



International Journal of Biological Innovations

Available online: <http://ijbi.org.in> | <http://www.gesa.org.in/journals.php>

DOI: <https://doi.org/10.46505/IJBI.2020.2101>



E-ISSN: 2582-1032

Review Article

COVID-19 : TOWARDS CONFRONTING AN UNPRECEDENTED PANDEMIC

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Received: 23.04.2019

Accepted: 30.04.2019

Published: 05.05.2020

Abstract: Latest 73rd report of COVID-19 from national authorities to WHO by April 2, 2020, there are 896450 confirmed cases with 45526 deaths globally. 0 to 14 days is the average range of incubation period. Recent study from China Center for disease control (CDC) showed that most of the patients were asymptomatic in its early days of infection that leads to widespread of virus. Nosocomial transmission is another serious problem the world is facing with this public health crisis. Coronaviruses are known to cause respiratory and enteric disease in human and animals. These are round or oval and pleomorphic in shape. Limited information is present till now about COVID-19. It suggests that its infection ranges from previous coronavirus encounters. Here in this review we summarize all information present till date and also a brief comparison to SARS and MERS. This is to identify the gaps in knowledge to share resources to recover from COVID-19. It also includes pharmaceutical drugs that showed a negative impact on SARS-CoV-2 in *in-vitro* studies that can be used for its treatment till a suitable vaccine candidate is available. The most important task at this hour is to find a vaccine for the infection. Moreover, the research needs to be conducted for finding measures to face this kind of challenges in future.

Keywords: Clinical manifestation, Epidemiology of COVID-19, Outbreak, Prevention, Viral mystery.

INTRODUCTION

According to wall street journal patient zero for COVID-19 has been identified as a 57 years old Shrimps seller, Wei Guixian in the Huanan sea food market of Wuhan, China. She developed common cold symptoms and visited local clinic on December 10, 2019. On December 16, 2019 she visited Wuhan Union Hospital where she didn't respond to the common cold treatment and she was quarantined by the end of December 2019. Till then a group of patients showing same

symptoms were observed in Wuhan, China. WHO identified the causative agents as corona virus and named the disease as COVID-19 (Corona Virus Disease 2019) on February 11, 2020. Based on the different similarity indices (e.g. phylogeny) to SARS (Severe acute respiratory syndrome) and MERS (Middle East respiratory syndrome) International Committee on Taxonomy of Viruses (ICTV) renamed it as SARS-CoV-2.

Originated in Wuhan sea food market the virus travelled internationally with the people moving out of transportation hub. Around 175000 people left Wuhan on January 1, 2020 only to celebrate lunar New Year and around 7 million in January, 2020. First overseas patient for COVID-19 was a 61 years old lady in Bangkok on January 13, 2020. The first death was recorded on January 11, 2020. As there were exponential rise in the cases Wuhan city (11 million people) was under lockdown on January 23, 2020. Very soon India and other countries evacuated their citizens from China and placed them under isolation for 14 days. According to a report in *The Lancet* the initial response of European countries was slow that leads to worse situations in these countries as compare to China while countries like Hong and South Korea had tested these earlier leaving them in better situation to tackle the infection.

The novel corona virus has no border, no religion, beyond cast and creed. It is highly contagious in nature and unpredictable. World was never prepared for this kind of pandemic, where we are in a race of developing a vaccine against its spread.

Epidemiology of COVID-19

As the cases for the disease are increasing with every passing hour more epidemiology features are revealed. Similarly to the SARS and MERS, COVID-19 is a zoonotic disease with intermediate host. Intermediate host for SARS-CoV and MERS-CoV is palm civets and camels while the possible intermediate host for SARS-CoV-2 is pangolin or snakes. The reserve host for all the three is bat. Bats carry so many viruses and around 200 corona viruses without getting sick.

So the primary mode of transmission is from bats to intermediate host to humans. Possible routes of transmission of 2019-nCoV is respiratory droplets and physical contact. It is also believed that it can spread fecal-oral transmission. Suspicion is there over aerosol possibility and pregnant woman to her child.

