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Letter to the Editor

Diagnostic strategy of SARS-CoV-2 for containment under China's zero-COVID-19 policy



Dear Editor,

Coronavirus disease 2019 (COVID-19) represents a serious global public health emergency.¹ Since late 2021, a new variant Omicron of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spread rapidly around the world, and raised a new global health concern.² The Omicron variant was characterized by substantially higher transmissibility, lower pathogenicity than the Delta variant, and resistance to vaccine-induced immunity and antiviral drugs.^{2,3} The elderly are still the highest risk group for the Omicron variant, and COVID-19-associated deaths. The Omicron variant had caused large outbreak in several cities/regions (e.g. Hong Kong, Shenzhen and Jilin) of China in early 2022, forming a huge challenge to the “zero-COVID-19 policy” of China. Currently, the Omicron variant is actively circulating in Shanghai, the largest city of China. To eliminate the pandemic, Shanghai implemented community closed-off management in late March 2022.

“zero-COVID-19 policy” is an effective route to reduce health damage in the mid- and long-term, and a cheaper path towards economic recovery.⁴ The current national situation, including a very large population size, many big cities (91 with over 5 million people, including 18 with over 10 million people) with high population density, aging society (age over 60 year-old: 18.7% of total population), and imbalanced medical resources, determines that China has to implement the “dynamic zero-COVID-19 policy”. If China allows the “living with COVID-19 policy”, outbreak of the Omicron variant in one or more cities will inevitably lead to not only the overwhelming of medical and public health resources, but also the shortage of quarantine facilities and daily necessities, thereby causing a humanitarian disaster.

SARS-CoV-2 nucleic acid testing plays a crucial role in the containment of COVID-19.^{5,6} Reverse transcription quantitative polymerase chain reaction (RT-qPCR) is widely used as the gold standard for detection and confirmation of SARS-CoV-2 infection due to its high sensitivity (>500–1000 copies/mL), specificity, and multiplex detection feature. However, RT-qPCR is time-consuming and costly, and requires sophisticated equipment and highly trained personnel. A city-wide broad RT-qPCR screening in a short timeframe will inevitably occupy substantial public health and medical resources, including a large numbers of specialists and volunteers, and a lot of PCR Labs. Frequent and/or daily population-based broad RT-qPCR screenings not only largely aggravate public health burden (e.g. cost, personnel and resources), but also increase the risk of exposure and infection due to large-scale concentrated sampling. The number of infected persons is high in COVID-19 affected areas at the early stage of closed-off manage-

ment, and early and rapid finding of infected individuals with high infectivity are of particular importance to control the spreading of COVID-19. However, concentrated sampling, sample transport, and large sample size will result in one or more days delay of the RT-qPCR results. As a cheap and easy process point-of-care testing (POCT) method, rapid antigen test (RAT) can well capture infected individuals with high viral load and infectivity in spite of relatively low detection sensitivity (10^4 – 5 copies/mL).⁷ When a city faces an outbreak of SARS-CoV-2, especially Omicron variant, which diagnostic strategies work best and should be implemented under community closed-off management should be carefully considered.

Dynamics of SARS-CoV-2 infection showed that the virus in nose and throat can be detected by RT-qPCR assay on the second day after infection, and then viral load rises steeply and reaches a peak at the level of 10^7 – 8 copies/mL about on the 5th–6th days (Fig. 1).⁸ Infected individuals remain high level of viral load (> 10^4 – 5 copies/mL), and are ready to spread the virus to other people during 3–9 days of infection,^{8,9} which is called transmission window (Fig. 1). Since day 10, most cases develop neutralizing antibodies to clear virus and become less or not contagious.

According to the dynamics of SARS-CoV-2 shedding, here we take the advantages of both RAT and RT-qPCR assays, and propose a high-efficacy and cost-effective diagnostic strategy that combines high-frequency self-RAT and low-frequency RT-qPCR assays to eliminate community transmission of SARS-CoV-2 under closed-off management (Fig. 1). The strategy suggests all persons to perform once self-RAT at home on the first day of implementing community closed-off management, followed by 3–4 times of population-based broad RT-qPCR screenings with intervals of 6 days (i.e. the 2nd, 8th, 14th and 20th day) since the second day, and at least two times of self-RAT at home within each 6-day interval (Fig. 1). The result of each self-RAT should be timely returned to community managers or volunteers, or uploaded to an online disease prevention and control platform (if available). With this strategy, most currently infected individuals (e.g. C1–C8) during transmission window can be captured by the first self-RAT at home, and timely quarantined, which avoids the potential risk of them to spread the virus to other people during concentrated sampling for RT-qPCR screening. Current cases (C–C10) on days 3–14 after infection will be identified by the first RT-qPCR screening (Fig. 1). Although the earlier cases with infection over 14 days might be missed by both the first self-RAT and RT-qPCR screenings, they either have very low viral load, or have returned to be negative, and are unable to or very less likely spread the virus.⁸ The cases C11 and newly infected individuals N1–N5, as well as any cases during transmission window (high viral load > 10^4 –

