Journal of Clinical Microbiology

Clinical Microbiology | Minireview

Proceedings of the Clinical Microbiology Open 2023: discussions about pandemic preparedness

Eleanor A. Powell,[1] Alexander L. Greninger,[2] Elizabeth M. Marlowe,[3] Samia N. Naccache,[4] Christopher D. Doern[5]

AUTHOR AFFILIATIONS See affiliation list on p. 10.

ABSTRACT The 4th Clinical Microbiology Open (CMO) took place in Carlsbad, California, on 10 and 11 February 2023. This event facilitated discussion between clinical and public health laboratory directors, government agencies, and industry representatives from the companies that make up ASM's Corporate Council. While many topics were discussed, much of the discussion focused on pandemic preparedness. There were four major questions addressed: (i) When is the perfect the enemy of good in pandemic testing? (ii) What other types of pathogens might cause another pandemic and how would this affect laboratory response? (iii) What research is needed to better understand the effectiveness of the pandemic response? (iv) What have we learned about the utility of self and at-home testing in future pandemics? This review serves as a summary of these discussions.

KEYWORDS pandemic preparedness, SARS-CoV-2

Representatives from infectious disease diagnostics companies, clinical and public health microbiology laboratories, and relevant government agencies met in Carlsbad, California, on 10 and 11 February 2023 to discuss important topics in clinical microbiology. Four major topics in pandemic preparedness were discussed and were a continuation of the conversation that began at the Clinical Microbiology Open (CMO) in Washington, DC, in June 2022. The discussion covered four primary questions: (i) When is perfect the enemy of good in pandemic testing? (ii) What other types of pathogens might cause another pandemic and how would this affect laboratory response? (iii) What research is needed to better understand the effectiveness of the pandemic response? (iv) What have we learned about the utility of self/home testing in controlling future pandemics?

One to two speakers introduced each topic, provided their perspective on the subject, and set the foundation for additional discussions. Following the presentations, attendees participated in small group breakout discussions, with each focusing on one question. At the conclusion of these group discussions, a speaker from each breakout session summarized their discussions for the larger group. The following is a detailed description of the proceedings.

WHEN IS PERFECT THE ENEMY OF GOOD?

One of the most challenging facets of managing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) testing was determining what were acceptable test characteristics for different clinical scenarios and patient populations. Often these decisions required a compromise between test performance, speed, and simplicity. Early in the pandemic, clinicians and patients favored highly sensitive tests to identify the maximum number of coronavirus disease 2019 (COVID-19) cases. As test capacity increased and asymptomatic testing became common, less sensitive tests were desirable as "falsely positive" results by detecting remnant SARS-CoV-2 nucleic acid became a

Editor Romney M. Humphries, Vanderbilt University Medical Center, Nashville, Tennessee, USA

Address correspondence to Eleanor A. Powell, powelleo@ucmail.uc.edu.

E.A.P. has received research funding from Roche GenMark. A.L.G. reports contract testing from Abbott, Cepheid, Novavax, Pfizer, Janssen, and Hologic and research support from Gilead, outside of the described work. E.M.M. is employed by and owns stock in Quest Diagnostics, a commercial clinical reference laboratory that offers SARS-CoV-2 testing. S.N.N. is employed by and owns stock in Labcorp, a commercial clinical reference laboratory that offers SARS-CoV-2 testing. C.D.D. consults for Qiagen and Shionogi.

Published 22 May 2024

concern. As with any laboratory test, the positive and negative predictive values of SARS-CoV-2 testing varied by patient population and clinical scenario (i.e., symptomatic versus asymptomatic testing). While these dynamics are common in diagnostic testing, the pandemic forced them into the public spotlight. Never before has there been a national conversation about the nuances and challenges of diagnostic testing. As the public confronted these complex dynamics, SARS-CoV-2 testing became a politically charged issue and brought with it an intensely emotional dialogue, complete with conspiracy theories and misinformation.

In other cases, the public health implications and level of scrutiny may have resulted in even stricter standards than normal. Outside of pandemic testing, many laboratory directors in attendance were comfortable testing rarely encountered, non-validated sample matrices, and adding a disclaimer to the result. This is supported by CAP standard MIC.64770 Validation Studies—Specimen Type/Collection Device. Despite this, many laboratories were reluctant to do this with SARS-CoV-2 testing due to strict Food and Drug Administration (FDA) regulations within Emergency Use Authorizations (EUAs). During both SARS-CoV-2 and Mpox virus test development, there was a movement toward including specimen acceptability controls to ensure adequate specimen collection. This typically involves the detection of a human gene to ensure an adequate amount of patient cells have been collected. While this adds benefit in determining specimen adequacy, it may decrease the amplification of pathogens near the limit of detection via competitive inhibition (1). Additionally, this may use additional reagents, require additional testing time, and has not been consistently included in previous respiratory viral testing or sexually transmitted infection diagnostics. In resource-limited pandemic testing scenarios, is this an unaffordable luxury?

