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India's Testing Strategy for COVID-19 – An Epidemiological Perspective

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ABSTRACT

India has responded to the current pandemic of coronavirus disease 2019 (COVID-19) in terms of systems development, capacity building, upgrading infrastructure along with highest political support, including implementation of testing for COVID-19 as per Indian Council of Medical Research (ICMR) guidelines. However, the strategy, which was earlier restricted due to several reasons has now been gradually scaled up and modified as per requirements of the country. The paper attempts to evaluate the testing strategies in place with an epidemiological perspective. Newer testing modalities of feces, saliva and radiological testing hold promising evidence and need validation for effective utilization. India must deploy the tests in hand rationally for the control of pandemic. Testing for COVID-19 must address resurgence of local outbreaks currently, provide immunity certificates and intelligence on epidemic evolution in long-term.

Keywords: India, COVID-19, Testing strategy

India has responded to the current pandemic of coronavirus disease 2019 (COVID-19) in terms of systems development, capacity building, upgrading infrastructure along with highest political support including implementation of testing for COVID-19 as per Indian Council of Medical Research (ICMR) guidelines.[1]

In the first phase of the epidemic, India attempted intensive screening of travelers, strict surveillance and contact tracing of imported cases. These measures were initiated with first travel restriction implemented/imposed for travel to China on 26th February 2020 and thereafter, from 2nd March 2020 advisories restricted movement of passengers from COVID-19-affected countries. Government closed entry for all international travelers to contain the spread of COVID-19 by 22nd March, 2020.[2] This was done with an intention to focus on the second stage of control wherein control measures will be targeted to active case finding and contact tracing within Indian subcontinent. The country went for total lockdown across all states on 24th March 2020 to prevent further spread of pandemic and prepare for the upcoming surge of cases. With rise in number of active cases to 25,007 and 1,147 deaths as on 1st May, 2020, country focused on the cluster containment strategy and measures that need to be adopted to exit lockdown, simultaneously preventing any surge of cases. The rapid surge in cases was; however, noticed in the following months thereafter with variation in numbers across states. As on 11th August, number of active cases reached to 6,39,929 with 45,257 deaths.[3]

India's response to the pandemic has been timely, tough and strategic, considering the pressures from the economic front.[4] Testing strategy of the country evolved as the pandemic progressed keeping in view the epidemiological measures, available logistics for testing and the warranted response. The strategy, which was earlier restricted due to several reasons was gradually scaled up as per requirements of the country. Appropriate testing strategy is essential to control the pandemic and optimally utilize the available resources.

The current paper attempts to study the evolution of testing strategy in Indian context with an epidemiological perspective.[5]

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TESTING FOR DIAGNOSIS

Right testing strategy is essential for rapid containment of outbreak and optimal utilization of resources. Under the aegis of ICMR, laboratory expansion is an ongoing process. ICMR is engaging with several non-ICMR, Ministry of Health & Family Welfare (MoHFW), Government laboratories and private labs to initiate testing facilities for COVID-19. As on 1st July, 2020, there were 1,049 labs - 761 Government and 288 Private laboratories.[6] Real-time reverse transcriptase polymerase chain reaction (RT-PCR) for COVID-19 is being done in 557 labs, TrueNat Test for COVID-19 is being done in 363 labs and CBNAAT Test for COVID-19 in 80 labs. To meet the surge in cases, diagnostic capacity is being strengthened by making optimum use of qRT-PCR and nucleic acid amplification test (NAAT)-based machines available with the Multidisciplinary Research Units (MRUs), National AIDS Control Organization (NACO) and National Tuberculosis Elimination Program (NTEP).[7] This has enabled country's daily testing capacity to scale up significantly to more than 5,00,000 tests/day. Mechanisms have been set up to ensure that central monitoring and reporting of all tests being done is conducted. An RT-PCR app has been introduced by ICMR which is used to generate SIRF (Specimen Referral Form) number for every test being performed. This SIRF number along with mobile contact is important for entering the test in the ICMR portal and is an essential pre-requisite by the ICMR for approved testing centers.

