Implementing U.S. Covid-19 Testing: Regulatory and Infrastructural Challenges

Health Policy Portal

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As COVID-19 cases continue to surge worldwide, more evidence is pointing towards asymptomatic transmission being a key driver of new infections, with studies showing it accounts for 17.9 to 30.8% of all infections.[1] Regions that have managed to contain the virus have relied on social distancing and aggressive efforts to test as many people as possible.[2] Unfortunately, delays in COVID-19 testing authorization and roll-out in the United States significantly hampered the country's response to the pandemic. Within the first four months of the pandemic, only around 125 people per million had been tested in the US, in comparison to 5000+ people per million in South Korea.[3] Although testing rates have improved since then, this initial lag in detection contributed to accelerated viral spread.

There were a few important reasons for the delays and challenges in the roll-out of COVID-19 testing in the United States. While FDA's Emergency Use Authorization (EUA) protocol was created for such public health emergencies, this unprecedented pandemic has revealed weaknesses in both the administrative process and the national testing infrastructure. This article draws potential lessons from other countries in how to optimize the process of reviewing and disseminating diagnostic testing in a public health crisis.

Initial Experience with Testing in the US

The outbreak of COVID-19 was first reported from Wuhan, China on December 31, 2019. Since then, the virus has spread around the world, causing more than 750,000 deaths and infecting more than 20 million people as of August 2020.[4] The viral genome was sequenced and made public by a laboratory in Shanghai as early as January 10, 2020, which allowed researchers to begin work on a molecular diagnostic test. A week later, German researchers announced that they had developed the first diagnostic tool using a polymerase chain reaction to amplify the virus' genetic code in patient sample for detection.[5] The testing protocol was made available through the World Health Organization (WHO), and it began shipping PCR assays to laboratories around the world.

In the US, local laboratories and hospitals oversee the majority of diagnostic tests. The FDA has long invoked its regulatory discretion to allow certain laboratories to develop their own tests without subjecting them to formal FDA review. These laboratory-developed tests are instead regulated indirectly by the Centers for Medicare and Medicaid Services, which does not review the specific test but certifies that the laboratory meets key quality standards. During past public health emergencies, however, the FDA has taken over the decision of whether an unapproved medical diagnostic can be used in the response.[6] The FDA's authority in these settings was clarified in the Project Bioshield Act of 2004, which authorized FDA to enact the EUA in emergencies based

About This Column

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on a demonstration that the product "may be effective" in diagnosing the disease.[7] Compared to FDA approval, there is more flexibility around amount and type of evidence required to support an EUA.[8] The first time an EUA was implemented was for the 2009 swine flu outbreak, when the FDA approved a test rapidly designed by the Centers for Disease Control and Surveillance (CDC).[9]

Just as the US had developed its own diagnostic tests in the context of the Ebola (2014) and Zika (2016) virus outbreaks, the US opted again to develop its own test instead of adopting the WHO test. The CDC publicly announced details of its own test on January 24, 2020, which was then approved by the FDA via an EUA on February 4, 2020.[10] Crucially for Covid-19, the FDA limited the initial approval to the CDC test and did not allow hospitals, academic centers, or companies to use any other test. While the goal was accurate surveillance, this decision limited the ability of the US public health system to develop rapid, widespread testing in the face of a virus spreading much faster than previous epidemics.[11]

The CDC started sending out its test kits to state public health laboratories the first week of February. Unfortunately, labs began reporting that many of the test kits were returning inconclusive results and that one of the chemicals used in the test needed to be remanufactured, leading the CDC to recall the test kits.[12] On February 28, dozens of clinical microbiologists sent a letter to Congress stating that due to FDA's restrictions on non-CDC tests, their own privately developed and validated tests were unable to be implemented — and since the CDC test at this point did not work, they were left with no other alternative. The following day, the FDA changed the EUA process to allow private labs to implement their own tests with the caveat that they had two weeks after implementation to submit data on the test's validity for the FDA to review.[13] By this time, however, crucial time had already passed without sufficient viral testing in the US.