From the industry perspective, a test may have been "good enough" for laboratories and providers, but businesses must protect their reputations. Mistakes or lower-quality EUA products can reflect poorly on the company and result in distrust. It can also pose operational challenges, as quality systems within the company are designed for non-EUA products. Applying less stringent standards to non-EUA product lines may not be feasible. Additionally, there must still be a justifiable business case for the creation of a test, and the test needs to fit into the company's diagnostic portfolio. Justification can be difficult when both the length and height of an outbreak are unpredictable. Developing tests that cater to a company's strengths and expertise can help minimize the pain and pitfalls of major change, especially in volatile times.

In an ideal scenario, test development and adoption would be an iterative process. At the beginning of a pandemic (or during surges when resources are limited), less-than-perfect tests—including suboptimal sample types like saliva and untested transport media like saline—may be an acceptable compromise. These unorthodox practices may also yield data that challenges previously held practices. As more information and resources become available, tests should evolve through improvements aimed at bringing testing up to the standards of non-pandemic testing.

While this flexible approach would allow manufacturers and laboratories to respond to evolving situations without sacrificing long-term quality, the regulatory systems in place are not set up for this. When test manufacturers wanted to add additional gene targets to their tests to ensure circulating variants were detected, laboratories using these tests had to perform new verification studies and individualized quality control plan testing, consuming precious reagents and time. Lack of guidance from regulatory agencies around new specimen types and transport media also makes laboratories reluctant to change practices. Clear regulatory guidance and reasonable accommodations for altering tests and acceptable specimen types (both for test developers and laboratories) will better enable new information to result in test improvement.

This flexibility should also be considered in the transition away from EUA status. Test manufacturers with broad claims included in an EUA may be unable to support the clinical trials to get these same claims in an FDA clearance. Currently, several tests with EUAs for asymptomatic screening do not include this in their *in vitro* diagnostics

(IVD) claims. Others have more limited specimen types and transport media options, despite years of use at this point. These restrictions also impact laboratories, who may find themselves unable to serve all the needed patient populations and test indications (pre-surgical screening, discharge to skilled nursing facility) without doing extensive and expensive clinical claims validations. This impact is likely to be felt most strongly by smaller laboratories without dedicated microbiology staff who may be limited to FDA-approved, sample-to-answer systems. The fact that there are several hundred COVID-19 EUA tests, many more laboratory-developed tests (LDTs), and only a handful of FDA-cleared tests, is a clear indicator that the expense and burden of obtaining regulatory approval limits test availability. This reality is particularly problematic in the face of the pending FDA regulation changes which promise to apply similar restrictions to LDTs, further limiting access to testing.

While the quest for a "perfect" test can delay and complicate test development and test implementation, there must also be balancing forces. Not all tests are "good enough" for use, and some tests may be inappropriate for certain populations and indications. While the clinical microbiologist can guide test utilization, communicating to the public that not all tests perform equally, is an ongoing challenge. Consider antigen testing before holiday celebrations—while a negative result reduces risk, it does not eliminate risk. Overconfidence in a negative result from an insensitive test may incorrectly drive discontinuation of safety measures. Furthermore, once the initial crisis stages of a pandemic have passed and testing needs for the future become clear, both test developers and laboratories must return to pre-pandemic standards (or better).

WHAT OTHER TYPES OF PATHOGENS MIGHT CAUSE ANOTHER PANDEMIC AND HOW WOULD THAT IMPACT LABORATORY RESPONSE?

In the wake of the COVID-19 pandemic, respondents agreed that novel respiratory RNA viruses are of particular concern for causing another pandemic, given (1) their ability to rapidly spread among people across the world (2), their high evolutionary rates (3), flexible glycoproteins, and (4) association of lower respiratory tract replication with high morbidity and mortality. Based on historical trends and the current spread of H5N1 in avian species, *Orthomyxoviridae* continues to be the most probable cause of the next pandemic. With hundreds of new recently discovered sarbecoviruses and the experiences of SARS-CoV, SARS-CoV-2, and Middle Eastern respiratory syndrome coronavirus (MERS-CoV) in the past two decades, *Coronaviridae* also remain likely pandemic drivers. *Paramyxoviridae* and *Pneumoviridae* already transmit well among humans with a variety of species such as human parainfluenza viruses, measles virus, mumps virus, human respiratory syncytial virus, and human metapneumovirus, and have long been concerns for new human outbreaks of high consequence with the henipaviruses. The ease of spread of *Adenoviridae* as well as *Picornaviridae* such as enteroviruses also cause a new pandemic, though we have had fewer recent examples of large-scale zoonotic infection and they are less evolutionarily pliable compared to viral families above. From a virological perspective, *Retroviridae* occupy a unique position in human pandemic history, given their ability to spread worldwide, evolve rapidly, and achieve latency and bide their time until it is clear how far they have spread, all while writing their evolutionary gains in human DNA. While not a discrete type of pathogen, the spread of bacterial antimicrobial resistance is now being appropriately rebranded as a pandemic and one which will require international cooperation and for which humankind has shown comparatively little success (2).

