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MAYO CLINIC

Screening for SARS-CoV-2: Health Policy Implications in Low- and Middle-Income Countries

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The current pandemic due to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus has paralyzed the global economy[1] and it is predicted that on average, each additional month of the continued pandemic would cost 2.5% to 3% of the global gross domestic product.[2] A plausible end to the pandemic would be the development of population-level immunity (herd immunity),[3] which can be achieved when the majority of a given population develops immunity to SARS-CoV-2, either via infection/recovery or via vaccination. To know how far we are from this goal, and to establish other strategies to respond to the pandemic, accurate epidemiology data are needed. Unfortunately, current data remain limited. For example, the case fatality rate requires knowing the number of people infected (the denominator of the rate). The early reported case fatality rates were exaggerated and uninterpretable (eg, rates in Italy and Germany were reported as >13% and 3%, respectively).[4] The early case fatality rate and other epidemiologic indicators were dependent on testing patterns and the accuracy of testing.

In low- and middle-income countries (LMICs), where the majority of the world population resides, the challenge is more prominent. Severe acute respiratory syndrome coronavirus 2 molecular diagnostic test (ie, reverse transcription polymerase chain reaction [RT-PCR]) access per 1000 individuals was approximately 0.25 in Bangladesh and 4.90 in Iran.[5] In contrast, many non-LMIC countries, such as the United Arab Emirates, have set up massive testing facilities with the capability of conducting tens of thousands RT-PCR tests daily.[6] Other countries have implemented sero-epidemiological investigations (serosurveys). A clear understanding of the differences between molecular RT-PCR and serologic testing, as well as knowledge of the characteristics of a good screening test, are necessary for patient- and country-level decision-making.

SEROLOGY VERSUS MOLECULAR TESTING FOR SARS-COV-2

A positive RT-PCR test means that the person has an active or recent case of coronavirus disease 2019. In contrast, depending on the serologic test used, a positive antibody test (immunoglobulin M, immunoglobulin G, or total antibodies) indicates that the patient has developed an immune response to the virus. Importantly, it does not necessarily indicate when the patient was infected — it may have occurred recently and they may still potentially be shedding live, infectious virus, or they may have been infected at some point in the past and are no longer infectious. There are multiple limitations for these tests. Most notably, for RT-PCR, although false-positive results are rare, the sensitivity of these tests is impacted by the quality of the collected specimen, when the specimen was collected relative to symptom onset, and the quality of the test itself. For serologic testing, false-negative results may occur if the sample is collected before the development of an immune response, if the individual is immunosuppressed, or in some cases, if the individual had mild or asymptomatic disease. False-positive antibody test results may also occur, which is why careful validation/verification of serologic tests is needed to fully understand their

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performance characteristics. Data from the related SARS coronavirus indicate that the presence of antibodies may confer protective immunity for approximately 2 years; however, we do not yet know if this is true for SARS-CoV-2. Despite this, early on in the pandemic, some countries considered provision of immunity cards for SARS-CoV-2.

THE AVAILABLE TESTS

The current pandemic has revealed significant concerns associated with the quality of some commercially available serologic tests. Many countries including the United Kingdom, Turkey, and the Czech Republic have reported that the imported serologic tests were flawed during the internal validation studies. Moreover, there has been a huge influx of diagnostic test manufacturers who claim that their analytic validation studies show high sensitivity and specificity; however, for some assays, these claims have not been independently confirmed or clinically validated. Validation procedures are not standardized across manufacturers, and test development may not undergo a similar degree of vigor; therefore, the accuracy of serologic tests from different manufacturers may vary when tested across the same population. Many manufacturers initially also promoted their assays by stating that it can be performed at the point-of-care or at home, although the US Food and Drug Administration (FDA) has not yet approved the use of any tests in such settings. To mitigate these concerns, the FDA updated their guidance, requiring that manufacturers apply for and receive Emergency Use Authorization of their test(s). This process allows the FDA to review and approve serologic tests for commercial use.