There were a few important reasons for the delays and challenges in the roll-out of COVID-19 testing in the United States. While FDA's Emergency Use Authorization (EUA) protocol was created for such public health emergencies, this unprecedented pandemic has revealed weaknesses in both the administrative process and the national testing infrastructure. This article draws potential lessons from other countries in how to optimize the process of reviewing and disseminating diagnostic testing in a public health crisis.

The early timeline of diagnostic test development displays two important characteristics: lack of regulatory flexibility and fragmented testing infrastructure. These features contributed to a vastly different experience with the coronavirus in the US than in other key geographic areas, such as South Korea and the EU.

Lack of Regulatory Flexibility

Regulatory bodies across the world, including the FDA, are faced with the challenge of maximizing efficient oversight. For medical diagnostics, it is critical to ensure optimal sensitivity/specificity and to properly validate testing. In the case of COVID-19, the FDA viewed testing validation as crucial towards preventing faulty lab tests from being used on patients. This, along with the goal of developing a test that can perform across a variety of testing platforms, is why the FDA focused most of its initial attention on the CDC test and did not allow private or academic labs to develop and use their own tests. Unfortunately, this approach combined with the faulty reagent led to important testing delays.[14]

Although no one could have predicted the initial CDC testing kit would encounter serious technical issues, the unexpected setback highlights the importance of speed and flexibility of regulatory approval during emergent crises. The FDA's approach worked well for prior outbreaks which was not as fast-moving and global in scale.[15] For example, in the case of the Zika outbreak, the disease had first surfaced in 2007 and then garnered international attention in mid-2015, but it was not declared a public health emergency until February 2016 by the WHO, giving scientists more time to work on diagnostics.

In the current case, the insidious nature and rapid pace of the coronavirus outbreak called for more flexibility in the early stages. Many privately-owned laboratories began developing their in-house tests, especially when the CDC test flaws caused significant delay. Flexibility around initial strategies, including simultaneously pursuing multiple options and allowing both state and private labs to work on testing, would have safeguarded against unexpected breakdowns within any one approach. It is also reasonable to ask why the CDC did not adopt the German-made WHO test being used by other countries when its own testing issues arose. If the WHO test had been included in the EUA pipeline from the beginning, it likely could have been substituted when the CDC test initially failed.

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Fragmented Testing Infrastructure

As the pandemic traveled across the US, the national testing infrastructure buried within a fragmented system of public and private health laboratories posed another major barrier towards widespread testing. Even if the testing approval process had gone according to plan and the CDC test was made available earlier, equipment compatibility, reagent kit availability, and processing capacity all served as potential bottlenecks.

The US diagnostic system is broken up into state and county public health laboratories, private laboratories, academic research institutions, and hospitals, all which have independent systems that may use different equipment. For example, one of the first coronavirus tests in the US developed by researchers at University of Washington were "lab-developed tests" that could only be used within their own institution. Most labs — particularly those at county hospitals — can only run a simpler type of test called "sample-to-answer" test, which does not require the same instruments that extract and amplify viral RNA.[16]

The lack of instrumentation standardization contributed to the initial period of reagent shortage that handicapped testing in the US for the first few weeks. Not all test kits work with all testing platforms; rather, the materials and components must match each platform.[17] For example, when one key product made by Qiagen, which is commonly used by research labs to isolate viral RNA, went on back-order, labs could not use the same product produced by Roche as these reagents are only compatible with laboratory equipment made by their respective manufacturers.[18]

Finally, while public health labs have limited testing capacity, private labs often lack the support required for massive roll-outs. When the CDC initially sent its test out to state public health laboratories, it became apparent that they would not be able to meet the demands. A public health lab is not intended to be a high-throughput clinical diagnostic lab, but rather as an initial identifier and surveyor of emerging disease.[19]

One solution to address the fragmented testing infrastructure would be public-private partnerships to coordinate the national testing effort. New York provides an example of a strong public-private partnership, where Governor Andrew Cuomo brokered a deal for the private company BioReference Laboratories to provide testing capacity for the state, which allowed 24-48 hour processing time for all drive-through test sites in NY. New York now holds almost 20 percent of all completed tests in the US.[20]

Lessons from Abroad

As the US continues to struggle with creating and meeting testing capacity, the European Union and South Korea offer examples of how regulatory flexibility and coordinated infrastructure helped their own causes.

