The Novel Coronavirus Pandemic 2020: The Origin, Transmission, Virion Properties and Diagnosis of COVID-19

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Abstract : COVID-19 caused by severe acute respiratory syndrome coronavirus- 2 (SARS-CoV-2) has affected human population at an alarming rate. Presently according to the World Health Organization, there are a reported 79 million cases worldwide, including over ~1.3 million deaths, since its discovery and outbreak in China, in December 2019. This is the third pandemic within 18 years by Coronaviruses, which are members of the family *Coronaviridae*. The first being severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002 followed by the Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012. The aim of this review article is to provide amalgamated information about the pandemic by elaborating on the history and the origin of Coronavirus. Furthermore, we have discussed transmission, symptoms, virion properties and diagnostics of COVID-19 available till date.
Keywords: COVID-19, SARS-CoV-2, Coronavirus, Lateral flow assay, RT-PCR

INTRODUCTION

The **C**oronavirus **D**isease 20**19** (COVID-19) has notoriously affected the lives of nearly 79 million people in 200 countries across six continents (Organization 2020a). The pandemic is caused by coronavirus initially called as the **n**ovel **co**rona**v**irus (2019-nCoV) by World Health Organization (WHO), and now referred as **S**evere **A**cute **R**espiratory **S**yndrome- **Co**rona**v**irus 2 (SARS-CoV-2) (Organization 2020a). It has been reported to be originated from Wuhan City, China, where within a short span of time infected nearly 83,000 people including 4000 deaths (Organization 2020b).

The crown-like enveloped coronavirus were first identified in 1960s (Caul and Clarke 1975). Coronavirus (CoV) are classified on the basis of genetic and serologic properties into four genera –alpha (α-), beta (β-), gamma (γ-), and delta (δ-), of which only α and β-CoV have origin in bats and are capable of infecting mammals (Maclachlan and Dubovi 2010) (fig. 1). Gamma and delta CoV have origin from birds and usually cause avian bronchitis. Furthermore, δ-CoV has been reported to infect pigs and leopards (Maclachlan and Dubovi 2010). Previously, there were six human-susceptible α and β-CoV reported in literature, of which four (HCoV-229E (α); HCoV-NL63 (α); HCoV-HKU1 (β) and HCoV-OC43 (β)) caused mild respiratory symptoms (less mortality rates in humans), while two (SARS-CoV (β) and MERS-CoV (β)) causes severe respiratory tract infections (higher mortality rates in humans) (Al-Tawfiq, et al. 2014; Yin and Wunderink 2018). The latest addition is SARS-CoV-2 which is also β-coronavirus (subgenus *sarbecovirus* and subfamily *Orthocoronavirinae*) and shares 82% similarity with SARS-CoV (Huang, et al. 2020; Zhu, et al. 2020). The first SARS-CoV was identified in November 2002 in Beijing, China (Liang, et al. 2004). The pandemic extended to nearly 30 countries and by March 2003, 8000 people were reported to be infected including 800 deaths (Drosten, et al. 2003; Liang, et al. 2004; Stadler, et al. 2003). Later, Middle East respiratory syndrome coronavirus (MERS-CoV) emerged in Saudi Arabia in 2012 and spread to 27 countries infecting nearly 2000 people including 800 deaths (Mohd, et al. 2016; Zaki, et al. 2012).

SARS-CoV-2 has spread to 200 countries and infected 79 million people including 44.5 million recoveries and 1.3 million deaths (Organization 2020b). It has been reported that MERS-CoV had higher mortality (~34%) rate in human population as compared to SARS-CoV (11%) and SARS-CoV-2 (2.6%) till date (Van Doremalen, et al. 2013; Yin and Wunderink 2018). This review will offer a perspective on features of SARS-CoV-2 in terms of its origin, modes of transmission, symptoms of infection and current diagnostics available for the same.

