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Corona Virus Epidemiology in India and Management Strategies: A Review

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ABSTRACT: The infection goes into the host body through the mouth, nose and eye. From that point, the infection advances down into the air sacs inside the lungs, known as alveoli. Once in the alveoli, the envelope spike glycoprotein present in the infection ties to its cell receptor, angiotensin-changing over catalyst 2 (ACE2) for SARS-CoV-2. There are two usually utilized nucleic corrosive recognition innovations forSARS-CoV-2 are ongoing quantitative polymerase chain response (RT-qPCR) and high-throughput sequencing. WHO and ECDC encouraged to maintain a strategic distance from open spot and close contact to contaminated people and pet animals.As the infection undermines network spread, there is a pressing need to improve foundation, create novel testing offices, get ready HR, support cutting edge wellbeing laborers and quest for a fix until the fight is won.

I. INTRODUCTION

HISTORY AND ORIGIN

The name "coronavirus" is gotten from Latin crown, signifying "crown" or "wreath because of the trademark appearance of virions , which have an edge of enormous, bulbous surface projections making a picture suggestive of a crown or of a sun based crown. Human coronaviruses were found during the 1960s. The third novel coronavirus to develop in this century is called SARS-CoV-2. It caused coronavirus disease (COVID-19), which rose up out of China in December 2019[1] . The first case of coronavirus disease gave pneumonia of obscure reason in the town of Wuhan, China. It was accounted for to the Country office of WHO, China on December 31, 2019. From that point forward, the infection had quickly spread to the remainder of the World representing high grimness and mortality. The sickness was reported a Public Health Emergency of International Concern on January 30, 2020. On February 11, 2020, the WHO proclaimed COVID-19 as another name for the sickness, while the International infection arrangement commission called the novel coronavirus as extreme intense respiratory disorder coronavirus 2 (SARS-CoV-2). It was proclaimed a worldwide pandemic by the World Health Organization on March 11, 2020[2].

MORPHOLOGY

The virus is estimated to have diameter of 0.12 micrometer and its shape is spherical and pleomorphic. The virus is enveloped with lipid bilayer with structural protein such as membrane, spike anchored on it. There are surface proteins resembling small spikes known as hemagglutanin esterase (HE). Multiple copies of nucIeocapsid protein are seen inside the envelope which for the nucleocapsid. The beads-on-a-string type conformation are bound to the positive-sense single-stranded RNA genome in a continuous. There is a 5′ methylated cap and a 3′ polyadenylated tail[3]in the genome with range of 26.4 to 31.7 kilobases. There are four structural proteins (spike (S), envelope (E), nucleocapsid (N) and membrane (M) proteins) and accessory proteins encoding the 1/3rd of genome while other 2/3rd genome ORF1a/b encodes polyproteins(which forms viral replicase transcriptase complex) [4].

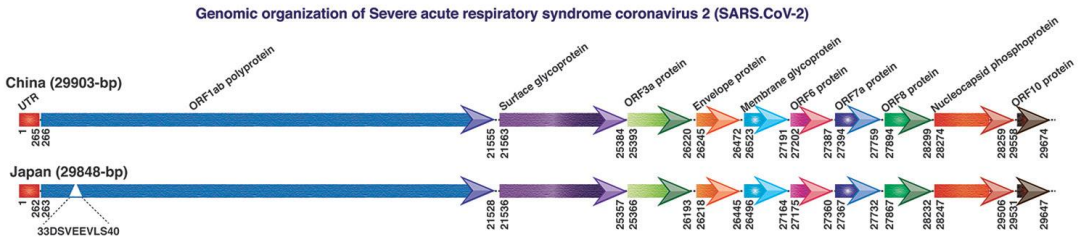

Fig. 1. Genomic organization of severe acute respiratory syndrome-coronavirus 2. ORF, open reading frame. *Source*: Refs 5,6.