The pathogens listed above constitute a list of usual suspects for pandemic-causing microbes. As such, these pathogens are associated with fewer analytical concerns for the clinical laboratory and industry response for the next pandemic due to changes made during the pandemic. The COVID-19 pandemic brought with it a significant capital outlay for automated sample-to-answer molecular platforms in clinical and public health laboratories as well as next-generation sequencing instruments, largely in public health laboratories, that both increased readiness for a future pandemic compared to 2019.

Industry likewise has scaled supply chains to levels not seen before, covering a significantly greater geographic footprint. During the pandemic, there was a paradigm shift in regulatory approaches and consumer demand for at-home testing that could be leveraged for future pandemics.

Despite the increased automation, the major concerns of the laboratory response for future laboratory response are staffing and exhaustion, as increased costs in hospitals have led to continued consolidation in the clinical laboratory industry. Automated instrumentation is useful when thousands of specimens per day need to be tested, but instrumentation does not address other complications such as increased call volume, writing of validation reports, or training the next generation of clinical laboratory technologists. Public health laboratories saw a boom in financing initially, but many have seen a subsequent bust in funding, leading to questions about whether the staff and equipment will still all be there for the next pandemic. True public health lab preparedness requires a baseline level of funding, even in the absence of active outbreaks, rather than reactionary increases in funding. Probably the biggest concerns for the industry response to future pandemics remain regulatory flexibility as well as the ability to obtain specimens for rapid validation and regulatory submissions, as demonstrated by recent authorizations for Mpox virus and influenza/SARS-CoV-2 diagnostic products that came well after each virus had peaked.

Regulatory concerns and specimen access are also concerns for laboratories. Though the VALID Act did not pass in 2022, the future regulatory paradigm for LDTs continues to be in flux, with the FDA promising new rulemaking in coming years without waiting for specific Congressional legislation. While governmental efforts (such as BEI Resources and World Reference Center for Emerging Viruses and Arboviruses) to make pathogen stocks available to the research and clinical laboratory community are essential, lack of access to clinical specimens for test development and validation studies continues to be a problem for clinical laboratories. Contrived specimens have historically been used by labs as part of LDT validations, particularly for low-incidence pathogens. Here, the FDA's clear signaling in the Mpox virus outbreak that entirely contrived specimens and synthetic materials were allowable for early validation studies was helpful. As SARS-CoV-2 so abruptly demonstrated, it is difficult for early-stage diagnostic testing to catch up to an entirely new pathogen and then diagnostic supply chain and staffing cannot keep up with an exponentially growing threat.

Given the global spread of *Candida auris*, white-nose syndrome in bats, and even the fictional pandemic in *The Last of Us*, a more distant yet possible concern for a future pandemic is a novel fungal pathogen. Testing of fungal pathogens presents special analytical issues as rapid fungal diagnostics are exceedingly limited compared to viral and bacterial pathogens, and few of the aforementioned rapid molecular platforms support fungal testing. More work is likely required for optimization of extraction on these platforms as well as standardization of molecular testing of fungal pathogens. While Clinical Microbiology Open participants hoped that this work would happen to diagnose today's endemic fungal infections, currently, we are less ready for a highly transmissible fungal pandemic from both a diagnostic and therapeutic angle.

Role of surveillance

While surveillance testing is critical for pandemic preparedness, the vast majority of public health surveillance is a collation of already performed diagnostic testing from clinical laboratories that is paid for by private and social insurance, and so diagnostic testing reimbursement and policy is a major driver of what monitoring is currently available. Participants were excited about the potential for metagenomic sequencing to allow for a more rapid and unbiased ability to detect novel pathogens early in a pandemic. Indeed, metagenomic sequencing was the method used to recover the SARS-CoV-2 genome in China and helped make specific PCR diagnostics available. Here, the hard part is identifying which specimens are worth subjecting to metagenomic analysis, since there are not a lot of novel pathogens circulating in humans that

fulfill this use case of metagenomics. Again, identifying specimens worthy of metagenomic sequencing for public health purposes is highly dependent on the widespread accessibility of (and reimbursement for) broad diagnostic molecular panels that can rapidly rule out common causes of infection, thus focusing efforts on clusters of unknown etiology. From an active monitoring standpoint, metagenomic sequencing of autopsy specimens from unexplained deaths would be more cost-efficient and be subject to less regulatory burden, while also informing on diagnostic misses of known but lesser common fatal pathogens (e.g., St. Louis encephalitis virus, *Balamuthia mandrillaris*, measles virus). Until the required instrumentation and expertise are more widespread and improvements have been made to reimbursement, metagenomic testing is likely to remain inaccessible to most institutions.

Participants also pointed out that future pandemics were most likely to start abroad, so any efforts at monitoring must be global, and international cooperation is essential. The widespread ability to rapidly recover and share pathogen sequences is a notable advance in the past decade, as illustrated by the vaccine designs and diagnostic tests that were ready within 72 hours of the global sharing of the SARS-CoV-2 genome. Greater international cooperation in specimen and data sharing would expedite diagnostic development and research. It was also suggested that existing networks in the military, which have significant global surveillance systems, could be leveraged. More work is also needed on regulatory standards for the use of synthetic material in early diagnostic test development and validation for a novel pathogen since this is likely our best hope to get a diagnostic test up and running before it arrives. As illustrated by SARS-CoV-2, by the time 20–30 positive specimens in the correct matrix have been detected domestically, it may be far too late to execute relevant diagnostic development and validation to forestall pathogen spread.