Origin and Transmission

CoVs are known to transmit across various species such as birds, bats, swine, camels, cattle, horses, cats, dogs, rabbits and rodents (Maclachlan and Dubovi 2010). Although speculations of SARS-CoV-2 origin from bat to an unknown source (such as turtles or pangolin) and finally to humans has been considered as it shares 96.2% similarity with Bat CoV RaTG13 (Guo, et al. 2020; Zhou, et al. 2020), however the source of SARS-CoV-2 to humans is elusive.

SARS-CoV-2 can be transmitted from human-to-human via three primary ways including close contact, touch and aerosol transmission with the infected person or incubation carriers. The virus infects other humans via respiratory droplets produced during coughing or sneezing by the infected person, which then enters mucous membranes of mouth, nose or eyes of the exposed person. The previous two β-CoVs could facilitate faecal-oral transmission and recently it has been reported that gastrointestinal tract may shed virus and faecal-oral transmission is plausible (Wu, et al. 2020b; Xu, et al. 2020). Furthermore, a study has indicated that the infection can be transferred from mother to the unborn child. The child on birth had high levels of IgM, which cannot cross placenta suggesting the vertical transfer of infection from mother to child (Dong, et al. 2020).

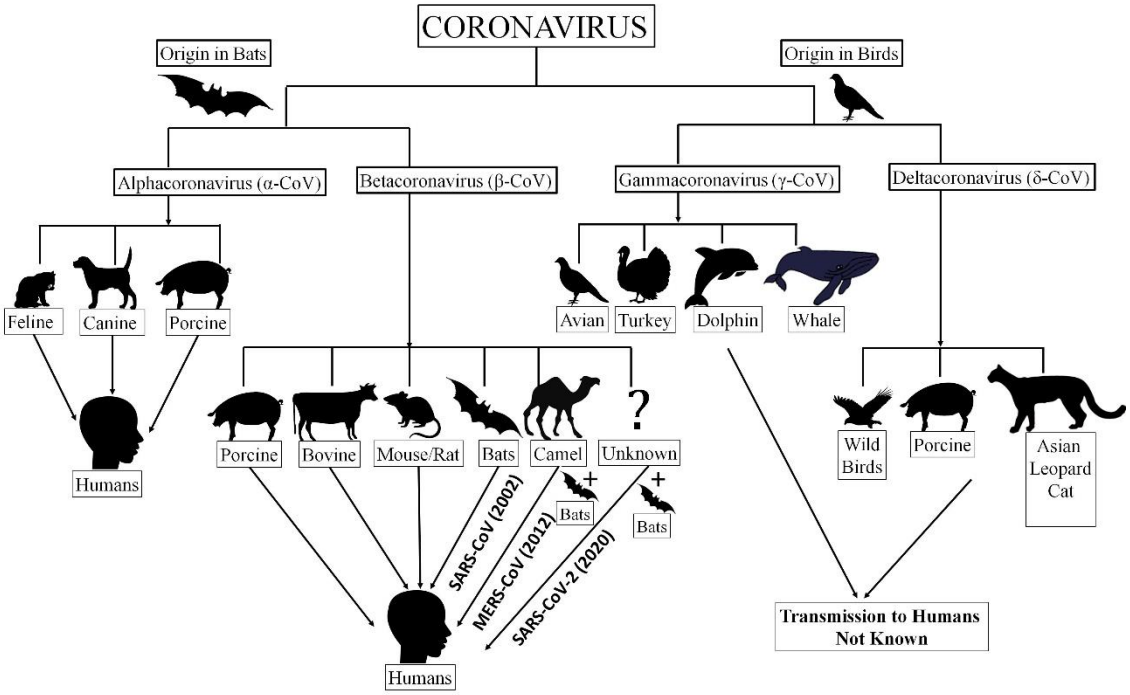

Figure 1: Schematic representation of four genera of Coronavirus with their origin and inter-species transmission.

The viability data for SARS-CoV suggests that it can survive up to 5 days at 22-25°C with 40-50% relative humidity, whereas MERS-CoV is viable at 20°C and 40% relative humidity for 48 hours. No viability data for SARS-CoV-2 is available at present, however a recent report suggests that half-lives of SARS-CoV and SARS-CoV-2 was similar in aerosols (van Doremalen, et al. 2020). Furthermore, the virus was reported to be stable and viable on plastic and stainless steel up to 72 hours, which can be another mode of transmission (van Doremalen, et al. 2020).