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TRANSMISSION

Airborne zoonotic droplets are responsible for the spread of coronavirus. The cellular damage is caused by replication of virus in ciliated epithelium that further leading to infection site of infection. According to a study published in 2019, it was seen that coronavirus in human cells uses Angiotensin converting enzyme 2 (ACE2), which is a membrane exopeptidase[7-9]. The age and immunity of the patient determines the severity and onset of COVID-19. The incubation period of COVID-19has a range from 2- 14 days and can be last for more than 2 weeks[10-11]. According to many studies high risk patients include patients with comorbidity such as hypertension, coronary heart disease, obesity[11,12]. The symptoms include fever, nonproductive cough, sneezing, dyspnea, myalgia, fatigue, normal or decreased leukocyte counts, shortness of breathing along with pneumonia on X-Ray similar to the symptoms of SARS-CoV and MERS-CoV infections[4].

PATHOGENESIS

Coronavirus infection has complex mechanism in the pathogenesis of disease[11]**.** There are four steps included in the life cycle of the COVID-19 infection i.e. attachment and entry, Replicase protein expression, replication and transcription and assembly and release[13]. The entry of virus in the human body occurs through the mouth, nose and eye. From there, the virus makes its way down into the air sacs inside your lungs, known as alveoli. Once in the alveoli, the envelope spike glycoprotein present in the virus binds to its cellular receptor, angiotensin-converting enzyme 2 (ACE2) for SARS-CoV-2. Once the virus' RNA has entered a cell, new copies are made and the host cell is killed in the process, releasing new viruses to infect neighboring cells in the alveolus and cause inflammation in lung which in turn activate the immune response.

Rodriguez-Morales et al.[14]analysed 19 different studies in a meta-analysis and reported that fever, cough and dyspnoea were the most common manifestations among the 656 COVID-19 patients. Around 32.8% developedARDS, 20.3% patients required critical care, and 6.2% developed shock. Fatal outcomes were observed in13.9% patients. Old age was significantly associated with the severity of the disease[14]. Similar clinical manifestations were observed in another meta-analysis by Yang et al. which included eight studies with 46,248 infected patients and reported that hypertension, diseases of respiratory and cardiovascular system may be significant risk factors for severity of COVID-19[14]. Later, these findings were supported by Emami et al. in another meta-analysis. After systematically analysing the data of 76,993 patients, smoking history and diabetes was also added to the list[16].

DIAGNOSIS

Clinical diagnosis of COVID-19 is mainly based on epidemiological history, clinical manifestations and some auxiliary examinations, such as nucleic acid detection, CT scan, immune identification technology (Point-of-care Testing (POCT) of IgM/IgG, enzyme-linked immunosorbent assay (ELISA) and blood culture. However, the clinical symptoms and signs of patients infected with SARS-CoV-2 are highly atypical, including respiratory symptoms, cough, fever, dyspnea, and viral pneumonia. Therefore, auxiliary examinations are necessary for the diagnosis of COVID-19, just as the epidemiological history. There are two commonly used nucleic acid detection technologies for SARS-CoV-2 are real-time quantitative polymerase chain reaction (RT-qPCR) and high-throughput sequencing[17].

The high throughput sequencing is limited due to its equipment dependency and highly expensive whereas RT-q PCR is effective and commonly used for the detection of viruses from the respiratory secretion of patients. In this RT q PCR techniques two primers and probes are used in ORF1ab and N gene region for the detection. RT qPCR has to detect both the targeted region of viral genome present in the patients to be confirmed as infected. Although RT qPCR are specific but false negative rate cannot be denied[17].

PREVENTION

In world, the cases of COVID 19 increases with high rate, so it is very much essential to opt the prevention. COVID 19 is inversely proportional to the immune system of the individual. Most of the people get infected with COVID-19 have mild symptoms and recover due to the proper medication, early stage or good immunity, whereas some patients are deceased due to the low immunity with having the previous diseases such as asthma, heart disease, diabetics, etc. there is no clinically proven drug for the treatment of COVID-19. Prevention is the only way to stay safe and healthy. As per the WHO guidelines, there are few prevention guidelines which need to be followed during this pandemic.