WHAT RESEARCH IS NEEDED TO BETTER UNDERSTAND THE EFFECTIVENESS OF THE PANDEMIC RESPONSE?

Looking through the available data on the COVID-19 pandemic can be overwhelming. An enormous body of literature has emerged from the pandemic and it can be difficult to sort through and translate the data into a valuable analysis that can tell a story. It is apparent that there is much we will continue to learn from the COVID-19 pandemic response. Some data may be available, while other data may be incomplete or not accessible. Many books, theses, and analyses are yet to be written about the COVID-19 pandemic and time will allow for thoughtful examination systematically so that appropriate evidence-based preparedness planning can occur. During the CMO discussions on this topic, the following major areas for research were identified.

How best to leverage and analyze big data

Many studies and programs were initiated in response to the pandemic. Looking back at those efforts with some distance and time, we can now begin to ask the right questions. In preparation for future pandemics, it is important to make the data available in real-time. Accurate real-time data analysis will allow for informed decision-making, policy-making, and timely activation of preparedness plans.

A critical question to answer is, what kinds of big data should be captured and analyzed. Early on in the COVID-19 pandemic, robust reporting mechanisms for COVID-19-related data did not exist. Each state had different mechanisms for reporting data to its public health laboratories, and in many cases, the systems that did exist were manual and error-prone. At a time when healthcare professionals were overwhelmed with managing the pandemic, there was neither time nor the resources to accommodate public health reporting. Yet these data would have been essential in assisting the public health response. Public health reporting from larger health systems has improved, but gaps remain in obtaining valuable data from smaller settings, such as urgent care clinics, physician offices, and most concerning, home-use testing data. Some examples of big data elements that could be useful in managing the next pandemic are listed in Table 1.

In addition to analyzing the data elements in Table 1, it would be helpful to be able to analyze the efficacy of pandemic control strategies both from within the US and outside the US, where different interventions may have been deployed.

Lastly, during the pandemic, clinical trials for new treatments to manage COVID-19 patients were conducted and data generated quickly. Learning from these experiences will allow us to plan and set frameworks for future needs with accelerated timelines.

Understanding the value of asymptomatic testing strategies and surveillance programs

SARS-CoV-2 diagnostic testing has been essential for disease identification, contact tracing, isolation, quarantining decisions, and treatment management. Initially, testing in the US focused on symptomatic patients with recent travel history, known close contacts, or those requiring inpatient care and who tested negative for other respiratory pathogens. Testing quickly turned to widespread asymptomatic screening programs. These programs were implemented in diverse environments such as nursing homes with high-risk patients, professional athletes who were quarantined in a bubble, to travel and entertainment venues. These asymptomatic screening programs came at a significant cost and required tremendous resources. Common sense would suggest that identifying asymptomatic cases should have helped control the pandemic, but there is little empirical evidence demonstrating that this was the case. Examining these data sets will help us to understand when these strategies worked, how often testing should occur, what test methods (molecular versus antigen) should be used, and at what intervals.

In August 2022 (updated November 2022) FDA issued a safety communication recommending repeat testing (serial testing) with at-home antigen testing. The recommendation is repeat testing following a negative result whether you have COVID-19 symptoms, 48 hours apart for up to three tests. Since antigen testing is less sensitive than molecular testing, repeat testing can increase the likelihood of an accurate result over the course of an infection (https://www.fda.gov/medical-devices/safety-communications/home-covid-19-antigen-tests-take-steps-reduce-your-risk-false-negative-results-fda-safety, accessed 26 February 2023). FDA collaborated with the NIH and the University of Massachusetts to assess serial at-home antigen testing in asymptomatic individuals and demonstrated that serial testing after a negative antigen test over a 2–3 day period decreased the likelihood of a false negative result (3–5). This can be an expensive strategy for patients purchasing antigen tests, and guidance around recommended patient behavior in the interim is unclear. Furthermore, there is a need for evidence-based data to understand the role and how best to use testing to enhance non-pharmaceutical interventions (NPI).

Beyond active screening programs, the role of other passive surveillance, such as wastewater testing, also needs to be examined more closely. Wastewater testing played a role in the early detection of cases in dormitories on college campuses that were trying to keep students in school (6–10). This strategy has also been used to detect other agents such as polio and the Mpox virus (7, 10–13). While there are many applications to this insightful technology, questions remain. What is the interpretation of these data and do

TABLE 1 Examples of big data sets that could be useful in managing a pandemic response

Laboratory data elements	Healthcare data elements
Tests performed	Emergency room visits for a given condition
Tests positive (ideally stratified by patient demographics—age, race, gender, zip code, underlying condition, symptom profile)	Intensive care unit (ICU) admissions for a given condition
Test capacity	Length of stay per visit for a given condition
Test turnaround time	Mortality rate
	Hospital bed capacity (stratified by setting such as Emergency Department, ICU, pediatric ICU, floor unit, rehabilitation)

they correlate with outcomes and actions? What benchmarks should be established so that an appropriate response infrastructure can be funded and sustained? What public health actions should be associated with the results of wastewater testing? What is the best use of surveillance resources and how can their effect be maximized? The long-term goal is to understand in a systematic, evidence-based manner what screening/surveillance testing programs make sense to employ.

