Technical paper

COVID 19

Testing strategy - Antigen Test or RTPCR Test

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Government of Kerala

Introduction

This paper is published in context of wide spread mis information regarding Antigen Testing and RTPCR testing in the public domain. Recently a new term commonly used in literature is – **infodemics** meaning overabundance of information, both online and offline. WHO describes it as "deliberate attempts to disseminate wrong information to undermine the public health response and advance alternative agendas of groups or individuals. Mis- and disinformation can be harmful to people's physical and mental health; increase stigmatization; threaten precious health gains; and lead to poor observance of public health measures, thus reducing their effectiveness and endangering countries' ability to stop the pandemic."

There is a special section in the WHO web site to inform correct information. The WHO calls on member states to "develop and implement action plans to manage the infodemic by promoting the timely dissemination of accurate information, based on science and evidence, to all communities, and in particular high-risk groups; and preventing the spread, and combating, mis- and disinformation while respecting freedom of expression". The whole world is not only fighting COVID19 pandemic but also the infodemics. World over all Health Experts and Leaders of the Sates are appealing not to spread misinformation based on individual perceptions and without detailed studies. Such infodemic can be tackled only by providing proper information to the readers and people.

This paper informs technical aspects of both the COVID testing technologies. In the pandemic situation, there is no either-or strategy. All the actions are to be taken based on the situation of the epidemic and the best approaches available at that point of time to control the epidemic.

There is also an impression given by some of the news articles stating that there is over emphasis on Antigen testing and less RTPCR tests done. Such thing has resulted in the increase in number of cases. All these arguments need to be seen in the context of each of the time period.

The scientific papers published are enclosed in this technical paper as an Annexure to give more clarity to the reader.

Testing Strategy of Kerala - Scientific Rationale

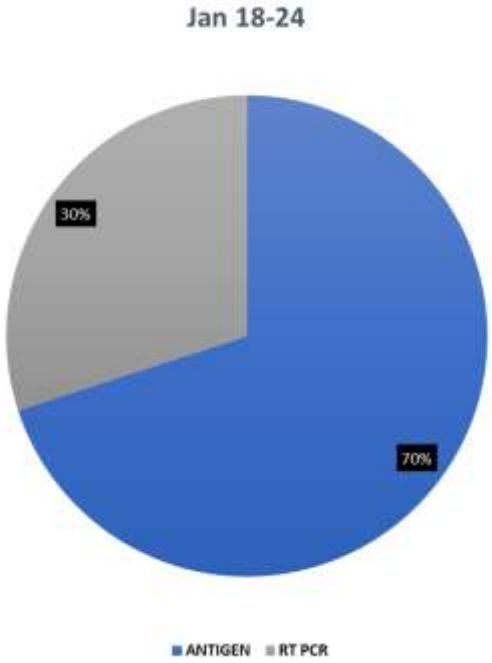
Background

The testing strategy of the state (https://dhs.kerala.gov.in/wp-content/uploads/2020/08/1597486460508_COVID-19-Revised-Testing-Guidelines-15th-August-2020.pdf) recommends rapid antigen tests to be performed at periphery for individuals with ILI and asymptomatic people in clusters where as RTPCR based tests are recommended for individuals with definite contact history, individuals with Severe Acute Respiratory Illness, symptomatic travellers, health care workers and before surgery. Symptomatic individuals who were rapid antigen negative are to undergo RTPCR based tests. ICMR recommends use of rapid antigen tests in combination with RT-PCR tests in such settings .

Table 1: Summary of COVID tests done in Kerala till 31st January 2021

TYPE OF TEST	TYPE OF SAMPLE	TOTAL SAMPLES TESTED	TOTAL NEW POSITIVES DETECTED
RTPCR- OPEN SYSTEM	Routine sample+ sentinel surveillance samples	2765823	319629
CBNAAT (RTPCR Closed System)	Priority samples	42800	3630
TRUENAT (RTPCR)	Priority samples	344619	23159
POCT PCR	Point of care test	2979	122
RT LAMP	Priority samples	1107	45
RAPID ANTIGEN TEST	Sentinel surveillance & Point-of care test	6391264	582593
ANTIBODY BASED TEST	Sero surveillance, Cluster surveillance, Airport surveillance	77321	Positives detected have been sent for RTPCR confirmation
		9625913	**929178**

Fig 1. Share of RTPCR Vs Rapid Antigen Tests Jan 18-24th, 2021



66% of total tests so far are being done using Rapid antigen tests. 62.6% of the total confirmed cases are also being found using Rapid antigen testing. RTPCR based tests (Open/NAAT) has an overall TPR of 10.9 % whereas rapid antigen tests have a positivity rate of 9.1%. Individuals with high probability of COVID (contacts) are being subjected to RTPCR

The current technical note justifies the testing strategy of Kerala with optimal use of antigen based and RTPCR based test.

