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Running Head

A close up on COVID-19

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Targeted Population, Strategy, Issues and Progress to Combat COVID-19

Authors and affiliations

Dheeraj Kumar Saini[1], Nikhil Rai[1], Prashant Kumar Jha[1], Mani Kant Jha[2]

[1]School of Minerals, Metallurgical and Material Engineering, Indian Institute of Technology Bhubaneswar, Argul 752050, Odisha, India

[2]Indira Gandhi Institute of Medical Science, Patna, Bihar, India

Corresponding Author:

Dheeraj Kumar Saini

School of Minerals, Metallurgical and Material Engineering

Indian Institute of Technology Bhubaneswar, Argul 752050, Odisha, India

Email: dks12@iitbbs.ac.in

Phone no. : +91-8273686154

Author contributions

Dheeraj Kumar Saini: layout of the manuscript, Writing original draft preparation

Nikhil Rai: Conceptulize economuic section

P**rashant Kumar Jha and Mani Kant Jha:** Formal analysis of manuscript

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Abstract

Introduction

A COVID-19 disease threatens the population and the economies of the countries significantly. Till now, this pandemic has affected 215 counties or territories. Unavailability of vaccine is the primary concern for the society. To avoid the spread of this disease, social isolation must be preserved and the inter and intra-population movement must be minimized. To reduce the possibility of transmission, the categorization of regions based on susceptibility to COVID-19 infection is a must.

Method

Due to the unavailability of a large amount of paper collection for this novel COVID-19 diseases, we used current literature available on a COVID-19 susceptibility of the diabetic patient, human reproductivity, hemodialysis patient's, pregnant women and meteorological factors and geographical location.

Results

Countries in the cold region are more susceptible to the risk of COVID-19 transmission. There was no evidence of the spread of this disease from non-respiratory bodies. Diabetic patients and pregnant women were found to be more susceptible to COVID-19 infection. Anosmia was observed in the majority of the COVID-19 infected cases in European countries. No evidence indicates COVID-19's impact on the human reproductive system explicitly. No cases of vertical transmission of this disease have been observed until now.

Conclusion

All the studies available till now is the small scale study. Correlation with something always does not mean causation. There are certain factor like pollution level, temperature Diurnal temperature range, geographical factor, humidity, pollution level, wind speed, population density, medical healthcare facilities social and political factor plays a critical role in transmitting the SARS-COV-2 virus. Besides the adverse effects, it has taught us to shed our selfish goals and to promote the welfare of all.

Highlights

- There was no evidence of the spread of this disease from non-respiratory bodies.
- There are certain factor like pollution level, temperature Diurnal temperature range, geographical factor, humidity, pollution level, wind speed, population density, medical healthcare facilities social and political factor plays a critical role in transmitting the SARS-COV-2 virus.
- Till now no evidence indicates COVID-19's impact on vertical transmission of disease.

Keywords

Cardiovascular disease; Human reproduction system; Meteorological factor; SARS-COV-2; Antigen testing

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Introduction

A Rapid spread of SARS-COV-2 (Severe Acute Respiratory syndrome) led to a pandemic COVID-19 (Coronavirus disease 2019). COVID-19 viral genes show 86.9% identity with the SARS-COV genome; therefore, it is known as SARS-COV-2 [1]. Zero patient of COVID-19 was found in Wuhan province of China on 8 December 2019. The global spread of SARS-COV-2, WHO declare COVID-19 as a pandemic on 1 March 2020. Globally as of 11 May 2020, there have been 4,006,257 confirmed cases of COVID-19, including 278,892 deaths reported by WHO [2]. Till now, the source of the origin of SARS-COV-2 is not known. There is an ambiguity regarding animal or human origin. Before this pandemic, all human coronavirus originated from mice or domestic animals [3]. SARS- COV-1, MERS (Middle East Respiratory Syndrome) are the previously originated respiratory syndrome, which has the same symptom as SARS-COV-2. These symptoms are associated with mild illness, severe acute respiratory syndrome distress, severe respiratory infection and death [4]. Real exposure to such disease defined by the R_0 number known as reproduction or transmission rate. In 2009 for seasonal influenza, H1N1 had R_0 value as 1.46 -1.48 and for COVID-19, it is reported as 2.24 - 3.58 [5]. R_o between 2.24 to 3.58 shows that 2-3 people infected from every index cause.

Structure or coronavirus

Coronavirus is a kind of large chain, single-stranded, enveloped RNA virus with a diameter of 80-120 nm [6, 7]. The envelope of the coronavirus consists of viral assembly (membrane protein, envelope protein) and spike protein, which mediate viral entry into the host cell [8]. Spike protein has a crown-like structure with two subunits. Where the S1 subunit/domain works as a host cell membrane for viral binding and the S2 subunit allows the SARS-COV-2 viral genome to enter into the host cell membrane. Spike protein consists of an amino-terminal. A part of the S2 domain (amino-terminal) bind to human Angiotensin-Converting Enzyme 2 (ACE 2) and responsible for the fusion of viral and host cell membrane [9].

How is it spreading?

The transmission of SARS-COV-2 takes place through the fomites and respiratory droplets and contact during human to human transmission [9, 10]. It targets the human lungs and causes severe damage to the lungs. The mildly infected patient shows symptoms like shortness of breath, headache, fever, cough, sputum production, myalgia and anosmia [11]. A critically ill patient shows symptoms like respiratory failure, cardiovascular disease, shock and multiorgan dysfunction. People with advanced age over 65 years of age with heart disease more likely to show severe symptoms of COVID-19 [7]. Approximately 80% of COVID-19 infected people show mild infection (flu-like symptom), 15-20% shows severe infection that requires oxygen supply and 5% shows the critical infection required ventilator [12]. SARS-COV-2 RNA had detected in human blood and stool. Therefore, for the detection of COVID-19, stool or blood sample of the patient is used. Yet no evidence is available that shows the spread through non-respiratory bodies [13]. The previous study shows that SARS-COV-2 was found in the aerosol for up to 3 hours with a half-life of 1.1 hours and on the surface of the plastic and stainless steel up to 72 hours [14].