Understanding the effectiveness of mitigation strategies

A Google search of the terms "COVID-19" and "mitigation strategies" will yield roughly 30,500,000 results (www.google.com, accessed 28 February 2023). These results range from mitigation at a community level to college campuses to keeping elementary schools open. Several factors go into deciding on a strategy. Looking back at the COVID-19 pandemic response, more questions arise. When is centralized testing with molecular methods better than at-home antigen testing? What is the role of antigens to rule-in and rule-out infectivity? Understanding the outcomes of test and trace, as well as test and treat programs, and how best to implement them is a key to future preparedness planning.

Analysis of studies on the role of NPI, such as masking, to reduce the spread of respiratory viruses such as SARS-CoV-2 and influenza virus has been published (14, 15). The quality, timing, viral pathogen studied, size, and primary objectives of these studies vary. A closer evaluation of data from elementary/private schools and universities would help understand real-world data outside of a more controlled healthcare setting. As with any real-world data set, understanding compliance with mitigation strategies will have a significant role in the outcome of the results. The results of some of these studies were published in a recent Cochrane review (16) which concluded, "In summary, more high-quality RCTs (Randomized control trials) are needed to evaluate the most effective strategies to implement successful physical interventions in practice, both on a small scale and at a population level. It is very unfortunate that more rigorous planning, effort, and funding was not provided during the current COVID-19 pandemic towards high-quality RCTs of the basic public health measures."

Executing a pandemic response that is equitable to underserved populations both locally and globally

Healthcare equity in underserved populations and community-based hospitals remains a problem, particularly among Hispanic and African American populations who continue to be disproportionately affected by COVID-19 and the resulting healthcare costs (17–25). The pandemic further highlighted these issues, often leaving our most vulnerable behind. It also highlighted the disparity in test access between large reference and academic health center laboratories capable of implementing high-complexity and lab-developed tests versus smaller community hospital laboratories which were limited in many cases to scarcely available sample-to-answer systems. We need to understand what allowed for a system that worked for those who lacked representation or resources. Furthermore, there is a need to identify effective programs, so that they can serve as a model to overcome barriers and improve access and outcomes. By identifying underserved populations and understanding the gaps and hurdles to their care, pandemic response efforts can be adjusted to facilitate more equitable responses.

Communicating science to influence policy and behavior

The scientific community must learn the importance of effective messaging for affecting change in policy and public behavior. While scientists communicate effectively with each other, they often fail at communicating their message when speaking to policymakers and the public. An appropriate scientific communication strategy is imperative to translate data and science to inform decision-making, and policies implemented, and gain public confidence. Additionally, we need to better understand the role of

behavioral science in successfully implementing mitigation strategies with the public. Funding in both behavior science and implementation science is required to address these concerns.

WHAT HAVE WE LEARNED ABOUT THE UTILITY OF SELF/HOME TESTING IN CONTROLLING THE PANDEMIC?

Sacrifices in test performance versus availability and rapidity of testing

While tests with acceptable performance characteristics were created within acceptable timeframes, self/home collect tests were not widely available within the first year of the pandemic. As discussed above, delays in the distribution of well-performing assays were due to challenges in regulatory pathways and in scaling up test production. Once rapid tests had been developed, there were no clear performance standards for at-home testing. The gold standard was established based on the kits that made it first to market; the performance of that first kit would set the bar for everyone else.

For future pandemics, establishing performance needs for different clinical scenarios is key. For diagnosis in the context of illness, even nucleic acid amplification testing (NAAT)-based testing can sometimes fall short. However, to aid in risk assessment for individuals seeking/needing to interact with others, testing twice serially within a defined period with a rapid antigen test was shown to be comparable clinically to PCR testing (26). When factoring decision-making surrounding an individual deciding to seek out testing, including the time spent obtaining lab-based testing and waiting on results, home-based testing was incredibly appealing. It became clear during peaks of testing that in determining whether an individual was safe to return to normal activities, waiting on results for days was unhelpful even if the results were accurate. When control and reduction of transmission were key, home tests needed to be in the community (1, 27).

Communication around test performance characteristics will be key both with the laboratory and the public. In retrospect, much of what we learned early on about the COVID-19 disease time course and optimal collection sources/specimens was borne out by larger studies. In future pandemics, it may be acceptable for the laboratory community to support testing based on assumptions gleaned from the first outbreaks, as long as we are communicating clearly about limitations. Applied to home testing and self-collection, it is important to also communicate about what testing characteristics we are optimizing for at distinct phases of a pandemic, including cost, performance, and scalability.