The transmission can be direct in the form of droplets produced during sneezing, coughing, speaking and accidentally inhaling the droplets in a

closed proximity of an infected person. Droplets are water holding entities of diameter more than 5 micrometer and these can be caught by a healthy person within a certain range of 1 m approximately. The indirect transmission is when virus is deposited on a dead surface like door bells, lift buttons, stairs, vegetables, fruits etc. which may come in contact with rest healthy persons frequently. From here the virus reaches to eyes, nose and mouth and finally leads to a new corona patient. Hence avoid touching your face frequently and wash your hands for 30 seconds under running water. Even fecal matter of infected patients is found to be the transmitting source. There is no proof of aerosol transmission has been reported. An investigation carried by Chen *et al.*, 2020 on 9 COVID-19 positive pregnant women showed all negative results from all possible sources (amniotic fluid, breast milk and neonatal throat swab etc.). One of these 9 babies was tested positive for the disease but that could be because of post-delivery negligence.

Nosocomial transmission is a serious problem related to all the three viruses. This property leads to extreme burden on the health system and hindered early detection of infected persons. Wang *et al.*, 2020 reported that 41% patients were suspected to be infected due to nosocomial transmission, 26% patient received ICU care and mortality of 43% from 138 COVID-19 hospitalized patients. WHO categorize COVID-19 into four stages on the basis of its spread. The four stages include Stage 1 (imported cases), Stage 2 (local transmission), Stage 3 (community transmission) and Stage 4 (transmission out of control). On the basis of severity it can be divided as mild, moderate, severe and critical. The main traits of this virus are highly penetrative and spread like a forest fire in jungle as we have witnessed with respect to China, Italy, Spain and now America already in community transfer. Initially it is out-breaking locally than community wise but now on the pave of global widespread pandemic.

Earlier epidemiological and laboratory studies on coronavirus showed that temperature has an impact on its transmission and survival (Doremalen *et al.*, 2013). Recently a study

conducted by Zhu and Xie on 122 affected cities of China showed that temperature relationship of novel coronavirus is positive linear up to 3°C mean temperature above which it becomes flat showing higher temperature can't have an impact on its transmission.

Studies showed that virus takes entry to the respiratory mucosa by Angiotensin receptor 2 (ACE₂) present in lower respiratory tract in abundance (Singhal 2020) mainly in type 2 alveolar cells. The same receptor is used by SARS-CoV (Zhou *et al.*, 2020). Death cases are mainly middle-aged and elderly patients with pre-existing diseases history (hypertension, coronary heart disease, and diabetes).

Etiology of COVID-19

On January 7, 2020 WHO recognized the virus as the corona virus with >96.2% similarity with bat corona virus CoV RaTG13, 79% to SARS-CoV and 50% to MERS-CoV (Wang *et al.*, 2020), table 1 showing comparison of three. Corona viruses are classified into four genera *i.e.* alpha corona virus,

beta corona virus, gamma corona virus and delta corona virus (Li 2016). The first two mainly infect the humans. Till now there are 7 strains of corona viruses that infect human being in upper respiratory tract and show common cold symptoms. These are HCoV- 229E, HCoV- NL63H (alpha), CoV- OC43, SARS-CoV, HCoV- HKV1, MERS-CoV and SARS-CoV- 2 (beta). The genera join the family *Coronaviridae* and order *Nidovirales*. Corona virus is an enveloped positive sense single stranded RNA virus with glycoprotein protrusions on the surface giving it a crown like appearance under microscope. On January 10, 2020 a research team led by Prof. Yong- Zhen Zhang published first genome of SARS-CoV-2. Its genome ranges from 29891-29903 ribonucleotide (Wang *et al.*, 2020) with one of the largest RNA genome among mammalian viruses (Woo *et al.*, 2009). SARS-CoV-2 genome possesses 14 open reading frames encoding 27 proteins. The four major structural genes encode for spike surface glycoprotein(S), small envelope protein (E), matrix protein (M) and nucleocapsid protein (N) (Wu *et al.*, 2020). The spike

Table 1: Epidemiological characteristic of three coronavirus diseases.