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2. SARS-COV-2 and Cardiovascular disease

Cardiovascular disease involves the blockage or narrowing of the blood vessel that leads to chest pain and heart attack. SARS-COV-2 attacks the human lungs and causes severe lung damage. It is suggesting the need to understand the potential mechanism of cardiovascular disease causes through SARS-COV-2.

2.1. Imbalance of Renin-Angiotensin System (RAS)

RAS is the hormone system responsible for the regulation of blood pressure and fluid balance. Spike protein of SARS-COV-2 binds the ACE-2 receptor that is homologs to ACE and the critical component of the RAS. ACE converts the Renin Hydrolyzes Angiotensinogen to Yield Angiotensin I to angiotensin II (Ang II). Ang II causes vasospasm that leads to higher blood pressure. Therefore ACE 2 binding with spike protein leads to the excessive release of Ang II, which in turn the heart loading by increasing blood pressure [7].

2.2. Cytokine storm

The fusion of spike protein and ACE 2 activates the immune response, which released pro-inflammatory cytokine. After the fusion of viral with the host cell membrane, the virus replicates it on the lung surface cell and causes lung inflammation. This infection causes downregulation of ACE 2 without affecting the ACE enzyme [15, 16]. Filtration of inflammatory cells from the blood and accumulation of cytokine at the injury site causes a cytokine storm. This leads to the over-activation of the immune system and increasing the damage of myocardial cells (muscle tissue) and increasing the risk of cardiovascular disease [17, 18].

2.3. Hypoxemia

It is the condition in which low arterial oxygen supply leads to the accumulation of oxygen free radical. To maintain an adequate level of oxygen, pump blood is intensified and prone to shortness of breath, rapid heart rate and myocardial infarction [19].

2.4. Stress response

In 20-30 % of COVID-19 patient severity of illness closely related to hypertension [7]. Interaction between the host cell and virus is a sophisticated process where interaction among the tissues and organs takes place. Meanwhile, a human response like fear, anxiety increases the human stress level. Catecholamine (monoamine neurotransmitter) reacts to stress in the body and mainly released in large quantities. That causes an increase in heart rate, breathing and blood pressure level. ACE I (Angiotensin-converting enzyme Inhibitors) are the class of medicine used for the treatment of high blood pressure. It caused a decrease in blood volume, therefore less oxygen demand from the heart, which leads to lower blood pressure. Animal studies show that ACE I drugs significantly increase the ACE 2 biological activity in rat cardiomyocytes [6, 20]. In the human body, it is unclear that these drugs increase the susceptibility of COVID-19. Therefore, the high blood pressure patient should not change the ACE I treatment plan without severe adverse reaction [7].

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3. COVID-19 and testing

Early detection of COVID-19 is essential for the prevention and control of this pandemic. The patient, which showing early onset of symptoms clinical characteristic (CT (Computed Tomography) image), cannot alone diagnose the COVID-19. Nucleic acid detection-based RT-PCR test more rapid, reliable and more sensitive toward early detection of COVID-19.

3.1. Reverse Transcription Polymer Chain Reaction (RT-PCR) test

RT-PCR testing technique used for the in-vitro diagnosis of COVID-19. This technique used for the qualitative detection of nucleic acid from the SARS-COV-2 RNA in the upper and lower respiratory tract during the acute phase of infection [21]. Tahamtan et al. perform an RT-PCR test for 2 patients for the detection of COVID-19. The test became undetectable for patient-1 after the 14-15 days and for patient-2 after the 18-20 days since the onset of symptoms. This suggested that COVID-19 disease shows different viral load kinetics in an individual patient. Therefore, the period of disease and sampling timing plays an essential role in the testing results [22]. False-negative and false-positive results are critical issues with RT-PCR. Negative results do not exclude the possibility of infection and false-positive results are the risk to the patient. Therefore, it is advisable to use a combination of CT image features and RT-PCR for the COVID-19 disease management that could reduce the inaccuracy in the results. It is advisable for all laboratories and hospitals should use standard guidelines and reporting procedures based on their public health policies to avoid any inconsistency in results. Sometimes contaminated sample leads to a false-positive or false-negative result. Therefore, the use of a sputum sample is suggested for the most accurate RT-PCR testing [23].

Due to the shortage of laboratory-based RT-PCR molecular testing and regent's, the manufacturer has begun to sell antibody test kit that can work outside the laboratory. These test kits are based on protein detection from the SARS-COV-2 and the human respiratory specimen like blood, sputum and throat swab.

3.2. Rapid test based on antigen detection from viral body

The rapid diagnostic test detects the viral protein (antigen) presence in the COVID-19 virus from the human respiratory tract. If the antigen present in the sufficient concentration in the human respiratory sample, it binds to a specific antibody enclosed in a device and starts to replicate it. Visible lines on the test kit paper show the detection of this antigen. This test is useful for the detection of early infection. The sensitivity of the test depends upon the time from the onset of symptoms, quality of the sample type, the concentration of the antigen in the respiratory tract and precise concentration of the reagents in the kits. Typically, the visual line is detectable on the test kit within 30 minutes. Bruning et al. found that the sensitivity of this test can be expected within the range of 34-80% [24]. Based on this information, it can be expected that more than half of the COVID-19 patients will be missed by such testing. There may be a chance of false-positive and negative results. If the person is suffering from human coronavirus that causes the common cold, such a test will detect the antigen and shows the false-positive result and further treatment of such a patient might be risky. Therefore, second-generation test kits are required for the detection of COVID-19 in the early stage, which needs adequate

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research and testing. Therefore, WHO currently not recommending the use of rapid diagnosis antigen kits for the detection of the SARS-COV-2 virus [25].