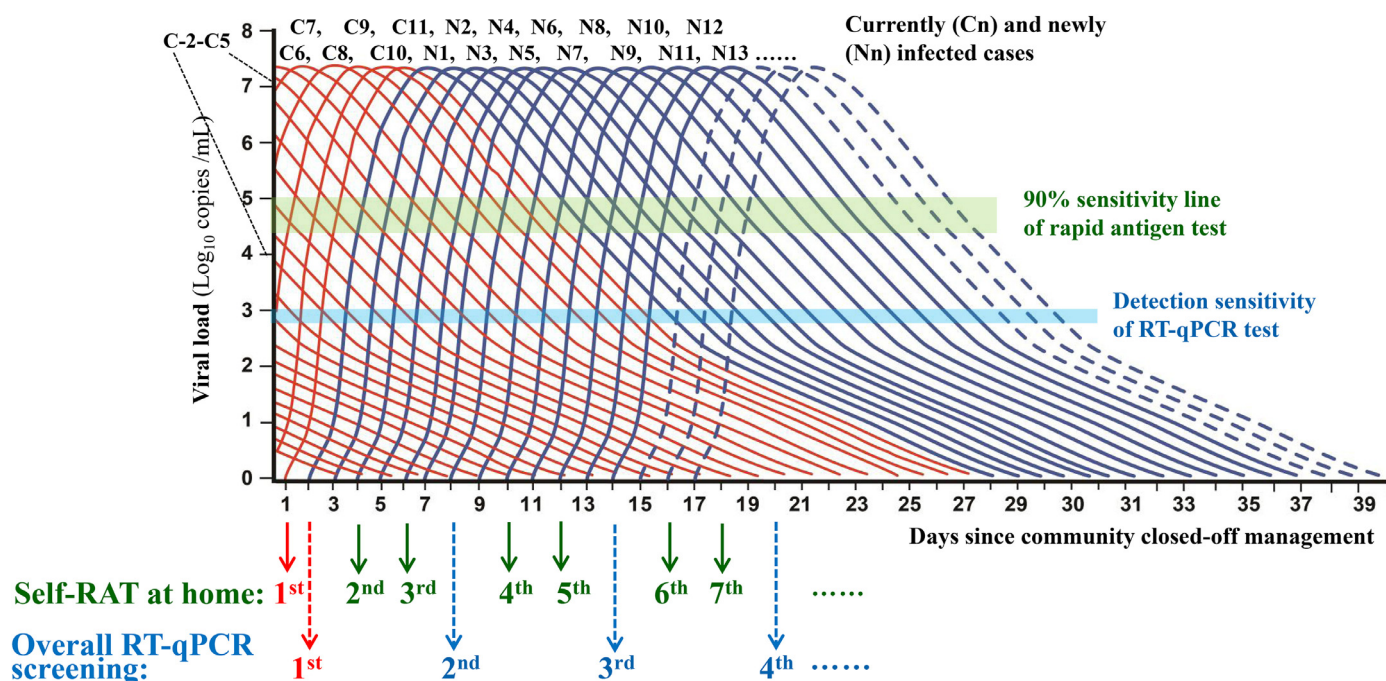


Fig. 1. Diagnostic schedule of SARS-CoV-2 under zero-COVID-19 policy. Colored lines shows the viral load dynamics of individuals infected by SARS-CoV-2 at different time-points. The curves were drawn based on the data from ref 8. The detection lines of both RAT and RT-qPCR assays are shown by colored thick lines. C1-n show currently infected cases, and N1-n show newly infected cases since community closed-off management. RAT: rapid antigen test.

5 copies/mL) but missed by both the first self-RAT and RT-qPCR screenings, can be found by subsequent self-RAT and RT-qPCR screenings. In theory, under strict community closed-off management, the vast majority of infected cases can be effectively found and quarantined after three rounds (about two weeks) of broad RT-qPCR and multiplex times of self-RAT screenings. Since then, new infections may occur sporadically, but can be picked up by further self-RAT and/or RT-qPCR screenings.

The pooling sample strategy with 5, 10 or even 20 samples in a pool is very effective in RT-qPCR screening for SARS-CoV-2 infection under low infection rate. To ensure the sensitivity of RT-qPCR test, multiple swabs pooling in a single tube, rather than media pooling, was widely used in China. Given the transmission feature of SARS-CoV-2, the pooling strategy can be optimized in a family unit, and a pool of 2–5 families can be used for population-based broad RT-qPCR screenings. Importantly, any pooling strategy should not be subjected to special groups including public health and healthcare workers, volunteers, drivers, deliveryman, and shop assistants.

Nucleic acid POCT methods have comparable sensitivity to RT-qPCR. Recently, RNA extraction-free probe-based RT-LAMP assays were developed for rapid, sensitive, and specific detection of SARS-CoV-2.^{10,11} The features of nucleic acid POCT assays, including easier operation, shorter sample-to-result time (about 30 min) and less dependence on sophisticated devices, enable their application at home. The use of nucleic acid POCT assays together with or as an alternative to RAT will further improve the efficiency of population-based broad SARS-CoV-2 screenings.

Declaration of Competing Interest

The authors declare that, they have no conflict of interests.

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