All eligible individuals are being offered tests at no cost in Government labs and at capped prices in private labs as per the recent directive of Supreme Court of India. Kits and assays used in the country are US Food and Drug Administration (FDA) approved or have undergone validation at the Apex laboratories of the country. Specimen collection and testing protocols follow the World Health Organization (WHO) guidelines and recommendations.

Currently, two types of tests are available for diagnosis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in India. RT-PCR assay of sample identifies people currently infected by testing for the presence of novel coronavirus. It is a quantitative assay; however, not being used in routine viral load assessment. It can identify the cases early and help in isolation and cluster containment. The test is time consuming (4-5 hours) with specific expertise and precautions required in sample collection and testing. The sensitivity varies with the type of sample increasing from oropharyngeal, nasopharyngeal to sputum and maximum with bronchoalveolar lavage (BAL). Sensitivity of RT-PCR, as reported by Wang et al varied, at 93% for BAL, 72% for sputum, 63% for nasal swabs and only 32% for throat swabs.[8] Pharyngeal RT-PCR tests for COVID-19 have a sensitivity and specificity of 78.2% and 98.8%, respectively.[9] Sampling of BAL is possible only for critical patients admitted with severe acute respiratory illness (SARI), leaving behind only the pharyngeal samples to be tested for RT-PCR.

A novel Rapid point of care antigen test from a South Korean firm (Rapid antigen test kits) is a safe, rapid chromatographic immunoassay for qualitative detection of specific antigens to SARS-CoV-2 at various levels. The test has a very high specificity ranging from 99.3% to 100%. Sensitivity of the test ranges from 50.6% to 84% in independent evaluations, based on the viral load of the patient. Higher viral load correlated with higher sensitivity.[10] To increase the testing capacity, it is recommended by ICMR to use rapid antigen tests as first-line tests, where RT-PCR is not available. Those positive are considered positive and managed accordingly. Those negative, if symptomatic with influenza-like illness (ILI) and strong exposure history, are advised for RT-PCR testing. If completely asymptomatic with insignificant exposure history, they can be considered negative, e.g., not suffering from the disease. Low level of re-testing with RT-PCR in those who are testing antigen negative with strong clinical suspicion will underestimate the cases and not give the true picture of the outbreak.[11]

Interpreting COVID-19 tests for diagnosis needs to be done with caution. Considering that the pretest probability may vary from the disease prevalence significantly, we cannot assume that the post-test probability or chances of acquiring the disease may remain same. Thus, the test result, positive or negative, must be analyzed keeping in view the exposure and symptomatic history of the individual (which in turn decides the pre-test probability). With knowledge of disease still in infancy and many lacunas remaining, it is difficult to give estimates of the same. The decision must be taken on case-to-case basis while interpreting the diagnostic test.[12]

WHO calls to isolate, test and treat intensively to break the chains of COVID-19 transmission.[13] Testing protocol in India underwent modifications to ensure that epidemiological strategies, disease surveillance and economic concerns are addressed. The country's testing capacity as on March 31 was nearly 5,500 tests/day crossing the capacity of 1 lakh/day in May,[14] 2 lakh/day by June end and 7 lakh/day by August.

S No.	Date	Testing Strategy	Rationale
1	17th March, 2020	1. Symptomatic people (fever, cough, difficulty in breathing, etc.) with history of international travel in the last 14 days. 2. Symptomatic in close contact with COVID laboratory confirmed cases.	To check for cases in people with travel history to affected countries and their contacts.
2	20th March, 2020	1. All symptomatic healthcare workers 2. All hospitalized patients with severe acute respiratory infection 3. Asymptomatic direct and high-risk contacts of confirmed case on Day 5 and Day 14 of contact.	1. Prevent nosocomial transmission of disease. 2. SARI surveillance done as a part of sentinel surveillance to understand the trend of disease across states in India. Also, it is marker for community transmission. 3. Asymptomatic contacts tested to further prevent community transmission.
3	9th April, 2020	Strategy for cluster containment: All symptomatic influenza-like illnesses (ILIs) to be tested with PCR assay within 7 days of illness and antibody test after 7 days of illness. It also advises the conduct of RT-PCR in cases with negative antibody tests when suspicion to suffer from SARS-CoV-2 is high. All asymptomatic direct contacts to be tested with RT-PCR between Day 5 and 14.	Ensure that effective cluster containment is done with mass testing for all people with ILI. Both RT-PCR and rapid antigen kits must be deployed for rapid results with accuracy.
4	18th May, 2020	Following additions were done in the testing strategy: 1. All symptomatic (ILI symptoms) individuals with history of international travel in the last 14 days. 2. All hospitalized patients who develop ILI symptoms. 3. All symptomatic ILI among returnees and migrants within 7 days of illness. 4. No emergency procedure (including deliveries) should be delayed for lack of test.	The required revisions were done to ensure that the internal migration and nosocomial transmission does not add to the disease burden of COVID-19 cases.
5	23rd June, 2020	Newer testing strategies introduced were expanded at country level e.g.,True-NAAT, CBNAAT, Rapid point of care Antigen tests.	Expansion of testing capacity to the labs at the level of district hospitals and at field level.
6	1st July, 2020	Test treat and track strategy emphasized: Testing capacity boosted and the process made simpler to ensure all individuals fitting into the criteria being tested with prescriptions from any Registered Medical Practitioner. Expansion of point of care rapid antigen tests for diagnosis in containment zones and in hospitals.	