1. **Washing of Hand Frequently:** Washing your hands with soap and water or using alcohol-based hand rub regularly and thoroughly kills viruses that may be on your hands[18-19].
2. **Maintain social distancing**: Maintain at least 1 metre (3 feet) distance between yourself and

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anyone who is coughing or sneezing. When someone coughs or sneezes, they spray small liquid droplets from their nose or mouth which may contain virus. If you are too close, you can breathe in the droplets, including the COVID-19 virus if the person coughing has the disease[18-19]. Avoid touching eyes, nose and mouth: Hands touch many surfaces and can pick up viruses. Once contaminated, hands can transfer the virus to your eyes, nose or mouth. From there, the virus can enter your body and can make you sick[18-19].

3. **Practice respiratory hygiene**: Make sure you, and the people around you, follow good respiratory hygiene. This means covering your mouth and nose with your bent elbow or tissue when you cough or sneeze. Then dispose of the used tissue immediately. Droplets spread virus. By following good respiratory hygiene, you protect the people around you from viruses such as cold, flu and COVID-19[18-19].
4. **Seek medical care early:** Stay home if you feel unwell. If you have a fever, cough and difficulty breathing, seek medical attention and call in advance[18].
5. **Cloth face covering:** Wear cloth face covering in the public setting where the social distance cannot be opted. It is additionally advised to use cloth mask rather than N95 mask to avoid spreading of the virus and help people who may have the virus and do not know it from transmitting it to others[20].
6. **Disinfecting surfaces:** Proper cleaning of frequently touched surfaces such as door, cabinet, etc. has to be performed using household detergent and water because COVID-19 virus survives on surfaces for many hours[21].

Apart from the aforementioned steps, there are several other steps, which can be opt by individual as a prevention such as resting and avoiding overexertion, drinking sufficient amount of water, avoiding smoking and smoky areas, etc.[1].

EPIDEMIOLOGY IN INDIA

COVID-19 has been the biggest public health crisis state since World War II. It has not limited itself as a medical emergency; it is affecting the global economy and if proper measures are not taken, it could have serious implications in socio-economic status and daily lives of mankind. It has deeply challenged the health care infrastructure especially in low- and middle-income countries. Every country is trying to protect its populations and the health workers as effectively as possible. India has already implemented nationwide lockdown since March 25, 2020 with the vision to 'break the chain' of infection and control its transmission. As the virus threatens community spread, there is an urgent need to improve infrastructure, develop novel testing facilities, prepare human resources, support frontline health workers and search for a cure until the battle is won.

On March 28, 2020, the total confirmed COVID-19 cases were 775 with 19 deaths. As on April 04, 2020, this number has increased to 3127 confirmed cases and 86 deaths[22].

Countries have introduced mobile-based apps and digital platforms to aid surveillance activities for COVID-19 control (Table 1). In some countries, the participation is voluntary and in others it is the basis for permitting movement in society. Apps for COVID-19 surveillance are made to perform two complementary functions: syndromic surveillance and contact tracing. They have been integrated with sectors beyond health such as law enforcement.

TABLE 1: Distribution of Mobile based applications in various countries

Country	Name of app	Contact tracing	Syndromic reporting	Consent	Geolocation or personal data collected	Comments
China	Alipay Health Code	Yes	Yes	No	Yes	Checklist would issue QR[a] code with one of three colors denoting quarantine status. The code is checked at various points of movement. Information is shared with the police for appropriate action, if

						required.
Russia	Social Monitoring	Yes	Yes	No	Yes	Government-issued QR code that needs to be presented to police, if required. It also ensures adequate check on people in quarantine and assesses their compliance with instructions.
South Korea	Corona 100m	Yes	Yes	No	Yes	Demographic data and location history is noted in the app at the time of COVID-19[b] diagnosis. It also alerts users if they come within 100 m (328 ft) of a location visited by confirmed case.
Singapore	Trace Together	Yes	Yes	No	No	Using Bluetooth, Trace Together identifies other nearby phones with the app during the period of infectiousness for SARS-CoV-2[c] (14 days). Data is stored in phone for 21 days and accessed only when the person is identified as being in close contact with a confirmed case of COVID-19 or has been diagnosed with COVID-19.
India	AarogyaSetu	No	Yes	Yes	No	Translated in 11 languages for use across all states of India. No mandatory government reporting and functions primarily as an app for self-assessment of COVID-19 risk and information if deemed necessary by an individual.