| Characteristics | SARS | MERS | COVID-19 | References |
|---------------------|----------------------------|---------------------------------------------|-----------------------------|----------------------------------------------------|
| Causative agent | SARS-CoV | MERS-CoV | SARS-CoV- 2 | WHO, Guo <i>et al.</i> , 2020 |
| Genus lineage | B | C | B | Song <i>et al.</i> , 2019, Wu <i>et al.</i> , 2020 |
| Time period | November 2002- July 2003 | April 2012- November 2019 | December 2019 | WHO |
| Incubation period | 10 days | 2- 14 days | 2- 14 days | WHO |
| Reproductive number | 2- 5 | 0.3- 0.8 | 2- 3.5 | WHO, Wang <i>et al.</i> , 2020 |
| Cases | 8098 | 2494 | 896450 | WHO |
| Deaths | 774 | 858 | 45526 | WHO |
| Origin | China | Saudi Arabia | China | WHO, Guo <i>et al.</i> , 2020 |
| Countries hit | 26 | 27 | 206 | WHO |
| Fatality rate | 9.6% | 34.4% | 5.17% | WHO |
| Intermediate host | Palm civets | Dromedary camels | Pangolin/ snakes | WHO, Wang <i>et al.</i> , 2020 |
| Reserve host | Bat | Bat | Bat | WHO, Wang <i>et al.</i> , 2020 |
| Median age | 41 | 53 | 47 | WHO |
| Sample collection | Upper respiratory specimen | Upper and lower respiratory specimen, blood | Upper respiratory and blood | WHO |

| | | | | |
|------------------------------|--------------------------------------------------------|-----------------------------------|-------------------------------------------|----------------------------------------------------|
| Diagnosis | RT-PCR, Serological testing of antibody, viral culture | RT-PCR, ELISA, IFA, viral culture | RT-PCR, blood testing, chest CT scan | WHO |
| Transmission | Human to human | Human to human | Human to human | WHO |
| Temperature effect | Yes | Yes | No | Zhu and Xie 2020 |
| Receptor | ACE ₂ (Angiotensin receptor 2) or CD209L | DPP4 (Dipeptidyl peptidase 4) | ACE ₂ (Angiotensin receptor 2) | WHO |
| Open reading frame in genome | 11 | 11 | 14 | Song <i>et al.</i> , 2019, Wu <i>et al.</i> , 2020 |
| Length of nucleotides | 29727 | 30119 | 29903 | Song <i>et al.</i> , 2019, Wu <i>et al.</i> , 2020 |
| Nonstructural protein | Atleast 5 | 16 | 16 | Song <i>et al.</i> , 2019, Wu <i>et al.</i> , 2020 |
| Accessory protein | 8 | 5 | 11 | Song <i>et al.</i> , 2019, Wu <i>et al.</i> , 2020 |

glycoprotein helps in the anchoring of virus to ACE₂. Spike protein is the most divergent and conserved protein for corona viruses so can be used for its detection. Nucleocapsid is the most abundant and easy to detect protein. A recent study by Wang *et al.*, 2020 showed that SARS-CoV-2 has a unique RRAR motif in spike protein that is not present in pangolin corona virus that confirms that the primary host of SARS-CoV-2 is different. Corona virus showed rapid mutation rate as per genome analysis from different patients of different provinces of China.

Clinical symptoms

The computerized tomographic chest scan of asymptomatic or mild disease patients is usually abnormal. The common symptoms experienced by moderate patients are high fever malaise and dry cough, shortness of breath (within 8 days of infection), fatigue, muscle pain, confusion, headache, sore throat, diarrhea, and vomiting (Guan *et al.*, 2020, Chen *et al.*, 2020) along with radiographic features. Some rare symptoms include runny nose. Severe patients show one of dyspnea, RR>30 times/min, oxygen saturation <93% or PaO₂/FiO₂<300 mmHg.

Critical patients show either one of the acute respiratory distress syndrome (ARDS), septic shock, metabolic acidosis, clotting disorders, and

multiple organ failure. Lymphopenia (depletion of CD4 and CD8 lymphocytes) is a deciding factor for disease severity and mortality.