TESTING STRATEGY FOR SURVEILLANCE

- Sentinel surveillance on SARI was initiated by ICMR across country. SARI testing for COVID-19 was the only testing strategy valid pan India, with reliable estimates and interstate comparisons. This is because with the advancement of pandemic and simultaneous shortage of logistics, adherence to ICMR criterion for testing varied across states at various stages of pandemic.[15]
- Pooled testing has been advocated to reduce the cost of screening large number of individuals for infectious diseases in disease locations across stages with low prevalence. If the pool tests negative, all individuals within it are diagnosed as negative. If the pool tests positive, retesting is required to identify the positive individuals.[16] In COVID-19 pandemic, pooled testing is permitted in areas with low prevalence of COVID-19 (low positivity of <2% from the existing data). In areas with positivity of 2-5%, sample pooling for PCR screening may be considered in community survey or surveillance among asymptomatic individuals.[17]

- Antibody test, using Rapid diagnostic kits, detect the host's immune response to the virus. An indigenous IgG ELISA test (COVID KAWACH) for antibody detection for SARS-CoV-2 was developed with sensitivity and specificity of 98.7% and 100%, respectively.[18] This was a rapid test with larger one-time processing of samples. Additionally, it is possible to do ELISA-based testing at district level as the ELISA kit has inactivated virus and it requires minimal biosafety and biosecurity. IgG ELISA and CLIA tests are recommended only for sero-surveys and survey in high-risk vulnerable population (healthcare workers, frontline workers, immunocompromised individuals, individuals in containment zones, etc.) to ascertain the proportion of people who have been infected in the past and have now recovered.

  Serial sero-surveys have been initiated across the country to know the prevalence of infection in the community. This will estimate and monitor the trend of infection in the adult population, ascertain the socio-demographic risk factors and outline the spread of the infection from a geographical viewpoint. Recent sero-surveys have been conducted by ICMR which found the past exposure of infection in 0.73% of the population. Risk in urban areas and urban slums was 1.09 and 1.89 times higher than rural areas, respectively.[19] Delhi sero-prevalence study by National Centre for Disease Control (NCDC) on 21,387 samples collected across Delhi found IgG antibodies in 23.48% of the population. The study also found that majority of the infected persons remained asymptomatic.[20] Sero-surveillance study conducted in an urban slum of Dharavi found 57% of surveyed people in the slums of Dahisar, Chembur and Matunga to have antibodies in blood.[21]

  The utilization of these tests is limited to criterions laid down by ICMR. It needs to be specified that they cannot be used for diagnosis of past infection of COVID-19 for the general population. The test has been advocated after 14 days of symptom onset when the level of antibody in blood peaks. Thereafter, it is shown to decline considerably with many studies reporting absence after 2 months from the days of onset of symptoms. Levels of antibody have been correlated with severity of disease with their presence in asymptomatics under research.[22]

TESTING STRATEGY FOR DISCHARGE

Revised discharge policy of the country, under the guidance of WHO, does not recommend testing for mild-to-moderate cases of COVID-19. The patient can be discharged after 10 days of symptom onset and no fever for 3 days for mild cases. For moderate cases, if the fever resolves within 3 days and the patient maintains saturation above 95% for the next 4 days (without oxygen support), such patient will be discharged after 10 days of symptom. For severe COVID-19 cases, a negative RT-PCR test is warranted along with resolution of symptoms.[23]