3.3 Rapid test based on antigen detection from the host body

Rapid test kits are the qualitative, immunochromatographic assay detects the IgG and IgM antibody present in the human respiratory sample. This test detects the antigen from human blood and believes that the patient has been infected from COVID-19 disease. The antibody response for all the individuals is not the same; it depends on several factors, including the severity of the disease, age, nutrition status and infection like HIV that suppress the immune system [25-28]. Figure 1 shows the antibody response with days of infection. Studies show that the majority of patients develop an antibody response in the second weak from the onset of symptoms. Therefore, this antibody kit should not use for the early body diagnosis of COVID-19. This suggests that antibody response is higher in the recovery phase, where most of the opportunities for clinical intervention transmission risk pass away. This test targets the antibody response that may also cross-react with the human pathogen, including coronavirus [27] and shows false-positive results. Eventually, the WHO does not recommend the use of this test for patient care. The testing can be continued in disease surveillance and epidemiological research [25]. A chart for the COVID-19 detection technique shown in Figure 2. Table 1 represents the clinical significance of testing results.

4. COVID-19 and meteorological factor

Currently, countries which are situated in the low-temperature region are suffering more from COVID-19 disease. Therefore, it is necessary to understand the effect of meteorological factors such as ambient temperature, humidity, diurnal temperature range, wind speed and geographical location of the countries. Apart from these factors, the transmission of the virus can be affected by many other parameters such as population density, medical care quality and policymaker decision, social and political factors [31]. Wang et al. [32] found that the transmission rate of COVID-19 disease in the warm and humid region of china was less as compared to the cold region. Arajo et al. [33] found that globally 95% of total cases occur in the dry climate where average temperature exists between 2-10 °C. A newsletter of MIT (Massachusetts Institute of Technology The Institute) on 19 March 2020 shows that transmission of COVID-19 frequently occurring in the countries where the annual average temperature lies in the range of 3 °C to 17 °C. Only 6% of the total causes observed in the region where the average annual temperature was above 18 °C [33]. Mohesen et al. [34] conducted the study in Iran and found that Alborz, Tehran, Mazandaran, Gilan and Qom cities were more susceptible to the COVID-19 transmission as compared to the Southern province of Iran. For this study, they considered several factors, including population density, number of infected people by COVID-19, average temperature, intra provincial movement, average precipitation, and infection days from the zero patient days, wind speed and solar radiation. They found that population density and interprovincial movement directly affect the COVID-19 transmission rate. Areas with low humidity, solar radiation exposure and wind speed were more susceptible to the COVID-19 outbreak. Jiangtao et al. [35] study the impact of the meteorological factor

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on the transmission of SARS-COV-2 in the 30 provincial capital cities in China. They found that pandemic might gradually decrease with rising temperatures with effective implementation of public health policies in the coming month. One more study was conducted to see the correlation between ambient temperature and COVID-19 infection in 122 cities from china. Based on this study, it was reported that no evidence could support the number of cases declining in warmer weather; but concluded that countries with temperatures below 3 °C at higher risk of SARS-COV-2 infection [36]. Oliveros et al. found that 82% variation in disease doubling time-related to the transportation, public health policies, migration and the remaining 18% variation may be due to the weather condition. Based on this study it can be suggested that temperature and weather condition is not the only factor that affects the spread of COVID-19 virus, there are some other factors like geographical and government decision and policies that affect the transmission rate.

Yueling et al. [37] conducted a study in the Wuhan and try to correlate the mortality rate with diurnal temperature range (DTR), average temperature, relative humidity and air pollution ($PM_{2.5}$, PM_{10}, CO, NO_2, O_3, and SO_2). They found that DTR positively related with the COVID-19 mortality rate and average daily temperature and relative humidity negatively associated with mortality rate. This can be justified by the previous study where respiratory disease mortality increases with a decrease in temperature [38] and heat and cold effect (related to DTR) harm the respiratory system [39]. Similar results found by Kim et al. [40], where they conducted a study on 30 East Asian countries and found that an increase in DTR increases the risk of respiratory and vascular disease that increases the mortality rate. Lower humidity or dry air causes contraction of mucociliary clearance and results in a respiratory infection [41]. So, it is essential to maintain a proper environment for the patient inside the hospitals. To avoid such risk situations in Wuhan, hospital windows were kept open for 24 hours for ventilation. Therefore, indoor meteorological factor variation could be the same as an outdoor and sudden change in temperature can be avoided [37].

5. COVID-19 and diabetic patient

It is known that diabetic Mellitus (disease related to a high level of sugar in the blood) is the common comorbidities in diabetic patients [42, 43] and poor glycemic control in the diabetic patient causes the infection [44]. This shows that a diabetic patient is more susceptible to infection. A study was conducted on the 1382 diabetic patient with an average age of 51.5 years in Italy to access the mortality risk due to COVID-19. The first outcome of this study shows that diabetic COVID-19 patient is at high risk of ICU admission. For second outcome study was conducted on 471 people with 56.6 average age. It shows that the mortality rate was higher for COVID-19 suspected diabetic patients as compared to others [45]. Therefore, diabetic patient requires extra medical care with standard medical guidelines.

6. COVID-19 and hemodialysis patient

For hemodialysis patients, a study was conducted in Zhongnam Hospital of Wuhan University in China. Among 201 hemodialysis patients, 5 patients (average age 47-67) got confirmed the RT-PCR testing. The most common symptoms in those patients were diarrhea, fever, fatigue, abdominal pain and dyspnea. Out of these 5 patients,

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no one has developed acute respiratory distress syndrome, shock and any other complication [46]. This result suggested that hemodialysis patient does not require extra medical attention. SARS-COV-2 is a novel virus; therefore, data availability limits the further conclusion regarding hemodialysis patients.