Laboratory symptoms

Studies have shown that no difference in viral burden between symptomatic and asymptomatic people while higher viral loads in the nasal cavity as compared to the throat (Zou *et al.*, 2020). Laboratory features of COVID-19 include increased activity of some enzymes like lactate dehydrogenase, alanine transaminase and creatinine kinase increased D-Dimer, increased C-reactive protein.

A case report by Xu *et al.*, 2020 biopsy study was done using the sample of lung, liver, and heart tissue of COVID-19 patient. The lung samples show following diagnostic characteristics: "bilateral diffuse alveolar damage with cellular fibromyxoid exudates, thickening of interlobular septa (Cobblestone changes). The lungs showed Interstitial mononuclear inflammatory infiltrates, dominated by lymphocytes, evident desquamation of pneumocytes, pulmonary oedema and hyaline membrane formation, indicating acute respiratory distress syndrome. Multi nucleated syncytial cells with atypical enlarged pneumocytes characterized by large nuclei, amphophilic granular cytoplasm, and

prominent nucleoli were identified in the intra-alveolar spaces, showing viral cytopathic-like changes. The liver biopsy samples showed moderate microvascular steatosis and mild lobular and portal activity. There were a few interstitial mononuclear inflammatory infiltrates, but no other substantial damage in the heart tissue. Peripheral blood was prepared for flow cytometric analysis. We found that the counts of peripheral CD4 and CD8 T cells were substantially reduced, while their status was hyper activated. Moreover, CD8 T cells were found to harbor high concentrations of cytotoxic granules.”

Diagnosis

Diagnosis of the COVID-19 is based on epidemiological features. Laboratory detections included for earlier coronaviruses include genomic sequencing, RT-PCR, enzyme-linked immunosorbent assay (ELISA) and blood (antibody) tests. As the present virus is new so the world is currently facing the problem related to its detection. Learning from previous encounters suspected patients, are diagnosed with chest CT, molecular technologies. Nucleic acid tests (RT-PCR) are fast and more reliable. However, there are certain limitation attached with these test as false results, contamination of nasal and throat swabs and short detection window. Enzyme-linked immunoassay (ELISA) was highly recommended as sampling through blood is much less stringent, quick results and cost effective as well. Antigens used in ELISA may react with antibodies against 4 other human coronaviruses that occurred in common colds. With the increasing number of cases the rapid detection kits are also being to be used in different countries. These kits use blood sample and look for the antibodies (IgM and IgG) because they provide longer detection window and also recognize the asymptomatic patients. Also antibody test can be used to verify vaccines under trial (table 3).

According to a study sensitivity of chest CT is more as compare to RT-PCR as in some cases the RT-PCR shows negative results initially (Fang *et al.*, 2020). A study published on *preprint bioRxiv* on March 14, 2020 claims that there can't be reinfection of SARS-CoV-2 in infected *Rhesus*

macaques. On contrary some patients are complaining about reinfection is just because of false nucleic acid test results.

Treatment

Till now there is no prescribed drug for treatment of COVID-19. Different approaches are used for different patients on the basis of severity. Four principles are important in patient management: “early recognition”, “early isolation”, “early diagnosis” and “early treatment” (Chen *et al.*, 2020). Based on earlier SARS and MERS encounter different antiviral drugs are being practiced in different combinations to combat COVID-19.

Bed rest; monitor the blood pattern, water-electrolytes balance, finger oxygen saturation, urine routine enzyme indications and chest CTs. According to oxygen saturation, give oxygen therapy by nasal catheter, noninvasive or invasive mechanical ventilation or mask.

For severe patients requirements are pulse oxymetry, oxygen therapy, non-invasive and invasive ventilator therapy. There are some drugs are under trial in clinics and *in-vitro* in laboratories (table 2).

Chloroquine phosphate (quinine derivative), an old drug (treatment of malaria) with new use is shown to have apparent higher success and admissible safety against COVID-19 in China. Chloroquine is a low cost and safe drug that has been used for more than 70 years. So any potential risk can be ruled out safely. While another derivative, hydroxychloroquine is less toxic earlier used against lupus, porphyria etc.