Bats have been implicated as reservoirs[23],and given their wide flight range in Asia, specific hostcontrol is difficult and unrealistic.

MANAGEMENT AND VACCINATION

There is no special vaccine for this yet. Only supportive therapy is the treatment strategy followed by health professionals. Supportive therapy includes administration of antipyretic and analgesic, maintenance of hydration, mechanical ventilation as respiratory support and uses of antibiotic in bacterial infections.The treatment course may warrant management of respiratory failure with non-invasive ventilation, mechanical ventilation and extracorporeal membrane oxygenation (ECMO). Additional intensive care therapies such as vasopressors and renal replacement therapy may be required while managing SARS-COV-2 infections[24].

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Many trials have been initiated along with the awareness of this outbreak out of which some trials focused on involving the patient recruitment to look for the effectivenessof using washed microbiota transplantation,remdesivir, ritonavir-lopinavir combination,

vitamin C infusion, darunavir and cobicistat,hydroxychloroquine for pneumonia, umifenovir andtraditional Chinese medicines, to name a few options[25].

Some guidelines in Chinahave recommended the use of α-interferon combinationwith the repurposed lopinavir/ritonavir combination (*Kaletra*) which have been used widely for the treatmentof patients admitted in hospitals[26]. Improvement in the first USpatient of COVID-19 after treatment with remdesivir[27],and subsequent experience of clinical response inanimal models has generated interest in the agent[28].

The WHO R&D blueprint and its Working Group conveyed an informal consultation on prioritization of vaccine candidates against SARS-CoV-2 in Geneva onJanuary 30, 2020[29,30]and identified at least five leading candidate vaccines for SARS-CoV-2[31].

As on February 13, 2020, the WHO expert group did not release a prioritization list, nor did the US Clinical Trials registry show any registered clinical trials on vaccines against SARS-COV-2. Among the different candidates in the pipeline, nucleic acids and viral vectored vaccine are being tried. INO-4800 is one of the leading candidates developed by Inovio Pharmaceuticals and Beijing Advaccine Biotechnology based on a DNA plasmid vaccine Electroporationdevice. Inovio aims to begin phase I clinical trial in the US simultaneously with Beijing Advaccine in China[25]. Clover Biopharmaceuticals is developing a recombinant subunit vaccine based on the trimeric S protein (S-Trimer)[25]. All the vaccine studies are currently in the preclinical phase.

CURRENT STRATEGIES AND ISSUES

Appropriatemeasures are required to keep laboratory staff safe while producing reliable test results.In the analytic stage, real-time reverse transcription-PCR (RT-PCR) assays remain the molecular test of choice for the etiologic diagnosis of SARS-CoV-2 infection while antibody-based techniques are being introduced as supplemental tools. In the postanalytical stage, testing results should be carefully interpreted using both molecular and serological findings. Finally, random-access, integrated devices available at the point of care with scalable capacities will facilitate the rapid and accurate diagnosis and monitoring of SARS-CoV-2 infections and greatly assist in the control of this outbreak.

There are certain current issues which should be known to clinicians, clinical microbiology laboratories and public health authorities for the laboratory diagnosis of COVID-19.