NEWER TESTING OPTIONS FOR COVID-19

In a retrospective study conducted by Bernheim et al in China, findings of chest computed tomography (CT) in relation to time between symptom onset and initial CT scan was reviewed for 121 symptomatic patients infected with COVID-19. Bilateral, peripheral ground-glass and consolidative pulmonary opacities were the hallmark findings. Majority of early patients had a normal CT whereas; however, as the time elapsed, more frequent CT findings like consolidation, total lung involvement, linear opacities, "crazy-paving" pattern and the "reverse halo" signs were observed.[24]

In a case series by Fang et al, the sensitivity of chest CT was observed to be greater than that of RT-PCR (98% vs. 71%, respectively, $p < 0.001$). Immature development of nucleic acid detection technique, low viral load or inadequate clinical sampling can be the probable reasons for the low efficiency of viral nucleic acid detection.[25] It has also been observed that patients who underwent both chest CT and RT-PCR tests, the sensitivity of chest CT in detecting COVID-19 was 97%, based on positive RT-PCR results. However, in patients with negative RT-PCR results, positive chest CT findings were evident in 75%.[26]

TESTING OF FECES AND SALIVA

SARS-CoV-2 is shed through multiple routes and testing of feces and saliva are being evaluated by several companies with kits for the same. However, there is a need to validate the results as currently studies have been conducted on small samples and results cannot be generalized. Persistent shedding of virus in feces is documented for a period of 5 weeks in adults and more than 4 weeks in children after the nasopharyngeal swabs turn negative.[27,28] The results of 2019-nCoV nucleic acid test of several biological samples during the treatment of confirmed COVID-19 shows positivity in feces to be 9.83%.[29] Fecal PCR testing was stated to be as accurate as respiratory sample PCR detection with fecal PCR becoming positive, 2-5 days later than sputum

PCR positive result in 36-53% cases.[30] Fecal testing for SARS-CoV-2 may be important from the aspect of environment surveillance and sewage sampling may be utilized indirectly to assess the circulation of virus in the community.

Salivary testing for COVID-19 has been advocated as being convenient, noninvasive and safe for patients as well as healthcare providers.[31] There has been documented evidence of saliva collected through coughing out as the most appropriate strategy for SARS-CoV-2 isolation.[32] Saliva has a high consistency rate of around 90% with nasopharyngeal specimens to detect respiratory viruses, including coronaviruses, and the presence of virus is reported in high titers.[33] Saliva has also been used in screening respiratory viruses among hospitalized patients without pyrexia or respiratory symptoms. In a study by Azzi et al, salivary testing has been advocated to be a reliable tool to detect SARS-CoV-2.[34] Another study demonstrated that despite having low sensitivity, saliva testing may be a suitable alternative first-line screening test in low resource settings.[35]

CONCLUSION

Rational and sound testing should form the basis of COVID-19 prevention and control. Testing strategy must be geographically tailored, pruned as per the COVID-19 statistics and epidemiological measures for disease control. Aggressive early testing allow for early identification of cases to allow for timely targeted isolation and social distancing measures. Moreover, in developing tropical countries, reports of false-positive tests for dengue have been informed in patients later diagnosed of COVID-19. Testing data with hospitalizations and mortality statistics can be surrogate markers of disease impact. Aggregated test results at community and state levels should support disease-surveillance system for moderating the stringency of infection prevention and control measures.[36]

Mass testing in countries alone cannot result in stemming or delaying the peak of COVID-19 outbreak. Right testing strategy as per WHO recommended standards with test, treat and track strategy will result in controlling the pandemic. India must deploy tests in hand rationally for the control of pandemic. Newer testing modalities like testing saliva, fecal samples and radiological imaging must be evaluated and systems established for the same. Testing for COVID-19 has multipronged outcomes, e.g., curbing the resurgence of local outbreaks, identifying people who have developed immunity and can return to work and obtaining information on how the epidemic is evolving, including information on when a threshold for herd immunity has been reached.

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