Intravascular immune globulin, corticosteroids can be used in certain mild or moderate cases. For respiratory support, ventilation technique and hemo (dia) filtration / plasma exchange can be applied.

According to a study published in *The Lancet* claims on the basis of artificial intelligence (AI), JAK-STAT signaling inhibitors can be used for the treatment of COVID-19. Baricitinib, fedratinib, and ruxolitinib are potent and selective JAK inhibitors which are also powerful anti-inflammatory in nature. . Other combination

Table 2: Drugs showing antiviral potential effect against COVID-19.

| Drug | Mode of administration | Mechanism | Earlier uses | Side effects | References |
|-------------------------|-------------------------------------------------|-------------------------------------------------|-----------------------------------|-----------------------------------------------------------------|-------------------------------------------------------------------|
| Lopinavir/ Ritonavir | Oral | Protease inhibitor. | HIV/SARS/ME RS | Diarrhea, vomiting, muscle pain headache, | Dong <i>et al.</i> , 2020 |
| Darunavir | Oral | Protease inhibitor | HIV | Liver and Pancreas damage | Dong <i>et al.</i> , 2020 |
| Arbidol | Oral | Inhibit viral and cell membrane fusion | Influenza/SARS/ Bronchitis | Allergic reaction | Dong <i>et al.</i> , 2020 |
| Nitazoxanide | Oral | Antiprotozoal agent | Antiviral | Vomiting, stomach pain, discolored urine | Rossignol 2014, 2016 |
| Favipiravir | Oral | Nucleoside analogue | Ebola/influenza/ H1N1 | Decrease RBC production, increased liver function | Furuta <i>et al.</i> , 2013 Cardile <i>et al.</i> , 2017 |
| Ganciclovir | Oral | Nucleoside analogue | Cytomegalovirus | Cardiac, eye, ear disorder | Singhal 2020 |
| Penciclovir | Topically, oral | Nucleoside analogue | Herpes simplex virus /VZV | Redness, burning, numbness | Guo <i>et al.</i> , 2020 |
| Oseltamivir | Oral | Neuraminidase inhibitor | Influenza | Nausea, vomiting | McQuade and Blair 2015 |
| Ribavirin | Intravenous infusion | Nucleoside analogue | HCV/SARS/ MERS | Nausea, fever, headache | Wang <i>et al.</i> , 2020, Tsang and Zhong 2003 |
| Nafamostat | Intravenous | Synthetic serine protease inhibitor | Influenza/ MERS/Ebola | Cardiac arrest | Nishimura and Yamaya 2015 |
| Remdesivir | Intravenous infusion | Nucleoside analogue | Ebola/SARS /MERS | Increased liver enzyme, nausea, vomiting | Dong <i>et al.</i> , 2020, Wang <i>et al.</i> , 2020 |
| Chloroquine | Oral | 9-aminoquinolin | Malaria/ Autoimmune disease | Vomiting, nausea, seizures, deafness, vision change | Vincent <i>et al.</i> , 2005 |
| Azithromycin | Oral, intravenous | Inhibit translation of RNA | Antibacterial infections | Anaphylaxis, QT prolongation, diarrhea | Indian government |
| Interferon α | Intravenous infusion and vapor inhalation | Inhibit DNA synthesis | Hepatitis, leukemia | Shortness of breath, depression, muscle pain | Dong <i>et al.</i> , 2020 |

suggested by same study is sunitinib and erlotinib, which are used for a wide range of virus treatment.