Sensitivity of testing regimen is important rather than sensitivity of individual tests

The key question is not how well molecules can be detected in a single sample but how effectively infections can be detected in a population by a given test as part of an overall testing strategy — the sensitivity of the testing regimen. Measuring the sensitivity of a testing regimen or filter requires us to consider a test in context: how often it's used, to whom it's applied, when in the course of an infection it works, and whether its results are returned in time to prevent spread. Researchers from HARVARD opined in New England Journal of Medicine that with Covid-19 cases accelerating or plateauing throughout much of the world, narrow focus on the analytic sensitivity of a test (the lower limit of its ability to correctly detect small concentrations of molecules in a

sample) to be replaced with the more relevant measure of a testing regimen's sensitivity to detect infections (the probability that infected persons learn they're infected in time to be filtered out of the population and prevent spread to others). [***https://www.nejm.org/doi/full/10.1056/NEJMp2025631***]

Rapid antigen tests-based regimens are efficient than RTPCR based testing regimens in containing the pandemic

After collection, PCR samples typically require transport to a centralized lab staffed by experts, which drives up costs, drives down frequency of testing, and can delay results by one or more days. This can delay rapid isolation of individuals who are actually infectious.

Testing regimen using rapid antigen tests which can be performed at the periphery and give results within 30 minutes is more sensitive than testing based on PCR techniques for containing the transmission. Public health experts across the globe opined the same. [***https://www.nejm.org/doi/full/10.1056/NEJMp2025631***]

Sensitivity of Rapid antigen tests are good to detect infectious cases

Study published in Journal of Clinical Virology by Tuna et al (attached) has demonstrated that even though overall sensitivity of antigen tests is low (50–77.6 %), its sensitivity to pick cases which are infectious (higher viral loads) are good (88.2-89.6%). Study results suggest that antigen tests have good potential in determining contagious individuals. For an effective COVID filter that will stop this pandemic, we need tests that can enable regimens that will capture most infections while they are still infectious.

Unwarranted use of RTPCR as a routine test will detect people who are non-infectious and add unnecessary burden to the people and system

RT-PCR will detect levels of viral nucleic acid that cannot be cultured, suggesting that the presence of viral nucleic acid does not always indicate contagiousness. RTPCR can be positive in individuals for up to 42 days, though the infectiousness will be maximum only for 7-8 days. This well-described long tail of RNA positivity after the transmissible stage means that if not used without right indication, most of the people whose infections are detected using RTPCR are no longer infectious at the time of detection. Long duration of the RNA-positive tail in RTPCR suggests that most infected people are being identified after the infectious period has passed. Crucially for the economy, it also means that thousands of people are being sent to isolation after positive RNA tests

despite having already passed the transmissible stage of infection. Comparing with the incremental benefits, burden to the people and the system are huge if we use RTPCR as a screening test.

Summary

Kerala has devised a testing strategy which was proven to be successful in saving lives of individuals and containment of infections. This testing strategy has helped the state to achieve low case fatality rate and stagnant Test Positivity Rates over weeks.

Rapid antigen tests which have good sensitivity in picking up infectious cases with minimal cost, minimal turnaround time and require minimal skill sets are being rightly deployed in a robust testing regimen. This helps in preventing transmission efficiently. RTPCR based tests are being done for individuals with high pre-test probability of having COVID. This testing strategy also reduces unnecessary burdens to the people and the system.

