Clinical Infectious Diseases

EDITORIAL COMMENTARY

Controlling the COVID-19 Pandemic Blindly: Silent Spread in Absence of Rapid Viral Screening

Hanalise V. Huff

Boston Children's Hospital, Harvard Medical School, Boston, MA, USA

(See the Major Article by Erlichster et al on pages e3047–52.)

Keywords. COVID-19; SARS-CoV-2; public health; transmission; testing.

Rapid identification of infected individuals in the early stages of an outbreak in order to isolate and prevent further transmission is of utmost importance. Public health responses utilized to accomplish this goal include identification and isolation of infected individuals based on symptom presentation then monitoring of contacts for symptoms before proceeding with further isolation. In the 2003 SARS-CoV epidemic, this strategy was effective given onset of symptoms occurred several days prior to infectivity and as a result the epidemic was contained rather quickly [1]. A critical difference between SARS-CoV and SARS-CoV-2 lies in the viral transmission dynamics. SARS-CoV-2 has demonstrated significant infectivity prior to symptom onset rendering the strategy of symptom onset for infection identification ineffective. A study on temporal patterns of viral shedding of SARS-CoV-2 by He et al found that the highest viral load in throat swabs was at the time of symptom onset suggesting infectiousness peaked on or before symptom onset [2]. The establishment that viral transmission occurs in presymptomatic and asymptomatic individuals and may be an important driver of the pandemic has important implications for the essential use of testing in the control of this pandemic [3]. As a result, testing to identify active infection is essential in preventing further viral transmission and therefore achieving pandemic control.

Widespread universal testing regardless of symptom early on would have identified those infected prior to transmission and would have offered a better chance at containment. The small town of Vo' in Italy locked down the city upon identification of first cases and tested a majority of the population regardless of symptoms [4, 5]. This town's mass testing demonstrated both the high proportion of asymptomatic yet infectious individuals and the utility of mass testing for transmission reduction and outbreak control [6].

Despite the fact that the SARS-CoV-2 genome was sequenced rapidly and distributed globally along with suggested PCR probes in January [6], testing still remains a challenge globally many months later. Many countries are incapable of testing the number of individuals needed to establish disease prevalence and curb transmission propagation. Stringent testing criteria are often imposed that exclude the population with the highest potential of transmitting; those that are yet to have symptoms. The initial delay to test and the continued limitations in sufficient testing capacity appear to be a multifactorial problem. In countries such as the United States, production of a novel test with additional primer sequences with goal of increased sensitivity led to a critical delay in testing. Delays also occurred due to restrictions on novel testing based on governmental regulations. In many countries, the ideal level of testing has still not been reached given testing supply shortages, insufficient amount of trained personnel and flaws in testing infrastructure.

The paper titled "Pan-Family Assays for Rapid Viral Screening: Reducing Delays in Public Health Responses During Pandemics" by Erlichster et al eloquently highlights the critical importance of rapid access to testing early in an outbreak and proposes the use of pan-family assays as a mechanism to expedited viral screening [7]. These assays would be prepared ahead of time, approved by relevant regulating bodies and stockpiled in mass quantity as a fail-safe way to more quickly build testing capacity for future novel-virus outbreaks. The present study proposes these pan-family assays as a screening mechanism to monitor early spread and uses the SARS-CoV-2 virus as a case study for the

Received 28 July 2020; editorial decision 31 July 2020; accepted 20 August 2020; published online August 25, 2020.

Correspondence: H. V. Huff, Boston Children's Hospital, 300 Longwood Avenue, Boston, MA 02115, USA (hanalise.huff@childrens.harvard.edu).

Clinical Infectious Diseases® 2021;73(9):e3053–4

DOI: 10.1093/cid/ciaa1251

utility of a pan-coronavirus (Pan-CoV) assay for detecting novel viruses within a family.

Within the study, specificity of the Pan-CoV assays is discussed in context of infection with viral members of the same family that are not the novel virus in question which would be detected as positive thereby resulting in a "false positive." In other words, individuals with infection by an endemic coronavirus would test positive despite the fact that they are not infected with the novel coronavirus. Specificity of the Pan-CoV assay will therefore depend on the population's likelihood of being infected with another coronavirus (ie, immunocompromised status, young age or "common-cold" season).