In the event of another pandemic, continued public familiarity with at-home testing/self-testing and what can or cannot be extrapolated from test results could be leveraged. An at-home testing culture that continues past the pandemic to include testing for other transmissible viral respiratory pathogens is on the horizon and will help protect the community from seasonal viruses affecting the vulnerable. These testing strategies must be paired with education regarding when home testing is appropriate. Laboratorians have a role in advocating for accurate and responsible testing within the home testing universe, as laboratories are already making these types of decisions. Continued involvement by laboratorians in home-testing policy will also keep home testing as part of our testing arsenal and would have the downstream effect of being able to leverage manufacturing capacity in the case of an emergent need.

Performance decreases with untrained operators versus the benefit of improved access

Even point-of-care testing performed within inpatient healthcare settings can be collected and performed incorrectly, despite controlled environments and access to training and quality programs. Transitioning similar testing to at-home use runs the risk that they will be used incorrectly in a home setting. The elderly and at-risk patients with co-morbidities may struggle more with self-tests, so there might be a need to categorize population needs regarding self-testing based on underlying conditions that may

hamper appropriate specimen collection and self-testing. Test design may also aid in ensuring correct performance; A move toward home tests with built-in readers, already in use in laboratories, would reduce the risk of misinterpreting testing. Adherence to testing algorithms, a challenge even in controlled laboratory settings, is also difficult if multiple testing events need to occur to achieve sensitivity. Telemedicine or monitored testing may increase adherence and reduce performance risks.

Readers, telemedicine, and monitored testing may also help with incidence tracking. During the pandemic, attempts at data reporting and tallying self/home testing ran into issues of compliance, privacy, traceability, and follow-up. There may be hesitancy surrounding sharing personal data with governmental entities and general privacy concerns, which would hinder the ability to require the reporting of self-testing results. Individuals might share a significant amount of personal data if the request for sharing self-testing data were to come from a trusted care provider (including a pharmacy). Despite these challenges, improved access to testing in the face of a pandemic was found to outweigh the inherent risks of performance loss with home testing.

Government distribution of testing kits: success or waste of resources?

Government distribution of rapid antigen testing began in January of 2022, 1 year after vaccination campaigns started, almost 2 years after the pandemic's start, and in the middle of the first Omicron wave. The tests distributed were EUA, well-performing assays.

At that point in time, therapeutics and vaccines were available, and the transmission dynamics of the virus were well understood. The Omicron variant showed infectious dynamics that decreased the ability of antigen tests to inform infectiousness, as people were often negative for SARS-CoV-2 by home testing while exhibiting symptoms and transmitting the virus (28, 29).

Discussion participants agreed that test distribution increased test availability, facilitated society's re-opening after the shutdowns, and promoted a return to pre-pandemic life. Furthermore, home testing became extremely useful as a signal for treatment once therapeutics were available. During the COVID-19 pandemic, therapeutics utilization in response to testing stayed limited, but it is likely to be the linchpin of future pandemic responses. Participants noted potential equity concerns in how home tests were used. For example, households with low incomes might not have had the resources to react to a positive test (by staying home from work/school) and might by necessity forego testing.

Would earlier access to home tests have saved lives?

At certain key periods in the COVID-19 pandemic, for example at the peaks of the alpha and delta waves, even the availability of an imperfect test to aid in mitigating shutdowns and helping to keep schools open would have improved life during the pandemic. Knowing if a child's symptoms were due to a transmissible virus such as RSV, influenza virus, or SARS-CoV-2, would be informative for the decision of whether to send a child to school within and beyond the pandemic. Accessibility to home testing hypothetically also allows for folks without access to clinical testing to take control of their family's health and measure risk accordingly.

If all individuals tested themselves prior to interacting with others, lives would have been saved by reducing forward transmission. Antigen testing would have been less effective in reducing forward transmission during the Omicron wave, due to changing infectious dynamics (28, 29). Ideally, manufacturing capacity will maintain the capability of ramping up quickly in the event of another pandemic.

CONCLUSIONS

Among the many topics discussed, several themes appeared. First, there is a need for a regulatory framework that empowers laboratories to utilize their unique expertise, especially early in a pandemic when widespread testing is not available. Next, test

development is an iterative process. While early versions of tests are stepping stones in the research and development process, these may need to be used in pandemic settings, with improvements made as they become available. The current regulatory framework makes this difficult, so appropriate adaptations should be considered. Third, home testing will play an increasingly significant role in infectious disease diagnostics. There needs to be a clear regulatory pathway for manufacturers to develop both at-home collection devices which can be mailed in for centralized testing and at-home testing devices. Additional studies will be needed to further understand the best use of these at-home tests. Finally, communication with the public is an essential component of pandemic preparedness. Clinical laboratorians must take an active role in ensuring the public has trust in diagnostics while understanding the weaknesses and appropriate uses of different testing options. It is important to note that small community hospital laboratories without dedicated microbiology staff are key to effectively managing past and future pandemics. Their unique needs and considerations were incorporated into the event discussions, but representation from and further consideration of this group will be essential in effectively preparing for future pandemics.