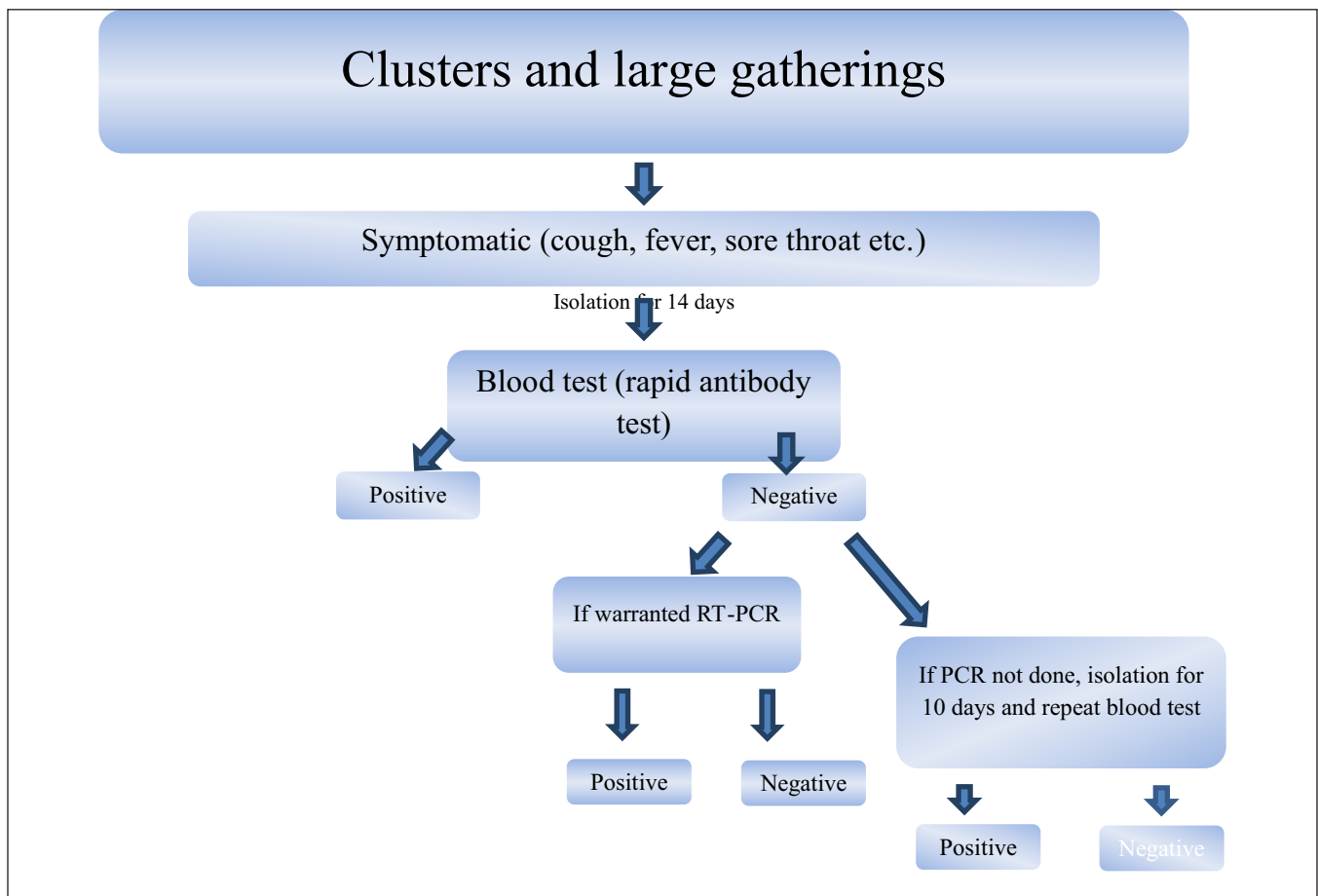
Recovery started in the 2nd or 3rd week with median stay in hospital was 10 days (Singhal 2020).

Prevention and control

Local transmission will lead to clustering of cases in time and space. The prevention strategy will

be: hand hygiene, testing, isolation, quarantine of suspected and close related contacts and social distancing. Contagious during the latency period, nosocomial transmission and asymptomatic transmission are some of cause of widespread of COVID-19.