Preanalytical issues. (i) Initial respiratory tract specimen collection for diagnosis and screening of patients with COVID-19 pneumonia. There is usually high viral loads in upper and lower respiratory tract within 5 to 6 days after the start of symptoms, onset of symptoms, patients with COVID-19 have demonstrated high viral loads in their upper and lower respiratory tracts32. For screening/diagnosis of early infection of COVID-19 the recommended specimens are nasopharyngeal (NP) swab and/or anoropharyngeal (OP) swab32. NP Swab (single specimen) as well tolerated by the patient and safe for operator has been considered as the preferred swab. NP swabs have an inherent qualitycontrol in that they usually reach the correct area to be tested in the nasal cavity. Wanget al. have just reported that OP swabs (n_398) were used much more frequently than nasal swabs (n_8) in China during the COVID-19 outbreak; however, the SARS-CoV-2 RNA was detected in only 32% of OP swabs, which was significantly lower than the level in nasal swabs (63%)33. While collection/testing of both nasal and OP swabs, either as independent specimens or together within a single aliquot of viral transport medium, might be an attractive option under normal circumstances, institutions must also consider the potential stress that this pandemic places on national/international supply chains. In this light, another excellent reason to limit testing with NP swabs is to prolong supplies of flocked swabs and/or transport media. However, as we understand more about respiratory and oral contact routes of transmission, we may learn that patients with pharyngitis as a dominant initial presenting symptom can be adequately sampled via the OP route. In order to properly obtain an NP swab specimen, the swab must be inserted deeply into the nasal cavity. Patients will likely flinch, but that means the swab has hit the target. Swabs should be kept in place for 10 s while being twirled three times. Swabs should have flocked nontoxic synthetic fibers, such as polyester, as well as synthetic nylon handles34. Collecting an NP/OP swab specimen may carry a theoretical risk of transmitting SARS-CoV-2, particularly if airborne transmission is demonstrated as the investigation of the COVID-19 outbreak continues. If personal protective equipment (PPE) cannot be utilized due to scarcity of such PPE, other means of collecting upper respiratory tract specimens will be needed35. One

alternative option for collecting an upper respiratory tract specimen to evaluate patients with suspected COVID-19 pneumonia is a self-collected saliva specimen32. Should the supply of swabs become scarce, other nonflocked swabs and transport media have been cleared equivalently by the Food and Drug Administration (FDA) under an emergency use authorization (EUA), but head-to-head comparisons are lacking currently. After collection, swabs should be placed in viral (universal) transport medium for rapid transportation to the clinical microbiology laboratory, ideally under refrigerated conditions34. It should be noted, however, that in some cases, saliva/NPs/OPs may miss early infection and that in later infection, the main site of replication may have shifted to the low respiratory tract. Repeated testing or obtaining lower respiratory tract specimens may be required. Repeated testing may be particularly important if a patient has a clinical picture of viral pneumonia, a potential exposure history, and/or radiographic findings (chest computed tomography [CT] or magnetic resonance imaging [MRI] scan) consistent with COVID-19 pneumonia. Equally challenging are how the results of a single undetected result should impact decisions regarding patient quarantine and social distancing, in particular when the patients themselves are health care providers (including clinical laboratory staff). Serology, as discussed in the postanalytical section, may assist in such situations32.

(ii) Late detection and monitoring of patients with severe COVID-19 pneumonia.

Ideally, sputum sampling or bronchoalveolar lavage should be used for collecting lower respiratory tract specimens as they have yielded the highest viral loads for the diagnosis of COVID-1935. A recent study revealed that samples bronchoalveolar lavage (BAL) fluid yielded the highest SARS-CoV-2 RNA rate although this study did not compare/evaluate results from NP swabs33. Patients who present with severe pneumonia and acute respiratory distress syndrome may require emergent intubation as well as respiratory isolation in a negative-pressure room. If possible, a lower respiratory tract sputum specimen should be collected during the intubation procedure. Alternatively, sputum and/or bronchoalveolar lavage fluid specimens can be collected after intubation36. However, some patients with COVID-19 pneumonia have demonstrated high viral RNA loads of SARS-CoV-2 in fecal material as well as delayed shedding from the respiratory tract late in their clinical course32. Thus, aside from direct respiratory sampling, the preferred method for detectingSARS-CoV-2 in advanced COVID-19 cases may be a rectal swab and real-time RT-PCR.

(iii) Safety measures for specimen processing for PCR processing and testing.

Processing of respiratory specimens should be done in a class II biological safety cabinet although some laboratories would argue that biosafety level three (BSL-3) work procedures should be used and that the safety cabinet should be in a negative-pressure room within the laboratory such as that used for mycobacterial cultures36,37. The clinicalspecimens/swabs should not be heated to 56°C for 30 min as evidence suggests that this process may also degrade the coronavirus RNA even as it inactivates viable coronavirus36. Once the clinical specimen in viral transport medium is transferred into a cartridge in a class II biosafety cabinet, the cartridge is sealed. Many of these random-access sealed devices are suitable for point-of-care testing for local hospitals and clinics without biosafety cabinets. In this situation, the specimen collector in appropriate protective gear (splash guard/goggles, mask, gloves, and disposable laboratory coat) could directly transfer the specimen into detection cartridges at bedside or in a location without a class II biosafety cabinet, and the closed cartridge could be safely placed on an instrument for testing. However, spills of transport solution during transfer to these cartridge-based tests should be avoided, and if they occur, decontamination should be performed as appropriate32.