Discussion

In the pandemic situation every new infection happens because of the previous infection. At both the ends or at one end the prevention activities are not followed and therefore the infection transmission happens. This is the most fundamental aspect one should understand. Infection does not happen because Antigen tests are done or not done. RTPCR test are done or not. Infections happen because people are complacent to the need for absolute follow up of COVID appropriate behaviour. Because infection transmission is seen even after RTPCR test done positives not following the protocol will end up spreading infection. Similarly, the individual coming in contact without following covid protocol will become positive. The individuals, irrespective of testing by RTPCR or ANTIGEN, always following all prevention activities and changed their behaviour will always have the least probability of contracting COVID 19 and even other viral diseases.

The efforts are taken to identify who is infected and ensure infected person is kept in isolation and is following the prevention aspects and covid appropriate behaviour.

The news report on the national level study https://www.indiatoday.in/coronavirus-outbreak/story/for-every-detected-covid-case-india-missed-90-infections-study-1750285-2020-12-17 has demonstrated that Kerala and Delhi might be missing out least percentage of positive cases in comparison to other States in the country.

The Antigen test if negative of the symptomatic person, is to be followed up by RTPCR test. For argument sake if it is assumed that the cases are getting missed out. Out of these missed cases, many(a proportion of missed cases) would have ended up in the Hospitals with serious symptoms. In the data analysis of the Hospitalization of serious cases, it is seen to be constant for the last six months. The missed out cases would have passed on infections and again these missed out cases would have in turn infected many more persons, this way in a geometric progression the new infections would have risen leading to a corresponding increase in hospitalizations. However, the new infection numbers and hospitalizations do not reflect the same.

There is another over emphasis on the test positivity rate of the day. In this regard, it must be kept in mind that the testing strategy clearly says that symptomatic cases to be tested. Out of general population if the tests are done the rate will be less. Out of symptomatic people if the tests are done the positivity rate will be always high (pre-test probability). This should be understood in the right perspective because such active case finding is assisting to reduce future transmission possibility and because the patient comes on the treatment track early, the probability of going to serious

condition reduces. The data also is suggesting the same obseravation in terms of less hospitalization and lower mortality rates.

Some news reports also say that the number of tests are inadequate. All the field officers, Collectors have been taking all measures to encourage testing. However, it is noticed that people are hesitant to come forward for testing even though in Government Laboratories all COVID tests are free. All Influenza like illness, severe acute respiratory illness patients, pregnant ladies, elderly above 60, people with morbidity, primary contact of the known positives, patient needing surgery, population prone for close social interactions such as front line workers etc should be undergoing testing.

Post October surge, the cases in November have come down. During pre-election period and elections, mixing of people was inevitable and as a result the spike in cases was anticipated. We see increase in cases than the previous month but not as we had experienced during October. Wherever the prevention measures were not followed by the groups and individuals, because of complacency, there the cases have gone up.

All these aspects take us back to the BASICS i.e. at population level, people should strictly follow wearing mask, maintain social distance and use hand sanitizer/ hand wash. People should bring in behaviour change by minimizing social interaction, during social interaction change the mode of it. At the health functionary level, we need to Screen – Test – Isolate- Contact trace – Quarantine – Symptom surveillance- Hospitalization – Treatment and care – Post covid care continuum to follow. Hence the campaign 'Back to the BASICS' is launched.

At the end, it is a Peoples' movement. We all have to collectively fight so that the health machinery shall be effectively able to provide much needed health services to COVID patients as well as non COVID patients.

We welcome the feedback from Health Experts, backed up by the scientific rationale to strengthen the fight against COVID.

Annexure 1: Available scientific evidences in literature regarding Rapid Antigen Tests and RTPCR based tests

Literature Review done by Dr Anish TS, Associate Professor, Govt. Medical College, Thiruvananthapuram

Search term used: ((COVID 19[Title/Abstract]) AND (Rapid Antigen [Title/Abstract])) AND (RTPCR[Title/Abstract])