7. COVID-19 and Anosmia

A French study reported the anosmia over half of the European COVID-19 patient (up to 24 March 2020) and often associated with dysgeusia. This study was conducted on 114 COVID-19 adult patients (age >18 years) conformed by RT-PCR testing. Children, pregnant women and patients with dementia were excluded from this study. Out of 114 patients, 47% of the patient detected with anosmia with an average age of 47 ± 16 years, and 67% of anosmia patients were female. Based on this result, it was reported that anosmia seems to be predominant in women and younger patients in the mean duration of 8.9 ± 6.3 days [47].

8. COVID-19 and human reproductivity

Till now, there has been no evidence that SARS-COV-2 directly affect the male and female gametes. There are no reports available that suggest the presence of the virus in female reproduction tract amniotic fluid in vaginal secretions. It was found that fever affects spermatogenesis in the male reproduction system. Therefore, maybe a chance of diminishes male fertility within 72-90 days followed by COVID-19 by reducing sperm concentration [48, 49]. Gametes obtained from COVID-19 patient does not require any special precaution (reducing exposure to cross-contamination of other laboratory tissues or non-infected partner) like HIV and hepatitis at laboratory scale due to lack of transmission of SARS-COV-2 through the blood or sexual content [50, 51]. Currently, there are no guidelines available for a sperm donor, infected by the COVID-19. This area required further investigation to ensure the safety of preserve gametes and the safety of patients undergoing reproduction [3].

9. COVID-19 and Pregnancy

A study reported that severe acute respiratory syndrome was the most severe disease for pregnant women. It was found that pregnant women require mechanical ventilation 3 times more than non-pregnant women [3]. Currently, no therapies are available for the pregnant COVID-19 patient; therefore, people are using mechanical ventilation to treat the complication. A study reported that Chloroquine (CQ) does not harm pregnancy [55]. A study was conducted in a New York City hospital on 43 SARS-COV-2 infected pregnant women. Out of 43 women, 29 were symptomatic and 14 were asymptomatic. By applying the disease severity index, it was found that 86% of women possess mild disease, 9.3 % exhibited severe disease and 4.7% shows critical disease. This result similar to the non-pregnant COVID-19 infected adult women, where 80% of women were subjected to mild diseases, 15% severe and 5% critical disease. There was no evidence of COVID-19 infection in neonates upon initial state on the very first day of life [52]. One more study was conducted in New York City tertiary care hospital on 7 pregnant COVID-19 confirmed patients with an average age of 32 years. Out of these, two of them were asymptomatic. It was found that symptomatic patient shows the cough, myalgia, fever, chest pain and headache as symptoms. Whereas asymptomatic patients after admission became symptomatic post-partum

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and requiring ICU admission [53]. Some study shows that due to characteristic immune response during pregnancy and potential risk form cytokine storm by COVID-19 infection, pregnant women may be infected by COVID-19 may face severe morbidity and even mortality. COVID-19 may alter the immune response at the maternal-fetal interface and affect the mothers and infants. Pregnant women more susceptible to respiratory pathogens; therefore, they may be more susceptible to COVID-19 infection than the general population. Till now, there is no evidence that infants born from the diseased COVID-19 mother have a higher mortality rate and vertical transmission of disease [3, 54].

10. COVID-19 and medication

10.1. Chloroquine (CQ) and Hydroxychloroquine (HCQ)

Chloroquine and its derivative Hydroxychloroquine are antimalarial drugs. The structure of both drugs is the same and works as a weak acid. These are the widely available drugs in countries like India, where malaria is endemic. It is also used for type II diabetic treatment patients in India since 2014 [55]. A Chinese center for disease control reported that the mortality rate in diabetic patients increases by 2.3% [56]; therefore, they need extra care and attention [43]. Due to the public health, emergency lot of medication is used to cure the COVID-19 patient. Some of these medications are the use of Chloroquine and Hydroxychloroquine. A study of Chloroquine and Hydroxychloroquine was conducted in vitro. Chloroquine is the potent anti-SARS-COV-1 effects in vitro. It interferes with the binding of viral to ACE 2 exists in the lungs and heart by creating a deficiency in the glycosylation receptor at the virus surface [55, 57]. It was found that the SARS-COV-2 virus also affects the ACE2 receptor. Therefore, recent study showing the use of Chloroquine and Hydroxychloroquine drugs for the treatment of COVID-19 patients. The use of these medicine affects cell signaling and produce a cytokine storm that regulates the immune system. A study reported that the standard dose of Chloroquine is highly effective in reducing the replication of the virus on the cell surface by penetrating the tissues [58, 59]. Some studies found that Hydroxychloroquine is the more favorable drug for the COVID-19 patient [60]. Therefore, the question arises whether these drugs have the same effect on the COVID-19 patient in all the stages like SARS-COV-1 patient. It was found that Hydroxyl molecule attached to Chloroquine makes it less permeable to the blood-retinal barrier and allows faster clearance from retinal pigment cells, thereby results in less risk of retinal toxicity [55, 61]. To check the effectiveness and safety of Chloroquine and Hydroxychloroquine, 15 clinical trials were conducted in China over more than 100 COVID-19 patients [62]. They conducted 8 clinical trials for Chloroquine, 6 clinical trials for Hydroxychloroquine and 1 clinical trial for a combination of Chloroquine and Hydroxychloroquine. They reported that chloroquine phosphate group efficiently reducing pneumonia and improving the lung's image findings. A dose of 500 mg chloroquine phosphate (300 mg dose of Chloroquine) recommended for adult COVID-19 patients, 2 times per day and not more than 10 days [63, 64]. Chloroquine and Hydroxychloroquine have the potential to prolongation of heart rate corrected QT interval (QTc). Prolongation of QTc increases the risk of sudden cardiac death. Therefore, a cardiograph is required before the starting of these drugs. QTc for a normal person may be less than or equal

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to 400ms [65], 410ms [66] and 420ms [67]. The risk of abnormal QTc for a male is above 450ms and in a female is above 470ms [68]. Therefore, a patient with 450-500ms QTc required ECG daily.

