far has adopted an elimination strategy to suppress COVID-19 circulation in the city (3). With a population of 7.5 million, Hong Kong so far has only 12 033 confirmed COVID-19 cases and about 21% of these patients were imported cases. The number of daily COVID-19 cases in the city has been reduced to a single digit level or 0 since late March 2021. Hong Kong has taken strict nonpharmaceutical measures (e.g., ban on mass gathering, mandatory mask wearing in public places, and closure of schools) to prevent major COVID-19 outbreaks in the city (4). Active contact tracing is performed for all confirmed COVID-19 cases if possible (5). Individuals in close contact with COVID-19 patients have to be subjected to a mandatory quarantine. Stringent travel restrictions have been imposed. All inbound passengers, irrespective of their vaccination status, must be quarantined.

Among these nonpharmaceutical measures, Hong Kong has heavily used nucleic acid amplification tests (NAATs) to control and monitor COVID-19. In addition to routine COVID-19 diagnosis, NAATs have been used extensively in various COVID-19 surveillance programs in Hong Kong. Mandatory COVID-19 RT–PCR testing before and after an inbound flight is requested for all inbound passengers. Individuals who are classified as high-risk cases in COVID-19 outbreak investigations have to be RT–PCR tested for SARS-CoV-2 repeatedly. Free NAATs are offered to all Hong Kong citizens who feel they have a higher risk of exposure or are experiencing clinical symptoms of respiratory infections. In addition, NAATs are used in different large-scale community COVID-19 screening programs. To prevent SARS-CoV-2 transmissions caused by asymptomatic patients in the community, NAATs have also been used in a citywide sewage surveillance program in Hong Kong. In this program, wastewater samples collected from different districts or individual buildings are RT–PCR tested for SARS-CoV-2 (6). Occupants from the so-called "COVID-19 positive buildings" are shortly subjected to mandatory COVID-19 NAATs. At the end of Wave 4 of COVID-19 in Hong Kong (April 2021), this sewage surveillance program identified >110 COVID-19 positive buildings and >50 previously unknown patients with COVID-19 in these buildings. In addition, to better understand the transmission dynamics of SARS-CoV-2 in the city, Hong Kong has conducted real-time molecular epidemiology of SARS-CoV-2 and studied about 20% of COVID-19 patients. Such analyses have provided information to relevant stakeholders for developing evidence-based COVID-19 control policy. In short, Hong Kong exemplifies the potential use of NAATs for controlling infectious diseases. There are ample opportunities to apply NAATs for robust disease surveillance, thereby providing timely results to inform public health policy making and practice.

Although guidelines for COVID-19 specific NAATs (7, 8) were released by the World Health Organization soon after the discovery of SARS-CoV-2, the potential use of NAATs for controlling COVID-19 has been severely affected by several practical hurdles at the beginning of this pandemic. In particular, with the "unexpected" huge surge in demand for testing, it was

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common to learn that COVID-19 RT–PCR testing activities in many laboratory settings were hampered by shortages of trained technical staff, consumables for sampling collection, and consumables for conducting NAATs for COVID-19. This prevented generation of timely and comprehensive results for real-time policy making. These limitations triggered unprecedented efforts from the global scientific and medical community to address this urgent problem. Solutions such as massive training of technical staff, use of alternative testing strategies (e.g., sampling pooling) (9), use of alternative platforms/assays (10), and increased production of consumables/reagents for NAATs have partially solved the problem. But for resource-limited settings, it is of great importance to make COVID-19 NAATs affordable for routine large-scale usage.

In this issue of *Clinical Chemistry*, Srivatsan and colleagues report a newly developed RT–PCR-based protocol for testing SARS-CoV-2 using self-collected nasal swab samples (SwabExpress) (11). This protocol has several advantages. First, collected dry swabs can be sent to a diagnostic laboratory without the need for virus transport medium or buffer. Second, a viral RNA extraction step is not needed in this protocol. Before the RT–PCR assays, clinical samples only need to be rehydrated in a low Tris-EDTA buffer, treated by a brief proteinase K digestion for 15 min to eliminate RT–PCR inhibitors and then heat treated at 95 °C for 15 min for virus inactivation. This testing protocol can avoid the need for several critical reagents, such as virus transport medium and expensive RNA extraction reagents or kits, thereby greatly reducing the diagnostic cost. In addition, this simple workflow can reduce the hands-on time for preparing input RNA samples for RT–PCR tests, which is highly attractive to laboratories that do not have automatic nucleic acid extraction systems for high throughput testing. Most importantly, this testing strategy does not compromise testing performance. According to the study, this testing protocol has a detection limit of 2–4 copies/μL. Using RT–PCR reactions with RNA purified from standard nucleic extraction protocol as references, the SwabExpress protocol has 100% sensitivity and 99.4% specificity. These findings demonstrate that SwabExpress has good potential for large-scale COVID-19 testing.

Although SwabExpress has highly promising features, further investigation of this testing approach is needed. Specifically, most samples tested in this study had a cycle threshold or C_T value of less than 35. It is therefore important to determine the testing performance of this approach by using clinical samples with low viral loads. It is also of interest to know whether other commonly used self-collected samples (e.g., saliva) can be tested by this protocol in a satisfactory manner. In addition, we need to know whether samples treated by this RNA extraction-free protocol can also be used in NAATs with different RT–PCR chemistries and beyond (e.g., isothermal NAATs) (12). Such investigations might help to reveal the full potential of this RNA extraction-free testing approach to detect SARS-CoV-2 and other respiratory virus infections.

The authors of this study found that viral RNA treated by this protocol is sensitive to freeze–thaw treatment, suggesting that archived samples collected by this approach would not yield reproducible results in repeated tests. Additionally, this kind of archived sample might have a limited use for full genome analyses. With the proteinase treatment in this protocol, these clinical samples are unlikely to be found useful for virus isolation for further characterization. Having said that, the primary objective of this study is to develop a robust and practical testing approach to identify patients with COVID-19 in a timely manner. Clearly, Srivatsan and colleagues have developed an excellent approach to address one of the major gaps in COVID-19 detection.

We are still facing a lot of challenges in the pandemic era. The virus has acquired additional adaptive mutations since its circulation in humans (e.g., D614G mutation in Spike) (13). COVID-19 vaccines have been developed for controlling this novel disease at an unprecedented speed and scale, but vaccine hesitancy and inequity still undermine the potential of these vaccines. Unfortunately, some of the circulating strains, such as the Delta variant of concern, have already acquired additional mutations that allow vaccine breakthrough (14). Nonetheless, COVID-19 vaccination still can reduce the risk of having severe clinical outcomes caused by these varaints. Nonpharmaceutical interventions are expected to have reduced effectiveness on COVID-19 transmission because of intervention fatigue. It is highly likely that SARS-CoV-2 will continue to circulate in humans as an endemic virus in future. A multipronged approach is needed to control its circulation in humans to a more manageable level. We need more affordable and accessible vaccine options to cope with the challenge of antigenic change in SARS-CoV-2. We need effective antivirals or therapeutics to treat severe COVID-19 patients or to prevent long-haul COVID-19 infections. We need more practical nonpharmaceutical interventions and better risk communication to reduce COVID-19 transmission between humans. Having cost-effective and highly sensitive NAATs for mass screening at the community level can help identify COVID-19 cases early, thereby allowing prompt and effective control measures to prevent major COVID-19 outbreaks. SwabExpress is a promising option to make such a community COVID-19 testing approach more feasible and sustainable.

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