Sensitivity for the Pan-CoV assays proposed was predicted by comparing the primer sequences to primer target sites in the genomes of 60 identified coronavirus species. It was found that 33% showed primer mismatches. Ideally a screening tool should have high sensitivity primarily in order to prevent missed cases in a population. A false negative SARS-CoV-2 patient would not isolate and therefore would continue transmitting the virus. As noted in the study, primer sequences for pan-CoV assays should target sequences highly conserved by the family so as not to miss detection in novel viruses.

For the pan-family assay concept to provide the best outcome, it would allow for detection of all coronavirus infections, regardless of species and with no missed infections. Depending on how many alternative coronavirus infections are out in the community at the time of testing, there would be resulting over-isolation due to "false positives" for novel coronavirus. However, in a screening scenario that has a goal of rapid isolation of all infectious cases, specificity is sacrificed for sensitivity given the epidemiologic consequences of a false negative.

The focus of this paper is on minimizing the delay to widespread test use that may result while species-specific tests are developed. This is an important consideration, however, as also noted by the authors, in most countries, the absence of a species-specific test early on in the pandemic was not the central issue given the early sequencing and identification of probe sequences. The problem, instead, was the lack of testing infrastructure, delays in government testing approval and limited testing resources. Developing countries may not have the machines necessary to process high throughput testing and global shortages in supplies needed for testing regardless of whether the test used is species-specific or a pan-family assay leads to hurdles in rapid viral testing. The need for future stockpiles of supplies, whether it is PPE or test kit resources, is evident as highlighted by the current global situation.

Whether the production and stock piling of mass amounts of pan-family assays in preparation for the next pandemic is feasible or not, the message of this paper is crucial. Public health strategies that focus on rapid viral screening are essential both for the current pandemic and in preparation for future pandemics and epidemics. As mentioned in the paper, a test that provides access to quick results in exchange for less sensitivity has epidemiologic value. The priority in rapid viral screening is identifying those infected in order to isolate as quick as possible to limit further transmission. Access to increased testing must be accompanied by fast turnaround time of results. Ramping up testing capacity is pointless if delay in test results increases. For a viral screen to serve its purpose, the asymptomatic SARS-CoV-2 infected individual must be informed of status immediately in order to isolate and provide the most substantial reduction in viral propagation [8].

Establishment of an effective test for identifying and/or confirming infection in an outbreak is essential. Insufficient testing capabilities early on can have dire downstream effects and are both necessary for prevention of escalation to pandemic state as well as controlling once pandemic state is reached. Given the transmission dynamics of the SARS-CoV-2 virus and its established ability to be transmitted prior to symptom onset, testing becomes even more essential. As more is understood about the transmission properties of the SARS-CoV-2 virus, it becomes clear that for optimized transmission prevention there is a need for mass surveillance testing that emphasizes frequent testing of asymptomatic individuals with rapid return of results. In order to take control of the COVID-19 pandemic, we can no longer operate blindly; we must illuminate the silent but infectious spreaders through rapid, frequent and early viral screening, thereby finally providing focus for our transmission prevention efforts.

Notes

Acknowledgments and compliance to ethical standards:

Financial support. No financial support was provided.

Potential conflicts of interest. The author: No reported conflicts of interest. The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

References

1. Fraser C, Riley S, Anderson RM, Ferguson NM. Factors that make an infectious disease outbreak controllable. Proc Natl Acad Sci U S A **2004**; 101:6146–51.
2. He X, Lau EHY, Wu P, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. Nat Med **2020**; 26:672–5.
3. Huff HV, Singh A. Asymptomatic transmission during the COVID-19 pandemic and implications for public health strategies [manuscript published online ahead of print 28 May 2020]. Clin Infect Dis **2020**.
4. Lavezzo E, Franchin E, Ciavarella C, et al; Imperial College COVID-19 Response Team. Suppression of a SARS-CoV-2 outbreak in the Italian municipality of Vo'. Nature **2020**; 584:425–9.
5. Day M. Covid-19: identifying and isolating asymptomatic people helped eliminate virus in Italian village. BMJ **2020**; 368:m1165.
6. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet **2020**; 395:565–74.
7. Erlichster M, Chana G, Zantomio D, Goudey B, Skafidas E. Pan-family assays for rapid viral screening: reducing delays in public health responses during pandemics [manuscript published online ahead of print 20 July 2020]. Clin Infect Dis **2020**.
8. Larremore DB, Wilder B, Lester E, et al. Test sensitivity is secondary to frequency and turnaround time for COVID-19 surveillance. medRxiv [Preprint]. June 27, **2020**; 2020.06.22.20136309.