Early Symptoms of the Disease

The signs and symptoms on the exposure of coronavirus are not highly specific and usually mimics that of the seasonal flu (Guan, et al. 2020; Organization 2020b). In early reports of patients with COVID-19, SARS-CoV-2 infection predominantly causes fever, cough and fatigue (Guo, et al. 2020; Huang, et al. 2020). However, patients have also reported symptoms including skin tingling, sputum production, headache, haemoptysis and nasal congestion (Guan, et al. 2020; Ling and Leo 2020; Ren, et al. 2020; Wu, et al. 2020a; Yuki, et al. 2020). Gastrointestinal symptoms including diarrhea, nausea, vomiting and abdominal pain were reported to be rare in COVID-19 patients, contradicting the major symptoms of SARS-CoV and MERS-CoV infections.

The symptoms of COVID-19 are described to appear after the incubation period of approximately 5.2 days (Rothan and Byrareddy 2020), however their appearance can vary between 6 to 41 days depending on age and susceptibility of the patient. Further radiological investigations such as CT-Scan and X-Ray of the chest can assist in diagnosis of COVID-19 (Huang, et al. 2020; Wu, et al. 2020a). X-Ray and CT scans suggests abnormalities such as peripheral consolidations, pneumonia, lesions and lung opacities in most patients however cannot be considered as confirmatory results as these are not specific to COVID-19 (Ai, et al. 2020; Hope, et al. 2020; Wong, et al. 2020; Wu, et al. 2020a; Yoon, et al. 2020). Furthermore, clinical examinations report the patients with decreased white blood cells and lymphocytopenia (count less than 1000 lymphocytes per microliter of blood in adults). Patients with severe infection had elevated blood urea and creatinine, neutrophil count, interleukin IL-6 (inflammatory factor) and tumour necrosis factor-α (TNF-α) (Guo, et al. 2020; Huang, et al. 2020).

Moreover, the recent reports suggest that patients with pre-existing history of diseases such as hypertension, respiratory system diseases, coronary heart disease and immunosuppressed patients (cancer patients) are prone to the SARS-CoV-2 infection as compared to healthy individuals (Clerkin, et al. 2020; D'Antiga 2020; Zheng, et al. 2020). Furthermore, recent studies have indicated that asymptomatic patients-who exhibit no physical symptoms of the infection and negligible abnormalities in the chest radiograph, gave positive results for viral nucleic acid test (Gasmi, et al. 2020). There are several reports of increase in number of asymptomatic patients who act as a reservoir and potent transmitters of COVID-19. This indicates that social distancing and trade and travel restrictions in the present scenario as a precautionary measure for restriction of the outbreak can be effective (Bai, et al. 2020; Lai, et al. 2020; Nishiura, et al. 2020).

Virion Properties of SARS-CoV-2

Members of *Coronviridae* are usually pleomorphic, enveloped and spherical in shape (80-220 nm in size). They have distinct 20 nm long large club shaped spiked structures (trimers of spike protein) over its surface, hence giving it characteristic crown like appearance. It is the largest known genome among RNA viruses with linear positive sense, single-stranded RNA ranging from 26000-37000 bases (Li, et al. 2017; Maclachlan and Dubovi 2010; Spaan, et al. 1988; Weiss and Navas-Martin 2005). The RNA genome codes for four proteins- spike (S), envelope (E), membrane (M) and nucleocapsid (N) (Maclachlan and Dubovi 2010) (fig. 2). The virus enters the host cells using spike protein and hence governs the zoonotic potential of the coronavirus. β-Coronaviruses have an additional fringe spikes (5 nm long) and is composed of the hemagglutinin-esterase (HE) protein. S protein which comprises of two functional subunits S1 and S2. S1 subunit enables binding of virus to host cell receptor as has receptor binding domain(s). The S1 subunit has four domains- domain A (S^A), domain B (S^B), domain C (S^C) and domain D (S^D), of which SA, SB or both domains are employed in receptor binding depending on the species of β- Coronavirus. The S2 subunit contains fusion machinery and hence is responsible of fusion of viral and cellular membrane (Kirchdoerfer, et al. 2016; Li, et al. 2017; Maclachlan and Dubovi 2010; Walls,