10.2. BCG (Bacillus Calmette Guerin) vaccine

BCG used as a vaccine against TB (tuberculosis). This vaccination is given to the children in most of the countries. Vaccination imitating pathogens leads to an expansion of memory T lymphocytes and B lymphocytes that can fight future exposure. During BCG vaccination, it was assumed that innate immune system, natural killer cell, compromising macrophages, white blood cells and neutrophils had no such memory to combat against future exposure. Netea et al. found that the innate immune system can develop memory known as "Trained Immunity." This helps in eliminating various non-mycobacterium infections, including staphylococci, candidiasis, yellow fever and influenza. Therefore, innate immune systems and trained immunity can be considered as a fighter against COVID-19 [69]. A study was conducted on the 179 countries to find the effect of BCG on COVID-19. They divided the country based on BCG vaccination (132 countries) and without BCG vaccination (21 countries) programme and the remaining 26 countries have unknown BCG status. They reported a 0.8 per million daily incidences of COVID-19 cases in countries with BCG vaccination and 34.8 per million in the without BCG vaccination. Such ecological studies confound too many biases, including the stage of the pandemic, disease burden, national demographics, and rate of COVID-19 testing. Here such co-relation does not mean causation. Till now, there is no evidence for the recommended of BCG vaccination for the prevention and control of COVID-19 disease. Therefore, WHO does not recommend the use of BCG for COVID-19 cure, but it continues the use of neonatal BCG vaccination in the countries at higher risk of tuberculosis [70].

11. COVID-19 challenges and strategies

11.1. Vaccine

Till now, there is no vaccine available for the SARS-COV-2. S1 domain of spike protein functions in the viral binding attachment of the host cell membrane; therefore, international research aimed at using the S1 domain of spike protein as a target for therapeutic anti-viral therapy for the vaccine development [3]. A total of 71 vaccines has been under review reported by WHO. Out of these 71, vaccine four vaccine has been prepared for the phase 1 trial and one vaccine has been prepared for phase 2 trial and the remaining vaccine is under clinical evaluation. Table 2 represents the details of these developed vaccines.

11.2. Asymptomatic patient

SARS-COV-2 proven exceptionally difficult due to asymptomatic and pro symptomatic spread as well as high person to person transmission. The asymptomatic person does not show any symptoms of COVID-19, including fever, shortening of breath, high heartbeat, headache, cough, sputum production, myalgia and anosmia. It is reasonable to say that asymptomatic represent a substantial contribution to disease spread [72, 73]. Due to this, healthcare workers are the vulnerable population at high risk of viral transmission. In Bhilwara's district

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of Rajasthan (India), one such case of viral transmission was observed wherein one private hospital 17 medical practitioners was infected by COVID-19, including doctors [74]. This hospital was largely responsible for the transmission of disease in this district. A study in New York City labor and delivery unit shows that out of 43 pregnant COVID-19 patients, around 32 % were asymptomatic during the admission [52]. Therefore, asymptomatic COVID-19 patient is a cumbersome task for the COVID-19 infected country. The only way to find such a patient is large scale testing.

11.3. Testing

The question comes in our mind that is testing the only strategy to control the transmission of COVID-19? Will a higher testing rate save more lives? Consider one example of Bolivia and Belgium, where the population of both countries is approximately the same. Bolivia tested 0.24 times the COVID-19 sample of Belgium. However, Bolivia has 866 confirmed cases with 46 deaths and Belgium have 45325 cases with 6917 death [77]. So, we can't think that more testing will save more life because transmission of disease may be featured as a geographical factor, meteorological factor, or public health policies. Some evidence shows that those infected with COVID-19 may be asymptomatic. It is challenging to track those asymptomatic patients unless public health organization testing in a cluster or individual gets tested on-demand [78].

A piece of digital video news in Boston reported that out of 397 people in a homeless shelter, 146 people were tested positive and all of them were not showing any symptoms of COVID-19. So, for such a situation, large-scale testing is required. In countries like India, wide-scale testing is neither feasible and nor advisable. Testing should be continued for the surveillance of COVID-19 patients to check the infected person is cured or not. Till now, all the available tests for COVID-19 are the first-generation ELISA **(**Enzyme-Linked Immunosorbent Assay**)**. We can't rely entirely on these tests because no test is entirely perfect and there is a possibility of a false-positive or false negative. So, extensive scale testing is not the only way of figuring out how the disease is spreading. There are some methods like syndromic surveillance [79], hotspot surveillance etc. that can be used to test the suspected COVID-19 patient. To control the transmission of COVID-19, one should follow the identify-track-trace and isolate strategy; just testing will not work alone.

11.4. Lockdown

India is the second-largest populated country in the world. Where community transfer would make the people panic and harm the population as well as the economy. Union government of India imposed lockdown over 1.32 billion people on 24 March 2020. It was an effort to put people in the biggest isolation. To find the effectiveness of lockdown, Raj and Prashant et al. [75] used a kinetic model theory for the qualitative understanding of the complete lockdown in India. They found that in case of complete lockdown after 60 days since the onset of lockdown, less than 4% of the population exposed to at high risk of transmission, whereas without lockdown, more than 40% of the Indian population would have got exposed to high risk of transmission. WHO report stated that most of the region of Americas like United States of America, Brazil, Canada, and Mexico comes in the category of community transfer whereas India comes in the category of a

cluster of cases [76]. Late implementation of lockdown in the USA could be the reason for the exponential increase in COVID-19 cases. So, lockdown is an effective strategy to control the transmission of COVID-19 causes.