South Korea's response to Covid-19 has been applauded for timely and pervasive roll-out of testing. The country has conducted over 300,000 tests, for a per-capita rate more than 40 times that of the US; its case fatality rate is just over 1%, among the lowest in the world.[21] Its regulatory process exemplifies certain features that were key in its response. In the aftermath of the 2015 Middle East Respiratory Syndrome (MERS) outbreak that killed 38 people and took a huge toll on the economy, South Korea found that a lack of testing had prompted people with the disease to travel from hospital to hospital in search of a diagnoses, spreading it in the process. At that time, the Korean Centers for Disease Control (KCDC) was the only institution authorized to do epidemiological testing.[22]

Since then, the KCDC reorganized to include a branch specifically in charge of testing and diagnostics to respond more dynamically to epidemics. Korean officials enacted key reforms that allowed government to give immediate approval to testing systems in an emergency. Within weeks of the first outbreak in Wuhan, four Korean companies had manufactured tests from the WHO guidelines, and the country quickly had a process of testing 10,000 people a day.[23]

South Korea also used public-private partnerships to bolster its testing infrastructure. As private institutions in South Korea account for 90% of the medical system and 90% of its testing capacity, KCDC was quick to understand the importance of private sector support. Since the MERS outbreak, the public and private sectors have cooperated more efficiently, coming together in voluntary collaboration.[24] The South Korean Health Ministry officials called a meeting with representatives from private medical companies in January when only four cases of virus had been confirmed, expressing urgency for testing development. In under one week, the government had approved a test kit developed by Kogene Biotech.[25]

Interestingly, the European Union, as a patchwork of nation-states, also faced a decentralized testing structure. Still, by as early as February 2020, an effort to assess the diagnostic capacity of specialized laboratories in 30 European Union/European Economic Area countries had been launched by the European Center for Disease Prevention and Control (ECDC). Through a detailed survey of 81 laboratories across 30 EU/EEA countries, they determined that although they had sufficient testing capacity, challenges include an initial lack of positive control and a lack of primers/probes.[26] A similarly detailed assessment within the US would have been very helpful in identifying early barriers towards testing.

Within the EU, Germany has stood out for its early effective testing and subsequent success in managing the epidemic. As of April 7, 2020, its death rate from coronavirus was only 1.5%, considerably lower than fellow EU members Spain (9.5%) and Italy (12%).[27] According to the Robert Koch Institute, Germany has carried out more than 1.3 million tests, compared to Italy's 807,000 and the UK's 335,000 tests.[28] The world's first coronavirus diagnostic test was created at Germany's Institute of Virology, and soon after implemented within the country, reflecting a fast speed of approval. The other key enabler of widespread testing was the effective coordination between the German federal government and local and state-level

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agencies in rolling out testing infrastructure.[29] As a result, Germany has a well-distributed network of testing through individual hospitals, clinics, and laboratories.

Conclusions

Since the FDA began allowing private labs and hospitals to develop their own coronavirus tests and submit evidence for EUA, more than 200 emergency authorizations have been granted for different tests as of August 2020.[30] Private companies such as Roche and ThermoFisher Scientific are ramping up production of coronavirus tests. Although much improved from the beginning stages of the pandemic, US is still behind in testing capacity. As initial areas of pandemic hotspots such as New Jersey and New York slowly recover, regions in the South and California are experiencing new surges. New CDC guidelines released on August 24, 2020 changed to say that individuals who had been in close contact with an infected person "do not necessarily need a test" if they do not have symptoms, which may promote increased asymptomatic transmission.[31] Issues in implementation and delivery of testing have led to difficulty in contact tracing and containing further spread. As the US continues to fight the pandemic, it will be important to re-assess the approach towards testing oversight and implement changes that will focus on regulatory adaptability and developing the infrastructure needed to efficiently respond in the time of such crises.

Note

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