The search retrieved 7 papers as follows

Sl No	Title of the paper	Result/Conclusion	Impression
1	Evaluation of a rapid antigen test (Panbio™ COVID-19 Ag rapid test device) for SARS-CoV-2 detection in asymptomatic close contacts of COVID-19 patients	The overall sensitivity and specificity of the RAD test was 48.1% (95% CI 37.4-58.9) and 100% (95% CI 99.3-100), respectively. Individuals testing positive by RAD test were more likely ($p < 0.001$) to become symptomatic than their negative counterparts.	Even if RAD is less sensitive, it can detect people with transmission potential and can prevent the spread. Figure 1 (Figure given below) shows that the cases missed by RAD is people having high CT value and low viral load (Means people less able to transmit the disease)
2	Evaluation of rapid antigen detection kit from the WHO Emergency Use List for detecting SARS-CoV-2	Generally RAD kit has got only 68.6% sensitivity. But RAD will be positive in high viral load and low CT value	Second paper is also giving the same result. The table is given as Table 1 for reference (Look at table 1, below)
3	Evaluation of clinical utility of novel coronavirus antigen detection reagent, Espline® SARS-CoV-2	Although the overall sensitivity of the Espline® SARS-CoV-2 reagent compared with RT-PCR is less, this antigen test can be useful in identifying people with high risk of virus transmission with high viral loads in order to prevent the pandemic and is useful for diagnosing COVID-19 within 30 min	The conclusion of the study clearly endorses the findings of the previous studies

4	Evaluation of Abbott BinaxNOW Rapid Antigen Test for SARS-CoV-2 Infection at Two Community-Based Testing Sites - Pima County, Arizona, November 3-17, 2020	Despite a lower sensitivity to detect infection, rapid antigen tests can be an important tool for screening because of their quick turnaround time, lower costs and resource needs, high specificity, and high positive predictive value (PPV) in settings of high pretest probability. The faster turnaround time of the antigen test can help limit transmission by more rapidly identifying infectious persons for isolation, particularly when used as a component of serial testing strategies.	
5	Performance Characteristics of BinaxNOW COVID-19 Antigen Card for Screening Asymptomatic Individuals in a University Setting	In individuals with presumably high viral loads (Ct < 23.0), a 95.8% positive agreement was observed between the RT-PCR assay and BinaxNOW. Due to the possibility of false negative results, caution must be taken when utilizing rapid antigen testing for screening asymptomatic individuals.	
6	Performance characteristics of a rapid SARS-CoV-2 antigen detection assay at a public plaza testing site in San Francisco	Using this Ct<30 threshold for Binax-CoV2 evaluation, the sensitivity of Binax-CoV2 was 93.3% (14/15), 95% CI: 68.1-99.8%, and the specificity was 99.9% (855/856), 95% CI: 99.4-99.9%.	Asserts the very important finding again. Antigen tests are capable of detecting cases with transmission potential. That is ct value less than 30

7	Comparison of the Quidel Sofia SARS FIA Test to the Hologic Aptima SARS-CoV-2 TMA Test for Diagnosis of COVID-19 in Symptomatic Outpatients	Using a C_T value of ≤35 as a surrogate for SARS-CoV-2 culture positivity, we estimate that the SOFIA test detected 87.2% of symptomatic patients tested ≤5 days from symptom onset who were likely to be culture positive.	

Figure 1

Differential CT values and Viral loads RTPCT diagnosed COVID 19 with respect to the RAD result