11.5. Body temperature measurement

To prevent the risk of transmission of the COVID-19 virus, most of the hospitals take adequate measures. These strategies include Personal Protective Equipment (PPE), information sharing, closure of multi entrances of the hospital building, establishment of outdoor quarantine station to check body temperature and completion of TOCC (Travel Occupation Contact Cluster) history for every individual entering to hospital. Fever is the respiratory symptoms of COVID-19 disease; therefore, most of the hospitals are using forehead thermometer and an infrared temperature detector. However, the thermometer shows typical reading in febrile conditions or even in hypothermia under the influence of environmental factors such as wind, rainfall, outdoor temperature. Ruan et al. found that accurate measurement of fever in cold environmental conditions requires at least 10 minutes for children to become acclimatized after coming from a cold environment [80]. Some patient takes antipyretics that decrease the body temperature to avoid outdoor quarantine. Interaction of such type of people in the hospital crowd may lead to the hospital staff at risk. In response to avoid such situations, a study was performed in Taiwan hospital. They made a rule of temperature checkup in the waiting area and again on the inside. During May 2020, hospital finds, out of 40887 visitors, only 5 patients were found temperature higher than 38 °C at the entrance of the hospital. However, 37 people were found to have fever inside the hospital during the second temperature measurement. Therefore, it is advisable for the hospital to takes repeated checkups of body temperature after acclimatizing to indoor. This simple strategy could play an important role in hospital prevention and control [81].

11.6. Economy

The biggest challenge for any COVID-19 affected country is to revive the economy from an unprecedented closure. It is expected that the pandemic will result in loss of skilled labor, a decrease in the pace of setting up infrastructure and even the scarcity of capital required for economic activities. The burden of high expenditure for containing the virus is going to affect the fiscal deficit target of the major countries. The temporary closure of industries, majorly MSMEs (Micro Small and Medium Enterprises), has made the workers cashless and this has led to a slump in demand. On top of this, to maintain social distancing, the restriction on agricultural activities has made the situation worse for marginal farmers.

The agricultural products sold to Mandi (Grain market) is also a major challenge and will affect the farmers strongly. To cope with COVID-19 and to practices social distancing in the workplace, countries have announced lockdown. The pandemic has resulted in a closure of factories other than those producing lifesaving drugs and other essentials. It is expected that pandemic will result in a loss of skilled laborers, as most of the workers are facing hardships and are returning to their native place. Even after the lockdown is lifted, the number of

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workers returning to their workplace is estimated to be low due to a lack of social security experienced in these hard times.

In a country like India, a large number of workers are daily wage laborers and are employed in the unorganized sector. Due to lockdown, these workers are facing a cash crisis and are likely to spend a very minimal amount on even the essentials. This could lead to a slump in demand, putting further strain on the economy. The lockdown has also impacted the small and marginal farmers in a big way. The agricultural activities are moving at a slow pace due to lockdown. In addition to this, due to restrictions on movements, it is difficult for farmers to sell their produce in agricultural markets. Farmers thus have to bear the excess inventory cost to their product for a more extended period. The procurement of urea and seeds required for agricultural activities have also become complicated and therefore, the farmers are likely to face a delay in their activities, which could affect the production. The farmers and workers constitute a large population of India and therefore, a major population of the country has to suffer due to the pandemic. Not only the laborers and farmers, but the pandemic has also hit the hospitality and tourism industry strongly. The hotels, taxi business, local artifacts have seen a slump in their business. It is estimated that pandemic can lead to the closure of around 50% of the small restaurants. The real estate sector is also facing difficulties in surviving. With almost no activities allowed in the real estate constructions, the industry has come to a standstill. The fact that the economy is cash-starved is making it difficult for real estate even to continue working. In these situations, the sector is expected to see a sharp decline in the demand leading to massive losses, as people are less likely to invest in properties. The lockdown has hit the aviation industry hard too. The aviation industry was already under immense pressure and losses. The halt in operations is increasing the troubles for the air carriers. The condition of the aviation industry is in such a fur moil that of the companies has announced a salary cut of up to 50% for their staff. With time, the companies might have to reduce their staff, resulting in job losses. All the industries under these strained conditions are expected to reduce their workforce leading to an unemployment crisis.

It would need both individual efforts and the government's determination to recover. While it would need considerable time to catch pace, the economy is expected to recover gradually. A behavioral change in consumer's choices is predicted to be seen concerning healthier items and organic products. International trade, tourism and transportation would require more time to scale up. Healthcare Industry has had the greatest advantage of the epidemic, although health professionals had to work for long hours, risking their own precious lives. Sanitizers, Face mask sales, have grown by more than 300%, and a behavioral change towards the use of sanitizers is expected. While we would face a high amount of loss due to the pandemic, it has given the economy a thought to work more on to date overlooked sectors, which have grown more important. COVID-19 pandemic has abrupt the supply chain between the major trading countries. In view of resuming the economic development and reducing the dependency of manufacturing products on China, the Japanese government has compiled a $2.2 billion package. This package for the help of Japanese manufacturing firms who wants to move out of China. Out of this $2 billion fund is for the manufacturing companies who want to shift their production from China to Japan and remain for the shifting of production to other countries [82]. The USA government is also previewing the support of manufacturing firms from China to other countries [83]. It

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shows that larger GDP countries are trying to reduce product dependency on other countries. During this pandemic, millions of people have lost their jobs; therefore, there is an urgent need to create employment opportunities. Now there is an opportunity for countries like India where land acquisition and skilled labor are easy to get. Now some states of India like Uttar Pradesh and Madhya Pradesh has modified the present labor laws to lure U. S. and Japanese manufacturing firm to move out from China.