et al. 2016). β- Coronavirus- SARS-CoV and SARS-CoV-2 interact directly with angiotensin-converting enzyme 2 (ACE2) to enter the target, while MERS-CoV employs dipeptidyl-peptidase 4 (DPP4 or CD26) (Li, et al. 2017; Maclachlan and Dubovi 2010). N protein is a structural protein and forms complexes with genomic RNA and interacts with M protein during virion assembly (McBride, et al. 2014).

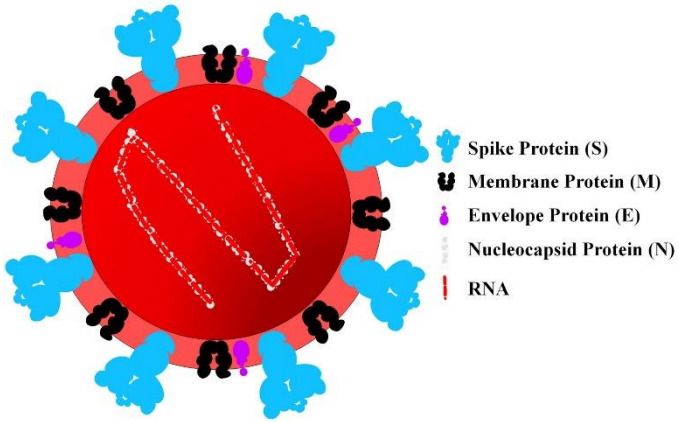

Figure 2: Schematic diagram of Novel Coronavirus- SARS-CoV-2 responsible for COVID-19.

Furthermore, N protein involves viral replication cycle and host cellular response. M protein (23-35 kDa) is the most abundant structural protein and is responsible for the virion envelope formation (McBride, et al. 2014). E protein (9-12 kDa) is the smallest structural protein of the virus and along with M protein is important for virion assembly and budding (Schoeman and Fielding 2019; Walls, et al. 2020). The response to CoV infection is produced by generating virus neutralizing antibodies principally for S and N proteins and hence have inclination for therapeutic and diagnostic applications (Fehr and Perlman 2015; Li, et al. 2017; Maclachlan and Dubovi 2010; Weiss and Navas-Martin 2005).

Diagnosis of COVID-19

The nonspecific symptoms on the onset of infection and absence of vaccines and therapeutics for SARS-CoV-2 till date has made diagnostics to be a principal way to identify infected persons and hence containment of COVID-19. The diagnosis of COVID-19 is based on evaluation of antibodies produced by the infected person to fight against the infection or the analysis of nucleic acid detection in samples collected from respiratory tract of the patients by reverse-transcriptase-based Polymerase Chain Reaction (RT-PCR) and further validation by next generation sequencing (NGS). The RT-PCR is presently the gold standard for confirmation of COVID-19, while the quantification or qualification of antibodies-IgM and IgG is rendered as a screening method (fig. 3).

Several lateral flow assays (LFA) for determination of levels of immunoglobulins-IgG and IgM from human serum using enzyme linked immunosorbent assay (ELISA) have been developed. The levels of IgM rise on the onset of infection within one week, followed by appearance of IgG (usually after two weeks). Moreover, IgG can persist up to detection levels for six months post infection indicating the history of infection in the patient. The lateral flow assay is developed on nitrocellulose membrane with conjugate pad. The conjugate pad contains both-SARS-CoV-2 antigen and anti-IgM conjugated bound to gold nanoparticles. The nitrocellulose membrane has two (one control and one test anti-SARS-CoV-2 IgG/IgM) or three (one control and two test- anti-SARS-CoV-2 IgG and anti-SARS-CoV-2 IgM) lines. On application of a positive sample and its migration, the antibodies bind to the SARS-CoV-2 antigen and adheres on the test line(s) which as anti-antibody IgG/IgM immobilized (fig. 3). The control line should always produce red colour as it indicates the validation of the lateral flow assay. Presence of only IgM indicates recent infection, while presence of only IgG suggests pervious infection. Positive for both, IgM and IgG will also indicate recent infection. However, the absence of both can be due to no infection or presence of antibodies not within detectable limits if the patient has physical signs and symptoms of the exposure to the virus. The LFA have absolute specificity (100%) for both IgG and IgM, however have less sensitivity and accuracy (57% and 69% for IgM; 81% and 86% for IgG). They have poor analytical sensitivity compared to RT-PCR, but due to high rise in number of infected patients they are being employed for primary screening.