During the drafting of this manuscript, both the United States Public Health Emergency and the World Health Organization Global Health Emergency for COVID-19 were declared to be over. More than 3 years after the emergence of SARS-CoV-2, government agencies, clinical and public health laboratories, and diagnostic manufacturers are shifting to a long-term strategy where SARS-CoV-2 is managed as other common respiratory viruses we regularly contend with. While the "emerging pandemic" phase of COVID-19 is behind us, it is critically important that we learn lessons from our experiences to be more prepared for the next pandemic. Chief among the lessons of COVID-19 is the importance of a frank and open dialogue among clinical and public health laboratories, government agencies, and diagnostic manufacturers. Events like the Clinical Microbiology Open focus and facilitate such discussions.

AUTHOR AFFILIATIONS

[1]Department of Pathology and Laboratory Medicine, University of Cincinnati, Cincinnati, Ohio, USA
[2]Department of Laboratory Medicine and Pathology, University of Washington Medical Center, Seattle, Washington, USA
[3]Quest Diagnostics, San Juan Capistrano, California, USA
[4]Department of Microbiology, LabCorp, Seattle, Washington, USA
[5]Department of Pathology, Virginia Commonwealth University Health System, Richmond, Virginia, USA

AUTHOR ORCIDs

Eleanor A. Powell http://orcid.org/0009-0005-8641-7708
Elizabeth M. Marlowe http://orcid.org/0000-0002-7023-5193

REFERENCES

1. Paltiel AD, Zheng A, Sax PE. 2021. Clinical and economic effects of widespread rapid testing to decrease SARS-CoV-2 transmission. Ann Intern Med 174:803–810. https://doi.org/10.7326/M21-0510
2. Mendelson M, Sharland M, Mpundu M. 2022. Antibiotic resistance: calling time on the 'silent pandemic'. JAC Antimicrob Resist 4:dlac016. https://doi.org/10.1093/jacamr/dlac016
3. Soni A, Herbert C, Baek J, Shi Q, Marquez J, Harman E, Kheterpal V, Nowak C, Suvarna T, Lin H, Heetderks W, Zai A, Cohen-Wolkowiez M, Corbie-Smith G, Kibbe W, Gerber BS, Hafer N, Barton B, Broach J, McManus D. 2022. Association of mass distribution of rapid antigen tests and SARS-CoV-2 prevalence: results from NIH-CDC funded say yes! covid test program in Michigan. medRxiv:2022.03.26.22272727. https://doi.org/10.1101/2022.03.26.22272727
4. Soni A, Herbert C, Filippaios A, Broach J, Colubri A, Fahey N, Woods K, Nanavati J, Wright C, Orwig T, et al. 2022. Comparison of rapid antigen tests' performance between delta (B.1.61.7; AY.X) and omicron (B.1.1.529; BA1) variants of SARS-CoV-2: secondary analysis from a serial home self-testing study. medRxiv:2022.02.27.22271090. https://doi.org/10.1101/2022.02.27.22271090
5. Soni A, Herbert C, Filippaios A, Broach J, Colubri A, Fahey N, Woods K, Nanavati J, Wright C, Orwig T, et al. 2022. Comparison of rapid antigen tests' performance between Delta and Omicron variants of SARS-CoV-2: a secondary analysis from a serial home self-testing study. Ann Intern Med 175:1685–1692. https://doi.org/10.7326/M22-0760
6. Barras C. 2020. Monitor sewage to track spread of the coronavirus. New Sci 246:7. https://doi.org/10.1016/S0262-4079(20)30833-2