12. COVID-19 is a lesson for society?

Despite being a deadly menace, COVID-19 has had some positive effects too. The concept of family, quality family time, friends, relatives, etc. has seen some positivity. The pandemic has taught us to be more sensitive towards our family members and well-wishers to find out time for people who matter in our lives. The disease has prompted us to be self-sufficient and self-reliant; it has made us understand the dignity of labor, the importance that our housemaids and other menial workers hold in our lives. As we discussed in the previous economic section that countries are trying to reduce their dependency on other countries. It taught the trading partners that self-sufficiency matters. Pandemic situation realizes the countries that without solidarity, it is not possible to combat COVID-19. Countries are helping each other during this crisis period by sharing medicine, PPE, test kits and other healthcare facilities. It creates a revolution in the field of education. During this period, most of the IT companies running on the concept of work from home. It realizes the less dependency on the IT sector on the infrastructure. Online classes, the meeting did a revolutionary digitally work in countries like India, where the digital divide is a major concern.

COVID-19 illuminate the strength and vulnerabilities of all the countries and taught a long-life lesson. It was observed that the prosperous economy had delayed the acceptance of the COVID-19 pandemic, therefore, failed miserably. Whereas those countries proactively accept the problem is safely combating with this pandemic. Every year millions of people dying because of air, water and land pollution. A global study reported the 23-lakh premature pollution-related death in India. Out of these, air pollution kills 12.4 lakh people, which is marginally behind from China (12.44 lakh). Globally half of the pollution-related premature death observed in India and China. One can imagine the enormity of the situation where 15 out of the top 20 cities are situated in India and most of them do not meet the WHO air quality standard [85]. Delhi (India) is one of the most polluted cities in India wherein the month of January (before transmission of COVID-19 disease) AQI was observed between 401-500, which remakes as severe conditions of air pollution and affects the healthy people by causing severe impacts on the existing disease. Now during lockdown 3.0, data shows the AQI between 51- 150 remarked as satisfactory to the moderate condition [86]. Such statistics show that COVID-19 has resulted in steep decline in pollution level in most of the cities of India. Therefore, it is feasible to say that COVID-19 saves millions of people living who were suffering from air and water pollution. This pandemic shows that there is much scope for research and development in the healthcare sector. A tremendous amount of infrastructure is required to combat such pandemic.

Conclusion

SARS-COV-2 has a mortality rate of 6.78 % worldwide, which is somewhat lower than that of MERS. A Higher R_0 value (2.24 - 3.58) of this disease spread it across the globe. There was no evidence of the spread of this disease from non-respiratory bodies. Diabetic patients and pregnant women were found to be more susceptible to COVID-19 infection. Anosmia was observed in the majority of the COVID-19 infected cases in European countries. No evidence indicates COVID-19's impact on the human reproductive system explicitly. No cases of vertical transmission of this disease have been observed until now. Statics and studies show a high risk of transmission for people living in cold countries. Pollution level, temperature Diurnal temperature range, geographical factor, humidity, pollution level, wind speed, population density, medical healthcare facilities social and political factor plays a critical role in transmitting the SARS-COV-2 virus. Higher levels of pollution cause severe effects on cardiovascular disease or disease that already exists. The imposition of lockdown not only helps to prevent the intra-movement and increase in the pollution level at the same time, it reduces the risk of severe condition and delays the transmission of risk. COVID-19 has been a lesson for humanity in the sense that it has faded the concept of Neo-determinism, and once again ushered environmental determinism. Climate Emergency seems very imminent now. Humankind has learned that sustainability and conservation efforts do matter. COVID-19 has taught us to shed off our welfare and work more towards the welfare of all.

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Conflict of Interest

We informed that the contributing authors do not have any conflict of interest related to this review article.

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Figures

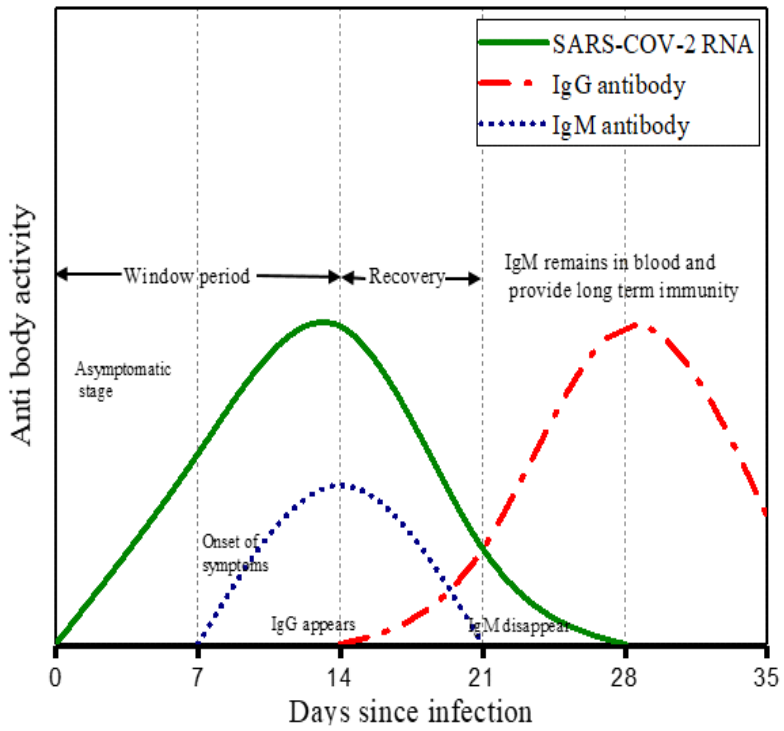

Figure 1: Schematic diagram of antibody response concerning with days of infection [29, 30]