Analytical issues. (i) Assay selection. Immunoassays have been developed forrapid detection of SARS-CoV-2 antigens or antibodies. These rapid point-of-care immunoassaysare generally lateral flow assays, for detecting antigens such as the SARS-CoV-2 virus or fordetecting antibodies (IgM and IgG) against COVID-19.

Rapid antigen lateral flow assays would theoretically provide the advantage of a fasttime toto result and low-cost detection of SARS-CoV-2but are likely to suffer from poorsensitivity early in infection, based on the experience with this method for influenza(Flu) viruses[38]. Thereis concern that, given the variability of viral loads in COVID-19 patients, antigendetection may miss cases due to low infectious burden or sampling variability.

(ii) Assay selection for molecular detection of SARS-CoV-2. Random-amplification deep-sequencing methods played a major role in the initial identification of SARSCoV- 239-40. Deep sequencing molecular methods such as next-generation sequencing and metagenomic next-generation sequencing will continue to be needed to determine future mutations of SARS-CoV-2 but are

currently impractical for diagnosing COVID-19. Most of the molecular diagnostics being developed for the diagnosis of COVID-19 involve real-time RT-PCR assays, including those from the U.S. Centers for Disease Control and Prevention41, Charité Institute of Virology in Berlin, Germany42, and Hong Kong University43. Other molecular methods are being developed and evaluated worldwide and include loop-mediated isothermal amplification, multiplex isothermal amplification followed by microarray detection, and CRISPR (clustered regularly interspaced short palindromic repeats)-based assays44.

(iii) Target selection for real-time RT-PCR assays. A real-time RT-PCR method is recommended for molecular testing45. A major advantage of real-time RT-PCR assays is that amplification and analysis are done simultaneously in a closed system to minimize false-positive results associated with amplification product contamination. There are a number of coronaviruses that cause respiratory and intestinal infections in humans. Among these coronaviruses are a group of SARS-like bat coronaviruses, including both SARS-CoV and SARS-CoV-2, that comprise a unique clade under the subgenus Sarbecovirus46. Postanalytical issues.

(i) Interpretation of molecular results. In the United States, initially if both of two targets in the CDC assay (nucleocapsid proteins N1 and N2) test positive, a case is considered to be laboratory confirmed47. A cycle threshold (CT) value of less than 40 is defined as a positive test, while a CT value of 40 or more is defined as a negative test. A CT value of _40 for only one of the two nucleocapsid protein (N1 and N2) is defined as indeterminant and requires confirmation by retesting47. Although some correlations have been revealed, viral loadsdetermined by real-time RT-PCR assays should not be used yet to indicate COVID-19severity or to monitor therapeutic response48-49. However, low CT valuesindicating high viral loads may be used as an indication of transmissibility50.

(ii) Test of cure and test of infectivity. Monitoring patients with resolution of COVID-19 pneumonia may also be important in terms of when they should be released from isolation and discharged. If discharged patients are still shedding viable coronavirus, they are likely to infect other people. Therefore, self-quarantine for up to 1 month has been recommended in some cases32

II. CONCLUSION

The role of rectal swabs in testing patients with late infection or as a test of infectivity/cure is currently not well studied but needs urgent attention. Equally unappreciated is theneed for broad screening/testing with molecular testing and/or serological testing inorder to determine the true mortality rate as well as other epidemiological markers.Finally, the importance of rapid development of integrated, random-access, point-ofcaremolecular devices for the accurate diagnosis of SARS-CoV-2 infections cannot beoveremphasized. These short turnaround-time (STAT) tests will be very important forreal-time patient management andinfection control decisions, especially when otherless infectious forms of pneumonia are present and respiratory isolate resources arescarce. These assays are safe, simple, and fast and can be used in local clinics andhospitals that already have the needed instruments and that are responsible foridentifying and treating such patients.

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