Seroprevalence studies require a highly specific and sensitive test, regardless of format (ie, enzyme-linked immunosorbent assay, immunofluorescent assay, chemiluminescent immunoassay, or immunochromatographic test). The FDA has outlined the expected performance characteristics of serologic tests which are used when determining whether to grant Emergency Use Authorization[7]; however, ideally, sensitivity and specificity in mass testing should approach 100%.[8]

THE APPROPRIATE ASSAYS FOR MASS TESTING AND SEROPREVALENCE STUDIES

Ideal Choice

A good diagnostic test should have sufficient (1) pre-analytic validity (ie, the test needs to conform to technical specifications that relate to the collection, handling, and storage of the specimen); (2) analytic validity (ie, the test needs to measure the biomarker in an accurate manner concordant with a gold or reference standard in a laboratory setting); (3) clinical validity (ie, the test needs to have diagnostic accuracy in classifying at risk population); and (4) clinical utility (ie, the test needs to improve outcomes or decisions).[9]

Pragmatic Choice

Although the above-mentioned criteria are necessary, in real-world experience, implementing an ideal test with utility and validity characteristics may not always be possible. Additional criteria are subsequently needed to use a test in mass surveillance, such as cost-effectiveness, ease of use, and acceptability by the population. This may itself be affected by political, cultural, and financial situations in each country.

Another question which commonly arises with respect to screening is whether the health care workers need to be routinely tested for this infection at defined intervals? Many experts are currently recommending RT-PCR screening of all asymptomatic health care personnel at defined intervals (frequency variable depending on the institutional policies), which may be a reasonable approach until further data is gathered, as a large study has indicated some utility of screening of health care workers.[10]

IMPLICATIONS

We have provided a summary of the role of mass serologic testing to help understand key epidemiologic concepts such as local, regional, and national transmission patterns, infection case fatality rates, and prevalence.

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REFERENCES

1. McKibbin WJ, Fernando R. The global macroeconomic impacts of COVID-19: seven scenarios. Brookings Institution website. https://www.brookings.edu/research/the-global-macroeconomic-impacts-of-covid-19-seven-scenarios. Published March 2, 2020. Accessed November 12, 2020.
2. Fernandes N. Economic effects of coronavirus outbreak (COVID-19) on the world economy. SSRN website. https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3557504. Published March 22, 2020. Revised November 5, 2020. Accessed November 12, 2020.
3. Metcalf CJE, Ferrari M, Graham AL, Grenfell BT. Understanding herd immunity. *Trends Immunol*. 2015;36(12):753-755.
4. Stafford N. COVID-19: why Germany's case fatality rate seems so low. *BMJ*. 2020;369:m1395.
5. Our World Data. Total COVID-19 Tests per 1000 people. https://ourworldindata.org/grapher/full-list-cumulative-total-tests-per-thousand. Accessed April 26, 2020.
6. Massive COVID-19 Testing Lab Set up in UAE in 14 days. Khaleej Times. https://www.khaleejtimes.com/coronavirus-pandemic/massive-covid-19-testing-lab-set-up-in-uae-in-14-days-. Accessed April 26, 2020.
7. US Food and Drug Administration. EUA Authorized Serology Test Performance. https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/eua-authorized-serology-test-performance. Accessed September 28, 2020.
8. US Food and Drug Administration. To Manufacturers and Other Stakeholders. https://www.fda.gov/media/137470/download. Accessed May 6, 2020.
9. Chang SM, Smetana GW, eds. *Methods Guide for Medical Test Reviews*. Rockville, MD: Agency for Healthcare Research and Quality (US); 2012.
10. Rivett L, Sridhar S, Sparkes D, et al. Screening of healthcare workers for SARS-CoV-2 highlights the role of asymptomatic carriage in COVID-19 transmission. *Elife*. 2020;9:e58728.