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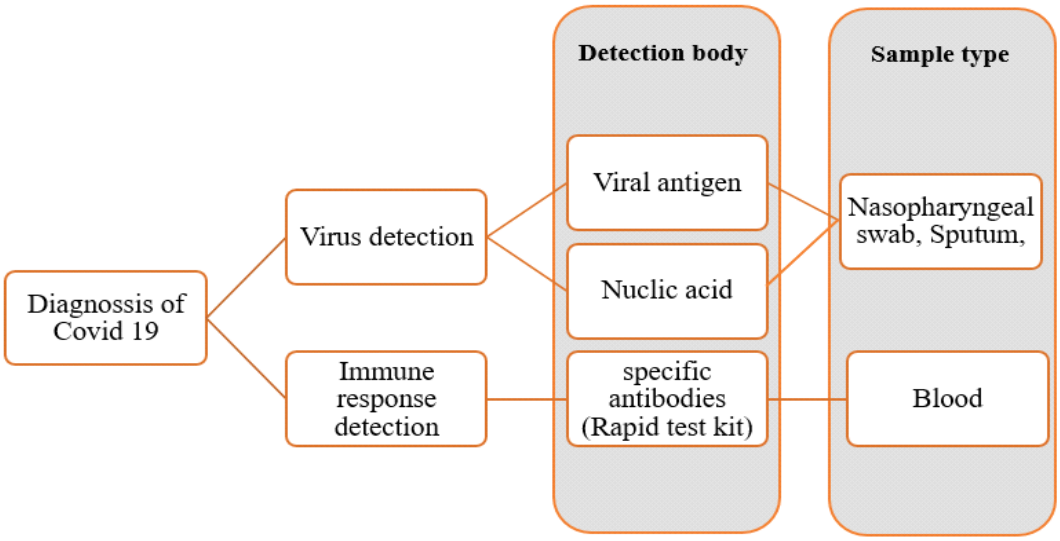

Figure 2: A Schematic diagram of COVID-19 diagnosis techniques [29].

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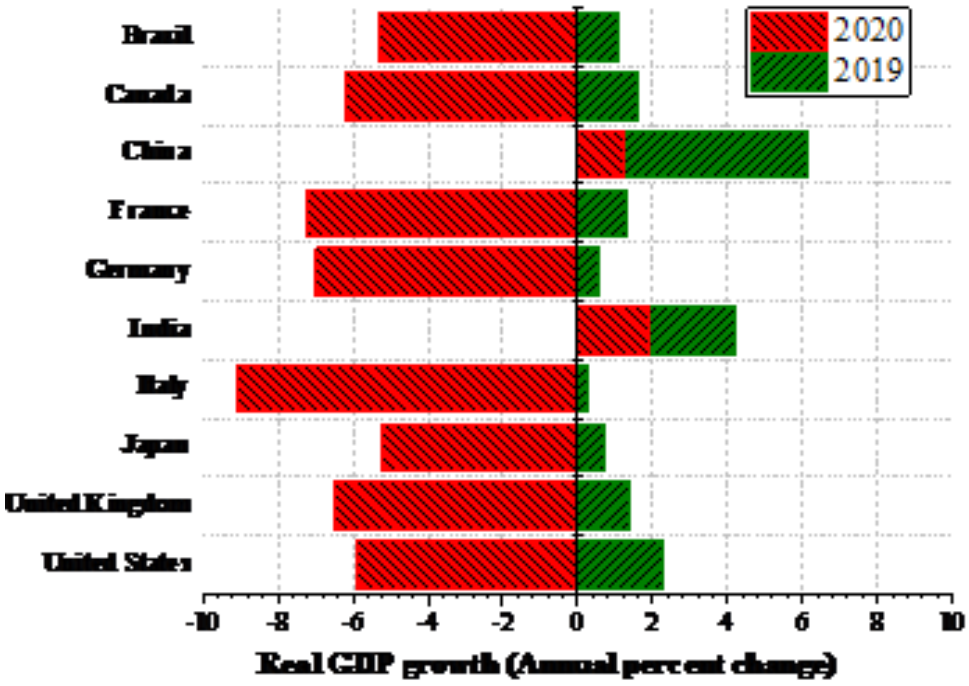

Figure 3: Annual percentage change in Real GDP growth for the nominal GDP countries [84]

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Tables

Table 1: Clinical significance of antigen and antibody test results [29, 30]

Test results			Clinical significance
RT-PCR	IgM	IgG	
+ve	-ve	-ve	A patient may be in the window period of infection.
+ve	+ve	-ve	A patient may be in the early stage of infection.
+ve	+ve	+ve	A patient is in the active phase of infection.
+ve	-ve	+ve	A patient may be in the late stage of infection.
-ve	+ve	-ve	A patient may be the early stage of infection. (RT-PCR may be false negative)
-ve	-ve	+ve	A patient may have a past infection or recovered.
-ve	+ve	+ve	A patient may be in the recovery stage of infection. (RT-PCR may be false negative)

Table 2: COVID-19 candidate vaccine [71]

Platform	Type of vaccine	Developer	The current stage of evaluation
Non-Replicating Viral Vector	Adenovirus Type 5 Vector	CanSino Biological Inc./Beijing Institute of Biotechnology	Phase 2 ChiCTR2000031781 Phase 1 ChiCTR2000030906
DNA	DNA plasmid vaccine Electroporation device	Inovio Pharmaceuticals	Phase 1 NCT04336410
Inactivated	Inactivated	Beijing Institute of Biological Products/Wuhan Institute of Biological Products	Phase 1 ChiCTR2000031809
Inactivated	Inactivated + alum	Sinovac	Phase 1
RNA	LNP encapsulated mRNA	Moderna / NIAID	Phase 1 NCT04283461