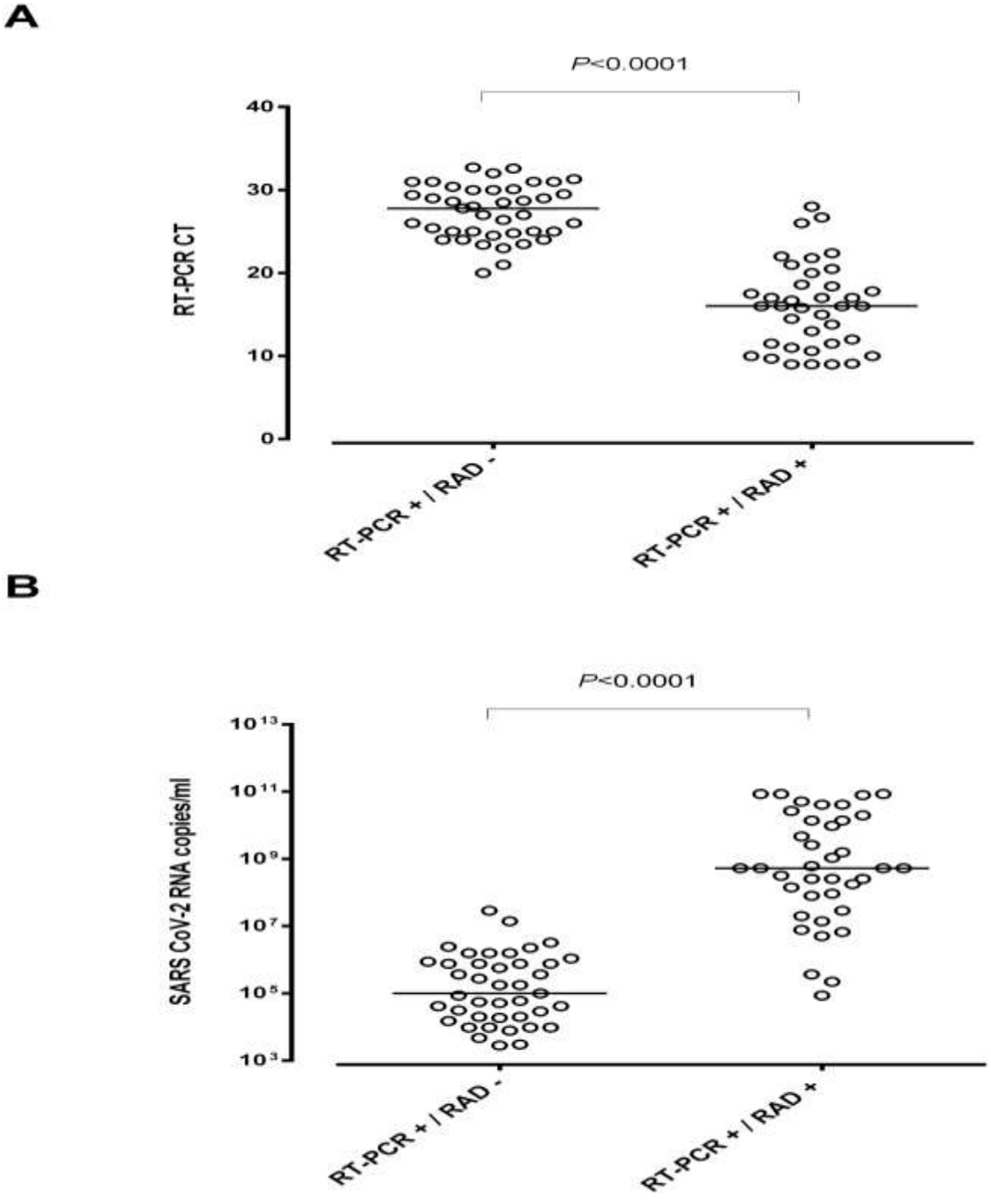


Table 1

Comparative CT value and viral load from paper 2

Table 1
Comparison of RT-PCR and rapid antigen detection kits for the limit of detection of SARS-COV-2 virus.

Dilution[b]	Test results[a]			
	RAD test			RT-PCR[e]
	Panbio (100 μL)[c]	Panbio (350 μL)[d]	Standard Q	
10^{-1}	POS	POS	POS	16.41
10^{-2}	POS	POS	POS	19.80
10^{-3}	POS	POS	POS	23.15
10^{-4}	POS	POS	POS	26.29
10^{-5}	NEG	NEG	NEG	28.80
10^{-6}	NEG	NEG	NEG	33.58
10^{-7}	NEG	NEG	NEG	NEG

[a] POS, positive; NEG, negative.
[b] Serial tenfold dilution of the respiratory specimen, NPS & TS, obtained from the Hong Kong COVID-19 patient, hCoV-19/Hong Kong/VM20031164/2020.
[c] Specimen volume of 100 μL was mixed with the extraction buffer. The subsequent procedures were carried out according to the manufacturer's instructions.
[d] Specimen volume of 350 μL was mixed with the extraction buffer. The subsequent procedures were carried out according to the manufacturer's instructions.
[e] RT-PCR were tested twice with identical results. The Ct values shown were the mean of both runs.

Conclusion:

From the evidences produced from the papers above, the advantage of RTPCR over Rapid Antigen test is mostly theoretical. Rapid antigen test is highly sensitive to diagnose cases with transmission potential (CT value less than 30) and has a clear advantage from a managerial point of view.