The nucleic acid testing employing reverse transcription PCR (RT-PCR) have been designed to identify SARS-CoV-2. The upper respiratory samples from the patients are recommended and obtained as nasopharyngeal and oropharyngeal swabs and nasal aspirates. However, lower respiratory samples (sputum and tracheal aspirates) can also be analysed for determination of viral load. The kit involves reverse transcription of RNA from SARS-CoV-2 into complementary DNA strands (cDNA). The specific regions of cDNA are then amplified using a set of primers and probes. Three regions which have conserved sequences have been discovered- (1) RNA-dependent RNA polymerase gene (*RdRp* gene), (2) the envelope protein gene (E gene) and (3) the nucleocapsid protein gene (N gene) and forward and reverse primers and probes from various institutions have been reported (Long, et al. 2020; Organization 2020c; Udugama, et al. 2020). RT-PCR is a one-step assay, which enables reverse transcription (step 1) followed by PCR amplification (step 2) in one reaction tube enabling the technique to be rapid and can be extended for high throughput analysis.

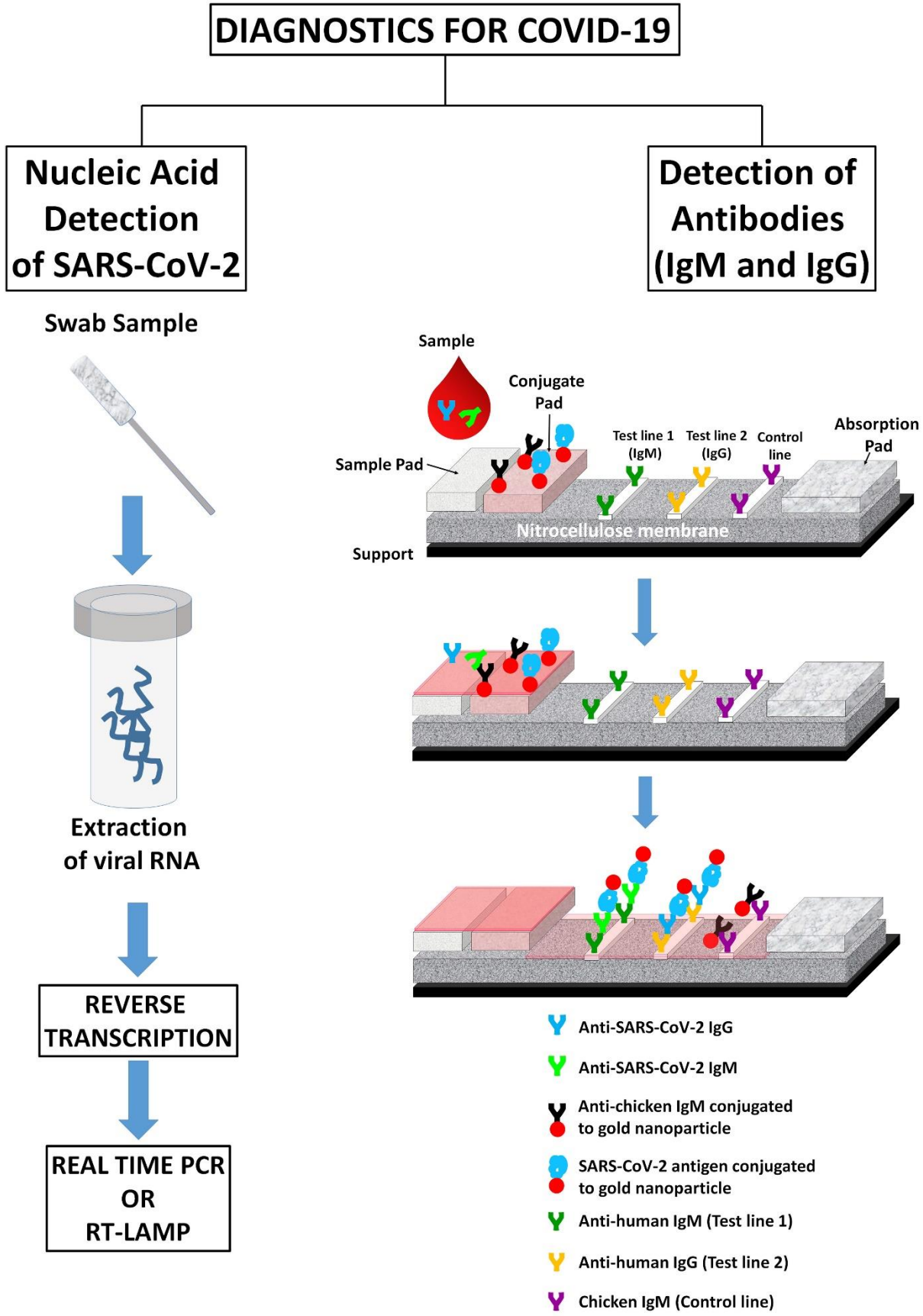

Figure 3: Schematic illustration of current diagnostics for COVID-19 by determination of SARS-CoV-2 using RT-PCR or RT-LAMP or antibodies (IgM and IgG) as an immune response to the infection using a lateral flow assay.

However, the sensitivity of one-step assay is reported to be less when compared to two-step assay involving two different tubes for each step. The Chinese Centre for Disease Control and Prevention (China CDC) recommended the RT-qPCR to detect two different regions of the viral genome. However, a varying sensitivity between 50-79% was reported for the same (Li, et al. 2020; Organization 2020c). The United States Centre for Disease Control and Prevention (CDC) recommends one-step real time reverse transcription PCR (rRT-PCR). The technique enables detection of the virus and quantification of the viral load in the sample as has higher