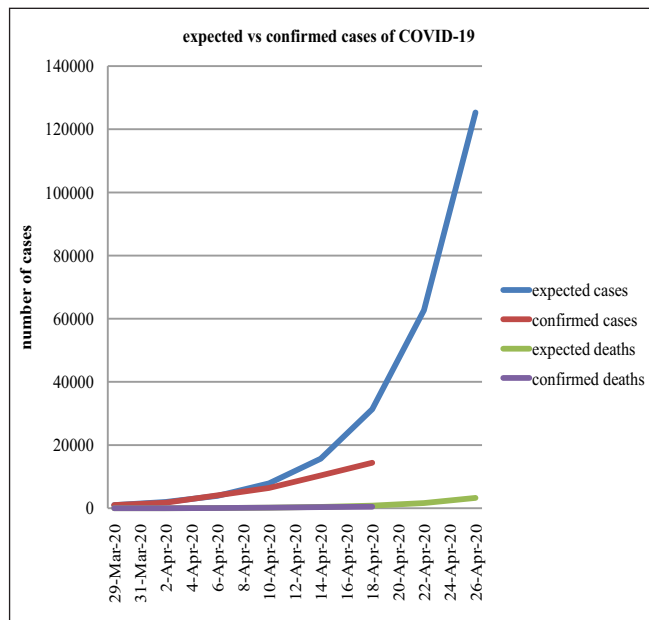
Coronaviruses are sensitive to heat (killed at 56°C for 30 min) and ultraviolet rays. These can be killed using ether, ethanol (75- 80% concentrate), chlorine disinfectant, peracetic acid, chlorine



Graph1: Strategy to use blood tests as recommended protocol by Indian Government. All tests that end at positive are probable COVID-19 cases and needs isolation and if symptoms worsen, move to designated COVID-19 hospitals while negative are non COVID-19 cases that are susceptible by Indian Council of Medical Research.

and chloroform can effectively inactivate the virus, but not chlorhexidine. Health caretakers shortages due to infection (due to poor or lack of PPE) put further pressure on already strained health systems. Hydroxychloroquine has been recommended as chemoprophylaxis drug for use by asymptomatic healthcare workers managing COVID-19 cases and asymptomatic contacts of

confirmed COVID-19 cases (Chen *et al.*, 2020). Along with whole world India is at a rescue mission to safeguard humankind from this deadly corona virus. All states of India are under complete lockdown for a period of 21 days under the Disaster Management Act, 2015. This step of social distancing is being appreciated globally. Measures taken by Indian government:



Graph 1: showing the comparison of expected to the confirmed cases of COVID-19 in India and also a prediction about the number of cases in next few days on the basis of mortality rate and doubling time (data from WHO). The change in the number is the positive effect of lockdown announced by Indian government.

- Tracing contact of infected persons
- Suspension of all transport medium (bus, train flights except the urgent ones)
- Economical help to poor, daily wage earners through a special budget
- Railways coaches converted to isolation wards
- Tasks to reduce mental stress
- Coordinated approach towards scientific community (collaboration, sharing and avoiding duplication of work)
- Sanitizing
- Walk in kiosk to test for COVID-19 to ensure safety of medical personals.

Personal measures include

- Maintaining cough hygiene
- Washing hands frequently
- Avoid touching eyes, mouth and nose with unwashed hands
- Wearing masks (as even saliva drops can transmit the virus)

- Regular decontamination of surfaces that can be possible source of infection
- People should stop spread of any COVID-19 related news instead back up by any scientific proof
- People should allay from panic and anxiety.

Discussion

The pandemic has made the world to stand united, with the sharing of assets, guidance and expertise from countries further ahead in the epidemic for better results in controlling the spread. Many nations have responded positively against COVID-19 while some yet have to take COVID-19 seriously. World's economy, education, social interactions and other global impacts are being significantly affected due to COVID-19.

To fight against COVID-19 pandemic, it is required to develop a vaccine against SARS-CoV-2. Recently WHO confirmed that as immediate response 2 vaccine candidates are under first phase of human trials and 60 on pre-clinical research table. According to a finding published by researcher Gonzalo Otazu in NYIT the Tuberculosis (TB) vaccine, Bacillus-Guerin (BCG) can be used as a potential weapon against COVID-19. They claimed that the countries having BCG vaccination has lower mortality rate.

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