7. Berchenko Y, Manor Y, Freedman LS, Kaliner E, Grotto I, Mendelson E, Huppert A. 2017. Estimation of polio infection prevalence from environmental surveillance data. Sci Transl Med 9:eaaf6786. https://doi.org/10.1126/scitranslmed.aaf6786
8. Martin J, Klapsa D, Wilton T, Zambon M, Bentley E, Bujaki E, Fritzsche M, Mate R, Majumdar M. 2020. Tracking SARS-CoV-2 in sewage: evidence of changes in virus variant predominance during COVID-19 pandemic. Viruses 12:1144. https://doi.org/10.3390/v12101144
9. Orive G, Lertxundi U, Barcelo D. 2020. Early SARS-CoV-2 outbreak detection by sewage-based epidemiology. Sci Total Environ 732:139298. https://doi.org/10.1016/j.scitotenv.2020.139298
10. Pöyry T, Stenvik M, Hovi T. 1988. Viruses in sewage waters during and after a poliomyelitis outbreak and subsequent nationwide oral poliovirus vaccination campaign in Finland. Appl Environ Microbiol 54:371–374. https://doi.org/10.1128/aem.54.2.371-374.1988
11. de Jonge EF, Peterse CM, Koelewijn JM, van der Drift A-MR, van der Beek RFHJ, Nagelkerke E, Lodder WJ. 2022. The detection of monkeypox virus DNA in wastewater samples in the Netherlands. Sci Total Environ 852:158265. https://doi.org/10.1016/j.scitotenv.2022.158265
12. La Rosa G, Mancini P, Veneri C, Ferraro GB, Lucentini L, Iaconelli M, Suffredini E. 2023. Detection of monkeypox virus DNA in airport wastewater, Rome, Italy. Emerg Infect Dis 29:193–196. https://doi.org/10.3201/eid2901.221311
13. Wolfe MK, Yu AT, Duong D, Rane MS, Hughes B, Chan-Herur V, Donnelly M, Chai S, White BJ, Vugia DJ, Boehm AB. 2023. Use of wastewater for Mpox outbreak surveillance in California. N Engl J Med 388:570–572. https://doi.org/10.1056/NEJMc2213882
14. Odusanya OO, Odugbemi BA, Odugbemi TO, Ajisegiri WS. 2020. COVID-19: a review of the effectiveness of non-pharmacological interventions. Niger Postgrad Med J 27:261–267. https://doi.org/10.4103/npmj.npmj_208_20
15. Etemad K, Mohseni P, Shojaei S, Mousavi SA, Taherkhani S, Fallah Atatalab F, Ghajari H, Hashemi Nazari SS, Karami M, Izadi N, Hajipour M. 2023. Non-pharmacologic interventions in COVID-19 pandemic management; a systematic review. Arch Acad Emerg Med 11:e52. https://doi.org/10.22037/aaem.v11i1.1828
16. Jefferson T, Dooley L, Ferroni E, Al-Ansary LA, van Driel ML, Bawazeer GA, Jones MA, Hoffmann TC, Clark J, Beller EM, Glasziou PP, Conly JM. 2023. Physical interventions to interrupt or reduce the spread of respiratory viruses. Cochrane Database Syst Rev 1:CD006207. https://doi.org/10.1002/14651858.CD006207.pub6
17. Alberti PM, Lantz PM, Wilkins CH. 2020. Equitable pandemic preparedness and rapid response: lessons from COVID-19 for pandemic health equity. J Health Polit Policy Law 45:921–935. https://doi.org/10.1215/03616878-8641469
18. Berkowitz SA, Cené CW, Chatterjee A. 2020. Covid-19 and health equity - time to think big. N Engl J Med 383:e76. https://doi.org/10.1056/NEJMp2021209
19. Essien UR, Eneanya ND, Crews DC. 2020. Prioritizing equity in a time of scarcity: the COVID-19 pandemic. J Gen Intern Med 35:2760–2762. https://doi.org/10.1007/s11606-020-05976-y
20. Ivers LC, Walton DA. 2020. COVID-19: global health equity in pandemic response. Am J Trop Med Hyg 102:1149–1150. https://doi.org/10.4269/ajtmh.20-0260
21. Medina-Walpole A. 2020. What it will take to equitably distribute a COVID-19 vaccine. Geriatr Nurs 41:1028–1029. https://doi.org/10.1016/j.gerinurse.2020.10.016
22. O'Connor MI. 2020. Equity360: gender, race, and ethnicity-COVID-19 and preparing for the next pandemic. Clin Orthop Relat Res 478:1183–1185. https://doi.org/10.1097/CORR.0000000000001282
23. Vanjani R, Martino S, Wunsch C. 2020. Health equity during COVID-19. J Gen Intern Med 35:3067–3068. https://doi.org/10.1007/s11606-020-06040-5
24. Wang Z, Tang K. 2020. Combating COVID-19: health equity matters. Nat Med 26:458. https://doi.org/10.1038/s41591-020-0823-6
Williams DR, CoopeR LA, , . 2020. COVID-19 and health equity-a new kind of "Herd Immunity". JAMA 323:2478–2480. https://doi.org/10.1001/JAMA.2020.8051
26. Soni A, Herbert C, Lin H, Yan Y, Pretz C, Stamegna P, Wang B, Orwig T, Wright C, Tarrant S, et al. 2023. Performance of rapid antigen tests to detect symptomatic and asymptomatic SARS-CoV-2 infection: a prospective cohort study. Ann Intern Med 176:975–982. https://doi.org/10.7326/M23-0385
27. Song W, Abudunaibi B, Zhao Z, Liu W, Wang X, Chen T. 2023. Analysis of the effect of PCR testing and antigen testing on controlling the transmission for Omicron based on different scenarios. Infect Dis Model 8:939–946. https://doi.org/10.1016/j.idm.2023.07.011
28. Cocherie T, Bastide M, Sakhi S, Zafilaza K, Flandre P, Leducq V, Jary A, Burrel S, Louet M, Calvez V, Marcelin AG, Marot S. 2022. Decreased sensitivity of rapid antigen test is associated with a lower viral load of Omicron than delta SARS-CoV-2 variant. Microbiol Spectr 10:e0192222. https://doi.org/10.1128/spectrum.01922-22
29. Marais G, Hsiao NY, Iranzadeh A, Doolabh D, Joseph R, Enoch A, Chu CY, Williamson C, Brink A, Hardie D. 2022. Improved oral detection is a characteristic of Omicron infection and has implications for clinical sampling and tissue tropism. J Clin Virol 152:105170. https://doi.org/10.1016/j.jcv.2022.105170