sensitivity (~83%) (Long, et al. 2020; Udugama, et al. 2020). In rRT-PCR, a fluorophore-quencher probe is employed which when cleaved generates a fluorescent signal thus enabling the real time analysis of the amplification process. The technique is high throughput and can be conducted in 96-well plate. However, due to the unavailability of the kits because of increasing demands and

lack of sophisticated infrastructure with PCR, several other nucleic acid testing methods are being explored such as isothermal amplification techniques. These techniques have an advantage of working on a single temperature and hence do not require specialized laboratory. Reverse Transcription Loop mediated isothermal amplification (RT-LAMP) is one such technique which has gained popularity for development of tests for SARS-CoV-2. The technique uses four to six primers and hence displays highly specificity. The amplified DNA is detected by observing turbidity of the sample, or change in coloration due to presence of pH sensitive dyes, or increase in fluorescence by addition of dyes specific for double stranded DNA (Li, et al. 2020; Shen, et al. 2020; Udugama, et al. 2020).

DISCUSSION

The COVID-19 pandemic has affected all the countries across the world and impacted the lives and health of humans. The chances of occurrence and development of the infection by SARS-CoV-2 depends on the interaction of virus and individual's immune system. Due to unavailability of vaccines and promising clinical treatment till date, social distancing is the most effective and preventive strategy for the containment of COVID-19. Furthermore, the outbreak can be regulated to some extend by identification of the infected patients using lateral flow assays as first line of diagnosis followed by RT-PCR, which is a gold standard and confirmatory test for COVID-19.

CONFLICT OF INTEREST

As the authors of the manuscript, we declare that we have no conflict of interest related to this article.

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